Evidence Synthesis
Number 86

Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHS-290-2007-10057-I, Task Order No. 3

Prepared by:
Oregon Evidence-based Practice Center
Portland, Oregon

Investigators:
Kimberly K. Vesco, MD, MPH
Evelyn P. Whitlock, MD, MPH
Michelle Eder, PhD
Jennifer Lin, MD, MCR
Brittany U. Burda, MPH
Caitlyn A. Senger, MPH
Rebecca S. Holmes, MD, MS
Rongwei Fu, PhD
Sarah Zuber, MSW

AHRQ Publication No. 11-05156-EF-1
May 2011

The literature search conducted for this systematic review was completed in September 2010. A manuscript that was derived from this systematic review was published in *Annals of Internal Medicine* on October 18, 2011. In preparing this manuscript, the review team conducted an ancillary search in PubMed (September 1, 2010 to August 3, 2011) to identify any updated information from trials included (or identified as pending) in this review We also queried three selected experts to determine their knowledge about recent relevant publications on August 8, 2011.

Our search identified nine additional studies, none of which provided additional data on trials included in this review. Instead, the studies represented four reports from previously identified cohorts that were contextually relevant[1,2] or unrelated[3,4] to the focus of this review, one performance study for a new human papillomavirus test,[5] two unrelated reports from trial authors,[6,7] and two public health reports.[8,9]

None of these reports added any new data to our review. Several were added to the discussion section in the *Annals* manuscript, which is available at www.annals.org.

Additional Identified Reports

1. Katki HA, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol*. 2011;12(7):663-72.
2. Schiffman M, et al. A long-term prospective study of type-specific human papillomavirus infection and risk of cervical neoplasia among 20,000 women in the Portland Kaiser Cohort Study. *Cancer Epidemiol Biomarkers Prev*. 2011;20(7):1398-409.
3. Castle PE, et al. Variable risk of cervical precancer and cancer after a human papillomavirus-positive test. *Obstet Gyencol*. 2011;117(3):650-6.
4. Littell RD, et al. Risk of cervical precancer and cancer in women aged 30 years and older with an HPV-negative low-grade squamous intraepithelial lesion screening result. *J Low Genit Tract Dis*. 2011;15(1):54-9.
5. Castle PE, et al. Evaluation of a new DNA test for detection of carcinogenic human papillomavirus. *J Clin Microbiol*. 2011;49(8):3029-32.
6. Kotaniemi-Talonen L, et al. Intensified screening among high risk women within the organised screening programme for cervical cancer in Finland. *Acta Oncol*. 2011;50(1):106-11.
7. Anttila A, et al. Cervical cancer patterns with automation-assisted and conventional cytological screening: a randomized study. *Int J Cancer*. 2011;128(5):1204-12.
8. Arbyn M, et al. Worldwide burden of cervical cancer in 2008. *Ann Oncol*. 2011 Apr 6. [Epub ahead of print]
9. Franceschi S, et al. Eurogin 2010 roadmap on cervical cancer prevention. *Int J Cancer*. 2011;128(12):2765-74.

This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHS-290-2007-10057-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

None of the investigators has any affiliation or financial involvement that conflicts with the material presented in this report.

Suggested Citation: Vesco KK, Whitlock EP, Eder M, Lin J, Burda BU, Senger CA, Holmes RS, Fu R, Zuber S. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 86. AHRQ Publication No. 11-05156-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; May 2011.

Structured Abstract

Purpose: We conducted this targeted systematic evidence review of five key questions to assist the U.S. Preventive Services Task Force (USPSTF) in updating its 2003 recommendation on cervical cancer screening.

Data Sources: We conducted literature searches of the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, PubMed, the Health Technology Assessment database, MEDLINE, the Cochrane Collaboration Registry of Clinical Trials, and PsycINFO from January 2000 through September 2010. We also wrote trial authors for unpublished data and searched for updated publications from trials of human papillomavirus (HPV) screening.

Study Selection: We reviewed a total of 4,262 abstracts and 641 complete articles. We included 35 studies reported in 66 articles (only one of which was published at the time of the previous USPSTF review): five related to initiating cervical cancer screening, four comparing liquid-based and conventional cytology, 12 evaluating HPV for primary cervical cancer screening, four evaluating the use of HPV plus cytology screening, one evaluating cytology triage of primary HPV testing, six evaluating HPV for triage of abnormal cytology to colposcopy, and four evaluating the harms of HPV testing.

Data Extraction: Two investigators independently reviewed all abstracts against a set of a priori inclusion criteria for all key questions. One investigator abstracted data from included studies into evidence tables and a second reviewer checked these data. At least two investigators critically appraised each study using design-specific quality criteria from the USPSTF, supplemented by the National Institute of Health and Clinical Excellence criteria for randomized controlled trials and systematic reviews and the QUADAS tool for quality assessment of diagnostic accuracy studies. Per the USPSTF methods, studies rated as poor quality were excluded.

Data Synthesis: Our results focus on trials and studies conducted in countries that have well-developed approaches to cervical cancer screening and are summarized primarily using qualitative synthesis due to incomplete reporting and clinical heterogeneity among included studies.

Key Question 1: Initiation of cervical cancer screening. The incidence of invasive cervical cancer (ICC) peaks among U.S. women aged 40 to 44 years, and few cases of cervical cancer are detected in women younger than age 20 (age-adjusted incidence rate of squamous cell carcinoma, 0.05 cases per 100,000 U.S. women). In contrast, HPV infection is most prevalent among women younger than age 20 years, occurring in about 20 percent of women, and is primarily transient in nature (median duration, 13.7 months), as are cytologic abnormalities (median duration, 8.7 months). Women younger than age 25 years have a higher proportion of false-positive Pap smears (age 15 to 19, 3.1%; age 20 to 24, 3.5%) than women aged 25 to 39 years (age 25 to 29, 2.1%; age 30 to 39, 2.6%). A large case-control study in the United Kingdom including 4,012 women with invasive cancer and 7,889 controls found that cervical cancer screening among women younger than age 25 was not associated with a decreased

incidence of cervical cancer diagnosis prior to the age of 30, although an impact on stage IB+ cervical cancer in women aged 25 to 27 years could not be ruled out. An overall protective effect of screening was not demonstrated until age 32 years, at which time screening was associated with a 45 percent reduction in the incidence of ICC diagnosis between the ages of 35 and 39 years (odds ratio, 0.55 [95% CI, 0.44 to 0.69]).

Key Questions 2 and 4: Liquid-based cytology compared to conventional cytology. Liquid-based cytology (LBC) and conventional cytology (CC) did not differ significantly in measures of relative sensitivity or absolute sensitivity or specificity for detection of cervical intraepithelial neoplasia (CIN)2+ or CIN3+ at any cytologic threshold. In two large randomized trials (n=134,162; age 25 to 64 years), LBC yielded a lower proportion of unsatisfactory slides than conventional cytology (0.4% and 2.6% of LBC slides vs. 1.1% and 4.1% of CC slides).

Key Question 3: HPV primary screening alone or followed by cytology triage.

Women aged 35 years and older. In a large fair-quality Italian randomized controlled trial (RCT) (NTCC Phase II) testing Hybrid Capture 2 (HC2) high-risk HPV screening against CC in 35,471 women aged 35 to 60 years, about twice as many CIN3+ or CIN2+ cases were detected in the HPV arm relative to CC after a single round, with relatively decreased CIN3+ in the second screening round (RR, 0.23 [95% CI, 0.07 to 0.82]). Cumulative relative CIN3+ detection was increased after a second screening round (which included cytology only) and 3.5 median years of followup (RR, 1.57 [95% CI, 1.03 to 2.40]), with about the same number of invasive cancer cases detected in both arms. Since women with a positive HPV test or atypical squamous cells of undetermined significance (ASC-US) cytology were immediately referred for colposcopy, baseline colposcopies were much higher in the HPV arm (5.8%), compared with cytology (2.5%). Trial investigators pooled invasive cancer from these primary HC2 results (NTCC Phase II) with HC2-CC co-testing results (NTCC Phase I) due to insignificant statistical heterogeneity between trials. Pooled results suggested decreased invasive cancer in women aged 35 years and older who were screened with HPV (6 total ICC cases in the HPV screening arms compared to 15 in the CC only arms; p=0.052). However, cancer outcomes would ideally come from comparable screening strategies and reflect clearly similar opportunities for diagnosis through comparable delivery of colposcopies and/or long enough followup with registry linkages to allow disease ascertainment outside the screening program. Reported data on cumulative burden or relative harms were lacking, since neither cumulative colposcopies nor cumulative relative positive predictive value (PPV) over the screening rounds were reported, nor compared between HPV and cytology screening. In absolute test performance studies, HC2 was much more sensitive (about 40% or higher relative sensitivity), but less specific (3 to 5% relatively less specific) than CC for CIN2+ or CIN3+ at a threshold of ASC-US or low-grade squamous intraepithelial lesion (LSIL) in women aged 30 years and older.

A very large fair-quality trial in 59,757 Finnish women aged 35 to 65 years compared primary HC2 screening (followed by CC triage for positive HPV tests) to CC screening alone at a colposcopy referral threshold of LSIL+. HPV with cytology triage tended to identify about one-third more CIN2+ or CIN3+ cases than CC alone after a single screening round (and at least 2 years of followup). However, extended followup (mean, 3.3 years) after this first screening round with linkage to registry data was required to demonstrate a significant increase in CIN3+ (RR, 1.77 [95% CI, 1.16 to 2.74], including 11 ICC/adenocarcinoma in situ (ACIS) cases in

HPV arm and 6 ICC/ACIS cases in CC only arm). In terms of colposcopy, cytology-triaged HPV screening and cytology screening alone resulted in about the same number of immediate referrals (about 1%), with slightly more women identified for retesting (and possible colposcopy referral in the future) in the HPV-cytology triage arm (7.2%), compared with CC (6.6%). Data for total colposcopies and compliance with colposcopy and retesting referrals for the entire first screening round are not yet reported, but will be important, since about half of CIN3+ cases found during extended followup came from those recommended for retesting. A second screening round at 3 years is planned. As more data from this trial are reported, differences with U.S. practice, including cytology referral and CIN treatment thresholds, will also need to be considered.

***Women younger than age 35 years*.** In the fair-quality Italian NTCC Phase II trial in 13,725 women aged 25 to 34 years, HC2 screening detected about four times the amount of CIN2+ and CIN3+ cases as CC after a single round, with relatively decreased CIN3+ in the second screening round (0.20 [95% CI, 0.05 to 0.93]). Cumulative detection of both CIN2+ and CIN3 was at least doubled in the HPV arm relative to CC (after a second round of CC screening only in both arms), with almost no invasive cancer cases in either arm. Pooled results for invasive cancer across the NTCC Phase I and II trials in younger women were not considered due to significant heterogeneity in age-specific protocols and statistical tests of between-trial results in younger women. Only baseline colposcopy referrals were reported, and these were markedly increased in the HPV primary screening arm (13.1%), compared with CC (3.6%). In the single study reporting absolute test performance for HPV alone in women younger than 30, sensitivity was relatively increased for CIN2+ or CIN3+ (23 to 27% higher than cytology at ASC-US+ threshold), while specificity was decreased to a much greater degree (11% relatively lower than cytology) than in older women.

Among 11,580 women aged 25 to 34 years old in the Finnish trial, HC2 with CC triage was little different from cytology in either CIN3+ detection or immediate colposcopy (2.8 vs. 2.7%), despite a higher percentage (16.7%) of HPV positive results initially. Complete colposcopy referrals for the entire first screening round will likely be greater in the HPV-cytology triage arm, since 15.8 percent of younger women—about twice the percentage in the cytology arm—were targeted for repeat testing. A second screening round at 3 years is planned.

Key Question 3: Combination HPV and cytology screening (co-testing).

***Women aged 30 or 35 years and older*.** Four large fair-quality RCTs (NTCC Phase I, POBASCAM, Swedescreen, ARTISTIC) compared combined HPV-cytology (co-testing) to cytology screening alone in 82,390 European women aged 30 to 64 years. Cumulative relative CIN3+ detection was the same between HPV-cytology co-testing and cytology alone after two screening rounds in all the RCTs, and most co-testing trials report differences in round-specific relative CIN detection (e.g., more CIN2+ with co-testing after Round 1, and less CIN3+ with co-testing after Round 2). Cumulative invasive cancer detection was similar or slightly higher in cytology alone compared with co-testing, with findings limited due to incomplete reporting of full followup for all participants, particularly after the second round of screening. Three of four co-testing trials (POBASCAM, Swedescreen, ARTISTIC) had a high threshold for colposcopy referral, generally referring women for high-grade squamous intraepithelial lesion (HSIL+) cytology, with colposcopy referral for HPV positive results (with normal cytology, ASC-US, or LSIL) only after repeat testing for persistent HPV positivity and/or abnormal cytology. Also,

none of these three trials has complete reporting for Round 2 (and therefore cumulatively) for a substantial proportion of trial participants (POBASCAM), for the complete followup period (Swedescreen), or for both (ARTISTIC). Data from a third screening round reported in 2011 from ARTISTIC do not correct these deficiencies, but address 6-year cumulative rates of CIN2+ and CIN3+ development by baseline screening test results.

In the only co-testing trial that found a cumulative increase in relative CIN detection for any CIN measure (NTCC Phase I), women were referred to colposcopy immediately at a lower cytology threshold (ASC-US+) or if HPV positive. Relative to cytology alone, this strategy increased both CIN2+ and CIN3+ after one screening round and cumulative CIN2+ overall; however, it did not significantly reduce CIN3+ in Round 2 or affect cumulative CIN3+. Invasive cancers were higher in the cytology arm in both rounds, and therefore cumulatively, but small numbers complicate interpretation. Cumulative CIN2+ was increased (RR, 1.50 [95% CI, 1.13 to 1.98]), perhaps reflecting overdiagnosis of regressive disease. Indirect comparisons between NTCC Phase I and II in older women suggest no additional benefit from co-testing above HPV primary screening alone, but possible increases in false positives. In NTCC Phase I, immediate colposcopies were much higher (10.6%) with co-testing than with cytology alone (3.0%), and neither phase of NTCC has reported cumulative colposcopies beyond those from immediate referral after initial screening in Round 1. Cumulative colposcopies are reported for only two trials (POBASCAM, ARTISTIC). Cumulative colposcopies were slightly higher in the co-testing arm (3.4%) of POBASCAM, compared with cytology (2.8%), although both arms received HPV testing with polymerase chain reaction (PCR) in Round 2, which might minimize differences. For women aged 30 to 64 years, cumulative colposcopy referrals after two screening rounds were 6.0 percent in the co-testing (HC2-LBC) arm in ARTISTIC, compared with 4.9 percent in the LBC only arm. Results from a third screening round are expected from at least one trial (ARTISTIC), which could be important, since ARTISTIC varied somewhat from other trials in several round-specific findings. Age-specific ARTISTIC data are not completely reported by rounds, thus some of these data include the 21 percent of women younger than age 30 years.

Two fair- or good-quality studies reported absolute sensitivity and specificity for HC2-CC co-testing among 17,885 women aged 30 to 60 years in countries with established cervical cancer screening programs. Studies used a positive definition from either co-test, so that all HPV positives met the threshold. For the detection of CIN3+ or CIN2+, HC2 plus cytology was 44 to 56 percent more sensitive than ASC-US+ cytology alone, but was 4.2 to 4.8 percent less specific. In these studies, the combination of HC2 plus cytology did not differ significantly from the use of HC2 alone in sensitivity (100% vs. 97 to 98%) or specificity (93 to 94% vs. 94 to 95%) for the detection of CIN2+ or CIN3+ lesions.

Indirect comparisons in trials and absolute test performance studies suggest that adding cytology to primary HPV screening (HPV-CC co-testing) does not significantly improve sensitivity but may decrease specificity compared to HPV alone. More rounds of screening could help determine if there may be other values for co-testing, such as identification of a cohort negative on both tests, that are appropriate for prolonged intervals before rescreening.

Women younger than age 30 or 35 years. Two co-testing trials included women younger than age 30 or 35 years (NTCC Phase I and ARTISTIC). Because complete age-specific results are not available from ARTISTIC, it is discussed with results for women older than 30, who

represent almost 80 percent of the total sample. Among 11,810 women aged 25 to 34 in NTCC Phase I, women were referred for ASC-US+ cytology but retested for HPV positive-cytology normal results. In contrast to other co-testing trials, no impact on CIN3+ in any round or cumulatively was seen in younger women. CIN2+ detection was relatively greater after Round 1 and cumulatively with co-testing, perhaps reflecting overdiagnosis of regressive disease. No cancer was found in the co-testing arm, although three cases were found in the cytology only arm. Although cumulative colposcopies are not yet reported, much higher initial colposcopies after co-testing compared with cytology (11.9 vs. 4.1%) are consistent with likely increased false positives and related harms in a co-testing strategy, compared with cytology alone, in younger women. Very limited absolute test performance data in younger women suggest a single co-test (with positive defined as LSIL+ or both ASC-US+/HPV+) decreased sensitivity relative to HPV testing alone, but remained similar to cytology alone, while specificity improved relative to either HPV testing alone or cytology alone. This strategy mimics triage if either test is positive (HPV+ or ASC-US+) using the other, and requires both to be positive for colposcopy referral.

KQ3: HPV for triage of ASC-US or LSIL cytology. Three cross-sectional (two of fair quality and one of good quality) and one prospective cohort study (of fair quality) compared HC2 with repeat cytology for the triage of women aged 15 to 78 years with ASC-US cytology results to colposcopy, two of which also compared HC2 with repeat cytology for triage of LSIL. Pooled estimates for the detection of CIN2+ among women with ASC-US cytology results demonstrated a 12 percent higher relative sensitivity for HC2 compared to repeat cytology (95% CI, 0 to 24) at a threshold of ASC-US, but no difference in specificity. One study evaluated HPV triage of ASC-US for the detection of CIN3+ and found no difference between HPV and repeat cytology. HPV testing strategies showed very poor absolute specificity for triaging LSIL (29.9 to 44.0% for CIN2+, 27.1% for CIN3+). In one small study (n=749) of ASC-US only, age-specific sensitivity for CIN2+ did not differ by age among women older and younger than age 35 years. However, in women aged 35 years and older, specificity for HC2 was better than for repeat cytology (84.8 vs. 74.7%), while specificity for HC2 in women younger than age 35 years tended to be lower than repeat cytology (60.4 vs. 65.5%).

Two good-quality RCTs evaluated HPV testing and repeat cytology versus repeat cytology alone for triage of ASC-US and LSIL Pap smears. Women were referred for HPV+ in either trial, for cytology of HSIL+ in the ALTS trial, or for ASC-US+ in the Swedish trial. Among women aged 18 to 35+ years (78% younger than age 35 years) in the ALTS trial, those triaged with HPV and repeat cytology for ASC-US screening results showed a nonsignificant increase in CIN3+ detection (RR, 1.24 [95% CI, 0.88 to 1.73]), compared to repeat cytology alone every 6 months for 2 years. Due to high prevalence of HPV in women with LSIL, 85 percent of women in the HPV-enhanced triage arm were referred to colposcopy, which was therefore discontinued as an unsuccessful triage strategy. The smaller Swedish trial mixed outcomes for women referred for either LSIL or ASC-US, but showed a similar impact on CIN3+ detection (RR, 1.20 [95% CI, 0.88 to 1.63]). Relative CIN3+ detection may be better in women aged 30 years or older compared to women younger than age 30 years. Both trials increased relative colposcopies. Neither trial exactly mimics current U.S. practice or guidelines.

*Key Question 5: Harms of HPV testing***.** Four studies that examined the psychological impact of HPV testing found increased levels of immediate anxiety and distress in women testing positive for HPV compared to HPV negative women. These differences, however, were resolved at 6-month followup.

Conclusions: The evidence we reviewed indicates that a reasonable age at which to initiate cervical cancer screening in women is age 21. Screening before this age is complicated by relatively high rates of transient HPV and regressive cervical abnormalities, with very few actual cancer cases. Current data cannot assure that beginning screening after this age is clearly safe, particularly in the United States, which has no centralized national cervical cancer screening program.

For cytology-based screening, LBC does not differ from CC in sensitivity, specificity, or relative CIN detection, but may yield a lower proportion of unsatisfactory slides. Cost, overall screening strategy, and other considerations may also pertain to local decisions on which approach to use for collecting cytology samples.

In women older than age 30 years, a single HC2 test is clearly more sensitive for CIN2+ and CIN3+ (about 40% greater) than cytology alone. However, a single HC2 test is also 3 to 5 percent less specific than cytology. Thus, while HPV-enhanced screening strategies offer a potential disease detection benefit compared with cytology alone, the potential burden due to increased false-positives is critical to understand, particularly given the relatively low incidence of cervical cancer and the established practice of repeated cervical screening.

Based on large trials, primary screening using a clinically validated HPV test, such as HC2, appears very promising in women aged 35 years and older, particularly when coupled with reflex cytology to triage positive HPV results before colposcopy. HPV testing enhances the detection of CIN3+, but also increases CIN2+ detection and immediate colposcopy referrals, compared with cytology alone. Cytology triage of positive HPV results identifies women with milder abnormalities for further followup and retesting, thus reducing the proportion immediately referred for diagnostic colposcopy. Eventually, after repeated screening rounds are reported, this strategy may be shown to reduce overall colposcopies and false-positive related harms—including some of the overdiagnosis and treatment of regressive disease—which both absolute test performance and existing trial data suggest are likely with primary HPV screening alone. While not yet reported, cumulative colposcopy requirements, treatments, and related harms are essential to determine net benefit from any enhanced CIN detection/cancer prevention with primary HPV screening. Thus, the net impact of primary HPV screening (with or without cytology triage) remains to be determined through completion of ongoing trials and more detailed reporting of potential harms, as well as benefits from completed trials.

Screening with combined HPV/cytology (co-testing) in women 30 years and older is much more sensitive than cytology alone, but may represent a strategy that adds little to HPV screening. Based on indirect comparisons between trials and on test performance data, one-time HPV/cytology co-testing appears to be very similar to HPV testing alone for the detection of CIN2+ or CIN3+, with similar (or slightly reduced) specificity. Compared with cytology alone, co-testing trials of repeated screening did not clearly report a consistent disease detection pattern indicating benefit, although most reported reduced relative CIN3+ detection in the second screening round, which may suggest benefit. Determination of net program impact is not possible, since most trials have not yet reported complete cumulative outcomes ascertainment for the entire study population, nor cumulative colposcopy requirements and related harms. Once trial data are more completely reported, judgment as to their applicability will be required, since co-testing trials to date used screening and retesting protocols that are not entirely relevant to U.S. practice.

In women younger than 30 years, there are much less data on primary HPV screening (with or without cytology triage) or co-testing with HPV-cytology. Where available, these indicate using HPV in any primary screening strategy is associated with a substantially inferior specificity (about 10 to 11% less specific) compared with cytology. Thus, HPV screening in younger women is likely to result in substantially more colposcopy referrals, greater regressive CIN2+ detection and treatment, and increased treatment-related harms, particularly compared with older women. Current data are inadequate to determine whether, and how much, cytology triage might mitigate specificity concerns with primary HPV screening performance in younger women, but caution is warranted.

For all HPV-enhanced primary screening approaches, results to date raise questions about possible overdiagnosis of regressive (or non-progressive) lesions and/or a high burden for a small net benefit in the context of frequently repeated screening as is typically done for cervical cancer in the United States. No available trials report adequate cumulative data on the proportion of women undergoing repeat testing, resulting colposcopy referrals, rates of treatment and diagnosis, or treatment-related harms, all of which are critical to addressing the issues of relative burden and harms of newer strategies relative to cytology. Thus, the net impact of HPV-enhanced primary screening remains elusive, but may become clearer after more in-depth reporting from trials reviewed here and reports from ongoing trials and studies, as well as international efforts to pool results of HPV-enhanced cervical cancer screening trials. Modeling exercises may also be useful.

A major benefit of HPV-enhanced primary screening could be identification of a low-risk cohort in whom a prolonged screening interval would be appropriate. Risk-stratifying approaches have not been directly incorporated into trials to date, and safety data for prolonged screening intervals in low-risk women based on baseline HPV testing (with or without cytology) are still accruing from trials and cohort studies. However, ensuring the acceptability of overall program requirements and feasibility would be important considerations in cervical cancer screening policy, even after it is shown that a large proportion of women could be safely risk-stratified to longer screening intervals. Ongoing research in HPV subtypes, as well as HPV-related biomarkers, could further advance efforts in risk stratification for appropriately targeted screening.

For the triage of women with ASC-US cytology to colposcopy, a single HC2 test has a higher sensitivity and similar specificity compared to single repeat cytology at a threshold of ASC-US for the detection of CIN2+. No additional benefit occurs when HC2 triage is combined with cytology, but this strategy increases false positives. HC2 does not appear useful for the triage of women with LSIL cytology because such a high proportion of women will test positive. HPV testing has few unique harms compared with cytology screening, but a positive HPV test may increase anxiety and distress, in the short-term only. Further research could be useful.

The most thoroughly studied HPV test for use in cervical cancer screening or triage is HC2. Data reported in this review primarily reflect results using HC2 at a positive threshold of 1 pg/ml and, to a lesser extent, PCR GP5+/6+. Careful consideration of all aspects of other tests' performance characteristics (sensitivity, specificity, PPV, negative predictive value) in screening settings is warranted before substituting tests, particularly in a population-based screening program.

Table of Contents

Chapter 1. Introduction 1
Scope and Purpose 1
Background 1
Condition Definition 1
Prevalence and Burden of Disease/Illness 2
Risk Factors 3
Etiology and Natural History 4
Current Screening Uptake in U.S. Women 5
Rationale for and Types of Screening/Screening Strategies 6
Management of Abnormal Cervical Cytology 7
Interventions/Treatment of Cervical Intraepithelial Neoplasia 8
Potential Harms Related to Diagnosis and Treatment of CIN 8
Efforts to Prevent HPV Infection 10
Current Clinical Practice 10
Previous USPSTF Recommendation 11
Chapter 2. Methods 12
Key Questions and Analytic Framework 12
Literature Search Strategy 13
Study Selection 13
Data Extraction and Quality Assessment 14
Data Synthesis and Analysis 14
USPSTF Involvement 15
Chapter 3. Results 16
Key Question 1. When Should Cervical Cancer Screening Begin, and Does This Vary By Screening Technology or By Age, Sexual History, or Other Patient Characteristics? 16
Key Question 2. To What Extent Does Liquid-Based Cytology Improve Sensitivity, Specificity, and Diagnostic Yield and Reduce Indeterminate Results and Inadequate Samples Compared to Conventional Cervical Cytology? 19
Unsatisfactory Slides 21
Key Question 3. What Are the Benefits of Using HPV Testing as a Screening Test, Either Alone or in Combination With Cytology, Compared With Not Testing for HPV? 21
1) Primary Screening With HPV Test Alone 22
2) HPV Testing With Cytology Triage of Positive HPV (Reflex Cytology) 25
3) Combination HPV and Cytology Testing (Co-Testing) 26
4) Cytology Testing With HPV Triage of Positive Cytology (Reflex HPV) 29
Key Question 4. What Are the Harms of Liquid-Based Cytology? 31
Key Question 5. What Are the Harms of Using HPV Testing as a Screening Test, Either Alone or in Combination With Cytology? 32
Chapter 4. Discussion 35
Summary of Review Findings 35
Initiation of Cervical Cancer Screening 35
Liquid-Based Cytology Compared to Conventional Cytology for Primary Cervical Cancer Screening 36
HPV-Enhanced Primary Cervical Cancer Screening 37
The Rationale and Potential Pitfalls of HPV-Enhanced Screening 38

Interim Conclusions about HPV-Enhanced Screening From Available Data 39
Potential Subgroup Considerations With HPV-Enhanced Cervical Cancer Screening..... 42
Cytology Screening With HPV Triage (Reflex HPV) for ASC-US or LSIL Cytology 44
Harms of HPV Testing..... 45
Are All HPV Tests the Same? 46
Age at Which to Stop Cervical Cancer Screening 46
Limitations 49
Emerging Issues/Next Steps 51
Future Research 52
Conclusions..... 53
References 55

Figures and Tables

Figure 1. U.S. Age-Adjusted Cervical Cancer Incidence Rates By Age and Race/Ethnicity 70
Figure 2. U.S. Age-Adjusted Incidence and Death Rates of Invasive Cervical Cancer By Age...71
Figure 3. U.S. Age-Adjusted Cervical Cancer Mortality Rates By Age and Race/Ethnicity.....72
Figure 4. Prevalence of High-Risk HPV By Age 73
Figure 5. Analytic Framework and Key Questions 74
Figure 6. High-Risk HPV Prevalence and CIN3+ Incidence 75
Figure 7. Comparison of HC2 and Repeat Cytology Sensitivity for the Detection of CIN2+ Among Women Referred With ASC-US Cytology..... 76
Figure 8. Comparison of HC2 and Repeat Cytology Specificity for the Detection of CIN2+ Among Women Referred With ASC-US Cytology..... 77

Table 1. Cervical Pathology: Comparison of Cytologic and Histologic Test Results and Current U.S. Guidelines for Management of Cytologic Abnormalities 78
Table 2. U.S. Age-Specific Crude Cervical Cancer Incidence Rates By Race 79
Table 3. Characteristics of Liquid-Based Cytology RCTs and Observational Studies (KQ2) 80
Table 4. Characteristics of Liquid-Based Cytology Test Performance for RCTs and Observational Studies (KQ2)..... 81
Table 5a. Population and Screening Program of RCTs of HPV Screening Strategies for Cervical Cancer Screening (KQ3) 82
Table 5b. Colposcopy Referral, Retesting, and Treatment Protocols of RCTs of HPV Screening Strategies for Cervical Cancer Screening (KQ3)..... 83
Table 5c. Quality Rating and Limitations of RCTs of HPV Screening Strategies for Cervical Cancer Screening (KQ3) 84
Table 6. Characteristics of RCTs of Cytology Testing With HPV Triage of Positive Cytology (KQ3). 86
Table 7. Characteristics of Studies Examining Absolute Test Performance of Primary Screening With HPV Test Alone and Combination HPV and Cytology Testing (KQ3) 87
Table 8a. Results for RCTs of HPV Screening Strategies in Cervical Cancer Screening, Women ≥30 or 35 Years of Age (KQ3)..... 89
Table 8b. Results for RCTs of HPV Screening Strategies in Cervical Cancer Screening, Women <30 or 35 Years of Age (KQ3) 91
Table 9a. Absolute Test Performance By Age of Primary Screening With HPV Test

Alone and Combination HPV and Cytology Testing Among Developed Countries Only, Women ≥30 Years of Age (KQ3) 93
Table 9b. Absolute Test Performance By Age of Primary Screening With HPV Test Alone and Combination HPV and Cytology Testing Among Developed Countries Only, Women <30 Years of Age (KQ3) 94
Table 10. Characteristics of Studies Examining Absolute Test Performance of Cytology Testing With HPV Triage of Positive Cytology (KQ3) 95
Table 11. Results of RCTs for Cytology Testing With HPV Triage of Positive Cytology 98
Table 12. Absolute Test Performance of Cytology Testing With HPV Triage of Positive Cytology (KQ3) 100
Table 13. Characteristics of HPV Harms Studies (KQ5) 102
Table 14. Outcomes of HPV Harms Studies (KQ5) 104
Table 15. Summary of Evidence By Key Question 105
Table 16a. Relative Detection Ratio By Screening Round for RCTs of HPV Screening Strategies in Cervical Cancer Screening (Women ≥30 or 35 Years) 111
Table 16b. Relative Detection Ratio By Screening Round for RCTs of HPV Screening Strategies in Cervical Cancer Screening (Women <30 Years). 113
Table 17. European Perspective in Interpreting Comparative HPV Screening Trials 114
Table 18. What Data Are Reported in RCTs of HPV Screening Strategies in Cervical Cancer Screening 115
Table 19. Cumulative Incidence of CIN3+ By Baseline Testing Status of RCTs and Cohort Studies With Long-Term Followup Data 117

Appendixes

Appendix A. Terminology and Abbreviations
Appendix B. Detailed Methods
Figure 1. Search Results and Article Flow
Table 1. Search Strategies
Table 2. Exclusion Criteria for Key Questions
Table 3. Quality Rating Criteria
Appendix C.
Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)
Table 2. Evidence Table for Liquid-Based Cytology (KQ2)
Table 3. Evidence Table for Benefits of HPV Testing (KQ3)
Table 4. Evidence Table for Harms of HPV Testing (KQ5)
Appendix D.
Table 1. Studies Excluded From the Review for KQ1
Table 2. Studies Excluded From the Review for KQ2
Table 3. Studies Excluded From the Review for KQ3
Table 4. Studies Excluded From the Review for KQ4
Table 5. Studies Excluded From the Review for KQ5
Appendix E. Screening Benefit Considerations Illustrated by NTCC Phase II Trial
Appendix F. Ongoing and Pending Trials
Appendix G. Recommendations of Other Groups
Appendix H. Cervical Cancer and HPV: Prevalence, Incidence, and Mortality Rates

Chapter 1. Introduction

Scope and Purpose

We undertook this systematic review to assist the U.S. Preventive Services Task Force (USPSTF) in updating its 2003 recommendation on cervical cancer screening. During the planning phase of this evidence review on cervical cancer screening, the Agency for Healthcare Research and Quality (AHRQ) decided to fund a separate modeling study to be conducted simultaneously. The USPSTF determined that the scope for both the systematic review and the modeling study would focus on important clinical questions that could inform effective use of screening in practice. This systematic review focuses on when to begin screening and on updating test accuracy and harms data on liquid-based cytology (LBC) and human papillomavirus (HPV) testing, either alone or in combination with cytology. The modeling study focuses on the effectiveness of strategies that use different ages at which to begin screening and different screening intervals.[1] These two reports are intended to provide the USPSTF with complementary information to update its recommendation on cervical cancer screening.

Background

Condition Definition

Two primary histologic abnormalities account for the majority of cancer of the uterine cervix—squamous cell carcinoma (SCC) and adenocarcinoma. The majority of cervical cancer cases (70% or more) are SCC, which is thought to arise from the transformation zone of the cervix.[2,3] The transformation zone is the region between the original and subsequent locations of the junction between the squamous and columnar cells of the cervix (squamocolumnar junction), which migrates from the exocervix to the distal endocervical canal with advancing age.[4] Adenocarcinoma, which develops from the mucus-producing cells of the endocervix, accounts for approximately 18 percent of cervical carcinomas. The remainder of cervical carcinomas are adenosquamous (4%) and other carcinomas (5%) or malignancies (1.5%).[4]

Cervical cancer does not develop suddenly[2] and is preceded by precancerous changes of the cervix. Precancerous changes of the cervix are histologically defined as cervical intraepithelial neoplasia (CIN) and are identified at varying levels of severity: CIN1, CIN2, and CIN3. The latter includes CIS (carcinoma in situ, a preinvasive carcinomatous change of the cervix).[5,6] Progression of neoplasia to invasive cervical cancer (ICC) is slow. The rate of progression of CIN3 to cancer has recently been estimated as 31.3 percent in 30 years. This rate was determined using retrospective data from an unethical clinical study in New Zealand between 1965 and 1974 that left a number of women with CIN3 disease incompletely treated or untreated.[6] Other rough estimates from early studies of precancer suggest a 20 to 30 percent risk of invasion over a 5- to 10-year timeframe.[7,8]

Screening for cancerous or precancerous changes of the cervix has traditionally been performed by scraping cells from the cervix and fixing them to a glass slide in a method developed by Papanicolaou called the Pap smear. The Pap smear is a cytologic screening test used to detect CIN and early cervical cancer so that these conditions can be managed or treated to prevent disease progression due to invasive cancer. Cervical cytology results are not

diagnostic of CIN or cancer, as biopsy and histologic confirmation are required for diagnosis. While the incidence of SCC of the cervix has declined significantly since the introduction of the Pap smear,[9] the incidence of adenocarcinoma has risen, leaving the optimal method of screening to detect adenocarcinoma of the cervix uncertain.[9]

The terminology for reporting the spectrum of cervical cytologic abnormalities is derived from the Bethesda System and is displayed in Table 1.[10] The 2001 Bethesda Workshop was convened to update terminology initially established in 1988 and revised in 1991.[11] Atypical squamous cells of undetermined significance, or ASC-US, is the least reproducible of all the cytologic categories and emphasizes that a specific diagnosis cannot be made. Atypical glandular cell (AGC) abnormalities (previously called AGUS) may be reported as endocervical, endometrial, or not otherwise specified. The percentage of AGC Pap smears associated with underlying high-grade disease (CIN2 or worse) is higher than for ASC-US.[10] High-grade squamous or glandular lesions can be seen in 10 to 39 percent of cases of AGC.[10] The term LSIL, or low-grade squamous intraepithelial lesion, includes cellular HPV changes and CIN1. The term HSIL, or high-grade squamous intraepithelial lesion, includes CIN2 and CIN3. While LSIL and HSIL are terms generally used to describe cytology, they have also been used to describe histology. The term CIN2+ is used to indicate CIN2 or worse (CIN2, CIN3, or cancer), and CIN3+ is used to indicate CIN3 or worse (CIN3 or cancer). Similarly, the term ASC-US+ is used to indicate ASC-US or worse cytology, LSIL+ to indicate LSIL or worse, and HSIL+ to indicate HSIL or worse.

Prevalence and Burden of Disease/Illness

The incidence and associated mortality of cervical cancer have continued to decrease in the United States since the introduction of cervical cytology screening programs in the 1950s and 60s. In 1950, the Centers for Disease Control (CDC) ―Vital Statistics of the United States" reported an unadjusted death rate of 10.2 per 100,000 for white women and 18.0 for nonwhite women (age-adjusted mortality not reported).[12] In 2007, age-adjusted mortality had dropped to 2.2 for white women, 4.3 for black women, and 2.4 overall.[13] Although these results are based on ecologic data, these changes have been seen in the United States and other countries with long-standing population screening and attributed to that screening.[14]

However, cervical cancer still remains a significant public health issue. Incidence figures for 2000 to 2008 from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database suggest that incidence varies significantly by age and race/ethnicity (Table 2 and Figure 1). The overall age-adjusted incidence rate of cervical cancer is 8.4 per 100,000 women per year. The incidence is highest among Hispanics (12.1 per 100,000 women) and blacks (10.7) and lowest among nonHispanic whites (7.5), American Indians and Alaska Natives (7.5), and Asian and Pacific Islanders (7.7) (Figure 1).[15] Based on 2004 to 2008 SEER data, the median age at diagnosis for cervical cancer in all women was 48 years.[16] Half of all incident cervical cancer cases between 2004 and 2008 occurred in women between the ages of 35 and 55 years. The age-adjusted death rate for cervical cancer was 2.5 per 100,000 women in 2007[17] and the median age for mortality was 57 years.[16] Mortality rates increase with age (Figure 2) and also vary by race and ethnicity (Figure 3).[17] The national target established in Healthy People 2010 was a mortality reduction to 2.0 deaths per 100,000 women. For 2010, SEER data estimate 12,200 new cases of cervical cancer and 4,210 deaths.[15]

Studies of screening history of women diagnosed with ICC repeatedly show that at least half have been inadequately screened. Studies of women diagnosed with ICC in the 1980s and 1990s in Connecticut[18] and California[19,20] showed that 50 to 60 percent had not been screened within 3 years of diagnosis. For comparison, the CDC's 2008 Behavioral Risk Factor Surveillance System found that just 17 percent of all adult women in the United States had not had a Pap test within the past 3 years.[21] In the Connecticut study, about half of women diagnosed with ICC had no screening within 5 years, and about 30 percent had never been screened.[18] A recent study of a high-risk urban population in London diagnosed with ICC between 1999 and 2007 showed very similar results, with 47 percent of women having no screening within 5 years and 31 percent with no prior screening.[22] Inadequate screening might be less of a contributing factor to cancer diagnosis for younger women. Sasieni and colleagues, for example, found that just 7 percent of women aged 20 to 24 years diagnosed with cervical cancer had never been screened or had had a lapse in screening.[23] These data also indirectly suggest that relatively rare rapid-onset cancer in younger women may be less amenable to earlier screening.[24]

Risk Factors

It is well recognized that infection with oncogenic HPV types is a necessary, although not sufficient, cause of virtually all cervical cancer.[25] The 12 HPV types most strongly associated with cervical cancer are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Other potentially carcinogenic HPV types include 26, 53, 66, 67, 68, 70, 73, and 82.[26-28] Eight HPV types (16, 18, 45, 31, 33, 35, 52, and 58) account for 95 percent of SCCs positive for HPV deoxyribonucleic acid (DNA).[26] HPV types 16 and 18 alone are responsible for approximately 70 percent of cervical cancer cases.[29,30] Results from a large international collection of cervical tumor specimens also revealed the presence of HPV DNA in 99.7 percent of cases.[31]

The prevalence of HPV infection declines with increasing age.[32-34] A cross-sectional study of 9,657 women screened for 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) in 26 sexually transmitted infection, family planning, and primary care clinics in six U.S. cities demonstrated that the prevalence of high-risk HPV was highest among women aged 14 to 19 years (35% [95% confidence interval (CI), 32 to 38]), and lowest among women aged 50 to 65 years (6% [95% CI, 4 to 8]) (Figure 4).[34]

Although we have not identified a published systematic review of other cervical cancer risk factors, pooled analyses of data from observational studies worldwide have been conducted by the International Collaboration of Epidemiological Studies of Cervical Cancer[35-37] and the International Agency for Research on Cancer.[38-41] Based on these and other reviews, cervical cancer risk factors may affect the risk of HPV acquisition, its persistence, or the likelihood of progression to neoplasia and cancer; however, the specific mechanisms underlying measured associations with risk are poorly understood.

The risk of acquiring HPV dramatically increases with the number of lifetime sexual partners.[35,42] Coinfection with other sexually transmitted agents such as chlamydia trachomatis and herpes simplex virus may also be associated with risk of HPV infection.[25,38,43,44] Other risk factors for cervical cancer include high parity (five or more pregnancies) and long-term oral contraceptive use, each associated with a two- to three-fold higher overall risk of precancer or cancer,[35,36,38,40,41,45] along with younger age at first intercourse and at first pregnancy.[35,36] Smoking is clearly associated with increased risk of SCC, but shows no association with the risk of cervical adenocarcinoma.[35,37-39] For SCC, the larger pooled studies show risk increases of 50

to 60 percent for current smokers.[35,37] In a pooled analysis restricted to HPV positive women, smoking was associated with a larger risk increase (relative risk [RR], 1.95 [95% CI, 1.43 to 2.65]), suggesting that smoking affects HPV persistence or disease progression more than HPV acquisition.[37] Reduced risk of both types of cervical cancer is seen with a history of cervical screening, although the reduction is larger for SCC than for adenocarcinoma.[35]

Etiology and Natural History

The progression from HPV infection to cervical cancer occurs over a series of four steps: 1) HPV transmission, 2) acute HPV infection, 3) persistent HPV infection leading to precancerous changes, and 4) ICC.[45] Transmission of HPV to the anogenital region occurs primarily as a result of skin-to-skin or mucosa-to-mucosa contact.[45] Malignant transformation of HPV-infected cells is believed to be mediated by the integration of the viral DNA into the host genome. The virus reproduces separately in most low-grade lesions, but the HPV genome may be integrated into the host's DNA in many advanced precancerous lesions and most cancer cases.[46]

A high proportion of sexually active women become infected with HPV, but only a small proportion of HPV infections become persistent. Among 4,504 women aged 18 years and older with a cytologic diagnosis of ASC-US or LSIL, 91 percent of prevalent HPV infections detected at enrollment cleared within 24 months.[47] The probability of persistent infection increased with duration of infection, such that about two-thirds of infections that had persisted to 18 months were still present at 24 months. Also, odds of persistent infection were highest in the 50 years and older age group, compared with those aged 20 years and younger (odds ratio [OR], 1.47 [95% CI, 1.11 to 1.94]).

HPV-associated risks are type-specific, with types 16 and 18 conferring the highest risk for HPV persistence and progression to high-grade lesions. In an HPV 16 vaccine trial, women aged 16 to 23 years had HPV DNA testing at 6-month intervals for up to 4 years. Among unvaccinated women in the placebo arm, the mean duration of incident HPV infections was 17.1 months (95% CI, 15.0 to 19.2) for HPV 16 and 16.6 months (95% CI, 13.4 to 19.7) for HPV 18.[48] The proportion cleared at 36 months was 85.3 percent (95% CI, 75.0 to 91.5) for HPV 16 and 91.1 percent (95% CI, 84.6 to 94.9) for HPV 18.[48] These studies illustrate that even high-risk HPV types are quite likely to clear in younger women.

In the same HPV 16 vaccination trial, the rate of progression to CIN2+ at 36 months was 16.5 percent for HPV 16 and 8.2 percent for HPV 18.[48] In a U.S. cohort of 20,514 women aged 16 years and older (median age, 34 years) tested at baseline for 13 oncogenic HPV types, the 10-year cumulative incidence rates of CIN3+ were 17.2 percent (95% CI, 11.5 to 22.9) among HPV 16 positive women and 13.6 percent (95% CI, 3.6 to 23.7) among HPV 18 positive women, but only 3 percent (95% CI, 1.9 to 4.2) among women who were positive for an HPV type other than 16 or 18.[49] Repeated HPV testing is required to identify type-specific incident infection and clearance.

These data illustrate that HPV infections are very likely to regress, and persistence of HPV infection is more likely to occur in older women. While HPV 16 and 18 are most likely to persist and be associated with CIN3 or cancer, a high proportion of HPV 16 and 18 infections also regress. Regression of HPV infection is presumably due to a successfully mounted immune response,[50,51] and increased incidence and persistence of HPV infections are observed in immunocompromised populations.[42,52] It is unknown whether viral infections resolve as a result

of complete clearance of the virus or by maintenance of the virus in a latent state.[45] While cohort studies have demonstrated that a viral type can reappear even after it has been thought to have cleared,[53] incident HPV infections may not confer a great deal of risk given the high probability of clearance and the long time period between HPV infection and cancer development, particularly among older women.[24]

Numerous analyses, including large cohort studies, have demonstrated that CIN not only progresses, but may also regress. In an historical cohort of about 20,000 Toronto women during a period when lesions were managed conservatively, CIN2 progression to ICC was 0.3 percent within 2 years, 0.7 percent within 5 years, and 1.2 percent within 10 years.[54] Rates of CIN3 progression to ICC were considerably higher (1.6% within 2 years, 2.6% within 5 years, and 9.9% within 10 years). Regression from CIN2 to a second normal smear occurred in 6.9 percent within 2 years, 29.0 percent within 5 years, and 53.7 percent within 10 years.

Using composite data from cytology, histology, or both to define CIN lesions, a review summarized studies published between 1950 and 1990 on persistence, regression, and progression of CIN.[55] Over followup from 1 to 25 years, regression or persistence was most common for CIN1 (57% regressed, 32% persisted, and 1% progressed). For CIN2, 43 percent regressed, 35 percent persisted, and 5 percent progressed to cancer. For CIN3, regression rates were 32 percent, persistence rates were 56 percent, and progression rates were greater than 12 percent. Neither the Holowaty[54] nor Ostor[55] reports discuss treatment for CIN3 specifically, or its effect on the results reported. The results from an unethical New Zealand study,[6] in which women with CIN3 were untreated or inadequately treated, estimated that 31.3 percent of these women progressed to cancer within 30 years, compared to 0.7 percent in those with adequate treatment.

Newer data suggest that CIN1 does not predict any meaningful risk of CIN3.[45,56] In addition, CIN1 diagnoses in the United States are poorly reproduced,[45,56] which has also been established recently for CIN2 diagnoses in the United States and other countries.[57,58] Despite poor reproducibility, data from the ASCUS-LSIL Triage Study (ALTS) trial have been used to estimate that up to 40 percent of CIN2 detected through colposcopy referral after positive primary screening tests (cytology and HPV) in younger women may regress, particularly in the presence of less severe cytology such as ASC-US+, LSIL+, or HPV positive tests that are not HPV 16 positive.[59]

Current Screening Uptake in U.S. Women

While it is estimated that around 80 percent of U.S. women have had cervical cytology screening within the past 3 years,[60] screening history varies by educational attainment, race/ethnicity, and age.[61] In 2008, women with low educational attainment (a high-school diploma, general equivalency diploma, or less) were less likely to report a Pap test within 3 years than those with some college or more; fewer Asian and American Indian/Alaskan Native women reported recent Pap smears than other racial/ethnic groups. While 80 to 85 percent of women aged 18 to 64 years reported at least one Pap test within 3 years in 2008, the proportion of women aged 65 years and older reporting a similarly recent Pap history was about 50 percent (down from about 65 percent in 2000). Given the 2003 USPSTF recommendation against ongoing cervical cancer screening in women aged 65 years and older with a previously adequate history, it is unclear how to interpret this age difference. Updated information on the screening

history of women with ICC in all age groups will continue to be important in monitoring the overall success of cervical cancer screening in the United States.

Rationale for and Types of Screening/Screening Strategies

While the great majority of U.S. women have had recent cytology screening, the majority of cervical cancer cases occur in those without such a history. Access to health care may be one concern.[62] Even among women with no health care access barriers to screening, however, the reasons for screening failures are similar. Among 833 women in a health maintenance organization diagnosed with ICC from 1995 to 2000, most (56%) had no Pap smear within the previous 36 months, while about one-third represented Pap test failures, and the remainder failure to followup.[63] Race/ethnicity was not a predictor of any type of failure, although high-poverty area of residence, lower education, and age older than 40 at diagnosis were associated with lack of recent screening. Data on false-negative results of one-time Pap smears suggest a failure rate of about 28 to 41 percent in developed countries.[20,64] Imperfect sensitivity as well as errors in sample collection and interpretation across settings underpin the need for frequent repeated screening and underscore interest in developing more accurate, reliable screening tests.[65] To address these issues, researchers have begun to look for technological advances, such as using LBC and high-risk HPV tests.[65]

LBC differs from CC in how the cervical specimen is sent to the cytology laboratory for evaluation. For CC, the cervical specimen is smeared onto a glass slide immediately after collection and the slide is either sprayed with or placed in fixative. For LBC, the sample collected from the cervix is suspended in fixative either by swirling the collection device in the fixative (ThinPrep, Hologic, Inc., Bedford, MA)[66] or by placing the collection device in the fixative (SurePath, TriPath Imaging, Burlington, NC).[67] In the laboratory, the cells in the fixative are dispersed and suspended, collected by filtration on a membrane, and then transferred onto a microscope slide in a monolayer.

In recent years, high-risk HPV testing has been incorporated into screening and screening triage algorithms by the American Society for Colposcopy and Cervical Pathology (ASCCP), as well as in post-colposcopy and post-treatment surveillance.[68,69] High-risk HPV testing is specified for use as a combined test (co-test) in women aged 30 years and older to determine rescreening interval in women who are cytology negative and as one possible triage strategy to determine colposcopy in women with ASC-US+ cytology (discussed more below). Additionally, HPV genotyping for types 16 and 18 is specified for use as a triage to colposcopy in women aged 30 years or older who have cytology negative, high-risk HPV positive screening results.

There are many methods available for detecting HPV, including in situ hybridization, polymerase chain reaction (PCR), and Hybrid Capture technology. Hybrid Capture technology uses specific ribonucleic acid (RNA) probes, hybridization, antibody capture, and signal amplification to allow rapid, standardized testing of genetic material. The Digene Hybrid Capture 2 (HC2) high-risk HPV DNA test (Qiagen Inc., Germantown , MD) is the most commonly used in the United States. In 2000, the Food and Drug Administration (FDA) approved HC2 for testing patients with ASC-US Pap smear results to determine the need for referral to colposcopy. In addition, the HC2 high-risk HPV DNA test was approved in 2003 for use in women aged 30 years or older in conjunction with the Pap smear to assess the absence or presence of high-risk HPV types.[70,71] The high-risk HPV types identified by HC2 include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. In 2009, the FDA approved Cervista HR HPV

(Hologic, Inc., Bedford, MA) for HPV testing for the same indications as HC2.[72] Cervista HR HPV tests for 14 high-risk HPV types, including type 66 as well as those identified by HC2. There is also an FDA-approved Cervista HPV 16/18 test that individually identifies these two high-risk HPV types.[73] Other HPV test systems are also under development. For example, Roche Diagnostics manufactures Amplicor HPV, a PCR-based test for 13 high-risk HPV types approved for use in Europe, Canada, and Japan. There are also two tests in use in Europe that identify specific HPV types—the Cobas 4800 HPV and Linear Array HPV genotyping tests. Roche has announced FDA reviews of all three of its tests, and received FDA approval in April 2011 for the Cobas 4800 HPV test (which reports results for HPV 16 and 18 and pooled results for 12 other high-risk HPV types [31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68]).[74]

Gen-Probe's APTIMA HPV assay detects 14 high-risk HPV types and also messenger RNA (mRNA) from viral oncogenes E6 and E7. The assay is approved for use in Europe, and Gen-Probe applied for FDA approval in late 2010.

Management of Abnormal Cervical Cytology

According to the American Congress of Obstetricians and Gynecologists (ACOG), colposcopy with directed biopsy has been the criterion for disease diagnosis and remains the technique of choice for treatment decisions.[75]

The process of triaging women with abnormal cytology to colposcopy is now being influenced by HPV testing.[76] Consensus guidelines developed by ASCCP in 2006 state that either HPV testing or repeat cytology at 6 and 12 months (or immediate colposcopy) are acceptable for managing ASC-US cytology in women older than age 20 years, although HPV testing is preferred if LBC or co-collection is available.[68] This is because HPV testing may be performed ~~"re~~flexively" if the cytologic specimen collected was liquid-based and a residual sample is still available for HPV testing, or if a separate specimen was collected at the time CC was performed.

According to the ASCCP algorithm, women with their first ASC-US cytology result and a negative high-risk HPV DNA test should undergo repeat cytology at 12 months. Women with a positive high-risk HPV DNA test or a second cytology result of ASC-US or worse within 6 or 12 months should undergo colposcopy. In 2009, ACOG generally supported a similar algorithm (i.e., immediate colposcopy, high-risk HPV DNA testing with colposcopy if positive, or repeat cytology in 6 and 12 months).[77] Neither ASCCP nor ACOG support HPV DNA testing in adolescents, and both recommend that adolescents with ASC-US or LSIL cytology have repeat cytology in 12 months and should only undergo colposcopy if followup cytology is HSIL or greater at 12 months or ASC-US or greater at 24 months.

According to ASCCP and ACOG, women with ASC-H (atypical squamous cells-cannot exclude HSIL), LSIL, HSIL, or AGC should undergo colposcopy.[68] There are two categories of women for which alternative strategies for management of LSIL cytology exist—adolescents and postmenopausal women. ASCCP now makes the same recommendations for LSIL in adolescents as they do for ASC-US. Postmenopausal women with LSIL may undergo reflex high-risk HPV DNA testing, repeat cytology at 6 and 12 months, or immediate colposcopy.

Interventions/Treatment of Cervical Intraepithelial Neoplasia

Once identified, CIN may be treated by ablative (cryotherapy or laser ablation) or excisional modalities (loop electrosurgical excision [LEEP], laser conization, or cold knife conization [CKC] of the cervix).[76] Current guidelines recommend observation of CIN1, as it is highly likely to regress spontaneously without treatment.[68] Treatment of CIN2 and CIN3 is advised, and both ablative and excisional modalities are acceptable. If CIN2 or CIN3 recurs, however, excision is preferred.[68] In adolescents, CIN2 may be observed and treated only if it persists for 24 months or progresses to CIN3.[68]

A randomized controlled trial (RCT) of cryotherapy, laser, and LEEP reported similar success rates (less than 5% rate of persistence of CIN, less than 20% rate of recurrence of CIN over approximately 3 years) and no significant difference in complication rates among the three treatment modalities.[78] Risk of persistent disease was higher among women with large lesions (risk ratio, 18.9 [95% CI, 3.2 to 110.6]). Recurrence risk was higher among women aged 30 years and older (risk ratio, 2.1 [95% CI, 1.2 to 4.3]), those with HPV type 16 or 18 (risk ratio, 2.1 [95% CI, 1.1 to 4.0]), and those who had had prior treatment for CIN (risk ratio, 2.1 [95% CI, 1.1 to 3.9]).

A systematic review published in 2000 of controlled and randomized studies of cone biopsy, cryotherapy, laser, and LEEP of the cervix found no substantive differences in the persistence or resolution of CIN among these modalities.[79] The pooled rates of resolution for low- and high-grade lesions or mixed histology ranged from 85 to 95 percent. The median duration of followup for these studies ranged from 2 to 45 months. A more recent Cochrane Collaboration review published in 2010 found no difference in residual disease between 1) LEEP, laser, or CKC or 2) laser ablation and laser, cold knife, or LEEP conization procedures.[80] There was no difference in residual disease between cryotherapy and laser ablation or between cryotherapy and LEEP at 6 months. However, there was a significantly lower risk of residual disease at 12 months among women who underwent LEEP compared to cryotherapy (risk ratio, 0.32 [95% CI, 0.13 to 0.78]).

A recently published retrospective cohort study used data from the British Columbia Cancer Agency cytology database to determine long-term risk of CIN recurrence among women with CIN1 to CIN3 treated by various modalities (cryotherapy, LEEP, CKC, and laser vaporization or excision).[81] The authors compared 37,142 women who underwent treatment for CIN1 to CIN3 between 1986 and 2000 with 71,213 women with normal cytology and no previous CIN using followup data through the end of 2004. The overall incidence of invasive cancer (per 100,000 woman-years) was higher among women with a history of CIN (37 cases [95% CI, 30.6 to 42.5]) than in the comparison cohort (6 cases [95% CI, 4.3 to 7.7]). Among all methods evaluated, cryotherapy was associated with the highest rate of subsequent disease (adjusted odds rate for invasive cancer, 2.98 [95% CI, 2.09 to 4.60]).

As the risk of ICC persists after treatment of CIN,[81-83] post-treatment followup is advised.[68,82] There is no specific treatment for HPV in the absence of CIN. Since current treatment only targets CIN after it has developed, the prevention of HPV infection and, consequently, the development of CIN is important.

Potential Harms Related to Diagnosis and Treatment of CIN

Risks of colposcopy and cervical biopsy include pain, bleeding, infection, failure to diagnose (inadequate sampling), and cost to the patient (e.g., time off work and psychological

impact). One large, multicenter trial of 4,439 women aged 20 to 59 years with low-grade cervical abnormalities who were randomized to cytologic surveillance versus immediate referral (Trial of Management of Borderline and Other Low-Grade Abnormal Smears [TOMBOLA]) attempted to quantify the potential harms (i.e., clinically significant anxiety and depression and self-reported after effects such as pain, bleeding, and vaginal discharge) associated with colposcopic evaluation versus surveillance.[84] Results from the TOMBOLA group indicated similar proportions of women with depression in the surveillance and immediate colposcopy groups at 6 weeks after the procedure, although women in the surveillance group were more likely to be anxious (13.4 vs. 7.9%; $p<0.001$). Significantly lower proportions of women in the surveillance group reported any pain (15.0 vs. 38.9%; $p<0.001$), bleeding (17.2 vs. 46.9%; $p<0.001$), or discharge (8.6 vs. 34.2%; $p<0.001$), compared with women in the immediate colposcopy arm. Within the TOMBOLA cohort, an observational study (n=929) compared the physical after effects (pain, bleeding, and discharge) of colposcopic examination only, cervical punch biopsies, and LEEP.[85] Among women aged 20 to 59 years with colposcopy and no biopsy, 14 to 18 percent reported pain, bleeding, or discharge at 6 weeks. In those with colposcopic biopsy, 53 percent reported pain, 79 percent reported bleeding, and 46 percent reported discharge. For women who had LEEP, these numbers were 67, 87, and 63 percent, respectively. The duration of bleeding and discharge was longer for women treated by LEEP than women in the other groups reporting these symptoms.

Potential harms of treatment of CIN include immediate, short-term, and long-term risks. These risks may include pain, injury to adjacent organs such as the bowel or bladder, infection, bleeding, adverse reactions to medications used during the treatment procedure, incomplete treatment (i.e., residual disease after treatment) requiring additional testing or treatment, cervical stenosis resulting in difficulties with future attempts at endocervical (or endometrial) assessment, and cervical shortening with possible subsequent increased risk for preterm birth. Other potential issues to consider are the cost to the patient for time off of work, treatment of lesions that might regress on their own, and the psychological impact of the diagnosis or procedure.

One review of obstetrical outcomes published in 2006 evaluated cold knife and laser conization, laser ablation, and LEEP. CKC was significantly associated with preterm delivery (less than 37 weeks: 8 studies; RR, 2.59 [95% CI, 1.80 to 3.72]), low birthweight (less than 2,500 grams: 4 studies; RR, 2.53 [95% CI, 1.19 to 5.36]), and cesarean delivery (4 studies; RR, 3.17 [95% CI, 1.07 to 9.40]), but no increase in perinatal mortality.[86] LEEP was also significantly associated with preterm delivery (8 studies; RR, 1.7 [95% CI, 1.24 to 2.35]), low birthweight (6 studies; RR, 1.82 [95% CI, 1.09 to 3.06]), and premature rupture of membranes (3 studies; RR, 2.69 [95% CI, 1.62 to 4.46]), but not cesarean delivery or perinatal mortality. Similar effects on preterm delivery were noted for laser conization, but these were not statistically significant. No increased risk for adverse obstetric outcomes was detected among women who underwent laser ablation.

A 2008 review of excisional or ablative therapies found that CKC was associated with an increased risk of preterm birth prior to 30 weeks (4 studies; RR, 5.33 [95% CI, 1.63 to 17.40]) and prior to 34 weeks (5 studies; RR, 2.78 [95% CI, 1.72 to 4.51]), birthweight less than 2,000 grams (1 study; RR, 2.86 [95% CI, 1.37 to 5.97]), and perinatal mortality (7 studies; RR, 2.87 [95% CI, 1.42 to 5.81]).[87] LEEP was not associated with an increased risk of perinatal mortality, preterm birth prior to 32 to 34 weeks, or preterm labor prior to 28 to 30 weeks. One included study evaluated the impact of LEEP on low birthweight and found no significant increased risk of low birthweight less than 2,000 or 1,500 grams. Ablative procedures (2 studies of cryotherapy

and 4 of laser ablation) were not associated with an increased risk of preterm birth, perinatal mortality, or low birthweight.

Neither of the two reviews addressed the relationship between the depth of the tissue specimen excised and preterm birth, or addressed important confounders such as socioeconomic status and previous preterm birth. One recent large retrospective U.S. cohort study, published after these two reviews, found no increased risk of preterm birth associated with LEEP.[88]

Efforts to Prevent HPV Infection

HPV vaccination may allow disease prevention early in the progression to cervical cancer, before persistent HPV infection is established. In 2006, the FDA approved the Merck vaccine GARDASIL for multiple indications, including use in females aged 9 to 26 years for prevention of diseases including CIN and cervical cancer. GARDASIL is a quadrivalent vaccine against HPV types 6, 11, 16, and 18 and is given in a three-dose schedule.[89] More recently (2009), CERVARIX by GlaxoSmithKline, a bivalent vaccine against HPV types 16 and 18, has also been approved for the prevention of CIN and cervical cancer in females aged 10 to 25 years.[90]

Clinical trials of GARDASIL,[91] CERVARIX,[92] and their precursors showed vaccine efficacy of close to 100 percent for prevention of CIN2+ related to HPV 16 or 18 among women who were HPV negative at enrollment. Among all women enrolled, regardless of baseline HPV status, efficacy was much lower: 44 percent for GARDASIL and 53 percent for CERVARIX. Thus, HPV vaccination[93] is expected to be most effective before HPV exposure. Sexually active women, however, can also receive and benefit from vaccination. Since the two approved vaccines protect against just two of the 15 common oncogenic HPV types, efficacy against cervical lesions irrespective of HPV type is also lower, about 20 to 30 percent among all women enrolled.

Current Clinical Practice

A 2004 survey of 2,980 nonfederal, nonmilitary U.S. clinicians performing cervical cancer screening indicates that LBC is the primary screening modality used by the majority of clinicians surveyed. In addition, the majority reported that they had ordered an HPV test in response to abnormal cytology. According to the survey, 22 percent (range, 8 to 42% by specialty) of clinicians used CC only, and 65 percent (range, 45 to 78%) used LBC only.[94] Of the various clinical specialties surveyed, 78 percent of obstetricians reported use of LBC only, versus 45 percent of adolescent medicine specialists. Overall, 21 percent of clinicians (range, 11 to 37%) ever ordered or collected an HPV DNA test as an adjunct to cytology to be run regardless of the cytology result, and 63 percent (range, 44 to 91%) ever ordered or collected an HPV DNA test to be run in response to abnormal or borderline cervical cytology results. Of the 21 percent of clinicians who reported ever using HPV tests as an adjunct to cytology, more reported testing women younger than age 30 years (35% [range, 27 to 46%]) than women aged 30 years or older (29% [range, 9 to 36%]). Currently, the FDA has only approved the HPV DNA test (HC2) for 1) screening patients with ASC-US cytology to determine the need for referral to colposcopy, and 2) use in women aged 30 years or older as an adjunct to cytology to assess the absence or presence of high-risk HPV types.[70,71] Clearly, current use is beyond FDA approval.

Previous USPSTF Recommendation

In 2003, the USPSTF found good evidence that screening with cervical cytology reduces incidence of, and mortality from, cervical cancer.[94] It strongly recommended screening for cervical cancer in women who have been sexually active and have a cervix (A recommendation). The USPSTF found limited evidence to determine the benefits of continued screening in women older than age 65 years and fair evidence that screening in this age group is associated with an increased risk for potential harms; thus, it recommended against routinely screening women older than age 65 years for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer (D recommendation). The USPSTF found fair evidence that the yield of cytologic screening in women after hysterectomy is very low. It found poor evidence that screening to detect vaginal cancer improves health outcomes, and recommended against routine screening in women who have had a total hysterectomy for benign disease (D recommendation). The USPSTF concluded that the evidence was insufficient to recommend for or against the routine use of new technologies (such as LBC or automated screening) to screen for cervical cancer (I statement). Finally, the USPSTF concluded that the evidence was insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer (I statement).

Chapter 2. Methods

Key Questions and Analytic Framework

Using the USPSTF's methods (detailed in Appendix B),[95] we developed an analytic framework (Figure 5) and five key questions (KQs) to guide our literature search. These KQs include:

KQ1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?

KQ2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?

KQ3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?

KQ4: What are the harms of liquid-based cytology?

KQ5: What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?

The scope of the review was set in early 2007 and was conducted in the intervening years without a change in scope. This report's scope differs from the 2002 USPSTF evidence report in several ways. KQ1, which was not included in the 2002 evidence report, addresses when cervical cancer screening should begin. Both LBC and automated screening technologies were evaluated in the prior review, and the evidence was determined to be insufficient to recommend for or against the use of these technologies in cervical cancer screening programs. For this review, we updated the evidence regarding LBC (KQ2) and focused on studies that evaluated either ThinPrep or SurePath, which are both FDA approved. However, we did not update the direct evidence for automated screening technologies because they are less relevant to primary care clinicians. These technologies are implemented by laboratories and not performed by the clinician at the time of cervical cytology collection. The previous review evaluated the sensitivity and specificity of the HPV test for detection of histologically proven HSIL and LSIL. The authors also evaluated the use of the HPV test as a tool to facilitate triage of women with abnormal cytology. The current review expanded the scope of KQ3 to evaluate the evidence regarding the use of HPV testing in the following scenarios:

1. Primary screening with HPV test alone.
2. HPV testing with cytology triage of positive HPV (reflex cytology).
3. Combination HPV and cytology testing (co-testing).
4. Cytology testing with HPV triage of positive cytology (reflex HPV).

We restricted the scope of KQ3 to include only HC2 or PCR methods for HPV testing. We did not evaluate the use of HPV testing for followup after treatment for CIN. KQs 4 and 5, neither of which was framed as a separate KQ in the prior review, address the harms of LBC and HPV testing.

We addressed one contextual question that evaluated the efficacy of screening in women older than age 65 years according to the USPSTF's specified nonsystematic approach.[96] The previous review addressed this question systematically, and the USPSTF recommended against routinely screening women older than age 65 years, based on limited evidence regarding the benefits of continued screening in these women. We did not update the direct evidence for

screening in women after a hysterectomy because the prior USPSTF recommendation to discontinue screening after hysterectomy for benign disease is clearly supported. Because the HPV vaccine is so new, data to determine the long-term efficacy of the vaccine or how the HPV vaccine will affect screening is limited. Therefore, the USPSTF did not include a KQ addressing the impact of the HPV vaccine on cervical cancer screening. This will be an important topic for future evidence reviews, when more data regarding this issue become available. The USPSTF judged that a thorough review of cost effectiveness analyses was beyond the scope of our review. We did not review evidence on appropriate screening intervals, as this issue is rarely studied directly and the concurrent modeling study addresses this topic. We did not systematically review the harms of treatment procedures such as LEEP, cryotherapy, and laser cone biopsy.

Literature Search Strategy

For all KQs, we searched for systematic reviews, meta-analyses, and evidence-based guidelines on cervical cancer screening in the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, PubMed, and the Health Technology Assessment database from 2000 through January 2007. We also conducted a series of searches for each KQ and reviewed the search results for applicability to all KQs. For KQs 1, 3, 4, and 5, we conducted searches to identify studies published since the previous USPSTF review (2000 through September 2010). We searched in MEDLINE and the Cochrane Collaboration Registry of Clinical Trials (CCRCT) without restrictions on study designs. For KQ5, we also searched PsycINFO to capture adverse psychological effects of HPV testing. The search period for LBC (KQ2) began in 2003 because two systematic reviews provided a complete and thorough search of the relevant literature through July 2003.[97,98] We used these reviews as source documents to locate relevant studies from before 2003 and bridged their searches for LBC using MEDLINE and CCRCT, without restrictions on study designs, from the beginning of 2003 through September 2010. We evaluated the studies included in the previous review by Hartmann and colleagues[99] against the inclusion and exclusion criteria for the current review, and found only one study was eligible for inclusion.[100] We also obtained articles from outside experts and bibliographies of other relevant articles and systematic reviews. In addition to these searches for published trials, we searched federal agency trial registries for unpublished trials of cervical cancer screening. All searches were limited to articles published in the English language.

Study Selection

While differences in inclusion, exclusion, and quality criteria precluded us from incorporating any of the existing systematic reviews or meta-analyses that were identified, the high-quality reviews and meta-analyses were used to check the completeness of our searches for primary studies.

For KQ1, in the absence of RCTs addressing when to begin screening, we included cohort studies that evaluated the incidence and prevalence of cervical cancer in young screened populations, natural history studies of CIN and HPV infection in young women, and studies reporting outcomes of population-based screening programs targeting young women.

For KQs 2 and 3, evaluating LBC and HPV testing, we included studies that provided evidence regarding absolute and relative test performance. Our specific criteria were as follows:

1. To determine absolute test performance, we required that the reference standard of colposcopy and/or biopsy was systematically applied to all those screening positive and at least a random sample of screen negatives, with valid adjustment for verification bias when necessary. The reference standard must have been independent of the screening test (i.e., the screening test results were not used to establish the final diagnosis).
2. If a study did not test negatives appropriately with the gold standard, we could not use their absolute test performance estimates. However, if the study was an RCT, compared test performance within the randomization scheme, and was of appropriate quality, then we included relative test performance measures.
3. To evaluate screening demands and potential harms, we abstracted the following data where available as absolute or relative measures: test positivity, colposcopy referrals, colposcopy compliance, positive predictive value (PPV), false-positive proportion, and appropriately calculated specificity. For trials with multiple screening rounds, we looked for round-specific and cumulative data. For all studies, we looked for age-specific data.
4. Many studies reported theoretical test performance by estimating results for different screening and management programs, rather than by what was actually done in the trials. We determined these calculations could not be included if the assumptions required to estimate performance introduced potential threats to validity. We usually could not determine how to fairly assess whether these assumptions affected the validity of the calculated test performance, and if they did, what direction or degree of bias was introduced.

Studies of LBC and HPV primary screening must have been conducted in routine screening populations. Other inclusion and exclusion criteria specific to each question are detailed in Appendix B.

Data Extraction and Quality Assessment

Two investigators independently reviewed all abstracts for all KQs. Two investigators evaluated articles against a set of inclusion/exclusion criteria. Each investigator independently reviewed articles for quality using design-specific quality criteria based on the USPSTF methods, supplemented by the National Institute of Health and Clinical Excellence criteria for quality of systematic reviews and the QUADAS tool for quality assessment of diagnostic accuracy studies (Appendix B, Table 3).[95,101,102] Two investigators critically appraised all studies and agreed when articles were excluded for quality reasons. One reviewer abstracted data from included studies into evidence tables, and a second reviewer checked the data.

Data Synthesis and Analysis

Except for cytology testing with HPV triage of positive cytology (KQ3), data synthesis for all questions was qualitative because heterogeneity in the samples, settings, study designs, and instruments did not allow for quantitative synthesis. In the results section, studies are summarized qualitatively within the KQs. For KQ3 addressing HPV testing, studies are categorized by four different uses of HPV testing in cervical cancer screening. For each question, we first describe RCTs comparing cytology with HPV-enhanced screening strategies within existing screening programs that report absolute and relative CIN2+/CIN3+ detection for one or two screening rounds, followed by cross-sectional studies reporting absolute test performance

data. Studies from countries with less developed cervical cancer screening programs are discussed separately due to their lower applicability to the U.S. population.

For evidence on the benefits of using HPV testing to triage women with ASC-US cytology, we estimated the combined difference in sensitivity and specificity between HPV and repeat CC. A random effects model was used to incorporate variation among studies. For the difference in sensitivity and specificity between HC2 and cytology, we used risk difference as the effect measure. Statistical heterogeneity was assessed by Cochran's *Q* test and the I^2 statistic.[103] All analyses were performed using Stata 10.0 (StataCorp, College Station, TX).

Many of the results reported in the evidence and summary tables are calculated from data provided in the articles using methods cited in Appendix B. Such calculations are indicated in the evidence tables by "(calc)." In the RCTs, results were generally reported using women screened (instead of women randomized, as in an "intention-to-screen" analysis, which also includes opportunistic screening results) within each arm and each round. To be consistent, we abstracted from the articles or calculated results using the number of women screened within each randomized arm as the denominator unless noted as otherwise in the tables. Consideration of program results among women screened only may be less appropriate to determine overall population impact, but acceptable when primarily evaluating the relative merits (including false positives and other adverse effects) of efficacious screening alternatives.

Evidence tables for all KQs are in Appendix C. Detailed methods can be found in Appendix B.

USPSTF Involvement

This research was funded by AHRQ under a contract to support the work of the USPSTF. The authors worked with eight USPSTF liaisons at key points throughout the review process to develop and refine the scope, analytic framework, and KQs; to resolve issues around the review process; and to finalize the evidence synthesis. AHRQ had no role in study selection, quality assessment, or synthesis, although AHRQ staff provided project oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review of content by outside experts, including representatives of professional societies and federal agencies. The final published systematic evidence review was revised based on comments from these external reviewers.

Chapter 3. Results

Key Question 1. When Should Cervical Cancer Screening Begin, and Does This Vary By Screening Technology or By Age, Sexual History, or Other Patient Characteristics?

Various factors should be considered when determining the age of onset for cervical cancer screening and type of screening test to be used. These factors include the prevalence and incidence of CIN2, CIN3, and cervical cancer among women in their teens and early 20s, as well as the rate of progression of CIN2 and CIN3 to cervical cancer. Screening for cervical cancer or CIN2 and CIN3 may be of little net benefit if these conditions are rare or progress slowly in younger age groups. This is particularly true if screening for and treatment of preinvasive disease causes excess harm. For screening to be beneficial, it should lead to earlier detection of disease that, when treated, results in decreased morbidity and mortality from cervical cancer. Given HPV's significant association with preinvasive and invasive disease of the cervix, the natural history of HPV infections in young women is also important, including persistence and progression from HPV infection to cervical cancer. All of this evidence informs whether women in their teens and early 20s should be screened for cervical cancer and, if so, how they should be screened.

The ideal study for determining when cervical cancer screening should begin would be an RCT in which women are randomized to begin screening at different ages and then followed for the development of CIN3 and cancer, including morbidity and mortality. We did not identify any RCTs evaluating the age at which screening should begin. We considered cohort studies that evaluated the incidence and prevalence of cervical cancer in young, screened populations by age and other risk factors, the natural history of CIN and HPV infection in young women, and the effects of population-based screening programs targeting young women. We identified one large, fair-quality, population-based, case-control study evaluating the association between cervical cancer screening at ages 20 to 69 and future cervical cancer detection among 11,901 women in the United Kingdom;[23] two fair-quality cohort studies (from the United States[104] and United Kingdom[32]) examining age-specific screening outcomes in 199,707 women aged 15 years and older; one fair-quality population-based correlational study evaluating screening in all 20- to 34-year-olds attending routine screening in Iceland;[105] and one good-quality prospective cohort study (from the United Kingdom) describing the natural history of incident HPV and CIN infection in 1,075 15- to 19-year-olds[106] (Appendix C Table 1). The best evidence comes from the case-control study and is supported by the cohort studies.

Although evidence is based on a limited number of studies, these studies show that high-risk HPV infections and cytologic abnormalities among women younger than age 20 years are common and transient, whereas CIN3+ is much less common in this group than in women aged 25 years and older. They also show that screening in younger women (younger than age 25) has lower detection rates and higher false positives than in older women. Screening these women also does not result in decreased incidence of cervical cancer among women younger than age 30 years.

A population-based, case-control study conducted within the United Kingdom's National Health Service (NHS) used prospectively recorded data on cervical cancer screening to estimate the association between having an adequate smear test taken in a particular 3-year age group

(such as ages 22 to 24) and the incidence of cervical cancer in a subsequent 5-year age group (such as ages 25 to 29).[23] The study cohort included 4,012 women with invasive cancer and 7,889 controls (two controls per case). The authors found that cervical cancer screening among women younger than age 25 years was not associated with a decreased incidence of cervical cancer diagnosis prior to age 30 years. However, the authors could not rule out the possibility that screening women in the age group of 20 to 24 years would be effective in reducing stage IB+ cervical cancer in women aged 25 to 27 years, because the group was small (65 women) and thus confidence intervals were wide (OR, 0.52 [95% CI, 0.23 to 1.2]). A statistically significant protective effect of screening was not demonstrated until age 32 years, when screening was associated with a 45 percent reduction (OR, 0.55 [95% CI, 0.44 to 0.69]) in the incidence of ICC diagnosis between ages 35 and 39 years.[23]

This study's major strength was that it was designed specifically to answer the question of when cervical screening should begin, measuring the association between age at screening and the outcome of greatest interest—cervical cancer incidence. Additional strengths of this study include a study population comparable to that of the United States and the extensive electronic database from which the data were abstracted. The authors' use of random control selection minimized selection bias, and their use of prospectively recorded data on screening history reduced the recall bias that would otherwise be a weakness of the study's retrospective design. However, confounding is another limitation of observational studies, and the authors did not report or adjust for many potential risk factors for cervical cancer.

A population-based study in Iceland evaluated the value of cervical cancer screening in the 20- to 34-year-old age group by analyzing trends in CIN2, CIN3, and cervical cancer.[105] Iceland's national cervical cancer screening program commenced in 1969 for women aged 25 to 69 years at 2- to 3-year intervals. After 1987, women aged 20 years or older were also invited to screening at 2-year intervals. In the years following the introduction of cervical cancer screening for women aged 20 to 24 years, the rate of ICC did not change among this age group. This rate did decrease significantly among women aged 35 to 39 years, however, with a stage shift toward earlier disease detection. In contrast, the detection rate of CIN2 and CIN3 increased among women aged 20 to 29 years, whereas detection of CIN2 increased among women aged 30 to 34 years but detection of CIN3 decreased.[105] In Iceland, the usual practice is to observe smears with low-grade cytologic abnormalities (≤LSIL) and refer women with high-grade smears for colposcopy with biopsy and endocervical curettage. However, screening and treatment practices may change over time or vary across institutions or providers. So, at an ecologic level, it is difficult to establish causality or to attribute changes in CIN2, CIN3, and cervical cancer detection rates solely to the initiation of screening younger women. This study's strength was the large timeframe over which the data were reviewed, which allowed for evaluation of shifts in trends of disease detection. This study and the UK study were rated fair quality. One advantage of the UK study's design is the use of prospectively collected individual-level data rather than population data. The Icelandic study supports initiation of screening in women in their early 20s, whereas the UK study was limited in power to determine whether screening among this group of women is beneficial. Neither study provided sufficient detail to allow determination of a specific age at which screening should be initiated.

A large cohort study conducted among 150,052 women aged 15 years or older enrolled in a Kaiser Permanente health plan between 1997 and 2002 examined age-specific cervical cancer screening outcomes.[104] In this population, the 25- to 29-year-old age group was the most frequently screened of all age groups—650 screened per 1,000 females enrolled compared to 217

per 1,000 for women aged 15 to 19 years.[104] The likelihood of detecting CIN3 was lower in women younger than age 25 years, compared to women aged 25 to 29 years, but the risk of having a false-positive smear was higher. The proportion of smears yielding CIN3 was 0.2 percent for women aged 15 to 19 years and 0.2 percent for women aged 20 to 24 years, compared to 0.6 percent for women aged 25 to 29 years and 0.4 percent for women aged 30 to 39 years. False-positive smears occurred in 3.1 percent of women aged 15 to 19 years, 3.5 percent of women aged 20 to 24 years, 2.1 percent of women aged 25 to 29 years, and 2.6 percent of women aged 30 to 39 years. One limitation of these data is that they were drawn from a screened population of women with relatively stable health insurance, and therefore may not be generalizable to the U.S. population. The remaining included studies also evaluated populations of women with health insurance.

A second large cohort study, which provides important evidence on the prevalence of high-risk HPV by age in a population of women similar to those in the United States, evaluated 49,655 British women of any age presenting for routine screening between 1988 and 1993.[32] This study's goal was to describe the relationship between HPV detection at entry and cytologic and histologic followup. The 78,062 cervical samples obtained during the study were stratified according to the 12-month period in which they were taken and into 5-year age groups. HPV testing (PCR) was performed on an age- and period-stratified random sample to limit cost (n=6,462). The authors found that the prevalence of high-risk HPV was greatest in women aged 15 to 19 years (20%) and decreased with increasing age to 2.6 percent among women aged 50 to 54 years (Figure 6).[32] Across all age groups, the prevalence of high-risk HPV positivity was much lower for women with normal smears than those with abnormal smears (17.2% vs. 73.7% among women aged 15 to 19 years; 1.6% vs. 40.7% for women aged 50 to 57 years). Although the prevalence of high-risk HPV peaked among adolescents, prevalent cases of CIN3+ peaked among women aged 35 to 39 years, and incident cases of CIN3+ peaked among women aged 25 to 29 years (Figure 6). Among women with no previous smear, the prevalence of CIN3+ was 0.2 percent among women aged 15 to 19 years compared to 1.7 percent among women aged 35 to 39 years. No prevalent cancer cases were identified among women younger than age 20 years. The annual incidence of new cases of CIN3+ for women with a screening interval of less than 5 years following a normal smear was 1.56/1,000 per year among women aged 15 to 19 years, peaked at 4.07/1,000 for women aged 25 to 29 years, and decreased with increasing age to the lowest incidence rate, which was 0.19/1,000 among women aged 60 to 64 years.

In a prospective cohort study of 1,075 British women aged 15 to 19 years with normal cytology and negative high-risk HPV tests, each woman was followed with serial smears and HPV testing at 6-month intervals.[106] The study's goal was to describe the natural history of incident HPV infection and its temporal relation to the occurrence of cytologic and histologic abnormality; it provides valuable information on the acquisition and remission of high-risk HPV among adolescents, and the risk of development of CIN2+ in relation to HPV status. All women with cytologic abnormalities underwent colposcopy and biopsy of abnormal areas. Treatment was postponed until there was histologic evidence of CIN2 or greater. The median number of visits was four, and median duration of followup was 29 months. This study demonstrated the frequent occurrence of new high-risk HPV infections and their transient nature as well as the transient nature of cytologic abnormalities among young women. The authors also identified a small percentage of young women who developed CIN2+ despite continuing to test negative for high-risk HPV.

During study followup, 38 percent of women became positive for any HPV type, and 26 percent of women became positive for high-risk HPV types (16, 18, 31, 33, 52, or 58). The cumulative risk at 3 years of any HPV type was 44 percent, and at 5 years the risk was 60 percent. The median duration of the first HPV positive episode was 13.7 months (interquartile range [IQR], 8.0 to 25.4) for any HPV type, 10.3 months (IQR, 6.8 to 17.3) for HPV 16, and 7.8 months (IQR, 6.0 to 12.6) for HPV 18. The cumulative risk at 3 years of any cytologic abnormality was 28 percent (95% CI, 25 to 32). The median duration of the first episode of cytologic abnormality was 8.7 months (IQR, 5.8 to 13.8). In this cohort, 28 women (2.6%) developed CIN2 (1.3%) or CIN3 (1.3%) during a median of 36 months of followup. Five of these women consistently tested HPV negative. The risk of being diagnosed with CIN2+ was 8 times greater for women who became HPV positive during followup than for those who remained negative (RR, 7.8 [95% CI, 2.7 to 22.0]).

Key Question 2. To What Extent Does Liquid-Based Cytology Improve Sensitivity, Specificity, and Diagnostic Yield and Reduce Indeterminate Results and Inadequate Samples Compared to Conventional Cervical Cytology?

We identified two RCTs,[107,108] one cohort,[109] and one cross-sectional study[110] that provide data comparing LBC (ThinPrep) and CC. Only one RCT, a cluster-randomized trial rated as good quality (Netherlands ThinPrep versus Conventional Cytology [NETHCON]), set out with the primary purpose of comparing LBC and CC.[108] The other RCT, the New Technologies for Cervical Cancer Study (NTCC) Phase I, rated as fair quality, was designed to compare CC with LBC in combination with HPV testing.[107] Both provide relative test performance data only. The two remaining observational studies, both rated as fair quality, provide absolute test performance data, since colposcopy and/or biopsy was systematically applied to all women.[109,110] The NTCC and NETHCON trials included a total of 134,162 eligible women, and the nonrandomized trials included a total of 7,404 women. All of the studies were conducted in primary care settings in nonU.S. populations (periurban South Africa, France, the Netherlands, and Italy) (Table 3).

The NTCC and NETHCON trials showed no difference between LBC and CC in relative detection ratio of CIN2+ or CIN3+ (Table 4).[107,108] The NETHCON trial demonstrated no difference between LBC and CC in relative PPV for detection of CIN2+ and a higher PPV of borderline statistical significance (p=0.036) favoring LBC for the detection of CIN3+,[108] while the NTCC trial demonstrated a lower PPV for LBC for the detection of both CIN2+ and CIN3+, compared to CC.[107] The NTCC trial found a higher relative proportion of false-positive test results for LBC compared to CC (1.97 for detection of CIN2+ and 1.93 for detection of CIN3+),[107] whereas the NETHCON trial found a slightly lower proportion of false-positive test results with LBC (0.90 for detection of CIN2+ and 0.89 for detection of CIN3+).[108]

The cluster-randomized NETHCON trial was designed to compare LBC to CC among women aged 30 to 60 years participating in the Dutch cervical screening program.[108] Overall, this is a well-designed study with good applicability to the United States, and it provides the best available evidence to address KQ2 in terms of the use of LBC in a large cervical cancer screening program. Randomization was by clinical site, with 88,988 women at 246 family practices included in the analysis. Exclusion criteria were not reported. Followup for screen-

positive women followed Dutch clinical guidelines, with colposcopy referral and directed biopsy for high-grade or persistent low-grade abnormalities.

Among 40,047 women with cytology results of ASC-US or worse, 280 cases of CIN2+ and 190 cases of CIN3+ were detected in the CC arm, of whom 420 underwent colposcopy only (n=2) or colposcopy and biopsy (n=418). In the LBC arm, 346 cases of CIN2+ and 253 cases of CIN3+ were detected among 48,941 women screened, of whom 484 underwent colposcopy only (n=4) or colposcopy and biopsy (n=480).[108]

The NETHCON trial found no significant difference between LBC and CC in the adjusted relative detection ratio (adjusted for age, site, urbanization, and study period) of either CIN2+ (1.00 [95% CI, 0.84 to 1.20]) or CIN3+ (1.05 [95% CI, 86 to 1.29]). The unadjusted relative PPV (adjusted results not provided by the authors) for CIN2+ was similar between the two screening tests (PPV for ASC-US+, 1.09 [95% CI, 0.95 to 1.25]; PPV for LSIL+, 1.04 [95% CI, 0.93 to 1.15]). For detection of CIN3+, the relative PPV for LBC bordered on statistical significance, compared to CC (PPV for ASC-US+, 1.17 [95% CI, 0.99 to 1.39]; PPV for LSIL+, 1.17 [95% CI, 1.01 to 1.36]). The relative false-positive proportion (RFPP) for LBC was 0.90 (95% CI, 0.82 to 0.99) for detection of CIN2+ and 0.89 (95% CI, 0.82 to 0.98) for detection of CIN3+, compared to CC.[108]

The NTCC study was not a randomized trial of LBC versus CC. Rather, this study was a randomized screening program of LBC plus the HC2 HPV test (experimental group) versus CC (control group).[107] The referral threshold for colposcopy was ASC-US for the experimental arm, and either ASC-US (72%) or LSIL (28%) for the control arm. Since the referral criterion differed for the two study groups, we present results for the centers that used the same referral criterion for both tests. In their comparison of LBC versus CC, the authors included CIN2 lesions or worse that were detected during the recruitment phase of the trial, within 1 year of referral to colposcopy.

Among women with cytology results of LSIL or worse, 70 cases of CIN2+ and 44 cases of CIN3+ were detected in the CC arm among 22,466 women, of whom 317 underwent colposcopy. In the LBC arm, 73 cases of CIN2+ were detected (relative detection ratio, 1.03 [95% CI, 0.74 to 1.43]; relative PPV, 0.58 [95% CI, 0.43 to 0.78]) and 32 cases of CIN3+ were detected (relative detection ratio, 0.72 [95% CI, 0.46 to 1.13]; relative PPV, 0.40 [95% CI, 0.26 to 0.62]) among 22,708 women screened, of whom 1,337 underwent colposcopy. Overall, more colposcopies were required in the LBC group (15/1,000 for CC vs. 27/1,000 for LBC). The relative detection ratio and PPV values noted for cytology results of ASC-US or worse (confidence intervals provided per correspondence with primary author, Dr. Ronco, on March 11, 2008) were also not significantly different.[111] The RFPP for LBC compared to CC was 1.97 (95% CI, 1.75 to 2.21) for detection of CIN2+ and 1.93 (95% CI, 1.72 to 2.21) for detection of CIN3+ for cytology results of ASC-US or worse, and 1.80 (95% CI, 1.48 to 2.19) for detection of CIN2+ and 1.72 (95% CI, 1.42 to 2.07) for detection of CIN3+ for cytology results of LSIL or worse.[107]

One substantial limitation of this study is that the colposcopists were not blinded to study arm. Therefore, they would have known the women's HPV test results.[107] Furthermore, no data were provided to determine that randomization provided comparable groups for this secondary analysis in which some women were excluded from the LBC arm because of positive HPV test results, but not from the control arm (since this group was not tested for HPV).

Two studies, one conducted in South Africa[109] and one in France,[110] provided absolute test performance results for comparison of LBC and CC for the detection of CIN2+ (Table 4).

Only the South African study provides data on detection of CIN3+.[109] For the detection of CIN2+ and CIN3+, the sensitivity of both LBC and CC decreased with increasing cytologic threshold, whereas specificity increased. LBC and CC did not significantly differ in sensitivity, specificity, false positive rates, or PPV for detection of CIN2+ and CIN3+, although wide, overlapping confidence intervals suggest limited power to detect a difference in sensitivity.

The French study was limited by a split-sample study design, which could bias the results because the smear prepared first may have the best sample of cells.[110] If that is so, then it might be expected that in this study, where the conventional smear was prepared first, the sensitivity of CC would be higher than LBC, but that was not the case. Both tests performed similarly.

The South African study has limited applicability, as the women in this study had never been screened prior to enrollment, which would be unusual for most U.S. women in the same age group.[109] Second, a high proportion of women in the study were infected with HIV. Finally, 14.5 percent had recently been treated for CIN. The proportion of women with HIV infection and/or recent CIN treatment was similar in both arms, so this is unlikely to bias the results in the direction of either cytology method; however, it is unclear how the absolute test performance of either method was impacted. The method of cervical sampling was not randomized or blinded, so there is some potential for introduction of bias through unequal allocation. The strength of this study lies in the fact that the gold standard was systematically applied to all study participants after collection of the screening test, therefore limiting differential application of the gold standard and verification bias.

Unsatisfactory Slides

Both the NETHCON and NTCC trials demonstrated a lower proportion of unsatisfactory cytology samples for LBC than CC, with 0.37 and 2.6 percent of LBC slides considered unsatisfactory, compared to 1.09 and 4.1 percent of CC slides, respectively (Table 4).[107,108] These findings are different than what had previously been demonstrated in the cohort and cross-sectional studies, in which LBC had more unsatisfactory samples. However, study design might explain these earlier results in at least one of the nonrandomized studies, in which the collected sample was first used to prepare the CC slide and the residual material was used to perform the LBC test.[110]

Key Question 3. What Are the Benefits of Using HPV Testing as a Screening Test, Either Alone or in Combination With Cytology, Compared With Not Testing for HPV?

We identified 22 unique studies in 48 publications that assessed the benefits of using HPV testing, either alone or in combination with cytology, as an initial screening or to triage abnormal initial screening cytology. These strategies were compared with cytology screening strategies that did not involve HPV testing. Results from these studies are summarized here, with more individual study details provided in Appendix C.

These studies address four different cervical cancer screening strategies using HPV: 1) primary screening with HPV test alone; 2) HPV testing with cytology triage of positive HPV (reflex cytology); 3) combination HPV and cytology testing (co-testing); and 4) cytology testing with HPV triage of positive cytology (reflex HPV). Within each HPV screening strategy, we found at least one fair- or good-quality RCT specifically testing that strategy compared with

cytology (Tables 5 and 6). Although most trials evaluated only one type of HPV screening strategy, the Italian NTCC trial addressed two different HPV screening strategies through separate recruitment phases—combined HPV and cytology testing (Phase I)[112] and HPV testing alone (Phase II).[113] The HPV test used in most trials was HC2, to detect 13 high-risk types of HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at a positive test cut-off of ≥1 pg/ml, except for two trials that tested PCR using general primers GP5+ and GP6+ to detect 14 high-risk HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).[114,115] Similarly, most trials compared various HPV screening strategies to cytology performed using CC, except for two that used LBC.[116,117] Colposcopy referral threshold varied between studies, and in three studies, different cytology thresholds were used by different study sites.[112,113,115]

All RCTs except one[118] (which enrolled previously unscreened women in rural India to evaluate one-time HPV testing versus cytology) were conducted in developed countries (i.e., United States, Italy, Sweden, England, the Netherlands, Finland) where cervical cancer screening is well established. The Sankaranarayanan trial is important in that it establishes a mortality benefit in reduced cervical cancer deaths (adjusted hazard ratio [HR], 0.52 [95% CI, 0.33 to 0.83]) with one-time HPV screening in never-screened Indian women aged 30 to 59 years compared to no screening. Trials addressed HPV screening strategies appropriate to unvaccinated women. Three trials limited recruitment to middle-aged women (excluding those younger than age 30 years or older than ages 56 to 64 years),[114,115,118] while six included women younger than age 30 years.[112,113,116,117,119,120] Only one study included women older than age 60 years.[116] We provide data stratified by age where possible for two primary reasons: 1) the FDA has approved the use of HC2 in women aged 30 years and older as an adjunct to cytology to assess the absence or presence of high-risk HPV types;[70,71] and 2) the prevalence of high-risk HPV is much lower in women aged 30 years and older than in women younger than age 30 years, dropping sharply from a prevalence of 35 percent for women aged 15 to 19 years to less than 15 percent for women aged 30 to 39 years (Figure 4).[34]

Five RCTs[112-115,117] reported program results after two rounds of screening, while the other four reported results after a single round of screening.[116,118-120] Treatment was generally offered for patients with CIN2+ histology, although in several studies this information was not clearly reported[114,115,118] or a different threshold was used.[119,120] Most RCTs reported relative results (estimating HPV screening strategy performance relative to cytology) by providing relative test performance characteristics and detection of CIN2+/CIN3+ for a single screening round and/or comparing cumulative disease detection after multiple screening rounds. The NTCC Phase I and II trials reported invasive cancer separately from CIN2 and CIN3,[112,113] but the author provided recalculated results for CIN2+ and CIN3+ by age to allow cross-study comparability. One trial was designed to allow randomized comparison of a differing order in which cytology and HPV specimens were collected.[121] This trial reported cross-sectional data most comparable with other observational studies, and is reported with these.

Primary Screening With HPV Test Alone

Countries with developed cervical cancer screening programs. One fair-quality RCT within the national screening program in Italy (NTCC Phase II) compared HC2 to cervical cytology for primary cervical cancer screening in 49,196 women aged 25 to 60 years (13,725 younger than age 35 years).[113] In the second screening round 3 years later, both groups were screened with cytology alone (Table 5a). Immediate colposcopy referral occurred for positive HC2 tests or for ASC-US+ cytology (Table 5b). The author provided data reported here for

CIN3+ and CIN2+, since published data separated out invasive cancer cases. Published outcome data reporting CIN3 and adenocarcinoma in situ (AIS) (with or without CIN2) are provided in Appendix C, along with authors' analyses combining ICC results across two protocols in NTCC (HPV screening and HPV-LBC co-testing). Trial data are supplemented by one good-quality[122] and five fair-quality cohort studies in community settings in the United States, Canada, Switzerland, Germany, and France (Table 7).[110,121,123-125] These studies compared the sensitivity and specificity of one-time HC2 screening to cervical cytology (primarily ASC-US+) in 40,732 women aged 17 to 93 years, with less than 10 percent (n=3,301) younger than age 30 years.

Women aged 30 or 35 years and older. After two rounds of screening in NTCC Phase II (one round of HPV screening) and a median of 3.5 years of followup, cumulative detection of CIN3+ (CIN3, AIS, or ICC) was increased in 17,724 women screened with HC2 relative to 17,747 women screened with cytology alone (55 vs. 35 CIN3+ lesions; RR, 1.57 [95% CI, 1.03 to 2.40]), with about the same number of invasive cancer cases detected in both arms (HC2 arm: 4 ICC/AIS cases; cytology alone: 5 ICC/AIS cases) (Table 8a).[113] Trial investigators pooled invasive cancer cases from these primary HC2 results (NTCC Phase II) with HC2-CC co-testing results (NTCC Phase I) due to insignificant statistical heterogeneity between trials.[113] Pooled results suggested decreased invasive cancer in women aged 35 years and older who were screened with HPV (6 total ICC cases in the HPV screening arms compared to 15 in the CC only arms; p=0.052). However, cancer outcomes would ideally come from comparable screening strategies and reflect clearly similar opportunities for diagnosis through comparable delivery of colposcopies and/or long enough followup with registry linkages to allow disease ascertainment outside the screening program. Because cumulative results are not reported for PPV, false-positive results, or colposcopy, it is difficult to assess the relative harms of HC2 versus cytology alone, or the net benefit of the two screening approaches.

Reported baseline colposcopy referrals were higher in HC2 screened women (5.8%), compared with cytology screened women (2.5%). Colposcopy referral data are not reported for the second screening round and are incomplete for the entire first round of screening. However, baseline colposcopy referrals in this trial may be a close approximation for the entire Round 1 screening, since women in both arms had a low threshold for immediate colposcopy referral, so few would undergo repeat testing strategies. Thus, there were about 3.3 percent more colposcopies after a single HPV test in Round 1, compared with cytology (ASC-US+ referral threshold) in women aged 35 years and older. In addition to incomplete reporting of harms and the use of different screening tests in Rounds 1 and 2 (with cytology alone in both arms in Round 2), another limitation of NTCC Phase II is that referral criteria differed by site in the control arm; two sites referred patients to colposcopy for LSIL+, and seven sites referred patients for ASC-US+.

Six community-based studies in both urban and rural settings in Europe, North America, and Asia reported absolute test performance of HPV alone compared with cytology. In a large study among women aged 30 years and older (n=7,908), one-time HC2 testing was much more sensitive than cytology (threshold of ASC-US+) for CIN3+ (HC2: 97.3% [95% CI, 83.2 to 99.6]; cytology: 46.0% [95% CI, 30.8 to 61.9]) and slightly less specific (HC2: 95.2% [95% CI, 93.4 to 96.5]; cytology: 98.0% [95% CI, 96.7 to 98.8]) (Table 9a).[123] A second, much smaller, study (n=774) provided similar estimates of greatly improved sensitivity with slightly reduced specificity, but with very wide confidence intervals.[122] This study's applicability to women older than age 30 years is limited, since more than 80 percent of women enrolled were younger than 30 years of age. More studies reported sensitivity and specificity for CIN2+, which generally

showed the same pattern of markedly higher sensitivity for HC2, with slightly decreased specificity (Table 9a and Appendix C).[110,121,123-128] One study with notably different sensitivity and specificity estimates for HC2 than the rest may have been affected by misclassification of women; this study attempted to report results for primary screening separately using an ~~-e~~nriched" screening sample (i.e., 26% of women were already referred for abnormalities detected in previous screening, while 74% were presenting for primary screening).

Women younger than age 30 or 35 years. The pattern of results in 13,725 younger women was similar to older women, but with a much higher rate of colposcopy referrals after HC2 screening (Table 8b). After two rounds of screening in NTCC Phase II, cumulative detection of CIN3+ also increased in younger women screened with HC2 relative to cytology alone (47 vs. 21 CIN3+ lesions; RR, 2.19 [95% CI, 1.31 to 3.66]), with few ICC cases detected in either arm (HC2 arm: 1 case; cytology arm: 0 cases). Relative CIN3+/CIN2+ detection was increased after HC2 screening in Round 1 to a much greater degree than in older women, with a possibly greater decrease in Round 2. Colposcopy referrals (reported for Round 1 only) were much higher in HC2 screened younger women (13.1%), compared to those screened with cytology (3.6%). One study (n=3,301) provided absolute test performance of HC2 compared with cytology in women younger than age 30 years.[122] HC2 sensitivity (for CIN3+ or CIN2+) was much higher (23 to 27%) than cytology, similar to markedly increased HC2 sensitivity in older women. Specificity of HC2, however, was relatively reduced compared to cytology to a much greater degree in younger women (about 11%) (Table 9b).

Countries without developed cervical cancer screening programs. A fair-quality cluster-randomized RCT of 131,806 never-screened women aged 30 to 59 years in rural India compared cervical cancer deaths and incidence up to 8 years after one-time HPV, CC, or visual inspection with acetic acid (VIA) screening to a never-screened control group.[118] One-time HPV testing significantly reduced the incidence of cervical cancer deaths (adjusted HR, 0.52 [95% CI, 0.33 to 0.83]) and Stage II or higher cervical cancer (adjusted HR, 0.47 [95% CI, 0.32 to 0.69]), compared to not screening. Neither VIA nor CC significantly reduced either cervical cancer deaths or incidence of Stage II or higher cervical cancer. Per 100,000 person-years of followup, there were 19.6 fewer Stage II or higher cervical cancer cases and 13.1 fewer cervical cancer deaths in the HPV screening group, compared with the unscreened controls. Since 25 percent of the cervical cancer deaths in the HPV screening group were in women who were not screened (about 20% of those randomized to the HPV arm), there is potential for even greater benefit if a larger proportion of never-screened women received a single HPV screening. This study's intent was to improve cervical cancer screening in a country developing its population-based screening, so applicability to the U.S. population or other developed countries is very limited (poor). Differences in treatment protocols and clinical care between rural India and the United States also suggest that cancer mortality data should be interpreted with caution. Another important limitation is that about 20 percent of eligible women randomized to one of the three screening interventions were neither screened nor included in the analysis.

We found four fair- or good-quality observational studies of primary HPV screening compared with cytology among 37,245 women aged 25 to 65 years in countries in the process of developing more robust cervical cancer screening.[129-132] All except one of these studies[130] show a pattern consistent with the observational studies conducted in developed countries (i.e., HPV testing is more sensitive but less specific than cytology). These studies were all judged to have poor[129-131] or fair-to-poor[132] applicability to the U.S. population, so they are not discussed further, but are included in Appendix C Table 3.

HPV Testing With Cytology Triage of Positive HPV (Reflex Cytology)

We identified one fair-quality RCT[120] of 71,337 women aged 25 to 65 years (approximately 16% younger than age 35 years) within the Finnish national screening program comparing HC2 testing (with CC testing to triage positive HPV results) to cytology alone.[133] HPV+ women with LSIL+ results on cytology triage were referred for immediate colposcopy, with retesting for ASC-US or HPV+/normal cytology results (Table 5b). Unlike most other studies, CIN1+ results were treated in all but the latter years of the trial, during which CIN1 in women younger than age 30 years was surveyed. A second round of screening (5 years after the initial round) is planned, but results from this second round have not yet been reported. Additional limitations of the Finnish trial include a high proportion of post-randomization loss (approximately one-third of women randomized to each study arm did not attend screening); unequal cross-over between study arms (more women in HPV arm screened with cytology [8%] than the converse [<0.1%]); and incomplete reporting of colposcopy referral rates (reported for baseline only) and false positives, particularly important for women aged 35 years and younger.

Women aged 35 years and older. After a single screening round (minimum 2 years of followup), HC2 testing with CC triage using an LSIL+ threshold nonsignificantly increased detection of CIN3+ after at least 2 years of followup, compared to cytology, in women older than 35 years (32 vs. 23 CIN3+ cases; RR, 1.38 [95% CI, 0.81 to 2.36]) and significantly increased CIN2+ detection (RR, 1.36 [95% CI, 0.98 to1.89]) (Table 8a). Six cases of invasive cancer were detected with HPV screening and four with conventional screening. Colposcopy referrals were modest in women older than age 35 years and similar between HPV screening (0.9%) and cytology alone (1.0%). Based on test positivity, these data appear to reflect immediate referrals for LSIL+ and appear not to include colposcopy due to retesting during initial or extended followup.

Extended followup (mean, 3.3 years; maximum, 5.0 years) of this first screening round with linkage to registry data in 38,670 screened women aged 30 to 64 years found significantly increased CIN3+ (and cancer) after cytology triage of HC2 testing, compared with cytology alone (HC2: 59 CIN3+ cases, including 11 ICC/ACIS; CC: 33 CIN3+ cases, including 6 ICC/ACIS; RR, 1.77 [95% CI, 1.16 to 2.74]).[134] Extended followup included just over half of the original cohort, with women from eight of the original nine municipalities and only women older than age 30 years. Additional cases were detected in those who were invited but did not attend program-based screening. However, relative detection of CIN3+ was also increased using an intention-to-screen analysis among all women invited (1.44 [95% CI, 1.01 to 2.05]). The majority of women who tested positive in both arms (1244/1354 in HPV with triage arm and 1053/1125 in cytology arm) were not referred for immediate colposcopy, but had retesting recommended (data not shown). Almost half of CIN3+ cases detected in both arms came from the groups recommended for retesting. It also took longer for a relative CIN3+ detection advantage to emerge between women immediately referred for colposcopy and those who underwent repeat testing. Within 1 year of initial screening, cases of CIN3+ from women with LSIL+ cytology were detected, while it took 3 to 3.5 years for all CIN3+ cases to accrue among women undergoing repeat testing for less abnormal results (HPV+ with or without ASC-US+ cytology). Thus, adequate length and completeness of followup appears important in determining the comparative detection impact of screening strategies. Women who screened HPV negative tended toward a relatively lower risk of CIN3+ compared with cytology negative women (0.28 [95% CI, 0.04 to 1.17]) (data not shown).

Women younger than age 35 years. Round 1 results (without extended followup) in 11,580 women younger than age 35 years found no enhanced CIN3+ or CIN2+ detection and little difference between HC2 screening with cytology triage and cytology alone in immediate colposcopy referrals (2.8 vs. 2.7%) (Table 8b). Complete Round 1 colposcopy referrals are likely higher in the HC2-cytology triage arm, since 15.8 percent of younger women in this arm were targeted for repeat testing, about twice as many as in the colposcopy arm alone (data not shown).

Combination HPV and Cytology Testing (Co-Testing)

We found four fair-quality RCTs within national screening programs in Italy, the United Kingdom, Sweden, and the Netherlands comparing cytology screening alone to combination testing (co-testing) in a total of 127,149 women aged 20 to 64 years (16,976 younger than age 30 or 35 years).[112,114,115,117] Trials tested HC2 plus LBC against CC (NTCC Phase I); HC2 plus LBC against LBC (A Randomised Trial in Screening to Improve Cytology [ARTISTIC]); or PCR using GP5+/6+ plus CC against CC (Population Based Screening Study Amsterdam Program [POBASCAM], Swedescreen). Colposcopy referral thresholds for cytology results varied considerably between trials (HSIL+ for ARTISTIC and POBASCAM, HSIL+ or ASC-US+ for different sites within Swedescreen, ASC-US+ or LSIL+ for different sites within NTCC Phase I). A cytology referral threshold of ASC-US+ or LSIL+ is probably most applicable to U.S. screening practice. Three trials (POBASCAM, Swedescreen, ARTISTIC) based immediate colposcopy referral on cytology results alone in both arms, using HPV positive results (alone or in combination with milder cytology abnormalities) to determine enhanced followup testing protocols (Table 5b).[114,117,115] NTCC Phase I followed a similar approach in women younger than age 35 years (retesting for HPV+ in persons with normal cytology), but referred older women with either HPV positive or ASC-US+ cytology results for immediate colposcopy.[112] No trials represented screening and retesting protocols identical to U.S. practice (as represented by ASCCP guidelines) for ASC-US or LSIL in combination with HPV results. Two trials changed screening strategies in the second round: POBASCAM screened both arms with PCR plus cytology after 5 years, while NTCC Phase I screened both arms after 3 years with cytology only (Table 5b).[112,114]

Duration of overall followup and completeness of followup for the whole sample varied between studies, which potentially affected complete ascertainment of outcomes. Followup interval from baseline was reported as 4.1 years (mean) in Swedescreen, up to 7 years in ARTISTIC, at least 6.5 years (median, 7.2) in POBASCAM, and up to 3.5 years after Round 2 invitation in NTCC Phase I. Based on incomplete followup, program impact could not be reported for a substantial portion of the sample in POBASCAM (not reported for the two-thirds without full 6.5 years of followup), while 29 percent of the sample in ARTISTIC had less than the minimal (2.5 years) followup after Round 2. Reporting of results after a third screening round in ARTISTIC did not remedy this.[135] Followup after a second screening round at 3 years in Swedescreen averaged less than 1 year, and did not include retesting of low-grade abnormalities. Another limitation of the co-testing trials was adherence to trial protocols. Just 50 to 60 percent of POBASCAM participants complied with repeat testing recommendations in each screening round. Twenty percent of POBASCAM participants in each arm had opportunistic screening outside the study, and 10 percent of ARTISTIC participants had no HPV test in Round 2; these deviations from protocol would be expected to attenuate measured differences between screening strategies. Given the variability in HPV-cytology co-testing strategies between trials and the lack

of complete implementation and reporting for all trials at this time, we did not try to quantitatively combine results.

We supplemented trial data with test performance data from four cohort studies (three of fair quality and one of good quality) in community settings in the United States, Canada, Germany, and France (Table 7).[110,121-123] These studies compared the sensitivity and specificity of one-time HC2 plus cervical cytology (defining a positive result using various combinations of test results) to cytology alone (ASC-US+) or HC2 alone in 25,040 women aged 18 to 69 **years** (3,301 younger than age 30 years) (Table 9).

Women older than age 30 or 35 years. In contrast with HPV screening alone, HPV plus cytology co-testing (using any of the variable screening, retest, and referral protocols) did not detect more CIN3+ after two rounds of screening than cytology alone in any of the trials (Table 8a). This finding may reflect the more stringent colposcopy referral protocols employed in most co-testing trials, compared with the one primary HPV screening trial (NTCC Phase II) (Table 5b). Round-specific screening results were somewhat mixed between trials, but generally detected relatively more CIN2+ with co-testing compared with cytology alone after Round 1, and less CIN3+ after Round 2. In all but one trial,[117] 51 to 78 percent more women with CIN2+ were detected in Round 1. ARTISTIC reported a 21 percent increase in CIN2+ detection that was not statistically significant, but also included all ages when reporting round-specific data (21% of women younger than age 30 years). All trials found 47 to 54 percent less CIN3+ detected in Round 2, although not all differences were statistically significant. Most trials detected the same or slightly fewer cancer cases overall in the HPV-tested arm, with few reporting impact on cancer incidence (i.e., second round relative cancer detection). Cumulative CIN2+ detection was relatively increased in the co-testing arm of a single trial (NTCC Phase I) that referred women with a positive HPV test or ASC-US+ cytology for immediate colposcopy.[112]

Given the many between-trial differences, it is difficult to interpret the mixed pattern of results. Findings to date do not reflect full followup of the second round of screening for any trial except NTCC Phase I (Table 5c). Reported results for colposcopy referral/attendance were also incomplete (NTCC Phase I, Swedescreen),[112,115] or round-specific colposcopy by age was not reported (ARTISTIC).[117] Colposcopy compliance was rarely reported. Cumulative colposcopies in ARTISTIC were higher in women randomized to co-testing (8.3%) than in those in the LBC only arm (6.4%), with a much higher colposcopy burden carried by women younger than age 30 years receiving co-testing (17.1%), compared with co-tested older women (6.0%) or with similarly young women receiving cytology only (12.0%) (Table 8).[117] Cumulative colposcopies reported in POBASCAM were low (3.4% for co-testing, 2.8% for cytology alone) and inadequate for estimating the burden associated with co-testing (compared with cytology alone), since both arms received HPV testing in Round 2.[114] Also, as with ARTISTIC, POBASCAM's immediate colposcopy referral threshold (HSIL+, with retesting protocols for ASC-US or LSIL results with or without HPV positivity) does not replicate recommended U.S. practice, so complete results will need to be judged for applicability. Nonetheless, most co-testing studies report reduced CIN3+ in the second round of screening compared with cytology screening. Reduced CIN3+ after a second screening round was used as the primary outcome for power calculations in several co-testing trials (ARTISTIC, POBASCAM) and an HPV with cytology triage trial (Finnish trial), indicating its perceived value.

Findings from trials are complemented by fair- or good-quality studies of one-time combined HC2 plus cytology (co-testing) test performance (Table 7). In these cross-sectional studies of 17,885 women aged 30 to 60 years, a one-time co-test was generally more sensitive than cytology (for detection of CIN2+ or CIN3+), but also less specific. Reported sensitivity and specificity are not completely comparable across studies since most used different thresholds for test positivity (Table 9a). Two studies, in which co-testing was positive if either HPV or cytology were abnormal, reported very high sensitivity for HC2 plus cytology co-testing that was clearly superior to cytology alone (44 to 56% more sensitive) at an ASC-US+ threshold, but not clearly more sensitive than HC2 alone.[121,123] This co-testing strategy (either test positive) was also 4 to 5 percent less specific than cytology alone, and appeared similar to HC2 testing alone.[121,123] Other co-testing strategies required both HPV and cytology tests to be positive, unless cytology met a threshold. One co-testing study based a positive result on HSIL+ cytology or a co-test result of HPV positive with ASC-US+ cytology,[110] while the other based a positive result on LSIL+ cytology or HPV+/ASC-US+ cytology results.[122] With these strategies, sensitivity of co-testing for CIN2+ or CIN3 was the same or somewhat better than cytology alone, but worse than HC2 alone (although confidence intervals were very wide). As expected, specificity for this more stringent definition of a positive co-test was better than HC2 alone, and similar or better than cytology alone. These co-test strategies are more similar to testing with either test alone, followed by triage if HPV+ or ASC-US cytology results using the other test, than to administering and acting on both tests.

Women younger than age 30 or 35 years. Only two co-testing trials (NTCC Phase I, ARTISTIC) included women younger than age 30 or 35 years (Table 8b).[112,117] Complete age-specific data were reported in NTCC Phase I only, and ARTISTIC is discussed with the results for women aged 30 or 35 years and older, since it largely reflects older women. NTCC Phase I compared one round of co-testing followed by cytology with two rounds of cytology. In contrast with the general pattern in older women (in NTCC Phase I and other co-testing trials), NTCC Phase I found no impact on CIN3+ in Round 1, Round 2, or cumulatively in 11,810 women aged 25 to 34 years. CIN2+ detection in younger women, however, was significantly increased in Round 1 and cumulatively. We had particular quality concerns for younger women in NTCC Phase I. Per protocol, the trial did not refer HPV positive/cytology negative younger women for immediate colposcopy, as it did with older women. Instead, younger women were retested at 1 year (Table 5b), a strategy reflecting the higher prevalence of HPV infection and likelihood of regression in young women. However, this difference in testing protocols led to differential loss to followup between the intervention and control arms, as many participants did not comply with repeat testing protocols. No cumulative data on colposcopy referrals in NTCC Phase I are available, and the higher baseline rate of colposcopy in younger women after co-testing compared with cytology alone (11.9 vs. 4.1%) is likely an underestimate, since these data reflect only immediate referrals.

In the only co-testing test performance study conducted primarily in younger women,[122] co-test positives were defined as both ASC-US+ and HPV+ (Table 9b). Co-testing was significantly less sensitive for CIN3+ (64.0% [95% CI, 51.1 to 77.6]) than HC2 alone (92.5% [95% CI, 83.5 to 97.3]), but not different than cytology alone (65.4% [95% CI, 51.9 to 79.1]). Specificity (87.6% [95% CI, 86.7 to 88.4]) was significantly higher than cytology alone (81.5% [95% CI, 80.7 to 82.3]) and HC2 alone (70.1% [95% CI, 66.5 to 73.1]). This strategy is dissimilar to that used in NTCC Phase I, and primarily mimics testing with either test alone,

followed by triage if HPV+ or ASC-US+ cytology results using the other test. Positive results on both tests would be considered necessary for immediate colposcopy referral.

Cytology Testing With HPV Triage of Positive Cytology (Reflex HPV)

We identified two good-quality RCTs in the United States[116] and Sweden[119] (Table 6) that addressed HPV triage of positive cytology. Neither study, however, compared HPV testing alone to repeat cytology in women referred with ASC-US or LSIL cytology. We also located four prospective cohort studies in countries with developed cervical cancer screening programs (United States, Sweden, France, Italy), three of fair quality[136-138] and one of good quality,[100] that evaluated the use of HPV testing using HC2 for triaging 2,261 women aged 15 to 78 years with ASC-US and LSIL cytology to colposcopy (Table 10). Three of the cohort studies compared one-time HPV screening to repeat cytology for triage of women referred with ASC-US or LSIL cytology.[100,136,137] In the fourth cohort study, women with ASC-US received repeat cytology and HPV testing at enrollment.[138] Women who tested positive on either test were invited for repeat HPV and cytology testing 6 months later. All women received HPV and cytology testing at 12-month followup. All studies compared HC2 to repeat CC, except ALTS, which compared HC2 and LBC to LBC alone (ThinPrep).

ALTS was a three-armed RCT that compared immediate colposcopy referral to HPV testing (HC2) plus repeat LBC or cytology (LBC) retesting alone (conservative management) to determine colposcopy referral in 5,060 U.S. women aged 18 to 81 years with community Pap smear diagnoses (69% ASC-US, 31% LSIL).[116] ALTS participants were primarily young (77.5% younger than age 35 years) and were racially and ethnically diverse. Criteria for immediate colposcopy referral was HSIL+ on repeat testing in either arm or positive HPV results in the intervention group. All women received colposcopy at 2 years. The reported sensitivity of the three arms for detection of CIN3+ was actually a calculation of the cases of CIN3+ detected using each of the management strategies within the a priori-defined period for the strategy (enrollment period for HPV arm and enrollment plus followup periods for conservative management) out of the total CIN3+ detected in that arm over the 2-year study period. This calculation focuses on comparing the efficacy of a single test event (HPV plus cytology) with ongoing testing (with cytology alone).

Within the a priori-defined periods for each strategy, CIN3+ was detected in 6.3 percent of women in the HPV-LBC triage arm and 5.1 percent in the cytology triage arm, for a relative CIN3+ detection ratio of 1.24 (95% CI, 0.88 to 1.73) (Table 11). CIN3+ included two cases of ICC and one case of AIS across all arms (one per arm) and similar cumulative CIN3+ cases (97 in immediate colposcopy arm, 101 in HPV triage, 109 in conservative management). HPV testing diagnosed a greater percentage of the CIN3+ cases at baseline, rather than during followup or at the exit visit (75.2% of all cases detected over the 2 years of the study), than immediate colposcopy (59.8%) or followup cytology (40.7%). At a cytology threshold of HSIL+, repeat cytology triage over 2 years referred significantly fewer women to colposcopy than HPV-cytology triage (12.3% vs. 55.6%; $p<0.001$), with no colposcopy referrals in the HPV arm based on cytology alone. Colposcopy compliance was reduced slightly when delayed (90.1% after HPV triage, 98.7% with immediate colposcopy referral).

Among women with LSIL enrolled in ALTS, HPV testing diagnosed a greater percentage of the CIN3+ cases at baseline, rather than during followup or at the exit visit (68.3% of all cases detected over the 2 years of the study), than immediate colposcopy (62.7%) or followup cytology (36.6%). HPV testing to triage LSIL, however, referred a vast majority of women (85%) to

colposcopy. CIN3+ was detected in 12.1 percent of women in the HPV-LBC triage arm and 6.7 percent in the cytology triage arm. The HPV arm was closed early due to very high HPV positivity, leading to an unequal number of women in each arm. Therefore, relative detection ratios are not valid in women with LSIL.

The ALTS trial was rated as good quality, but had some limitations, particularly related to applicability. The study design does not likely reflect current standard practice for ASC-US cytology in U.S. practice. This study used a repeat cytology threshold of HSIL for referral to colposcopy, while recent guidelines recommend referral of women to colposcopy if ASC-US or worse is identified on repeat cytology.[68] The results of the ALTS trial are reasonable estimates of what the study arms would produce in real life. While theoretical estimates are reported by the authors, the data provided do not allow for calculation of realistic estimates of comparative referral rates for usual care. More women would potentially have been referred to colposcopy, and sensitivity for CIN3+ might have been higher in the conventional management arm if a lower cytology threshold for referral had been employed. Whether this would have differed from the HPV triage strategy is unknown.

A second, smaller RCT compared HPV testing (HC2) plus repeat CC to repeat CC alone in 674 women aged 23 to 60 years with ASC-US or LSIL Pap smears identified through the Swedish national screening program.[119] After one round of triage, 132 CIN3+ lesions (including one ICC) were detected, and relative CIN3+ detection tended to be higher with HPV-CC triage than CC triage alone (1.20 [95% CI, 0.88 to 1.63]) (Table 11). These results were very similar in magnitude to the single round in ALTS, but nonstatistically significant. Although power was limited, HPV-CC triage tended to improve relative CIN3+ detection primarily in women aged 30 years and older. HPV-CC triage significantly improved CIN2+ detection compared with CC alone (1.32 [95% CI, 1.04 to 1.67]), with relatively greater detection of CIN2+ in younger women. A very large proportion of women (62% in the HPV-CC triage arm and 41% of women in the CC triage arm) were referred to colposcopy after triage. The relative false-positive proportion for CIN3+ was 1.74 (95% CI, 1.38 to 2.20), meaning there were seven false positives in the HPV-CC triage arm for every four in the CC-only triage arm. Age-specific results suggested worse relative false-positive performance for women younger than age 30 years, compared with older women.

This trial differed from ALTS in several important ways: 1) women were referred at a threshold of ASC-US (and/or HPV positive results) after one triage test, rather than through a program of repeat testing; and 2) all triage positive women were treated with LEEP, laser conization, or hysterectomy, providing good histological confirmation of disease. While this trial was rated as good quality, its small sample size limits its power. Additionally, the applicability of this trial to U.S. practice is limited because the authors do not present results separately for women referred with ASC-US versus LSIL cytology. As seen in the ALTS trial and the observational studies discussed below, the HPV test does not perform well as a triage test in women referred with LSIL cytology due to low specificity, whereas the specificity of HPV is similar to repeat cytology in the triage of women with ASC-US cytology to colposcopy.

Three fair-quality studies[136-138] and one good-quality study[100] that included 2,299 women aged 15 to 78 years with ASC-US on initial CC screening compared the absolute sensitivity and specificity of HPV alone or combined with cytology to repeat cytology alone for the detection of CIN2+ (Table 12). Studies primarily reported CIN2+ using a referral threshold of ASC-US+ or HC2 >1 pg/ml. All but one of these studies trended toward higher sensitivity for HPV.[136] The confidence intervals, however, were wide, and the differences were not statistically

significant.[100,137,138] HPV tended to have similar[100]or worse specificity[136,137] than repeat cytology in all but one study that showed slightly improved specificity with HPV,[138] although power was an issue in most comparisons. HPV plus cytology tended to improve sensitivity but reduce specificity (with limited power, because fewer than 1,000 women with ASC-US were evaluated for these comparisons).[136,138]

The cohort studies were small (total n=2,299), but data could be pooled for three of the studies (n=1,550) to provide combined test performance estimates for the comparison of HPV testing to repeat cytology for the detection of CIN2+ among women with ASC-US referral cytology (Figures 7 and 8).[100,137,138] The pooled difference in sensitivity between HC2 and repeat cytology was estimated to be 12 percent (95% CI, 0.2 to 23.9), suggesting a better sensitivity for HC2. The confidence interval was wide even after pooling due to small sample sizes. No difference in specificity between HC2 and repeat cytology was observed (*P*=0.65 for the combined difference).

The fourth cohort study was not pooled because it provided cumulative test performance over 1 year for detection of CIN2+ among women with ASC-US cytology results.[138] In this study, HC2 alone was more sensitive than cytology for the detection of CIN2+ (93.1% [95% CI, 91.3 to 94.9] vs. 74.1% [95% CI, 70.9 to 77.3]) and more specific (78.6% [95% CI, 75.7 to 81.6] vs. 72.3% [95% CI, 69.0 to 75.6]). The combination of both cytology and HPV testing was 100 percent sensitive, but less specific (62.5% [95% CI, 58.9 to 66.0]) than either HC2 alone or cytology alone. Age-specific results showed significantly better sensitivity and a tendency toward better specificity (but worse PPV) with repeat cytology in women aged 35 years and older, compared with younger women. In older women, HPV triage had a significantly higher area under the curve (AUC) (0.92) than in younger women (AUC, 0.74).

One study confirmed worsened sensitivity of immediate colposcopy that ALTS also found when compared to HPV testing (but not repeat Pap testing) in all women with ASC-US, regardless of age.[138] When data were reported for triaging initial LSIL results using HPV,[137] with or without repeat cytology,[136] these studies confirmed findings from ALTS of very poor specificity of HPV testing strategies for triaging LSIL.

Findings from observational studies generally represented older women (mean or median age, 34 to 42 years) and confirmed an increased detection of CIN2+ with HPV triage of ASC-US cytology (compared with repeat CC) and no further sensitivity advantage of adding CC to HPV triage. Trial results suggest reduced specificity (more false positives and colposcopies) with an HPV triage strategy, and most observational studies agree. In one small study (n=749) of ASC-US only that reported age-specific results for women younger and older than age 35 years, sensitivity for CIN2+ did not differ by age. However, in women aged 35 years and older, specificity for HC2 was better than for repeat cytology (84.8% vs. 74.7%), while in women younger than age 35 years, specificity for HC2 tended to be lower than for repeat cytology (60.4% vs. 65.5%).[138]

Key Question 4. What Are the Harms of Liquid-Based Cytology?

Potential harms of screening with LBC (which are also potential harms of CC) include harm from collecting the cytologic sample itself, harm from unnecessary evaluation of false-positive smears, psychological distress associated with a false-positive result, and the economic burden related to recall for repeated sampling due to an inadequate or insufficient LBC

specimen. We did not identify any studies that specifically addressed direct harm from collection of the LBC sample or psychological distress. Additionally, we did not systematically review the harms of diagnosis with colposcopy and biopsy.

Key Question 5. What Are the Harms of Using HPV Testing as a Screening Test, Either Alone or in Combination With Cytology?

Potential harms of HPV testing include harm from collecting the sample, psychological distress associated with a false-positive result or unnecessary evaluation of a false-positive result, partner discord, and the economic burden related to recall for repeated sampling due to an inadequate or insufficient specimen. Seven of the studies included for KQ3 reported on insufficient HPV test samples (Appendix C Table 3).[112,113,115-117,122,132] The range of insufficient HPV test samples from these studies (including both HC2 and PCR) ranged from 0.08 to 6.0 percent of samples taken. No studies reported direct harm from collection of the cervical sample itself.

We found four fair-quality observational studies that examined the psychological impact of HPV testing (Tables 13 and 14).[139-142] Three were conducted in the United Kingdom, two cross-sectional surveys[140,141] and one consecutive series[139] of patients evaluated from a randomized trial of combined HPV and LBC testing, which included 4,155 women aged 20 to 64 years presenting for routine cervical screening. These three studies focused on the psychological impact of knowing HPV test results. The fourth, a randomized trial of HPV triage of ASC-US Pap smears conducted in Australia (n=314), evaluated the psychological impact of HPV triage versus repeat cytology versus having an informed choice of either an HPV test or repeat cytology.[142] All study details are included in Appendix C.

Two of the three studies evaluating the psychological impact of knowing HPV test status (known test positive versus test negative, known test result versus no test result) evaluated only the immediate impact of the HPV test results.[139,141] The third evaluated participants both at 1 week and 6 months after receiving test results.[140] These studies found testing positive resulted in short-term increases in anxiety and distress among women who knew their HPV test result, but these findings resolved by 6-month followup (Table 14). Among women who did not know their test results, there were no differences in anxiety and distress between women who tested positive. In the fourth study that evaluated the short- and long-term psychological impact of HPV triage of ASC-US cytology versus repeat cytology, long-term followup suggested greater satisfaction with care and less distress among women undergoing HPV testing.[142]

A fair-quality study by McCaffery and colleagues evaluated adverse psychological effects in 428 women attending routine cervical screening at a NHS well-woman clinic after being given standard information about HPV (Table 13).[141] Seventy-three percent of women enrolled were included in the final analysis. The analysis compared psychological outcomes by screening test results using four study groups: 1) normal cytology, HPV negative (n=185); 2) normal cytology, HPV positive (n=46); 3) abnormal/unsatisfactory cytology, HPV negative (n=17); and 4) abnormal/unsatisfactory cytology, HPV positive (n=23). Baseline State-Trait Anxiety Inventory (STAI) scores did not differ.[141] Among those with normal cytology results, women who tested positive for HPV were significantly more anxious (mean STAI score, 43.5 vs. 29.8; F=39; p<0.0001) and distressed (mean Coping Strategy Questionnaire [CSQ] score, 13 vs.

8.9; F=69; p<0.0001) than those whose tests were negative (Table 13).[141] Among participants with abnormal or unsatisfactory cytology, women who tested positive for HPV did not differ in anxiety, but women who were HPV positive were significantly more distressed (mean CSQ score, 17 vs. 14; F=8.8; p=0.002).[141]

A second study evaluated the short-term psychological impact of HPV testing in a consecutive sample of women enrolled in the ARTISTIC trial with normal or mildly abnormal cytology (Table 13).[139] Women in the ARTISTIC trial underwent both cytology and HPV testing, but in one arm the HPV test result was concealed. Overall, 2,700 women in the revealed arm and 882 women in the concealed arm were mailed questionnaires assessing psychological distress, anxiety, and sexual satisfaction at 2 weeks after they had received the results of their baseline cytology. This study was rated as fair quality, with the primary concern that no baseline General Health Questionnaire (GHQ), STAI, or Sexual Rating Scale (SRS) testing was assessed for study participants prior to undergoing cervical cancer screening. In addition, the followup questionnaire had a response rate of about 70 percent.[139] The primary comparison was made among women with normal cytology who either knew (revealed arm) or did not know (concealed arm) they were HPV positive.[139]

The two groups did not differ in distress or anxiety (Table 14). Women in the HPV revealed arm did indicate lower sexual satisfaction with their current partner (adjusted mean difference in SRS score, -7.28 [95% CI, -12.60 to -1.96]). Planned subgroup analyses of women who had borderline or mild abnormalities on cervical cytology revealed no significant differences in distress, anxiety, or sexual satisfaction between the two groups. The study also compared women within the revealed arm of the study who knew their HPV test result.[139] Among women with negative cytology results, the odds of psychological distress (GHQ score ≥4) were increased (age adjusted OR, 1.70 [95% CI, 1.33 to 2.17]), and mean GHQ scores were higher (mean difference, 1.43 [95% CI, 0.75 to 2.10]) for women who knew they were HPV positive compared to women who knew they were negative. STAI scores indicated higher state (mean difference, 2.90 [95% CI, 1.40 to 4.39]) and trait (mean difference, 1.53 [95% CI, 0.16 to 2.92]) anxiety levels for women who were HPV positive. There were no statistically significant differences between HPV positive and negative women with mild or borderline cytology results, except that women who were HPV positive had higher odds of sexual satisfaction with their current partners than those who were HPV negative (mean difference, 8.66 [95% CI, 4.30 to 13.02]; p<0.0001).

The third study evaluating the psychological impact of HPV test results was conducted by Maissi and colleagues,[140,143] who evaluated 2,183 women attending routine cervical screening at two of the three centers taking part in an English HPV/LBC pilot study (Table 14). In addition to assessing distress and anxiety, they also assessed health-related quality of life (EuroQol EQ-5D). Outcomes were assessed by mailed questionnaire within 1 week after women had received their HPV and cytology results. Sixty-three percent of women returned the 1-week questionnaire, and 74 percent completed a followup questionnaire at 6 months. No data were provided to assess differences between responders and nonresponders. The analysis compared psychological outcomes among four groups of participants: women with 1) normal cytology results and no HPV test, 2) borderline or mildly abnormal cytology results and no HPV test, 3) borderline or mildly abnormal cytology results and an HPV negative test, and 4) borderline or mildly abnormal cytology results and an HPV positive test.[140,143] The study groups varied significantly in baseline characteristics; however, attempts were made to control for potential confounders in multivariate analyses.[140,143]

Results from immediate followup showed that the groups differed significantly in anxiety ($F=4.44$; $p=0.004$), distress ($F=5.37$; $p=0.001$), and concern about test result scores ($F=242.46$; $p<0.001$) (Table 14).[140,143] Women with abnormal cytology who were HPV positive had significantly higher anxiety (mean, 39.6 vs. 37.6; $p<0.00$), distress (mean, 2.8 vs. 2.1; $p<0.05$), and concern (mean, 9.7 vs. 8.8; $p<0.05$) than women who were HPV negative. There was no difference in anxiety, distress, or concern between women who had negative HPV tests and women who were not tested for HPV.

At 6 months, the groups still differed significantly in concern about test results ($F=83.39$; $p<0.001$), but not in anxiety or distress (Table 14).[140,143] Levels of anxiety, distress, and concern did not differ significantly between the HPV positive and HPV negative groups. Groups did not differ in health-related quality of life scores at baseline or followup. All four groups had low scores on the Psychological Effects of Abnormal Pap Smears Questionnaire, indicating low levels of sexual health worries, but women who were HPV positive had significantly higher scores than women who were HPV negative ($p<0.05$).

The fourth study, by McCaffery and colleagues, evaluated the psychological impact of HPV triage versus repeat cytology versus having an informed choice of either an HPV test or repeat cytology among women from family planning clinics across Australia with ASC-US equivalent cytology results (Table 13).[142] Overall, this was a well-designed, pragmatic, nonblinded RCT with good followup. Outcomes were assessed by questionnaire at baseline and at 2 weeks, 3 months, 6 months, and 12 months after the triage test. The primary outcome measure was health-related quality of life (36-Item Short-Form Health Survey, mental health combined score). They also assessed cognitive measures (perceived disease severity and risk, intrusive thoughts, worry, and satisfaction with care), emotional measures (anxiety, distress, and concerns about infectivity and effects on relationships), and behavioral measures (effects on sexual health, help seeking behavior, and visits to primary care physician).

At 2 weeks, no significant differences were seen between the three groups in psychosocial outcomes, except in proportion reporting intrusive thoughts (57%, 43%, and 32% for the HPV, informed consent, and repeat cytology groups, respectively; $p=0.02$) and satisfaction with care ($p=0.04$). Over 1 year, however, distress was significantly less in the HPV group than either the repeat cytology or informed choice groups, with mean CSQ scores of 16.6 in the HPV group, 18.4 in the cytology group, and 17.5 in the informed choice group ($p<0.01$).[142] Mean satisfaction scores were highest among women randomized to HPV testing and informed choice. The authors hypothesized that the longer wait for results in those who chose or were assigned to cytology likely accounted for higher distress and lower satisfaction in this group.

Chapter 4. Discussion

Summary of Review Findings

Cervical cancer screening's impact on reducing cervical cancer rates has been well-established by epidemiological evidence.[144] Evidence to evaluate the most efficient and effective screening approaches, however, has changed substantially since the 2003 USPSTF review and recommendation.[145] At that time, there was insufficient evidence to evaluate newer technologies, including LBC and high-risk HPV DNA screening. Largely within the past 5 years, results from eight RCTs evaluating HPV-enhanced screening strategies have been reported, with ongoing results as additional screening rounds are completed.[112-117,119,120] Another updated body of evidence addresses whether LBC and CC are generally equivalent. A large RCT compared LBC to CC,[108] and another large RCT compared these two cytological approaches using data from an HPV-cytology co-testing trial.[107] Data from trials for newer technologies are supplemented by well-done observational studies evaluating absolute test performance. When well-done, observational studies can be viewed as superior in some ways, since they compare test performance in the same women. However, since their results represent only cross-sectional histological findings, longitudinal followup with rescreening (as in trials) is needed to determine whether any differences in detected cervical lesions represent true (likely to progress) predisease.

The USPSTF began formulating its update in 2006 with a focus primarily on evidence for newer cervical cancer screening technologies. This report also focuses primarily on studies applicable to the United States or other countries with well-developed, population-based cervical cancer screening. Thus, while some promising trials and studies have been performed in India[118,129] and China,[130-132] their results have not been discussed, nor do they inform our discussion and conclusions.

Table 15 presents a summary of evidence for each KQ in order, which we briefly discuss next.

Initiation of Cervical Cancer Screening

The available evidence from five studies (four of fair quality and one of good quality) cumulatively suggests no benefit to cervical cancer screening for women before the age of 21 years. The goal of cervical cancer screening is detecting and treating preinvasive lesions, and incidence of CIN2 and CIN3 does not begin to peak until women reach their late 20s. The findings of Woodman and colleagues[106] and Peto and colleagues[32] confirm the findings of other studies[146] indicating that the prevalence and incidence of HPV infections in women younger than age 20 years is high, but most infections and cytologic abnormalities are transient. Moreover, a study by Insinga and colleagues found that the risk of false-positive smears is higher for women younger than age 25 years than for women aged 25 to 29 years (3.1 to 3.5% vs. 2.1%, respectively).[104] U.S. incidence data demonstrate that ICC is rare in women younger than age 20 years.[17] Overall, between 2000 and 2008, the age-adjusted incidence rate of cervical cancer among women younger than age 20 years was 0.05 cases per 100,000 U.S. women.[17] By comparison, the annual age-adjusted incidence rate for breast cancer in men of all ages was 1.1/100,000.[147] The high prevalence of HPV, the transient nature of cytologic abnormalities, and the rare occurrence of cervical cancer in adolescents argue against cytologic screening for

women younger than age 20 years, irrespective of timing of coitarche or presence of high-risk sexual practices. In fact, screening in this population may be harmful, as it could lead to unnecessary intervention. Since CIN1 and CIN2 are likely to regress, overtreatment could potentially occur.[68] Colposcopy and biopsy, which are currently the gold standard for evaluation of cervical cytologic abnormalities, and treatment of CIN may be associated with anxiety, pain, and cervical bleeding.[84,85,148,149] Furthermore, certain types of CIN treatment procedures may affect subsequent reproductive outcomes. Two systematic evidence reviews of obstetric outcomes in women with a history of CKC to treat CIN demonstrate a significantly increased risk of preterm birth (at less than 30-, 34-, and 37-weeks' gestation) and low birthweight in infants (less than 2,000 grams and less than 2,500 grams).[86,87] The two reviews differed in the impact of LEEP on obstetrical outcomes. In one review, pooled estimates demonstrated a 1.7-fold increased risk of preterm birth prior to 37 weeks and a 1.8-fold increased risk of birthweight less than 2,500 grams.[86] In the other, pooled estimates demonstrated no impact of LEEP on preterm birth prior to 34 weeks or birthweight less than 2,000 grams.[87] Other harms to consider are the psychological impact of labeling a woman as HPV positive, especially in a population in which HPV infections are highly prevalent and likely to regress.[150-152]

Whether initiation of screening in the United States should begin later than age 21 is unclear. The UK NHS Cervical Screening Programme does not commence cervical cancer screening until age 25. The large case-control study by Sasieni and colleagues was designed to determine whether screening should begin prior to age 25 in the United Kingdom.[23] While the authors concluded that screening women aged 20 to 24 years would have little or no impact on rates of ICC up to age 30, there was still some uncertainty regarding its impact on advanced stage tumors (IB+) in women younger than 30.[23] In June 2009, the UK Advisory Committee on Cervical Screening reviewed the practice of initiation of screening at age 25 years, and there was unanimous agreement that there should be no change in their current policy.[153] However, whether this practice should be adopted in the United States is uncertain. The Icelandic study by Sigurdsson and colleagues[105] supports initiation of screening in women in their early 20s, whereas the UK study was limited in power to definitively determine whether screening among this group of women is beneficial.[23] Neither study provided sufficient detail to allow determination of a specific age at which screening should be initiated. Furthermore, no studies were identified that provided information on age at which to initiate cervical cancer screening using U.S. data.

Liquid-Based Cytology Compared to Conventional Cytology for Primary Cervical Cancer Screening

The studies we reviewed demonstrated that LBC and CC do not differ in relative sensitivity or absolute sensitivity and specificity. False-positive rates varied among studies. They were not significantly different between LBC and CC in the nonrandomized trials. False-positive proportions in randomized trials were slightly lower in one study and slightly higher in the other, and both results bordered on statistical significance. The randomized trials included over 130,000 women combined and, thus, were well powered to detect significant differences. Our findings that LBC and CC do not differ in sensitivity and specificity are consistent with two recently completed systematic evidence reviews of LBC with more liberal inclusion criteria.[154,155] However, the systematic evidence review by Davey and colleagues performed in 2006, prior to the release of data from the NTCC and NETHCON trials, found that LBC did not reduce the

proportion of unsatisfactory slides compared to CC.[155] Data from the NTCC and NETHCON trials, in which thousands of women were randomized to LBC or CC, has since been published and demonstrates that LBC yields fewer unsatisfactory slides than CC.[107,108] We were unable to identify any studies that identified direct harms resulting from collecting the cervical sample for LBC.

Studies of clinical practice in the United States suggest that LBC has been widely adopted despite lack of available data to support greater accuracy with LBC testing, compared to CC.[94] One potential reason for the adoption of LBC is the ability to add reflex HPV testing without requiring an additional examination and specimen collection. Currently, the FDA has approved HC2 for testing patients with ASC-US cytology to determine the need for referral to colposcopy, and for use in women aged 30 years or older in conjunction with cytology to assess the absence or presence of high-risk HPV types. Since specimens for HPV testing can be collected at the time of cytologic testing without the use of LBC, sophisticated decision analysis models would need to be developed to determine whether or not the use of LBC is preferable to CC when HPV testing is desired, as there appears to be no advantage in terms of test performance to the use of LBC over CC in the absence of HPV testing. An editorial commentary by Schiffman and Solomon noted that other factors now influence the choice between LBC and CC, including issues related to laboratory productivity (LBC specimen slides are easier and quicker to scan under the microscope), slide adequacy (impact of fewer unsatisfactory slides), relative cost (LBC is more expensive than CC), and ease of ancillary molecular testing.[156]

HPV-Enhanced Primary Cervical Cancer Screening

The most extensive new data for cervical cancer screening technologies evaluate four potential roles for HPV in primary cervical cancer screening. However, despite recent detailed reports from five large RCTs within national screening programs in Italy, England, Finland, Sweden, and the Netherlands, available data are not yet complete, consistent, or relevant enough to determine a clear role for HPV testing as a primary cervical cancer screening method in the United States. One trial (NTCC Phase II) compared HC2 screening alone to CC alone (49,196 women screened; 27.9% younger than age 35 years),[113] four trials (NTCC Phase I, POBASCAM, Swedescreen, ARTISTIC) compared co-testing (with HC2 or PCR and CC or LBC) to CC or LBC alone (127,149 women; 13.4% younger than age 30 to 35 years),[113-115,117] and one trial (Finnish trial) compared primary HPV screening with cytology triage to CC alone (71,337 women; 16.2% younger than age 35).[120]

While all but one[120] of these trials of primary HPV-enhanced screening have reported results after two rounds of screening, data needed to determine benefit, harms, and net benefit remain incompletely reported. As shown in Table 5c, reported benefits (for CIN3+ detection, Table 16) as a cumulative or second-screening round outcome (Table 17) are considered possible surrogates for cancer; however, these data also represent incomplete followup of a significant proportion of study participants in three of four co-testing trials (POBASCAM, Swedescreen, ARTISTIC).[114,115,117] In addition, a planned second screening round is not yet conducted or reported in one trial (Finnish trial),[120] and recent reporting of a third round in ARTISTIC does not rectify data or other concerns affecting its validity.[135]

Regarding potential burden or harms, four of six trials (NTCC Phase I and II, Swedescreen, Finnish trial) representing all types of HPV-enhanced primary screening do not include data for each screening round and cumulative data, as would be necessary to interpret

screening burden and potential harms (Table 18).[112,113,115,120] Missing data include: proportion referred and receiving colposcopy immediately or after retesting protocols, proportion referred for retesting, compliance with retesting referrals, proportion receiving treatment, and, ideally, proportion experiencing diagnostic and treatment-related harms. Because age-specific data are critical in HPV-enhanced screening, lack of complete age-specific reporting for important benefit and harm-related measures in two of three trials including women younger than age 30 or 35 years (ARTISTIC, Finnish trial) further limits their current interpretation.[117,120] Reporting of these data will more fully inform the balance between potential benefits and harms from HPV-enhanced primary screening strategies, which will be particularly important since some available metrics (i.e., colposcopy) may appear ―worse" after one round of HPV testing (compared with cytology), but may look better over time if the more sensitive HPV test detected and treated earlier disease. It will also be particularly important to consider these trials' applicability, since none of their screening strategies mimics recommended U.S. practice.

How can we have so much data and yet still not know enough? The answer lies in our inability to answer two critical questions: 1) how much benefit does incorporating the more sensitive HPV test into routine screening approaches for cervical cancer provide? and 2) what are the tradeoffs in order to achieve this benefit? These issues also must be framed in a programmatic screening perspective focused specifically on cervical cancer. We illustrate these considerations using one trial, NTCC Phase II (Appendix E).

The Rationale and Potential Pitfalls of HPV-Enhanced Screening

Fair- or good-quality test performance studies (without verification or other serious biases) of one-time screening test performance clearly indicate that HC2 testing is much more sensitive than cytology alone for detecting CIN2+ (and CIN3+, based on more limited data). These data come primarily from women aged 30 to 69 years, within countries with well-developed cervical cancer screening programs. In the case of one-time co-testing (combined HPV-cytology screening), sensitivity is also superior to cytology alone, but not clearly better than HPV alone. For co-testing, test performance studies are fewer and more variable, and each study reflects a somewhat different test combination for a positive result (Table 9). There is also a potential bias toward inflated sensitivity when an adjunctive test is added to a conventional test and this combination is compared to the conventional test in the same women.[14] Therefore, based on test performance studies alone, some improvement in sensitivity compared with cytology is likely if HPV testing were substituted for (or added to) cytology in primary cervical cancer screening, but the magnitude of increase is uncertain.

While some improvement in sensitivity with primary HPV screening may be likely, the degree of benefit in preventing invasive cancer cannot be determined from test performance studies alone for a number of reasons.[14] First, the cross-sectional data suffer from determining sensitivity, specificity, and related predictive values for a surrogate outcome (CIN2+) and not true disease (ICC). Cervical cancer has a long preclinical period with predisease (CIN) regression, as well as progression that cannot be easily or directly studied. Regression can happen in any preclinical lesion, but appears much more likely in CIN2 or milder abnormal histological findings than in CIN3.[55] If a disease that is destined to regress is detected, it represents true overdiagnosis and potentially overtreatment. As a surrogate, we can be more confident in the detection of CIN3+, given that it includes carcinoma in situ, adenocarcinoma, or ICC, and is more likely to progress and less likely to regress than CIN2+.[55] Nonetheless, all CIN3+ is not clearly destined to quickly progress, leaving some uncertainty about whether

increased detection and treatment confers a clear benefit in preventing ICC.[55] Since cervical cancer screening consists of a program of repeated screening over time, earlier detection of precancerous lesions that would not have progressed and could be detected at a subsequent screening is not a clear benefit. Thus, for many reasons, one-time comparative test performance studies cannot provide full information on benefit, and complete data from repeated screening over time are needed. On the other hand, very high sensitivity (and corresponding negative predictive value [NPV]) is informative when considering screening interval. This concept will be covered more thoroughly in the section titled ―Potential Subgroup Considerations With HPV-Enhanced Cervical Cancer Screening."

While we are confident there is a meaningful potential benefit from HPV screening, we also recognize the potential for harms. The same test performance studies suggesting increased sensitivity also show specificity is generally reduced (between 2.8 and 4.5%). Given that screening test specificity is critically important when the prevalence of disease is low (as is the case with cervical cancer overall, but particularly in younger age groups),[17] test performance studies suggesting any decrease in specificity demand further research.[157] For example, even a 2 percent decrease in specificity for a one-time screening test in 10,000 U.S. women (with 0.8/1,000 CIN2, 0.7/1,000 CIN3, 0.1/1,000 cervical cancer) would result in 200 additional women receiving further unnecessary and even harmful testing and/or treatment, compared with cytology alone.[104] No more than one case of cervical cancer could be detected (even with increased sensitivity), although more predisease would be detected and treated. Given that the reduced specificity with HPV testing is for a surrogate outcome (CIN2), it cannot be determined whether any (or how much) of the presumed false-positives actually represent predisease that was appropriately detected and prevented through ongoing enhanced surveillance stimulated by a positive screening test and negative colposcopy. This is particularly possible since colposcopy is also an imperfect test. Colposcopy is the accepted reference standard, but one that can generate a false-negative or false-positive result, leading to overtreatment. A study of 1,176 community histology CIN1 or CIN2+ diagnoses from the NTCC trial suggested a 15 percent estimate of overtreatment, since 15 percent of CIN2 or worse diagnoses were downgraded to CIN1 or better after blinded review of all surgical and histological samples available within 1 year of colposcopy referral.[158] Similarly, in the United Kingdom, possible overtreatment occurred in 26 percent of histologically confirmed CIN1 and in 18 percent of women with biopsy showing less than CIN1 findings.[159] Thus, additional cumulative disease detection results, along with more complete reporting of retesting, colposcopies, treatments, and related harms from RCTs could help answer important questions about the comparative impact on benefits and harms of different screening strategies for cervical cancer in a program of repeated screening.

Interim Conclusions About HPV-Enhanced Screening From Available Data

While incomplete, trial results to date—in combination with results from rigorous test performance studies in applicable populations—allow us to draw a few conclusions and point out some important caveats to interpreting trial results as they are reported going forward

First, HPV-enhanced primary screening strategies appear most promising when focused in women aged 30 or 35 years and older, but not younger women. Women older than age 30 or 35 years represent the primary age of study participants, and also show a better balance between improved test sensitivity and reduced test specificity than do younger women (Appendix E).

Second, some HPV-enhanced screening strategies look more promising and more relevant to U.S. practice than others. Although it is premature to determine which HPV-enhanced protocol(s) might be preferable, some trial designs are more directly relevant to U.S. practice (NTCC Phase I and II, Finnish trial), primarily due to the colposcopy referral thresholds employed. According to NTCC Phase II, HPV screening alone in women aged 35 years and older may provide a benefit relative to a cytology-only strategy, but this benefit would require some initial increase in colposcopy (Appendix E). Whether some of this increase will be offset by fewer tests in subsequent screening rounds, and determining what proportion of excess colposcopy is due to increased false positives (and their related harms), cannot be determined with available data (Table 18). Also, it remains to be determined whether proportional benefits and harms reported from this trial will be directly applicable to the United States, given this study tended to use a lower cytology threshold for immediate colposcopy referral and also referred all women to colposcopy for a single HPV positive test. Based on possibly reducing the degree of relative increase in colposcopy in HPV screening versus cytology, HPV testing followed by cytology triage appears promising given its superior specificity for CIN2+ or CIN3+ lesions, compared to cytology screening alone, in women of all ages. For women aged 35 years and older only, simulations suggest relative PPV for HPV with cytology triage was the same or significantly greater than with cytology alone, while HPV screening showed significantly reduced relative PPV.[121,133,160] These simulated data are interesting but preliminary, since they reflect only baseline screening results and not a full screening round (with ongoing rescreening and colposcopy referral) or cumulative screening rounds. Also, data from the HPV-cytology triage trial come from cytology referral protocols that are similar but not identical to U.S. practice—that is, immediate colposcopy referral threshold for LSIL+ cytology with HPV+ (ASC-US or normal cytology) managed through repeat testing. Thus, more complete results from this trial could be relatively applicable to the United States.

Third, and in contrast to the other HPV-enhanced strategies, it is not clear if any co-testing strategy reviewed here offers a clear potential for additional benefit, particularly compared with primary HPV screening (alone or followed by cytology triage). Test performance data suggest no additional benefit above primary HPV screening alone for co-testing using cytology thresholds similar to U.S. practice, although increased cost would be expected for the additional test. European trials compared co-testing strategies to cytology alone (never to HPV screening), although indirect comparisons in the NTCC Phase I and II trials in women older than age 35 years suggest HPV-cytology co-testing did not detect more CIN that HPV testing alone, but did require twice the number of colposcopies at baseline. Finally, none of these trials employed strategies to directly evaluate the other main potential benefit from co-testing, which would be a prolongation in screening interval for cytology negative, HPV negative women (as recommended in U.S. practice). Unless co-testing is completely superior to HPV testing in appropriately determining those at lowest risk for prolongation in screening interval, it is difficult to see how administering both tests will ultimately be more valuable than other HPV-enhanced screening strategies. The issue of NPV is discussed more thoroughly below (“Potential Subgroup Considerations With HPV-Enhanced Cervical Cancer Screening”).

Fourth, there is no current consensus on how to interpret these comparative effectiveness trials of cervical cancer screening. Their interpretation is impacted by the many years and large sample sizes necessary to determine true disease outcomes (cancer). Thus, available data primarily represent surrogate outcomes (precancer or combined precancer and cancer). The European trials have offered considerable expertise and perspective on the acceptability and

hierarchy of program outcomes—including surrogates—which is informative (Table 17). These experts suggest that reduced CIN3+ in Round 2 or beyond may be an acceptable surrogate measure for screening program benefit,[161] while also clearly acknowledging the preference for demonstrating an impact on invasive cancer incidence or mortality.[162] However, these perspectives may be most applicable in countries with uniform national screening policies. The degree of confidence that U.S. clinicians and policymakers are willing to place in surrogate outcomes is key.

Similarly, interpretation of round-specific and cumulative trial results is complex. As suggested by experts, Round 1 of screening detects prevalent disease and predisease, and increased detection of predisease in one strategy relative to another may represent early diagnosis and/or overdiagnosis of regressive predisease.[117] In Round 2 of screening, incident, missed, or progressive disease and predisease are detected.[117] Over at least two rounds, therefore, there is some way to compare the patterns of disease and predisease detection and infer overall program performance, as well as to compare round-specific patterns between trials to explain different results. Longer followup of Round 2 results (or additional screening rounds) may be necessary, particularly to allow for more complete ascertainment in both arms and to detect an impact on cancer. Some experts evaluate the pattern of screening results by round, suggesting that increased relative CIN2+ detection in Round 1 followed by decreased relative CIN3+ in Round 2 suggests prevention of disease progression.[163] Others suggest that similar cumulative CIN2+ disease detection between arms after at least two screening rounds would indicate lack of overdiagnosis[144] if the same screening test (ideally including HPV) was applied in both study arms at Round 2 and after.[163] Only one trial applied HPV testing using PCR to both arms in the second screening round.[114] Many other differences between trials (besides whether the second round applied HPV testing or not)—including type of HPV screening strategy, colposcopy referral and repeat screening protocols, and approaches to compiling and reporting outcomes—complicate applying these types of theoretical interpretations to the current body of evidence. Some commentators point out that the co-testing trials (with the exception of NTCC Phase I) actually test primary HPV screening with cytology triage, since all the trials use a cytological referral threshold only for immediate colposcopy.[163] However, these trials actually have a safety-net in place for women with HPV-cytology-positive lesions, since all women receive both tests with referral for high-grade cytology alone.

Fifth, there are a number of important potential biases that will need to be carefully considered when interpreting more complete reporting from trials. Large comparative effectiveness trials of cervical cancer screening embedded in national screening programs use a pragmatic design that offer many advantages.[164] However, there are several important biases to consider in their ultimate interpretation. As is well recognized, there is a potential for verification bias in any screening study that does not apply the gold standard to all who are screened, regardless of outcome.[102] In these real-world trials, only those screening positive possibly receive the diagnostic colposcopic evaluation. Therefore, as with observational studies, their main value in terms of estimating test performance is limited to relative test performance results. Similar, any outcome interpretation is affected by the proportion receiving the diagnostic test. Possible ascertainment bias could occur if there are between-arm differences in the proportion complying with the recommended diagnostic test. Sufficient time for followup is also critical, given that diagnostic tests can be recommended immediately after screening or after a year or so of retesting and confirmation of initially abnormal screening results. Finally, the comparison of two tests (HPV vs. cytology) or the use of adjunctive tests (HPV plus cytology vs. cytology) in a

randomized design can still be complicated by asymmetry bias in ascertainment if results do not represent sufficient long-term followup.[14] Between-arm differences in predisease detection can occur even if the new test performs at random, when more women are selected for colposcopy due to the detection of incipient lesions that would not otherwise have been found. Thus, sufficient long-term followup and use of outside registry data to get a better estimate of the rates of true disease and predisease is important.

Potential Subgroup Considerations With HPV-Enhanced Cervical Cancer Screening

Beyond the impact on disease detection, there may be other subgroup considerations for an HPV-enhanced screening strategy. HPV screening introduces potential individual patient-level as well as population-level benefits, such as using negative test results to stratify women into low-risk groups in which screening intervals may be safely lengthened. International experts have noted that the NPV of adding an HPV test to cytology (or substituting HPV for cytology) may be a major utility of HPV-enhanced primary screening.[165] Thus, this is an important endpoint for ongoing European trials, which has been partially reported to date.[166] On the other hand, issues of how to best manage women with mixed results—particularly those who are HPV positive but cytology negative—are equally critical. For all women with inconclusive testing results, safety of any tailored screening strategies along with data on psychological effects, including compliance with rescreening, will be critical.

HPV negative/cytology negative subgroup considerations (Table 19). Meta-analyses of cross-sectional results have confirmed the high NPV of negative results for combined HPV/cytology testing.[165,166] Some European trials have reported longitudinal results for this subgroup. The POBASCAM trial estimated that after a combined negative high-risk HPV test result and negative cytology, the 5-year cumulative risk of CIN3+ lesions per woman screened was 0.1 percent (95% CI, 0.1% to 0.2%), which was lower than the risk for women who did not receive an HPV test at baseline but had negative cytology (0.8% [95% CI, 0.6 to 1.0]).[114] Almost half of CIN3+ cases (3/8) detected in the subsequent screening round 5 years later in those initially HPV negative/cytology negative were in women who tested HPV+ in the second round.[114] Post hoc analyses demonstrated little prognostic benefit for co-testing above HPV testing alone, since the 5-year cumulative risk of CIN3+ after a negative high-risk HPV test was 0.2 percent (95% CI, 0.1 to 0.3). Two other trials (ARTISTIC, Swedescreen) have reported interim data that are consistent with a very low risk of CIN3+ in those negative for HPV and cytology at rescreening after 2 to 3 years.[115,117] However, a lower proportion of HPV negative/cytology negative women completed Round 2 screening in ARTISTIC (60%) than women with at least one positive test did. This affects assessment of true CIN3+ risk, but also raises questions about whether women who test double-negative might not comply with future screenings. Reporting from a third screening round in ARTISTIC confirms a longer-term (6-year) reduced risk of CIN3+ (0.28%) in those women who were HPV negative that is indistinguishable from those who were HPV negative/cytology negative.[135] Since these data are reported only in those women undergoing three rounds of testing, however, they represent only 36.2 percent of the original cohort, and could represent selective ascertainment due to incompletely reported data.

These short-term, trial-specific data are supplemented by large, longitudinal cohort studies and pooled data. A multinational European joint cohort study with pooled data on 24,295

women examined cumulative incidence of CIN3+ among women with adequate cytology and HPV testing at baseline and at least one followup cytological or histological test.[167] During 6 years of followup, 1.6 percent of women developed histologically-confirmed CIN3+. The cumulative CIN3+ incidence rate among women that tested negative for HPV (generally HC2) and on cytology (less than ASC-US) was 0.28 percent (95% CI, 0.12 to 0.45). There was little difference in CIN3+ development between women with negative results on both tests and women negative for HPV only. The rate of CIN3+ development over 6 years in women who were HPV negative was significantly lower than among women who had negative cytology results (0.97% developed CIN3+ over 6 years). Results for CIN2+ were essentially the same, but with a higher number of cases. These data are limited by verification bias (only test positives according to initial and rescreening protocols were uniformly assessed for disease outcomes), with between-study differences in protocol, as seen in trials in this review. Nonetheless, CIN3+ detection rates were generally consistent and low across studies in HPV negative/cytology negative women, despite their likely participation in ongoing cervical cancer screening.

In a prospective study of 20,810 women (mean age, 35.9 years) in Kaiser Permanente Northwest, the risk of CIN3+ was 0.16 percent (95% CI, 0.08 to 0.24) after almost 4 years of followup in 17,592 women with negative cytology and high-risk HPV tests.[168] In women who were HPV negative, the 10-year cumulative incidence of CIN3+ was 0.87 (95% CI, 0.62 to 1.12) and lower than the cumulative incidence in women with ASC-US+ baseline cytology (1.38 [95% CI, 1.10 to 1.67]).

Among Danish women who tested negative for high-risk HPV, only 8 percent of those aged 22 to 32 years and 7 percent of those aged 40 to 50 years developed an abnormal Pap smear over 10 years, with each woman receiving a median of three tests. For both age groups, most abnormal smears were atypia only, with about one-third reflecting severe dysplasia.[169] The absolute risk of CIN3+ in HPV negative/cytology negative women at 3 years was 0.2 percent in younger women and 0.08 percent in older women, at 5 years it was 0.8 percent in younger women and 0.4 percent in older women, and by 10 years it was 3.1 percent in younger women and 1.7 percent in older women. Compared with women with two negative tests, age cohorts that were cytology negative but HPV positive had markedly increased relative risk for CIN3+ at 3 years (younger women: RR, 11.0; older women: RR, 53.8), 5 years (younger women: RR, 6.9; older women: RR, 23.3), and 10 years (younger women: RR, 4.4; older women: RR, 12.5).

Among 8,735 women aged 30 to 60 years participating in the United Kingdom HPV in Addition to Routine Test (HART) trial, a randomized evaluation of management strategies for women who tested positive after co-testing, the high NPV of a negative HPV test was confirmed.[159] After a minimum of 5 years, cumulative CIN2+ was about half as common in women who were HPV negative at baseline compared with those who were cytology negative (0.23% and 0.48%, respectively). Since most differences between the two tests occurred in the first year, differences may reflect poorer sensitivity of cytology. The hazards ratio for cumulative CIN2+ increased dramatically with the HPV relative light unit (RLU) levels. Compared with a typical negative result (<1 pg/ml), the hazards ratio for an HPV RLU of 1-10 pg/ml was 5.4 (95% CI, 1.7 to 18.2) and 25.2 (95% CI, 13.6 to 47.9) for an HPV RLU $\geq$10 pg/ml ($p<0.00l$ for trend). Data were not reported for CIN3+.

These trial and cohort data clearly indicate that one potential value of a screening program with initial HPV testing could be reduced screening intervals for the majority of women who test negative. Among participants in co-testing trials, this group represents a very significant proportion of those screened at baseline: from 78 percent in both arms (combined) in ARTISTIC,

to 88 to 93 percent in the co-testing arms of Swedescreen, NTCC, and POBASCAM. Thus, if a reduced interval for repeat screening is shown to be safe and effective—as well as workable within the clinical, social, and political realities of cervical cancer screening in the United States—it would be appropriate for the vast majority of women aged 35 years and older after a single round of screening that included HPV testing.[24]

HPV negative subgroup considerations. Based on the data discussed above, women screening negative on HPV testing have a nearly identical reduced long-term risk of developing CIN3+ as women that are HPV negative/cytology negative. The high NPV associated with HPV negative testing alone, particularly in older women, might inform extended screening intervals for such women, with no need for cytology testing at all in HPV negative women.

HPV positive/cytology negative subgroup considerations. A concern among programs that involve combined HPV-cytology screening initially or in sequence is how best to manage HPV positive/cytology negative individuals. Data from large cohort studies show that women with HPV positive/cytology negative results experience a continuously increasing cumulative incidence rate that reaches 10 percent (95% CI, 6.2 to 15.1) after 6 years.[167] As indicated in Table 5b, trials varied in their approach to management of these individuals in terms of timing of repeat screening, rescreening tests utilized, and colposcopy referral thresholds. A detailed analysis and comparison of these differences and associated outcomes in this important subgroup would be important, but our review (consistent with others' findings)[170] suggests that additional details beyond those currently published would be needed to fairly compare different protocols. Any modeling of co-testing would need to carefully consider between-study details about rescreening protocols, compliance, and the impact on results. Furthermore, research continues to identify the role of specific HPV subtypes (particularly 16, but also 18, 31, and 33) and persistent infection by these types in further specifying high risk for CIN3+.[171] More specific management of this subgroup could be informed by better risk prediction. Similarly, genotyping may also play an important role in the future for risk-stratification into tailored screening strategies.[172]

Cytology Screening With HPV Triage (Reflex HPV) for ASC-US or LSIL Cytology

Overall, results from observational studies suggest that HC2 is somewhat more sensitive than repeat cytology at a colposcopy referral threshold of ASC-US+ for the detection of CIN2+ (but not clearly CIN3+) lesions among women with ASC-US referral cytology, with no further advantage when CC is added to HPV triage, but a possible increase in false positives. Age-stratified results were generally not available, but many studies (besides ALTS) represent women primarily older than age 30 years. Our findings from a much more limited meta-analysis agree with previous meta-analysis results reported by Arbyn and colleagues.[173,174] HPV testing was more sensitive and equally specific for detection of CIN2+ for the triage of ASC-US+ results, compared to repeat cytology, with no benefit for HPV triage of LSIL+ cytology.

Trial results suggest reduced specificity (more false positives and colposcopies) for CIN2+ or CIN3+ with HPV compared with CC triage—particularly, but not exclusively, in women younger than age 30 years. The higher prevalence of transient HPV infections in younger women may play a role here. In contrast, the use of an HPV triage test clearly provided no substantial advantage for referring women with LSIL to colposcopy. This may reflect a high prevalence of HPV among women with LSIL cytology results (58.9 to 94.8%). Other studies have suggested potential value for HPV triage of LSIL in women older than ages 45-50 years, if

they represent a group in whom the co-occurrence of HPV is lower and if the HPV negative group has a low-risk of CIN3+ over the time period until the next screening.[175] In women aged 30 years and older, one small study suggests an HPV triage strategy for ASC-US or LSIL would produce three false positives for every two with repeated cytology, and four false positives with HPV triage for every two with cytology in younger women (Appendix C Table 3).[119] These estimates are imprecise due to the small number of women in the study and because the authors include both ASC-US and LSIL triage in their calculation, which inflated the number of referrals in the HPV arm. Trials reviewed here reported simulations of various triage and repeat testing strategies following primary HPV screening or primary cytological screening.[117,119,121] None of these had (or reported) cumulative screening round data to simulate different triage strategies within a program of screening.

The studies we included to evaluate HPV triage of abnormal cytology included women from a broad age range (range, 15 to 78 years; mean or median range, 27 to 35 years), but provided minimal age-stratified data. While these studies found that overall HPV testing was not useful for the triage of LSIL cytology due to the high prevalence of HPV among women with LSIL cytology, one might postulate that the low HPV prevalence among older women could potentially render HC2 useful for triage of LSIL cytology in the older age groups. However, the study by Peto and colleagues, included for KQ1, demonstrated that there was no trend of decreasing high-risk HPV prevalence with age among women with abnormal cytology.[32] In an article from the ALTS trial, the authors concluded that HPV triage of LSIL cytology was not useful at any age range, since the proportion of HPV positivity among women with LSIL did not decline dramatically with age.[176]

Harms of HPV Testing

In addition to concerns about false-positive testing and related harms, we identified four studies that described potential psychological harm from HPV testing.[139-142] In the short term (first few weeks after receiving test results), women who test positive for HPV had higher levels of anxiety and distress and greater concerns about their health and health risks. In the long term, however, these results did not persist. In fact, when considering triage of ASC-US cytology with an HPV test versus repeat cytology, long-term followup suggests greater satisfaction with care and less distress among women undergoing HPV testing. This may be because women who undergo repeat cytology have to wait for additional results before it is determined whether or not they need colposcopy, whereas women undergoing HPV testing are triaged much more quickly.

The evidence about harms of HPV testing is limited. Only two of the four included studies present long-term followup, there was a small number of women included in the followup, only one study administered questionnaires prior to cytology and HPV testing, and all studies had large proportions of women who did not return the study questionnaires. Larger studies with longer-term followup, assessment of psychological measures pre- and post-test, and adjustment for baseline psychological measures and appropriate confounders are needed to determine the psychological impact of HPV testing.

Are All HPV Tests the Same?

HPV testing has been approved by the FDA for cervical cancer screening in women older than age 30 years as co-testing and for triage of ASC-US cytology. Whether HPV testing was a

more sensitive indicator than cytology for recurrent or residual CIN following treatment was not included in this review.[166]

The vast majority of data reviewed in this report, from both trials and observational studies, reflects a clinically validated commercial assay, HC2, with a much smaller body of evidence evaluating PCR testing using GP5+/6+ probes. Newer FDA-approved tests were not part of our original scope, although we did not exclude any trials for that reason. As evidence on HPV testing is translated into practice—particularly into screening programs—users should consider whether tests other than HC2 will produce similar results as shown in research. In widespread screening, even small differences in test performance may have large detrimental impact.[177] HPV is a very complex molecular diagnostic assay whose analytic and clinical validity are affected by issues such as the number of HPV genotypes tested,[177] number of viral copies required, and other factors.[178] Users should be aware of potential differences in expected test performance between validated well-studied tests and other, less-well-studied tests. Those choosing to use a less-well-studied test should ensure the minimal performance standards of these tests, as discussed below.

Some data suggest that PCR may not be equivalent to HC2 in absolute test performance[122] or have shown heterogeneous sensitivity and specificity estimates when pooled, perhaps due to use of different primers in detection of amplified sequences.[144] Although differences may be amenable to better quality control, care should be taken to ensure expected test performance before substituting another HPV assay for proven tests in large-scale screening programs. Furthermore, as outlined in a recent article, FDA approval of newer HPV technologies may not always include a complete consideration of its comparative performance relative to HC2, or its overall clinical performance (both sensitivity and specificity) in a program of screening.[179] Kinney provides a cogent argument, with examples taken from package insert data for one recently approved HPV test, illustrating that HPV tests with good analytic sensitivity should not be assumed to have clinically equivalent test performance as HC2, and that differences in clinical performance, particularly related to specificity, could have a large impact on cervical cancer screening programs in terms of costs and potential harms.[179]

An international group of experts has proposed minimum relative sensitivity (0.90) and specificity (0.98) thresholds to be determined in direct test performance comparisons with HC2 before clinical use of newer high-risk HPV tests in cervical cancer screening. Newer tests should also be highly reproducible (agreement >87%, minimum 500 samples).[162,180] U.S. experts have made similar recommendations.[163] Criteria have also been articulated to guide policymakers about when good clinical test performance data can allow substitution of a diagnostic test into proven clinical use without new RCTs.[157,162] These same standards should apply to the substitution of different screening tests than those proven in RCTs or convincing epidemiological evidence.

Age at Which to Stop Cervical Cancer Screening

We did not systematically evaluate the literature regarding the age at which cervical cancer screening should be discontinued. This topic was systematically reviewed in the previous USPSTF evidence review.[99] Based on fair-quality evidence obtained from 12 cohort studies, the review reported the following conclusions.

1. The incidence and prevalence of high-grade cervical lesions and cancer decreased with age. The peak incidence or prevalence varied with type of lesion (e.g., CIN1 and

CIN2 versus CIN3), but in general, women older than age 65 years had the lowest burden of disease.

2. The age-related decrease in cervical disease was similar in previously unscreened women.
3. There was no difference in the aggressiveness of invasive cancer in older women compared with younger women.
4. Repeat screening after negative smears was associated with a reduced risk of high-grade cytologic abnormalities.

Evidence identified during the course of our review confirms the previous review's findings of reduced rates of abnormal cytology and detection rates for CIN3+ as women age and with subsequent screenings.[32,104,181] Data from two rounds of cervical cancer screening (750,591 cytology tests from the first round and 373,851 from the second) from the CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) demonstrate that the percentage of abnormal cytology results decreases with age and with subsequent screenings.[181] The percentage of cytology results that were classified as abnormal on first screening decreased fairly linearly with increasing age, from 33 percent of cytology tests in women aged 18 to 29 years to 14 percent in those aged 65 years and older. The percentage with HSIL or SCC also decreased with age from a high of 2.4 percent in 18- to 29-year-olds, but plateaued and was similar among those aged 40 years and older (0.4 to 0.6%). Age-specific detection rates for CIN3+ decreased linearly with age from 14.6 per 1,000 cytology tests in women aged 18 to 29 years to 2.0 per 1,000 in those aged 65 years or older. CIN3+ rates were fairly similar among all women aged 50 years and older. For all ages, rates of abnormal cytology or histology were reduced on second screening, but the age gradient was maintained, with relatively higher rates of cervical abnormalities in younger women than older women. Women aged 40 years and older, particularly those aged 65 years or older, experienced a smaller proportional reduction from first to second screening in rates of abnormal cytology and biopsy-confirmed CIN than younger women.

In a study from a UK cohort screened between 1988 and 1993 and less than 5 years after a normal screening smear, the annual incidence of CIN3+ decreased as women aged, from a high of 4.07 per 1,000 per year for ages 25 to 29 years to 0.19 per 1,000 per year for ages 60 to 64 years.[32] Incidence of CIN3+ in those women aged 65 to 69 years was somewhat higher (1.39 per 1,000 per year), but was comparable to the incidence in young women aged 15 to 19 years (1.56 per 1,000 per year). Similarly, in the Kaiser Permanente Northwest population, the highest incidence of CIN3 (6 per 1,000 routine smears) was in women aged 25 to 29 years, with 0 to 1 CIN3 cases per 1,000 routine smears in women aged 60 to 79 years, which was lower than the 15- to 19-year-olds (2 per 1,000).[104] In this study, there was a sharp decline in the yield of CIN2 and CIN3 with screening in women older than age 30 years, with only 2 cases of high-grade CIN identified in 5,488 routine smears in women aged 60 years and older.[104] Incidence of cervical cancer after three consecutive negative screening tests was found to be the same after 10 years followup in 445,000 women aged 30 to 44 years compared to 219,000 women aged 45 to 54 years, suggesting that the risk among well-screened women is the same among middle-aged women (30 to 65 years).[182]

At present, there remains no consensus regarding the age at which to discontinue cervical cancer screening,[183,184] and countries with screening policies recommend stopping after an adequate screening history at different ages: ages 59 to 60 years (Sweden, Finland, Japan), ages 64 to 65 years (England, Spain), and age 69 years (Australia, Canada, Norway).[183] The United

States may be the only country consistently screening some women older than age 65 years (an estimated 43 to 66% during one 3-year period), and one epidemiologist has recently noted that ecologic data from all of these countries suggest that the United States is also the only one of these countries that has achieved a relative downward trend in the incidence of cervical cancer in women older than age 65 years.[183]

However, improving the burden of cervical cancer on older women is likely best achieved by focusing on screening those who have not been adequately screened. In a recent review on screening intervals and age limits, Sasieni and Castanon note that a Markov model for disease progression produced by Fahs and colleagues determined that screening women older than age 65 years with previously adequate screening history would be inefficient;[185] in contrast, screening women who have not been adequately screened triennially would reduce mortality by 74 percent.[183] Sasieni and Castanon state that the inefficiency is primarily because more smears are required, less CIN is detected as women age, and there are other competing causes of death. In addition, disease progression from CIN to cancer is believed to be relatively slow, and only a proportion of CIN cases will progress to cancer (20 to 30% within 5 to 10 years).[183] These authors point out that most guidelines around the world suggest that screening should cease by age 65 years, provided women have an adequate screening history.[183]

Defining an ―adequate screening history" is not entirely clear-cut, except among those who have never been screened. Published reviews suggest that about half of all invasive cervical cancer cases are diagnosed in women who have never been screened or have not been screened within 5 years.[18,186,187] Given this, the NBCCEDP program has shifted its focus to target women older than age 40 years who are at greater risk for never or rarely having been screened.[181] Among the 465 cases of ICC detected between 1995 and 2001 in the NBCCEDP program, 31 percent reported no prior screening before entry into the program. Among women aged 18 to 29 years, 25 percent reported no previous screening, compared to 42 percent among those aged 65 years and older. Data from the UK Audit of Screening Histories also suggest that older women with cervical cancer are less likely to have ever been screened than younger women with cervical cancer or age-matched controls.[183] According to the UK data, approximately 70 to 80 percent of women aged 20 to 49 years with cervical cancer had ever been screened, compared to fewer than 50 percent of women aged 60 to 69 years. The proportion ever screened among the young women with cervical cancer did not appear to differ from their age-matched controls, whereas the proportion of women aged 60 to 69 years with cancer who had ever been screened was 20 percent less than age-matched controls. Only about 25 percent of women aged 60 to 69 years with invasive cancer had a negative smear within 5 years, compared with 60 percent of age-matched controls.

The results of previous screening episodes may also be associated with risk. As already discussed, a large observational study in the Netherlands found the same cumulative incidence of ICC after three consecutive negative smears in women aged 45 to 54 years as in women aged 30 to 44 years.[182] Another observational study in Italy found nearly an eight-fold lower cumulative risk of CIN2+ in women aged 50 to 64 years compared to those aged 25 to 49 years after three previous negative screens.[188] The effect of a history of negative screening results on risk in older women is not clear from these studies, although differences between older and younger women may be less for cervical cancer than for precancerous lesions. Researchers are beginning to factor in considerations such as new sexual partners in increasing risk for HPV infection (or re-infection) in older adults.[189]

Women previously treated for CIN have a higher risk of later cervical cancer. A cohort study in Finland found increased risk of cervical cancer in women treated for any CIN, compared to a standard population (standardized incidence ratio, 2.8 [95% CI, 1.7 to 4.2]),[83] although no increase in cervical cancer mortality was found in the same cohort.[190] Another cohort study in Sweden found increased cervical cancer risk after CIN3 treatment (standardized incidence ratio, 2.34 [95% CI, 2.18 to 2.50]), with greater risk for women aged 50 years and older, compared to younger women.[191]

Older women are currently disproportionately represented in the unscreened and underscreened population—with 83.1 percent of those aged 60 to 64 years receiving recommended screening versus 87.6 percent overall, according to 2008 Behavioral Risk Factor Surveillance System data—as are some minority (American Indian/Alaska Native and Asian/Pacific Islander) and non-English speaking women.[184,192] Black women, despite having slightly higher than average rates of compliance with recommended cervical screening,[192] have increased age-specific cervical cancer incidence that does not peak but continues to increase with age[193,194] to about 26 per 100,000 women at ages 85 years and older (Table 2 and Figure 1). Both black and Hispanic women have higher age-adjusted incidence rates for cervical cancer than nonHispanic whites,[17,193,194] and these minority groups, along with American Indian/Alaskan Natives, also have higher age-adjusted cervical cancer death rates.[17] Therefore, these groups remain important populations in which to ensure adequate screening, both for older and younger women. Age-adjusted incidence rates for Asian and Pacific Islander women were somewhat higher than for nonHispanic white women from 2000 to 2008, but mortality was similar between the two groups.[17]

In summary, newly available data do not contradict current USPSTF recommendations to discontinue routine cervical cancer screening for women older than age 65 years who have had adequate screening with negative results and who are not otherwise at high risk for cervical cancer. Older women with a history of treatment for CIN represent one high-risk group who could continue screening. In the future, factors such as the use of HPV testing, HPV genotyping, and sexual history might help further define a cohort of older HPV negative women for whom screening could be safely discontinued.[32,195,196]

Limitations

This review has several limitations. While our literature search was extensive and the included studies covered an international population of women, we only included studies that were written in the English language. We further focused our results and discussion to primarily consider studies most relevant to the United States, which excluded countries without well-developed population screening for cervical cancer in place. Most included studies addressed women aged 30 to 60 years, with almost no data in women older than age 65 years and limited data in younger women. Age-specific data were not always reported or did not always use the same thresholds when reported. Thus, women aged 30 to 34 years were variously grouped with older or younger women, depending on study reporting. We did not systematically review data related to screening intervals, age at which to stop screening, or automated cytologic screening technologies, of which the latter two were covered in the previous review by Hartmann and colleagues.[99] Automated cytologic screening technologies were excluded from this review due to the limited audience for these data among primary care providers. Furthermore, HC2 was the

only HPV test available in the United States when the scope of this review was determined, and thus we limited our review to use of HC2 and PCR only.

Two large studies, one evaluated for inclusion in KQ2 (Guanacaste study) and one for KQ3 (HART), did not meet eligibility criteria for this review. Appendix D delineates the rationale for their exclusion. Briefly, the final histologic diagnosis in the Guanacaste study included results of the screening tests. Additionally, the reference standard of colposcopy and biopsy was not systematically applied. The main limitation of the HART study is that it is a randomized trial of management options after co-testing or HPV with cytology triage rather than a test of an HPV-enhanced screening strategy compared with cytology. HART also has risk of verification bias, given that there was differential loss to followup for colposcopy referral among the study arms. Other issues in using results to estimate absolute test performance include uncertainty about the timeframe within which colposcopy and biopsy were provided and lack of blinding of colposcopists to cytology results (with perhaps the ability to guess HPV results). Longer-term followup with linkage to registries can overcome some of these limitations, particularly for examining NPV.

Our review made a dedicated effort to consistently analyze and report the most policy-relevant data from recent trials of screening programs involving HPV for the USPSTF's recommendation process. However, there are many publications associated with each of these trials, with updated results coming out over time. Some of the data that we indicate as not reported might have been missed in an ancillary publication or could become available through author requests or soon-to-be-available publications. Thus, findings from this report will need frequent updating with more complete data from trials. We found little data on age at which to begin screening or risk factors that may modify when screening should begin, such as age at first intercourse. While the available studies did not present data with sufficient granularity to make a specific age recommendation at which to commence screening, they do suggest that screening women younger than age 20 years is of little value, given the low incidence of cervical cancer in this age group and the potential harms of unnecessary evaluation and treatment.

Providing data related to the cost-effectiveness of HPV in any screening strategy was beyond the scope of our review. ARTISTIC investigators have conducted an extensive economic evaluation associated with that trial.[197] Results suggest it would not be cost-effective to screen with cytology plus HPV (co-testing) compared with cytology alone. In this analysis, however, simulated primary HPV screening with cytology triage (or HPV triage of cytology) was cheaper than cytology screening without any HPV. A head-to-head trial comparing these two strategies is currently under way in Canada, with results expected in 2014 (Appendix F).[198] Studies of HPV triage of ASC-US and LSIL cytology were limited by the lack of age-stratified results, and only two studies provided data for the outcome of CIN3+. The results of the ALTS trial were limited by a study design that does not mirror current clinical practice. In the ALTS trial, women were referred for colposcopy if their cytologic diagnosis was HSIL, which is a higher threshold for referral than what is commonly used in clinical practice.[68] In addition, the immediate colposcopy arm would represent the results of colposcopy after one abnormal cytology result. In the clinical setting, among women with no prior history of CIN, colposcopy is usually performed after two ASC-US cytology results have occurred.

Another potential limitation of this review is that most trials and studies used colposcopy and/or biopsy as the reference standard. In some included studies, the biopsy was taken at standard cervical positions, but in many studies only abnormalities visible on colposcopy were biopsied, with a negative colposcopy interpreted as absence of disease. Colposcopically-directed

biopsy is not 100 percent sensitive for the detection of preinvasive disease. The Shanxi Province Cervical Cancer Screening Study, for example, found that colposcopically-directed biopsy was more accurate in detecting large lesions compared to small ones, and identified 62.5 percent of lesions covering zero to two quadrants of the cervix and 100 percent of lesions involving three to four quadrants.[199] In addition, only 62 of 83 women with CIN2 were detected by colposcopically-directed biopsy: 19 were detected by random biopsy and 2 solely by endocervical curettage. Analysis of data from the placebo arms of Merck's GARDASIL trials also showed low correlation between results of colposcopically-directed biopsy and excisional specimens. The trial included women who were referred based on concerning cytology, biopsy and/or endocervical curettage results for LEEP, or other definitive therapy, and who had a cervical biopsy taken within 6 months before treatment (about 7% of all those in the placebo arms). The biopsy and definitive diagnosis (negative, CIN1, CIN2, or CIN3/AIS) coincided for just 42 percent of these participants; biopsy underestimated disease for 21 percent and overestimated (or removed) disease for 36 percent.[200]

Finally, the use of detected disease without full ascertainment of undetected disease does not accurately reflect sensitivity or true test performance. However, in the context of trials, it reflects real-world impact. Almost all trials reported results without using an intention-to-screen analysis, in which all women in the randomized arm are in the denominator for all calculations. Thus, for comparability, we used the number of women screened (or other comparable measures) for the denominator in our calculations. For trials nested within ongoing screening programs, either denominator has a rationale, although intention-to-screen would be most conservative. It is reassuring, however, that long-term disease detection was not substantially different using intention-to-screen analysis than when calculated using only women screened in one study reporting both.[134]

Emerging Issues/Next Steps

An international effort to pool data from HPV-based primary screening trials has been recently announced, recognizing the need to provide complete, uniformly reported, age-stratified data to inform evidence-based guideline development.[201] These efforts are critical and could provide the best simulations of various possible HPV-based screening strategies, considering between-trial differences in screening and rescreening protocols. When available, their results will greatly enhance what we found through our systematic review.

Studies under way could impact the findings of this review and perhaps necessitate an update. These include a Canadian RCT comparing HPV with cytology triage to cytology followed by HPV triage among women aged 25 to 65 years.[198] Results after two rounds of screening after implementation of the FDA-approved co-testing strategy in Kaiser Permanente Northern California in over 300,000 women are also expected.[202] Initial HMO experience suggests that co-testing every 3 years is acceptable to both patients and providers,[24] and that the average interval between negative tests is appropriately lengthened.[203] Data from a nationally representative sample, however, suggests that U.S. primary care providers are not likely to extend the screening interval to 3 years, as suggested.[203]

This review excluded several emerging HPV testing methods, including tests that detect HPV-16 and HPV-18 only, p16 immunostaining, in situ hybridization, tests of mRNA or protein expression, and tests of viral load, which we felt to be of less clinical significance to the primary care setting when our review started. Since that time, more data are emerging to suggest that

these may be important strategies to evaluate in the future. Recently, additional new technologies beyond the scope of our review have been approved by the FDA. These include the Cervista HPV HR and Cervista HPV 16/18 tests and Roche Diagnostics' Cobas 4800 HPV test. Cervista HPV HR tests for 14 high-risk HPV types and Cervista HPV 16/18 individually identify two high-risk HPV types. The Cobas 4800 HPV Test simultaneously detects 14 high-risk HPV types (the same as those detected by Cervista HR HPV) and specifically identifies types 16 and 18.[74] We found no studies on the Roche technologies that met our inclusion criteria. However, this test is in use abroad and approved in early 2011 for as yet undocumented indications. Triage strategies that allow immediate colposcopy referral for the highest-risk women, such as HPV genotyping and/or p16 immunostaining in HPV positive women, could improve overall compliance with colposcopy and potentially improve HPV-based screening program performance.[170] Emerging technologies such as Roche Diagnostics' Amplicor HPV test and Linear Array HPV genotyping test and Gen-Probe's APTIMA HPV test will require future consideration, if submitted to and approved by the FDA. Gen-Probe's APTIMA HPV, which detects 14 high-risk HPV types and also mRNA from viral oncogenes E6 and E7, is approved for use in Europe and has been submitted for FDA approval.

Future Research

Future research and future reviews will need to address the long-term impact of the HPV vaccine on the incidence of CIN and cervical cancer and on cervical cancer screening strategies. Reports from trials of GARDASIL and CERVARIX include about 3 years of followup, but longer-term efficacy is unknown.[92,204] Brisson and colleagues used a cohort model of the natural history of HPV infection to estimate the number needed to vaccinate to prevent HPV-related disease and death, and found that results were highly dependent on the vaccine's duration of protection.[205] As discussed earlier, none of the HPV screening studies included in this review included HPV-vaccinated women; therefore, the impact of HPV vaccines on the effectiveness of cervical cancer screening programs is also currently unknown. Similarly, whether screening strategies should be modified in the face of known (or uncertain) vaccination histories will need study.

Additional research on the appropriate age at which to start screening (with year-specific data reported for younger women rather than 5-year age groups) and exploration of risk-stratification tools for targeted, earlier screening would extend the limited findings from this report. Similarly, given the relatively high proportion of women aged 65 years and older who are unscreened or underscreened and the apparent downward trend in cervical cancer screening (as recommended) among this age group, continuing research to determine screening history and other characteristics of women who develop ICC before and after age 65 years will be informative.

Ongoing population screening program research in Canada is under way to directly compare the efficacy of primary HPV screening (with cytology triage using LBC) to primary LBC with HPV triage, using tests and protocols similar to those in current use in North America.[198] Results could help inform screening policy in the United States and Canada, including safety of an HPV primary screening approach and prolonged intervals for HPV negative women. Other research confirming the long-term low risk of high-grade cervical lesions in screening-negative women, along with research and modeling studies which incorporate sociodemographic and medical factors, may help further risk stratify women for more or less

aggressive cervical cancer screening regimens. Ongoing research evaluating type-specific high-risk HPV testing, mRNA, or p16INK4A and other molecular markers has the potential to further clarify future risk in women and to improve the specificity of targeted screening approaches.[144] Additionally, other future research should continue to address means to encourage screening in women who often ignore invitations to screening visits; one promising approach could be self-sampling for HPV testing, among other innovations.[206]

Conclusions

In summary, our systematic review supports the following conclusions:

1. Due to the high prevalence of HPV, the regressive nature of prevalent cervical abnormalities, and the low prevalence of cervical cancer in women younger than age 21 years, cervical cancer screening in women younger than age 21 years does not appear to offer substantial benefit. No studies provided specific information on which risk factors beyond age should influence the decision of when to start screening, and we found no sufficient data on screening interval specific to younger women.
2. In terms of cervical cytology approaches, LBC did not differ from CC in absolute test performance (sensitivity, specificity) or improve relative CIN detection. Most data suggest that LBC yields a lower proportion of unsatisfactory slides compared to CC and also allows for several different screening strategies with one specimen (i.e., reflex HPV after an ASCU-US cytology result, co-testing with both LBC and HPV, or reflex cytology after a positive HPV result). Cost and feasibility were not part of our review, but may be considerations, along with other local factors.
3. The use of the HC2 HPV test as a primary cervical cancer screening tool appears very promising in women aged 30 years and older, particularly when coupled with cytology triage of HPV positive results. HC2 clearly is more sensitive for the detection of CIN2+ or CIN3+, compared with cytology alone, but somewhat less specific, with some uncertainty about overdiagnosis of regressive lesions. Use of cytology triage may reduce the increase in false positives (and their related harms) seen with HC2 testing alone. The net benefit of a primary HPV-screening strategy (with or without cytology triage) appears promising, but the net impact of such a program remains to be confirmed through more complete reporting of cumulative program results and requirements and modeling exercises.
4. HPV testing in combination with cytology for women aged 30 years and older is also more sensitive than cytology alone for the detection of CIN2+ and CIN3+, but round-specific and cumulative impact on CIN3+ detection is still incompletely reported in RCTs, with mixed results at present. An acceptable measure of comparative benefit for a cervical cancer screening program has not been specified, although some European RCTs suggest decreased CIN3+ in a second screening round. However, available RCTs primarily test protocols that may not be very applicable to current U.S. practice. Also, through indirect comparisons and observational studies, HPV-cytology co-testing appears to be no more sensitive than HPV alone, and is possibly less specific; current RCTs do not completely report round-specific and cumulative colposcopy or related harms. Thus, from available data, there appears to be no additional advantage of HPV testing in combination with cytology compared to HPV testing alone, unless an advantage is conferred by assigning a subgroup of women who are negative on both tests to a program

of less-intensive screening. Modeling would be needed to inform this possibility, also considering the similarly high NPV of HPV negativity alone.

5. A single HC2 HPV test is more sensitive but equally or slightly less specific than repeat cytology for the detection of CIN2+ among women with ASC-US cytology. There is no benefit to combined cytology and HPV triage over HPV triage alone, and this strategy is associated with more false positives. Two trials (that actually tested HC2 plus CC triage) suggest non-significantly increased detection of CIN3+ with HC2 HPV triage; results apply particularly to women aged 30 or 35 years and older, with less data in younger women. HPV testing is not useful for the triage of LSIL or higher grade cytology, and HPV testing in women younger than age 21 years is clearly not advised.
6. The best studied test for any HPV-enhanced screening program is HC2. Data reported here primarily refer to results with HC2 at a positive threshold of 1 pg/ml, and to a lesser extent, PCR GP5+/6+. Some trials simulate screening program results using a 2 pg/ml threshold for HC2 screening. In the absence of adequate RCT data, substitution of other types of HPV testing in cervical cancer screening programs based on these trials should be based on careful consideration of clinical test performance (test positivity, sensitivity, and specificity) when directly compared with HC2, on evidence of test-retest and inter-laboratory test reliability, other quality control issues, and cost.

References

1. Kulasingam SL, Havrilesky L, Ghebre R, Myers ER. Screening for Cervical Cancer: A Decision Analysis for the U.S. Preventive Services Task Force. AHRQ Publication No. 11-05157-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
2. American Cancer Society. Cervical Cancer. Atlanta, GA: American Cancer Society; 2006. Accessed at http://www.cancer.org/cancer/cervicalcancer/index on 19 April 2011.
3. Saraiya M, Ahmed F, Krishnan S, et al. Cervical cancer incidence in a prevaccine era in the United States, 1998-2002. *Obstet Gynecol.* 2007;109:360-370.
4. Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG (eds). *Clinical Oncology*. 3rd ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2004.
5. Richart RM. Cervical intraepithelial neoplasia. *Pathol Annu.* 1973;8:301-328.
6. McCredie M, Sharples K, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet.* 2008;9:425-434.
7. Chang AR. Carcinoma in situ of the cervix and its malignant potential: a lesson from New Zealand. *Cytopathology.* 1990;1:321-328.
8. Kinlen LJ, Spriggs AI. Women with positive cervical smears but without surgical intervention: a follow-up study. *Lancet.* 1978;2:463-465.
9. Smith HO, Tiffany MF, Qualls CR, et al. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. *Gynecol Oncol.* 2000;78:97-105.
10. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002;287:2114-2119.
11. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: revised after the second National Cancer Institute Workshop, April 29-30, 1991. *Acta Cytol.* 1993;37:115-124.
12. National Office of Vital Statistics, U.S. Department of Health, Education, and Welfare. Vital Statistics of the United States, 1950. Volume III: Mortality Data. Washington, DC: U.S. Government Printing Office; 1953. Accessed at http://www.cdc.gov/nchs/data/vsus/VSUS_1950_3.pdf on 19 April 2011.
13. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: final data for 2007. *Natl Vital Stat Report*. 2007;58:1-135.
14. International Agency for Research on Cancer. *IARC Handbooks of Cancer Prevention: Cervix Cancer Screening*. Vol. 10. Lyon, France: IARC Press; 2005.
15. National Cancer Institute, Surveillance Epidemiology and End Results (SEER) Program. SEER Stat Fact Sheets: Cervix Uteri. Bethesda, MD: National Cancer Institute; 2011. Accessed at http://seer.cancer.gov/statfacts/html/cervix.html#incidence-mortality on 21 April 2011.
16. Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2008. Bethesda, MD: National Cancer Institute; 2011. Accessed at http://www.seer.cancer.gov/csr/1975_2008/index.html on 21 April 2011.
17. SEER incidence and U.S. death rates by race/ethnicity: cancer of the cervix uteri. In: SEER Cancer Statistics Review, 1975-2008. Howlader N, Noone AM, Krapcho M, et al (eds). Bethesda, MD: National Cancer Institute; 2011.
18. Janerich DT, Hadjimichael O, Schwartz PE, et al. The screening histories of women with invasive cervical cancer, Connecticut. *Am J Public Health.* 1995;85:791-794.

19. Kinney W, Sung HY, Kearney KA, et al. Missed opportunities for cervical cancer screening of HMO members developing invasive cervical cancer (ICC). *Gynecol Oncol.* 1998;71:428-430.
20. Sung HY, Kearney KA, Miller M, et al. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. *Cancer.* 2000;88:2283-2289.
21. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System: Prevalence and Trends Data. Atlanta, GA: Centers for Disease Control and Prevention; 2010. Accessed at http://apps.nccd.cdc.gov/brfss/ on 19 April 2011.
22. Herbert A, Anshu, Culora G, et al. Invasive cervical cancer audit: why cancers developed in a high-risk population with an organised screening programme. *BJOG.* 2010;117:736-745.
23. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *BMJ.* 2009;339:b2968.
24. Schiffman M, Wentzensen N, Wacholder S, et al. Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst.* 2011;103:368-383.
25. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine.* 2006;24(Suppl 1):S1-S15.
26. Munoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003;348:518-527.
27. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Human Papillomaviruses*. Vol. 90. Lyon, France: World Health Organization; 2007.
28. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—part B: biological agents. *Lancet Oncol.* 2009;10:321-322.
29. Clifford GM, Smith JS, Aguado T, et al. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *Br J Cancer.* 2003;89:101-105.
30. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer.* 2007;121:621-632.
31. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189:12-19.
32. Peto J, Gilham C, Deacon J, et al. Cervical HPV infection and neoplasia in a large population-based prospective study: the Manchester cohort. *Br J Cancer.* 2004;91:942-953.
33. Cotton SC, Sharp L, Seth R, et al. Lifestyle and socio-demographic factors associated with high-risk HPV infection in UK women. *Br J Cancer.* 2007;97:133-139.
34. Datta SD, Koutsky LA, Ratelle S, et al. Human papillomavirus infection and cervical cytology in women screened for cervical cancer in the United States, 2003-2005. *Ann Intern Med.* 2008;148:493-500.
35. Berrington de Gonzáles A, Sweetland S, Green J. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer.* 2007;120:885-891.
36. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563

women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer.* 2006;119:1108-1124.

37. Appleby P, Beral V, Berrington de Gonzáles A, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer.* 2006;118:1481-1495.
38. Castellsagué X, Díaz M, de Sanjosé S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst.* 2006;98:303-315.
39. Plummer M, Herrero R, Franceschi S, et al. Smoking and cervical cancer: pooled analysis of the IARC multi-centric case—control study. *Cancer Causes Control.* 2003;14:805-814.
40. Muñoz N, Franceschi S, Bosetti C, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *Lancet.* 2002;359:1093-1101.
41. Moreno V, Bosch FX, Muñoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet.* 2002;359:1085-1092.
42. Cox JT. The development of cervical cancer and its precursors: what is the role of human papillomavirus infection? *Curr Opin Obstet Gynecol.* 2006;18(Suppl 1):S5-S13.
43. Bosch FX, de Sanjosé S. The epidemiology of human papillomavirus infection and cervical cancer. *Dis Markers.* 2007;23:213-227.
44. Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol.* 2006;2006(Suppl):40470.
45. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. *Lancet.* 2007;370:890-907.
46. Ziegert C, Wentzensen N, Vinokurova S, et al. A comprehensive analysis of HPV integration loci in anogenital lesions combining transcript and genome-based amplification techniques. *Oncogene.* 2003;22:3977-3984.
47. Plummer M, Schiffman M, Castle PE, et al. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis.* 2007;195:1582-1589.
48. Insinga RP, Dasbach EJ, Elbasha EH, et al. Incidence and duration of cervical human papillomavirus 6, 11, 16, and 18 infections in young women: an evaluation from multiple analytic perspectives. *Cancer Epidemiol Biomarkers Prev.* 2007;16:709-715.
49. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst.* 2005;97:1072-1079.
50. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 61: human papillomavirus. *Obstet Gynecol.* 2005;105:905-918.
51. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci (Lond).* 2006;110:525-541.

52. De Vuyst H, Lillo F, Broutet N, et al. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev.* 2008;17:545-554.
53. Schiffman M, Kjaer SK. Chapter 2: natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Monogr.* 2003;14-19.
54. Holowaty P, Miller AB, Rohan T, et al. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst.* 1999;91:252-258.
55. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol.* 1993;12:186-192.
56. Cox JT, Schiffman M, Solomon D. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *Am J Obstet Gynecol.* 2003;188:1406-1412.
57. Dalla PP, Giorgi RP, Collina G, et al. The reproducibility of CIN diagnoses among different pathologists: data from histology reviews from a multicenter randomized study. *Am J Clin Pathol.* 2009;132:125-132.
58. Carreon JD, Sherman ME, Guillen D, et al. CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population-based cervical samples. *Int J Gynecol Pathol.* 2007;26:441-446.
59. Castle PE, Schiffman M, Wheeler CM, et al. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstet Gynecol.* 2009;113:18-25.
60. National Center for Health Statistics. Health, United States, 2009: with special feature on medical technology. Hyattsville, MD: National Center for Health Statistics; 2010. Accessed at http://www.cdc.gov/nchs/data/hus/hus09.pdf on 19 April 2011.
61. Centers for Disease Control and Prevention. Cervical Cancer Screening Rates. Atlanta, GA: Centers for Disease Control and Prevention; 2011. Accessed at http://www.cdc.gov/cancer/cervical/statistics/screening.htm on 19 April 2011.
62. Freeman WP, Wingrove BK. Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities. Rockville, MD: National Cancer Institute, Center to Reduce Cancer Health Disparities; 2005. Accessed at http://crchd.cancer.gov/attachments/excess-cervcanmort.pdf on 19 April 2011.
63. Leyden WA, Manos MM, Geiger AM, et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. *J Natl Cancer Inst.* 2005;97:675-683.
64. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol.* 1995;141:680-689.
65. Arbyn M, Antilla A, Jordan J, et al (eds). *European Guidelines for Quality Assurance in Cervical Cancer Screening*. 2nd ed. Luxembourg: European Commission; 2008.
66. Cytyc Corporation. ThinPrep Pap Test Quick Reference Guide: Endocervical Brush/Spatula Protocol. Boxborough, MA: Cytyc Corporation; 2004. Accessed at http://www.thinprep.com/pdfs/pap_quick_reference.pdf on May 12 2011.

67. TriPath Imaging, Inc. SurePath Technology is Changing Cervical Cancer Screening for the Better. Burlington, NC: TriPath Imaging; 2004. Accessed at http://www.bmpath.com/documents/Surepath%20Visual%20Sheet.pdf on 19 April 2011.
68. Wright TC Jr, Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*. 2007;197:346-355.
69. American Society for Colposcopy and Cervical Pathology. Management Algorithm for Using HPV Genotyping to Manage HPV High-risk Positive/Cytology Negative Women 30 Years and Older. Hagerstown, MD: American Society for Colposcopy and Cervical Pathology; 2009. Accessed at http://www.asccp.org/Portals/9/docs/pdfs/Consensus%20Guidelines/hpv_genotyping_20090320.pdf on 19 April 2011.
70. Approval Letter: Digene Hybrid Capture 2 High-Risk HPV DNA Test–P890064/S007. Rockville, MD: Center for Devices and Radiological Health, U.S. Food and Drug Administration; 2000.
71. Approval Letter: Digene Hybrid Capture 2 High-Risk HPV DNA Test–P890064/S009. Rockville, MD: Center for Devices and Radiological Health, U.S. Food and Drug Administration; 2003. Accessed at http://www.accessdata.fda.gov/cdrh_docs/pdf/p890064s009a.pdf on 19 April 19, 2011.
72. Approval Letter: Cervista HPV High-Risk and Genfind DNA Extraction Kit–P080014. Rockville, MD: Center for Devices and Radiological Health, U.S. Food and Drug Administration; 2009. Accessed at http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080014A.pdf on 19 April 2011.
73. Approval Letter: Cervista HPV 16/18–P080015. Rockville, MD: Center for Devices and Radiological Health, U.S. Food and Drug Administration; 2009. Accessed at http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080015A.pdf on 19 April 2011.
74. Approval Letter: Cobas HPV Test–P100020. Rockville, MD: Center for Devices and Radiological Health, U.S. Food and Drug Administration; 2011. Accessed at http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100020a.pdf on 11 May 2011.
75. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 99: management of abnormal cervical cytology and histology. *Obstet Gynecol.* 2008;112:1419-1444.
76. Wright TC Jr, Cox JT, Massad LS, et al. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA.* 2002;287:2120-2129.
77. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 109: cervical cytology screening. *Obstet Gynecol.* 2009;114:1409-1420.
78. Mitchell MF, Tortolero-Luna G, Cook E, et al. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstet Gynecol.* 1998;92:737-744.
79. Nuovo J, Melnikow J, Willan AR, et al. Treatment outcomes for squamous intraepithelial lesions. *Int J Gynaecol Obstet.* 2000;68:25-33.
80. Martin-Hirsch PP, Paraskevaidis E, Bryant A, et al. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev.* 2010;CD001318.

81. Melnikow J, McGahan C, Sawaya GF, et al. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *J Natl Cancer Inst.* 2009;101:721-728.
82. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer.* 2006;118:2048-2055.
83. Kalliala I, Anttila A, Pukkala E, et al. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ.* 2005;331:1183-1185.
84. TOMBOLA Group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial. *BMJ.* 2009;339:b2546.
85. Sharp L, Cotton S, Cochran C, et al; TOMBOLA Group. After-effects reported by women following colposcopy, cervical biopsies and LLETZ: results from the TOMBOLA trial. *BJOG.* 2009;116:1506-1514.
86. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet.* 2006;367:489-498.
87. Arbyn M, Kyrgiou M, Simoens C, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ.* 2008;337:a1284.
88. Werner CL, Lo JY, Heffernan T, et al. Loop electrosurgical excision procedure and risk of preterm birth. *Obstet Gynecol.* 2010;115:605-608.
89. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007;356:1915-1927.
90. Approval Letter: Cervarix. Rockville, MD: Center for Biologics Evaluation and Research, U.S. Food and Drug Administration; 2009. Accessed at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186959.htm on 19 April 2011.
91. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet.* 2007;369:1861-1868.
92. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet.* 2009;374:301-314.
93. Committee on Adolescent Health Care; ACOG Working Group on Immunization. ACOG Committee Opinion No. 344: human papillomavirus vaccination. *Obstet Gynecol.* 2006;108:699-705.
94. Irwin K, Montano D, Kasprzyk D, et al. Cervical cancer screening, abnormal cytology management, and counseling practices in the United States. *Obstet Gynecol.* 2006;108:397-409.
95. Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20:21-35.

96. U.S. Preventive Services Task Force. USPSTF Procedure Manual. AHRQ Publication No. 08-05118-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
97. Noorani HZ, Brown A, Skidmore B, Stuart GC. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. Technology Report No. 40. Ottawa, Ontario: Canadian Coordinating Office of Health Technology Assessment; 2003.
98. Medical Services Advisory Committee. Liquid Based Cytology for Cervical Screening. MSAC Reference 12a. Canberra: Australia Department of Health and Ageing; 2002.
99. Hartmann KE, Hall SA, Nanda K, Boggess JF, Zolnoun D. Screening for Cervical Cancer. Systematic Evidence Review No. 25. Rockville, MD: Agency for Healthcare Research and Quality; 2002.
100. Manos MM, Kinney WK, Hurley LB, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA.* 1999;281:1605-1610.
101. National Institute for Health and Clinical Excellence. *The Guidelines Manual*. London: National Institute for Health and Clinical Excellence; 2006.
102. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003;3:25.
103. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539-1558.
104. Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. *Am J Obstet Gynecol.* 2004;191:105-113.
105. Sigurdsson K, Sigvaldason H. Is it rational to start population-based cervical cancer screening at or soon after age 20? Analysis of time trends in preinvasive and invasive diseases. *Eur J Cancer.* 2007;43:769-774.
106. Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet.* 2001;357:1831-1836.
107. Ronco G, Cuzick J, Pierotti P, et al. Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. *BMJ.* 2007;335:28.
108. Siebers AG, Klinkhamer PJ, Grefte JM, et al. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. *JAMA.* 2009;302:1757-1764.
109. Taylor S, Kuhn L, Dupree W, et al. Direct comparison of liquid-based and conventional cytology in a South African screening trial. *Int J Cancer.* 2006;118:957-962.
110. Coste J, Cochand-Priollet B, de Cremoux P, et al. Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ.* 2003;326:733.
111. Ronco G. Questions regarding publication of NTCC study. Vesco KK. March 11, 2008.
112. Ronco G, Segnan N, Giorgi-Rossi P, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the New Technologies for Cervical Cancer randomized controlled trial. *J Natl Cancer Inst.* 2006;98:765-774.

113. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncology.* 2010;11:249-257.
114. Bulkmans NW, Berkhof J, Rozendaal L, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet.* 2007;370:1764-1772.
115. Naucler P, Ryd W, Tornberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *New Engl J Med.* 2007;357:1589-1597.
116. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol.* 2003;188:1383-1392.
117. Kitchener HC, Almonte M, Thomson C, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncology.* 2009;10:672-682.
118. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *New Engl J Med.* 2009;360:1385-1394.
119. Bjerre P, Silfverdal L, Dillner L, et al. A randomized trial of basing treatment on human papillomavirus and/or cytology results in low-grade cervical lesion triage. *Am J Obstet Gynecol.* 2008;199:24-27.
120. Kotaniemi-Talonen L, Anttila A, Malila N, et al. Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3. *Eur J Cancer.* 2008;44:565-571.
121. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *New Engl J Med.* 2007;357:1579-1588.
122. Kulasingam SL, Hughes JP, Kiviat NB, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. *JAMA.* 2002;288:1749-1757.
123. Petry KU, Menton S, Menton M, et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br J Cancer.* 2003;88:1570-1577.
124. Bigras G, de Marval F. The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. *Br J Cancer.* 2005;93:575-581.
125. Cárdenas-Turanzas M, Nogueras-Gonzalez GM, Scheurer ME, et al. The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. *Cancer Epidemiol Biomarkers Prev.* 2008;17:2865-2871.
126. Mayrand MH, Duarte-Franco E, Coutlee F, et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian Cervical Cancer Screening Trial (CCCaST). *Int J Cancer.* 2006;119:615-623.
127. Cochand-Priollet B, Le Galès C, de Cremoux P, et al. Cost-effectiveness of monolayers and human papillomavirus testing compared to that of conventional Papanicolaou smears for

cervical cancer screening: protocol of the study of the French Society of Clinical Cytology. *Diagn Cytopathol.* 2001;24:412-420.

128. de Cremoux P, Coste J, Sastre-Garau X, et al. Efficiency of the Hybrid Capture 2 HPV DNA test in cervical cancer screening: a study by the French Society of Clinical Cytology. *Am J Clin Pathol.* 2003;120:492-499.
129. Sankaranarayanan R, Chatterji R, Shastri SS, et al. Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: results from a multicenter study in India. *Int J Cancer.* 2004;112:341-347.
130. Pan Q, Belinson JL, Li L, et al. A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma: a cross-sectional, comparative study. *Acta Cytol.* 2003;47:45-50.
131. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncology.* 2008;9:929-936.
132. Moy LM, Zhao FH, Li LY, et al. Human papillomavirus testing and cervical cytology in primary screening for cervical cancer among women in rural China: comparison of sensitivity, specificity, and frequency of referral. *Int J Cancer.* 2010;127:646-656.
133. Leinonen M, Nieminen P, Kotaniemi-Talonen L, et al. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. *J Natl Cancer Inst.* 2009;101:1612-1623.
134. Anttila A, Kotaniemi TL, Leinonen M, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. *BMJ.* 2010;340:c1804.
135. Kitchener HC, Gilham C, Sargent A, et al. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. *Eur J Cancer*. 2011;47:864-71.
136. Andersson S, Dillner L, Elfgren K, et al. A comparison of the human papillomavirus test and Papanicolaou smear as a second screening method for women with minor cytological abnormalities. *Acta Obstet Gynecol Scand.* 2005;84:996-1000.
137. Bergeron C, Jeannel D, Poveda J, et al. Human papillomavirus testing in women with mild cytologic atypia. *Obstet Gynecol.* 2000;95:821-827.
138. Del Mistro A, Frayle-Salamanca H, Trevisan R, et al. Triage of women with atypical squamous cells of undetermined significance (ASC-US): results of an Italian multicentric study. *Gynecol Oncol.* 2010;117:77-81.
139. Kitchener HC, Fletcher I, Roberts C, et al. The psychosocial impact of human papillomavirus testing in primary cervical screening—a study within a randomized trial. *Int J Gynecol Cancer.* 2008;18:743-748.
140. Maissi E, Marteau TM, Hankins M, et al. Psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: cross sectional questionnaire study. *BMJ.* 2004;328:1293.
141. McCaffery K, Waller J, Forrest S, et al. Testing positive for human papillomavirus in routine cervical screening: examination of psychosocial impact. *BJOG.* 2004;111:1437-1443.

142. McCaffery KJ, Irwig L, Turner R, et al. Psychosocial outcomes of three triage methods for the management of borderline abnormal cervical smears: an open randomised trial. *BMJ.* 2010;340:b4491.
143. Maissi E, Marteau TM, Hankins M, et al. The psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: 6-month follow-up. *Br J Cancer.* 2005;92:990-994.
144. Cuzick J, Arbyn M, Sankaranarayanan R, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine.* 2008;26(Suppl 10):K29-41.
145. U.S. Preventive Services Task Force. Screening for Cervical Cancer: Recommendations and Rationale. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
146. Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338:423-428.
147. Chan PG, Sung HY, Sawaya GF. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstet Gynecol.* 2003;102:765-773.
148. Galaal KA, Deane K, Sangal S, et al. Interventions for reducing anxiety in women undergoing colposcopy. *Cochrane Database Syst Rev.* 2007;CD006013.
149. Massad SL, Markwell S, Cejtin HE, et al. Risk of high-grade cervical intraepithelial neoplasia among young women with abnormal screening cytology. *J Low Genit Tract Dis.* 2005;9:225-229.
150. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet.* 2004;364:1757-1765.
151. Lewin SA, Dick J, Pond P, et al. Lay health workers in primary and community health care. *Cochrane Database Syst Rev.* 2005;CD004015.
152. Montanari G, Confortini M, Bellomi A, et al. Assessment of specimen adequacy reproducibility: an Italian experience. *Diagn Cytopathol.* 2003;28:224-226.
153. National Health Service. NHS Cervical Screening Programme: About Cervical Screening. Sheffield, UK: NHS Cancer Screening Programmes; 2011. Accessed at http://www.cancerscreening.nhs.uk/cervical/about-cervical-screening.html on 19 April 2011.
154. Arbyn M, Bergeron C, Klinkhamer P, et al. Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. *Obstet Gynecol.* 2008;111:167-177.
155. Davey E, Barratt A, Irwig L, et al. Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. *Lancet.* 2006;367:122-132.
156. Schiffman M, Solomon D. Screening and prevention methods for cervical cancer. *JAMA.* 2009;302:1809-1810.
157. Lord SJ, Irwig L, Simes RJ. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? *Ann Intern Med.* 2006;144:850-855.

158. Dalla PP, Giorgi RP, Collina G, et al. The risk of false-positive histology according to the reason for colposcopy referral in cervical cancer screening: a blind revision of all histologic lesions found in the NTCC trial. *Am J Clin Pathol.* 2008;129:75-80.
159. Mesher D, Szarewski A, Cadman L, et al. Long-term followup of cervical disease in women screened by cytology and HPV testing: results from the HART study. *Br J Cancer.* 2010;102:1405-1410.
160. Naucler P, Ryd W, Tornberg S, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. *J Natl Cancer Inst.* 2009;101:88-99.
161. Arbyn M, Anttila A, Jordan J, et al. European Guidelines for Quality Assurance in Cervical Cancer Screening: second edition—summary document. *Ann Oncol.* 2010;21:448-458.
162. Arbyn M, Ronco G, Cuzick J, et al. How to evaluate emerging technologies in cervical cancer screening? *Int J Cancer.* 2009;125:2489-2496.
163. Ronco G, Meijer C. HPV screening: available data and recommendations for clinical practice. *Curr Cancer Ther Rev*. 2010;6:104-109.
164. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA.* 2003;290:1624-1632.
165. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119:1095-1101.
166. Arbyn M, Sasieni P, Meijer CJ, et al. Clinical applications of HPV testing: a summary of meta-analyses. *Vaccine.* 2006;24(Suppl 3):S78-S89.
167. Dillner J, Rebolj M, Birembaut P, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ.* 2008;337:a1754.
168. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst.* 2003;95:46-52.
169. Kjaer S, Hogdall E, Frederiksen K, et al. The absolute risk of cervical abnormalities in high-risk human papillomavirus-positive, cytologically normal women over a 10-year period. *Cancer Res.* 2006;66:10630-10636.
170. Rebolj M, Lynge E. Incomplete follow-up of positive HPV tests: overview of randomised controlled trials on primary cervical screening. *Br J Cancer.* 2010;103:310-314.
171. Kjaer SK, Frederiksen K, Munk C, et al. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst.* 2010;102:1478-1488.
172. Franco EL. Persistent HPV infection and cervical cancer risk: is the scientific rationale for changing the screening paradigm enough? *J Natl Cancer Inst.* 2010;102:1451-1453.
173. Arbyn M, Buntinx F, Van Ranst M, et al. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. *J Natl Cancer Inst.* 2004;96:280-293.
174. Arbyn M, Paraskevaidis E, Martin-Hirsch P, et al. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN—an update of pooled evidence. *Gynecol Oncol.* 2005;99:S7-11.

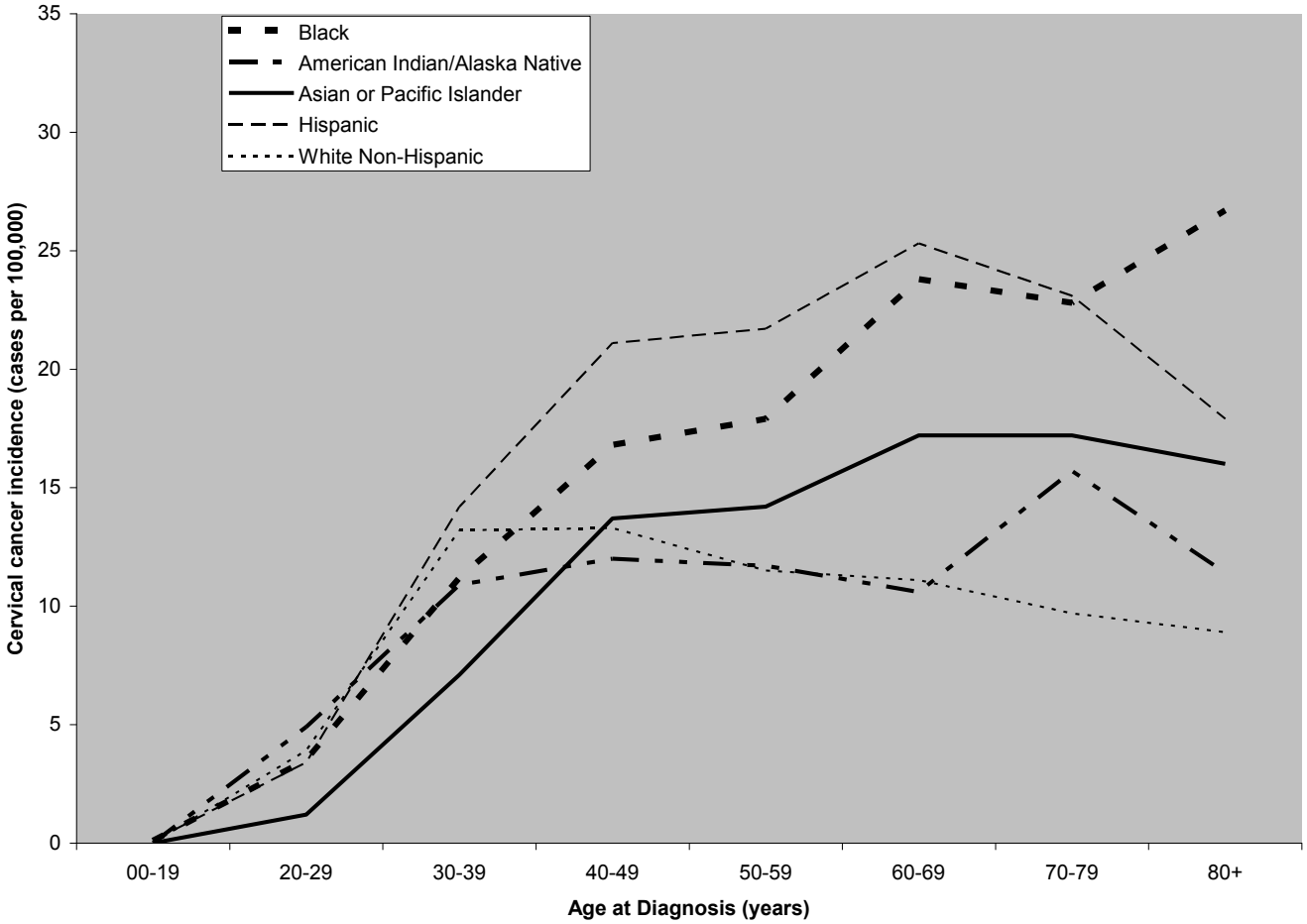
175. Castle PE, Fetterman B, Thomas CJ, et al. The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. *Obstet Gynecol.* 2010;116:76-84.
176. Sherman M, Schiffman M. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst.* 2002;102-107.
177. Schiffman M, Khan MJ, Solomon D, et al. A study of the impact of adding HPV types to cervical cancer screening and triage tests. *J Natl Cancer Inst.* 2005;97:147-150.
178. Stoler MH, Castle PE, Solomon D, et al. The expanded use of HPV testing in gynecologic practice per ASCCP-guided management requires the use of well-validated assays. *Am J Clin Pathol.* 2007;127:335-337.
179. Kinney W, Stoler MH, Castle PE. Special commentary: patient safety and the next generation of HPV DNA tests. *Am J Clin Pathol.* 2010;134:193-199.
180. Meijer CJ, Berkhof J, Castle PE, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer.* 2009;124:516-520.
181. Benard VB, Eheman CR, Lawson HW, et al. Cervical screening in the National Breast and Cervical Cancer Early Detection Program, 1995-2001. *Obstet Gynecol.* 2004;103:564-571.
182. Rebolj M, van Ballegooijen M, Lynge E, et al. Incidence of cervical cancer after several negative smear results by age 50: prospective observational study. *BMJ.* 2009;338:b1354.
183. Sasieni P, Castanon A. Call and recall cervical screening programme: screening interval and age limits. *Curr Diagn Pathol*. 2006;12:114-126.
184. Mandelblatt J, Lawrence W, Yi B, et al. The balance of harms, benefits, and costs of screening for cervical cancer in older women: the case for continued screening. *Arch Intern Med.* 2004;164:245-247.
185. Fahs MC, Mandelblatt J, Schechter C, et al. Cost effectiveness of cervical cancer screening for the elderly. *Ann Intern Med.* 1992;117:520-527.
186. Hutchinson ML, Agarwal P, Denault T, et al. A new look at cervical cytology: ThinPrep multicenter trial results. *Acta Cytol.* 1992;36:499-504.
187. Hildesheim A, Hadjimichael O, Schwartz PE, et al. Risk factors for rapid-onset cervical cancer. *Am J Obstet Gynecol.* 1999;180:571-577.
188. Armaroli P, Gallo F, Bellomi A, et al. Do women ≥50 years of age need as much screening as women <50 years after they have had negative screening results? *Br J Cancer.* 2008;99:239-244.
189. Trottier H, Ferreira S, Thomann P, et al. Human papillomavirus infection and reinfection in adult women: the role of sexual activity and natural immunity. *Cancer Res.* 2010;70:8569-8577.
190. Kalliala I, Dyba T, Nieminen P, et al. Mortality in a long-term follow-up after treatment of CIN. *Int J Cancer.* 2010;126:224-231.
191. Strander B, Andersson-Ellström A, Milsom I, et al. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. *BMJ.* 2007;335:1077.

192. Henley SJ, King JB, German RR, et al. Surveillance of screening-detected cancers (colon and rectum, breast, and cervix)—United States, 2004-2006. *MMWR Surveill Summ.* 2010;59:1-25.
193. Barnholtz-Sloan J, Patel N, Rollison D, et al. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. *Cancer Causes Control.* 2009;20:1129-1138.
194. McDougall JA, Madeleine MM, Daling JR, et al. Racial and ethnic disparities in cervical cancer incidence rates in the United States, 1992-2003. *Cancer Causes Control.* 2007;18:1175-1186.
195. Strander B, Ryd W, Wallin KL, et al. Does HPV-status 6-12 months after treatment of high grade dysplasia in the uterine cervix predict long term recurrence? *Eur J Cancer.* 2007;43:1849-1855.
196. Verguts J, Bronselaer B, Donders G, et al. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conisation. *BJOG.* 2006;113:1303-1307.
197. Kitchener HC, Almonte M, Gilham C, et al. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. *Health Technol Assess.* 2009;13:1-150.
198. Ogilvie GS, van Niekerk DJ, Krajden M, et al. A randomized controlled trial of human papillomavirus (HPV) testing for cervical cancer screening: trial design and preliminary results (HPV FOCAL Trial). *BMC Cancer.* 2010;10:111.
199. Pretorius RG, Kim RJ, Belinson JL, et al. Inflation of sensitivity of cervical cancer screening tests secondary to correlated error in colposcopy. *J Low Genit Tract Dis.* 2006;10:5-9.
200. Stoler MH, Vichnin MD, Ferenczy A, et al. The accuracy of colposcopic biopsy: analyses from the placebo arm of the Gardasil clinical trials. *Int J Cancer.* 2010;128:1354-1362.
201. Arbyn M, Cuzick J. International agreement to join forces in synthesizing evidence on new methods for cervical cancer prevention. *Cancer Lett.* 2008;278:1-2.
202. Solomon D. Personal communication. Whitlock EP. May 2, 2011.
203. Saraiya M, Berkowitz Z, Yabroff KR, et al. Cervical cancer screening with both human papillomavirus and Papanicolaou testing vs Papanicolaou testing alone: what screening intervals are physicians recommending? *Arch Intern Med.* 2010;170:977-985.
204. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007;356:1915-1927.
205. Brisson M, Van de Velde N, De Wals P, et al. Estimating the number needed to vaccinate to prevent diseases and death related to human papillomavirus infection. *CMAJ.* 2007;2007:464-468.
206. Gök M, Heideman DA, van-Kemenade FJ, et al. HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. *BMJ*. 2010;340:c1040.
207. American Society for Colposcopy and Cervical Pathology. Algorithms for the 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests. *J Lower Genital Tract Dis.* 2007;11:201-222.

208. National Cancer Institute, Surveillance Epidemiology and End Results (SEER) Program. Age-Specific (Crude) Cervical Cancer Incidence Rates By Race. Bethesda, MD: National Cancer Institute; 2011. Accessed at http://seer.cancer.gov/ on 21 April 2011.
209. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. *J Natl Cancer Inst.* 2008;100:492-501.
210. Ronco G, Cuzick J, Segnan N, et al. HPV triage for low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology. *Eur J Cancer.* 2007;43:476-480.
211. Ronco G, Brezzi S, Carozzi F, et al. The New Technologies for Cervical Cancer Screening randomised controlled trial: an overview of results during the first phase of recruitment. *Gynecol Oncol.* 2007;107(Suppl 1):S230-232.
212. Anttila A, Hakama M, Kotaniemi-Talonen L, et al. Alternative technologies in cervical cancer screening: a randomised evaluation trial. *BMC Public Health.* 2006;6:252.
213. Kotaniemi-Talonen L, Nieminen P, Anttila A, et al. Routine cervical screening with primary HPV testing and cytology triage protocol in a randomised setting. *Br J Cancer.* 2005;93:862-867.
214. Bulkmans NW, Rozendaal L, Snijders PJ, et al. POBASCAM, a population-based randomized controlled trial for implementation of high-risk HPV testing in cervical screening: design, methods and baseline data of 44,102 women. *Int J Cancer.* 2004;110:94-101.
215. Elfgren K, Rylander E, Rådberg T, et al. Colposcopic and histopathologic evaluation of women participating in population-based screening for human papillomavirus deoxyribonucleic acid persistence. *Am J Obstet Gynecol.* 2005;193:650-657.
216. Kitchener HC, Almonte M, Wheeler P, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. *Br J Cancer.* 2006;95:56-61.
217. Sargent A, Bailey A, Turner A, et al. Optimal threshold for a positive Hybrid Capture 2 test for detection of human papillomavirus: data from the ARTISTIC trial. *J Clin Microbiol.* 2010;48:554-558.
218. Sargent A, Bailey A, Almonte M, et al. Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial. *Br J Cancer.* 2008;98:1704-1709.
219. ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol.* 2003;188:1393-1400.
220. ASCUS-LSIL Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst.* 2000;92:397-402.
221. Schiffman M, Adrianza ME. ASCUS-LSIL Triage Study: design, methods and characteristics of trial participants. *Acta Cytol.* 2000;44:726-742.
222. Solomon D, Schiffman M, Tarone R; ALTS Study Group. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst.* 2001;93:293-299.

223. American Cancer Society. Cancer Glossary. Atlanta, GA: American Cancer Society; 2008. Accessed at http://www.cancer.org/Cancer/CancerGlossary/index on 12 May 2011.
224. U.S. Food and Drug Administration. A-Z Subject Index. Rockville, MD: U.S. Food and Drug Administration; 2008. Accessed at http://www.fda.gov on 12 May 2011.
225. Sigurdsson K. Cervical cancer: cytological cervical screening in Iceland and implications of HPV vaccines. *Cytopathology.* 2010;21:213-222.
226. Belinson J, Qiao YL, Pretorius R, et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecol Oncol.* 2001;83:439-444.
227. Shastri SS, Dinshaw K, Amin G, et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bull World Health Organ.* 2005;83:186-194.

Figure 1. U.S. Age-Adjusted Cervical Cancer Incidence Rates By Age and Race/Ethnicity (SEER 2000-2008)[17]



Rates are expressed as cases per 100,000 women; age-adjusted to 2000 US Standard Population
*American Indian/Alaska Native statistics only include cases from the Contract Health Service Delivery Area (CHSDA) counties.
†Hispanic and NonHispanic are not mutually exclusive from white, black, American Indian/Alaska Native, and Asian or Pacific Islander.

Figure 2. U.S. Age-Adjusted Incidence and Death Rates of Invasive Cervical Cancer By Age (SEER 2000-2008)[17]

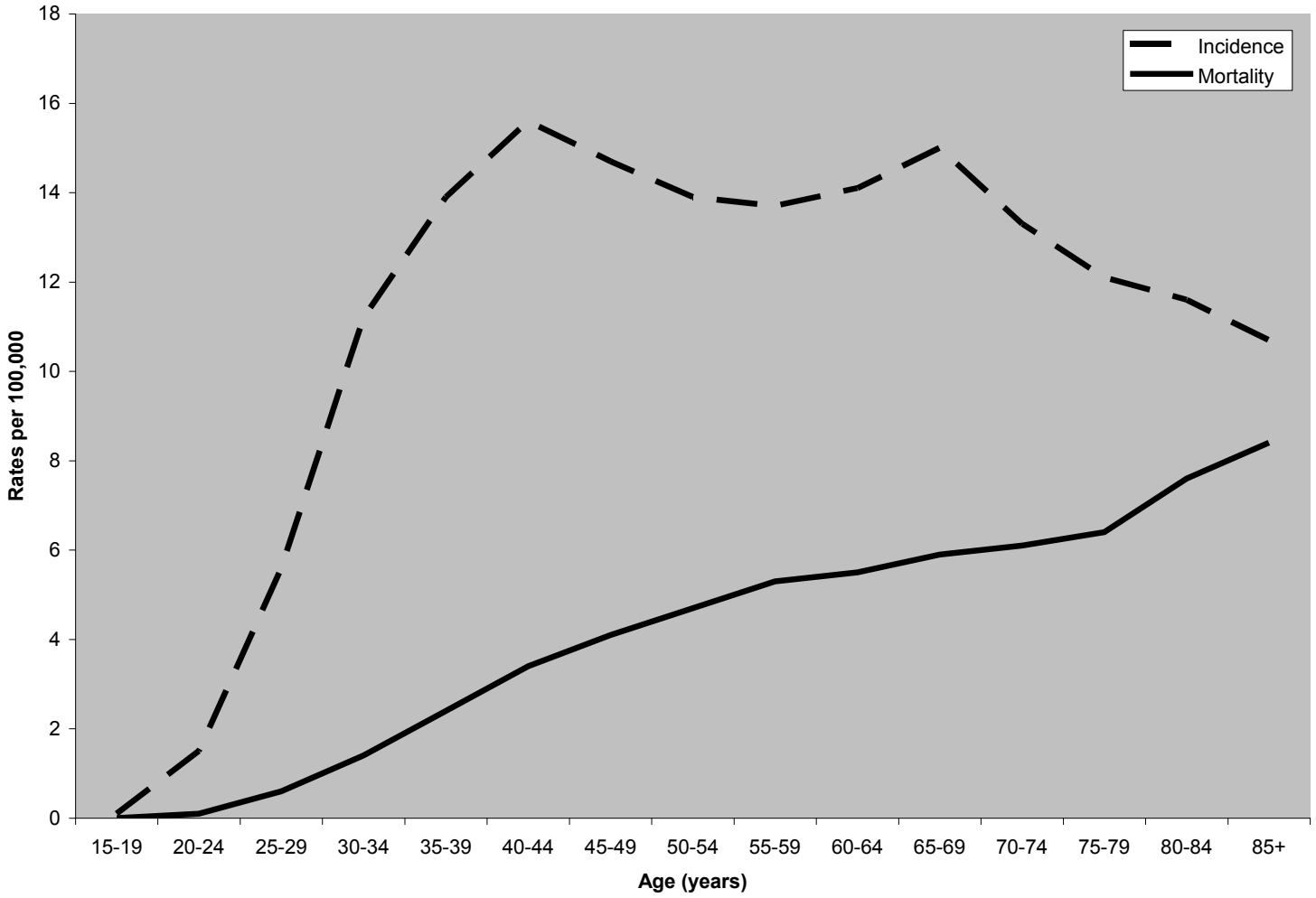
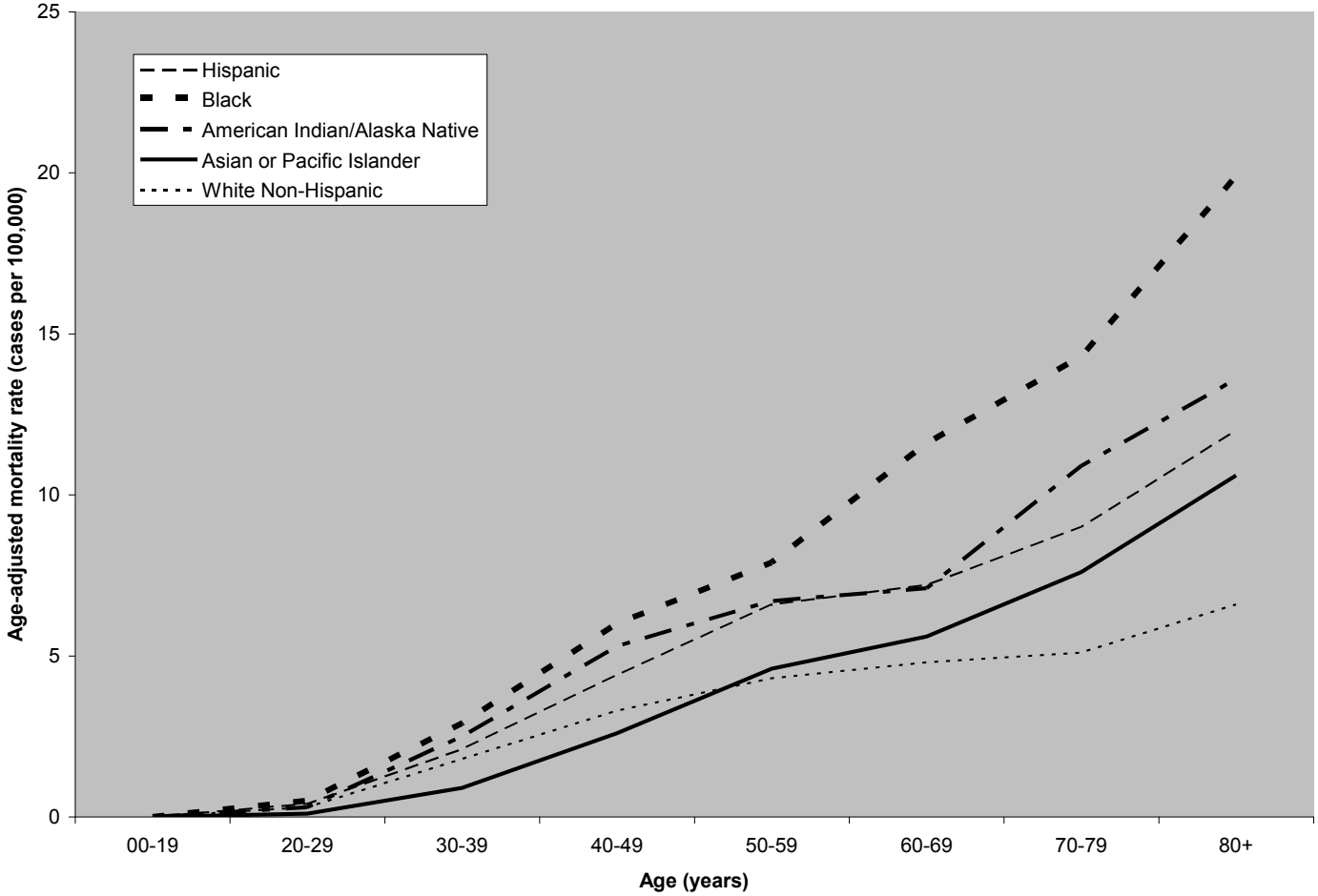


Figure 3. U.S. Age-Adjusted Cervical Cancer Mortality Rates By Age and Race/Ethnicity (SEER 2000-2008)[17]



Rates are expressed as cases per 100,000 women; age-adjusted to 2000 U.S. Standard Population. Data not yet updated for 2008.
*American Indian/Alaska Native statistics only include cases from the Contract Health Service Delivery Area (CHSDA) counties.
†Hispanic and nonHispanic are not mutually exclusive from white, black, American Indian/Alaska Native, and Asian or Pacific Islander.

Figure 4. Prevalence of High-Risk Human Papillomavirus By Age[34]

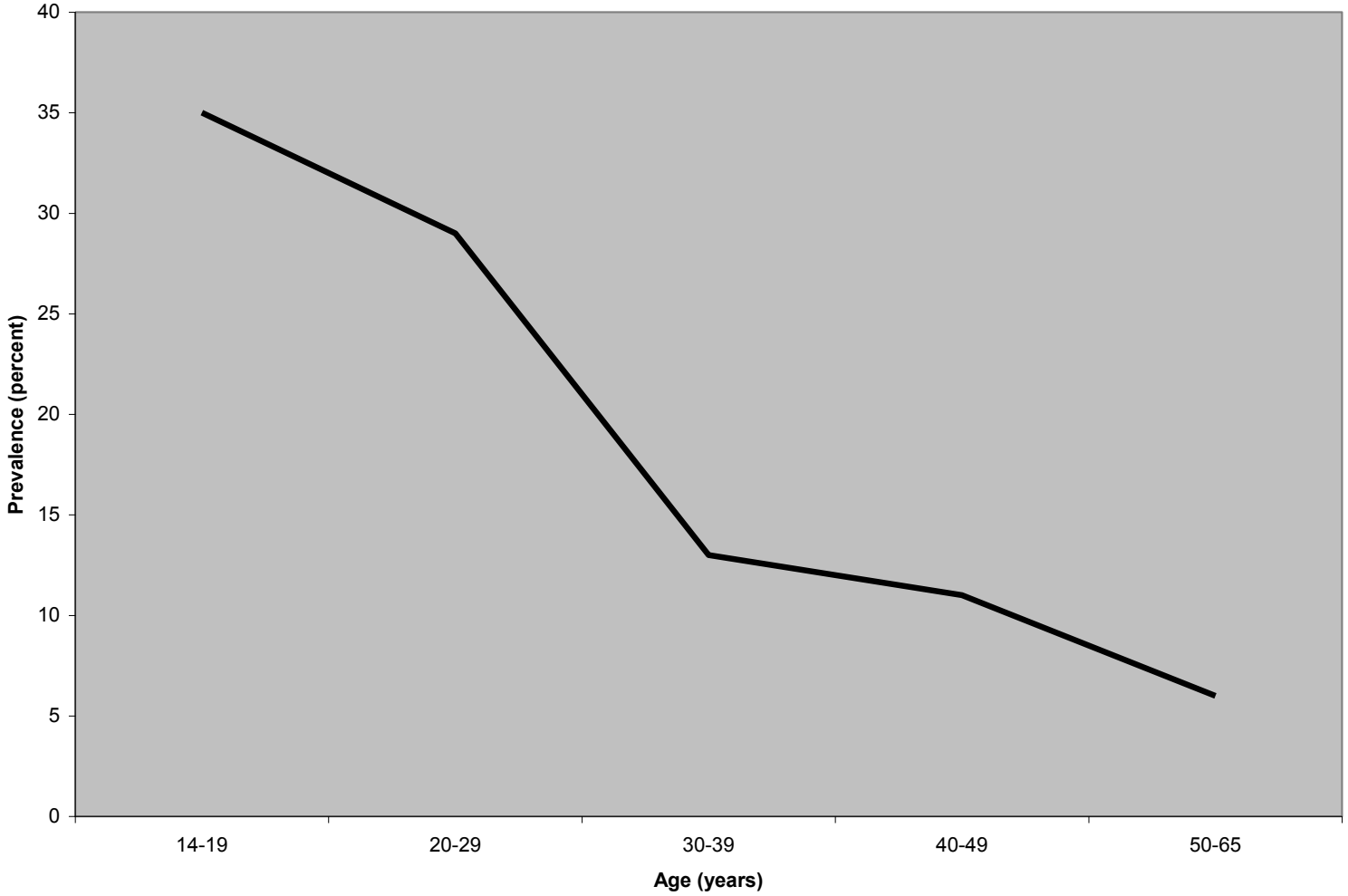
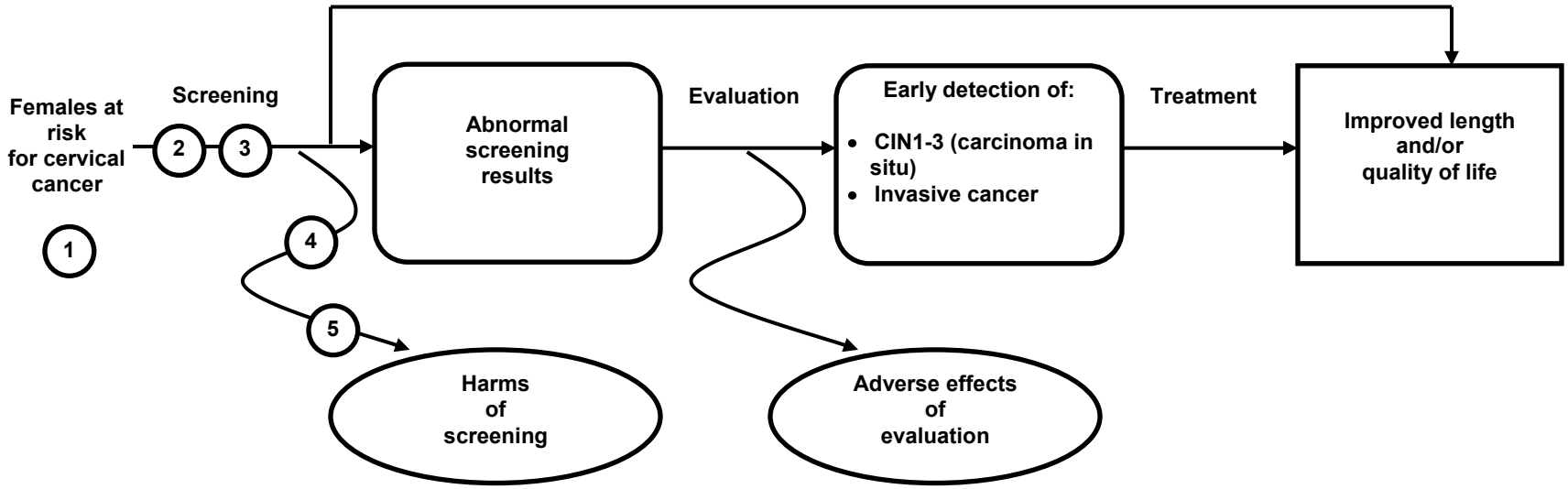


Figure 5. Analytic Framework and Key Questions



Key Questions

KQ1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?

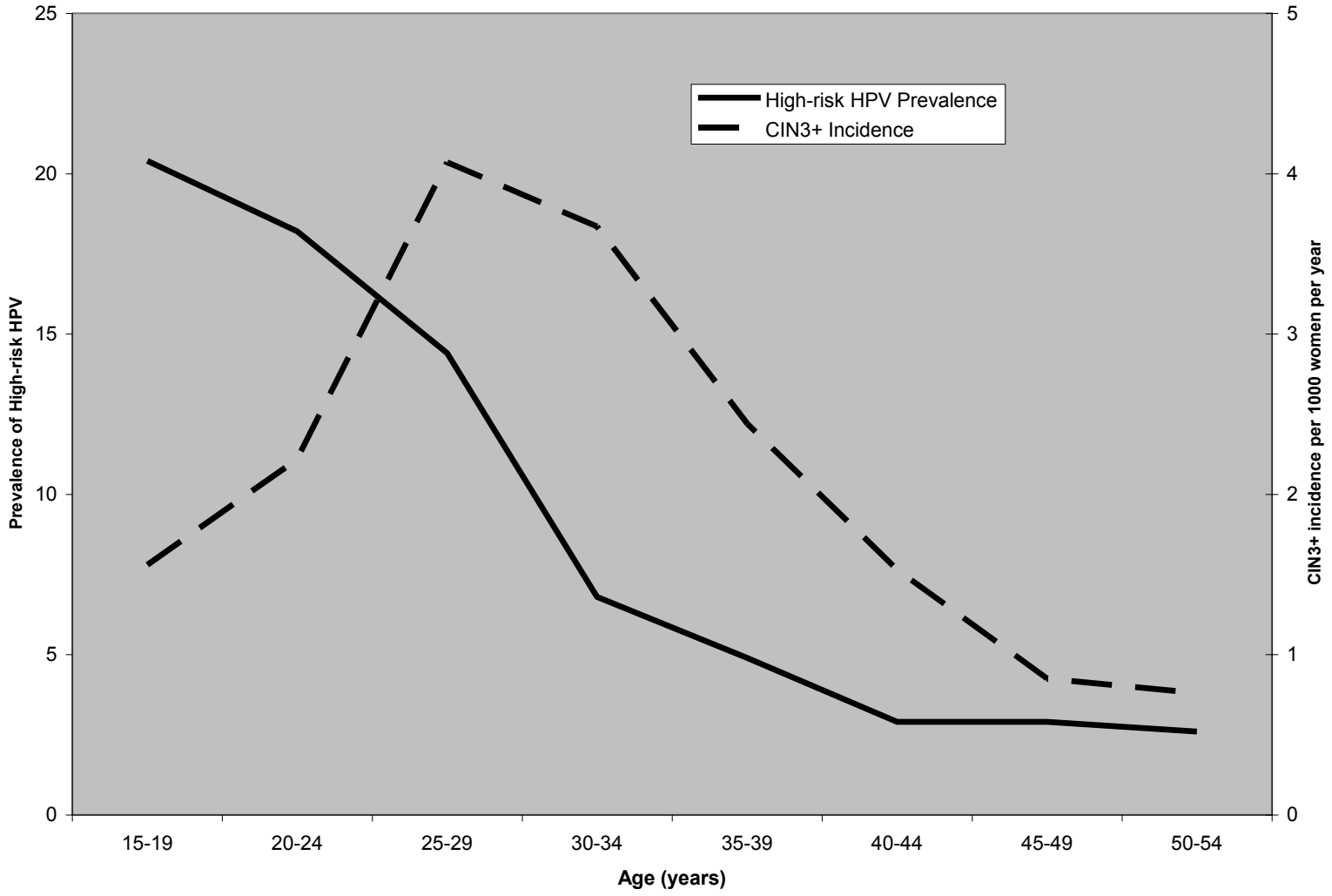
KQ2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?

KQ3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?

KQ4: What are the harms of liquid-based cytology?

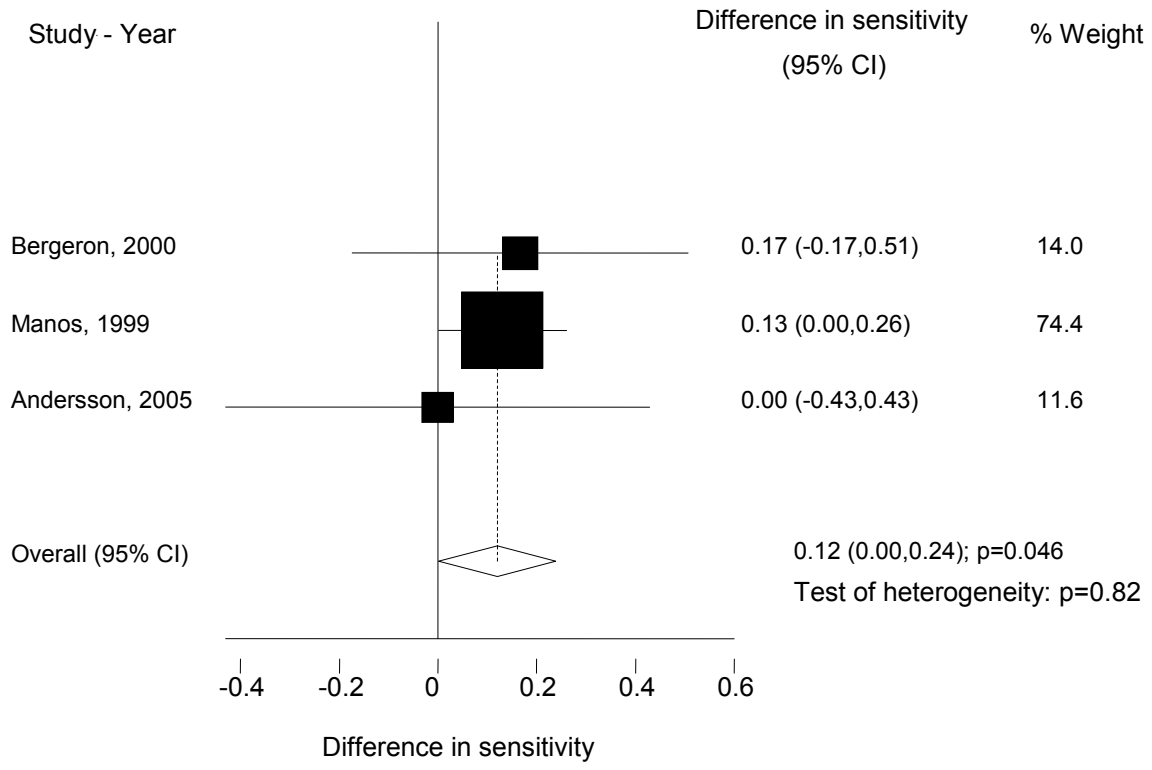
KQ5: What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?

Figure 6. High-Risk HPV Prevalence and CIN3+ Incidence[32]



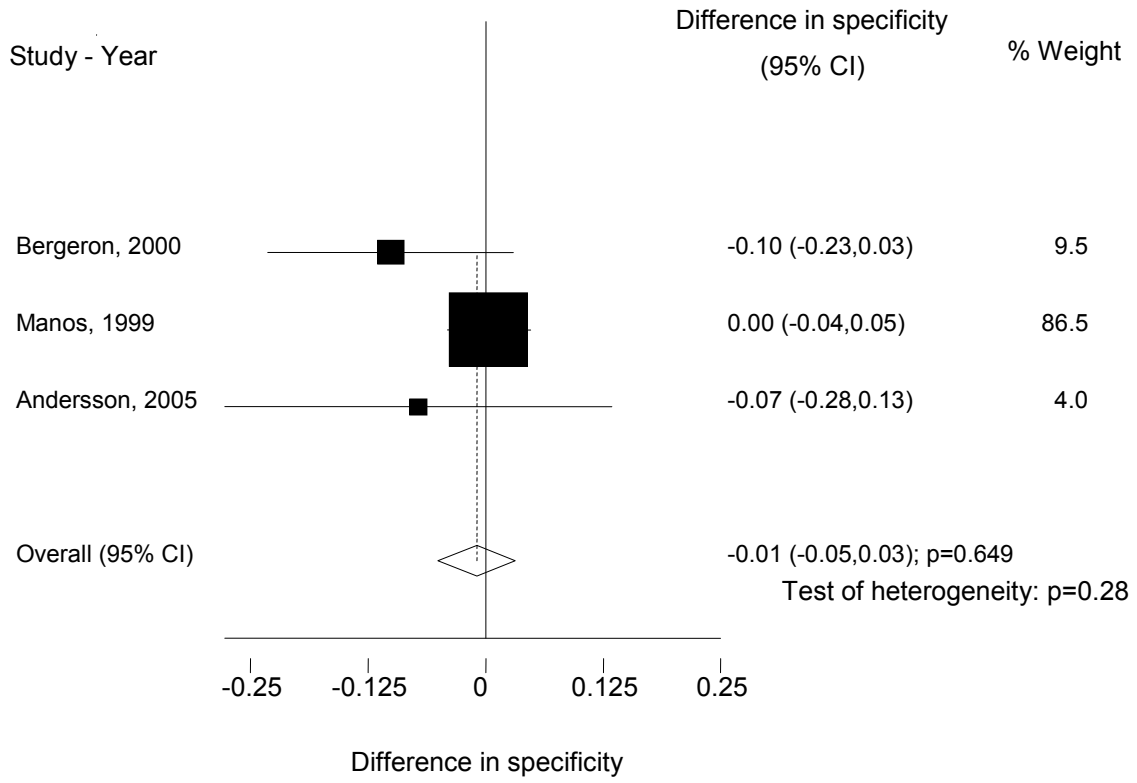
High-risk HPV types: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68[32]

Figure 7. Comparison of HC2 and Repeat Cytology Sensitivity for the Detection of CIN2+ Among Women Referred With ASC-US Cytology



ASC-US: atypical squamous cells of undetermined significance; CI: confidence interval ; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2

Figure 8. Comparison of HC2 and Repeat Cytology Specificity for the Detection of CIN2+ Among Women Referred With ASC-US Cytology



ASC-US: atypical squamous cells of undetermined significance; CI: confidence interval; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2

Table 1. Cervical Pathology: Comparison of Cytologic and Histologic Test Results[10] and Current U.S. Guidelines for Management of Cytologic Abnormalities

Abnormal cervical cytology: the Bethesda System, 2001	Corresponding cervical histology
ASC-US[1] (Atypical Squamous Cells of Undetermined Significance)	
ASC-H[2] (Atypical Squamous Cells – cannot exclude HSIL)	
LSIL[3] (Low-Grade Squamous Intraepithelial Lesion) Previous terminology: mild dysplasia	**CIN1** (Cervical Intraepithelial Neoplasia 1)
HSIL[2] (High-Grade Squamous Intraepithelial Lesion) Previous terminology: moderate dysplasia (CIN2) Severe dysplasia and carcinoma in situ (CIN3)	**CIN2** **CIN3**
SCC[2] (Squamous Cell Carcinoma)	
AGC[2] (Atypical Glandular Cells; specify endocervical or not otherwise specified)	
Atypical Glandular Cells, favor neoplastic (specify endocervical or not otherwise specified)	
AIS[2] (Adenocarcinoma in Situ [endocervical])	
Adenocarcinoma[2]	

Management options and referral thresholds (based on ASCCP guidelines[207]):

1. Women ≤ 20 years : Repeat cytology
   Women ≥ 20 years: Colposcopy is one option
2. All women: Receive at least immediate colposcopy
3. Women ≤ 20 years: Repeat cytology
   Women ≥ 20 years: Colposcopy

Table 2. U.S. Age-Specific Crude Invasive Cervical Cancer Incidence Rates By Race, 2000-2008[208]

Age-Group	White NonHispanic	Black	American Indian/Alaska Native*	Asian or Pacific Islander	Hispanic†
00	0	0	0	0	0
01-04	0	0	0	0	0
05-09	0	0	0	0	0
10-14	0	0.1	0	0	0
15-19	0.1	0.2	0	0	0.2
20-24	1.5	1.9	3.8	0.5	1.6
25-29	6.4	5.2	6.0	1.8	5.2
30-34	12.4	9.6	12.9	5.6	11.2
35-39	13.9	12.5	9.2	8.3	16.9
40-44	13.8	16.9	12.3	12.2	21.5
45-49	12.6	16.6	11.6	15.5	20.7
50-54	11.8	17.3	8.9	14.0	21.0
55-59	11.1	18.7	15.2	14.5	22.5
60-64	10.7	23.3	10.4	17.3	24.1
65-69	11.4	24.3	10.8	17.1	26.7
70-74	10.3	21.7	12.3	16.1	24.1
75-79	9.0	24.1	19.8	18.4	21.9
80-84	9.4	24.7	8.7	16.7	17.8
85+	8.3	28.9	14.5	15.1	18.0

Rates are expressed as cases per 100,000 women.
*American Indian/Alaska Native statistics only include cases from the Contract Health Service Delivery Area (CHSDA) counties.
†Hispanic and nonHispanic are not mutually exclusive from white, black, American Indian/Alaska Native, and Asian or Pacific Islander.

Table 3. Characteristics of Liquid-Based Cytology Studies (RCTs and Observational Studies) (KQ2)

	NETHCON[108]	NTCC[107]	Taylor 2006[109]	Coste 2003[110]
Setting	The Netherlands	Italy	Periurban South Africa	France
Design	Cluster RCT, randomized) to LBC vs. CC	RCT: HPV (HC2) & LBC vs. CC	Cytology method (LBC vs. CC) rotated on 6 month basis	Consecutive series, split sample
Years of Study	April 2004 to January 2008	February 2002 to 2005	June 2000 to December 2002	September 1999 to May 2000
Sample Size (N)	88,988	45,174	5,647	1,757
Patient Age	<30 ≥30 LBC 0.7% 99.3% CC 0.6% 99.4%	Median: 41	35-39 40-49 50-65 LBC 39.4% 41.4% 19.3% CC 37.5% 43.7% 18.8%	Mean (SD): 33.3 (11.1)
Primary Screening Test Evaluated	ThinPrep	ThinPrep	ThinPrep	ThinPrep
Primary Outcomes	CIN2+, CIN3+	CIN2+, CIN3+	CIN2+, CIN3+	CIN2+
Test Positivity Rate	LBC (ASC-US/AGUS+): 2.7% CC (ASC-US/AGUS+): 2.8%	LBC (ASC-US/AGUS+): 6.3% CC (ASC-US/AGUS+): 3.8%	LBC (ASC-US+): 16.4% CC (ASC-US+): 16.4%	LBC (ASC-US+): 13.4% CC (ASC-US+): 12.4%
Disease Detection	CIN2+ CIN3+ ICC LBC 0.71% 0.52% 0.06% CC 0.70% 0.47% 0.03%	CIN2+ CIN3+ LBC 0.44% 0.20% CC 0.37% 0.24%	CIN2 1.0% CIN3+ 1.2%	CIN2 or CIN3: 2.0% Invasive cancer: 0.3%
USPSTF Quality	Good	Fair	Fair	Fair

ASC-US: atypical squamous cells of undetermined significance; AGUS: atypical glandular cells of undetermined significance; CC: conventional cytology; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; LBC: liquid-based cytology; SD: standard deviation; RCT: randomized controlled trial; USPSTF: United States Preventive Services Task Force

Table 4. Liquid-Based Cytology Test Performance Characteristics for Studies (RCTs and Observational Studies) (KQ2)

Study ID	Cytology Cutoff	Sensitivity/ Relative Detection Ratio (95% CI)*		Specificity (95% CI)		Positive Predictive Value (95% CI)*		False Positive Rate (95% CI)*		Unsatisfactory Samples†	
		LBC	CC	LBC	CC	LBC	CC	LBC	CC	LBC	CC
Detection of CIN3+											
NETHCON[108]	**ASC-US+**	1.05 (0.86-1.29) (adjusted)		NA		1.17 (0.99-1.39)		0.89 (0.82-0.98)		0.37%	1.09%
	LSIL+	NR		NA		1.17 (1.01-1.36)		NR			
NTCC[107]	**ASC-US+**	0.84 (0.56-1.25)		NA		0.42 (0.29-0.62)		1.93 (1.72-2.21)		2.6%	4.1%
	LSIL+	0.72 (0.46-1.13)		NA		0.40 (0.26-0.62)		1.72 (1.42-2.07)			
Taylor 2006[109]	**ASC-US+**	75.8 (57.7-88.9)	87.9 (71.8-96.6)	84.2 (82.9-85.5)	84.5 (83.0 -86.0)	4.9 (3.2-7.1)	7.2 (4.9-10.2)	15.8 (14.5-17.1)	15.5 (14.0-17.0)	2.2%	0.8%
	LSIL+	66.7 (48.2-82.0)	72.7 (54.5-86.7)	93.6 (92.6-94.4)	93.9 (92.9-94.9)	10.0 (6.4-14.7)	14.1 (9.3-20.3)	6.4 (5.6-7.4)	6.1 (5.1-7.1)		
	HSIL+	54.5 (36.4-71.9)	63.6 (45.1-79.6)	97.8 (97.2-98.3)	97.1 (96.4-97.8)	21.2 (13.1-31.4)	23.3 (15.1-33.4)	2.2 (1.7-2.8)	2.9 (2.2-3.6)		
Detection of CIN2+										--	--
NETHCON[108]	**ASC-US+**	1.00 (0.84-1.20) (adjusted)		NA		1.09 (0.95-1.25)		0.90 (0.82-0.99)		--	--
	LSIL+	NR		NA		1.04 (0.93-1.15)		NR			
NTCC[107]	**ASC-US+**	1.11 (0.81-1.52) ‡		NA		0.65 (0.49-0.88) ‡		1.97 (1.75-2.21)		--	--
	LSIL+	1.03 (0.74-1.43)		NA		0.58 (0.43-0.78)		1.80 (1.48-2.19)			
Taylor 2006[109]	**ASC-US+**	70.6 (58.3-81.0)	83.6 (71.2-92.2)	84.8 (83.5-86.1)	85.1 (83.6-86.5)	9.4 (7.0-12.3)	11.4 (8.5-15.0)	15.2 (13.9-16.5)	14.9 (13.5-16.4)	--	--
	LSIL+	60.3 (47.7-71.9)	69.1 (55.2-80.9)	94.1 (93.2- 94.9)	94.5 (93.5-95.4)	18.6 (13.7-24.4)	22.4 (16.3-29.4)	5.9 (5.1-6.8)	5.5 (4.6-6.5)		
	HSIL+	44.1 (32.1-56.7)	58.2 (44.1-71.3)	98.2 (97.7-98.6)	97.6 (96.9-98.2)	35.3 (25.2-46.4)	35.6 (25.7-46.3)	1.8 (1.4-2.3)	2.4 (1.8-3.1)		
Coste 2003[110]	**ASC-US+**	87.5 (73.2-95.8)	87.8 (73.8-95.9)	88.3 (86.7-89.8)	89.4 (87.9-90.9)	14.9 (10.6-20.1)	16.6 (11.9-22.2)	11.7 (10.2-13.3)	10.6 (9.1-12.1)	0.4%	0.1%
	LSIL+	80.0 (64.4-90.9)	73.2 (57.1-85.8)	93.1 (91.8-94.3)	94.6 (93.4-95.6)	21.3 (15.1-28.8)	24.4 (17.1-33.0)	6.9 (5.7-8.2)	5.4 (4.4-6.6)		
	HSIL+	65 (50-80)	60 (45-75)	98 (98-99)	99 (99-99)	49.1 (35.1-63.2)	58.5 (42.1-73.7)	1.6 (1.0-2.3)	1.0 (0.6-1.6)		

*Relative detection ratio, relative PPV, and relative false positive proportion for RCTs
†Unsatisfactory samples across all, not specific to CIN diagnosis
‡Restricted to centers with ASC-US+ referral criteria
ASC-US: atypical squamous cells of undetermined significance; CC: conventional cytology; CI: confidence interval; CIN: cervical intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial lesion; LBC: liquid-based cytology; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable; NETHCON; Netherlands ThinPrep vs. Conventional Cytology; NTCC: New Technologies for Cervical Cancer; NR: not reported

Table 5a. Population and Screening Program of RCTs of HPV Screening Strategies for Cervical Cancer Screening (KQ3)

	NTCC Phase II[112,113,209-211]	**Finnish Trial**[120,133,134,212,213]	**NTCC Phase I**[112,113,210,211]	**POBASCAM**[114,214]	**Swedescreen**[115,160,215]	**ARTISTIC**[117,197,216-218]
Country	Italy	Finland	Italy	The Netherlands	Sweden	UK
Total randomized and screened	49,196	71,337	45,174	44,938	12,527	24,510
Ages recruited	25-60	25-65	25-60	30-56	32-38	20-64
Older women	35,471	59,757	33,364	44,938	12,527	19,344
Younger women	13,725	11,580	11,810	NA	NA	5,166
Number of Rounds	2	1	2	2	2	2
Round Interval (y)	3	2-4	3	5	3	3
Followup (y)	3.5*	3.3 (mean)	3.5*	6.5†	4.1 (mean)‡	7§
Screening Approach Round 1	HC2 vs. CC	HC2 with cytology triage (CC) vs. CC	HC2+LBC vs. CC	PCR+CC vs. CC	PCR+CC vs. CC	HC2+LBC vs. LBC
Screening Approach Round 2	CC vs. CC	NA	CC vs. CC	PCR+CC vs. PCR+CC	PCR+CC vs. CC	HC2+LBC vs. LBC
Difference between rounds	All women had CC alone in Round 2 No women were excluded from Round 2 based on Round 1 histologic outcomes Some women who did not comply with repeat screening or post-colposcopy followup in Round 1 were not invited to Round 2	NA	All women had CC alone in Round 2 No women were excluded from Round 2 based on Round 1 histologic outcomes Some women who did not comply with repeat screening or post-colposcopy followup in Round 1 were not invited to Round 2	At Round 2, all women (both arms) had IG protocol (HPV & CC co-testing) Women with CIN2+ histology at Round 1 excluded from analyses of Round 2 results	Second (–incidence”) round screening occurred in the next screening round under the Swedish cervical cancer screening program, scheduled 3 years after baseline, or other screening not complying with the study protocol No exclusions from second round reported based on first-round histologic outcomes	Women with CIN2+ histology at Round 1 excluded from analyses of Round 2 results

Table 5b. Colposcopy Referral, Retesting, and Treatment Protocols of RCTs of HPV Screening Strategies for Cervical Cancer Screening (KQ3)

	ASCCP‖	NTCC Phase II[112,113,209-211]	Finnish Trial[120,133,134,212,213]	NTCC Phase I[112,113,210,211]	POBASCAM[114,214]	Swedescreen[115,160,215]	ARTISTIC[117,197,216-218]
Criteria for immediate colposcopy referral	LSIL+ (includes LSIL, HSIL, ASC-H)¶ Immediate colposcopy also acceptable for ASC-US	IG: HPV+ CG: ASC-US+ LSIL+#	IG: HPV+&LSIL+ CG: LSIL+	IG: HPV+ ASC-US+** CG: ASC-US+ LSIL+#	IG: HSIL+ CG: HSIL+	IG: ASC-US+ HSIL+†† CG: ASC-US+ HSIL+††	IG: HSIL+ CG: HSIL+
Repeat testing protocol	ASC-US → either immediate colposcopy, repeat cyto at 6 and 12m, or HPV test→ if ≥ ASC or HPV+ → colposcopy HPV testing in women ≥ 30y: Cyto- → HPV test, if HPV+ → repeat cytology and HPV at 12m, if cytology- & HPV+ → colposcopy	IG: None CG: Baseline ASC-US (2 sites) → repeat cytology (timing NR), if LSIL+ → colposcopy	IG: Baseline HPV+ and CC- or ASC-US → repeat screening (including HPV) at 12 months → repeat ASC-US, or three consecutive HPV+ results if CC- → colposcopy CG: Baseline ASC-US → repeat screening at 12 months (referral criteria NR)	IG: Baseline HPV+ and cytology negative → repeat HPV and cytology in one year, if HPV+ or ASC-US+ → colposcopy‡‡ CG: Baseline ASC-US (2 sites)→ repeat cytology (timing NR), if LSIL+ → colposcopy	IG: Baseline HPV+, ASC-US, ASC-H or LSIL → repeat testing at 6 and 18 months, at 6 months- if abnormal CC and HPV+, or for HSIL+ alone → colposcopy, at 18 months- HPV+ or HSIL+ → colposcopy CG: Baseline ASC-US, ASC-H or LSIL → repeat CC at 6 and 18 months, at repeat any abnormality → colposcopy	IG: Baseline HPV+ (CC-) → repeat HPV and CC annually, persistent HPV+ (type specific) → colposcopy; CC: Baseline ASC-US or LSIL → repeat CC only (timing and referral criteria NR) CG: Baseline ASC-US or LSIL → repeat CC only (timing and referral criteria NR)	IG: HPV+ (LBC-): Baseline, repeat only HPV at 12 months, if HPV+ → patient choice of colposcopy at 12 months or repeat HPV at 24 months, if HPV+ at 24 months → colposcopy; LBC: Same as CG CG: Baseline ASC-US or LSIL → repeat LBC at 6 and 12 months, if 3 consecutive ASC-US → colposcopy, or if 2 consecutive LSIL → colposcopy
Treatment threshold		CIN2+	CIN1+ CIN2+§§	CIN2+	NR	High-grade CIN	CIN2+
Treatment		NR	LEEP	NR	NR	Conization, loop excision	Excision, ablation‖‖

Table 5c. Quality Rating and Limitations of RCTs of HPV Screening Strategies for Cervical Cancer Screening (KQ3)

	NTCC Phase II[112,113,209-211]	Finnish Trial[120,133,134,212,213]	NTCC Phase I[112,113,210,211]	POBASCAM[114,214]	Swedescreen[115,160,215]	ARTISTIC[117,197,216-218]
USPSTF Quality	Fair	Fair	Fair	Fair	Fair	Fair
Quality Issues	-Participants not blinded -Cytology may be relatively poor if community standards not good (14 labs) -Colposcopists, local histologists not blind to HPV results; but blinded central review. -Community colpos repeated if normal but —learly abnormal cytology"; no clear biopsies taken in negative colpos -Non-compliant women in Rd 1 not invited to Rd 2 (2.8% in IG vs 0.7% in CG)	-Single screening round thus far -Cytologist, colposcopists, and pathologists not blinded to HPV results; community colposcopy; no biopsies in normal colpos -Randomization scheme not reported -Eligibility not clear, except age	-Cytology may be relatively poor if community standards not good, especially for LBC (14 labs); were blind to HPV. -Colposcopists, histologists not blind to HPV results. -Community colpos repeated if normal but —learly abnormal cytology"; no clear biopsies taken in negative colpos. -Non-compliant women in Rd 1 not invited to Rd 2 (2.7% in IG vs 0.6% in CG).	-In Round 2, all women had HPV with cytology; doesn't really test repeat HPV screening. -Round 2 results for 2/3 of sample still not reported. -Blinding not reported for participants, but in place for cytology and HPV, not reported for histology.	-Cytology reading not described -Patient unblinding to HPV at year 3 due to high CIN2+/3+ in those HPV+. -Round 2 followup is limited to one year—doesn't include retesting results.	-Colposcopists aware of HPV+/cyto neg results. -No biopsies in neg colpos. -Incomplete Rd 2 screening and followup. -Round 2 data ignored CIN2+ histology following normal cytology to make diagnostic criteria the same in both arms—reduces impact of retesting (HPV+/cyto-) -Women linked to NHS registries only for cancer incidence & mortality, not intermediate outcomes as was done in the other trials

*NTCC Phase I and NTCC Phase II, maximum followup after invitation to Round 2 reported
†POBASCAM, followup among a subset of the population
‡Swedescreen, median followup years between enrollment and colposcopy
§ARTISTIC, maximum followup reported
‖ASCCP details for reference only: For HSIL, immediate LEEP is an alternative to colposcopy with endocervical assessment. ASCCP guidelines for adolescent women (20 years and younger), recommendations for AGC, and post-colposcopy management are not summarized here. May use HPV 16/18 genotyping for women ≥30 years who are cytology negative and HPV+, refer immediately to colposcopy if positive for HPV 16 or 18.
¶ASCCP guidelines: Pregnant women with LSIL may defer colposcopy, post-menopausal women with LSIL may follow ASC-US protocol

#NTCC Phase I and NTCC Phase II, colposcopy threshold varied by site: ASC-US+ (7 sites) or LSIL+ (2 sites)

**NTCC Phase I, colposcopy threshold varied by age
††Swedescreen, colposcopy threshold varied by site
‡‡NTCC Phase I, repeat testing protocol varied by age, currently reporting women aged < 35, older women had none
§§Finnish, treatment threshold varied by date and age
‖‖ARTISTIC, treatment method varied by site

ASC-H: atypical squamous cells cannot exclude HSIL; ASC-US: atypical squamous cells of undetermined significance; CC: conventional cytology; CG: control group; CIN: cervical intraepithelial neoplasia; cyto: cytology; HC2: Hybrid Capture 2; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; IG: intervention group; LBC: liquid based cytology; LEEP: loop electrosurgical excision procedure; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable, NR: not reported, NTCC: New Technologies for Cervical Cancer Screening; PCR: polymerase chain reaction, Rd: round, y: years

Table 6. Characteristics of RCTs of Cytology Testing With HPV Triage of Positive Cytology (KQ3)

	ALTS[116,176,219-222]	Bjerre[119]
Country	United States	Sweden
Total randomized and screened	5,060	674
Ages recruited	18-81	22-60
Older women	NR	IG: 172 CG: 162
Younger women	NR	IG: 165 CG: 175
Number of Rounds	1	1
Round Interval (y)	NA	NA
Followup	2 years	7 months
Screening Approach	IG: LBC w/ HPV (HC2) triage CG: LBC	IG: CC w/ HPV (HC2) triage CG: CC
Criteria for immediate colposcopy referral	IG: HPV+ (or missing), or HSIL+ CG: HSIL+	IG: HPV+ CG: ASC-US+
Repeat testing protocol	IG: Followup cytology at 6 month intervals (HPV results masked), HSIL → colposcopy CG: Followup cytology at 6 month intervals (HPV results masked), HSIL → colposcopy	None
Treatment threshold	CIN2+, in addition to women with persistent lesions (CIN1+ and cytology results from ≥ of the previous two visits showed LSIL or HPV+ASC-US)	All women with positive triage test
Treatment	LEEP	LEEP, laser conization
USPSTF Quality	Good	Good
Quality Issues	-Repeat cyolgoy threshold of HSIL for referral colposcopy versus ASC-US in recent guidelines	- Small sample size

ASC-US: atypical squamous cells of undetermined significance; CC: conventional cytology; CG: control group; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; IG: intervention group; LBC: liquid based cytology; LEEP: loop electrosurgical excision procedure; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable, NR: not reported

Table 7. Characteristics of Studies Examining Absolute Test Performance of Primary Screening With HPV Test Alone and Combination HPV and Cytology Testing (KQ3)

Study ID Years of study	Setting	Study Design	Primary Screening Test Evaluated	Primary Outcomes	Number of Patients	Patient Age	Test Positivity Rate	Prevalence of Disease (in women with colposcopy/ biopsy results)	USPSTF Quality
Bigras 2005[124] April 2002 to January 2004	Switzerland Private practice Routine screening	Consecutive series HC2 performed on residual LBC sample	Hybrid Capture 2	HSIL+	13,842	Mean: 44.4 yr (range 17-93) ≥30 years: 96.4%	HC2 (HR): 8.2% LBC (ASC-US+): 3.6%	CIN2: 1.5% CIN3: 3.7% AIS: 0.2% Invasive carcinoma: 0	Fair
Kulasingam 2002[122] December 1997 to October 2000	U.S. 3 Planned Parenthood clinics in Washington State Routine screening	Consecutive series Swab of cervix collected after cytology for HC2 or PCR testing After Jan 2000, HC2 performed on residual LBC sample	Hybrid Capture 2 & PCR	CIN2+, CIN3+	4,075	Mean: 25 yr (SD 5.7) <30 yr: 81% ≥30 yr: 19%	HC2 (HR): 28.4% PCR (HR): 18.3% LBC (ASC-US+): 16.6%	CIN2: 4.9% CIN3+: 8.6% CIN3+ (corrected for colposcopy attendance and verification bias): 3.2%	Good
CCCast[121,126] September 2002 to February 2005	Canada Medical practices in Quebec & Newfoundland Routine screening	RCT with 2 arms: 1) Focus on HPV: HC2 followed by CC 2) Focus on Pap: CC followed by HC2 Both screening tests included in each arm, order of collection was randomized	Hybrid Capture 2	CIN2+	5,020 Focus on Pap 4,957 Focus on HPV	30-39 yr: 38.5% 40-49 yr: 35.0% 50-59 yr: 20.4% 60-69 yr: 6.1%	HC2 (HR): 6.3% in Focus on HPV 5.8% in Focus on Pap CC (ASC-US+): 2.7% in Focus on HPV 3.0% in Focus on Pap	CIN2+: 3.0%	Fair

Study ID Years of study	Setting	Study Design	Primary Screening Test Evaluated	Primary Outcomes	Number of Patients	Patient Age	Test Positivity Rate	Prevalence of Disease (in women with colposcopy/ biopsy results)	USPSTF Quality
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127] September 1999 to May 2000	France Two public university hospitals and two private practices Routine screening	Consecutive series, split sample LBC slide prepared from CC sample and HC2 assay performed on residual sample from LBC	Hybrid Capture 2	CIN2+	1,323 HC2 1,757 CC & LBC	Mean (SD): 33.3 yr (11.1)	HC2 (HR): 16.02% LBC (ASC-US+): 12.1% CC (ASC-US+): 10.0%	CIN2 or CIN3: 2.0% Invasive cancer: 0.3%	Good
Cardenas-Turanzas 2008[125] October 1998 to November 2005	U.S. and Canada (cancer center & community hospital) Women recruited through advertising in local media	Consecutive series, split sample	Hybrid Capture 2	CIN2+	1,850	Mean: 46.7 yr	HC2: 7.9% CC (ASC-US+): 7.1%	CIN 2/3 or cancer: *Screening:* 1.9% *Diagnosis:* 25.9%	Fair
Petry 2003[123] December 1998 to December 2000	Germany 28 urban, suburban or rural, office-based gynecological practices Routine screening	Consecutive series HC2 sample collected following CC sample at same visit	Hybrid Capture 2	CIN2+, CIN3+	7,908	Mean: 42.7 yr 30-60 years: 94.6%	HC2 (HR): 6.4% CC (PapIIw+): 3.1%	CIN2+: 8.6% CIN3+: 6.9%	Fair

AIS: adenocarcinoma in situ; ASC-US: atypical squamous cells of undetermined significance; CC: conventional Papanicolaou test; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2; HPV: human papillomavirus; HR: high risk; HSIL: high-grade squamous intraepithelial lesion; LBC: liquid-based cytology; LSIL: low-grade squamous intraepithelial lesion; PapIIw: Munich cytology classification approximately equivalent to borderline/ASC-US; PCR: polymerase chain reaction; RCT: randomized controlled trial; SCC: squamous cell carcinoma; SD: standard deviation; U.S.: United States; USPSTF: United States Preventive Services Task Force

Table 8a. Results for RCTs of HPV Screening Strategies in Cervical Cancer Screening, Women ≥30 or 35 Years of Age (KQ3)

Parameter	Rd	NTCC Phase II[112,113,209-211]	Finnish Trial[120,133,134,212,213‡‡]	NTCC Phase I[112,113,210,211]	POBASCAM[114,214]	Swedescreen[115,160,215]	ARTISTIC[117,197,216-218]
N Randomized and Screened (All Ages)		49,196	71,337	45,174	44,938	12,527	24,510
Ages Recruited		25-60	25-65	25-60	30-56	32-38	20-64**
Screened Women aged ≥ 30-35y		35,471 (35-60y)	59,757 (35-65y)	33,364 (35-60y)	17,155 (30-56y)	12,527 (32-38y)	19,344 (30-64y)
Sample Size	**R1**	IG: 17,724 CG: 17,747	IG: 29,968 CG: 29,789	IG: 16,706 CG: 16,658	IG: 8,575 CG: 8,580	IG: 6,257 CG: 6270	IG: 14,507 CG: 4,837
	R2	IG: 17,401 CG: 17,658	NR	IG: 16,332 CG: 16,561	IG: 6,887 CG: 6,838	IG: 6,257 CG: 6,270	NR**
Screening Approach	**R1**	IG: HC2 CG: CC	IG: HC2 w/CC triage CG: CC	IG: HC2+LBC CG: CC	IG: PCR+CC CG: CC	IG: PCR+CC CG: CC	IG: HPV+LBC CG: LBC
	R2	IG: CC CG: CC	NA	IG: CC CG: CC	IG: PCR+CC CG: PCR+CC	IG: PCR+CC CG: CC	IG: HPV+LBC CG: LBC
Test Positivity	**B**	IG: 1,029 (5.8%) CG: 555 (3.1%)* 182 (1.0%)†	NR	IG: 1,789 (10.7%) CG: 594 (3.6%)* 212 (1.3%)†	NR	NR	NR
	R1	NR	IG: 258 (0.9%) CG: 293 (1.0%)	NR	IG: 56 (0.7%) CG: 54 (0.6%)	IG: 146 (2.3%)‡ CG: 150 (2.4%)	248 (1.3%)§
	R2	NR	NA	NR	IG: 38 (0.6%) CG: 50 (0.7%)	NR	IG: 47 (0.40%)# CG: 16 (0.41%)#
	C	NR	NA	NR	IG: 94 (1.1%) CG: 104 (1.2%)	NR	IG: 405 (2.2%)# CG: 121 (2.0%)#
Colposcopy Referrals‖‖	**B**	IG: 1,029 (5.8%) CG: 435 (2.5%)	NR	IG: 1,773 (10.6%) CG: 498 (3.0%)	NR	NR	NR
	R1	NR	IG: 258 (0.9%) CG: 293 (1.0%)	NR	IG: 201 (2.3%) **CG: 115 (1.3%)**	NR	IG: 707 (4.9%) CG: 197 (4.1%)
	R2	NR	NA	NR	IG: 87 (1.3%) **CG: 129 (1.9%)**	NR	IG: 160 (NR)** CG: 42 (NR)**
	C	NR	NA	NR	IG: 288 (3.4%) CG: 244 (2.8%)	NR	IG: 867 (6.0%) CG: 239 (4.9%)
Positive Predictive Value for CIN3+	**B**	0.80 (0.55-1.18)	NR	0.34 (0.21-0.54)	NR	NR	NR
	R1	NR	See footnote††	NR	NR	NR	**0.63 (0.44-0.90)**
	R2	NR	NR	NR	NR	NR	**0.32 (0.18-0.55)#**
	C	NR	NA	NR	NR	NR	**0.54 (0.44-0.66)#**

Parameter	Rd	NTCC Phase II[112,113,209-211]	Finnish Trial[120,133,134,212,213‡‡]	NTCC Phase I[112,113,210,211]	POBASCAM[114,214]	Swedescreen[115,160,215]	ARTISTIC[117,197,216-218]
Absolute Detection for CIN3+	**B**	NR	NR	NR	NR	NR	NR
	R1	IG: 52 (0.29%) CG: 22 (0.12%)	IG: 32 (0.11%) CG: 23 (0.08%)	IG: 52 (0.31%) CG: 33 (0.20%)	IG: 68 (0.79%) CG: 40 (0.47%)	IG: 72 (1.15%) CG: 55 (0.88%)	IG: 116 (0.80%) CG: 38 (0.79%)
	R2	IG: 3 (0.02%) CG: 13 (0.07%)	NR	IG: 5 (0.03%) CG: 11 (0.07%)	IG: 24 (0.35%) CG: 54 (0.79%)	IG: 16 (0.26%) CG: 30 (0.48%)	IG: 29 (0.25%)[#] CG: 18 (0.47%)[#]
	C	IG: 55 (0.31%) CG: 35 (0.20%)	NR	IG: 57 (0.34%) CG: 44 (0.26%)	IG: 92 (1.07%) CG: 94 (1.10%)	IG: 88 (1.41%) CG: 85 (1.36%)	IG: 262 (1.51%)[#] CG: 98 (1.77%)[#]
Relative Detection Ratio for CIN3+	**B**	NR	NR	NR	NR	NR	NR
	R1	**2.37 (1.44-3.89)**	1.38 (0.81-2.36)	**1.57 (1.02-2.43)**	**1.70 (1.15-2.51)**	1.31 (0.92-1.87)	1.02 (0.71-1.47)
	R2	**0.23 (0.07-0.82)**	NR	0.46 (0.16-1.33)	**0.45 (0.28-0.72)**	**0.53 (0.29-0.98)**	**0.53 (0.30-0.96)**[#]
	C	**1.57 (1.03-2.40)**	NR	1.30 (0.87-1.91)	0.98 (0.74-1.30)	1.04 (0.77-1.39)	0.85 (0.67-1.08)[#]
Relative Detection Ratio for CIN2+	**B**	NR	NR	NR	NR	NR	NR
	R1	**2.13 (1.51-3.00)**	1.36 (0.98-1.89)	**1.78 (1.30-2.44)**	**1.56 (1.14-2.13)**	**1.51 (1.13-2.02)**	1.21 (0.91-1.60)
	R2	**0.25 (0.10-0.68)**	NR	0.59 (0.28-1.24)	**0.53 (0.36-0.78)**	**0.58 (0.36-0.96)**	**0.63 (0.42-0.96)**[#]
	C	**1.58 (1.16-2.13)**	NR	**1.50 (1.13-1.98)**	1.00 (0.79-1.27)	1.17 (0.92-1.49)	0.99 (0.83-1.19)[#]
Invasive Cervical Cancer	**B**	NR	NR	NR	NR	NR	NR
	R1	IG: 4 (0.02%)[§§] CG: 2 (0.01%)[§§]	IG: 6 (0.02%)[#,,§§] CG: 4 (0.01%)[#,,§§]	IG: 2 (0.01%)[§§] CG: 6 (0.04%)[§§]	IG: 5 (0.06%) CG: 2 (0.02%)	NR	NR
	R2	IG: 0 (0%)[§§] CG: 3 (0.02%)[§§]	NR	IG: 0 (0%)[§§] CG: 4 (0.02%)[§§]	IG: 2 (0.03%) CG: 7 (0.10%)	NR	NR
	C	IG: 4 (0.02%)[§§] CG: 5 (0.03%)[§§]	NR	IG: 2 (0.01%)[§§] CG: 10 (0.06%)[§§]	IG: 7 (0.08%) CG: 9 (0.10%)	IG: 1 (0.02%) CG: 2 (0.03%)	IG: 8 (0.04%)[#,§§] CG: 4 (0.07%)[#,§§]

Bold indicates statistical significance
*NTCC Phase I and NTCC Phase II, colposcopy referral threshold varied by site: ASC-US+ (7 sites)
†NTCC Phase I and NTCC Phase II, colposcopy referral threshold varied by site: LSIL+ (2 sites)
‡Swedescreen, colposcopy referral threshold (ASC-US+ or HSIL+): only ASC-US+ reported
§ARTISTIC, colposcopy referral threshold (HSIL+) pooled across both arms
#ARTISTIC, all age data reported (n=15,542), incomplete round 2 followup
**ARTISTIC, sample size for age-specific data not reported as Round 2 is incomplete
†† Finnish Trial, PPV reported across three age-groups in IG: 35-44 [1.81 (0.84-3.89)], 45-54 [1.63 (0.57-4.65)], and ≥ 55 [1.13 (0.36-3.51)]; CG: referent
‡‡Finnish Trial, extended 5-year followup data for a subset of the screened population (n=38,670); PPV for CIN3+, 1.49 (0.98-2.26); absolute detection for CIN3+, IG: 59 (0.30%), CG: 33 (0.17%); relative detection ratio for CIN3+, 1.77 (1.16-2.74); invasive cervical cancers, IG: 6 (0.03%), CG: 3 (0.02%)
§§Invasive cervical cancers include adenocarcinoma and/or squamous cell carcinoma for NTCC Phase I, NTCC Phase I and ARTISTIC – all others ICC only
‖ ‖Colposcopy compliance reported in NTCC Phase I (IG: 1669, CG: 453) and NTCC Phase II (all women, IG: 1813, CG: 615)
ASC-US: atypical squamous cells of undetermined significance; B: baseline; C: cumulative; CC: conventional cytology; CG: control group; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2; HPV: human papillomavius; HSIL: high-grade squamous intraepithelial lesion; ;IG: intervention group; LBC: liquid-based cytology; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable; NR: not reported; NTCC: New Technologies for Cervical Cancer Screening; PCR: polymerase chain reaction; Rd: Round; R1: Round 1; R2: Round 2

Table 8b. Results for RCTs of HPV Screening Strategies in Cervical Cancer Screening, Women <30 or 35 Years of Age (KQ3)

Parameter	Rd	NTCC Phase II[112,113,209-211]	Finnish Trial[120,133,134,212,213]	NTCC Phase I[112,113,210,211]	ARTISTIC[117,197,216-218]
N Randomized and Screened (All Ages)		49,196	71,337	45,307	24,510
Ages Recruited		25-60	25-65	25-60	20-64
Screened Women ≤30-35 years of age		13,725 (25-34y)	11,580 (25-34y)	11,810 (25-34y)	5,166 (20-29y)
Sample Size	**R1**	IG: 6,937 CG: 6,788	IG: 5,869 CG: 5711	IG: 6,002 CG: 5,808	IG: 3,879 CG: 1,287
	R2	IG: 6,577 CG: 6,714	NA	IG: 5,761 CG: 5,769	NR[¶]
Screening Approach	**R1**	IG: HC2 CG: CC	IG: HC2 w/CC triage CG: CC	IG: HC2+LBC CG: CC	IG: HPV+LBC CG: LBC
	R2	IG: CC CG: CC	NA	IG: CC CG: CC	IG: HPV+LBC CG: LBC
Test Positivity	**B**	IG: 907 (13.1%) CG: 270 (4.0%)[*] 136 (2.0%)[†]	NR	IG: 530 (8.8%) CG: 261 (4.5%)[*] 129 (2.2%)[†]	NR
	R1	NR	IG: 166 (2.8%) CG: 127 (2.2%)	NR	215 (4.2%)[‡]
	R2	NR	NA	NR	NR
	C	NR	NA	NR	NR
Colposcopy Referral[‖‖]	**B**	IG: 907 (13.1%) CG: 244 (3.6%)	NR	IG: 712 (11.9%) CG: 237 (4.1%)	NR
	R1	NR	IG: 166 (2.8%) CG: 127 (2.7%)	NR	IG: 540 (13.9%) CG: 123 (9.6%)
	R2	NR	NR	NR	IG: 124 (NR)[¶] CG: 32 (NR)[¶]
	C	NR	NR	NR	IG: 664 (17.1%) CG: 115 (12.0%)
Positive Predictive Value for CIN3+	**B**	0.66 (0.31-1.40)	NR	0.80 (0.55-1.18)	NR
	R1	NR	0.70 (0.30-1.64)	NR	**0.50 (0.36-0.69)**
	R2	NR	NA	NR	NR
	C	NR	NA	NR	NR
Absolute Disease Detection for CIN3+	**B**	NR	NR	NR	NR
	R1	IG: 45 (0.65%) CG: 11 (0.16%)	IG: 10 (0.17%) CG: 11 (0.19%)	IG: 23 (0.38%) CG: 25 (0.43%)	IG: 117 (3.02%) CG: 42 (3.26%)
	R2	IG: 2 (0.03%) CG: 10 (0.15%)	NR	IG: 8 (0.14%) CG: 8 (0.14%)	NR

Parameter	Rd	NTCC Phase II[112,113,209-211]	Finnish Trial[120,133,134,212,213]	NTCC Phase I[112,113,210,211]	ARTISTIC[117,197,216-218]
	C	IG: 47 (0.68%) CG: 21 (0.31%)	NR	IG: 31 (0.52%) CG: 33 (0.57%)	NR
Relative Disease Rate for CIN3+	B	NR	NR	NR	NR
	R1	**4.00 (2.07-7.73)**	0.88 (0.38-2.08)	0.89 (0.51-1.57)	0.93 (0.65-1.31)
	R2	**0.20 (0.05-0.93)**	NR	1.00 (0.38-2.67)	NR
	C	**2.19 (1.31-3.66)**	NR	0.91 (0.56-1.48)	NR
Relative Disease Rate for CIN2+	B	NR	NR	NR	NR
	R1	**4.54 (2.95-6.99)**	1.29 (0.88-1.89)	**1.99 (1.35-2.92)**	1.07 (0.83-1.38)
	R2	**0.40 (0.17-0.95)**	NR	0.73 (0.34-1.60)	NR
	C	**2.80 (1.98-3.95)**	NR	**1.63 (1.16-2.28)**	NR
Invasive Cervical Cancer	B	NR	NR	NR	NR
	R1	IG: 1 (0.01%)[§§] CG: 0 (0%)[§§]	NR	IG: 0 (0%)[§§] CG: 1 (0.02%)[§§]	NR
	R2	IG: 0 (0%)[§§] CG: 0 (0%)[§§]	NR	IG: 0 (0%)[§§] CG: 2 (0.03%)[§§]	NR
	C	IG: 1 (0.01%)[§§] CG: 0 (0%)[§§]	NR	IG: 0 (0%)[§§] CG: 3 (0.05%)[§§]	NR

Bold indicates statistical significance
*NTCC Phase I and NTCC Phase II, colposcopy referral threshold varied by site: ASC-US+ (7 sites)
†NTCC Phase I and NTCC Phase II, colposcopy referral threshold varied by site: LSIL+ (2 sites)
‡ARTISTIC, colposcopy referral threshold (HSIL+) pooled across both arms
¶ ARTISTIC, sample size for age-specific data not reported as Round 2 is incomplete
#All age data reported, majority of participants were older women
§§Invasive cervical cancers include adenocarcinoma and/or squamous cell carcinoma
‖ ‖Colposcopy compliance reported in NTCC Phase I (IG: 666, CG: 219) and NTCC Phase II (all women, IG: 1813, CG: 615)

ASC-US: atypical squamous cells of undetermined significance; B: baseline; C: cumulative; CC: conventional cytology; CG: control group; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; IG: intervention group; LBC: liquid-based cytology; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable; NR: not reported; NTCC: New Technologies for Cervical Cancer Screening; PCR: polymerase chain reaction; Rd: Round; R1: Round 1; R2: Round 2

Table 9a. Absolute Test Performance By Age of Primary Screening With HPV Test Alone and Combination HPV and Cytology Testing Among Developed Countries Only, Women ≥30 Years of Age (KQ3)

Study Reference	Sample Size (N)	Sensitivity			Specificity			Positive Predictive Value			Negative Predictive Value		
		HC2	Cytology ASC-US+	HC2 & Cytology	HC2	Cytology ASC-US+	HC2 & Cytology	HC2	Cytology ASC-US+	HC2 & Cytology	HC2	Cytology ASC-US+	HC2 & Cytology
Detection of CIN3+													
Petry 2003[123]	7,908	97.3 (83.2-99.6)	46.0 (30.8-61.9)	100 (93.7-100)*	95.2 (93.4-96.5)	98.0 (96.7-98.8)	94.9 (93.1-96.2)*	8.7 (6.3-11.8)	9.7 (6.1-15)	8.4 (6.2-11.4)*	100 (55.3-100)	99.7 (98.8-99.9)	100 (99.1-100)*
Kulasingam 2002[122]	774	86.0 (59.7-96.9)	49.7 (32.9-71.5)	49.7 (32.9-71.5)†	83.0 (76.8-87.1)	86.4 (84.8-88.1)	94.7 (92.8-96.1)†	NR	NR	NR†	NR	NR	NR†
Detection of CIN2+													
Bigras 2005[124]	13,842	97.0 (91.8-99.4)	58.7 (48.6-68.2)	NR	92.4 (91.9-92.9)	96.9 (96.6-97.2)	NR	8.8 (7.3-10.6)	12.4 (9.6-15.6)	NR	99.98 (99.96-100)	99.75 (99.67-99.83)	NR
Cardenas-Turanzas 2008[125]	1,850	69 (41-89)	44 (20-70)	NR	93 (91-95)	94 (92 - 95)	NR	17 (95% CI NR)	12 (95% CI NR)	NR	99 (95% CI NR)	99 (95% CI NR)	NR
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]‖	3,080	96 (88-100)	65 (50-80)	76 (59-93)‡	85 (83-87)	98 (98-99)	97 (97-98)‡	NR	NR	NR‡	NR	NR	NR‡
Kulasingam 2002[122]	774	62.7 (31.4-93.2)	38.3 (19.3-63.3)	38.3 (19.3-63.3)†	83.0 (76.6-87.2)	86.4 (84.7-88.3)	95.0 (93.0-96.4)†	NR	NR	NR†	NR	NR	NR†
Mayrand 2007[121] Mayrand 2006[126]	9,977	97.4 (95% CI NR)	56.4 (95% CI NR)	100 (95% CI NR)§	94.3 (95% CI NR)	97.3 (95% CI NR)	92.5 (95% CI NR)§	7.0 (95% CI NR)	8.5 (95% CI NR)	5.5 (95% CI NR)§	100 (95% CI NR)	99.8 (95% CI NR)	100 (95% CI NR)§
Petry 2003[123]	7,908	97.8 (86.3-99.7)	43.5 (30.0-58.0)	100 (93.7-100)	95.3 (93.5-96.6)	98.0 (96.7-98.8)	93.8 (91.8-95.3)	10.9 (8.2-14.2)	11.4 (7.5-16.9)	8.6 (6.5-11.3)	100 (55.3-100)	99.7 (98.7-99.9)	NR

Table 9b. Absolute Test Performance By Age of Primary Screening With HPV Test Alone and Combination HPV and Cytology Testing Among Developed Countries Only, Women <30 Years of Age (KQ3)

Study Reference	Sample Size (N)	Sensitivity			Specificity			Positive Predictive Value			Negative Predictive Value		
		HC2	Cytology ASC-US+	HC2 & Cytology	HC2	Cytology ASC-US+	HC2 & Cytology	HC2	Cytology ASC-US+	HC2 & Cytology	HC2	Cytology ASC-US+	HC2 & Cytology
Detection of CIN3+													
Kulasingam 2002[122]	3,301	92.5 (83.5-97.3)	65.4 (51.9-79.1)	64.0 (51.1-77.6)†	70.1 (66.5-73.1)	81.5 (80.7-82.3)	87.6 (86.7-88.4)†	NR	NR	NR†	NR	NR	NR†
Detection of CIN2+													
Kulasingam 2002[122]	3,301	73.5 (53.3-87.7)	50.1 (35.2-62.2)	47.9 (34.1-60.0)†	71.1 (67.3-74.0)	82.1 (81.3-83.0)	88.3 (87.4-89.2)†	NR	NR	NR†	NR	NR	NR†

*Petry: HC2 and cytology reported as positive on either test with cytology threshold of Pap IIw+ (equivalent to ASC-US+) for CIN2+ and PapIII+ for CIN3+.
†Kulasingam: HC2 and cytology reported as ASC-US+ and hrHPV+
‡Coste: HC2 and cytology reported as HSIL+ or RLU/cut-off value ratio > 1.0 if ASC-US or AGUS.
§Mayrand: HC2 and cytology reported as Pap result of ASC-US+ or HPV ≥ 1 pg HPV DNA/ml
‖Coste: Data was not stratified by age, study included women > 18 years of age; average age was 33.3 years

ASC-US: atypical squamous cells of undetermined significance, AGUS: atypical glandular cells of undetermined significance, CC: conventional cytology, CI: confidence interval, CIN: cervical intraepithelial neoplasia, DNA: deoxyribonucleic acid, HC2: Hybrid Capture 2, HPV: human papillomavirus, hr: high-risk; LBC: liquid-based cytology, LSIL: low-grade squamous intraepithelial lesion, ml: milliliter, NR: not reported, RLU: relative light units

Table 10. Characteristics of Studies Examining Absolute Test Performance of Cytology Testing With HPV Triage of Positive Cytology (KQ3)

Study ID Years of Study	Setting	Study Design	Primary Screening Test Evaluated	Primary Outcomes	Number of Patients	Patient Age	Test Positivity Rate	Prevalence of Disease (in women with colposcopy/biopsy results)	USPSTF Quality
Andersson 2005[136] Dates NR	Sweden Gynecologic departments of three university hospitals of Stockholm 4-6 months after referral cytology Women with low-grade atypia (ASC-US or LSIL) detected at a population-based screening	Consecutive series, split sample HC2 assay performed on CC sample	Hybrid Capture 2	CIN2+, CIN3+	177	Mean: 34 yr (range 23-60)	All HC2 (HR): 65.5% CC (ASC-US+): 47.5% Referred with ASC-US HC2 (HR): 44.2% CC (ASC-US+): NR Referred with LSIL HC2 (HR): 74.4% CC (ASC-US+): NR	All CIN2: 15.3% CIN3: 6.2% Referred with ASC-US CIN2: 11.5% CIN3: 7.7% Referred with LSIL CIN2: 16.8% CIN3: 5.6%	Fair
Bergeron 2000[137] March 1996 to August 1998	France 41 participating gynecologists; number of clinics NR Within two months after referral cytology Women referred for ASC-US or LSIL smears in the Laboratoire Pasteur Cerba, a private laboratory	Consecutive series HC2 sample collected following CC sample at same visit	Hybrid Capture 2	CIN2+	378	Mean: 35 yr (range 15-75)	All HC2 (HR): 53.7% CC (ASC-US+): 49.7% Referred with ASC-US HC2 (HR): 43.2% CC (ASC-US+): 32.4% Referred with LSIL HC2 (HR): 58.1% CC (ASC-US+): 56.9%	All CIN2+: 6.9% Referred with ASC-US CIN2+: 10.8% Referred with LSIL CIN2+: 5.2%	Fair

Study ID Years of Study	Setting	Study Design	Primary Screening Test Evaluated	Primary Outcomes	Number of Patients	Patient Age	Test Positivity Rate	Prevalence of Disease (in women with colposcopy/biopsy results)	USPSTF Quality
DelMistro 2010[138] 2005-2007	Italy Five centers in Veneto region in Northeast Italy participating in organized cervical screening program	Comparison of: (1) immediate colposcopy, (2) repeat Pap, and (3) HPV test for triage of ASC-US All participants received all three tests at baseline and 12 months later Women with any positive screening test invited for repeat Pap and HPV test at 6 months	Hybrid Capture 2	CIN2+	749	Median Age: 42 yr (range: 25-64)	HPV+: 24.2% Pap (ASC-US+): 29.4%	CIN2: 1.9% CIN3: 2.0% ICC: None reported	Fair
Manos 1999[100] October 1995 to June 1996	U.S. Participants identified from cohort of 46,009 women belonging to Kaiser Permanente Medical Care Program, Northern California Region, who had routine cervical screening at 1 of 12 gynecology clinics at 4 participating medical centers	Consecutive series HC2 sample collected following CC sample at initial visit (referral cytology) Repeat CC collected at colposcopy examination and used to estimate results of a repeat	Hybrid Capture 2 (prototype)	HSIL+	973 HC2 957 CC	Median: 37 yr (range 15-78)	HC2 (HR): 39.5% CC (ASC-US+): 38.9%	HSIL (CIN2-3): 6.6% Invasive cancer: 0.1%	Good

Study ID Years of Study	Setting	Study Design	Primary Screening Test Evaluated	Primary Outcomes	Number of Patients	Patient Age	Test Positivity Rate	Prevalence of Disease (in women with colposcopy/biopsy results)	USPSTF Quality
	Median of 67 days (range 12-240 days) after referral cytology Women with initial ASC-US cytology results	cytology conducted within 6 months							

ASC-US: atypical squamous cells of undetermined significance; CC: conventional Papanicolaou test; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2; HPV: human papillomavirus; HR: high risk; HSIL: high-grade squamous intraepithelial lesion; LBC: liquid-based cytology; LSIL: low-grade squamous intraepithelial lesion; NR: not reported; U.S.: United States; USPSTF: United States Preventive Services Task Force

Table 11. Results of RCTs for Cytology Testing With HPV Triage of Positive Cytology (KQ3)

Parameter	ALTS[116,176,219-222]	Bjerre[119]
All ages		
N Randomized and Screened (All Ages)	5,060	674
Ages Recruited	18-81	22-60
Sample Size	IG: 1161 CG: 1164	IG: 337 CG: 336
Screening Approach	IG: LBC w/ HPV (HC2) triage CG: LBC	IG: CC w/ HPV (HC2) triage CG: CC
Test Positivity	HPV+: 1767 (50.7%) ASC-US+: 2019(57.9%)	IG: 207 (61.4%) CG: 148 (43.9%)
Colposcopy Referral	**IG: 645 (55.6%)** **CG: 143 (12.3%)**	IG: 208 (62%) CG: 138 (41%)
Positive Predictive Value for CIN3+	NR	0.80 (0.61-1.04)
Absolute Disease Detection for CIN3+	IG: 73 (6.3%) CG: 59 (5.1%)	IG: 72 (21.4%) CG: 60 (17.8%)
Relative Disease Rate for CIN3+	1.24 (0.88-1.73)	1.20 (0.88-1.63)
Relative Disease Rate for CIN2+	NR	**1.32 (1.04-1.67)**
Invasive Cervical Cancer	IG: 0 (0%) CG: 1 (0.09%)	IG: 0 (0%) CG: 1 (0.3%)
Women < 35 years of age		
Screened Women < 35 years of age	NR	IG: 165 CG: 175
Test Positivity	NR	IG: 126 (76.4%) CG: 88 (50.3%)
Colposcopy Referral	NR	NR
Positive Predictive Value for CIN3+	NR	NR
Absolute Disease Detection for CIN3+	NR	IG: 40 (24.2%) CG: 39 (22.3%))
Relative Disease Rate for CIN3+	NR	1.09 (0.38-2.08)
Relative Disease Rate for CIN2+	NR	**1.34 (1.00-1.79)**
Invasive Cervical Cancer	NR	IG: 0 (0%) CG: 0 (0.0%)
Women ≥ 35 years of age		
Screened Women ≥ 35 years of age	NR	IG: 172 CG: 162
Test Positivity	NR	IG: 75 (43.6%) CG: 60 (37.0%)
Colposcopy Referral	NR	NR
Positive Predictive Value for CIN3+	NR	NR
Absolute Disease Detection for CIN3+	NR	IG: 32 (18.6%) CG: 21 (13.0)

Parameter	ALTS[116,176,219-222]	Bjerre[119]
Relative Disease Rate for CIN3+	NR	1.44 (0.86-2.38)
Relative Disease Rate for CIN2+	NR	1.32 (0.89-1.97)
Invasive Cervical Cancer	NR	IG: 0 (0%) CG: 1 (0.62%)

Bold indicates statistical significance
ALTS: ASCUS-LSIL Triage Study; ASC-US, atypical squamous cells of undetermined significance; CC: conventional cytology; CIN: cervical intraepithelial neoplasia; CG: control group; HC2: Hybrid Capture 2; HPV: human papillomavirus; IG: intervention group; LBC: liquid-based cytology; NR: not reported; R1: Round 1

Table 12. Absolute Test Performance of Cytology Testing With HPV Triage of Positive Cytology (KQ3)

Study ID	Sensitivity						Specificity						False Positive Rate					
	Triage of ASC-US			Triage of LSIL			Triage of ASC-US			Triage of LSIL			Triage of ASC-US			Triage of LSIL		
	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC
Detection of CIN3+																		
Andersson 2005[136]	75.0 (19.4-99.4)	75.0 (19.4-99.4)	NR	100 (59.0-100.0)	71.4 (29.0-96.3)	NR	58.3 (43.2-72.4)	64.6 (49.5-77.8)	NR	27.1 (19.3-36.1)	50.0 (40.7-59.3)	NR	41.7 (27.6-56.8)	35.4 (22.2-50.5)	NR	72.9 (63.9-80.7)	50.0 (40.7-59.3)	NR
Detection of CIN2+																		
Andersson 2005[136]	60.0 (26.2-87.8)	60.0 (26.2-87.8)	NR	89.3 (71.8-97.7)	60.7 (40.6-78.5)	NR	59.5 (43.3-74.4)	66.7 (50.5-80.4)	NR	29.9 (21.0-40.0)	51.5 (41.2-61.8)	NR	40.5 (25.6-56.7)	33.3 (19.6-49.5)	NR	70.1 (60.0-79.0)	48.5 (38.2-58.8)	NR
Bergeron 2000[137]	83 (51.6-97.9)	66 (34.9-90.1)	92 (61.5-99.8)	93 (66.1-99.8)	100 (76.8-100.0)	100 (76.8-100.0)	62 (51.3-71.2)	71 (61.8-80.3)	46 (36.4-56.8)	44 (37.7-50.2)	45 (39.2-51.8)	32 (25.9-37.7)	38 (28.8-48.7)	29 (19.7-38.2)	54 (43.2-63.6)	56 (49.8-62.3)	55 (48.2-60.8)	68 (62.3-74.1)
Manos 1999[100]	89.2 (78.4-95.2)	76.2 (63.5-85.7)	NR	NA	NA	NA	64.1 (60.9-67.2)	63.8 (60.5-66.9)	NR	NA	NA	NA	35.9 (32.8-39.1)	36.2 (33.1-39.5)	NR	NA	NA	NA
DelMistro 2010[138]	93.1 (91.3-94.9)	74.1 (70.9-77.3)	100 (100-100)	NA	NA	NA	78.6 (75.7-81.6)	72.3 (69.0-75.6)	62.5 (58.9-66.0)	NA	NA	NA	21.4 (95% CI NR)	27.7 (95% CI NR)	37.5 (95% CI NR)	NA	NA	NA

Table 12. Absolute Test Performance of Cytology Testing With HPV Triage of Positive Cytology (KQ3) (cont.)

Study ID	Positive Predictive Value (95% CI)						Negative Predictive Value (95% CI)					
	Triage of ASC-US			Triage of LSIL			Triage of ASC-US			Triage of LSIL		
	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC	HC2	CC	HC2 & CC
Detection of CIN3+												
Andersson 2005[136]	13.0 (2.8-33.6)	15.0 (3.2-37.9)	NR	7.5 (3.1-14.9)	7.8 (2.6-17.3)	NR	96.6 (82.2-99.9)	96.9 (83.8-99.9)	NR	100 (89.1-100.0)	96.7 (88.7-99.6)	NR
Detection of CIN2+												
Andersson 2005[136]	26.1 (10.2-48.4)	30.0 (11.9-54.3)	NR	26.9 (18.2-37.1)	26.6 (16.3-39.1)	NR	86.2 (68.3-96.1)	87.5 (71.0-96.5)	NR	90.6 (75.0-98.0)	82.0 (70.0-90.6)	NR
Bergeron 2000[137]	20.8 (10.5-35.0)	22.2 (10.1-39.2)	17.2 (8.9-28.7)	8.4 (4.5-13.9)	9.2 (5.1-15.0)	7.5 (4.2-12.2)	96.8 (89.0-99.6)	94.7 (86.9-98.5)	97.9 (88.7-99.9)	99.1 (95.1-100.0)	100 (96.8-100.0)	100 (95.5-100.0)
Manos 1999[100]	15.1 (11.7-19.2)	12.9 (9.8-16.8)	NR	NA	NA	NA	98.8 (97.4-99.5)	97.4 (95.7-98.5)	NR	NA	NA	NA
DelMistro 2010[138]	14.9 (12.4-17.5)	9.5 (7.3-11.6)	9.4 (7.3-11.6)	NA	NA	NA	NR	NR	NR	NA	NA	NA

ASC-US: atypical squamous cells of undetermined significance; CC: conventional Papanicolaou test; CI: confidence interval; CIN: cervical intraepithelial neoplasia; HC2: Hybrid Capture 2; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable; NR: not reported

Table 13. Characteristics of HPV Harms Studies (KQ5)

Study ID	USPSTF Quality	Setting Study Design	Population Details
Kitchener 2007[139]	Fair	Manchester, England General practices in primary care within the National Cervical Screening Program Women with normal or mildly abnormal cytology who had been recruited into the ARTISTIC trial were mailed a booklet of questionnaires approximately two weeks after they had received the results of their baseline cytology Two study groups: HPV-revealed HPV-concealed	N: 2,508 Patient Age: NR
Maissi 2004[140] Maissi 2005[143]	Fair	England Two of the three centers taking part in the English HPV/LBC pilot study Cross sectional questionnaire sent within one week of research team being informed that smear test results had been sent. Second questionnaire sent six months after receipt of test results	N: 1,376 Baseline 1,011 Followup Patient Age: Baseline: Mean (SD) Normal: 40.2 yr (12.2) HPV-: 40.5 yr (11.3) HPV+: 31.6 yr (9.7) No HPV test: 35.4 yr (10.4) Followup: Mean (SD) Normal: 40.5 yr (12.1) HPV-: 41.6 yr (11.1) HPV+: 32.7 yr (9.8) No HPV test: 36.6 yr (11.1)
McCaffery 2004[141]	Fair	London, UK National Health Service well-woman clinic Cross sectional survey using postal questionnaire sent one week after receipt of HPV and cytology screening results	N: 271 Patient Age: Mean: 32 yr (SD 8.0, range 20-61) <30 yr: 55% 30-34 yr: 18% 35-39 yr: 10% ≥40 yr: 17%

Table 13. Characteristics of HPV Harms Studies (KQ5) (cont.)

Study ID	USPSTF Quality	Setting Study Design	Population Details
McCaffery 2010[142]	Fair	Australia 18 urban and rural family planning clinics across the country Multi-center RCT of triage testing Randomized to three arms: HPV: HPV testing (HC2) arranged as soon as possible IC: Choice of HPV or repeat smear, informed by decision aid RS: Repeat smear 6 months after randomization Baseline questionnaire assessing psychosocial wellbeing was conducted immediately after consent, close to receipt of first abnormal smear result Followup questionnaires conducted at regular intervals during the 12 months after triage testing Baseline questionnaire assessing psychosocial wellbeing was conducted immediately after consent, close to receipt of first abnormal smear result	N: 314 women randomized HPV: 104 IC: 104 RS: 106 235 (75%) included in primary analysis, 305 (97%) in sensitivity analysis Patient Age: 30 yr and over: 66% Under 30 yr : 34%

HC2: Hybrid Capture 2, HPV: human papillomavirus, IC: informed choice, LBC: liquid-based cytology, NS: not significant, RS: repeat smear; SD: standard deviation, USPSTF: United States Preventive Services Task Force, UK: United Kingdom, Wks: weeks, Yr: year

Table 14. Outcomes of HPV Harms Studies (KQ5)

Study ID	Timing of assessment after screening results given & comparison groups	Anxiety (STAI)	Distress (CSQ or GHQ)	Concern	Sexual health or relationships (SRS or PEAPS)	Quality of life (EuroQOL or SF-36)
McCaffery et al, 2004[141]	*1 week*					
	Normal cytology: HPV+ vs HPV-	Higher	Higher	NA	Worse feelings about past, present, future sexual partners*	NA
	Abnormal or unsatisfactory cyto: HPV+ vs HPV-	No difference	Higher	NA	Worse feelings about past/future sexual partners*	NA
Kitchener et al, 2007[139]	*2 weeks*					
	Normal cytology: known HPV+ vs unknown HPV+	No difference	No difference	NA	Lower sexual satisfaction with current partner	NA
	Mildly abnormal cytology: known HPV+ vs unknown HPV+	No difference	No difference	NA	No difference	NA
	Normal cytology: Known HPV+ vs known HPV-	Higher	Higher	NA	No difference	NA
	Mild abnormal cytology: Known HPV+ vs. known HPV-	No difference	No difference	NA	Higher sexual satisfaction with current partner	NA
Maissi et al, 2004, 2005[140]	*1 week*					
	Normal cytology: no HPV test Borderline cytology: no HPV test, HPV-, HPV+	Higher for HPV+ group	Higher for HPV+ group	Greater concern & higher perceived risk HPV+†	Not evaluated	No difference
	6 months					
	Normal cytology: no HPV test Borderline cytology: no HPV test, HPV-, HPV+	No difference	No difference	Greater concern and higher perceived risk abnormal pap no HPV test†	Higher level sexual health worries among women with abnormal pap who were HPV+	No difference
McCaffery et al, 2010[142]	*2 weeks*					
	HPV test (immediate) Repeat Cytology (6 mo.) Informed choice	No difference	No difference	More intrusive thoughts among HPV test group	No difference	No difference
	Over 1 year (average daily score)					
	HPV test (immediate) Repeat Cytology (6 mo.) Informed choice	No difference	Lower for HPV test group	Greater satisfaction with care in HPV test group	No difference	No difference

*Study specific assessment tool
†Scale not reported
CSQ: Cervical Screening Questionnaire, EuroQOL: European Quality of Life, GHQ: General Health Questionnaire, HPV: human papillomavirus; Mo: months; NA: not available; SF-36: Short Form 36; STAI: State-Trait Anxiety Inventory

Table 15. Summary of Evidence By Key Question

Number and Design of Studies	Major Limitations	Validity of Evidence	Summary of Findings
KQ1. When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?			
5 studies • 3 population-based cohort studies • 1 prospective cohort study • 1 case-control study	Lack of RCT level evidence, lack of information regarding the influence of risk factors on cervical cancer screening in young women	Overall fair quality Good consistency across studies Applicable to U.S.	Cervical cancer in teens is rare, whereas HPV infections and cytologic abnormalities are common and are usually transient. False positive cytology results are more common in women under age 25 (3.1 to 3.5%) than in women aged 26 to 39 (2.1 to 2.6%). Results from a large, case-control study (n=11, 901 women aged 20 to 69 years) found screening women under age 25 was not associated with a decreased incidence of cervical cancer diagnosed prior to the age of 30, although an impact on stage IB+ cervical cancer could not be ruled out. In this study, an overall protective effect of screening on invasive cervical cancer (ICC) incidence was not demonstrated until age 32.
KQ2. To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cytology?			
4 studies • 1 RCT of LBC + HPV vs. CC • 1 RCT of LBC vs. CC • 1 consecutive series, split-sample study • 1 prospective cohort study (derived from RCT)	RCTs provide relative test performance data comparing LBC and CC. One RCT was not directly designed to answer the KQ, but is supplemented by another larger RCT that was. Studies performed in nonU.S. primary care settings.	Overall good quality Good consistency across studies Mostly applicable to U.S. (especially RCTs)	In two RCTs (n=134,162 women aged 25 to 60 years), liquid-based cytology (LBC) and conventional cytology (CC) did not differ significantly at any cytologic threshold in measures of relative sensitivity or of absolute sensitivity or specificity for detection of CIN2+ or CIN3+. LBC yields a lower proportion of unsatisfactory slides than CC. Absolute test performance studies (n=7,404) largely confirm trial findings.
KQ3. What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV? (See also Tables 16a and 16b for age-specific round specific screening program detection for each HPV-enhanced primary screening trial)			
Primary screening with HPV test alone			
12 studies (7 in countries similar to U.S. in cervical cancer screening) • 2 RCTs of HC2 vs. CC (1 relevant to U.S.) • 1 RCT and 9 cross-sectional studies of absolute test performance of HC2 or HPV	Only about half (7/12) of studies were conducted in countries with population cervical cancer screening similar to U.S. (1 RCT; 6 observational/RCT of	One large fair-quality RCT (NTCC Phase II) of HC2 vs. CC in women aged 25 to 60 years (28% aged 25 to 34	After a single screening round in NTCC Phase II among 35,471 Italian women aged 35 to 60 years, about twice as many CIN3+ and CIN2+ were detected in the HC2 arm compared with CC. During the second screening round using CC in both arms, CIN3+ was relatively decreased in women initially screened with HC2 compared with cytology (0.23, 95%

Number and Design of Studies	Major Limitations	Validity of Evidence	Summary of Findings
PCR (6 relevant to U.S.)	absolute test performance). RCT didn't report outcomes as CIN2+ or CIN3+, but author provided data on request. RCT does not report cumulative data on false positives, relative PPVs, colposcopies or related harms, only cumulative disease detection. RCT tests one round of HPV screening only as second screening round is conventional cytology (CC) in both arms. Very limited evidence available on HC2 HPV primary screening in women under 30 years of age.	years), with a second round of CC only ; 6 fair- or good-quality cross-sectional studies. Consistently improved sensitivity or detection of CIN2+/CIN3+ with HPV testing vs. CC; consistently reduced test specificity. Uncertain screening program impact on possible harms, but likely worse in younger women. Fair applicability, primarily for women > 30 to 35 years. Small number of younger women in test performance studies and less than 1/3 of trial under 35 years.	CI 0.07 to 0.82). Relative cumulative detection of both CIN2+ and CIN3+ were increased about 57% in the HC2 screened arm. In 13,725 women aged 25 to 34 years, about four times as many CIN3+ and CIN2+ were detected after initial HC2 screening compared with cytology. During Round 2, CIN3+ was relatively decreased in the HC2 arm (0.20, 95% CI 0.05 to 0.93). Relative cumulative detection of CIN2+ and CIN3+ was about doubled. Experts suggest excess relative CIN2+ may reflect over-diagnosis. Cumulative colposcopies are not reported, however baseline referrals were more than doubled in HC2-screened women aged 35 to 60 years (5.8%) compared with CC only (2.5%). In younger women, baseline colposcopies were markedly increased with HC2 screening (13.1%) compared with CC (3.6%). Trial investigators pooled invasive cancers from these primary HC2 results (NTCC Phase II) with HC2-CC co-testing results (NTCC Phase I) due to insignificant statistical heterogeneity between trials.[113] Pooled results suggested decreased invasive cancers in women aged 35 years and older screened with HPV (6 total invasive cervical cancers in the HPV screening arms compared to 15 in the CC only arms [p=0.052]). However, cancer outcomes would ideally come from comparable screening strategies and reflect clearly similar opportunities for diagnosis through comparable delivery of colposcopies and/or long enough followup with registry linkages to allow disease ascertainment outside the screening program. For women over 30, one-time HC2 HPV test is relatively much more sensitive (40% or more) but less specific (3 to 5%) than cytology for the detection of CIN2+ and CIN3+. Much less evidence in women under 30, suggests HC2 is 23 to 27% more sensitive, but much less specific (11%) compared with cytology for the detection of CIN2+/3+.
HPV testing with cytology triage of positive HPV (reflex cytology)			
1 study • 1 RCT of HC2 with CC triage vs. CC triage alone (Finnish Trial)	Only one RCT with a single round of screening reported as of yet, although a second round	Fair quality One large RCT with a single round of	A very large trial (n=71,337) of screened Finnish women aged 25 to 64 years compared a single round of cytology triage of a positive HPV test with cytology alone for the detection of CIN2+. After 2 to 4 years, the use of cytology to triage positive

Number and Design of Studies	Major Limitations	Validity of Evidence	Summary of Findings
	is planned. Cumulative Impact on colposcopy referrals or PPV not reported.	screening reported, and 5 year followup recently reported in a subset of women (aged 30 to 64 years). Fair applicability to the U.S. (tests used); Finnish population is not multi-racial and has lower cervical cancer incidence and mortality	HC2 HPV tests resulted in identification of more CIN2+ lesions (RR 1.34, CI 1.04 to 1.72), with a trend towards more CIN3+ lesions (RR 1.22, 95% CI 0.78 to 1.92), than cytology alone at a threshold of LSIL. After 5 years of followup, CIN3+ was significantly increased in intention-to-screen analyses (1.44, 95% CI 1.01 to 2.05) as well as among women screened (1.77, 95% CI 1.16 to 2.74, including 11 ICC/ACIS in HPV arm and 6 ICC/ACIS in CC only arm). Time until detection of benefit is about one year for those referred to colposcopy immediately, but approximately 3 years for those undergoing repeat screening and surveillance. Almost half of cases of CIN3+ detected during extended followup came from women undergoing repeat screening and surveillance. In women 35 and older, baseline colposcopies were similarly small (1%) between arms, with higher repeat testing in HPV-cytology triage arm (7.2%) than CC (6.0%). Authors report simulated relative PPV, but need full Round 1 results and further rounds. In younger women, overall colposcopies were higher in both arms that in older women (2.8%), with twice the retesting in HPV (15.8%) than in CC. Evidence is somewhat supplemented by co-testing trial results since 3 of 4 RCTs retested for HPV+ results if cytology was below colposcopy threshold. However, these trials used different, higher cytology thresholds, and theoretically have a cytology testing safety net in place since cytology was done in all women.
Combination HPV and cytology testing (co-testing)			
4 RCTs (all in countries similar to U.S., within national cervical cancer screening) • 2 RCTs of HPV PCR + CC vs. CC alone (POBASCAM, Swedescreen) • 2 RCTs of HC2 + LBC vs. LBC or CC alone (NTCC Phase I, ARTISTIC)	Data apply primarily to women aged 30 and older. About 2/3 of data reflect HC2 usage, and 1/3 PCR. All trials use CC co-testing and for control group screening (except ARTISTIC). Trials used different screening/rescreening, retesting, and referral	Overall fair quality All report after two screening rounds, but three are incomplete for Round 2. Some unexplained inconsistency in results (see limitations) – may	European trials evaluated HPV-cytology co-testing versus cytology in 127,149 screened women aged 20 to 64 (16,976 younger than 30 to 35 years) through two rounds of screening within national screening programs. In women older than 30 years, no trials showed an impact on relative CIN3+ for HPV-cytology co-testing compared with cytology. Only one trial (NTCC Phase I) that referred co-tested women for ASC-US+ or HPV+ showed an impact on cumulative CIN2+ detection (1.55, 95% CI 1.25 to 1.93), which some believe may indicate over-diagnosis of regressive disease. All but NTCC Phase I showed a significant decrease in relative CIN3+ detection in Round 2 of screening among co-tested women compared with

Number and Design of Studies	Major Limitations	Validity of Evidence	Summary of Findings
	protocols, including variable colposcopy referral thresholds from ASC-US+ to HSIL+ that differ from U.S. recommended practice and from one another. Only 1 RCT referred women immediately for HPV+ results when cytology was below threshold. Thus, trials primarily test HPV screening with cytology triage. Only two trials used same testing strategy in Round 2 as in Round 1. Trials did not consistently report cumulative false positives, relative PPVs, or colposcopies. About two-thirds of data reflect HC2 use, one-third reflect HPV PCR use.	reflect incomplete reporting Protocols for colposcopy referrals, possible differences in compliance with referrals or retesting, or other differences. Conducted in countries applicable to the U.S. using HPV and cytology technologies available in the U.S.	cytology. Experts propose this as one surrogate for enhanced true disease impact in programs of ongoing cervical cancer screening. Impact on ICC was limited due to few cases and relatively short time frames. Two trials included women under 35 years, but only one (NTCC Phase I) reported complete age-specific results. HPV-cytology co-testing did not impact CIN3+ detection, but increased cumulative CIN2+ in younger women to about the same degree as in older women (RR 1.63, 95% CI 1.16 to 2.28). Indirect comparisons between NTCC Phase I and II in women 35 to 64 years suggest no additional benefit to co-testing above HPV screening alone, although immediate colposcopies were higher in co-testing (10.6%) than in cytology (3.0%) or indirectly compared to HPV primary screening (5.8%) in these trials all using the same cytology and HPV tests and thresholds. In the single trial that reported cumulative PPV/colposcopies (ARTISTIC) reflecting repeat co-testing, cumulative relative PPV was significantly reduced for CIN2+ or CIN3+ (1.86 false positive results with HC2-LBC co-testing for every one with LBC alone). Women in the co-testing arm under 35 years of age had twice (17.1%) the cumulative colposcopy referral rate as women 35 to 60 years (6.0%). Three of four co-testing trials (ARTISTIC, POBASCAM, Swedescreen) have not completely reported Round 2 (and therefore cumulative) screening results (i.e., relative detection, relative colposcopies, relative treatment rates, relative harms), thus limiting current interpretation. In cross-sectional studies of 17,885 women over 30 years, a single HC2 test with CC (co-testing) was more sensitive for CIN2+ or CIN3+, but less specific than CC alone. These studies varied in their definitions of a positive co-test. In two studies defining a positive cotest as HPV+ or ASC-US+, co-test was 44 to 56 percent more sensitive but 4 to 5 percent less specific than ASC-US+ cytology alone.

Number and Design of Studies	Major Limitations	Validity of Evidence	Summary of Findings
			The 5-year cumulative risk of CIN3+ lesions per woman screened was lower (0.1 percent) after a combined negative high-risk HPV test result and negative cytology or a negative HPV test alone (0.2 percent) than after negative cytology alone (0.8 percent). Large cohort studies suggest very low cumulative risk of CIN3+ in women HC2 negative with cytology less than ASC-US+: 0.16% after 4 years and 0.28% after six years—with similar 6-year results in HC2 negative women, but higher 6-year CIN3+ in cytology negative women (0.97%). After 10 years in 20,810 U.S. women (mean age 35.9 years), cumulative incidence of CIN3+ among HPV negative women was 0.87 (95% CI, 0.62 to 1.12) compared with cytology<ASC-US+ women (1.38, 95% CI 1.10 to 1.67).
Cytology testing with HPV triage of positive cytology (reflex HPV)			
6 studies • 2 RCTs of repeat cytology and HPV versus cytology alone • 1 prospective cohort and 3 cross-sectional studies of absolute test performance	RCTs do not address the most important clinical question regarding the value of a one time high-risk HPV test versus repeat cytology. Observational studies had small numbers but overall findings were consistent with other systematic reviews on this topic. No data available to assess impact of age on value of HPV triage of ASC-US or LSIL cytology.	Overall fair quality Protocol and colposcopy referral threshold inconsistency, particularly with U.S. practice across studies Fair to poor applicability of trials, good applicability of observational studies	A single HPV test is more sensitive than a single repeat cytology test for the detection of CIN2+ among women with ASC-US referral cytology and appears to have equal specificity. Testing strategies involving either 1) HPV testing plus cytology versus cytology alone or 2) HPV testing plus cytology once versus repeat cytology every 6 months for 2 years demonstrated a non-significant increase in CIN3+ detection among women with ASC-US referral cytology but resulted in more colposcopies. HPV testing is not useful for the triage of LSIL cytology due to the high proportion of positive HPV tests among women with LSIL cytologic diagnoses and referral of the majority of women to colposcopy.
KQ4. What are the harms of liquid-based cytology?			
No evidence other than that provided in studies included for Key Question 2, which show no difference in false positive rates between LBC and conventional cytology.			
KQ 5. What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?			
4 studies • 1 RCT • 1 prospective cohort study • 2 cross-sectional studies	Small studies and only two evaluating symptoms both in short term and long term. High	Overall fair quality Good consistency across studies	A positive result for HPV is associated with transient increases in anxiety and distress as well as increased concern about sexual health, but these symptoms do not persist at 6 month followup. No short-term differences in anxiety or distress were

Number and Design of Studies	Major Limitations	Validity of Evidence	Summary of Findings
	proportions of nonresponders on surveys.	Applicable to U.S.	shown among women randomized to triage of ASC-US Pap with HPV test versus repeat cytology versus choice of either HPV test or repeat cytology; however, women who underwent HPV testing had less distress at one-year followup.

ASC-US: atypical squamous cells of undetermined significance; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; KQ: key question; LSIL: low-grade squamous intraepithelial lesion; No: number; RCT: randomized controlled trial

Table 16a. Relative Detection Ratio By Screening Round for RCTs of HPV Screening Strategies in Cervical Cancer Screening (Women ≥30 or 35 Years)

Study ID Screening Approach N Total & by Age	Round	CIN3+	CIN2+	Invasive Cervical Cancer
Primary screening with HPV test alone				
NTCC Phase II[112,113,209-211] ***Round 1: Primary HC2 vs. CC*** ***Round 2: CC vs. CC*** Total: 49,196 <35: 13,725 >35: 35,471	Round 1	**↑ 2.37 (1.44-3.89)**	**↑ 2.13 (1.51-3.00)**	ICC-AD IG: 4, CG: 2
	Round 2	**↓ 0.23 (0.07-0.82)**	**↓ 0.25 (0.10-0.68)**	ICC-AD IG: 0, CG: 3
	Cumulative	**↑ 1.57 (1.03-2.40)**	**↑ 1.58 (1.16-2.13)**	ICC-AD IG: 4, CG: 5
HPV testing with cytology triage of positive HPV (reflex cytology)				
Finnish Trial[120,133,134,212,213] ***Round 1***: HPV with cytology triage vs. CC Total: 71,337 <30: 11,580 >30: 59,757 ***Extended Round 1 Followup***: Total: 38,670 30-39: 9,201 40-64: 29,469	Round 1	1.38 (0.81-2.36)	1.36 (0.98-1.89)	ICC-AD† IG: 6, CG: 4
	Extended Round 1 Followup (up to 5-years)	**↑ 1.77 (1.16-2.74)**		IG: 6 ICC/ 5 ACIS/ 11 total CG: 3 ICC/ 3 ACIS/ 6 total
	Cumulative			
Combination HPV and cytology testing (co-testing)				
NTCC Phase I[112,113,210,211] ***Round 1: Co-testing: HC2 + LBC vs. CC*** ***Round 2: CC vs. CC*** Total: 45,174 <35: 11,810 >35: 33,364	Round 1	**↑ 1.57 (1.02-2.43)**	**↑ 1.78 (1.30-2.44)**	ICC-AD IG: 2, CG: 6
	Round 2	0.46 (0.16-1.33)	0.59 (0.28-1.24)	ICC-AD IG: 0, CG: 4
	Cumulative	1.30 (0.87-1.91)	**↑ 1.50 (1.13-1.98)**	ICC-AD IG: 2, CG: 10
Swedescreen[115,160,215] ***Rounds 1 & 2: Co-testing: PCR + CC vs. CC*** Total: 12,527 <30: None >30: 12,527	Round 1	1.31 (0.93-1.86)	**↑ 1.51(1.13-2.01)**	Pooled data only IG: 1 ICC/ 4 ACIS-AD/ 5 total CG: 5 ICC/ 4 ACIS-AD/ 9 total
	Round 2	**↓ 0.53 (0.29-0.98)**	**↓ 0.58 (0.36-0.95)**	
	Cumulative	1.04 (0.77-1.39)	1.17 (0.92-1.49)	
POBASCAM[114,214] ***Round 1: Co-testing: PCR + CC vs. CC*** ***Round 2: PCR + CC vs. PCR + CC*** Total: 17,155 <30: None >30: 17,155	Round 1	**↑ 1.70 (1.15-2.51)**	**↑ 1.56 (1.14-2.13)**	IG: 5 ICC/ 3 ACIS / 8 total CG: 2 ICC / 1 ACIS / 3 total
	Round 2	**↓ 0.44 (0.27-0.71)**	**↓ 0.52 (0.36-0.77)**	IG: 2 ICC/ 0 ACIS/ 2 total CG: 7 ICC/ 3 ACIS/ 10 total
	Cumulative	0.98 (0.74-1.30)	1.00 (0.79-1.27)	IG: 7 ICC/ 3 ACIS/ 10 total CG: 9 ICC/ 4 ACIS/ 13 total

Study ID Screening Approach N Total & by Age	Round	CIN3+	CIN2+	Invasive Cervical Cancer
ARTISTIC[117,197,216-218] ***Rounds 1 & 2: Co-testing: HC2 + LBC vs. LBC*** Total: 24,510 <30: 5,166 >30: 19,344	Round 1	1.02 (0.71-1.47)	1.21 (0.91-1.60)	ICC-AD† IG: 8, CG: 4
	Round 2	**↓ 0.53 (0.30-0.96)***	**↓ 0.63 (0.42-0.96)***	
	Cumulative	0.85 (0.67-1.08)*	0.99 (0.83-1.19)*	

Bold: Statistically Significant
*ARTISTIC CIN3+ and CIN2+ pooled across all ages at Round 2 and Cumulative, majority of participants (79%) were women aged > 30 years
†Invasive cervical cancer cases pooled across all ages and rounds; majority of participants were women aged > 30 years

ACIS: Adenocarcinoma in situ; AD: adenocarcinoma; CC: Conventional cytology; CG: control group; HC2: Hybrid capture 2; ICC: invasive cervical cancer; IG: intervention group; LBC: liquid based cytology

Table 16b. Relative Detection Ratio By Screening Round for RCTs of HPV Screening Strategies in Cervical Cancer Screening (Women <30 or 35 Years)

Study ID Screening Approach N Total & by Age	Round	CIN3+	CIN2+	Invasive Cervical Cancer
Primary screening with HPV test alone				
NTCC Phase II[112,113,209-211] ***Round 1: Primary HC2 vs. CC*** ***Round 2: CC vs. CC*** Total: 49,196 <35: 13,725 >35: 35,471	Round 1	**↑ 4.00 (2.07-7.73)**	**↑ 4.54 (2.95-6.99)**	ICC-AD IG: 1, CG: 0
	Round 2	**↓ 0.20 (0.05-0.93)**	**↓ 0.40 (0.17-0.95)**	ICC-AD IG: 0, CG: 0
	Cumulative	**↑ 2.19 (1.31-3.66)**	**↑ 2.80 (1.98-3.95)**	ICC-AD IG: 1, CG: 0
HPV testing with cytology triage of positive HPV (reflex cytology)				
Finnish Trial[120,133,134,212,213] ***Round 1***: HPV with cytology triage vs. CC Total: 71,337 <30: 11,580 >30: 59,757 ***Extended Round 1 Followup***[‡]: Total: 38,670 (> 30 years)	Round 1	0.88 (0.38-2.08)	1.29 (0.88-1.89)	NR†
	Round 2			
	Cumulative			
Combination HPV and cytology testing (co-testing)				
NTCC Phase I[112,113,210,211] ***Round 1: Co-testing: HC2 + LBC vs. CC*** ***Round 2: CC vs. CC*** Total: 45,174 <35: 11,810 >35: 33,364	Round 1	0.89 (0.51-1.57)	**↑ 1.99 (1.35-2.92)**	ICC-AD IG: 0, CG: 1
	Round 2	1.00 (0.38-2.67)	0.73 (0.34-1.60)	ICC-AD IG: 0, CG: 2
	Cumulative	0.91 (0.56-1.48)	**↑ 1.63 (1.16-2.28)**	ICC-AD IG: 0, CG: 3
ARTISTIC[117,197,216-218] ***Rounds 1 & 2: Co-testing: HC2 + LBC vs. LBC*** Total: 24,510 <30: 5,166 >30: 19,344	Round 1	0.92 (0.65-1.31)	1.07 (0.83-1.38)	NR†
	Round 2	NR*	NR*	
	Cumulative	NR*	NR*	

Bold: Statistically Significant
*ARTISTIC CIN3+ and CIN2+ pooled across all ages at Round 2 and Cumulative, majority of participants (79%) were women aged > 30 years, see Table 18a
†Invasive cervical cancer cases pooled across all ages and rounds; majority of participants were women aged > 30 years, see Table 18a
‡Finnish Trial, extended 5-year followup data for a subset of the screened population (n=38,670); relative detection ratio for CIN3+, 1.77 (1.16-2.74); invasive cervical cancers, IG: 6 (0.03%), CG: 3 (0.02%)
ACIS: adenocarcinoma in situ; AD: adenocarcinoma; CC: conventional cytology; CG: control group; HC2: hybrid capture 2; ICC: invasive cervical cancer; IG: intervention group; LBC: liquid based cytology

Table 17. European Perspective in Interpreting Comparative HPV Screening Trials[162]

Suggested hierarchy of outcomes for new cervical cancer screening methods	
Rank	***Outcome***
1	Cervical cancer mortality (QALY gained)
2	Cervical cancer morbidity / Stage IB+ incidence
3	Cervical cancer incidence (including microinvasive)
4	Reduced CIN3+ incidence*
5	Increased detection of CIN3+ (or CIN2+)* • More CIN3+ detection overall (cumulative CIN3+) • More CIN2+ followed by less CIN3+ at subsequent screening • CIN2+ may exaggerate benefit through including overdiagnosis
6	Increased test positivity with increase, similar, or hardly reduced PPV*

*Surrogates may need to suffice for purposes of health policy, followed by modeling.

CIN: cervical intraepithelial neoplasia; PPV: positive predictive value; QALY: quality-adjusted life years

Table 18. What Data Are Reported in RCTs of HPV Screening Strategies in Cervical Cancer Screening

		Primary HPV Screening	HPV with Cytology Triage	Combined HPV/Cytology Co-testing			
		NTCC Phase II	Finnish Trial	NTCC Phase I	ARTISTIC	Swedescreen	POBASCAM
Test positives	B	X		X			
	R1		X		X	X	X
	R2				X		X
	C				X		X
Colpo referrals	B	X		X			
	R1		X		X		X
	R2				X		X
	C				X		X
PPV	B	X		X			
	R1		X		X		
	R2				X		
	C				X		
CIN 2+/3+ Detection	B						
	R1	X	X	X	X	X	X
	R2	X		X	X	X	X
	C	X		X	X	X	X
ICC	B						
	R1	X	X	X			X
	R2	X		X			X
	C	X		X	X	X	X

Table 18. What Data Are Reported in RCTs of HPV Screening Strategies in Cervical Cancer Screening (cont.)

	NTCC Phase II [112,113,209-211]	Finnish Trial[120,133,134,212,213]	NTCC Phase I [112,113,210,211]	ARTISTIC[117,197,216-218]	Swedescreen[115,160,215]	POBASCAM[114,214]
Additional Limitations / Considerations	• Different tests in R1 and R2: HC2 vs CC in R1, CC vs CC in R2 • Does not exclude women with CIN2+ in R1 from R2 • Cytology referral threshold differed by site (2 sites LSIL+, 7 sites ASC-US+)	• Only one screening round reported to date, second planned at 5 years • Study includes few participants age <30 (5% each arm)	• Different tests in R1 and R2: HC2 & LBC vs CC in R1, CC vs CC in R2 • Does not exclude women with CIN2+ in R1 from R2 • Cytology referral threshold differed by site (2 sites LSIL+, 7 sites ASC-US+) • Younger women had different referral protocol and larger and differential attrition	• Interval between R1 and R2 ranged from 26 to 54 months • Incomplete R2 FU, with 34% not yet attending R2 at time of analysis • For those attending R2, histology FU after screening shortened (<30 months) for 29% • Maximum FU from baseline of 7 years, but mean FU NR	• Mean FU 4.1 years, incomplete for R2 (only immediate colposcopy referrals complete) • Number of women with incomplete FU not quantified • R2 occurs outside study with registry FU only • Referral threshold differed by site (about half ASC-US+, half HSIL+) • Study includes ages ≥ 30 years only (range just 32-38)	• 5-year interval between rounds (3 in most trials) • 59% of participants had not completed 6.5 years' FU at time of analysis • For both R1 and R2, data reported only for those completing all 6.5 years' FU • In R2 all women received both HPV and cytology tests • Study includes ages ≥ 30 years only

§Data reported in age-specific strata

ASC-US: atypical squamous cells of undetermined significance; B: Baseline; C: Cumulative; CC: conventional cytology; CIN: cervical intraepithelial neoplasia; colpo: colposcopy; FU: followup; ICC: invasive cervical cancer; HC2: Hybrid Capture 2; HSIL: high-grade squamous intraepithelial lesion; HPV: human papillomavirus; LSIL: low-grade squamous intraepithelial lesion; NR: not reported; NTCC: New Technologies in Cervical Cancer, R1: Round 1; R2: Round 2; PPV: positive predictive value

Table 19. Cumulative Incidence of CIN3+ By Baseline Testing Status of RCTs and Cohort Studies With Long-Term Followup Data

Baseline Testing Status	European Cohort Study[167]† (all ages)	POBASCAM[114,214] Aged 30+ years	ARTISTIC[117,135,197,216-218] All ages and age-specific	Swedescreen[115,160,215] Aged 30+ years	Kaiser Permanente NW Cohort Study[168] (all ages)	Finnish Trial[134] Aged 30+ years	Danish Study[169] Aged 30+ years
HPV-/Cyto+ (FU yrs)	27/1000 (95% CI 6 to 60) (6 yrs)	2/1000 (5 yrs)	*All Ages* 8.3/1000 (95% CI 4.0 to 15.2) (6 yrs)	48/1000 (2 yrs)			
HPV- (FU yrs)	2.7/1000 (95% CI 1.2 to 4.5) (6 yrs)		*All Ages* 1.5/1000 (6 yrs) *< 30 yrs* 3.5/1000 (6 yrs) *≥ 30 yrs* 1.1/1000 (6 yrs)		8.7/1000 (95% CI 6.2 to 11.2) (10 yrs)	0.1/1000 (5 yr extended FU)	
HPV-/Cyto- (FU yrs)	2.8/1000 (95% CI 1.0 to 4.7) (6 yrs)	1/1000 (5 yrs)	*All Ages* 0.7/1000 (3 yrs)* 2.3/1000 (95% CI 1.4 to 3.6) (6 yrs)	0/1000 (2 yrs)	1.6/1000 (95% CI 0.8 to 2.4) (4 yrs)		0.8/1000 (3 yrs) 4/1000 (5 yrs) 17/1000 (10 yrs)
Cyto- (FU yrs)	9.7/1000 (95% CI 5.3 to 13.4) (6 yrs)		*All Ages* 2.9/1000 (6 yrs)		13.8/1000 (95% CI 11.0 to 16.7) (10 yrs)	0.4/1000 (5 yr extended followup)	
Cyto-/HPV+ (FU yrs)	100/1000 (95% CI 62 to 151) (6 yrs)	6/1000 (5 yrs)	*All Ages* 40.5/1000 (95% CI 29.8 to 53.6) (6 yrs)	39/1000 (2 yrs)			43/1000 (3 yrs) 93/1000 (5 yrs) 212/1000 (10 yrs)

*A lower proportion of baseline HPV negative/cytology negative women completed Round 2 screening (60%) than among groups with some test positivity at baseline. Therefore, results are not completely representative.
† Limited by verification bias (only test positives according to initial and rescreening protocols were uniformly assessed for disease outcomes)
CI: confidence interval; Cyto: cytology; FU: followup; HPV: human papillomavirus; NW: northwest; Yrs: years

Appendix A. Terminology and Abbreviations

Adenocarcinoma[223]: Cancer that begins in cells that line certain internal organs and that have gland-like (secretory) properties.

Baseline screening: Initial cross-sectional results from a screening episode, with associated histologic results from immediate colposcopy referrals. Does not include complete retesting results (repeat screens after an initial equivocal result) or associated histology. For example, in Phase 1 of the NTCC trial, baseline results included histologic lesions detected up to one year after initial colposcopy referral, but not lesions detected over the full three-year interval between screening rounds.

Cervical cancer[223]: Cancer that forms in tissues of the cervix (the organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests.

Cervix[223]: The lower, narrow end of the uterus that forms a canal between the uterus and vagina.

Colposcopy[223]: Examination of the vagina and cervix using a lighted magnifying instrument called a colposcope.

Cone biopsy[223]: Surgery to remove a cone-shaped piece of tissue from the cervix and cervical canal. Cone biopsy may be used to diagnose or treat a cervical condition. Also called conization.

Cryotherapy[223]: Any method that uses cold temperature to treat disease.

Cytology[223]: The study of cells using a microscope.

False positive: A patient with an abnormal screening test but a normal gold standard test for disease. Depending on the outcome of interest, the definition of a normal disease outcome will vary. For example, in analyzing the performance of a cytology screening test result of LSIL+ to predict CIN3+ detected by colposcopically-directed biopsy, false positives would be women with LSIL+ cytology and either normal colposcopy (no biopsy), normal biopsy, or biopsy showing CIN1 or CIN2.

Histology[223]: The study of tissues and cells under a microscope.

HPV testing[224]: Detects presence of HPV genetic material (DNA) high-risk for cervical cancer.

HPV vaccine[223]: A vaccine being studied in the prevention of human papillomavirus infection and cervical cancer. Infection with certain types of HPV increases the risk of developing cervical cancer. Also called human papillomavirus vaccine.

Liquid-based cytology[223]: A method for screening for cancerous or precancerous changes of the cervix performed by scraping cells from the cervix and rinsing the sampling device into a vial containing a liquid preservative.

Loop electrosurgical excision procedure[223]: A technique that uses electric current passed through a thin wire loop to remove abnormal tissue. Also called loop excision and LEEP.

Pap smear[223]: A method developed by Dr. George Papanicolaou for screening for cancerous or precancerous changes of the cervix performed by scraping cells from the cervix and fixing them on a glass slide. Also known as conventional cytology.

Primary cervical cancer screening test(s)[163]: A first test (historically cervical cytology) that, if abnormal and meets a pre-established threshold (such as LSIL+), leads to referral for a diagnostic procedure (usually colposcopy and biopsy).

Rescreening: The next routine screening episode after a negative screening test result.

Retesting[163]: After a primary cervical cancer screening test, those with abnormal results who do not reach the threshold for diagnostic referral go through a repeated protocol of follow-up screening with later colposcopy referral based on persistent or advancing abnormalities.

Round 1 screening: Screening test results (both initial Round 1 results and retesting results) and associated histology for the full duration of Round 1.

Round 2 screening: Screening test results (both initial Round 2 results and restesting results) and associated histology for the full duration of Round 2.

Appendix A. Terminology and Abbreviations

Screening: Testing asymptomatic individuals in order to detect disease at an earlier, more treatable stage and minimize adverse outcomes.

Screening interval (or rescreening interval): Time between routine screening episodes (e.g. three years).

Screening program: A comprehensive screening plan including routine screening intervals and protocols for retesting after equivocal tests and for referral to colposcopy, represented by the designs of national screening programs or of randomized controlled trials.

Squamous cell carcinoma[223]: Cancer that begins in squamous cells, which are thin, flat cells that look like fish scales. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts. Also called epidermoid carcinoma.

Triage test[163]: A test applied to those with a positive primary test to further select women before referral for a diagnostic procedure (colposcopy and biopsy).

List of acronyms and abbreviations

Abbreviation/Acronym	Phrase, term, name of instrument
AGC	Atypical glandular cells (specify endocervical or not otherwise specified [NOS])
AGUS	Atypical glandular cells of undetermined significance
ACIS	Endocervical adenocarcinoma in situ
ASC-H	Atypical squamous cells – cannot exclude HSIL
ASC-US	Atypical squamous cells of undetermined significance
CC	Conventional cytology
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CKC	Cold knife conization
CSQ	Cervical Screening Questionnaire
DR	Detection rate
ECC	Endocervical curettage
GHQW-12	General Health Questionnaire
HC2	Digene Hybrid Capture 2 high-risk HPV DNA test
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
hrHPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesion encompassing: moderate and severe dysplasia, CIN2, CIN3, and carcinoma in situ
ICC	Invasive cervical cancer
IQR	Interquartile range
LBC	Liquid-based cytology
LEEP	Loop electrosurgical excision procedure
LSIL	Low-grade squamous intraepithelial lesion encompassing: human papillomavirus/ mild dysplasia/CIN1
OR	Odds ratio
PCR	Polymerase chain reaction
PEAPS-Q	Psychosocial Effects of Abnormal Pap Smear Questionnaire
PPV	Positive predictive value
RCT	Randomized controlled trial
RFPP	Relative false positive proportion
RLU	Relative light unit
RR	Relative risk
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SONE	Strips of neoplastic endocervix
S-STAI-6	Short form of Spielberger State-Trait Anxiety Inventory
STI	Sexually transmitted infection
VIA	Visual inspection with acetic acid

Appendix B. Detailed Methods

Literature Search Strategy

For all key questions (KQs), we used existing systematic evidence reviews and meta-analyses to the extent possible and supplemented with primary systematic literature searches bridging the time period covered by the prior review. Results are presented in a cumulative fashion, incorporating the relevant studies from the prior review. We evaluated the studies included in the previous review by Hartmann and colleagues against the inclusion and exclusion criteria for the current review, and found only one study was eligible for inclusion.100 For all key questions, we initially searched for systematic reviews, meta-analyses, and evidence-based guidelines on cervical cancer screening in the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews (CDSR), PubMed, and the Health Technology Assessment database (HTA) from 2000 through 2007. Subsequent searches specific to each key question supplemented evidence found in the search of reviews and meta-analyses. Two reviewers independently examined abstracts from all searches for relevance to all key questions.

For KQs 1, 3, 4, and 5 (addressing age to begin screening, benefits of HPV testing, and harms of liquid-based cytology and HPV testing), we found no systematic reviews or meta-analyses that met our inclusion criteria. Therefore, we conducted primary literature searches to cover the time period since the previous USPSTF review (2000 through September 2010) in MEDLINE and the Cochrane Collaboration Registry of Clinical Trials (CCRCT) without restrictions on study designs. For KQ5, we also searched PsycINFO to capture adverse psychological effects of HPV testing. Search terms are listed in Appendix B, Table 1.

For KQ2, we found two systematic reviews of liquid-based cytology providing coverage through July 2003.97,98 We used these reviews as source documents and bridged their searches for liquid-based cytology. Therefore, for KQ2, we searched MEDLINE and CCRCT, without restrictions on study designs, from the beginning of 2003 through September 2010.

We also obtained articles from outside experts and through reviewing bibliographies of other relevant articles and systematic reviews. In addition to these searches for published trials, we searched the following sources for unpublished trials: Computer Retrieval of Information on Scientific Projects (CRISP), ClinicalStudyResults.org, Current Controlled Trials, ClinicalTrials.gov.

Inclusion and Exclusion Criteria

We developed the following set of inclusion/exclusion criteria that were applied to the key questions. Differences in inclusion, exclusion, and quality criteria precluded us from incorporating any of the existing systematic reviews or meta-analyses that were identified; however, the high-quality reviews and meta-analyses were used to check the completeness of our searches for primary studies.

Populations: This review addresses all females at risk for cervical cancer. Studies focusing only on high-risk populations (e.g., HIV-infected women) or women who have had a hysterectomy were excluded.

Settings: This review includes studies conducted in primary care or other settings generalizable to primary care (e.g., family planning clinics, STI clinics, school-based health clinics). No studies were excluded based on geographic location.

Screening interventions: This report addresses the following screening interventions:

1. Liquid-based cytology (obtained as a screening test or adjunct to screening rather than followup of documented disease)
2. Conventional cytology
3. Primary screening with HPV test alone
4. HPV testing with cytology triage of positive HPV (reflex cytology)
5. Combination HPV and cytology testing (co-testing)
6. Cytology testing with HPV triage of positive cytology (reflex HPV)

For KQ3, we focused on the high-risk HPV types as identified by Hybrid Capture 2 (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). We included studies that used HC2 or PCR (including Linear Array and Amplicor) to identify these 13 HPV types. We excluded studies that focused exclusively on HPV types not listed above. We also excluded studies of in-situ hybridization, p16 immunostaining, and viral load.

Outcomes: For KQ1, we included studies reporting age-specific incidence and prevalence of CIN2, CIN3, invasive carcinoma, or death. For KQs 2 and 3, we included studies reporting detection of histologically-confirmed CIN2,

CIN3, and invasive cervical cancer. For KQ4, we included studies of psychological distress and the consequences of false positive results (e.g., colposcopy/biopsy, unnecessary treatment). For KQ5, we included studies reporting the following harms of HPV testing: stigma and under-screening due to association with sexually-transmitted disease, partner discord, unnecessarily labeling some women as high risk, anxiety from and consequences of high-risk labeling, and undermined importance of cytologic screening. We did not systematically review the harms of treatment procedures such as LEEP, cryotherapy, and laser cone biopsy. Instead, we report the results of two systematic reviews on the harms of cervical cancer treatment procedures.

Study designs: For KQ1, addressing when to begin screening, we included RCTs, CCTs, population-based prospective and retrospective cohort studies, case-control studies, ecological-level reports correlating population-based rates of CIN and cancer detection with screening, systematic reviews, and meta-analyses. We only included studies in routine screening populations that present age-specific outcomes, report screening-related denominators, and use age intervals that allow for evaluation of young women separately.

For KQs 2 and 3, evaluating liquid-based cytology and HPV testing, we included studies that provided evidence regarding absolute and relative test performance. Our specific criteria are as follows:

1) To determine absolute test performance, we required that the reference standard of colposcopy and/or biopsy was systematically applied to all those screening positive and at least a random sample of screen negatives, with valid adjustment for verification bias when necessary. The reference standard must have been independent of the screening test (i.e., the screening test results were not used to establish the final diagnosis).
2) If a study did not test negatives appropriately with the gold standard, we could not use their absolute test performance estimates. However, if the study was a randomized controlled trial, compared test performance within the randomization scheme, and was of appropriate quality, then we included relative test performance measures.
3) Many studies reported theoretical test performance by estimating results for different screening and management programs than what was actually done in the trials. We determined these calculations could not be included if the assumptions required to estimate performance introduced potential threats to validity. We usually could not determine how to fairly assess whether these assumptions affected the validity of the calculated test performance, and if they did, what direction or degree of bias was introduced.

For HPV testing in primary screening, we included studies conducted in routine screening populations that compared HC2 or PCR to cytology (conventional or liquid based). For HPV triage of women with ASC-US or LSIL cytology, we included studies in women referred with a single ASC-US or LSIL cytology result that compared HPV triage to repeat cytology.

For KQs 4 and 5, addressing the harms of liquid-based cytology and HPV testing, we included RCTs, CCTs, case-control studies, systematic reviews, and high-quality observational studies.

Quality: We excluded studies that met criteria for “Poor” quality using the USPSTF design-specific criteria (Appendix B, Table 3).

Language: We excluded non-English language abstracts and articles.

Article Review and Data Abstraction

We reviewed a total of 4,262 abstracts and 641 complete articles for all KQs (Appendix B, Figure 1). While we conducted three searches to cover age to begin screening, liquid-based cytology, HPV testing, and harms of liquid-based cytology and HPV testing, we reviewed all abstracts for potential inclusion for any of the KQs. Two investigators independently reviewed all abstracts.

Two investigators independently reviewed articles against inclusion/exclusion criteria specific for each key question and marked articles for exclusion as soon as an exclusion criterion was met. Included studies that met all criteria were then independently rated for quality by two investigators, using the USPSTF’s study design-specific criteria[95] supplemented by National Institute for Health and Clinical Excellence (NICE) criteria for quality assessment[101] and the QUADAS tool for quality assessment of diagnostic accuracy studies[102] (Appendix B, Table 3). The Methods Work Group of the USPSTF has defined a three-category rating of “good,” “fair,” and “poor” based on these criteria. In general, a good study meets all criteria well. A fair study does not meet, or it is not clear that it meets, at least one criterion, but has no known important limitation that could invalidate its results. A poor study has important limitations. Articles were rated as good, fair, or poor by each rater, and disagreements were settled by consensus. Studies receiving a poor final quality rating were excluded from the review. Listings of excluded articles for each key question, along with the reason for exclusion, are in Appendix D Tables 1-5. A list of all exclusion criteria is in Appendix B Table 2.

Appendix B. Detailed Methods

There are 35 studies (reported in 66 articles) included in this review. For KQ1, we found 5 studies reported in 6 articles, none of which were included in the previous USPSTF report. For KQ2, we found 4 studies reported in 7 articles, none of which were included in the previous USPSTF report. For KQ3, we found 22 studies reported in 48 articles, 1 of which was included in the previous USPSTF report. For KQ4, we found no studies. For KQ5, we found 4 studies reported in 5 articles, none of which were included in the previous USPSTF report. One primary reviewer abstracted relevant information such as study setting, population, screening method, and outcomes into standardized evidence tables for each included article (Appendix C Tables 1-4). A second reviewer checked the abstracted data for accuracy and completeness.

Data Synthesis

We found no data for KQ4. Except for cytology testing with HPV triage of positive cytology (KQ3), data synthesis for all questions was qualitative because heterogeneity in the samples, settings, study designs, and instruments did not allow for quantitative synthesis. In the results text, studies are summarized qualitatively within the key questions. For KQ3 addressing HPV testing, studies are categorized by the four different uses of HPV testing in cervical cancer screening. In addition, randomized controlled trials providing primarily relative test performance measures within screening programs are described first, followed by studies reporting absolute test performance data. Studies from countries with less developed cervical cancer screening programs are discussed separately due to their lower applicability to the US population. Where possible, the data is provided stratified by age for two primary reasons: 1) the FDA has approved the use of HC2 in women 30 years and older as an adjunct to cytology to assess the absence or presence of high-risk HPV types,[70,71] and 2) the prevalence of high-risk HPV is much lower in women aged 30 and older than in women under age 30, dropping sharply with age from a prevalence of 35 percent for women aged 15-19 to <15 percent for women aged 30-39 (Figure 3). For evidence on the benefits of using HPV testing to triage women with ASC-US cytology, we estimated the combined difference in sensitivity and specificity between HPV and repeat conventional cytology. A random effects model was used to incorporate variation among studies. For the difference in sensitivity and specificity between HC2 and cytology, we used risk difference as the effect measure. Statistical heterogeneity was assessed by Cochran's Q test and the I^2 statistic.[103] All analyses were performed using Stata 10.0 (StataCorp, College Station, TX, 2007).

Many of the results reported in the evidence and summary tables are calculated from data provided in the articles. Such calculations are indicated in the evidence tables by '(calc)' following the results. In the randomized controlled trials, results were generally reported using women screened (instead of women randomized as in an "intention-to-screen" analysis) within each arm and each round. To be consistent, we abstracted from the articles or calculated results using the number of women screened within each randomized arm as the denominator unless noted as otherwise in the evidence tables. Consideration of program results only among women screened may be less appropriate to determine overall population impact, but acceptable when primarily evaluating the relative merits (including false positives and other adverse effects) of efficacious screening alternatives.

The trials reviewed generally applied the histology reference standard to screen-positive but not systematically to screen-negative participants. The numbers of true positive versus false positive screening test results are thus known (if not always fully reported), represented in the tables below as "a" and "b" respectively. However, the numbers of true versus false negative results ("d" and "c") and the total numbers of participants with (a+c) and without (b+d) disease are unknown (collectively, all the shaded cells below).

Intervention arm		Disease		
		+	—	
Test 1	+	a_1	b_1	a_1+b_1
	—	c_1	d_1	c_1+d_1
		a_1+c_1	b_1+d_1	$n_1 = a_1+b_1+c_1+d_1$

Absolute test performance in the intervention group:
$\text{Sensitivity}_1 = a_1/a_1+c_1$
$\text{Specificity}_1 = d_1/b_1+d_1$

Control arm		Disease		
		+	—	
Test 2	+	a_2	b_2	a_2+b_2
	—	c_2	d_2	c_2+d_2
		a_2+c_2	b_2+d_2	$n_2 = a_2+b_2+c_2+d_2$

Appendix B. Detailed Methods

Absolute test performance in the control group:
Sensitivity$_2$ = a_2/a_2+c_2
Specificity$_2$ = d_2/b_2+d_2

As a result, absolute sensitivity and specificity as defined above cannot be derived. However, clinically relevant relative test performance measures can be calculated. In a randomized trial where disease prevalence is expected to be the same between study arms, if the number of participants in each arm of the trial are the same then the number of participants with disease (a+c) should be the same in the intervention and control groups, i.e., $(a_1+c_1) = (a_2+c_2)$. The relative detection rate (RDR, which could also be called relative sensitivity) can then be calculated:

Relative detection rate (RDR) = $[a_1/(a_1+c_1)]/a_2/(a_2+c_2)] = a_1/a_2$

Where the number of participants in each arm of the trial differs, the RDR can be calculated instead as:

Relative detection rate (RDR) = $[(a_1/n_1)/(a_2/n_2)]$

Where
a_1 = cases of disease detected (or true positives) in the intervention arm
n_1 = number of participants in the intervention arm
a_2 = cases of disease detected (or true positives) in the control arm
n_2 = number of participants in the control arm

We used the latter formula, correcting for differences in number of participants between arms, in all our RDR calculations. Inclusion of CIN outcomes from opportunistic screening varied between trials, and was not always clearly reported. For example, detection rates (a/n) and relative detection rates reported for the POBASCAM trial used the numerator of all CIN or cancer cases detected in each study arm, regardless of screening test result, including cases detected by opportunistic screening in screen-negative women. ARTISTIC publications included only screen-detected CIN in reported detection rates, and we did the same in calculating age-specific RDRs. For the Finnish trial, initial publications appeared to include only screen-detected CIN in detection rates, though CIN outcomes were not reported by screening test result. Extended followup published in 2010 reported RDRs in both screen-positive women and all attendees, and we reported the results in all attendees as better representing the real-world effectiveness of the screening program. Swedescreen appeared to report screen-detected CIN in Round 1 RDRs, while including opportunistic screening from both rounds with Round 2.

Less often reported, but analogous to the RDR, is another relative test performance measure, which we have called the relative false positive proportion (RFPP). The RFPP is an estimate of the relative harms of screening tests, specifically the relative proportion of women referred unnecessarily to colposcopy.

Relative False Positive Proportion (RFPP) = $[(b_1/n_1)/(b_2/n_2)]$

Where
b_1 = false positives in the intervention arm (i.e., those with a positive screening test not found by histology to have true disease)
n_1 = number of participants in the intervention arm
b_2 = false positives in the control arm
n_2 = number of participants in the control arm

A similar calculation of "relative specificity" is not possible, as it would require information on true versus false negatives which these trials do not obtain (specifically, d_1 and d_2 or the true negatives in the tables above). We therefore neither abstracted nor calculated any specificity measure from the trials. Both absolute and relative positive predictive value (PPV) should be calculable for all trials since this measure describes screen-positive women only, for whom full histology data were obtained. Wherever reported data allowed, we abstracted or calculated both PPV measures as well.

Absolute PPV in the intervention group = $PPV_1 = a_1/(a_1+b_1)$

Where
a_1 = cases of disease detected (in screen-positive participants, i.e., true positives) in the intervention arm

a_1+b_1 = all participants in the intervention arm with a positive screening test

Absolute PPV in the control group = $PPV_2 = a_2/(a_2+b_2)$

Where
a_2 = cases of disease detected (in screen-positive participants, i.e., true positives) in the control arm
a_2+b_2= all participants in the control arm with a positive screening test

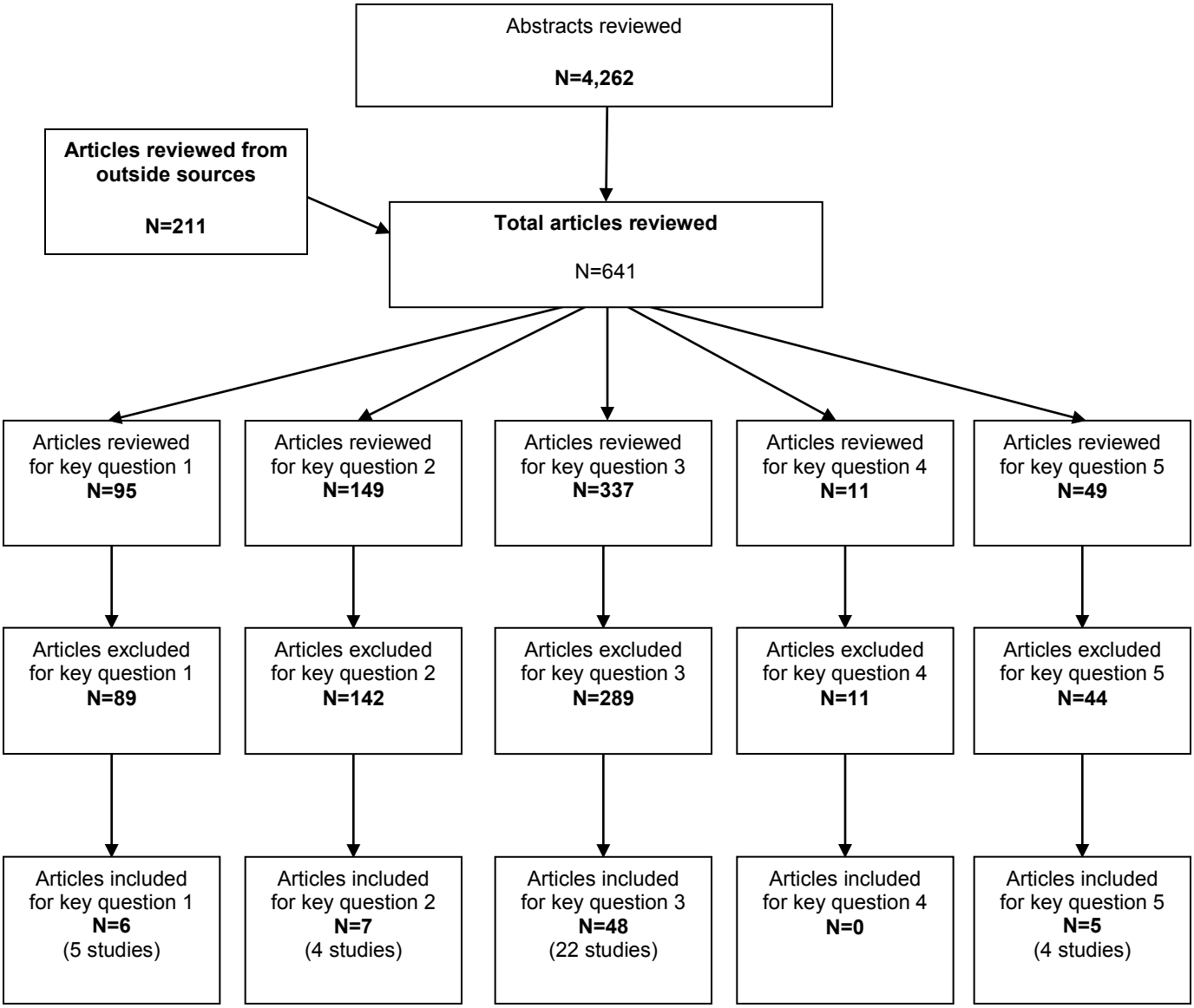
Relative PPV (intervention vs. control arm) = PPV_1/PPV_2

The randomized controlled trials of HPV testing include complicated, different protocols for followup retesting and referral to colposcopy among those with positive results not meeting the threshold for immediate colposcopy referral. In some cases, studies used different colposcopy referral thresholds; therefore, we performed PPV and RFPP calculations using the lowest referral criterion for cytology, HPV+ and/or ASC-US+, to define a positive screening test. This is a conservative strategy that may overestimate false positives for trials with higher initial referral criteria such as POBASCAM, ARTISTIC (both HSIL+), and the Finnish trial (LSIL+), though the relative test performance measures available from these trials may be less affected than would absolute test performance measures. A conservative definition of a positive screening test is consistent with the cumulative CIN outcomes reported in the trials and used in test performance calculations, including results from intensified followup as well as from immediate colposcopy. It is also consistent with clinical practice, in which an ASC-US+ cytology result or positive HPV test triggers additional followup, even if not immediate referral to colposcopy.

External Review Process

The USPSTF appointed eight liaisons to guide the scope and reporting of this review. The work plan for the review was sent to four experts on cervical cancer screening, whom we asked to comment on the general proposed approach, scope of the review, and adequacy of the identified questions. In addition, ten outside experts provided feedback on a draft version of this evidence synthesis.

Appendix B Figure 1. Search Results and Article Flow



Appendix B Table 1. Search Strategies

Systematic Reviews
Databases: CDSR, DARE, HTA, Pubmed
2000 to January 2007

1. "Uterine Cervical Neoplasms"[MeSH] OR "Uterine Cervical Dysplasia"[MeSH] OR "Cervical Intraepithelial Neoplasia"[MeSH] OR "Papillomavirus Infections"[MeSH] OR "Papillomaviridae"[MeSH]
2. "Mass Screening"[MeSH:NoExp] OR "Vaginal Smears"[MeSH]
3. screen*[tiab] OR "vaginal smear"[tiab] OR "vaginal smears"[tiab] OR Papanicolaou[tiab] OR Papanicolau[tiab] OR pap[tiab]
4. "cervical smear"[tiab] OR "cervical smears"[tiab]
5. 2 OR 3 OR 4
6. 1 AND 5
7. "cervical cancer screening"[tiab]
8. "hpv testing"[tiab]
9. "cervical screening"[tiab]
10. "Vaginal Smears"[MeSH]
11. "liquid based cytology"[tiab]
12. "human papillomavirus testing"[tiab]
13. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. 13 AND systematic[sb] Limits: English, Publication Date from 2000 to 2007

When to Begin Screening (KQ1)
Databases: Medline, CCRCT
2000 to September 2010

1. uterine cervical diseases/ or uterine cervical dysplasia/ or uterine cervical neoplasms/
2. Cervical Intraepithelial Neoplasia/
3. Vaginal Smears/
4. 1 or 2 or 3
5. mass screening/
6. screen$.ti,ab.
7. 5 or 6
8. 4 and 7
9. cervical cancer screening.ti,ab.
10. cervical neoplas$ screening.ti,ab.
11. cervical screening.ti,ab.
12. 8 or 9 or 10 or 11
13. Coitus/
14. (first adj4 intercourse).ti,ab.
15. (first adj4 coitus).ti,ab.
16. (initi$ adj4 intercourse).ti,ab.
17. (sexual$ adj4 activ$).ti,ab.
18. chronologic$ age.ti,ab.
19. different age$.ti,ab.
20. (young$ adj2 wom#n).ti,ab.
21. (age adj2 specific).ti,ab.
22. (beg#n$ adj4 screen$).ti,ab.
23. (start$ adj4 screen$).ti,ab.
24. (age adj4 beg#n$).ti,ab.
25. (age adj4 start$).ti,ab.
26. (age adj4 first).ti,ab.
27. age factors/
28. age distribution/
29. (old$ adj2 wom#n).ti,ab.
30. (stop$ adj4 screen$).ti,ab.
31. (age adj4 stop$).ti,ab.
32. age restrict$.ti,ab.
33. (withdraw$ adj4 screen$).ti,ab.
34. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 12 and 34
36. limit 35 to english language

37. limit 36 to yr="2000 - 2010"

Liquid-based Cytology Benefits (KQ2) & Harms (KQ4)
Databases: Medline, CCRCT
2003 to September 2010 (KQ2), 2000 to September 2010 (KQ4)

1. Cervix Uteri/cy [Cytology]
2. Uterine Cervical Diseases/pa, di [Pathology, Diagnosis]
3. Uterine Cervical Neoplasms/pa, di [Pathology, Diagnosis]
4. Cervical Intraepithelial Neoplasia/pa, di [Pathology, Diagnosis]
5. Uterine Cervical Dysplasia/pa, di [Pathology, Diagnosis]
6. Vaginal Diseases/pa, di [Pathology, Diagnosis]
7. Vaginal Smears/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Cytological Techniques/
10. Histocytological Preparation Techniques/
11. Cytodiagnosis/
12. 9 or 10 or 11
13. cervix.ti,ab,hw.
14. cervical.ti,ab,hw.
15. vaginal.ti,ab,hw.
16. 13 or 14 or 15
17. 12 and 16
18. ((cervical or cervix or vaginal) adj3 cytolog$).ti,ab.
19. 8 or 17 or 18
20. liquid$.ti,ab.
21. fluid based.ti,ab.
22. thinprep.ti,ab.
23. thin prep.ti,ab.
24. surepath.ti,ab.
25. autocyte.ti,ab.
26. cytorich.ti,ab.
27. monolayer.ti,ab.
28. mono layer.ti,ab.
29. thin layer.ti,ab.
30. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 19 and 30
32. "Sensitivity and Specificity"/
33. "Predictive Value of Tests"/
34. ROC Curve/
35. False Negative Reactions/
36. False Positive Reactions/
37. Diagnostic Errors/
38. "Reproducibility of Results"/
39. Reference Values/
40. Reference Standards/
41. Observer Variation/
42. Quality Control/
43. Quality Assurance, Health Care/
44. standards.fs.
45. specificit$.ti,ab.
46. sensitiv$.ti,ab.
47. predictive value.ti,ab.
48. accurac$.ti,ab.
49. false positive$.ti,ab.
50. false negative$.ti,ab.
51. miss rate$.ti,ab.
52. error rate$.ti,ab.
53. comparison$.ti.
54. compare$.ti.
55. comparing.ti.
56. comparative study.pt.

57. detection rate$.ti,ab.
58. diagnostic yield$.ti,ab.
59. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
60. 31 and 59
61. limit 60 to english language
62. limit 61 to humans
63. limit 61 to animals
64. 63 not 62
65. 61 not 64
66. limit 65 to yr="2003 - 2010"
67. harm$.ti,ab.
68. adverse$.ti,ab.
69. adverse effects.fs.
70. inadequate$.ti,ab.
71. 67 or 68 or 69 or 70
72. 31 and 71
73. limit 72 to english language
74. limit 73 to humans
75. limit 73 to animals
76. 75 not 74
77. 73 not 76
78. limit 77 to yr="2000 - 2010"
79. 66 or 78

HPV DNA Testing Benefits (KQ3) & Harms (KQ5)
Databases: Medline, CCRCT, PsycINFO
2000 to September 2010

1. Papillomavirus Infections/di [Diagnosis]
2. Papillomaviridae/ip [Isolation & Purification]
3. Alphapapillomavirus/ip [Isolation & Purification]
4. Human papillomavirus 16/ip [Isolation & Purification]
5. Human papillomavirus 18/ip [Isolation & Purification]
6. (hpv$ adj3 test$).ti,ab.
7. (hpv$ adj3 detect$).ti,ab.
8. (papillomavirus$ adj3 test$).ti,ab.
9. (papillomavirus$ adj3 detect$).ti,ab.
10. (papilloma virus$ adj3 test$).ti,ab.
11. (papilloma virus$ adj3 detect$).ti,ab.
12. DNA Probes, HPV/
13. hybrid capture.ti,ab.
14. hc2.ti,ab.
15. hc 2.ti,ab.
16. hcII.ti,ab.
17. hc II.ti,ab.
18. digene.ti,ab.
19. pcr.ti.
20. polymerase chain reaction$.ti.
21. polymerase chain reaction/
22. Reverse Transcriptase Polymerase Chain Reaction/
23. linear array.ti,ab.
24. amplicor.ti,ab.
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. papillomavirus$.ti,ab,hw.
27. papillomaviridae$.ti,ab,hw.
28. papilloma virus$.ti,ab,hw.
29. hpv$.ti,ab,hw.
30. 26 or 27 or 28 or 29
31. 25 and 30
32. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 31
33. cervix.ti,ab,hw.

Appendix B Table 1. Search Strategies

34. cervical.ti,ab,hw.
35. vaginal.ti,ab,hw.
36. (pap or Papanicolaou).ti,ab.
37. "Diagnostic Techniques, Obstetrical and Gynecological"/
38. female.sh.
39. 33 or 34 or 35 or 36 or 37 or 38
40. 32 and 39
41. "Sensitivity and Specificity"/
42. "Predictive Value of Tests"/
43. ROC Curve/
44. False Negative Reactions/
45. False Positive Reactions/
46. Diagnostic Errors/
47. "Reproducibility of Results"/
48. Reference Values/
49. Reference Standards/
50. Quality Control/
51. Quality Assurance, Health Care/
52. specificit$.ti,ab.
53. sensitiv$.ti,ab.
54. predictive value.ti,ab.
55. accurac$.ti,ab.
56. false positive$.ti,ab.
57. false negative$.ti,ab.
58. miss rate$.ti,ab.
59. error rate$.ti,ab.
60. comparison$.ti.
61. compare$.ti.
62. comparing.ti.
63. comparative study.pt.
64. detection rate$.ti,ab.
65. diagnostic yield$.ti,ab.
66. performance.ti,ab.
67. triage/
68. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69. 40 and 68
70. limit 69 to english language
71. limit 70 to yr="2000 - 2010"
72. limit 71 to humans
73. limit 71 to animals
74. 73 not 72
75. 71 not 74

Appendix B Table 2. Exclusion Criteria for Key Questions

Exclusion Criteria Applied to All Key Questions

Population:
- Studies focusing only on high-risk populations (e.g., HIV-infected women) or women who have had a hysterectomy

Setting:
- Screening not conducted in primary care or other setting with primary care-comparable population

Design:
- Editorials; Letters; Non-systematic reviews; Opinions

Quality:
- Does not meet quality criteria

No relevant outcomes
Precedes search period
Article covered by an included systematic review
Systematic review used as source document only
Non-English

Additional Exclusion Criteria Specific to Each Key Question

Key Question 1 - When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?

Population:
- Conducted solely in referred population

Design:
- Data not stratified by age
- Denominators for outcomes unknown
- Age intervals presented don't allow evaluation of young women separately
- Modeling study
- Ecological study reporting incidence/mortality in total population without link to screening
- Provides prevalence data only

Key Question 2 - To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?

Relevance:
- Does not focus on cervical cancer screening
- Focused on treatment of CIN, carcinoma in situ, or invasive cervical cancer
- Focused on methods to promote uptake and continuance of appropriate screening
- Focused on methods to improve follow up of abnormal screening findings
- Focused on comparison of tools for collection of cytologic samples (e.g., type of spatula, brush, or swab)
- Focused on patient education, satisfaction, or test acceptability

Population:
- Conducted solely in referred population or doesn't report outcomes in routine screening population separately

Design:
- Case-control study
- Does not systematically apply reference standard of colposcopy and/or biopsy
- Reference standard applied to screening test positives only (for studies of absolute test performance)
- Physician choice of cytology
- No comparison to conventional cytology

Screening intervention:
- Obtained as follow up of documented disease
- Home self-test
- See and treat
- Automated screening technologies

Key Question 3 - What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?

Relevance:
- Does not focus on cervical cancer screening

Appendix B Table 2. Exclusion Criteria for Key Questions

- Focused on treatment of CIN, carcinoma in situ, or invasive cervical cancer
- Focused on methods to promote uptake and continuance of appropriate screening
- Focused on methods to improve follow up of abnormal screening findings
- Focused on patient education, satisfaction, or test acceptability

Population:

- For primary screening, conducted solely in referred population or doesn't report outcomes in routine screening population separately
- For triage studies, includes women with repeated abnormal smears or abnormal smear other than ASC-US or LSIL

Design:

- Case-control study
- Does not systematically apply reference standard of colposcopy and/or biopsy
- Reference standard applied to screening test positives only (for studies of absolute test performance)
- Physician choice of cytology
- No comparison to cytology

Screening intervention:

- Home self-test
- See and treat
- HPV testing conducted to follow up on treatment
- In-situ hybridization
- p16 immunostaining
- Tests of viral load
- Focus on HPV types other than: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
- Hybrid Capture I

Key Question 4 - What are the harms of liquid-based cytology?

Relevance:

- Focus on harms of treatment procedures (e.g., LEEP, cryotherapy, laser cone biopsy)

Screening intervention:

- Obtained as follow up of documented disease
- Home self-test
- See and treat
- Automated screening technologies

Key Question 5 - What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?

Relevance:

- Focus on harms of treatment procedures (e.g., LEEP, cryotherapy, laser cone biopsy)

Screening intervention:

- Home self-test
- See and treat
- HPV testing conducted to follow up on treatment
- In-situ hybridization
- p16 immunostaining
- Tests of viral load
- Focus on HPV types other than: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
- Hybrid Capture I

Appendix B Table 3. Quality Rating Criteria

Design	United States Preventive Services Task Force quality rating criteria[95]	National Institute for Health and Clinical Excellence methodology checklists[101]	The QUADAS Tool[102]
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• The study addresses an appropriate and clearly focused question • A description of the methodology used is included • The literature search is sufficiently rigorous to identify all the relevant studies • Study quality is assessed and taken into account • There are enough similarities between the studies selected to make combining them reasonable	Not applicable
Case-control studies	• Accurate ascertainment of cases • Nonbiased selection of cases/controls with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Measurement of exposure accurate and applied equally to each group • Appropriate attention to potential confounding variables	• The study addresses an appropriate and clearly focused question • The cases and controls are taken from comparable populations • The same exclusion criteria are used for both cases and controls • What percentage of each group (cases and controls) participated in the study? • Comparison is made between participants and non-participants to establish their similarities or differences • Cases are clearly defined and differentiated from controls • Is it clearly established that controls are non-cases? • Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment • Exposure status is measured in a standard, valid and reliable way • The main potential confounders are identified and taken into account in the design and analysis • Have confidence intervals been provided?	Not applicable

Appendix B Table 3. Quality Rating Criteria

Design	United States Preventive Services Task Force quality rating criteria[95]	National Institute for Health and Clinical Excellence methodology checklists[101]	The QUADAS Tool[102]
Randomized controlled trials (RCTs)	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups is randomized • An adequate concealment method is used • Subjects and investigators are kept 'blind' about treatment allocation • The treatment and control groups are similar at the start of the trial • The only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid and reliable way • What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? • All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • Where the study is carried out at more than one site, results are comparable for all sites	Not applicable

Appendix B Table 3. Quality Rating Criteria

Design	United States Preventive Services Task Force quality rating criteria[95]	National Institute for Health and Clinical Excellence methodology checklists[101]	The QUADAS Tool[102]
Cohort studies	• Initial assembly of comparable groups employs consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes considered	• The study addresses an appropriate and clearly focused question • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed? • Comparison is made between full participants and those lost to follow-up, by exposure status • The outcomes are clearly defined • The assessment of outcome is made blind to exposure status • Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • The measure of assessment of exposure is reliable • Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Exposure level or prognostic factor is assessed more than once • The main potential confounders are identified and taken into account in the design and analysis • Have confidence intervals been provided?	Not applicable

Appendix B Table 3. Quality Rating Criteria

Design	United States Preventive Services Task Force quality rating criteria[95]	National Institute for Health and Clinical Excellence methodology checklists[101]	The QUADAS Tool[102]
Diagnostic accuracy studies	• Screening test relevant, available for primary care, adequately described • Study uses a credible reference standard, performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate result in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test	• The nature of the test being studied is clearly specified • The test is compared with an appropriate gold standard • Where no gold standard exists, a validated reference standard is used as a comparator • Patients for testing are selected either as a consecutive series or randomly, from a clearly defined study population • The test and gold standard are measured independently (blind) of each other • The test and gold standard are applied as close together in time as possible • Results are reported for all patients that are entered into the study • A pre-diagnosis is made and reported	• The spectrum of patients are representative of the patients who will receive the test in practice • Selection criteria are clearly described • The reference standard is likely to correctly classify the target condition • The time period between the reference standard and the index test is short enough to be reasonably sure that the target condition did not change between the two tests • The whole sample or a random selection of the sample receives verification using a reference standard of diagnosis • Patients receive the same reference standard regardless of the index test result • The reference standard is independent of the index test • The execution of the index test is described in sufficient detail to permit replication of the test • The execution of the reference standard is described in sufficient detail to permit its replication • The index test results are interpreted without knowledge of the results of the reference standard • The reference standard results are interpreted without knowledge of the results of the index test • The same clinical data is available when test results are interpreted as would be available when the test is used in practice • Uninterpretable/ intermediate test results are reported • Withdrawals from the study are explained

Appendix C Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)

Study ID	Objective	Study design	Setting	Prevalence	Number of patients Inclusion & exclusion criteria	Patient characteristics
Insinga 2004[104]	To examine routine cervical cancer screening diagnoses and outcomes on an age-specific basis in a US population	Observational cohort study 1997-2002 health plan inpatient and outpatient administrative and laboratory data for women enrolled at Kaiser Permanente Northwest (KPNW) in 1998 Incident episode of care associated with particular routine smear defined to begin with initial smear and end when at least nine months had passed without receipt of follow-up smear or other related cervical service	US KPNW histology files -- HMO serving greater Portland, OR region Women attending routine screening	NA - see outcomes	227,915 total 1998 KPNW female population 150,052 eligible sample with 2 years continuous health insurance enrollment over 1997-1998 103,476 outcome analysis sample with continuous health plan enrollment over 1997-2002	(Total KPNW enrolled population) **Ethnicity** White: approx. 90% Asian: 2.6% Hispanic: 2.3% African American: 1.6% Native American: 0.8% Other minority: 1.1%
Sigurdsson 2010[225] Sigurdsson 2007[105]	To evaluate the value of screening in the age group 20-34 by analyzing trends in preinvasive and invasive disease	Correlational study Data from Cancer Detection Clinic registry (preinvasive disease) and Cancer Registry of the Icelandic Cancer Society (invasive disease) Includes both organized and spontaneous screening results Screening program characteristics: 1964 organized screening began 1969 became nationwide, with screening at 2-3 year intervals in 25- to 69-year-olds 1979 intensified with improved call-recall system and improved quality assurance 1988 lower age limit decreased to 20 years	Iceland Nationwide screening program registry Women attending routine screening	NA - see outcomes	NA - see outcomes	NR

Appendix C Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)

Study ID	Funding source	Outcomes	Other outcomes	Quality rating	Applicability
Insinga 2004[104]	Merck Research Laborator-ies	**Outcomes of 1998 abnormal routine smears as % of routine smears** Age / Routine Smears (N) / CIN2 / CIN3 / False positive smear 15-19: 1,046 / 0.5 / 0.2 / 3.1 20-24: 852 / 0.6 / 0.2 / 3.5 25-29: 1,952 / 0.6 / 0.6 / 2.1 30-39: 5,992 / 0.3 / 0.4 / 2.6 40-49: 8,405 / 0.1 / 0.1 / 2.4 50-59: 7,162 / 0.1 / 0.0 / 2.3 60-69: 3,543 / 0.0 / 0.0 / 1.6 70-79: 1,657 / 0.0 / 0.1 / 1.8 80+: 288 / 0.0 / 0.0 / 2.1 Overall: 30,936 / 0.3 / 0.2 / 2.4 Only 15 cases of invasive cancer so age-specific rates not reported	**Screening attendance in 1998** Age / Screening per 1,000 female enrollees 15-19: 217.0 20-24: 468.0 25-29: 649.9 30-39: 508.7 40-49: 403.4 50-59: 360.8 60-69: 280.7 70-79: 164.1 80+: 53.3 Overall: 294.7	Fair	Good
Sigurdsson 2010[225] Sigurdsson 2007[105]	NR	**Incidence of invasive cancer per 100,000 women in population** Time Period / Age / Incidence 1964-1988: 20-24: 2.1 25-29: 11.8 30-34: 21.4 35-39: 38.5 1989-2008: 20-24: 2.8 25-29: 16.6 30-34: 20.3 35-39: 22.5* Time Period / Age / Stage IA / Stage IB / Stage IIA+ 1964-1988: 20-29: 2.7 / 2.7 / 1.1 20-34: 4.7 / 3.6 / 2.4 1989-2008: 20-29: 6.6* / 2.8 / 0.2 20-34: 8.9* / 4.0 / 0.2* *Significant rate difference between time periods **Detection rate of CIN2 and CIN3 per 1,000 women screened** Age / Time Period / Women Screened (N) / CIN2 N / CIN2 Rate / CIN3 N / CIN3 Rate 20-24: 1979-1988: 11,658 / 30 / 2.6 / 94 / 8.1 1989-2003: 36,224 / 253 / 7.0 / 522 / 14.4 25-29: 1979-1988: 22,123 / 66 / 2.9 / 430 / 19.4 1989-2003: 38,921 / 179 / 4.6 / 928 / 23.8 30-34: 1979-1988: 21,077 / 35 / 1.7 / 403 / 19.1 1989-2003: 40,062 / 108 / 2.7 / 690 / 17.2 Data not reported for 2004-2008	**Screening attendance** 1979-1988 Age 20-24: 23% Age 25-29: 62% Age 30-34: 72% 1989-2003 Age 20-24: 62% Age 25-29: 78% Age 30-34: 82% 2008 Age 20-24: 51% Age 25-39: 63% Age 30-34: NR	Fair	Good

Appendix C Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)

Study ID	Objective	Study design	Setting	Prevalence	Number of patients Inclusion & exclusion criteria	Patient characteristics
Peto 2004[32]	To describe the relationship between HPV detection at entry and cytologic and histologic followup	Prospective cohort study Recruitment between 1988 and 1993 Smear and histology results in study database updated from laboratory records at 6-monthly intervals during recruitment and through 1998 for histology results Date of diagnosis defined as date of first abnormal smear in 2 years preceding histological confirmation of CIN2, CIN3, or cancer HPV at entry assayed in age- and period-stratified random sample	UK Over 100 general practitioners and screening clinics in Greater Manchester area who used Christie Hospital cytology laboratory Women attending routine screening	**High-risk HPV prevalence** (in random cohort of 6,462 HPV-typed women) Age / N / % 15-19 / 69 / 20.4 20-24 / 92 / 18.2 25-29 / 93 / 14.4 30-34 / 86 / 6.8 35-39 / 47 / 4.9 40-44 / 28 / 2.9 45-49 / 15 / 2.9 50-54 / 29 / 2.6 55-69 / 1 / 0.9 Overall / 460 / 7.1	54,060 women provided samples 49,655 met inclusion criteria **Inclusion:** Women of any age attending for routine screening **Exclusion:** Inadequate entry smear (3,391), previous CIN3 (505), abnormal smear in preceding year (509)	NR

Study ID	Funding source	Outcomes	Other outcomes	Quality rating	Applicability
Peto 2004[32]	Cancer Research UK	**Prevalence of CIN2 and CIN3+ as % of total smears** Age at smear / CIN2 Prevalence (n) / CIN2 OR (95% CI) / CIN3 Prevalence (n) / CIN3 OR (95% CI) 20-24 / 0.59% (56) / 1.15 (0.79-1.68) / 0.69% (65) / 0.84 (0.61-1.15) 25-29 / 0.57% (63) / 1.00 / 0.96% (107) / 1.00 30-34 / 0.48% (42) / 0.81 (0.54-1.20) / 1.23% (107) / 1.18 (0.90-1.55) 35-39 / 0.42% (31) / 0.68 (0.44-1.05) / 0.78% (57) / 0.71 (0.51-0.98) 40-44 / 0.31% (21) / 0.48 (0.29-0.80) / 0.67% (45) / 0.58 (0.40-0.82) 45-49 / 0.08% (4) / 0.17 (0.04-0.32) / 0.37% (19) / 0.30 (0.19-0.50) 50-54 / 0.24% (10) / 0.35 (0.18-0.68) / 0.28% (12) / 0.23 (0.13-0.42) 55+ / 0.04% (3) / 0.05 (0.02-0.16) / 0.20% (16) / 0.15 (0.09-0.26) Overall / 0.38% (230) / 0.70% (428)	**Annual incidence of new cases of CIN3+ in women with a screening interval of less than 5 years following a normal smear** (estimated by dividing number of cases by woman-years of followup since last smear) Age / Incidence per 1,000 per year 15-19 / 1.56 20-24 / 2.22 25-29 / 4.07 30-34 / 3.67 35-39 / 2.44 40-44 / 1.53 45-49 / 0.85 50-54 / 0.76 55-59 / 0.58 60-64 / 0.19 65-69 / 1.39	Fair	Good

Appendix C Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)

Study ID	Objective	Study design	Setting	Prevalence	Number of patients Inclusion & exclusion criteria	Patient characteristics
Woodman 2001[106]	To describe the natural history of incident HPV infection and its temporal relation to the occurrence of cytologic abnormality and development of high-grade CIN	Prospective cohort study Recruitment between 1988 and 1992 At study entry, obtained risk factor profile and cervical smear; women asked to reattend at six month intervals for updated risk factor profiles and further cervical and serum samples; median number of visits = 4; median duration of followup = 29 months Women with cytologic abnormalities referred for colposcopy and biopsy; colposcopic and cytologic surveillance maintained in these patients; treatment postponed until histological evidence of CIN2+, at which point women left study All stored cervical samples tested for HPV using PCR after clinical followup had ended; tested for 2 low-risk types (6 or 11) and 6 high-risk types (16, 18, 31, 33, 52, and 58); additional tests assigned numerical types not identified by type-specific PCR	UK One Birmingham Brook Advisory Centre Women who had recently become sexually active	(during followup) **HPV+ (any):** 407/1,075 (37.9%) **HPV+ (HR):** 276/1,075 (25.7%) **CIN2:** 14/1,075 (1.3%) **CIN3:** 14/1,075 (1.3%)	2,011 enrolled 1,075 in final sample **Inclusion:** Aged 15-19 years **Exclusion:** Abnormal smear at entry (148), HPV+ at entry (244), HPV+ and abnormal smear at entry (138), provided only 1 sample evaluable for cytology & HPV testing (406)	**Mean Age (SD):** 17.5 (1.2) **Ethnicity** White: 94% Afro-Caribbean: 3% South Asian: 2% Other: 0.2% **Education:** NR **Socioeconomic Class (Father's Occupation)** Professional: 6% Intermediate: 23% Skilled, Non-manual: 7% Skilled, Manual: 37% Partly Skilled: 8% Unskilled: 2% Armed Services: 0.1% Unoccupied: 5% Inadequately Described: 11% **HIV+:** NR **Attended STD Clinic:** 2% **Smoking** Non-smoker: 59% Ex-smoker: 9% Smoker: 33% **Median duration of sexual activity before study entry:** 1 year (range 0-7)

Study ID	Funding source	Outcomes	Other outcomes	Quality rating	Applicability
Woodman 2001[106]	Cancer Research Campaign	**Cumulative risk at three years (95% CI)** Any HPV type: 43.8 (40.1-47.5) HPV 16: 10.5 (8.3-12.7) HPV 18: 6.6 (4.8-8.4) Any cytologic abnormality: 28 (25-32) Incident cytologic abnormality after first detection of HPV: 33 (26-40) CIN2+ (after any type of HPV infection): 7.8 (2.7-22.0) CIN2+ (after HPV 16 infection): 8.5 (3.7-19.2)* CIN2+ (after HPV 18 infection): 3.3 (1.4-8.1)*	**Median duration of detectability (IQR)** Any HPV type: 13.7 months (8.0-25.4) HPV 16: 10.3 months (6.8-17.3) HPV 18: 7.8 months (6.0-12.6) **Median duration of first episode of cytologic abnormality (IQR):** 8.7 months (5.8-13.8) **Median time to diagnosis of CIN2+ from**	Good	Good

Appendix C Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)

		Cumulative risk at five years Any HPV type: 60% **Risk of CIN2+ by time since first exposure to HPV 16** Relative hazards ratio (95% CI) Unexposed: 1.00 ≤6 months: 5.98 (1.33-26.85) 6-12 months: 18.02 (5.50-59.03) 12-18 months: 14.22 (3.76-53.86) >18 months: 2.60 (0.75-8.99) *Controlling for any other HPV exposure	**study entry:** 36.1 months (range 6.6-104.0) **Median time to diagnosis of CIN2+ from first detection of HPV:** 26 months (range 0-69) **Timing of progression to CIN2+:** During 1st HPV+ episode: 13/28 (46.4%) During 2nd HPV+ episode: 8/28 (28.6%) During 3rd HPV+ episode: 1/28 (3.6%) During 4th HPV+ episode: 1/28 (3.6%) Remained HPV-: 5/28 (17.9%)		

Study ID	Objective	Study design	Setting	Prevalence	Number of patients Inclusion & exclusion criteria	Patient characteristics
Sasieni 2009[23]	To study the effect of cervical screening on incidence of cervical cancer as a function of age	Case-control study Cases with invasive cervical cancer (including micro-invasive) diagnosed between 1990 and 2008 Controls were women ever registered with an NHS GP; in most cases selected randomly Controls matched to cases on age and area of residence, and half of controls matched by GP Data on screening history abstracted from cervical cytology records in the UK national cervical screening call/recall system (NHS and many private providers) Smears taken between 1988 and 2008	UK Population based Women diagnosed with ICC identified from histology records at various centers in the UK over differing time periods, a year at a time Controls identified from NHS records	NR	4,012 cases 7,889 controls **Inclusion:** Age 20-69 **Exclusion:** Cases not in the cervical cancer call/recall system	NR

Appendix C Table 1. Evidence Table for Age at Which to Begin Screening (KQ1)

Study ID	Funding source	Outcomes	Other outcomes	Quality rating	Applicability
Sasieni 2009[23]	Cancer Research UK and NHS cervical screening programme	**Protective effect of screening in past against developing cancer in future** Age at diagnosis with ICC / Age at screening / OR* (95% CI) 25-29 / 20-21 / 1.51 (0.95-2.38) 22-24 / 1.11 (0.83-1.50) 35-39 / 30-31 / 0.79 (0.57-1.1) 32-34 / **0.55** (0.44-0.69) 45-49 / 40-41 / **0.40 (0.27-0.58)** 42-44 / **0.37 (0.29-0.48)** 55-59 / 50-51 / **0.27 (0.17-0.43)** 52-54 / **0.26 (0.19-0.36)** *Odds ratio estimating risk of cervical cancer in those with screening (in one of two time periods before diagnosis) vs. risk in those without screening in either time period **Bold indicates statistically significant risk reduction associated with screening	**Screening history for women aged 20-24 at diagnosis (73 participants)** Most cases (93%) younger than 25 were diagnosed with cancer despite screening: Screen-detected: 32 (44%) (calc) Interval (last result normal): 15 (21%) History of abnormal cytology: 21 (29%) Never screened or lapsed: 5 (7%) **Benefit associated with being screened twice by age 26** Age at diagnosis with ICC / Age at screening / OR for stage IB+ (95% CI) / OR for all stages (95% CI) 26.5-29 / 20-22 and 23-25 / 0.90 (0.38-2.2) / 1.1 (0.62-2.0) 23-25 only / 1.00 (Ref.) / 1.00 (Ref.)	Fair	Good

CI-confidence interval; CIN-cervical intraepithelial neoplasia; GP- general practitioner; HMO-health maintenance organization; HPV-human papillomavirus; ICC- invasive cervical cancer; IQR-inter-quartile range; KPNW-Kaiser Permanente Northwest; NHS- National Health Service; NR-not reported; OR-odds ratio; NA-not applicable; PCR- Polymerase chain reaction; UK-United Kingdom, US-United States

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Primary screening test evaluated Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion and exclusion criteria	Patient characteristics	Application of gold standard (histological verification)
Taylor 2006[109]	ThinPrep Ayre's type spatula and cytobrush	Samples collected at clinic visit six months after enrollment in screen and treat RCT Cytology method (LBC vs. CC) rotated on six month basis	South Africa Three primary care clinical sites in Khayelitsha (periurban, informal settlement outside Cape Town) High-risk, previously unscreened women enrolled in cervical cancer prevention trial	**CIN2:** 57/5,558 = 1.0% **CIN3+:** 66/5,558 = 1.2% (CIN3+ includes 14 SONE cases)	5,647 total **LBC:** 3,184 (56.4%) **CC:** 2,463 (43.6%) **Inclusion:** Ages 35-65, previously unscreened **Exclusion:** Pregnant, history of hysterectomy or prior treatment for CIN	**Age** 35-39: LBC 39.4%, CC 37.5% 40-49: LBC 41.4%, CC 43.7% 50-65: LBC 19.3%, CC 18.8% **Ethnicity:** NR **Employed:** LBC 24.8%, CC 26.5% **Education** No school: LBC 9.3%, CC 9.0% Some primary school: LBC 38.1%, CC 36.6% Some high school: LBC 44.2%, CC 46.8% High school graduate: LBC 8.4%, CC 7.6% **Treated with cryotherapy in prior 6 mos:** LBC 14.1%, CC 14.7% **HIV+:** LBC 12.8%, CC 12.4% **Trichomonas vaginalis:** LBC 10.7%, CC 10.6% **Current smoker:** LBC 7.1%, CC 8.4%	Colposcopy with endocervical curettage and biopsy of all colposcopic abnormalities in all women

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Funding source	Quality rating	Applicability	Yield	Insufficient samples	Sensitivity (95% CI)
Taylor 2006[109]	NR	Fair	Poor for absolute test performance, but not for relative test performance High-risk population, HIV prevalent, includes only women never screened for cervical cancer, 14.5% with previous treatment	**ASC-US** LBC: 9.3% CC: 9.5% **LSIL** LBC: 4.3% CC: 3.3% **≥HSIL** LBC: 2.7% CC: 3.7% **Test Positivity Rate (ASC-US+):** LBC = 16.4% CC = 16.4%	Unsatisfactory **LBC:** 2.2% **CC:** 0.8%, p<.01 Satisfactory but limited **LBC:** 6.5% **CC:** 27.9%, p<.01	**Detection of CIN2+:** ASC-US+ **LBC:** 70.6 (58.3-81.0) **CC:** 83.6 (71.2-92.2) LSIL+ **LBC:** 60.3 (47.7-71.9) **CC:** 69.1 (55.2-80.9) HSIL+ (calc) **LBC:** 30/68 = 44.1 (32.1-56.7) **CC:** 32/55 = 58.2 (44.1-71.3) **Detection of CIN3+ (calc):** ASC-US+ **LBC:** 25/33 = 75.8 (57.7-88.9) **CC:** 29/33 = 87.9 (71.8-96.6) LSIL+ **LBC:** 22/33 = 66.7 (48.2-82.0) **CC:** 24/33 = 72.7 (54.5-86.7) HSIL+ **LBC:** 18/33 = 54.5 (36.4-71.9) **CC:** 21/33 = 63.6 (45.1-79.6)

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics	Comments
Taylor 2006[109]	**Detection of CIN2+:** ASC-US+ **LBC:** 2583/3046 = 84.8 (83.5-86.1) **CC:** 2033/2389 = 85.1 (83.6-86.5) LSIL+ **LBC:** 2867/3046 = 94.1 (93.2-94.9) **CC:** 2257/2389 = 94.5 (93.5-95.4) HSIL+ (calc) **LBC:** 2991/3046 = 98.2 (97.7-98.6) **CC:** 2331/2389 = 97.6 (96.9-98.2) **Detection of CIN3+ (calc):** ASC-US+ **LBC:** 2595/3081 = 84.2 (82.9-85.5) **CC:** 2038/2411 = 84.5 (83.0-86.0) LSIL+ **LBC:** 2883/3081 = 93.6 (92.6-94.4) **CC:** 2265/2411 = 93.9 (92.9-94.9) HSIL+ **LBC:** 3014/3081 = 97.8 (97.2-98.3) **CC:** 2342/2411 = 97.1 (96.4-97.8)	**Detection of CIN2+:** ASC-US+ **LBC:** 9.4 (7.0-12.3) **CC:** 11.4 (8.5-15.0) LSIL+ **LBC:** 18.6 (13.7-24.4) **CC:** 22.4 (16.3-29.4) HSIL+ (calc) **LBC:** 30/85 = 35.3 (25.2-46.4) **CC:** 32/90 = 35.6 (25.7-46.3) **Detection of CIN3+ (calc):** ASC-US+ **LBC:** 25/511 = 4.9 (3.2-7.1) **CC:** 29/402 = 7.2 (4.9-10.2) LSIL+ **LBC:** 22/220 = 10.0 (6.4-14.7) **CC:** 24/170 = 14.1 (9.3-20.3) HSIL+ **LBC:** 18/85 = 21.2 (13.1-31.4) **CC:** 21/90 = 23.3 (15.1-33.4)	**Detection of CIN2+:** ASC-US+ **LBC:** 99.2 (98.8-99.5) **CC:** 99.6 (99.2-99.8) LSIL+ **LBC:** 99.1 (98.7-99.4) **CC:** 99.3 (98.8-99.6) HSIL+ (calc) **LBC:** 2991/3029 = 98.7 (98.3-99.1) **CC:** 2331/2354 = 99.0 (98.5-99.4) **Detection of CIN3+ (calc):** ASC-US+ **LBC:** 2595/2603 = 99.7 (99.4-99.9) **CC:** 2038/2042 = 99.8 (99.5-99.9) LSIL+ **LBC:** 2883/2894 = 99.6 (99.3-99.8) **CC:** 2265/2274 = 99.6 (99.3-99.8) HSIL+ **LBC:** 3014/3029 = 99.5 (99.2-99.7) **CC:** 2342/2354 = 99.5 (99.1-99.7)	**Detection of CIN2+ (calc):** ASC-US+ **LBC:** 15.2 (13.9-16.5) **CC:** 14.9 (13.5-16.4) LSIL+ **LBC:** 5.9 (5.1-6.8) **CC:** 5.5 (4.6-6.5) HSIL+ **LBC:** 1.8 (1.4-2.3) **CC:** 2.4 (1.8-3.1) **Detection of CIN3+ (calc):** ASC-US+ **LBC:** 15.8 (14.5-17.1) **CC:** 15.5 (14.0-17.0) LSIL+ **LBC:** 6.4 (5.6-7.4) **CC:** 6.1 (5.1-7.1) HSIL+ **LBC:** 2.2 (1.7-2.8) **CC:** 2.9 (2.2-3.6)	No significant differences in sensitivity or specificity when stratified by HIV status or age group (<40 years vs. ≥40 years) Sensitivity and specificity results similar when subset of women randomized to no cryotherapy arm analyzed separately	CIN2+ and CIN3+ include SONE = women diagnosed with strips of neoplastic endocervix on their endocervical curettage who either were not diagnosed with CIN2 or CIN3 on their biopsy or had no biopsy

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Primary screening test evaluated Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion and exclusion criteria	Patient characteristics	Application of gold standard (histological verification)
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]	ThinPrep Cervexbrush or appropriate brushes and spatulas	Consecutive series, split sample	France Two public university hospitals and two private practices Women attending for routine screening and women referred for colposcopy due to abnormalities detected on prior screening smears* *We report results for routine screening sample only	**CIN 2-3:** 35/1,754 = 2.0% **Invasive cancer:** 6/1,754 = 0.3%	2,585 Total **1,757 women attending for routine screening** 828 women referred for colposcopy **Inclusion:** Women ≥18 years old undergoing spontaneous screening for cervical cancer **Exclusion:** Pregnant, no cervix, recent (<1 year) history of surgery or laser treatment of the cervix, cervix not visible by physician, mentally retarded, clinical or psychological status not allowing collection of required samples	**Mean age (SD):** 33.3 (11.1) **Ethnicity:** NR **Education** No schooling or primary only: 4% Secondary: 53% Higher: 43% **HIV+:** 0% **Previous documented Chlamydia trachomatis infection:** 1% **Current smoker:** 31%	Colposcopy and directed biopsy of abnormalities in all women

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Funding source	Quality rating	Applicability	Yield		Insufficient samples	Sensitivity (95% CI)	
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]	French Ministry of Health and the Association de Recherche contre le Cancer	Fair	Probably fairly comparable to a US population, although lack of experience with ThinPrep may mean results aren't comparable	**CLINICAL READING** **ASC-US/AGUS** LBC: 5.6% CC: 4.1% **LSIL** LBC: 4.2% CC: 4.0% **HSIL** LBC: 2.3% CC: 1.8% **Invasive Cancer** LBC: 0% CC: 0.1% **Test Positivity Rate (ASC-US+):** LBC: 12.1% CC: 10.0%	**OPTIMIZED INTERPRETATION** **ASC-US/AGUS** LBC: 4.8% CC: 5.4% **LSIL** LBC: 5.5% CC: 4.7% **HSIL** LBC: 3.0% CC: 2.3% **Invasive Cancer** LBC: 0% CC: 0.1% **Test Positivity Rate (ASC-US+):** LBC: 13.4% CC: 12.4%	Satisfactory for evaluation **LBC:** 87% **CC:** 91%, p<.0001 Unsatisfactory for evaluation **LBC:** 0.4% **CC:** 0.1% Satisfactory for evaluation but limited by **LBC:** 12.7% **CC:** 9.1%	**CLINICAL READING** **Detection of CIN2+:** ASC-US+ (calc) **LBC:** 32/41 = 78.0 (62.4-89.4) **CC:** 35/41 = 85.4 (70.8-94.4) LSIL+ (calc) **LBC:** 28/41 = 68.3 (51.9-81.9) **CC:** 30/41 = 73.2 (57.1-85.8) HSIL+ **LBC:** 51 (36-67) **CC:** 51 (36-67)	**OPTIMIZED INTERPRETATION** **Detection of CIN2+:** ASC-US+ (calc) **LBC:** 35/40 = 87.5 (73.2-95.8) **CC:** 36/41 = 87.8 (73.8-95.9) LSIL+ (calc) **LBC:** 32/40 = 80.0 (64.4-90.9) **CC:** 30/41 =30/41 = 73.2 (57.1-85.8) HSIL+ **LBC**: 65 (50-80) **CC:** 60 (45-75)

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Specificity (95% CI)		Positive predictive value (95% CI)		Negative predictive value (95% CI)		False positive rate (95% CI)		Other performance characteristics	Comments
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]	**CLINICAL READING** **Detection of CIN2+:** ASC-US+ (calc) **LBC:** 1529/1709 = 89.5 (87.9-90.9) **CC:** 1573/1714 = 91.8 (90.4-93.0) LSIL+ (calc) **LBC:** 1623/1709 = 95.0 (93.8-96.0) **CC:** 1640/1714 = 95.7 (94.6-96.6) HSIL+ **LBC:** 99 (98 to 99) **CC:** 99 (99 to 100)	**OPTIMIZED INTERPRE-TATION** **Detection of CIN2+:** ASC-US+ (calc) **LBC:** 1515/1715 = 88.3 (86.7-89.8) **CC:** 1532/1713 = 89.4 (87.9-90.9) LSIL+ (calc) **LBC:** 1597/1715 = 93.1 (91.8-94.3) **CC:** 1620/1713 = 94.6 (93.4-95.6) HSIL+ **LBC:** 98 (98 to 99) **CC:** 99 (99 to 99)	**CLINICAL READING** **Detection of CIN2+ (calc):** ASC-US+ **LBC:** 32/212 = 15.1 (10.6-20.6) **CC:** 35/176 = 19.9 (14.3-26.6) LSIL+ **LBC:** 28/114 = 24.6 (17.0-33.5) **CC:** 30/104 = 28.8 (20.4-38.6) HSIL+ **LBC:** 21/41 = 51.2 (35.1-67.1) **CC:** 21/34 = 61.8 (43.6-77.8)	**OPTIMIZED INTERPRE-TATION** **Detection of CIN2+ (calc):** ASC-US+ **LBC:** 35/235 = 14.9 (10.6-20.1) **CC:** 36/217 = 16.6 (11.9-22.2) LSIL+ **LBC:** 32/150 = 21.3 (15.1-28.8) **CC:** 30/123 = 24.4 (17.1-33.0) HSIL+ **LBC:** 26/53 = 49.1 (35.1-63.2) **CC:** 24/41 = 58.5 (42.1-73.7)	**CLINICAL READING** **Detection of CIN2+ (calc):** ASC-US+ **LBC:** 1529/1538 = 99.4 (98.9-99.7) **CC:** 1573/1579 = 99.6 (99.2-99.9) LSIL+ **LBC:** 1623/1636 = 99.2 (98.6-99.6) **CC:** 1640/1651 = 99.3 (98.8-99.7) HSIL+ **LBC:** 1689/1709 = 98.8 (98.2-99.3) **CC:** 1701/1721 = 98.8 (98.2-99.3)	**OPTIMIZED INTERPRE-TATION** **Detection of CIN2+ (calc):** ASC-US+ **LBC:** 1515/1520 = 99.7 (99.2-99.9) **CC:** 1532/1537 = 99.7 (99.2-99.9) LSIL+ **LBC:** 1597/1605 = 99.5 (99.0-99.8) **CC:** 1620/1631 = 99.3 (98.8-99.7) HSIL+ **LBC:** 1688/1702 = 99.2 (98.6-99.5) **CC:** 1696/1713 = 99.0 (98.4-99.4)	**CLINICAL READING** **Detection of CIN2+ (calc):** ASC-US+ **LBC:** 10.5 (9.1-12.1) **CC:** 8.2 (7.0-9.6) LSIL+ **LBC:** 5.0 (4.0-6.2) **CC:** 4.3 (3.4-5.4) HSIL+ **LBC:** 1.2 (0.7-1.8) **CC:** 0.8 (0.4-1.3)	**OPTIMIZED INTERPRE-TATION** **Detection of CIN2+ (calc):** ASC-US+ **LBC:** 11.7 (10.2-13.3) **CC:** 10.6 (9.1-12.1) LSIL+ **LBC:** 6.9 (5.7-8.2) **CC:** 5.4 (4.4-6.6) HSIL+ **LBC:** 1.6 (1.0-2.3) **CC:** 1.0 (0.6-1.6)	Interobserver Reliability (assessed in 30% random sample) **LBC:** κ = 0.57 (0.52,0.63) Moderate **CC:** κ = 0.69 (0.64,0.74) Good	*Optimized interpretation: if CC and LBC readings disagree, reread to reach consensus diagnosis, or read by independent expert if disagreement not resolved

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Primary screening test evaluated Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion and exclusion criteria	Patient characteristics	Application of gold standard (histological verification)	Funding source
NTCC[107,112]	ThinPrep Plastic Ayre's spatula and cytobrush	Randomized screening program with two arms IG: HPV (HC2) & LBC at baseline CG: CC at baseline HC2 assay performed on residual cytology sample	Italy Nine organized cervical screening programs Women presenting for routine screening	**CIN2+** ASC-US+ **LBC:** 99/22,708 = 0.44% **CC:** 84/22,466 = 0.37% LSIL+ **LBC:** 73/22,708 = 0.32% **CC:** 70/22,466 = 0.31% **CIN3+** ASC-US+ **LBC:** 45/22,708 = 0.20% **CC:** 53/22,466 = 0.24% LSIL+ **LBC:** 32/22,708 = 0.14% **CC:** 44/22,466 = 0.20%	45,307 randomized 22,760 IG 22,547 CG 45,174 eligible 22,708 IG 22,466 CG **Inclusion**: Aged 25-64 **Exclusion**: Pregnant, hysterectomy, or treated for CIN within five years	**Median age:** 41 **Ethnicity:** NR **Education**: NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	Serious areas identified by colposcopy were biopsied Referral to colposcopy: IG: ASC-US+ CG: ASC-US+ at seven centers (72%), LSIL+ at two centers (28%) % of women who had colposcopy: IG: 5.9% CG: 2.9%	European Union, Italian Ministry of Health, Special Project "Oncology," Compagnia di S. Paolo FIRMS, and participating Italian regions

Study ID	Quality rating	Applicability	Yield	Insufficient samples	Relative detection ratio (95% CI)	Relative false positive proportion (95% CI)	Relative positive predictive value (95% CI)
NTCC[107,112]	Fair	Fair	**ASC-US/AGUS** LBC: 3.59% CC: 2.29% Relative frequency (95% CI): 1.57 (1.41-1.75) **LSIL** LBC: 2.32% CC: 1.26% Relative frequency (95% CI): 1.84 (1.60-2.13) **HSIL** LBC: 0.41% CC: 0.26% Relative frequency (95% CI): 1.57 (1.13-2.18)	Unsatisfactory results (any reason): **LBC:** 2.57% **CC:** 4.11%	LBC vs. CC **Detection of CIN2+** ASC-US+: 1.17 (0.87-1.56) ASC-US+ (restricted to centers with ASC-US+ referral criteria): 1.11 (0.81-1.52) LSIL+: 1.03 (0.74-1.43) **Detection of CIN3+** ASC-US+: 0.84 (0.56-1.25) LSIL+: 0.72 (0.46-1.13)	LBC vs. CC ASC-US+ **Detection of CIN2+ (calc):** (783/16,706)/(397/16,658) = 1.97 (1.75-2.21) **Detection of CIN3+ (calc):** (806/16,706)/(417/16,658) = 1.93 (1.72-2.21) LSIL+ **Detection of CIN2+ (calc):** (278/16,706)/(154/16,658) = 1.80 (1.48-2.19) **Detection of CIN3+ (calc):** (293/16,706)/(170/16,658) = 1.72 (1.42-2.07)	LBC vs. CC **CIN2+** ASC-US+: 0.58 (0.44-0.77) ASC-US+ (restricted to centers with ASC-US+ referral criteria): 0.65 (0.49-0.88) LSIL+: 0.58 (0.43-0.78) **CIN3+** ASC-US+: 0.42 (0.29-0.62) LSIL+: 0.40 (0.26-0.62)

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Primary screening test evaluated Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion and exclusion criteria	Patient characteristics	Application of gold standard (histological verification)	Funding source
NETHCON[108]	ThinPrep Rovers Cervex-Brush	Cluster RCT, randomized by family practice (clinical site) to LBC vs. CC Screen-positive women followed prospectively for 18 mo.	The Netherlands Women participating in Dutch cervical screening program at 246 family practices All women screened at one of the participating practices were included in study	**CIN2+:** LBC: 346/48,941= 0.71% CC: 280/40,047= 0.70% **CIN3+:** LBC: 253/48,941= 0.52% CC: 190/40,047= 0.47% **Carcinoma:** LBC: 30/48,941= 0.06% CC: 14/40,047= 0.03%	89,784 women had baseline cytology **LBC:** 49,222 **CC:** 40,562 88,988 included in primary analysis **LBC:** 48,941 **CC:** 40,047 **Inclusion:** All women screened at one of the participating family practices **Exclusion:** NR	**Age (calc):** <30: LBC 0.7%, CC 0.6% 30-34: LBC 21.1%, CC 20.3% 35-39: LBC 14.7%, CC 14.0% 40-44: LBC 18.2%, CC 17.7% 45-49: LBC 12.1%, CC 12.1% 50-54: LBC 12.6%, CC 13.4% 55-59: LBC 17.7%, CC 18.7% >59: LBC 3.1%, CC 3.1% **Ethnicity:** NR **Education:** NR **Monthly income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	Screen-positive women followed for 18 months according to guidelines of the Dutch Society of Pathologists and Dutch Society of Obstetrics and Gynecology Women with equivocal or low-grade cytologic abnormalities on initial test offered repeat cytology at 6 and 18 months Those whose initial abnormality persists or progresses at followup referred for colposcopy Women with high-grade abnormalities at baseline or followup referred for colposcopy 898 women had histology (36.3% of those with abnormal cytology, in each arm and overall); 6 additional women had colposcopy only Relative test performance measures comparing LBC to CC use histology outcomes alone (“primary final outcome”) PPVs reported use a combined histology/follow-up cytology outcome (“secondary final outcome”)	European Commission, Dutch Ministry of Health, and Belgian Foundation Against Cancer

Appendix C Table 2. Evidence Table for Liquid-Based Cytology (KQ2)

Study ID	Quality rating	Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+ (95% CI)	Relative detection ratio (95% CI)	Relative false positive proportion (95% CI)	Relative positive predictive value (95% CI)
NETHCON[108]	Good	Good	**ASC-US/AGUS and LSIL (calc):** LBC: 1,019/49,222= 2.07% CC: 899/40,562= 2.22% **HSIL (calc):** LBC: 302/49,222= 0.61% CC: 254/40,562= 0.63%	Inadequate baseline cytology**:** **LBC:** 0.37% **CC:** 1.09% Excluded from analysis	**Detection of CIN2+:** LBC (ASC-US+): 0.71 (0.63-0.78) CC (ASC-US+): 0.70 (0.62-0.78) **Detection of CIN3+:** LBC (ASC-US+): 0.52 (0.45-0.58) CC (ASC-US+): 0.47 (0.41-0.54)	LBC vs. CC (both ASC-US+) **Detection of CIN2+:** 1.01 (0.86-1.18) (crude) 1.00 (0.84-1.20) (adjusted)* **Detection of CIN3+:** 1.09 (0.90-1.31) (crude) 1.05 (0.86-1.29) (adjusted)* Intention to treat analysis *Adjusted for age, study site, urbanization, and study period and taking cluster design into account	LBC vs. CC (both ASC-US+) **Detection of CIN2+ (calc):** (878/48,941)/(799/40,047) = 0.90 (0.82-0.99) **Detection of CIN3+ (calc):** (971/48,941)/(889/40,047) = 0.89 (0.82-0.98)	LBC vs. CC (unadjusted) **CIN2+ (calc)** ASC-US+: 28.3%/25.9% = 1.09 (0.95-1.25) LSIL+: 62.8%/60.7% = 1.04 (0.93-1.15) **CIN3+ (calc)** ASC-US+: 20.7%/17.6% = 1.17 (0.99-1.39) LSIL+: 48.9%/41.9% = 1.17 (1.01-1.36)

AGUS-Atypical Glandular Cells of Undetermined Significance; ASC-US-atypical squamous cells of undetermined significance; calc-calculated; CC-conventional cytology; CG-control group; CI-confidence interval; CIN-cervical intraepithelial neoplasia; FU-follow-up; HIV-human immunodeficiency virus; HSIL-high-grade squamous intraepithelial lesion; IG-intervention group; LBC-liquid-based cytology; LSIL-low-grade squamous intraepithelial lesion; mos-months; NR-not reported; PPV-positive predictive value; RCT-randomized controlled trial; SD-standard deviation; SONE-strips of neoplastic endocervix; US-United States

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Primary Screening with HPV Test Alone: Studies reporting absolute test performance measures						
Bigras 2005[124]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** Cervex brush **LBC (Surepath):** Cervex brush	Consecutive series, split sample	Switzerland Recruited by 113 gynecologists from six Swiss cantons (Genève, Vaud, Neuchâtel, Fribourg, Valais, and Tessin), most of whom are in private practice; recruitment was not from sexually transmitted disease clinics Women at low risk -- most had been screened yearly at least 5 years before the study	***All women (calc):*** **CIN2:** 23/13,842 = 0.2% **CIN3:** 56/13,842 = 0.4% **AIS:** 3/13,842 = 0.02% **Invasive carcinoma:** 0 ***Women with colposcopy/biopsy results:*** **CIN2:** 23/1,533 = 1.5% **CIN3:** 56/1,533 = 3.7% **AIS:** 3/1,533 = 0.2% **Invasive carcinoma:** 0	13,842 included in analysis **Inclusion:** Women attending for routine screening at the practice of 1 of 113 participating gynecologists **Exclusion:** NR	**Mean Age:** 44.4 (17-93) **Age ≥ 30 years:** 96.4% **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Bigras 2005[124]	Colposcopy and biopsy in 77% (1,031/1,334) of women positive for at least one test and 4% (502/12,508) random sample of women negative for both tests Biopsy was requested on all patients undergoing colposcopy; the biopsy was directed if a lesion was noted or random by strongly brushing the proximal	Unclear	Fair	Good - low risk population and most screened yearly prior to study	**Test Positivity Rate** HC2: 8.2% LBC (ASC-US+): 3.6% **Concordance (calc)** 26.4% of HPV+ samples were ASC-US+ 61.3% of ASC-US+ samples were HPV+	NR

	endocervical canal if no lesion was visualized All women positive for at least one test (1,334) were referred for colposcopy/biopsy, but 248 (18.5%) refused, missed appointments, or underwent follow up in other labs and 55/1,086 (5%) biopsies were unsatisfactory for evaluation				**% HPV+ by LBC diagnosis:** HSIL: 96.4% LSIL: 89.9% ASC-US: 37.7% ASC-H: 83.3% AGC: 50.0% Negative: 57.1% **HPV/LBC categories:** HPV-LBC-: 90.4% HPV-LBC+: 1.4% HPV+LBC+: 2.2% HPV+LBC-: 6.1%	

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Bigras 2005[124]	**Detection of HSIL+:** HC2 (HR HPV+): 100.8/103.9 = 97.0 (91.8-99.4) LBC (ASC-US+): 61.0/103.9 = 58.7 (48.6-68.2) All estimates corrected for verification bias	**Detection of HSIL+:** HC2 (HR HPV+): 12,695.9/13,738.1 = 92.4 (91.9-92.9) LBC (ASC-US+): 13,306.1/13,738.1 = 96.9 (96.6-97.2) All estimates corrected for verification bias	**Detection of HSIL+ (calc):** HC2 (HR HPV+): 100.8/1,143 = 8.8 (7.3-10.6) LBC (ASC-US+): 61/493 = 12.4 (9.6-15.6) All estimates corrected for verification bias	**Detection of HSIL+:** HC2 (HR HPV+): 99.98 (99.96-100) LBC (ASC-US+): 99.75 (99.67-99.83) All estimates corrected for verification bias	**Detection of HSIL+ (calc):** HC2 (HR HPV+): 7.6 (7.1-8.1) LBC (ASC-US+): 3.1 (2.8-3.4) All estimates corrected for verification bias	**% of HSIL+ biopsies by HPV/LBC category:** HPV-LBC-: 0% HPV-LBC+: 3.0% HPV+LBC+: 55.7% HPV+LBC-: 41.3% All estimates corrected for verification bias

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Kulasingam 2002[122]	PCR (NR) Hybrid Capture 2 **PCR:** Positive for high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 55,	Consecutive series Separate samples for LBC followed by PCR Prior to January	US Three Planned Parenthood clinics in Washington State	***All women (calc):*** **CIN2:** 50/4,075 = 1.2% **CIN3+:** 87/4,075 = 2.1% (includes 1 case of AIS; 3 of these 87 women found to have	4,358 eligible 4,075 consented to participate **Inclusion:** Age 18-50	**Age:** Mean: 25 (SD 5.7) <30: 81% ≥30: 19% **Ethnicity** African American: 10% American Indian: 1%

	56, 58, 59, 68, 73, 82, and 84) **HC2:** Positive for high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 RLU **PCR:** Dacron-tipped swab **HC2:** Dacron-tipped swab (prior to Jan. 2000); Ayres spatula and cytobrush (starting in Jan. 2000) **LBC (ThinPrep):** Ayres spatula for transformation zone and cytobrush for endocervical cells	2000, HC2 assay performed on residual STM samples after aliquot for PCR removed Starting in January 2000, HC2 assay performed on residual LBC liquid	Women presenting for annual examinations	microinvasive cancer in LEEP specimen) ***Women with colposcopy/biopsy results:*** **CIN2:** 50/1,015 = 4.9% **CIN3+:** 87/1,015 = 8.6% **CIN3+ (corrected for colposcopy attendance and verification bias):** 3.2%	**Exclusion:** History of hysterectomy, chronic immune suppression, or treatment for cervical neoplasia	Asian: 3% Hispanic: 4% White: 72% Other: 10% **Education** ≤ high school: 40% > high school: 60% **Monthly Income** ≤$400: 25% $401-$800: 27% $801-$1,300: 24% >$1,300: 24% **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Kulasingam 2002[122]	Colposcopy and biopsy in women screening positive on cytology, PCR, or HC2 and in a random sample of 202 (7.7%) women with negative cytology and PCR test results Ectocervical biopsies of visible lesions or the 12 o'clock location if no lesion was visible	National Cancer Institute	Good	Good	**Test Positivity Rate** PCR: 18.3% HC2: 28.4% LBC (ASC-US+): 16.6% **Concordance* (calc)** (based on 3,996 with satisfactory LBC tests) **PCR** 45.9% of HPV+ samples were ASC-US+ 49.9% of ASC-US+ samples were HPV+ **HC2** 38.2% of HPV+ samples were ASC-US+ 62.1% of ASC-US+ samples were HPV+ **% HPV+ by LBC diagnosis:** HSIL: PCR 82.0%, HC2 85.6% LSIL: PCR 62.7%**, HC2 81.9% ASC-US: PCR 35.7%, HC2 47.4% Negative: PCR 12.0%, HC2 20.5% **HPV/LBC categories:** HPV-LBC-: PCR 73.1%, HC2 66.0%	**Insufficient** PCR: 3.9% HC2: 2.1% **Unsatisfactory** LBC: 1.9%

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

					HPV-LBC+: PCR 8.5%, HC2 6.4% HPV+LBC+: PCR 8.5%, HC2 10.5% HPV+LBC-: PCR 10.0%, HC2 17.0% *All estimates corrected for verification bias and bias due to loss to follow up **Reported as 64.4% (104/166) in text	

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value	False positive rate	Other performance characteristics
Kulasingam 2002[122]	All Ages **Detection of CIN3+:** PCR (HR HPV+): 88.2 (78.9-93.8) HC2 (HR HPV+): 90.8 (83.1-95.8) LBC (ASC-US+): 61.3 (48.5-70.9) HC2&LBC: 60.3 (47.4-69.6) *Age <30 years* **Detection of CIN2+:** PCR: 69.9 (49.4-85.2) HC2: 73.5 (53.3-87.7) LBC: 50.1 (35.2-62.2) HC2&LBC: 47.9 (34.1-60) **Detection of CIN3+:** PCR: 91.1 (81.0-97.2) HC2: 92.5 (83.5-97.3) LBC: 65.4 (51.9-79.1) HC2&LBC: 64.0 (51.1-77.6) *Age ≥30 years* **Detection of CIN2+:** PCR: 56.5 (30.3-85.5) HC2: 62.7 (34.1-93.2) LBC: 38.3 (19.3-63.3) HC2&LBC: 38.3 (19.3-63.3) **Detection of CIN3+:** PCR: 80.0 (58.8-92.2) HC2: 86.0 (59.7-96.9) LBC: 49.7 (32.9-71.5)	All Ages **Detection of CIN3+:** PCR (HR HPV+): 78.8 (77.9-79.7) HC2 (HR HPV+): 72.6 (69.4-75.0) LBC (ASC-US+): 82.4 (81.8-83.1) HC2&LBC: 88.9 (88.1-89.6) Age <30 years **Detection of CIN2+:** PCR: 77.8 (76.7-78.9) HC2: 71.1 (67.3-74.0) LBC: 82.1 (81.3-83.0) HC2&LBC: 88.3 (87.4-89.2) **Detection of CIN3+:** PCR: 76.8 (75.7-77.8) HC2: 70.1 (66.5-73.1) LBC: 81.5 (80.7-82.3) HC2&LBC: 87.6 (86.7-88.4) Age ≥30 years **Detection of CIN2+:** PCR: 87.3 (85.5-89.5) HC2: 83.0 (76.6-87.2) LBC: 86.4 (84.7-88.3) HC2&LBC: 95.0 (93.0-96.4) **Detection of CIN3+:** PCR: 87.4 (85.7-89.6) HC2: 83.0 (76.8-87.1) LBC: 86.4 (84.8-88.1)	NR	All Ages **Detection of CIN3+:** (95% CI NR) PCR (HR HPV+): 99.5 HC2 (HR HPV+): 99.6 LBC (ASC-US+): 98.5 HC2&LBC: 98.5 All estimates corrected for verification bias and bias due to loss to follow up	All Ages **Detection of CIN3+ (calc):** PCR (HR HPV+): 21.2 HC2 (HR HPV+): 27.4 LBC (ASC-US+): 17.6 Age <30 years **Detection of CIN2+ (calc):** PCR: 22.2 HC2: 28.9 LBC: 17.9 **Detection of CIN3+ (calc):** PCR: 23.2 HC2: 29.9 LBC: 18.5 Age ≥30 years **Detection of CIN2+ (calc):** PCR: 12.7 HC2: 17.0 LBC: 13.6 **Detection of CIN3+ (calc):** PCR: 12.6	All Ages **% Referred for Colposcopy:** PCR (HR HPV+): 23.4% HC2 (HR HPV+): 29.4% LBC (ASC-US+): 19.0% HC2&LBC: 12.7%

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

	HC2&LBC: 49.7 (32.9-71.5) All estimates corrected for verification bias and bias due to loss to follow up	HC2&LBC: 94.7 (92.8-96.1) All estimates corrected for verification bias & loss to followup bias			HC2: 17.0 LBC: 13.6 All estimates corrected for verification bias and bias due to loss to follow up	

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
CCCaST Mayrand 2007[121] Mayrand 2006[126]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** Digene cervical sampler kit **CC:** Per protocol at each medical practice	RCT with 2 arms: **Focus on HPV:** HC2 followed by CC **Focus on Pap:** CC followed by HC2 Both screening tests included in each arm, but order of collection was randomized. Tests performed sequentially at same visit	Canada 30 selected medical practices in Montreal and surrounding municipalities (province of Quebec) and St. John's (province of Newfoundland) Physicians recruited from medical practices identified by cytology laboratories as active in cervical cancer screeningWomen attending routine cervical cancer screening	***All women (calc):*** **CIN2+** Conservative Case Definition*: 41/10,154 = 0.4% Liberal Case Definition*: 54/10,154 = 0.5% ***Women with colposcopy/biopsy results:*** **CIN2+** Conservative Case Definition*: 41/1,365 = 3.0% Liberal Case Definition*: 54/1,365 = 4.0%	14,953 assessed for eligibility 10,154 randomly assigned to screening 5,059 assigned to Focus on Pap group 5,095 assigned to Focus on HPV group 9,977 received assigned intervention 5,020 in Focus on Pap group 4,957 in Focus on HPV group **Inclusion:** Age 30-69 **Exclusion:** Attending colposcopy clinic for evaluation, treatment or follow up of a cervical lesion, without a cervix, pregnant, previous history of invasive cervical cancer, received cytology test within 12 months	**Age** 30-39: 38.5% 40-49: 35.0% 50-59: 20.4% 60-69: 6.1% **Ethnicity** (10,019 participants) French Canadian: 36.7% English Canadian: 56.9% Other: 6.4% **Education** (10,064) Elementary school: 10.3% High school: 22.7% Junior college: 29.0% University: 38.0% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Application of reference standard (histologic verification)	Funding source	Yield	Insufficient samples	Sensitivity (95% CI)		Specificity (95% CI)	
CCCaST Mayrand 2007[121] Mayrand 2006[126] Fair Good	Colposcopy and biopsy in 90.9% (723/795) of women positive for at least one test and 7.1% (665/9,359) random sample of women negative for both tests	Canadian Institutes of Health Research, Merck Frosst Canada, National Cancer Institute of Canada, Fonds de la Recherche en Santé due Québec	**Test Positivity Rate** HC2: 6.3% in Focus on HPV 5.8% in Focus on Pap CC: 2.7% in Focus on HPV 3.0% in Focus on Pap **Concordance:** NR	**HC2:** NR **CC:** 1.4% in both arms	Group-Specific Comparison **Detection of CIN2+:** Conservative Case Definition* **HC2:** 94.6 (84.2-100.0) **CC:** 55.4 (33.6-77.2) Liberal Case Definition* **HC2:** 45.9 (18.9-72.9) **CC:** 43.4 (13.2-73.6) All estimates corrected for verification bias	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **HC2:** 97.4 **CC (ASC-US+):** 56.4 **CC (LSIL+):** 42.2 All estimates corrected for verification bias	Group-Specific Comparison **Detection of CIN2+:** Conservative Case Definition* **HC2:** 94.1 (93.4-94.8) **CC:** 96.8 (96.3-97.3) Liberal Case Definition* **HC2:** 94.2 (93.5-94.9) **CC:** 96.9 (96.4-97.4) All estimates corrected for verification bias	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **HC2:** 94.3 **CC (ASC-US+):** 97.3 **CC (LSIL+):** 99.1 All estimates corrected for verification bias

Study ID	Positive predictive value (95% CI)		Negative predictive value (95% CI)		False positive rate		Other performance characteristics	Comments
CCCaST Mayrand 2007[121] Mayrand 2006[126]	**Detection of CIN2+:** Conservative Case Definition* **HC2:** 6.4 (5.0-8.0) **CC:** 7.1 (4.8-	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who	**Detection of CIN2+:** Conservative Case Definition* **HC2:** 100.0 (98.6-100.0) **CC:** 99.8 (99.7-	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who	**Detection of CIN2+ (calc):** Conservative Case Definition* **HC2:** 5.9 **CC:** 3.2	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who	**Test Performance by Sampling Order** Performance of HC2 and CC not influenced by order of specimen collection (i.e., first or	*According to the conservative definition, cases were considered only if confirmed on the LEEP specimen or in the

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

	10.3) Liberal Case Definition* **HC2:** 8.0 (5.6-11.3) **CC:** 9.1 (4.7-16.7) All estimates corrected for verification bias	had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **HC2:** 7.0 **CC (ASC-US+):** 8.5 **CC (LSIL+):** 17.5 All estimates corrected for verification bias	99.9) Liberal Case Definition* **HC2:** 99.4 (99.1-99.5) **CC:** 99.6 (99.3-99.8) All estimates corrected for verification bias	had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **HC2:** 100.0 **CC (ASC-US+):** 99.8 **CC (LSIL+):** 99.7 All estimates corrected for verification bias	Liberal Case Definition* **HC2:** 5.8 **CC:** 3.1 All estimates corrected for verification bias	had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* **HC2:** 5.7 **CC (ASC-US+):** 2.7 **CC (LSIL+):** 0.9 All estimates corrected for verification bias	second), as judged by test positivity, unsatisfactory smears or those showing ASC-US, viral load, and sensitivity or specificity **Referrals for Colposcopy**(using combined groups) Conservative Case Definition* **HC2:** 6.1 **CC (ASC-US+):** 2.9 **CC (LSIL+):** 1.0 All estimates corrected for verification bias	confirmatory biopsy when ablative treatment was used. The liberal definition includes all cases of CIN2-3, adenocarcinoma in situ, or cervical cancers confirmed by histologic examination of any of the ectocervical or endocervical biopsy specimens.

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Petry 2003[123]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** Digene cervical sample device **CC:** Followed routine procedure in each gynacologocal practice (most, but not all, used	Consecutive series HC2 sample collected following CC sample at same visit	Germany 28 urban, suburban or rural, office-based gynacological practices from Hannover and Tuebingen and the surrounding areas Women attending routine cervical cancer screening	***All women (calc):*** **CIN2+:** 46/7,908 = 0.6% **CIN3+:** 37/7,908 = 0.5% (includes 1 case of invasive cervical carcinoma) ***Women with colposcopy/biopsy results:*** **CIN2+:** 46/536 = 8.6% **CIN3+:** 37/536 = 6.9%	8,466 recruited 8,101 met inclusion criteria 8,083 with cytology and HC2 results 7,908 included in test performance analysis (excludes 175 with positive test who refused colposcopy) **Inclusion:** Attending for routine annual screening **Exclusion:** Genital warts (43), history of conization or hysterectomy (13), pregnant	**Mean Age:** 42.7 **Age 30-60 years:** 94.6% **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

	cotton-tipped swab)				(11), abnormal cytology within 1 year of study entry (8), under age 30 (167), no written consent (123)	
Pan 2003[130] Belinson 2001[226]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at 1.0 pg/mL **HC2 and LBC (ThinPrep):** Plastic spatula and endocervical brush	Consecutive series, split sample	China Recruited from villages in 4 communes in Xiangyuan County in Shanxi Province Previously unscreened women from rural, low-resource setting	**CIN2:** 43/1,993 = 2.2% **CIN3:** 31/1,993 = 1.6% **SCC:** 12/1,993 = 0.6%	2,047 recruited 50 excluded (44 had cytology and colposcopy only, 2 <35 years old, 2 having menses, 1 pregnant, 1 screened in pilot study) 1,997 in study sample 1,993 included in LBC analyses (4 with insufficient epithelial cells) 1,836 included in HPV analyses (4 with insufficient epithelial cells, 157 without HPV data) **Inclusion:** Age 35-45 **Exclusion:** Pregnant, history of cervical screening, pelvic radiation, or hysterectomy	Characteristics of 1,997 in study sample **Mean age (SD):** 39.1 (3.16) **Ethnicity:** NR **Education:** NR **HIV+:** NR **History of condyloma:** 0.3% **Trichomoniasis on cytology:** 20.6% **Never smoked:** 93.3%

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Petry 2003[123]	Colposcopy and punch biopsy of any regions suspicious for CIN in women with any degree of cytologic abnormality and/or positive for HPV test and a random sample of 3.4% of women who were negative on both screening tests	Cancer Society of Lower Saxony, Hannover, Germany, the Ria-Freifrau von Fritsch Stiftung, and an unconditional formal grant from DIGENE corporation to the University of Hannover and Tuebingen	Fair	Good	**Test Positivity Rate** HC2: 6.4% CC (PapIIw+): 3.1% **Concordance (calc)** 11.7% of HPV+ samples were PapIIw+ 24.3% of PapIIw+ samples were HPV+ **% HPV+ by CC diagnosis:** PapIV+V: 100% PapIIId: 50.8% PapIII: 21.4% PapIIw: 10.8% Negative: 5.9% **HPV/CC categories (calc):** HPV-CC-: 91.2% HPV-CC+: 2.4% HPV+CC+: 0.8% HPV+CC-: 5.7%	NR
Pan 2003[130]	Colposcopy and biopsy in all women	Taussig Cancer Center Cleveland	Good	Fair to Poor	**Test Positivity Rate** HC2: 17.8%	Insufficient **HC2:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Belinson 2001[226]	If the colposcopic examination was normal, four 2-mm biopsies were taken from positions 2,4,8, and 10 o'clock on the exocervix at the squamocolumnar junction; endocervical curettage was also performed on all subjects; any abnormalities revealed on colposcopy were also biopsied, and it was acceptable to take more than one biopsy per quadrant	Clinic Foundation, Cancer Institute/Hospital, Chinese Academy of Medical Sciences, Terry Fox Foundation, Transamerica Corporation, Digene Corp., Cytyc Corp., Optical Biopsy Tech, LLC, and Carl Zeiss, Inc.		Reports high incidence of cervical cancer in Shanxi Province and high age-adjusted mortality rate from cervical cancer (52/100,000); low resource setting	LBC (ASC-US+): 25.7% **Concordance** 60.2% of HPV+ samples were ASC-US+ 40.8% of ASC-US+ samples were HPV+ **% HPV+ by LBC diagnosis (p<.01):** SCC: 100% HSIL: 91.3% LSIL: 58.9% ASC-US/AGUS: 16.6% Negative: 9.6% **HPV/LBC categories:** HPV-LBC-: 66.6% HPV-LBC+: 15.6% HPV+LBC+: 10.7% HPV+LBC-: 7.1%	**LBC:** 0.2% Unsatisfactory **HC2:** NR **LBC:** 7.9%* *These samples were reprocessed for LBC without HPV testing

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Petry 2003[123]	**Detection of CIN2+:** HC2 (HR HPV+): 45/46 = 97.8 (86.3-99.7) CC (PapIIw+): 20/46 = 43.5 (30.0-58.0) HC2 and CC: 100.0 (93.7-100) **Detection of CIN3+:** HC2: 36/37 = 97.3 (83.2-99.6) CC: 17/37 = 46.0 (30.8-61.9) HC2 and CC (PapIII+): 100.0 (93.7-100)	**Detection of CIN2+:** HC2 (HR HPV+): 7,493/7,862 = 95.3 (93.5-96.6) CC (PapIIw+): 7,706/7,862 = 98.0 (96.7-98.8) HC2 and CC: 93.8 (91.8-95.3) **Detection of CIN3+:** HC2: 7,493/7,871 = 95.2 (93.4-96.5) CC: 7,712/7,871 = 98.0 (96.7-98.8) HC2 and CC: 94.9 (93.1-96.2)	**Detection of CIN2+:** HC2 (HR HPV+): 10.9 (8.2-14.2) CC (PapIIw+): 11.4 (7.5-16.9) HC2 and CC: 8.6 (6.5-11.3) **Detection of CIN3+:** HC2: 8.7 (6.3-11.8) CC: 9.7 (6.1-15) HC2 and CC (PapIII+): 8.4 (6.2-11.4)	**Detection of CIN2+:** HC2 (HR HPV+): 100.0 (55.3-100) CC (PapIIw+): 99.7 (98.7-99.9) HC2 and CC: 100.0 (98.8-100) **Detection of CIN3+:** HC2: 100.0 (55.3-100) CC: 99.7 (98.8-99.9) HC2 and CC (PapIII+): 100.0 (99.1-100)	**Detection of CIN2+ (calc):** HC2 (HR HPV+): 4.7 (3.4-6.5) CC (PapIIw+): 2.0 (1.2-3.3) HC2 and CC: 6.2 (4.7-9.2) **Detection of CIN3+ (calc):** HC2: 4.8 (3.5-6.6) CC: 2.0 (1.2-3.3) HC2 and CC (PapIII+): 5.1(3.8-6.9)	**% referred to colposcopy:** HC2: CIN2+ 5.2, CIN3+ 5.2 CC: CIN2+ 2.2, CIN3+ 2.2 HC2 and CC: CIN2+ 6.8, CIN3+ 5.6 **Quality control:** 719/925 (77.7%) of CC samples reviewed by an independent expert were in agreement 96.6% of 600 HC2 samples retested were in agreement (κ 0.75)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Pan 2003[130] Belinson 2001[226]	**Detection of CIN2+ (calc):** HC2 (HR): 79/83 = 95.2 (88.1-98.7) LBC (ASC-US+): 81/86 = 94.2 (87.0-98.1) LBC (LSIL+): 75/86 = 87.2 (78.3-93.4) LBC (HSIL+): 66/86 = 76.7 (66.4-85.2) **Detection of CIN3+ (calc):** HC2 (HR): 40/41 = 97.6 (87.1-99.9) LBC (ASC-US+): 42/43 = 97.7 (87.7-99.9) LBC (LSIL+): 40/43 = 93.0 (80.9-98.5) LBC (HSIL+): 39/43 = 90.7 (77.9-97.4)	**Detection of CIN2+ (calc):** HC2 (HR): 1505/1753 = 85.9 (84.1-87.5) LBC (ASC-US+): 1475/1907 = 77.3 (75.4-79.2) LBC (LSIL+): 1783/1907 = 93.5 (92.3-94.6) LBC (HSIL+): 1865/1907 = 97.8 (97.0-98.4) **Detection of CIN3+ (calc):** HC2 (HR): 1508/1795 = 84.0 (82.2-85.7) LBC (ASC-US+): 1479/1950 = 75.8 (73.9-77.7) LBC (LSIL+): 1791/1950 = 91.8 (90.5-93.0) LBC (HSIL+): 1881/1950 = 96.5 (95.5-97.2)	**Detection of CIN2+ (calc):** HC2 (HR): 79/327 = 24.2 (19.6-29.2) LBC (ASC-US+): 81/513 = 15.8 (12.7-19.2) LBC (LSIL+): 75/199 = 37.7 (30.9-44.8) LBC (HSIL+): 66/108 = 61.1 (51.3-70.3) **Detection of CIN3+ (calc):** HC2 (HR): 40/327 = 12.2 (8.9-16.3) LBC (ASC-US+): 42/513 = 8.2 (6.0-10.9) LBC (LSIL+): 40/199 = 20.1 (14.8-26.3) LBC (HSIL+): 39/108 = 36.1 (27.1-45.9)	**Detection of CIN2+ (calc):** HC2 (HR): 1505/1509 = 99.7 (99.3-99.9) LBC (ASC-US+): 1475/1480 = 99.7 (99.2-99.9) LBC (LSIL+): 1783/1794 = 99.4 (98.9-99.7) LBC (HSIL+): 1865/1885 = 98.9 (98.4-99.4) **Detection of CIN3+ (calc):** HC2 (HR): 1508/1509 = 99.9 (99.6-100.0) LBC (ASC-US+): 1479/1480 = 99.9 (99.6-100.0) LBC (LSIL+): 1791/1794 = 99.8 (99.5-100.0) LBC (HSIL+): 1881/1885 = 99.8 (99.5-99.9)	**Detection of CIN2+ (calc):** HC2 (HR): 14.1 (12.5-15.9) LBC (ASC-US+): 22.7 (20.8-24.6) LBC (LSIL+): 6.5 (5.4-7.7) LBC (HSIL+): 2.2 (1.6-3.0) **Detection of CIN3+ (calc):** HC2 (HR): 16.0 (14.3-17.8) LBC (ASC-US+): 24.2 (22.3-26.1) LBC (LSIL+): 8.2 (7.0-9.5) LBC (HSIL+): 3.5 (2.8-4.5)	**ASC-US/AGUS to SIL ratio:** 1.47

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Sankaranarayanan 2004[129] Shastri 2005[227]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** Digene cervical sampler brush	4 cross-sectional studies HC2 sample collected following CC sample at same visit Opportunistic recruitment via	India Primary health centers or mobile field clinics in residential locations in Kolkata (2 studies), the slums of Mumbai, and Trivandrum in the State of Kerala	**CIN2:** 99/18,085 = 0.5% **CIN3:** 89/18,085 = 0.5% **Invasive cancer:** 51/18,085 = 0.3%	20,053 eligible and consented 1,968 excluded from analysis (1,945 had abnormal colposcopy but no biopsy taken due to refusal of women and 23 had inconclusive biopsy results) 18,085 included in analysis **Inclusion:** Apparently healthy, asymptomatic, aged 25-65	**Age** 25-39: 56.5% 40-49: 31.1% 50-65: 12.4% **Ethnicity:** NR **No formal education:** 28.3% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
	CC: Cervex broom brush or Ayre's spatula and cotton-tipped swab	publicity and individual or group health education	Apparently healthy asymptomatic women		**Exclusion:** Hysterectomy, history of cervical neoplasia	
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at 1.0 pg/mL **HC2, LBC (ThinPrep), and CC:** Cervexbrush or appropriate brushes and spatulas	Consecutive series, split sample LBC slide prepared from CC sample and HC2 assay performed on residual sample from LBC	France 2 public university hospitals and 2 private practices Women attending for routine screening and women referred for colposcopy due to abnormalities detected on prior screening smears* *We report results for routine screening sample only	**CIN 2-3:** 35/1,754 = 2.0% **Invasive cancer:** 6/1,754 = 0.3%	CC and LBC: 2,585 Total **1,757 routine screening** 828 referred for colposcopy HC2: 1,785 Total (enough residual material) **1,323 routine screening** 462 referred for colposcopy **Inclusion:** Women ≥18 years old undergoing spontaneous screening for cervical cancer **Exclusion:** Pregnant, no cervix, recent (<1 year) history of surgery or laser treatment of the cervix, cervix not visible by physician, mentally retarded, clinical or psychological status not allowing collection of required samples	**Mean age (SD):** 33.3 (11.1) **Ethnicity:** NR **Education** No schooling or primary only: 4% Secondary: 53% Higher: 43% **HIV+:** 0% **Previous documented Chlamydia trachomatis infection:** 1% **Current smoker:** 31%

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Sankaranarayanan 2004[129] Shastri 2005[227]	Colposcopy in all women, and punch biopsies from any colposcopically-assessed abnormal areas on the cervix	Bill & Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention	Fair	Poor Training of specimen collectors widely vary and include high school graduates	**Test Positivity Rate** HC2 Overall: 7.0% Range across sites: 6.1% - 9.0% CC (LSIL+): 5.9% **Concordance** NR	NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

				Variability in quality of specimen collection and reference standards		
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]	Colposcopy and directed biopsy of abnormalities in all women	French Ministry of Health and the Association de Recherche contre le Cancer	Fair	Fair to Good Probably fairly comparable to a US population, although lack of experience with ThinPrep may mean results aren't comparable	**Test Positivity Rate** HC2: 16.02% LBC (ASC-US+): 12.1% CC (ASC-US+): 10.0% **Concordance (calc)** (Routine and referred samples combined, unclear whether cytologic comparison is LBC or CC) 63.9% of HPV+ samples were ASC-US+ 67.8% of ASC-US+ samples were HPV+ **% HPV+ by LBC diagnosis:** Carcinoma: 92.3% HSIL: 82.6% LSIL: 68.0% ASC-US/AGUS: 42.6% Negative: 13.0% **HPV/LBC categories:** HPV-LBC-: 64.9% HPV-LBC+: 8.1% HPV+LBC+: 17.2% HPV+LBC-: 9.7%	Satisfactory for evaluation **HC2:** NR **LBC:** 87% **CC:** 91% Unsatisfactory for evaluation **HC2:** NR **LBC:** 0.4% **CC:** 0.1% Satisfactory for evaluation but limited by **HC2:** NR **LBC:** 12.7% **CC:** 9.1%

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Sankarana-rayanan 2004[129] Shastri 2005[227]	**Detection of CIN2+ (calc):** HC2 (HR HPV+): 163/239 = 68.2 (61.9-74.1) CC (LSIL+): 109/166 = 65.7 (57.9-72.8) **Detection of CIN3+ (calc):** HC2: 113/140 = 80.7 (73.2-86.9) CC: 81/101 = 80.2 (71.1-87.5) **Detection of CIN2-3 (excl. inv. cancer):**	**Detection of CIN2+ (calc):** HC2 (HR HPV+): 16,736/17,846 = 93.8 (93.4-94.1) CC (LSIL+): 9,909/10,425 = 95.1 (94.6-95.5) **Detection of CIN3+ (calc):** HC2: 16,785/17,945 = 93.5 (93.2-93.9) CC: 9,946/10,490 = 94.8 (94.4-95.2)	**Detection of CIN2+ (calc):** HC2 (HR HPV+): 163/1,273 = 12.8 (11.0-14.8) CC (LSIL+): 109/625 = 17.4 (14.5-20.6)	**Detection of CIN2+ (calc):** HC2 (HR HPV+): 16,736/16,812 = 99.5 (99.4-99.6) CC (LSIL+): 9,909/9,966 = 99.4 (99.3-99.6) **Detection of CIN3+ (calc):** HC2:	**Detection of CIN2+ (calc):** HC2 (HR HPV+): 6.2 (5.9-6.6) CC (LSIL+): 4.9 (4.5-5.4) **Detection of CIN3+ (calc):** HC2: 6.5 (6.1-6.8) CC: 5.2 (4.8-5.6)	Quality assessment to investigate statistically significant variability in sensitivity across study sites **Rate of normal biopsy:** Range = 40.5% (Kolkata1) - 79.8% (Mumbai) **Interobserver**

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

	HC2 (HR HPV+) **Kolkata1:** 45.7 (30.9 - 61.0) **Kolkata2:** 69.8 (55.7 - 81.7) **Mumbai:** 69.1 (52.9 - 82.4) **Trivandrum:** 80.9 (66.7 - 90.9) CC (LSIL+) **Kolkata1:** 36.6 (22.1 - 53.1) **Kolkata2:** No cytology **Mumbai:** 70.0 (53.5 - 83.4) **Trivandrum:** 72.3 (57.4 - 84.4) **Detection of HSIL:*** HC2 and CC **Both results positive:** 46.8 (32.1 - 61.9) **Either result positive:** 72.3 (57.4 - 84.4) *From Shastri 2005: Sample of 4,039 women from Mumbai site only; excludes invasive cancer cases	**Detection of CIN2-3 (excl. inv. cancer):** HC2 (HR HPV+) **Kolkata1:** 91.7 (90.7 - 92.6) **Kolkata2:** 94.5 (93.9 - 95.0) **Mumbai:** 93.6 (92.7 - 94.4) **Trivandrum:** 94.6 (93.9 - 95.3) CC (LSIL+) **Kolkata1:** 87.2 (85.9 - 88.4) **Kolkata2:** No cytology **Mumbai:** 98.6 (98.1 - 99.0) **Trivandrum:** 97.9 (97.4 - 98.3) **Detection of HSIL:*** HC2 and CC **Both results positive:** 99.4 (99.1 - 99.7) **Either result positive:** 92.8 (91.8 - 93.6) *From Shastri 2005: Sample of 4,039 women from Mumbai site only; excludes invasive cancer cases	**Detection of CIN3+ (calc):** HC2: 113/1,273 = 8.9 (7.4-10.6) CC: 81/625 = 13.0 (10.4-15.8)	16,785/16,812 = 99.8 (99.8-99.9) CC: 9,946/9,966 = 99.8 (99.7-99.9)		**agreement from review of 182 histology slides:** 96.5% (κ 0.90) in Kolkata 1&2, 88.2% (κ 0.60) in Trivandrum **Overall agreement from reanalysis of 298 HPV samples:** 85.9% (range 81.0 - 92.9); κ 0.72 (range 0.62 - 0.86)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	False positive rate	Other performance characteristics	Comments
Coste 2003[110] de Cremoux 2003[128] Cochand-Priollet 2001[127]	**Detection of CIN2+:** HC2 (HR): 96 (88-100) LBC (optimized interpretation)*: 65 (50-80) CC (optimized interpretation)*: 60 (45-75) LBC & HC2 when ASC-US/AGUS: 76 (59-93)	**Detection of CIN2+:** HC2 (HR): 85 (83-87) LBC (optimized interpretation)*: 98 (98-99) CC (optimized interpretation)*: 99 (99-99) LBC & HC2 when ASC-US/AGUS: 97 (97-98)	NR	NR	**Detection of CIN2+ (calc):** HC2 (HR): 15 LBC (optimized interpretation)*: 1 CC (optimized interpretation)*: 1 LBC & HC2 when ASC-US/AGUS: 3	Likelihood Ratio (+/-) **Detection of CIN2+:** HC2 (HR): 6.52/0.05 LBC (optimized interpretation)*: 41.29/0.36 CC (optimized interpretation)*: 60.46/0.40 LBC & HC2 when ASC-US/AGUS: 29.71/0.25	*Optimized interpretation: if CC and LBC readings disagree, reread to reach consensus diagnosis, or read by independent expert if disagreement not resolved

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Cardenas-Turanzas 2008[125]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **CC and HC2:** Cervical brush	Consecutive series of women participating in a phase II clinical trial of spectroscopic cervical inspection Split sample; HC2 sample obtained by immersing cervical brush in solution after preparing smear **Screening group:** no history of abnormal cytology by patient's report **Diagnosis group:** self-reported abnormal cytology at any previous time	3 sites: U.S. (a cancer center and a community hospital), and Canada (cancer center) Women recruited to trial through advertising in local media, expected to increase minority participation	**CIN 2/3 or cancer (calc)**: **Screening:** 16/835=1.9% **Diagnosis:** 134/518= 25.9%	1,850 enrolled 1,000 in screening group 850 in diagnosis group 1,444 ≥ 30 years old 873 in screening group 571 in diagnosis group 1,353 with complete data included in analysis 835 in screening group 518 in diagnosis group **Inclusion:** Nonpregnant women ≥ 18 years **Exclusion:** History of CIN or cervical cancer	For women ≥ 30 years: **Screening:** **Mean Age:** 46.7 y **Ethnicity:** Non-Hispanic white: 51.1% African-American: 14.7% Hispanic: 26.1% Asian: 6.6% Other: 1.4% **Education:** ≤High school: 24.0% Some college: 38.4% College: 23.0% Graduate: 14.6% **Income:** NR **HIV+/Other STIs:** NR **Smoking:** Ever: 34.9% Current: 9.8% **Diagnosis:** **Mean Age:** 42.3y **Ethnicity:** Non-Hispanic white: 63.9% African-American: 9.5% Hispanic: 13.7% Asian: 9.3% Other: 3.7% **Education:** ≤High school: 27.8% Some college: 34.4% College: 23.0% Graduate: 14.9% **Income:** NR **HIV+:** NR **Smoking:** Ever: 43.6%,Current: 20.7%

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Cardenas-Turanzas 2008[125]	All women had colposcopic examination and biopsies If colposcopy abnormal, 1-2 biopsies taken of area with worst colposcopic impression 1-2 biopsies also taken of squamous and columnar epithelium from an area of normal appearance, typically at the 6 o'clock and 12 o'clock positions, regardless of whether abnormal area identified by colposcopy	National Cancer Institute	**Fair**	**Fair** Separate reporting of "screening" and "diagnosis" groups; risk in each may differ from that in an unselected screening population	**Test positivity:** Screening HC2: 66/835=7.9% (calc) CC (ASC-US+): 59/835=7.1% Diagnosis: HC2: 203/518=39.2% (calc) CC (ASC-US)+: 208/518=40.2% **Concordance:** % of HPV+ samples that were ASC-US+: NR 100% of ASC-US+ samples were HPV+	NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Cardenas-Turanzas 2008[125]	Screening group **Detection of CIN2+:** HC2+: 0.69 (0.41-0.89) CC (ASC-US+): 0.44 (0.20-0.70) CC (ASC-US+) or HC2+:0.69 (0.41-0.89) Diagnosis group **Detection of CIN2+:** HC2+: 0.89 (0.82-0.94) CC (ASC-US+): 0.78 (0.70-0.85) CC (ASC-US+) or HC2+: 0.96 (0.92-0.99)	Screening group **Detection of CIN2+:** HC2+: 0.93 (0.91-0.95) CC (ASC-US+): 0.94(0.92-0.95) CC (ASC-US+) or HC2+: 0.88 (0.86-0.91) Diagnosis group **Detection of CIN2+:** HC2+: 0.78 (0.74-0.82) CC (ASC-US+): 0.73 (0.68-0.78) CC (ASC-US+) or HC2+: 0.65 (0.60-0.69)	Screening group **Detection of CIN2+:** (95% CI NR) HC2+: 0.17 CC (ASC-US+): 0.12 CC (ASC-US+) or HC2+: 0.10 Diagnosis group **Detection of CIN2+:** (95% CI NR) HC2+: 0.66* CC (ASC-US+): 0.50 CC (ASC-US+) or HC2+: 0.49 *According to HPV and histology results in Table 2, should be 119/203 = 0.59	Screening group **Detection of CIN2+:** (95% CI NR) HC2+: 0.99 CC (ASC-US+): 0.99 CC (ASC-US+) or HC2+: 0.99 Diagnosis group **Detection of CIN2+:** (95% CI NR) HC2+: 0.95 CC (ASC-US+): 0.91 CC (ASC-US+) or HC2+: 0.98	Screening group **Detection of CIN2+ (calc):** HC2+: 0.07 CC (ASC-US+): 0.06 CC (ASC-US+) or HC2+: 0.12 Diagnosis group **Detection of CIN2+ (calc):** HC2+: 0.22 CC (ASC-US+): 0.27 CC (ASC-US+) or HC2+: 0.35	Screening group **Area under ROC:** HC2+: 0.81 CC (ASC-US+):0.70 CC (ASC-US+) or HC2+: 0.79 **LR+:** HC2+: 10.24 CC (ASC-US+): 6.89 CC (ASC-US+) or HC2+: 5.93 **LR-:** HC2+: 0.34 CC (ASC-US+): 0.60 CC (ASC-US+) or HC2+: 0.35 Diagnosis group **Area under ROC:** HC2+: 0.83 CC (ASC-US+): 0.78 CC (ASC-US+) or HC2+: 0.80 **LR+:** HC2+: 4.06 CC (ASC-US+):2.92 CC (ASC-US+) or HC2+: 2.72 **LR-:** HC2+: 0.14 CC (ASC-US+): 0.30 CC (ASC-US+) or HC2+:0.06

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Qiao 2008[131]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2 and LBC (SurePath)**: Collection method NR	Two communes selected from each of two counties using randomized cluster sampling; all eligible women from the four selected communes invited Consecutive series, split sample Provider-obtained cervical specimens for LBC and HC2 followed self-obtained vaginal specimens	China Rural Shanxi province, two women and children's hospitals Unscreened population	**CIN2:** 47/2,388= 2.0% **CIN3:** 22/2,388= 0.9% **Cancer:** 1/2,388=0.04%	3,721 recruited 2,530 enrolled (68%) 2,388 with complete data **Inclusion:** Age 30-54 years, married **Exclusion:** pregnant; menstruating; history of CIN, pelvic radiation, or hysterectomy	**Mean Age:** 43.4y (SD 6.2, range 30-55) **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** 98.7% had never smoked

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Qiao 2008[131]	All women had colposcopy, with directed biopsy and endocervical curettage as necessary 441 women with negative colposcopy but unsatisfactory or abnormal screening test were recalled for second colposcopy and 4-quadrant biopsy at the squamo-columnar junction	Bill & Melinda Gates Foundation	**Fair**	Poor Population-based, but in an unscreened population in rural Chinese villages	**Test positivity (calc):** HC2: 401/2,388 = 16.8% LBC (ASC-H+): 127/2,388 = 5.3% **Concordance (calc):** 31.8% of HPV+ samples were ASC-H+ (based on 2,338 with satisfactory LBC) 96.1% of ASC-H+ samples were HPV+ **%HPV+ by LBC diagnosis (calc):** <ASC-H: 11.8% ASC-H+: 96.1% Unsatisfactory: 34.0% **HPV/LBC(ASC-H+) categories (calc):** (based on 2,338 with satisfactory LBC) HPV-LBC-: 83.4% HPV-LBC+: 0.2% HPV+LBC-: 11.2% HPV+LBC+: 5.2%	**Unsatisfactory** LBC: 50/2,388 = 2.1% (calc) HC2: NR

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Qiao 2008[131]	**Detection of CIN2+:** HC2: 97.1 (93.2-100.0) LBC (ASC-H+): 85.3 (76.9-93.7) **Detection of CIN3+:** HC2: 95.7 (87.3-100.0) LBC (ASC-H+): 87.0 (73.2-100.0)	**Detection of CIN2+:** HC2: 85.6 (84.2-87.1) LBC (ASC-H+): 97.0 (96.3-97.7) **Detection of CIN3+:** HC2: 84.0 (82.5-85.5) LBC (ASC-H+): 95.4 (94.5-96.2)	**Detection of CIN2+:** HC2: 17.0 (13.3-20.6) LBC (ASC-H+): 45.7 (37.0-54.3) **Detection of CIN3+:** HC2: 5.5 (3.3-7.7) LBC (ASC-H+): 15.7 (9.4-22.1)	**Detection of CIN2+:** HC2: 99.9 (99.8-100.0) LBC (ASC-H+): 99.5 (99.3-99.8) **Detection of CIN3+:** HC2: 99.9 (99.9-100.0) LBC (ASC-H+): 99.9 (99.7-100.0)	**Detection of CIN2+ (calc):** HC2: 14.4 LBC (ASC-H+): 3.0 **Detection of CIN3+ (calc):** HC2: 16.0 LBC (ASC-H+): 4.6	**Area under ROC:** **Detection of CIN2+:** HC2: 0.96 (0.94-0.97) LBC (ASC-H+): 0.95 (0.92-0.99) **Detection of CIN3+:** HC2: 0.94 (0.89-0.99) LBC (ASC-H+): 0.94 (0.87-1.00)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Moy 2009[132]	Pap: LBC (ThinPrep/Autocyte) HR-HPV DNA test: HC2 HR-HPV DNA testing for HR types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) with standard RLU cutoff ratio ≥ 1 (equivalent to 1 pg of HR-HPV DNA). Sensitivity analysis conducted for cutoffs of 2.0, 3.0, 4.0, 10.0 and 20.0 Gynecologists used cytology brush to collect cervical specimens from transformation zone for **LBC** and **HC2** tests after women self-collected 3 vaginal specimens using plastic-shafted swab or brush	Screening Technologies to Advance Rapid Testing (START) Project: age-eligible women in selected counties in the 3 provinces identified by census and recruited door-to-door All consenting women had both screening tests (LBC and HC2), with referral to colposcopy according to screening result and year of study 5 screening strategies evaluated: 1) Pap only (referral for ASC-US+) 2) HC2 only 3) Reflex (referral for either LSIL+, or ASC-US+ with HC2+) 4) Cotesting LSIL 5) Cotesting HSIL	Rural China 4 women's and children's hospitals in 3 provinces (Shanxi, Jiangxi, and Gansu) Counties selected based on high rates of cervical cancer mortality Unscreened population	**CIN3+:** Unadjusted prevalence: 140/9,057= 1.5% (calc) Adjusted prevalence among all women enrolled (9,057): 1.8%	11,424 invited to participate (eligible by census data) 9,057 confirmed eligible, available, and consented **Inclusion:** age 30-49 y 2003-2005, age 30-54 y 2006; married or history of sexual activity; able to give informed consent **Exclusion:** history of cervical cancer screening; history of CIN, cervical cancer, or hysterectomy; pregnancy (LMP required to be less than 5 weeks before); menstruating women invited to return to participate; no debilitating disease	**Mean age:** 39 y **Age:** 30-34: 24.5% 35-39: 26.8% 40-44: 27.5% 45-54: 21.1% **Ethnicity:** NR (assumed nonWhite) **Education:** None: 20.7% Primary: 35.3% Middle/Junior: 34.5% High/Sr. High: 8.9% College: 0.5% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Moy 2009[132]	**2003 and 2005:** Women with positive VIA, VILI, Pap (LSIL+) or HC2 referred to colposcopy **2004 and 2006:** All women had colposcopy, with directed biopsy of visible lesions; women with Pap of ASC-H, AGUS, LSIL or higher, or HPV+, had 4-quadrant biopsy. Overall colposcopy attendance (calc): 5,905/9,057 = 65.2%	NR	Fair	Poor Unscreened population in rural Chinese counties with high rates of cervical cancer mortality	**Test positivity:** LBC (ASC-US+): 1,035/9,057=11.4% HC2+: 1,242/9,057=13.7% **Concordance (calc)*:** 515/985=52.3% of those ASC-US+ were HPV+ 515/1215=42.4% of those HPV+ were ASC-US+ **%HPV+ by LBC diagnosis:** Negative: 9.5% ASC-US: 32.7% ASC-H: 79.3% AGUS: 62.5% LSIL: 89.6% HSIL: 97.5% Cancer: 94.4% Missing: 17.4% **HPV/LBC categories (calc):** HPV-LBC-: 79.8% HPV-LBC+: 5.6% HPV+LBC-: 8.4% HPV+LBC+: 6.2% *Note: data in text on p. 5 used to calculate concordance. However, there is a discrepancy in data presented: sum of denominators for cytology results in women with HPV results (including missing cytology category) is 8,507, vs. 8,517 reported elsewhere (text p. 5, Table 2) as total number of participants with HPV results.	**Missing*:** LBC: 169 (1.9%) HC2: 540 (6.0%) *Table 2 lists as missing, while text on p. 3 (Data analysis) groups missing and inadequate; study coded these as test positive, with sensitivity analysis coding as test negative

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Moy 2009[132]	**Detection of CIN2+:** Pap only (ASC-US+): 71.2 (65.7-76.4) HC2 only (cutoff 1.0): 93.6 (90.5-96.4) Reflex: 67.2 (61.5-72.6) Cotesting LSIL: 95.5 (93.2-98.0) Cotesting HSIL: 95.5 (93.2-98.0) **Detection of CIN3+:** Pap only (ASC-US+): 80.2 (74.1-86.2) HC2 only (cutoff 1.0): 96.3 (93.6-99.2) Reflex: 75.4 (68.7-81.9) Cotesting LSIL: 99.4 (98.2-100) Cotesting HSIL: 99.4 (98.2-100) All estimates corrected for verification bias	**Detection of CIN2+:** Pap only (ASC-US+): 93.5 (93.2-93.8) HC2 only (cutoff 1.0): 85.8 (85.4-86.2) Reflex: 96.9 (96.7-97.2) Cotesting LSIL: 85.1 (84.6-85.5) Cotesting HSIL: 85.1 (84.7-85.6) **Detection of CIN3+:** Pap only (ASC-US+): 93.3 (93.0-93.6) HC2 only (cutoff 1.0): 85.5 (85.0-85.9) Reflex: 96.7 (96.5-96.9) Cotesting LSIL: 84.8 (84.3-85.3) Cotesting HSIL: 84.8 (84.3-85.3) All estimates corrected for verification bias	**Detection of CIN2+:** Pap only (ASC-US+): 14.7 (12.0-17.4) HC2 only (cutoff 1.0): 9.4 (7.9-10.9) Reflex: 25.7 (21.2-30.2) Cotesting LSIL: 9.1 (7.6-10.6) Cotesting HSIL: 9.2 (7.7-10.7) **Detection of CIN3+:** Pap only (ASC-US+): 15.8 (13.1-18.5) HC2 only (cutoff 1.0): 9.4 (7.9-10.9) Reflex: 26.6 (22.3-30.9) Cotesting LSIL: 9.3 (7.8-10.8) Cotesting HSIL: 9.3 (7.8-10.8) All estimates corrected for verification bias	**Detection of CIN2+:** Pap only (ASC-US+): 99.5 (99.3-99.7) HC2 only (cutoff 1.0): 99.9 (99.8-100.0) Reflex: 99.5 (99.4-99.6) Cotesting LSIL: 99.9 (99.8-100.0) Cotesting HSIL: 99.9 (99.8-100.0) **Detection of CIN3+:** Pap only (ASC-US+): 99.6 (99.5-99.7) HC2 only (cutoff 1.0): 100 (NR) Reflex: 99.6 (99.5-99.7) Cotesting LSIL: 100 (NR) Cotesting HSIL: 100 (NR) All estimates corrected for verification bias	**Detection of CIN2+ (calc):** Pap only (ASC-US+): 6.5 (6.2-6.8) HC2 only (cutoff 1.0): 14.2 (13.8-14.6) Reflex: 3.1 (2.8-3.3) Cotesting LSIL: 14.9 (14.5-15.4) Cotesting HSIL: 14.9 (14.4-15.3) **Detection of CIN3+ (calc):** Pap only (ASC-US+): 6.7 (6.4-7.0) HC2 only (cutoff 1.0): 14.5 (14.1-15.0) Reflex: 3.3 (3.1-3.5) Cotesting LSIL: 15.2 (14.7-15.7) Cotesting HSIL: 15.2 (14.7-15.7)	**ROC AUC:** 0.9 for all five screening strategies **HC2 cutoffs:** Test performance also reported for HC2 cutoffs from 2.0 to 20.0 Authors identify 10.0 pg as having high specificity and low referral rate Do not use ROC to assess cutoffs **Proportion referred to colposcopy:** Pap only (ASC-US+): 7.8 (7.2-8.4) HC2 only (cutoff 1.0): 15.8 (15.0-16.6) Reflex: 4.4 (4.0-4.8) Cotesting LSIL: 16.5 (15.7-17.3) Cotesting HSIL: 16.5 (15.7-17.3) All estimates corrected for verification bias

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Primary Screening with HPV Test Alone: RCTs reporting relative test performance measures						
NTCC Phase II Ronco 2010[113] Ronco 2008[209] Ronco 2006[112] Ronco 2007[210] Ronco 2007[211]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL Results for 2 pg/mL cutoff also assessed (not reported here) **CC:** plastic Ayre's spatula and a cytobrush **HC2:** Digene Corporation cervical sampler (a broomlike device)	RCT with two recruitment phases, each with two rounds of screening Phase 2 reported here (primary HPV testing), Phase 1 reported below with HPV cotesting **Study arms:** Round 1: IG: HPV (HC2) alone CG: CC Round 2: CC for all women	Italy Nine organized cervical screening programs Women presenting for routine screening	Results at recruitment **CIN2+ (calc):** IG: 137/24,661 = 0.6% CG: 55/24,535 = 0.2% **CIN3+ (calc):** IG: 59/24,661 = 0.2% CG: 26/24,535 = 0.1%	**All ages:** 49,196 randomized eligible 24,661 IG 24,535 CG **Age 25-34:** 13,725 randomized eligible 6,937 IG 6,788 CG **Age 35-60:** 35,471 randomized eligible 17,724 IG 17,747 CG **Inclusion:** Age 25-60 **Exclusion:** Pregnant, hysterectomy, or treated for CIN in last five years	**Median age:** 42 years **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Application of reference standard (histologic verification)	Funding source	Yield	Insufficient samples
NTCC Phase II Ronco 2010[113] Ronco 2008[209] Ronco 2006[112] Ronco 2007[210] Ronco 2007[211] Fair Fair	Suspicious areas identified by colposcopy were biopsied **<u>Cross-sectional data at Phase 2 recruitment:</u>** <u>Referral to colposcopy (calc):</u> IG: for HPV+; 1,936/24,661 = 7.9% referred CG: for ASC-US+ at seven centers, LSIL+ at two centers; 679/24,535 = 2.8% referred <u>Compliance with colposcopy (calc):</u> IG: 1,813/1,936 = 93.6% complied with referral CG: 615/679 = 90.6% complied **<u>Cumulative Phase 2 colposcopy data:</u>** NR	European Union, Italian Ministry of Health, Special Project "Oncology," Compagnia di S. Paolo FIRMS, and participating Italian regions	**Test positivity (at recruitment, varied by site):** <u>All ages (calc):</u> *IG* (HPV+): 1,936/24,661 = 7.9% *CG* (ASCUS+): 825/24,535 = 4.6% *CG* (LSIL+): 318/24,535 = 1.3% <u>Age 25-34 (calc):</u> *IG* (HPV+): 907/6,937 = 13.1% *CG* (ASCUS+): 270/6,788 = 4.0% *CG* (LSIL+): 136/6,788 = 2.0% <u>Age 35-60 (calc):</u> *IG* (HPV+): 1,029/17,724 = 5.8% *CG* (ASCUS+): 555/17,747 = 3.1% *CG* (LSIL+): 182/17,747 = 1.0% **Concordance:** NR **Referred to colposcopy (at recruitment):** <u>All ages (calc)</u> *IG:* 1,936/24,661 =7.9% *CG:* 679/24,535 = 2.8% <u>Age 25-34 (calc)</u> *IG:* 907/6,937 = 13.1% *CG:* 244/6,788 = 3.6% <u>Age 35-60 (calc)</u> *IG:* 1,029/17,724 =5.8% *CG:* 435/17,747 = 2.5% **Compliance with colposcopy (at recruitment):** <u>All ages (calc)</u> *IG:* 1,813/1,936 =93.6% *CG*: 615/679 = 90.6% **Invasive cancers** (ICC-AD), n: <u>All ages</u> **R1:** *IG:* 5, *CG:* 2 **R2:** *IG:* 0, *CG:* 3 **C:** *IG: 5*, *CG:* 5 <u>Age 25-34 (author provided data)</u> **R1:** *IG: 1*, *CG:* 0 **R2:** *IG:* 0, *CG:* 0 **C:** *IG:* 1, *CG:05*	HC2: no valid test for 96/24,661 = 0.4% CC: 442/24,535 = 1.8% with unsatisfactory result

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Application of reference standard (histologic verification)	Funding source	Yield	Insufficient samples
			Age 35-60 (author provided data) **R1:** *IG:* 4, *CG:* 2 **R2:** *IG:* 0, *CG:* 3 **C:** *IG: 4*, *CG:* 5	

Study ID	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)
NTCC Phase II Ronco 2010[113] Ronco 2008[209] Ronco 2006[112] Ronco 2007[210] Ronco 2007[211]	**Cross-sectional results at Phase 2 recruitment (per 1000):** ***Age 25-34:*** **CIN2+†** IG (HPV ≥ 1 pg/mL): 9.80 CG (ASCUS+): 2.80 **CIN3+‡** IG (HPV ≥ 1 pg/mL): 3.46 CG (ASCUS+): 1.33 ***Age 35-60:*** **CIN2+†** IG (HPV ≥ 1 pg/mL): 3.89 CG (ASCUS+): 2.03 **CIN3+‡** IG (HPV ≥ 1 pg/mL): 1.97 CG (ASCUS+):0.96 **Cumulative Phase 2 results (calc):** ***Age 25-34:*** **CIN2+ (author provided data)**	**Cross-sectional results at Phase 2 recruitment:** HPV ≥ 1 pg/mL vs. CC ≥ ASCUS ***Age 25-34:*** **CIN2+†** 3.50 (2.11-5.82) **CIN3+‡** 2.61 (1.21-5.61) ***Age 35-60:*** **CIN2+†** 1.92 (1.28–2.87) **CIN3+‡** 2.06 (1.16-3.68) **Cumulative Phase 2 results:** HPV group vs. cytology group ***Age 25-34:***	**Cross-sectional results at Phase 2 recruitment (calc):** HPV ≥ 1 pg/mL vs. CC ≥ ASCUS ***Age 25-34:*** **CIN2+†** (782/6,937)/(191/6,788) = 4.01 (3.43-4.68)	**Cross-sectional results at Phase 2 recruitment:** (95% CI NR) ***Age 25-34:*** **CIN2+†** IG (HPV ≥ 1 pg/mL): 8.0% CG (ASCUS+): 9.0%	**Cross-sectional results at Phase 2 recruitment:** HPV ≥ 1 pg/mL vs. CC ≥ ASCUS ***Age 25-34:*** **CIN2+†** 0.89 (0.55-1.44)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)
	Round 1 IG: 116/6,937 = 1.67% CG: 25/6,788 = 0.37% Round 2 IG: 7/6,577 = 0.11% CG: 18/6,714 = 0.27% Both rounds IG: 123/6,937 = 1.77% CG: 43/6,788 = 0.63%	**CIN2+ (author provided data)** Round 1 4.54 (2.95-6.99) Round 2 0.40 (0.17-0.95) Both rounds 2.80 (1.98-3.95)			

Study ID	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)
NTCC Phase II Ronco 2010[113] Ronco 2008[209] Ronco 2006[112] Ronco 2007[210] Ronco 2007[211]	**CIN3+ (author provided data)** Round 1 IG: 45/6,937 = 0.65% CG: 11/6,788 = 0.16% Round 2 IG: 2/6,577 = 0.03% CG: 10/6,714 = 0.15% Both rounds IG: 47/6,937 = 0.68% CG: 21/6,788 = 0.31% ***Age 35-60:*** **CIN2+ (author provided data)** Round 1 IG: 105/17,724 = 0.58% CG: 48/17,747 = 0.27% Round 2 IG: 5/17,401 = 0.03% CG: 20/17,658 = 0.11% Both rounds IG: 107/17,724 = 0.60% CG: 68/17,747 = 0.38% **CIN3+ (author provided data)** Round 1 IG: 52/17,724 = 0.29%	**CIN3+ (author provided data)** Round 1 4.00 (2.07-7.73) Round 2 0.20 (0.05-0.93) Both rounds 2.19 (1.31-3.66) ***Age 35-60:*** **CIN2+ (author provided data)** Round 1 2.13 (1.51-3.00) Round 2 0.25 (0.10-0.68) Both rounds 1.58 (1.16-2.13) **CIN3+ (author provided data)** Round 1 2.37 (1.44-3.89)	**CIN3+‡** (826/6,937)/(201/6,788) = 4.02 (3.46-4.67) ***Age 35-60:*** **CIN2+†** (893/17,724)/(365/17,747) = 2.45 (2.17-2.76) **CIN3+‡** (927/17,724)/(384/17,747) = 2.42 (2.15-2.72)	**CIN3+‡** IG (HPV ≥ 1 pg/mL): 2.8% CG (ASCUS+): 4.3% ***Age 35-60:*** **CIN2+†** IG (HPV ≥ 1 pg/mL): 7.2% CG (ASCUS+): 8.9% **CIN3+‡** IG (HPV ≥ 1 pg/mL): 3.6%	**CIN3+‡** 0.66 (0.31-1.40) ***Age 35-60:*** **CIN2+†** 0.80 (0.55-1.18) **CIN3+‡** 0.86 (0.49-1.52)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)
	CG: 22/17,747 = 0.12% Round 2 IG: 3/17,401 = 0.02% CG: 13/17,658 = 0.07% Both rounds IG: 55/17,724 = 0.31% CG: 35/17,747 = 0.20%	Round 2 0.23 (0.07-0.82) Both rounds 1.57 (1.03-2.54)	**Cumulative Phase 2 results:** Neither PPV nor the number of participants with false positive results reported	CG (ASCUS+): 4.2% **Cumulative Phase 2 results:** Neither PPV nor the number of participants with false positive results reported	**Cumulative Phase 2 results:** Neither PPV nor the number of participants with false positive results reported

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient character-istics	Application of reference standard (histologic verification)	Funding source
Sankaran-arayanan 2009[118]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) at ≥1.0 pg/mL **HC2:** Collection device NR **CC:** Cervex brushes Nurse-midwives trained using IARC manuals in the collection of cervical cells for HPV and	Cluster randomized trial, 497 villages in 52 clusters, assigned to four groups of 13 clusters each (HPV, cytology, VIA, control) Study reports baseline data (screening test results, colposcopy rates, and CIN and baseline cancer outcomes) collected within 3 months of screening, and cumulative data over 8 years for cancer outcomes only	India Rural Osmanabad district Unscreened population (except for eight individuals)	**CIN2 or 3:** HC2: 245/27,192 = 0.9% CC: 262/25,549 = 1.0% **Cancer:** HC2: 73/27,192 = 0.3% CC: 83/25,549 = 0.3%	131,806 women eligible and randomized (52 clusters) 110,994 women completed screening or were assigned to control group: HC2: 27,192 CC: 25,549 VIA: 26,765 Control: 31,488 **Inclusion:** Ages 30-59 years, "healthy," currently or previously married, intact uterus, living in study cluster	**Mean age (range):** HC2: 39 (38-40) CC: 39 (39-40) Control: 40 (39-41) **Ethnicity:** NR **Education:** (average proportion in clusters with no formal education]) HC2: 70% CC: 73% Control: 71% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	Women with positive screening tests evaluated with colposcopy and directed biopsy of abnormal areas. **Baseline colposcopy data** (within 3 months of screening): Colposcopy rates among women screened (calc): HC2: 2,505/27,192 = 9.2% CC: 1,570/25,549 = 6.1% Colposcopy rates among women with positive screening tests:	Bill & Melinda Gates Foundation

	cytologic testing				**Exclusion:** Pregnant, uterine prolapse, history of cervical cancer		HC2: 2,505/2,812 = 89.1% CC: 1,570/1,787 = 87.9%	

Study ID Quality rating	Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value (95% CI)	Relative positive predictive value (95% CI)
Sankarana-rayanan 2009 [118] Fair	Fair to Poor Unscreened population in rural India 3 weeks' to 3 months' special training as part of study for nurse-midwives, doctors, and laboratory technicians, plus periodic refresher courses	**Test positivity (baseline screening):** HC2: 2,812/27,192 = 10.3% CC: 1,787/25,549 = 7.0% **Concordance:** NR **Colposcopy rates among women screened** **R1 (calc):** *IG:* 2,505/27,192 = 9.2% *CG*: 1,570/25,549 = 6.1% **Colposcopy rates among women with positive screening tests:** **R1:** *IG*: 2,505/2,812 = 89.1% *CG:* 1,570/1,787 = 87.9%	NR	**Baseline detection of CIN2+ (calc):** HC2: 318/27,192 = 1.17% (1.05-1.30) CC: 345/25,549 = 1.35% (1.21-1.50) **Cumulative incidence rate of all cervical cancer (per 100,000 p/y)** HC2 47.4 CC 60.7 *Stage II or higher* HC2 14.5 CC 23.2	HC2 vs. CC **CIN2+ (baseline, calc):** 1.17%/1.35 % = 0.87 (0.74-1.01)	HC2 vs. CC **CIN2+ (baseline, calc):** (2,187/27,192)/ (1,225/25,549) = 1.68 (1.57-1.80)	**Baseline PPV for CIN2+ (CIs calc):** HC2: 318/2,812 = 11.3% (10.2-12.5) CC: 345/1,787 = 19.3% (17.5-21.2) Denominators include all participants with positive screening tests, though not all of these underwent colposcopy	HC2 vs. CC **CIN2+ (baseline, calc)**: 11.3%/19.3% = 0.59 (0.51-0.67)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
HPV Testing with Cytology Triage of Positive HPV (Reflex Cytology): RCTs reporting relative test performance measures						
Finnish Trial Kotaniemi-Talonen 2008[120] Anttila 2006[212] Kotaniemi-Talonen 2005[213] Leinonen 2009[133] Anttila 2010[134]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2**: Cervical sampler brush from HC2 test kit **CC**: Ayre spatula and cytobrush	RCT with two arms: IG: HPV screening with cytology triage, split sample (smears analyzed only for women testing positive for HPV) CG: Conventional cytology alone	Finland Nine municipalities within the Finnish cervical screening program Data from eight municipalities included in 2010 report of extended Round 1 follow-up (five years maximum) Women presenting for routine screening	**CIN2+ (calc):** IG: 146/35,837 = 0.41% CG: 108/35,500 = 0.30% **CIN3+ (calc):** IG: 42/35,837 = 0.12% CG: 34/35,500 = 0.10%	108,425 randomized 71,337 attended screening IG: 35,837 CG: 35,500 *Extended follow-up:* 58,282 randomized 38,670 attended screening IG: 19,449 CG: 19,221 **Inclusion**: Aged 25-65 years *Extended follow-up:* Aged 30-64 years **Exclusion**: NR	**Mean Age:** IG: 45.2 years CG: 45.3 years **Ethnicity:** NR **Education:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Finnish Trial Kotaniemi-Talonen 2008[120] Anttila 2006[212] Kotaniemi-Talonen 2005[213] Leinonen 2009[133] Anttila 2010[134]	Referred for colposcopy IG: 424/35,837=1.2% CG:420/35,500=1.2%	European Union action program Europe Against Cancer, Academy of Finland, and Finnish Cancer Organizations HPV tests provided at reduced price by Digene Corporation	Fair	Fair	**Test positivity rate (calc)** *All ages*: IG (HPV+): 2,628/35,837 = 7.3% IG (LSIL+): 424/35,387 = 1.2% CG (LSIL+): 420/35,500 = 1.2% *Women < 35* IG (HPV+): 983/5,869 = 16.7% IG (LSIL+): 166/5,869 = 2.8% CG (LSIL+): 127/5,711 = 2.2% *Women 35+* IG (HPV+): 1,645/29,968 = 5.5% IG (LSIL+): 258/29,968 = 0.9% CG (LSIL+): 293/29,789 = 1.0% CC (ASC-H or LSIL+) IG: 7.9% CG: 1.2% **Concordance** NR **Colposcopy Referrals** *All ages*: IG: 424/35,837= 1.2% CG: 420/35,500=1.2% *Women < 35 (calc)* IG: 166/5,869 = 2.8% CG: 127/5,711 = 2.2% *Women 35+ (calc)* IG: 258/29,968 = 0.9% CG: 293/29,786 = 1.0% **Invasive cancers**, n: **R1***: IG*: 6, *CG*: 4 **Extended R1 Followup:** ICC: *IG:* 6, *CG*: 3 ACIS: *IG:* 5, *CG :* 3	IG: HPV not available for 2,737/35,837 = 7.6%, mostly because of technical reasons (e.g. proper brush or tube missing) Cytology uninterpretable for 16/5,363 = 0.3% of those with primary or triage cytology (calc) CG: 79/35,475 = 0.2% with uninterpretable cytology (calc)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Detection of CIN	Relative Detection Ratio (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)	Relative Risk of Colposcopy Referral (95% CI)	Comments
Finnish Trial Kotaniemi-Talonen 2008[120] Anttila 2006[212] Kotaniemi-Talonen 2005[213] Leinonen 2009[133] Anttila 2010[134]	**CIN2+ (calc):** IG: 146/35,837 = 0.41% CG: 108/35,500 = 0.30% **CIN3+ (calc):** IG: 42/35,837 = 0.12% CG: 34/35,500 = 0.10% *Extended follow-up:* **CIN3+ (calc):** IG: 59/19,449 = 0.30% CG: 33/19,221 = 0.17%	HPV & CC vs. CC: **CIN2+ (calc):** 0.41%/0.30% = 1.34 (1.04-1.72) *Women < 35* 1.29 (0.88-1.89) *Women 35+* 1.36 (0.98-1.89) **CIN3+:** 1.22 (0.78-1.92) *Women < 35 (calc)* 0.88 (0.38-2.08) *Women 35+ (calc)* 1.38 (0.81-2.36) *Extended follow-up:* **CIN3+:** 1.77 (1.16-2.74)	**CIN2+** HPV + CC triage: 34.4% (29.9-39.2) HPV alone: 5.6% (4.7-6.5) CC: 25.7% (21.6-30.2) **CIN3+** HPV + CC triage: 9.9% (7.2-13.2) HPV alone: 1.6% (1.1-2.2) CC: 8.1% (5.7-11.1) *Extended follow-up:* **CIN3+ (calc)** HPV + CC triage: 59/1,354 = 4.36% (3.4-5.6) CC: 33/1,125 = 2.34% (2.1-4.1)	**CIN2+** HPV + CC triage: 1.34 (1.04-1.72) HPV alone: 0.21 (0.16-0.27) CC: 1.00 (Ref) *RFPP* **R1:** IG: 0.88 (0.75-1.04) CG: 1.00 (Ref) Women aged *25-34* *IG:* 1.26 (0.95-1.69) *CG:* 1.00 (Ref) **CIN3+** HPV + CC triage: 1.22 (0.78-1.92) HPV alone: 0.19 (0.12-0.30) CC: 1.00 (Ref) *RFPP* IG:0.98(0.85-1.13) CG: 1.00 (NR) *IG:* *Aged 35-44* 0.98(0.77-1.26) *45-54* 0.57(0.40-0.82) *≥55* 0.88(0.61-1.26) *CG:* 1.00 (Ref) *Extended follow-up:*	HPV & CC vs. CC: 1.00 (0.87-1.14)	

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Detection of CIN	Relative Detection Ratio (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)	Relative Risk of Colposcopy Referral (95% CI)	Comments
				CIN3+ (calc) HPV + CC triage: 4.21%/2.31% - 1.49 (0.98-2.26) CC: 1.00 (Ref) *RFPP (calc)* IG: (1,297/19,449)/ (1,099/19,221) = 1.17 (1.08-1.27) CG: 1.00 (Ref)		

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Combination HPV and Cytology Testing (Co-Testing): Studies reporting absolute test performance measures						
Petry 2003[123]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** Digene cervical sample device **CC:** Followed routine procedure in each gynacologocal practice (most, but not all, used cotton-tipped swab)	Consecutive series HC2 sample collected following CC sample at same visit	Germany 28 urban, suburban or rural, office-based gynacological practices from Hannover and Tuebingen and the surrounding areas Women attending routine cervical cancer screening	***All women (calc):*** **CIN2+:** 46/7,908 = 0.6% **CIN3+:** 37/7,908 = 0.5% (includes 1 case of invasive cervical carcinoma) ***Women with colposcopy/biopsy results:*** **CIN2+:** 46/536 = 8.6% **CIN3+:** 37/536 = 6.9%	8,466 recruited 8,101 met inclusion criteria 8,083 with cytology and HC2 results 7,908 included in test performance analysis (excludes 175 with positive test who refused colposcopy) **Inclusion:** Attending for routine annual screening **Exclusion:** Genital warts (43), history of conization or hysterectomy (13), pregnant (11), abnormal cytology within 1 year of study entry (8), under age 30 (167), no written consent (123)	**Mean Age:** 42.7 **Age 30-60 years:** 94.6% **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Petry 2003[123]	Colposcopy and punch biopsy of any regions suspicious for CIN in women with any degree of cytologic abnormality and/or positive for HPV test and a random sample of 3.4% of women who were negative on both screening tests	Cancer Society of Lower Saxony, Hannover, Germany, the Ria-Freifrau von Fritsch Stiftung, and an unconditional formal grant from DIGENE corporation to the University of Hannover and Tuebingen	Fair	Good	**Test Positivity Rate** HC2: 6.4% CC (PapIIw+): 3.1% **Concordance (calc)** 11.7% of HPV+ samples were PapIIw+ 24.3% of PapIIw+ samples were HPV+ **% HPV+ by CC diagnosis:** PapIV+V: 100% PapIIId: 50.8% PapIII: 21.4% PapIIw: 10.8% Negative: 5.9% **HPV/CC categories (calc):** HPV-CC-: 91.2% HPV-CC+: 2.4% HPV+CC+: 0.8% HPV+CC-: 5.7%	NR

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Petry 2003[123]	**Detection of CIN2+:** CC (PapIIw+): 20/46 = 43.5 (30.0-58.0) HC2 and CC: 100.0 (93.7-100) **Detection of CIN3+:** CC: 17/37 = 46.0 (30.8-61.9) HC2 and CC (PapIII+): 100.0 (93.7-100)	**Detection of CIN2+:** CC (PapIIw+): 7,706/7,862 = 98.0 (96.7-98.8) HC2 and CC: 93.8 (91.8-95.3) **Detection of CIN3+:** CC: 7,712/7,871 = 98.0 (96.7-98.8) HC2 and CC: 94.9 (93.1-96.2)	**Detection of CIN2+:** CC (PapIIw+): 11.4 (7.5-16.9) HC2 and CC: 8.6 (6.5-11.3) **Detection of CIN3+:** CC: 9.7 (6.1-15) HC2 and CC (PapIII+): 8.4 (6.2-11.4)	**Detection of CIN2+:** CC (PapIIw+): 99.7 (98.7-99.9) HC2 and CC: 100.0 (98.8-100) **Detection of CIN3+:** CC: 99.7 (98.8-99.9) HC2 and CC (PapIII+): 100.0 (99.1-100)	**Detection of CIN2+ (calc):** CC (PapIIw+): 2.0 (1.2-3.3) HC2 and CC: 6.2 (4.7-9.2) **Detection of CIN3+ (calc):** CC: 2.0 (1.2-3.3) HC2 and CC (PapIII+): 5.1(3.8-6.9)	**% referred to colposcopy:** CC: CIN2+ 2.2, CIN3+ 2.2 HC2 and CC: CIN2+ 6.8, CIN3+ 5.6 **Quality control:** 719/925 (77.7%) of CC samples reviewed by an independent expert were in agreement 96.6% of 600 HC2 samples retested were in agreement (κ 0.75)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
CCCaST Mayrand 2007[121] Mayrand 2006[126]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** Digene cervical sampler kit **CC:** Per protocol at each medical practice	RCT with 2 arms: **Focus on HPV:** HC2 followed by CC **Focus on Pap:** CC followed by HC2 Both screening tests included in each arm, but order of collection was randomized. Tests performed sequentially at same visit	Canada 30 selected medical practices in Montreal and surrounding municipalities (province of Quebec) and St. John's (province of Newfoundland) Physicians recruited from medical practices identified by cytology laboratories as active in cervical cancer screeningWomen attending routine cervical cancer screening	***All women (calc):*** **CIN2+** Conservative Case Definition*: 41/10,154 = 0.4% Liberal Case Definition*: 54/10,154 = 0.5% ***Women with colposcopy/biopsy results:*** **CIN2+** Conservative Case Definition*: 41/1,365 = 3.0% Liberal Case Definition*: 54/1,365 = 4.0%	14,953 assessed for eligibility 10,154 randomly assigned to screening 5,059 assigned to Focus on Pap group 5,095 assigned to Focus on HPV group 9,977 received assigned intervention 5,020 in Focus on Pap group 4,957 in Focus on HPV group **Inclusion:** Age 30-69 **Exclusion:** Attending colposcopy clinic for evaluation, treatment or follow up of a cervical lesion, without a cervix, pregnant, previous history of invasive cervical cancer, received cytology test within 12 months	**Age** 30-39: 38.5% 40-49: 35.0% 50-59: 20.4% 60-69: 6.1% **Ethnicity** (10,019 participants) French Canadian: 36.7% English Canadian: 56.9% Other: 6.4% **Education** (10,064) Elementary school: 10.3% High school: 22.7% Junior college: 29.0% University: 38.0% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Application of reference standard (histologic verification)	Funding source	Yield	Insufficient samples	Sensitivity (95% CI)	Specificity (95% CI)
CCCaST Mayrand 2007[121] Mayrand 2006[126] Fair Good	Colposcopy and biopsy in 90.9% (723/795) of women positive for at least one test and 7.1% (665/9,359) random sample of women negative for both tests	Canadian Institutes of Health Research, Merck Frosst Canada, National Cancer Institute of Canada, Fonds de la Recherche en Santé due Québec	**Test Positivity Rate** HC2: 6.3% in Focus on HPV 5.8% in Focus on Pap CC: 2.7% in Focus on HPV 3.0% in Focus on Pap **Concordance:** NR	**HC2:** NR **CC:** 1.4% in both arms	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **CC (ASC-US+):** 56.4 **CC (LSIL+):** 42.2 **HC2 and Pap:** 100.0 All estimates corrected for verification bias	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **CC (ASC-US+):** 97.3 **CC (LSIL+):** 99.1 **HC2 and Pap:** 92.5 All estimates corrected for verification bias

Study ID	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate	Other performance characteristics	Comments
CCCaST Mayrand 2007[121] Mayrand 2006[126]	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **CC (ASC-US+):** 8.5 **CC (LSIL+):** 17.5 **HC2 and Pap:** 5.5 All estimates corrected for verification bias	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* (95% CI NR) **CC (ASC-US+):** 99.8 **CC (LSIL+):** 99.7 **HC2 and Pap:** 100.0 All estimates corrected for verification bias	Comparison of Screening Approaches Using Combined Groups (n = 9,959 women in two groups who had available HC2 and CC results) **Detection of CIN2+:** Conservative Case Definition* **CC (ASC-US+):** 2.7 **CC (LSIL+):** 0.9 **HC2 and Pap:** 7.5 All estimates corrected for verification bias	**Test Performance by Sampling Order** Performance of HC2 and CC not influenced by order of specimen collection (i.e., first or second), as judged by test positivity, unsatisfactory smears or those showing ASC-US, viral load, and sensitivity or specificity **Referrals for**	*According to the conservative definition, cases were considered only if confirmed on the LEEP specimen or in the confirmatory biopsy when ablative treatment was used. The liberal definition includes all cases of CIN2-3, adenocarcinoma in situ, or cervical cancers confirmed

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

				Colposcopy(using combined groups) Conservative Case Definition* **CC (ASC-US+):** 2.9 **CC (LSIL+):** 1.0 **HC2 and Pap:** 7.9 All estimates corrected for verification bias	by histologic examination of any of the ectocervical or endocervical biopsy specimens.

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics	Application of reference standard (histologic verification)	Funding source
Combination HPV and Cytology Testing (Co-Testing): RCTs reporting relative test performance measures								
NTCC Phase I Ronco 2006[112] Ronco 2007[210] Ronco 2007[211] Ronco 2010[113]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2, LBC (*ThinPrep*) & CC:** plastic Ayre's spatula and a cytobrush	RCT with two recruitment phases, each with two rounds of screening Phase 1 (cotesting) reported here, Phase 2 reported above with primary HPV testing **Study arms:** Round 1: IG: HPV (HC2) & LBC	Italy Nine organized cervical screening programs Women presenting for routine screening	Results at Phase 1 recruitment: **CIN2+ (calc)** IG 75/16,706 = 0.4% CG 51/16,658 = 0.3% **CIN3+ (calc)** IG 39/16,706 = 0.2% CG 31/16,658 = 0.2%	33,364 randomized (age ≥ 35) 16,706 IG 16,658 CG 32,638 completed baseline testing 16,255 IG 16,383 CG **Inclusion:** Age 35-60 Women age 25-34 years also included, but protocol for colposcopy referral in the intervention group differed for this age group in	**Median age at recruitment:** 45 **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	Suspicious areas identified by colposcopy were biopsied Referral to colposcopy (women with complete baseline testing): IG: ASC-US+ or HPV+; 1,730/16,255 = 10.6% CG: ASC-US+ at seven centers (72%), LSIL+ at two centers (28%); 495/16,383 = 3.0% (calc) Compliance with	European Union, Italian Ministry of Health, Special Project "Oncology," Compagnia di S. Paolo FIRMS, and participating Italian regions

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

		HC2 assay performed on residual cytology sample CG: CC Round 2: CC for all women			Phase 1 **Exclusion:** Pregnant, hysterectomy, or treated for CIN in last five years		colposcopy (women with complete baseline testing) (calc): IG: 1,625/1,730 = 93.9% CG: 449/495 = 90.7%	

Study ID Quality rating Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative positive predictive value (95% CI)
NTCC Phase I Ronco 2006[112] Ronco 2007[210] Ronco 2007[211] Ronco 2010[113] Fair Fair	**Test Positivity Rate (at recruitment, varied by site and age)** All ages (calc): *IG(HPV+):* 2,021/22,708 = 8.9% *IG (ASC-US+):* 1435/22,708 = 6.3% *CG (ASC-US+):* 855/22,466=3.8% *CG (LSIL+)*: 341/22,466 = 1.5% Age 25-34 (calc): *IG (ASC-US+):* 530/6,002 = 8.8% *CG (ASC-US+)*: 261/5,808 = 4.5% *CG (LSIL+)*: 129/5,808 = 2.2% Age 35-60: *IG (ASC-US+ or HPV+) (calc):*	**Results at Phase 1 recruitment:** **≥1 Unsatisfactory smear** IG: 2.5% CG: 3.7% p<0.001 **No valid HPV test due to insufficient material (calc)** 14/16,706 = 0.08%	**Cross-sectional results at Phase 1 recruitment (per 1000):** **CIN2+†** IG LBC (ASC-US+) **or** HPV+: 4.49 HPV: 4.37 LBC (ASC-US+): 3.23 LBC (LSIL+): 2.39 LBC (ASC-US+) **and** HPV+: 3.11 CG ASC-US+: 3.06 LSIL+: 2.52 **CIN3+‡** IG LBC (ASC-US+) **or** HPV+: 2.33 HPV: 2.27 LBC (ASC-US+): 1.86 LBC (LSIL+): 1.50 LBC (ASC-US+) **and** HPV+: 1.80 CG ASC-US+: 1.86 LSIL+: 1.56 **Cumulative Phase 1 results (calc):** *All ages* **CIN3+(author provided data)**	**Cross-sectional results at Phase 1 recruitment:** **CIN2+†** IG LBC (ASC-US+) **or** HPV+: 1.47 (1.03-2.09) LBC (ASC-US+) **or** HPV+ (restricted to centers with ASC-US+ referral criteria)*: 1.44 HPV: 1.43 (1.00-2.04) LBC (ASC-US+): 1.06 (0.72-1.55) LBC (LSIL+): 0.78 (0.52-1.18) LBC (ASC-US+) **and** HPV+: 1.02 (0.69-1.50) CG ASC-US+: 1.00 (referent) LSIL+: 0.82 (0.69-0.95) **CIN3+‡** IG LBC (ASC-US+) **or** HPV+: 1.25 (0.78-2.01) LBC (ASC-US+) **or** HPV+ (restricted to centers with ASC-US+ referral criteria)*: 1.28 HPV: 1.22 (0.76-1.96)	**Cross-sectional results at Phase 1 recruitment:** **CIN2+†** IG LBC (ASC-US+) **or** HPV+: 0.40 (0.23-0.66) LBC (ASC-US+) **or** HPV+ (restricted to centers with ASC-US+ referral criteria)*: 0.43 HPV: 0.58 (0.33-0.98) LBC (ASC-US+): 0.57 (0.39-0.82) LBC (LSIL+): 1.11 (0.75-1.64) LBC (ASC-US+) **and** HPV+: 1.66 (1.16-2.36) CG ASC-US+: 1.00 (referent) LSIL+: 1.88 (1.60-2.06) **CIN3+‡** IG LBC (ASC-US+) **or** HPV+: 0.34 (0.21-0.54) LBC (ASC-US+) **or** HPV+ (restricted to centers with ASC-US+ referral criteria)*: 0.38 HPV: 0.50 (0.32-0.79) LBC (ASC-US+): 0.54 (0.33-0.87)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative positive predictive value (95% CI)
	1,789/16,706 = 10.7% *CG (ASC-US+):* 594/16,658 = 3.6% *CG (LSIL+)(calc):* 212/16,658 = 1.3% **Concordance (calc):** HPV+ samples that were ASC-US+: 300/1,185 = 25.3% HPV+ samples that were LSIL+: 167/1,185 = 14.1% ASC-US+ samples that were HPV+: 300/894 = 33.6% LSIL+ samples that were HPV+: 167/345 = 48.4% **Referred to colposcopy (calc):** All ages: *IG*: 2,485/22,708 = 10.9% *CG*: 735/22,466 = 3.3% Age 25-34: *IG:* 712/6,002 = 11.9% *CG*: 237/5,808 = 4.1% Age 35-60:		**R1:** *IG:* 75/22,708 = 0.33% (0.26-0.41) *CG:* 58/22,466 = 0.26% (0.20-0.33) **R2:** *IG:* 13/22,093 = 0.06% (0.03-0.10) *CG:* 19/22,330 = 0.09% (0.05-0.13) **C**: *IG:* 88/22,708 = 0.39% (0.31-0.48) *CG:* 77/22,466 = 0.34% (0.27-0.43) **CIN2+(author provided data)** **R1:** *IG:* 187/22,708 = 0.82% (0.71-0.95) *CG:* 99/22,466 = 0.44% (0.36-0.54) **R2:** *IG:* 22/22,093 = 0.09% (0.06-0.15) *CG:* 34/22,330 = 0.15% (0.11-0.21) **C**: *IG:* 209/22,708 = 0.92%(0.80-1.05) *CG:* 133/22,466 = 0.59%(0.50-0.70) *Women 35-60:* **CIN3+(author provided data)** Round 1 IG*: 52/16,706 = 0.31% CG: 33/16,658 = 0.20% Round 2 IG*: 5/16,332 = 0.03% CG: 11/16,561 = 0.07% Both rounds IG*: 57/16,706 = 0.34% CG: 44/16,658 = 0.26% **CIN2+(author provided data)** Round 1 IG*: 109/16,706 = 0.65% CG: 61/16,658 = 0.37% Round 2 IG*: 11/16,332 = 0.07%	LBC (ASC-US+): 1.00 (0.61-1.64) LBC (LSIL+): 0.80 (0.48-1.36) LBC (ASC-US+) **and** HPV+: 0.96 (0.58-1.59) CG ASC-US+: 1.00 (referent) LSIL+: 0.84 (0.66-0.95) *data received from author, 95% CI not provided **Cumulative Phase 1 results:** HPV group vs. cytology group **CIN2+(author provided data)** *All ages (calc)* **R1:** 1.87 (1.47-2.38) **R2:** 0.65 (0.38-1.12) **C:** 1.55 (1.25-1.93) *Women 35-60 (from author)* **R1:** 1.78 (1.30-2.44) **R2:** 0.59 (0.28-1.24) **C:** 1.50 (1.13-1.98) *Women 25-34 (from author)* **R1:** 1.99 (1.35-2.92) **R2:** 0.73 (0.34-1.60) **C:** 1.63 (1.16-2.28) **CIN3+(author provided data)** *All ages (calc)* **R1:** 1.28 (0.91-1.80) **R2**: 0.69 (0.34-1.40) **C:** 1.13 (0.83-1.53) *Women 35-60*	LBC (LSIL+): 1.14 (0.69-1.90) LBC (ASC-US+) **and** HPV+: 1.57 (0.97-2.54) CG ASC-US+: 1.00 (referent) LSIL+: 1.92 (1.53-2.13) *data received from author, 95% CI not provided **Cumulative Phase 1 results:** Neither PPV nor the number of participants with false positive results reported

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative positive predictive value (95% CI)
	IG: 1,773/16,706 = 10.6% *CG*: 498/16,658=3.0% **Invasive cancers** (ICC-AD), All ages **R1:** *IG:* 2, *CG:* 7 **R2:** *IG:* 0, *CG:* 6 **C:** *IG:* 2, *CG:* 13 Age 25-34 (author provided data) **R1:** *IG:* 0, *CG:* 1 **R2:** *IG:* 0, *CG:* 2 **C:** *IG:* 0, *CG:* 3 Age 35-60 (author provided data) **R1:** *IG:* 2, *CG:* 6 **R2:** *IG:* 0, *CG:* 4 **C:** *IG:* 2, *CG:* 10		CG: 19/16,561 = 0.11% Both rounds IG*: 120/16,706 = 0.72% CG: 80/16,658 = 0.48% *Women 25-34* **CIN3+(author provided data)** Round 1 IG*: 23/6,002 = 0.38% CG: 25/5,808 = 0.43% Round 2 IG*: 8/5,761 = 0.14% CG: 8/5,769 = 0.14% Both rounds IG*: 31/6,002 = 0.52% CG: 33/5,808 = 0.57% **CIN2+(author provided data)** Round 1 IG*: 78/6,002 = 1.30% CG: 38/5,808 = 0.65% Round 2 IG*: 11/5,761 = 0.19% CG: 15/5,769 = 0.26% Both rounds IG*: 89/6,002 = 1.48% CG: 53/5,808 = 0.91% *LBC (ASC-US+) **or** HPV+	**R1:** 1.57 (1.02-2.43) **R2:** 0.46 (0.16-1.33) **C:** 1.30 (0.87-1.91) *Women 25-34* **R1:** 0.89 (0.51-1.57) **R2:** 1.00 (0.38-2.67) **C:** 0.91 (0.56-1.48)	

†Data include CIN2, CIN3, and AIS
‡Data include CIN3 and AIS

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
POBASCAM Bulkmans 2007[114] Bulkmans 2004[214]	PCR (GP5+/GP6+) Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) **CC and PCR:** Cervex-Brush or cytobrush	RCT with two arms: **IG:** Conventional cytology and HPV Women with normal cytology and HPV- recalled at 5 years. Repeat testing at 6 and 18 months advised for normal cytology/HPV+ and ASC-US+ cytology. Women HPV- and LSIL or better at 18 months were recalled at 5 years. **CG:** Conventional cytology alone (HPV test results blinded) Women with normal cytology recalled at 5 years. Women with ASC-US+ at baseline were recalled at 6 and 18 months. Women with normal cytology at 6 and 18 months recalled at 5 years. At 5 years, all women managed according to protocol for IG PCR assay performed on CC specimen	The Netherlands Conducted within the Dutch nationwide screening program	***Round 1:*** **CIN2+** IG: 98/8,575 = 1.1% CG: 63/8,580 = 0.7% **CIN3+** IG: 68/8,575 = 0.8% CG: 40/8,580 = 0.5% ***Both rounds:*** **CIN2+** IG: 137/8,575 = 1.6% CG: 137/8,580 = 1.6% **CIN3+** IG: 92/8,575 = 1.1% CG: 94/8,580 = 1.1%	49,220 eligible 44,938 enrolled IG: 22,420 CG: 22,518 18,403 enrolled and ≥6.5 yrs follow up by Feb 2007 17,155 eligible at baseline IG: 8,575 CG: 8,580 16,869 eligible at round 2 IG: 8,413 CG: 8,456 **Inclusion:** women aged 30-56 years, live in a defined semi-urbanized region to the southwest of Amsterdam **Exclusion:** history of CIN2+ or abnormal cytology in last 2 years, hysterectomy	**Median age:** 41.0 (range 29-56) **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Application of reference standard (histologic verification)	Funding source	Yield	Insufficient samples	Detection of CIN2+/CIN3+
POBASCAM Bulkmans 2007[114] Bulkmans 2004[214] Fair Fair	Colposcopically directed biopsies from suspected areas on cervix according to standard procedures in the Netherlands Referral criteria: **IG:** HSIL+ at any time; ASC-US+ at baseline and ASC-US+/HPV+ at 6 months; HPV+ on 2nd repeat smear at 18 months **CG:** HSIL+ at any time; ASC-US+ at baseline and 6 or 18 months. Round 1 IG: 201/8,575 = 2.3% (2.0-2.7) CG: 115/8,580=1.3% (1.1-1.6), p<0.0001 Round 2 IG: 87/6,887=1.3% (1.0-1.6) CG: 129/6,838 = 1.9% (1.6-2.2), p=0.003 Both rounds (calc) IG: 288/8,575=3.4% CG: 244/8,580=2.8%	Zorg Onderzoek Nederland (Netherlands Organization for Health Research and Development)	**Test Positivity Rate** HSIL+ Round 1: IG: 56/8,575 = 0.7% CG: 54/8,580 = 0.6% Round 2: IG: 38/6,887 = 0.6% CG: 50/6,838 = 0.7% Both rounds (calc): IG: 94/8,575 = 1.1% CG: 104/8,580 = 1.2% **Concordance** % of ASC-US+ that were HPV+ (calc) Round 1: IG: 46.1% CG: 44.7% Round 2: IG: 36.6% CG: 41.8% % of HSIL+ that were HPV+ Round 1: IG: 85.7% CG: 84.9% Round 2: IG: 77.8% CG: 77.8%	**Inadequate cytology** IG: 0.1% Round 1, 0.3% Round 2 CG: 0.1% Round 1, 0.4% Round 2	**CIN2+ (95% CI)** Round 1 IG: 98/8,575 = 1.1% (0.9-1.4) CG: 63/8,580 = 0.7% (0.6-0.9) p=0.006 Round 2 IG: 39/8,413 = 0.5% (0.3-0.6) CG: 74/8,456 = 0.9% (0.7-1.1) p=0.001 Both rounds IG: 137/8,575 = 1.6% (1.4-1.9) CG: 137/8,580 = 1.6% (1.4-1.9) **CIN3+ (95% CI)** Round 1 IG: 68/8,575 = 0.8% (0.6-1.0) CG: 40/8,580 = 0.5% (0.4-0.6) 70% higher in IG (15-151), p=0.007 Round 2 IG: 24/8,413 = 0.3% (0.2-0.4) CG: 54/8,456 = 0.6% (0.5-0.8) 55% lower in IG (28-72), p=0.001 Both rounds IG: 92/8,575 = 1.1% (0.9-1.3) CG: 94/8,580 = 1.1% (0.9-1.3) p=0.89 **Invasive cancers**, n: ICC: **R1:** *IG:* 5, *CG:* 2 **R2:** *IG:* 2, *CG:* 7 **C:** *IG:* 7, *CG:* 9 ACIS: **R1:** *IG:* 3, *CG:* 1 **R2:** *IG:* 0, *CG:* 3 **C:** *IG:* 3, *CG:* 4

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Relative Detection Ratio (95% CI)	Positive Predictive Value (95% CI)	Relative Positive Predictive Value (95% CI)	5-Year Cumulative Risk of CIN2+/CIN3+ per Woman Screened	Colposcopy Referral Rates and CIN2+/CIN3+ Rate per Woman Referred
POBASCAM Bulkmans 2007[114] Bulkmans 2004[214]	IG vs. CG **CIN2+ (calc)** Round 1 1.1%/0.7% = 1.56 (1.14-2.13) Round 2 0.5%/0.9% = 0.52 (0.36-0.77) Both rounds 1.6%/1.6% = 1.00 (0.79-1.27) **CIN3+ (calc)** Round 1 0.8%/0.5% = 1.70 (1.15-2.51) Round 2 0.3%/0.6% = 0.44 (0.27-0.71) Both rounds 1.1%/1.1% = 0.98 (0.74-1.30)	Neither PPV nor the number of participants with false positive results reported	Neither PPV nor the number of participants with false positive results reported	% (95% CI)* **CIN2+** IG: Normal cytology and HPV negative: 0.4% (0.2-0.5) HPV negative: 0.5% (0.3-0.6) CG: Normal cytology: 1.1% (0.8-1.4) **CIN3+** IG: Normal cytology and HPV negative: 0.1% (0.1-0.2) HPV negative: 0.2% (0.1-0.3) CG: Normal cytology: 0.8% (0.6-1.0) *Adjusted for loss to follow-up	**Colposcopy Referral Rate per Woman Screened (95% CI)** IG: Round 1: 201/8575 = 2.3% (2.0-2.7) Round 2: 87/6887 = 1.3% (1.0-1.6) CG: Round 1: 115/8580 = 1.3% (1.1-1.6), p<0.0001 Round 2: 129/6838 = 1.9% (1.6-2.2), p=0.003 **CIN2+ Rate per Woman Referred (95% CI)** IG: Round 1: 47% (40-54) Round 2: 40% (31-51) CG: Round 1: 49% (40-58) Round 2: 52% (43-60) **CIN3+ Rate per Woman Referred (95% CI)** IG: Round 1: 33% (27-40) Round 2: 25% (17-35) CG: Round 1: 32% (24-41), p=0.90 Round 2: 40% (32-48), p=0.03

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Swedescreen Naucler 2007[115] Naucler 2009[160] Elfgren 2005[215]	PCR (GP5+/GP6+) Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) CC and PCR: cytologic brush	RCT with two arms: **IG:** Conventional cytology plus HPV test (HPV+ women with no record of abnormal cytology were offered 2nd round of HPV testing and cytology ≥ 12 months later; women with persistent type-specific HPV infection were offered colposcopy) **CG:** Conventional cytology alone (similar number of randomly selected women offered 2nd cytology screening and colposcopy) Follow up included annual cytology and HPV tests, with colposcopy in cases of persistent high-risk HPV infection in addition to routine clinical practice for abnormal cytology	Sweden Conducted within the Swedish cervical cancer screening program	***First screening:*** **CIN2+ (calc)** IG: 114/6,257 = 1.8% CG: 76/6,270 = 1.2% **CIN3+ (calc)** IG: 72/6,257 = 1.2% CG: 55/6,270 = 0.9% ***Entire study (calc):*** **CIN2+** IG: 139/6,257 = 2.2% CG: 119/6,270 = 1.9% **CIN3+** IG: 88/6,257 = 1.4% CG: 85/6,270 = 1.4% **Invasive cancers**, pooled data only: ICC: *IG:* 1, *CG:* 2 ACIS-AD: *IG:* 4, *CG:* 4	12,527 randomized IG: 6,257 CG: 6,270 **Inclusion:** women aged 32-38 years participating in the screening program from May 1997-November 2000 in 5 Swedish cities **Exclusion:** none	**Mean age:** 35.1 **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Application of reference standard (histologic verification)	Funding source	Yield	Insufficient samples	Detection of CIN (95% CI)	Relative Detection Ratio (95% CI)	Positive Predictive Value	Relative Positive Predictive Value
Swedescreen Naucler 2007[115] Naucler 2009[160] Elfgren 2005[215] Fair Fair	Ectocervical biopsy specimens taken from all lesions that turned white when treated with acetic acid and lesions that were not stained by Lugol's iodine solution. If no lesions seen, 2 specimens taken at 12 o-clock and 6 o'clock positions on ectocervix, close to squamo-columnar junction. Endocervical cell sample also obtained from all women ASC-US+ referred to colposcopy in Stockholm; in other cities, repeat cytology was option for ASC-US or LSIL In IG, women with persistent type-specific HPV infection referred to colposcopy Random sample of 111 women in control group also referred to colposcopy	Swedish Cancer Society and Europe against Cancer	**Test Positivity Rate (varied by site)** **R1:** *IG (ASC-US+):* 146/6,257 = 2.3% *IG (HSIL+)*: NR *CG (ASC-US+):* 150/6270=2.4% *CG (HSIL+)*: NR **R2:** NR **C:** NR **Concordance** NR **Colposcopy referrals** **R1**: NR **R2:** NR **C:** NR **Compliance with referral:** **R1:** NR **R2:** NR **C:** NR	PCR (calc) 2.7% inadequate at baseline 0.7% inadequate at second test CC NR	**CIN2+ (calc)** First screening IG: 114/6,257 = 1.82% (1.51-2.18) CG: 76/6,270 = 1.21% (0.96-1.51) Second screening IG: 25/6,257 = 0.40% (0.26-0.59) CG: 43/6,270 = 0.69% (0.50-0.92) Entire study IG: 139/6,257 = 2.22% (1.87-2.62) CG: 119/6,270 = 1.90% (1.57-2.27) **CIN3+ (calc)** First screening IG: = 72/6,257 = 1.15% (0.90-1.45) CG: = 55/6,270 = 0.88% (0.66-1.14) Second screening IG: 16/6,257 = 0.26% (0.15-0.41) CG: 30/6,270 = 0.48% (0.32-0.68) Entire study IG: 88/6,257 = 1.41% (1.13-1.73) CG: 85/6,270 = 1.36% (1.08-1.67)	IG vs. CG **CIN2+** First screening 1.51 (1.13-2.02) Second screening 0.58 (0.36-0.96) Entire study (calc) 2.22%/1.90% = 1.17 (0.92-1.49) **CIN3+** First screening 1.31 (0.92-1.87) Second screening 0.53 (0.29-0.98) Entire study (calc) 1.41%/1.36% = 1.04 (0.77-1.39)	Neither PPV nor the number of participants with false positive results reported	Neither PPV nor the number of participants with false positive results reported

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics	Application of reference standard (histologic verification)	Funding source
ARTISTIC Kitchener 2009[117] Kitchener 2006[216] Sargent 2010[217] Sargent 2008[218] Kitchener 2009[197]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) at ≥1.0 pg/mL **HPV and LBC (ThinPrep):** Collection method NR	ARTISTIC trial randomized participants in 3:1 ratio to two arms: HPV-revealed: LBC + HPV results acted on HPV-concealed: LBC results alone acted on Two screening rounds; participants invited for 2nd screen 36 months after 1st screen Round 2 defined as first cytologically adequate sample taken 26 to 54 months after Round 1 sample	England Greater Manchester county Women recruited in general practice and family planning clinics during routine screening (National Health Service Cervical Screening Programme)	***Round 1:*** **CIN2+:** Revealed: 2.46% Concealed: 2.17% **CIN3+:** Revealed: 1.27% Concealed: 1.31% ***Both rounds:*** **CIN2+:** Revealed: 3.01% Concealed: 3.03% **CIN3+:** Revealed: 1.51% Concealed: 1.77% Prevalence over both rounds combines prevalence over Rounds 1 and 2 using the formula: $\log(1-p) = \log(1-p_1) + \log(1-p_2)$	Round 1: 25,078 enrolled and randomized 24,856 confirmed eligible after randomization 24,510 analyzed Revealed (IG): 18,386 Concealed (CG): 6,124 Round 2: 16,080 with follow-up data at time of analysis Women with CIN2+ histology at R1 excluded from analysis of R2 results 15,542 analyzed Revealed: 11,676 Concealed: 3,866 **Inclusion:** age 20-64 years at round 1 **Exclusion:** NR	**Age:** Mean: NR <30: 21% (calc) ≥30: 79% (calc) **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	**Referral protocol:** Colposcopy for positive screening test only, with biopsy of abnormalities Colposcopy in those with HSIL in both arms ASC-US or LSIL followed with repeat screening, with colposcopy for persistent abnormality Those with HPV+ test had repeat HPV at 12-month intervals, with colposcopy for persistent positive test With this protocol, histology obtained up to 30 months after corresponding screening test **Colposcopy data:** Colposcopies	National Institute of Health Research Health Technology Assessment Programme

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics	Application of reference standard (histologic verification)	Funding source
							among women screened, unclear whether referred or attending (calc): *All ages* **R1:** *Revealed:* 1,247/18,386 = 6.8% *Concealed:* 320/6,124 = 5.2% **R2:** *Revealed:* 284/11,676 = 2.4% *Concealed:* 74/3,866 = 1.9% **C:** *Revealed:* 1,531/18,386 = 8.3% *Concealed:* 394/6,124 = 6.4% *Women <30* **R1:** *Revealed:* 540/3879=13.9% *Concealed:* 123/1287=9.6% **R2:** *Revealed:* 124 *Concealed:* 32 (sample size NR for	

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics	Application of reference standard (histologic verification)	Funding source
							R2) **C:** *Revealed:* 664/3879-17.1% *Concealed:* 115/1287=12.0% *Women ≥ 30* **R1:** *Revealed:* 707/14507=4.9% *Concealed:* 197/4837=4.1% **R2:** *Revealed:* 160 *Concealed:*42 (sample size NR for R2) **C:** *Revealed:* 867/14507=6.0% *Concealed:* 239/4837=4.9%	

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Quality rating	Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value (95% CI)	Relative positive predictive value (95% CI)
ARTISTIC Kitchener 2009[117] Kitchener 2006[216] Sargent 2010[217] Sargent 2008[218] Kitchener 2009[197]	Fair	Good	**Test positivity (calc):** HSIL+ **R1:** *Revealed* 358/18,386 = 2.0% *Concealed:* 105/6,124 = 1.7% **R2:** *Revealed* : 47/11,676 = 0.4% *Concealed:* 16/3,866 = 0.4% **C:** *Revealed* : 405/18,386 = 2.2% *Concealed:* 121/6,124 = 2.0% *Women aged <30* **R1:** *Revealed* : 164/3,879 = 4.2% *Concealed:* 51/1,287 = 4.0%	Round 1 (calc) 346/24,856 = 1.4% with inadequate *or* missing screening tests Round 2 (calc) 90/16,080 = 0.6% with no adequate cytology	**CIN2+ (95% CI)** Round 1 Revealed:453/18,386 = 2.46% (2.24-2.70) Concealed: 133/6,124 = 2.17% (1.82-2.57) Round 2 Revealed: 65/11,676 = 0.56% (0.43-0.71) Concealed: 34/3,866 = 0.88% (0.61-1.23) Both rounds *See prevalence above for methods* Revealed: 3.01% (2.75-3.28) Concealed: 3.03% (2.59-3.53) **CIN3+ (95% CI)** Round 1 Revealed: 233/18,386 = 1.27% (1.11-1.44) Concealed: 80/6,124 = 1.31%	**CIN2+ (95% CI, p-value)** Round 1 1.14 (0.94-1.38) p>0.2 Round 2 0.63 (0.42-0.96) p=0.035 Both rounds 0.99 (0.83-1.19) p>0.2 Women <30 (calc): 1.07(0.83-1.38) Women ≥30 (calc): 1.21(0.91-1.60) **CIN3+ (95% CI. p)** Round 1 0.97 (0.75-1.25) p>0.2 Round 2 0.53 (0.30-0.96) p=0.042 Both rounds 0.85 (0.67-1.08) p>0.2	***All ages:*** **CIN2+ (calc)** Round 1 (3,566/18,386)/(653/6,124) = 1.82 (1.68-1.97) Round 2 (1,178/11,676)/(139/3,866) = 2.81 (2.36-3.33) Both rounds (4,744/18,386)/(792/6,124) = 2.00 (1.86-2.14) **CIN3+ (calc)** Round 1 (3,786/18,386)/(706/6,124) = 1.79 (1.66-1.93) Round 2 (1,224/11,676)/(192/3,866) = 2.11 (1.82-2.45) Both rounds (5,010/18,386)/(898/6,124) = 1.86 (1.74-1.98) ***Age 20-29:*** **CIN2+ (calc)** Round 1 (1,318/3,879)/(205/1,287) = 2.13 (1.87-2.44)	**CIN2+ (95% CI NR)** Round 1 Revealed: LBC (ASCUS+): 421/2,344 = 18.0% (16.4-19.6) LBC (ASCUS+) **or** HPV+ (calc): 453/4,019 = 11.3% (10.3-12.3) Concealed: LBC (ASCUS+): 133/786 = 16.9% (14.4-19.7) Round 2 Revealed: LBC (ASCUS+): 65/575 = 11.3% (8.8-14.2) (p<0.001 comparing R1 and R2) LBC (ASCUS+) **or** HPV+ (calc): 80/1,258 = 6.4% (5.1-7.9) Concealed: LBC (ASCUS+): 34/210 = 16.2% (11.5-21.9) **CIN3+ (calc)** Round 1 Revealed: LBC (ASCUS+):	**CIN2+ (calc)** Round 1 Revealed: LBC (ASCUS+): 18.0%/16.9% = 1.06 (0.89-1.27) LBC (ASCUS+) **or** HPV+: 11.3%/16.9% = 0.67 (0.56-0.80) Concealed: 1.00 (Ref) Round 2 Revealed: LBC (ASCUS+): 11.3%/16.2% = 0.70 (0.48-1.02) LBC (ASCUS+) **or** HPV+: 6.4%/16.2% = 0.39 (0.27-0.57) Concealed: 1.00 (Ref) **CIN3+ (calc)** Round 1 Revealed: LBC (ASCUS+): 9.5%/10.2% = 0.93 (0.73-1.19) LBC (ASCUS+) **or** HPV+: 5.8%/10.2% = 0.57 (0.45-0.73) Concealed: 1.00 (Ref)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Quality rating	Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value (95% CI)	Relative positive predictive value (95% CI)
			R2: NR **C:** NR *Women aged ≥30* **R1:** *Revealed* 194/14,507 = 1.3% *Concealed:* 54/4,837 = 1.1% **R2:** NR **C:** NR **Concordance (calc):** % of HPV+ samples that were ASC-US+ Round 1: Revealed: 1,185/2,860 = 41.4% Concealed: 402/953 = 42.2% Round 2: Revealed: 249/932 = 26.7% Concealed: 92/316 = 29.1%		(1.04-1.62) Round 2 Revealed: 29/11,676 = 0.25% (0.17-0.36) Concealed: 18/3,866 = 0.47% (0.28-0.73) Both rounds *See prevalence above for methods* Revealed: 1.51% (1.33-1.71) Concealed: 1.77% (1.43-2.16)	Women <30 (calc): 0.92 (0.65-1.31) Women ≥30 (calc): 1.02 (0.71-1.47) Reported as Odds Ratio in Table 4 of manuscript (revealed vs. concealed)	Round 2 NR Both rounds NR **CIN3+ (calc)** Round 1 (1,437/3,879)/ (236/1,287) = 2.02 (1.79-2.28) Round 2 NR Both rounds NR ***Age 30-64:*** **CIN2+ (calc)** Round 1 (2,248/14,507)/ (448/4,837) = 1.67 (1.52-1.84) Round 2 NR Both rounds NR **CIN3+ (calc)** Round 1 (2,349/14,507)/ (470/4,837) = 1.67 (1.52-1.83) Round 2 NR Both rounds NR	223/2,344 = 9.5% (8.4-10.8) LBC (ASCUS+) **or** HPV+: 233/4,019 = 5.8% (5.1-6.6) Concealed: LBC (ASCUS+): 80/786 = 10.2% (8.2-12.5) Round 2 Revealed: LBC (ASCUS+): 29/575 = 5.0% (3.4-7.2) LBC (ASCUS+) **or** HPV+: 34/1,258 = 2.7% (1.9-3.8) Concealed: LBC (ASCUS+): 18/210 = 8.6% (5.2-13.2)	Round 2 Revealed: LBC (ASCUS+): 5.0%/8.6% = 0.59 (0.33-1.04) LBC (ASCUS+) **or** HPV+: 2.7%/8.6% = 0.32 (0.18-0.55) Concealed: 1.00 (Ref)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Quality rating	Applicability	Yield	Insufficient samples	Detection of CIN2+/CIN3+	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value (95% CI)	Relative positive predictive value (95% CI)
			% of ASC-US+ that were HPV+ Round 1: Revealed: 1,185/2,344 = 50.6% Concealed: 402/786 = 51.1% Round 2: Revealed: 249/575 = 43.3% Concealed: 92/210 = 43.8% **Invasive cancers**, (ICC-AD), pooled from both rounds, n: *IG*: 8 *CG*: 4						

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Cytology Testing with HPV Triage of Positive Cytology (Reflex HPV): Studies reporting absolute test performance measures						
Andersson 2005[136]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at 1.0 pg/mL **HC2 and CC:** Cervical brush	Consecutive series, split sample HC2 assay performed on CC sample	Sweden Gynecologic departments of three university hospitals of Stockholm 4-6 months after referral cytology Women with low-grade atypia (ASC-US or LSIL) detected at a population-based screening	All **CIN2:** 27/177 = 15.3% **CIN3:** 11/177 = 6.2% Referred with ASC-US **CIN2:** 6/52 = 11.5% **CIN3:** 4/52 = 7.7% Referred with LSIL **CIN2:** 21/125 = 16.8% **CIN3**: 7/125 = 5.6%	177 enrolled **Inclusion:** Referred with low-grade atypia (ASC-US or LSIL) **Exclusion:** NR	**Mean Age:** 34 (23-60) **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Andersson 2005[136]	Colposcopy and biopsy in all women Punch biopsies were obtained from acetowhite areas; if no acetowhite area was observed, a biopsy was taken close to the squamocolumnar junction, at 12 o'clock	Swedish Cancer Foundation, the Karolinska Institutet Foundation, and AFA, Sweden	Fair	Good	**Test Positivity Rate** HC2 **All:** 65.5% **Referred with ASC-US:** 44.2% **Referred with LSIL:** 74.4% CC (ASC-US+) **All:** 47.5% **Referred with ASC-US (calc):** 38.5% **Referred with LSIL (calc):** 51.2% **Concordance** 72.4% of HPV+ samples were ASC-US+ 81.0% of ASC-US+ samples were HPV+ **% HPV+ by CC diagnosis:** ASC-US+: 81.0% Negative: 51.6%	NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

					HPV/CC categories: HPV-CC-: 25.4% HPV-CC+: 9.0% HPV+CC+: 38.4% HPV+CC-: 27.1%	

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics	Comments
Andersson 2005[136]	**Detection of CIN2+:** HC2 (all) : 82 (67-91) CC (all) (ASC-US+): 61 (45-74) HC2 (referred with ASC-US, calc): 6/10 = 60.0 (26.2-87.8) CC (referred with ASC-US, calc): 6/10 = 60.0 (26.2-87.8) HC2 (referred with LSIL, calc): 25/28 = 89.3 (71.8-97.7) CC (referred with LSIL, calc): 17/28 = 60.7 (40.6-78.5) **Detection of CIN3+ (calc):** HC2 (all): 10/11 = 90.9 (58.7-99.8) CC (all) (ASC-US+): 8/11 = 72.7 (39.0-94.0) HC2 (referred with ASC-US): 3/4 = 75.0 (19.4-99.4) CC (referred with ASC-US): 3/4 = 75.0 (19.4-99.4) HC2 (referred with LSIL): 7/7 = 100.0 (59.0-100.0) CC (referred with LSIL):	**Detection of CIN2+:** HC2 (all): 39 (31-47) CC (all, calc): 78/139 = 56.1* (47.5-64.5) HC2 (referred with ASC-US, calc): 25/42 = 59.5 (43.3-74.4) CC (referred with ASC-US, calc): 28/42 = 66.7 (50.5-80.4) HC2 (referred with LSIL, calc): 29/97 = 29.9 (21.0-40.0) CC (referred with LSIL, calc): 50/97 = 51.5 (41.2-61.8) **Detection of CIN3+ (calc):** HC2 (all): 60/166 = 36.1 (28.8-44.0) CC (all): 90/166 = 54.2 (46.3-62.0) HC2 (referred with ASC-US): 28/48 = 58.3 (43.2-72.4) CC (referred with ASC-US): 31/48 = 64.6 (49.5-77.8) HC2 (referred with LSIL): 32/118 = 27.1 (19.3-36.1) CC (referred with LSIL): 59/118 = 50.0 (40.7-59.3)	**Detection of CIN2+:** HC2 (all): 27 (18-35) CC (all, calc): 23/84 = 27.4 (18.2-38.2) HC2 (referred with ASC-US, calc): 6/23 = 26.1 (10.2-48.4) CC (referred with ASC-US, calc): 6/20 = 30.0 (11.9-54.3) HC2 (referred with LSIL, calc): 25/93 = 26.9 (18.2-37.1) CC (referred with LSIL, calc): 17/64 = 26.6 (16.3-39.1) **Detection of CIN3+ (calc):** HC2 (all): 10/116 = 8.6 (4.2-15.3) CC (all): 8/84 = 9.5 (4.2-17.9) HC2 (referred with ASC-US): 3/23 = 13.0 (2.8-33.6) CC (referred with ASC-US): 3/20 = 15.0 (3.2-37.9)	**Detection of CIN2+:** HC2 (all): 89 (80-97) CC (all, calc): 78/93 = 83.9 (74.8-90.7) HC2 (referred with ASC-US, calc): 25/29 = 86.2 (68.3-96.1) CC (referred with ASC-US, calc): 28/32 = 87.5 (71.0-96.5) HC2 (referred with LSIL, calc): 29/32 = 90.6 (75.0-98.0) CC (referred with LSIL, calc): 50/61 = 82.0 (70.0-90.6) **Detection of CIN3+ (calc):** HC2 (all): 60/61 = 98.4 (91.2-100.0) CC (all): 90/93 = 96.8 (90.9-99.3) HC2 (referred with ASC-US): 28/29 = 96.6 (82.2-99.9) CC (referred with ASC-US): 31/32 = 96.9 (83.8-99.9)	**Detection of CIN2+ (calc):** HC2 (all): 61.2 (52.5-69.3) CC (all): 43.9 (35.5-52.5) HC2 (referred with ASC-US): 40.5 (25.6-56.7) CC (referred with ASC-US): 33.3 (19.6-49.5) HC2 (referred with LSIL): 70.1 (60.0-79.0) CC (referred with LSIL): 48.5 (38.2-58.8) **Detection of CIN3+ (calc):** HC2 (all): 63.9 (56.0-71.2) CC (all): 45.8 (38.0-53.7) HC2 (referred with ASC-US): 41.7 (27.6-56.8) CC (referred with ASC-US): 35.4 (22.2-50.5) HC2 (referred with LSIL): 72.9 (63.9-80.7)	42% of women ≤30 years old without any signs of CIN were HPV positive, compared to 23% of women >30	HPV accuracy available grouped by referral smear (ASC-US vs LSIL), but repeat cytology accuracy only presented for all patients combined (ASC-US and LSIL referral smears)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics	Comments
	5/7 = 71.4 (29.0-96.3)	*Reported as 34% in text	HC2 (referred with LSIL): 7/93 = 7.5 (3.1-14.9) CC (referred with LSIL): 5/64 = 7.8 (2.6-17.3)	HC2 (referred with LSIL): 32/32 = 100.0 (89.1-100.0) CC (referred with LSIL): 59/61 = 96.7 (88.7-99.6)	CC (referred with LSIL): 50.0 (40.7-59.3)		

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
Bergeron 2000[137]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at 1.0 pg/mL **HC2:** Cone brush **CC:** Wooden spatula (ectocervix) and cytobrush (endocervix)	Consecutive series HC2 sample collected following CC sample at same visit	France 41 participating gynecologists; number of clinics NR Within 2 months after referral cytology Women referred for ASC-US or LSIL smears in the Laboratoire Pasteur Cerba, a private laboratory	All **CIN2+:** 26/378 = 6.9% Referred with ASC-US **CIN2+:** 12/111 = 10.8% Referred with LSIL **CIN2+:** 14/267 = 5.2%	1,037 eligible 404 consented 378 included (26 inadequate biopsy specimens) **Inclusion:** Referred with ASC-US or LSIL **Exclusion:** NR	**Mean Age:** 35 (15-75) **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR
Manos 1999[100]	Hybrid Capture 2 (prototype) Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58) at 1.0 pg/mL **HC2:** Conical brush **CC:** Cervical broom	Consecutive series HC2 sample collected following CC sample at initial visit (referral cytology) Repeat CC collected at colposcopy examination and used to estimate	US Participants identified from cohort of 46,009 women belonging to Kaiser Permanente Medical Care Program, Northern California Region, who had routine cervical cytology at 1 of 12 gynecology clinics at 4 participating centers	**HSIL (CIN2-3):** 64/973 = 6.6% **Invasive cancer:** 1/973 = 0.1%	1,632 women with ASC-US 1,340 returned for colposcopy 995 participated in study 973 definitive histologic diagnosis and HPV result available 957 repeat cytology results available **Inclusion:** ASC-US cytology results	**Median Age:** 37 (15-78) **Ethnicity** (850 participants) White: 64% Black: 9% Hispanic: 14% Asian/Pacific Islander: 11% Other: 2% **Education:** NR **Income:** NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

		results of repeat cytology conducted within 6 months	Median of 67 days (range, 12-240 days) after referral cytology Women with initial ASC-US cytology results		**Exclusion:** Pregnant, treated for CIN within previous 6 m, no longer Kaiser Permanente members, moved, provider deemed them ineligible (e.g., due to serious illness)	**HIV+:** NR **Other STIs:** NR **Smoking:** NR

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
Bergeron 2000[137]	All women had colposcopies, and biopsy specimens were taken from the abnormal transformation zone seen in all but 20 women	Digene Diagnostics, Inc.	Fair	Good	**Test Positivity Rate** HC2 **All:** 53.7% **Referred with ASC-US: 43.2**% **Referred with LSIL:** 58.1% CC (ASC-US+) **All:** 49.7% **Referred with ASC-US:** 32.4% **Referred with LSIL:** 56.9% HC2 and CC **All:** 66.4% **Referred with ASC-US:** 57.7% **Referred with LSIL:** 70.0% **Concordance** NR	NR
Manos 1999[100]	Colpsocopy with biopsy and/or ECC in all women In cases in which no lesion requiring biopsy was seen, an ECC was performed. In other cases, ECCs were performed at the discretion of the colposcopist	Kaiser Permanente Innovations Program, Cytyc Corporation, Digene Corporation	Good	Good	**Test Positivity Rate** HC2: 39.5% CC (ASC-US+): 38.9% **Concordance** NR	NR

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics
Bergeron 2000[137]	**Detection of CIN2+:** All **HC2:** 23/26 = 88 (69.8-97.6) **CC:** 22/26 = 85 (65.1-95.6) **HC2 and CC:** 25/26 = 96 (80.4-99.9) p = 0.17 (vs CC) Referred with ASC-US **HC2:** 10/12 = 83 (51.6-97.9) **CC:** 8/12 = 66 (34.9-90.1) p = 0.31 (vs HC2) **HC2 and CC:** 11/12 = 92 (61.5-99.8) p = 0.13 (vs CC) Referred with LSIL **HC2:** 13/14 = 93 (66.1-99.8) **CC:** 14/14 = 100 (76.8-100.0) **HC2 and CC:** 14/14 = 100 (76.8-100.0)	**Detection of CIN2+:** All **HC2:** 172/352 = 49 (43.5-54.2) **CC:** 186/352 = 53 (47.5-58.2) **HC2 and CC:** 126/352 = 36 (30.8-41.0) p<.001 (vs CC) Referred with ASC-US **HC2:** 61/99 = 62 (51.3-71.2) **CC:** 71/99 = 71 (61.8-80.3) **HC2 and CC:** 46/99 = 46 (36.4-56.8) p<.001 (vs CC) Referred with LSIL **HC2:** 111/253 = 44 (37.7-50.2) **CC:** 115/253 = 45 (39.2-51.8) **HC2 and CC:** 80/253 = 32 (25.9-37.7) p=.001 (vs CC)	**Detection of CIN2+ (calc):** All **HC2:** 23/203 = 11.3 (7.3-16.5) **CC:** 22/188 = 11.7 (7.5-17.2) **HC2 and CC:** 25/251 = 10.0 (6.5-14.4) Referred with ASC-US **HC2:** 10/48 = 20.8 (10.5-35.0) **CC:**8/36 = 22.2 (10.1-39.2) **HC2 and CC:** 11/64 = 17.2 (8.9-28.7) Referred with LSIL **HC2:** 13/155 - 8.4 (4.5-13.9) **CC:** 14/152 = 9.2 (5.1-15.0) **HC2 and CC:** 14/187 = 7.5 (4.2-12.2)	**Detection of CIN2+:** All **HC2:** 172/175 = 98.3 (95.1-99.6) **CC:** 186/190 = 97.9 (94.7-99.4) **HC2 and CC:** 126/127 = 99.2 (95.7-100.0) Referred with ASC-US **HC2:** 61/63 = 96.8 (89.0-99.6) **CC:** 71/75 = 94.7 (86.9-98.5) **HC2 and CC:** 46/47 = 97.9 (88.7-99.9) Referred with LSIL **HC2:** 111/112 = 99.1 (95.1-100.0) **CC:** 115/115 = 100.0 (96.8-100.0) **HC2 and CC:** 80/80 = 100.0 (95.5-100.0)	**Detection of CIN2+ (calc):** All **HC2:** 51 (45.8-56.5) **CC:** 47 (41.8-52.5) **HC2 and CC:** 64 (59.0-69.2) Referred with ASC-US **HC2:** 38 (28.8-48.7) **CC:** 29 (19.7-38.2) **HC2 and CC:** 54 (43.2-63.6) Referred with LSIL **HC2:** 56 (49.8-62.3) **CC:** 55 (48.2-60.8) **HC2 and CC:** 68 (62.3-74.1)	
Manos 1999[100]	**Detection of HSIL+:** HC2: 58/65 = 89.2 (78.4-95.2) CC: 48/63 = 76.2 (63.5-85.7) p = 0.09	**Detection of HSIL+:** HC2: 582/908 = 64.1 (60.9-67.2) CC (calc): 570/894 = 63.8 (60.5-66.9)	**Detection of HSIL+:** HC2: 15.1 (11.7-19.2) CC: 12.9 (9.8-16.8)	**Detection of HSIL+:** HC2: 98.8 (97.4-99.5) CC: 97.4 (95.7-98.5)	**Detection of HSIL+ (calc):** HC2: 35.9 (32.8-39.1) CC: 36.2 (33.1-39.5)	**Referral to colposcopy** HC2: 39.5% CC: 38.9%

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics
DelMistro 2010[138]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at 1.0 pg/mL **HC2 and CC:** Collection methods NR	Comparison of: (1) immediate colposcopy, (2) repeat Pap, and (3) HPV test for triage of ASC-US All participants received all three tests at baseline and 12 months later Women with any positive screening test invited for repeat Pap and HPV test at 6 months	Italy Five centers in Veneto region in Northeast Italy participating in organized cervical screening program	**CIN2 (calc):** 14/749=1.9% **CIN3 (calc):** 15/749=2.0% **ICC:** None reported	749 enrolled **Inclusion:** ASC-US result in routine screening in past 12 months (median was 72.2 days)	**Median Age:** 42 **Age range:** 25-64 y <35y: 26.4% >35y: 73.6% **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR

Study ID	Application of reference standard (histologic verification)	Funding source	Quality rating	Applicability	Yield	Insufficient samples
DelMistro 2010[138]	All women received colposcopy at baseline and at 12 months, with biopsy when indicated Biopsies (cervical and/or vaginal) taken in 338 women (45.1%) either at enrollment or during follow-up; histology data appear to pool results from different time points.	NR	Fair	Good	**Test positivity:** HPV+: 24.2% Pap (ASC-US+): 29.4% **Concordance:** NR	Pap smears at enrollment were inadequate for 16 women (2.2% of those tested)

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	False positive rate (95% CI)	Other performance characteristics	Comments
DelMistro 2010[138]	**Detection of CIN2+:** All women: Pap test: 74.1 (70.9-77.3) HC2: 93.1 (91.3-94.9) HC2 + Pap: 100 (100-100) <35 years: Pap test: 66.7 (60.0-73.3) HC2: 87.5 (82.9-92.1) HC2 + Pap: 100 (100-100) >35 years: Pap test: 83.3 (80.1-86.5) HC2: 100 (100-100) HC2 + Pap: 100 (100-100)	**Detection of CIN2+:** All women: Pap test: 72.3 (69.0-75.6) HC2: 78.6 (75.7-81.6) HC2 + Pap: 62.5 (58.9-66.0) <35 years: Pap test: 65.5 (58.8-72.3) HC2: 60.4 (53.6-67.2) HC2 + Pap: 50.3 (43.2-57.3) >35 years: Pap test: 74.7 (70.9-78.4) HC2: 84.8 (81.8-87.8) HC2 + Pap: 66.7 (62.6-70.7)	**Detection of CIN2+:** All women: Pap test: 9.5 (7.3-11.6) HC2: 14.9 (12.4-17.5) HC2 + Pap: 9.4 (7.3-11.6) <35 years: Pap test: 14.1 (9.2-19.0) HC2: 16.3 (11.1-21.4) HC2 + Pap: 14.6 (9.6-19.6) >35 years: Pap test: 7.1 (4.9-9.3) HC2: 13.7 (10.8-16.6) HC2 + Pap: 6.6 (4.4-8.7)	**NR**	**Detection of CIN2+ (calc):** All women: Pap test: 27.7 HC2: 21.4 HC2 + Pap: 37.5 <35 years: Pap test: 34.5 HC2: 39.6 HC2 + Pap: 49.7 >35 years: Pap test: 25.3 HC2: 15.2 HC2 + Pap: 33.3	**ROC area:** Pap: 0.73 HC2: 0.85	

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics	Application of reference standard (histologic verification)	Funding source
Cytology Testing with HPV Triage of Positive Cytology (Reflex HPV): RCTs reporting relative test performance measures								
ALTS 2003[116] ALTS 2003[219] ALTS 2000[220] Schiffman 2000[221] Solomon 2001[222] Sherman 2002[176]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at 1.0 pg/mL **LBC (ThinPrep) and HC2:** Papette broom	RCT with 3 arms: **IC:** Immediate colposcopy (all referred to colposcopy) **CM:** Conservative management (cytologic follow up at 6 month intervals, referral to colposcopy if HSIL or carcinoma) **HPV triage** (addition of one-time HPV triage to cytologic follow up, referral to colposcopy if HPV test positive or missing or cytologic	US 4 clinical centers: University of Alabama, University of Oklahoma, Magee-Women's Hospital of the University of Pittsburgh Medical Center, and University of Washington Within 6 months after referral cytology (average of 2 months) Women with cytologic diagnosis of ASC-US or	***Baseline data:*** Referred with ASC-US (calc) **CIN2:** 143/3,488 = 4.1% **CIN3+:** 180/3,488 = 5.2% (CIN3+ includes 1 case of SCC and 1 case of AIS) Referred with LSIL (IC arm only; 4 did not attend colposcopy) **CIN2:** 76/669 = 11.4% **CIN3:** 34/669 = 5.1% ***Cumulative diagnoses over course of study:***	5,060 total 3,488 with ASC-US 1,163 IC 1,161 HPV 1,164 CM 1,572 with LSIL 673 IC 224 HPV* 675 CM 4,234 had exit colposcopy (retention did not differ by study arm) **Inclusion:** Community-read cytologic diagnosis of ASC-US or LSIL within six months of enrollment, age ≥18 years, able to provide informed consent, likely	Overall **Mean Age:** 27 (18-81) **History of Other STIs** Chlamydia trachomatis: 21% Vulvar warts: 13% Trichomonas vaginalis: 13% Neisseria gonorrhoeae: 8% Genital herpes simplex virus: 6% Syphilis: 1%	Colposcopically-directed cervical biopsies obtained from any lesion suspicious for SIL, taken in order from worst to least severity. ECC performed according to clinician's judgment in cases where transformation zone or proximal extent of a cervical lesion not adequately visualized. After histologic interpretation at the clinical center, all slides sent to Pathology QC group at Johns Hopkins Hospital for re-evaluation; however, the	National Cancer Institute Support in the form of equipment or supplies at reduced or no cost from: Cytyc Corporation, DenVu, National Testing Laboratories, Digene Corporation, NeoPath, Roche Molecular Systems Inc., and TriPath Imaging

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics		Application of reference standard (histologic verification)	Funding source
		diagnosis of HSIL or carcinoma) HC2 assay performed on LBC specimen All women followed every six months for two years with LBC, masked HPV testing, and cervicography; all women received colposcopy at 24-month exit visit	LSIL from each clinical center's referral base consisting of gynecology, general practice, and family planning clinics in its immediate geographical location	Referred with ASC-US **CIN2:** 232/3,488 = 6.7% **CIN3+:** 306/3,488 = 8.8% (CIN3+ includes 2 cases of invasive cancer and 1 case of AIS) Referred with LSIL **CIN2:** 165/1,572 = 10.5% **CIN3+:** 236/1,572 = 15.0% (CIN3+ includes 5 cases of invasive cancer and 1 case of AIS)	to participate for full duration of trial **Exclusion:** Prior hysterectomy, history of ablative or excisional therapy to cervix, pregnant *HPV triage arm closed for LSIL referrals in first year because majority of women with LSIL tested positive	Referred with ASC-US **Age** Mean: 29 <35: 77.5% ≥35: 22.5% **Ethnicity** White: 63.6% Black: 31.2% Nat Am/Alaskan nat: 1.9% Asian/Pacific Islander: 3.4% **Education** Elementary: 14.9% High school/GED: 30.3% Vocational/some college: 37.7% Completed college: 12.4% Some graduate work: 4.7% **Income:** NR **Smoking** Never: 54.5% Former: 13.3% Current: 32.2%	Referred with LSIL **Age** Mean: 25, p<0.001 <35: 91.4% ≥35: 8.6% **Ethnicity** White: 63.4% Black: 30.4% Nat Am/Alaskan nat: 2.8% Asian/Pacific Islander: 3.4% **Education** (initially significant difference explained by younger age) Elementary: 18.8% High school/GED: 31.5% Vocational/some college: 37.5% Completed college: 8.8% Some graduate work: 3.4% **Smoking** Never: 49.8% Former: 9.7% Current: 40.5%	management of the participant was based on the clinical center reading. Any case with a CIN2+ diagnosis by either pathology QC or clinical center automatically went to panel review composed of 2 of 4 QC pathologists unmasked to previous histology diagnoses. For all other cases, first QC review diagnosis compared with clinical center diagnosis and, if concordant, served as final diagnosis. If disagreement between clinical center and first QC reviewer, case sent to panel review and that review constituted the final diagnosis.	

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID	Primary screening test evaluated Screening cutoff Collection method	Study design	Setting	Prevalence of disease	Number of patients Inclusion & exclusion criteria	Patient characteristics	Application of reference standard (histologic verification)	Funding source
Bjerre 2008[119]	Hybrid Capture 2 Positive for high oncogenic risk viruses (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) at ≥1 pg/mL **HC2:** collected from cervical canal with cervical brush **CC:** Collected with wooden spatula from posterior fornix and ectocervix, and CytoBrush Plus from endocervix	Women with ASC-US or LSIL detected in routine screening randomized to treatment for (1) positive repeat Pap and/or HPV test or (2) positive repeat Pap only Repeat screening conducted 4 mo (±1) after index smear, treatment 7 mo (±1) after index	Sweden Trial nested in population-based screening program in two counties, with 74% population coverage in one county and 83% in the other in 2002	**CIN2+ (calc):** 197/674=29.2% **CIN3+ (calc; one case of ICC):** 132/674=19.6%	803 identified with ASC-US or LSIL 674 fulfilled the inclusion criteria, consented and were randomized, 337 in each arm **Inclusion:** Age 23-60 y (invitations to cervical screening program) **Exclusion:** Pregnant or treated for dysplasia in last two years	**Mean Age:** 36.7 y **Age range:** 22-60y **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** Non-smoker: 61.4% Smoker: 38.6% (calc)	Women with positive repeat screening tests treated with LEEP (n=275), laser conization (n=70), or hysterectomy (n=1) (procedures which also provided tissue for histology), regardless of colposcopy findings IG: 62% treated CG: 41% treated	Health Authorities of Värmland and Örebro Counties

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Yield		Insufficient samples	Detection of CIN	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value	Relative positive predictive value (95% CI)
ALTS 2003[116] ALTS 2003[219] ALTS 2000[220] Schiffman 2000[221] Solomon 2001[222] Sherman 2002[176] Good Good	Referred with ASC-US **Test Positivity Rate** HC2: 50.7% LBC (ASC-US+): 57.9% **Concordance (calc)** 74.3% of HPV+ samples were ASC-US+ 68.0% of ASC-US+ samples were HPV+ **% HPV+ by LBC diagnosis (p<0.001):** HSIL (CIN3): 100% HSIL (CIN2): 96.5% LSIL: 88.6% ASC-US: 50.6% Negative: 32.6% **HPV/LBC categories:** HPV-LBC-: 28.2% HPV-LBC+: 18.6% HPV+LBC+: 39.5% HPV+LBC-: 13.7% **Referral to colposcopy (%)** Referred with ASC-US **IC:** 100 (99.7-100) **CM:** 12.3 (10.5-14.3) **HPV:** 55.6 (52.6-58.4) p < 0.001 **Compliance with colposcopy (%) (calc)** Referred with ASC-US **IC:** 1148/1163 (98.7%) **CM:** 94/100 (94%)	Referred with LSIL **Test Positivity Rate** HC2: 84.1% LBC (ASC-US+): 81.2% **Concordance (calc)** 86.7% of HPV+ samples were ASC-US+ 90.3% of ASC-US+ samples were HPV+ **% HPV+ by LBC diagnosis (p<0.001):** HSIL (CIN3): 100% HSIL (CIN2): 98.8% LSIL: 94.8% ASC-US: 77.1% Negative: 58.4% **HPV/LBC categories:** HPV-LBC-: 8.0% HPV-LBC+: 7.9% HPV+LBC+: 72.9% HPV+LBC-: 11.2% **Referral to colposcopy (%)** Referred with LSIL **IC:** 100 (99.4-100) **CM:** 18.8 (15.9-22.0)	**HC2** (missing results due to insufficient residual material after ThinPrep) ASC-US: 4.6% LSIL: 5.0% **LBC** (unsatisfactory or missing) ASC-US: 0.5% LSIL: 0.4%	CIN3+ Referred with ASC-US **IC:** 52/1163 = 4.5% (3.4-5.9) **HPV:** 73/1161 = 6.3% (5.0-7.9) **CM:** 59/1164 = 5.1% (3.9-6.5) Referred with LSIL **IC:** 57/673 = 8.5% **HPV:** 27/224 = 12.1% **CM:** 45/675 = 6.7% ‡Includes 2 cases of invasive cancer (1 in IC & 1 in CM) & 1 case of ACIS in the HPV arm	(HPV/CM) **Referred with ASC-US** 6.3%/5.1% = 1.24 (0.88-1.73) **Referred with LSIL** 12.1%/6.7% = 1.81* *Unequal number of women in groups makes this number invalid **Timing of CIN3+ diagnosis** Referred with ASC-US **Enrollment:** IC 59.8%, CM 40.7%, HPV 75.2% **Follow up:** IC 14.4%, CM 20.4%, HPV 5.9% **Exit:** IC 25.8%, CM 38.9%, HPV 18.8% p < 0.001 Referred with LSIL **Enrollment:** IC 62.7%, CM 36.6%, HPV 68.3% **Follow up:** IC 19.6%, CM 26.9%, HPV 9.8% **Exit:** IC 17.6%, CM 36.6%, HPV 22.0% p < 0.001 The management strategy performance calculations consider as "successes" only those cases of CIN3+	**NR**	**NR**	**NR**

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Yield		Insufficient samples	Detection of CIN	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value	Relative positive predictive value (95% CI)
	V: 585/649 (90.1%)	**HPV:** 85.3 (79.9-89.6) p < 0.001			detected by the clinical application of the management strategy at the centers within the a priori-defined period for that strategy (i.e., enrollment period for IC and HPV triage, and enrollment plus follow up periods for CM). Cases of CIN3+ missed by the strategy but detected by safety net interventions and cases detected after the defined period for that strategy are not included in the numerator for calculating sensitivity.			

Appendix C Table 3. Evidence Table for Benefits of HPV Testing (KQ3)

Study ID Quality rating Applicability	Yield	Insufficient samples	Detection of CIN	Relative Detection Ratio (95% CI)	Relative False Positive Proportion (95% CI)	Positive predictive value	Relative positive predictive value (95% CI)
Bjerre 2008[119]	**Test positivity:** *HPV+:* 201/337=59.6% *Pap (ASC-US+):* 291/674=43.2% (calc) *IG (ASC-US+):* 143/337= 42.4% *CG (ASC-US+):* 148/337= 43.9% Women <35 *IG (HPV+):* 126/165= 76.4% *IG* (ASC-US+): 77/165=46.7% *CG* (ASC-US+): 88/175=50.3% Women ≥35 *IG (HPV+):* 75/172= 43.6% *IG* (ASC-US+)*:* 66/172= 38.4% *CG* (ASC-US+)*:* 60/162= 37.0% **Concordance (calc):** 113/187 = 60.4% of HPV+ samples were ASC-US+ 113/134 = 85.0% of ASC-US+ samples were HPV+ **HPV/CC categories (calc):** HPV-CC-: 35.8% HPV-CC+: 6.5% HPV+CC-: 22.4% HPV+CC+: 35.2%	Cytology*: For 2 women in HPV/Pap group (and no women in the Pap-only group), Pap was unreadable (2/673 = 0.3%, calc) *Table 3; reported as 3 unsatisfactory samples in Methods	**CIN2+ (calc)** IG (HPV+ or ASC-US+): 112/337 = 33.2% CG (ASC-US+): 85/337 = 25.2% **CIN3+ (calc)*** IG (HPV+ or ASC-US+): 72/337 = 21.4% CG (ASC-US+): 60/337 = 17.8% *includes 1 case of invasive cancer	IG (HPV+ or ASC-US+) vs. CG (ASC-US+) **CIN2+ (calc)** 33.2%/25.2% = 1.32 (1.04-1.67) Women <35: 1.34 (1.00-1.79) Women ≥35: 1.32 (0.89-1.97) **CIN3+ (calc)** 21.4%/17.8% = 1.20 (0.88-1.63) Women <35: 1.09 (CI) Women ≥35: 1.44 (0.86-2.38)	IG (HPV+ or ASC-US+) vs. CG (ASC-US+) ***All ages:*** **CIN2+ (calc)** (96/337)/(53/337) = 1.81 (1.34-2.44) **CIN3+ (calc)** (136/337)/(78/337) = 1.74 (1.38-2.20) ***Age < 35 years:*** **CIN2+ (calc)** (50/165)/(28/175) = 1.89 (1.26-2.86) **CIN3+ (calc)** (77/165)/(42/175) = 1.94 (1.43-2.65) ***Age ≥ 35 years:*** **CIN2+ (calc)** (46/172)/(28/162) = 1.55 (1.02-2.35) **CIN3+ (calc)** (59/172)/(39/162) = 1.42 (1.01-2.01)	**CIN2+ (calc)** IG (HPV+ or ASC-US+): 112/208 = 53.8% (46.8-60.8) CG (ASC-US+): 85/138 = 61.6% (52.9-69.7) **CIN3+ (calc)** IG (HPV+ or ASC-US+): 72/208 = 34.6% (28.2-41.5) CG (ASC-US+): 60/138 = 43.5% (35.1-52.2)	IG (HPV+ or ASC-US+) vs. CG (ASC-US+) **CIN2+ (calc)** 53.8%/61.6% = 0.87 (0.73-1.05) **CIN3+ (calc)** 34.6%/43.5% = 0.80 (0.61-1.04)

ACIS-adenocarcinoma in situ; AGC-atypical glandular cells; AGUS-atypical glandular cells of undetermined significance; AIS-adenocarcinoma in situ; ALTS-ASC-US-LSIL Triage Study; ASC-H-atypical squamous cells cannot exclude HSIL; ASC-US- atypical squamous cells of undetermined significance; calc-calculation; B: baseline; C-cumulative; CC-conventional cytology; CI- confidence interval; CIN-cervical intraepithelial neoplasia; CM-conservative management; ColpoBx-colposcopically directed biopsy; ECC-endocervical curettage; HC2-Hybrid Capture 2; HIV-human immunodeficiency virus; HPV-human papillomavirus; HR-high risk; HSIL- high-grade squamous intraepithelial lesion; IARC-International Agency for Research on Cancer; IC- immediate colposcopy; LBC-liquid-based cytology; LEEP-loop electrosurgical excision procedure; LMP-last menstrual period; LR-likelihood ratio; LSIL- low-grade squamous intraepithelial lesion; Mo-month; NR-not reported; PCR-polymerase chain reaction; pg/mL-picogram/milliliter; PPV-positive predictive value; QC-quality control; R1-round one; R2-round two; RLU-relative light unit; SCC-squamous cell carcinoma; SD-standard deviation; STI-sexually transmitted infection; STM-standard transport medium; VIA-visual inspection with acetic acid;VILI-visual inspection with Lugol's Iodine; y-year

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Study design	Setting	Number of patients Inclusion & exclusion criteria	Patient characteristics		Funding source
Maissi 2004[140] Maissi 2005[143]	Cross sectional questionnaire Recruited all women with borderline or mildly dyskaryotic test results over five month period and the first 13 women each week who received a normal test result; all borderline or mildly dyskaryotic smear samples tested for HPV; after pilot completed, recruited the first 42 women each week over a five week period with borderline or mildly dyskaryotic results but no HPV results, half from each center Questionnaires sent to women within one week of research team being informed that smear test results had been sent to them Second questionnaire sent 6 months after receipt of test results Four study groups: 1) Normal cytology 2) Borderline/mildly dyskaryotic cytology, HPV- 3) Borderline/mildly dyskaryotic cytology, HPV+ 4) Borderline/mildly dyskaryotic cytology, not tested for HPV	England Two of the three centers taking part in the English HPV/LBC pilot study Women presenting for routine cervical smear	**Initial Sample** 2,183 sent questionnaires 1,376 (63%) returned questionnaire Normal cytology: 366 Borderline/mildly dyskaryotic cytology, HPV-: 331 Borderline/mildly dyskaryotic cytology, HPV+: 536 Borderline/mildly dyskaryotic cytology, not tested for HPV: 143 **Follow-up Sample** 1,011 completed 2nd questionnaire (74%)* Normal cytology: 288 Borderline/mildly dyskaryotic cytology, HPV-: 252 Borderline/mildly dyskaryotic cytology, HPV+: 369 Borderline/mildly dyskaryotic cytology, not tested for HPV: 102 **Inclusion:** Normal or borderline or mildly dyskaryotic cytology test result **Exclusion:** NR *Response rate varied significantly between groups (p = 0.006)	**Initial Sample** **Mean Age (SD)** Normal: 40.2 (12.2) HPV-: 40.5 (11.3) HPV+: 31.6 (9.7) No HPV test: 35.4 (10.4) **White Ethnicity** Normal: 96% HPV-: 96% HPV+: 97% No HPV test: 98% **College Education** Normal: 45% HPV-: 36% HPV+: 50% No HPV test: 42% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	**Follow-up Sample** **Mean Age (SD)** Normal: 40.5 (12.1) HPV-: 41.6 (11.1) HPV+: 32.7 (9.8) No HPV test: 36.6 (11.1) **White Ethnicity** Normal: 97.9% HPV-: 96.8% HPV+: 97.0% No HPV test: 97.9% **College Education** Normal: 46.7% HPV-: 37.5% HPV+: 48.5% No HPV test: 46.8% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	Policy Research Programme of the Department of Health

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Outcome measures	Results		Other results		Quality rating	Applicability
Maissi 2004[140] Maissi 2005[143]	**Initial questionnaire:** Short form of Spielberger State-Trait Anxiety Inventory (S-STAI-6); General Health Questionnaire (GHQ-12) to measure general distress; EuroQoL EQ-5D to measure health-related quality of life; concern about the smear result; perceived risk of developing cervical cancer; understanding of smear result **6 month followup:** Short form of Spielberger State-Trait Anxiety Inventory (S-STAI-6); General Health Questionnaire (GHQ-12); EuroQoL EQ-5D to measure health-related quality of life; concern about smear result; perceived risk of developing cervical cancer; Psychosocial Effects of Abnormal Pap Smear (PEAPS-Q) to measure sexual health worries	Baseline adjusted mean scores (SE) **S-STAI-6** Normal: 36.4 (0.7) HPV-: 37.6 (0.7) HPV+: 39.6 (0.6) No HPV test : 37.7 (1.2) F=4.44, p=0.004 for all groups t=3.11, p=0.002 for HPV+ vs. other groups p<.05 for HPV+ vs. HPV- **GHQ-12** Normal: 2.0 (0.1) HPV-: 2.1 (0.2) HPV+: 2.8 (0.2) No HPV test: 2.4 (0.3) F=5.37, p=0.001 for all groups t=3.252, p=0.001 for HPV+ vs. other groups p<.05 for HPV+ vs. HPV- **Concern about test result** Normal: 5.2 (0.1) HPV-: 8.8 (0.1) HPV+: 9.7 (0.1) No HPV test: 9.1 (0.2) F=242.46, p<0.001 for all groups t=13.391, p<0.001 for HPV+ vs. other groups p<.05 for HPV+ vs. HPV- **HRQoL (EQ-5D)*** Normal: 0.91 (0.02) HPV-: 0.89 (0.02) HPV+: 0.88 (0.02) No HPV test: 0.87 (0.02) F=0.91, p=0.340 *In followup sample (n = 1,011)	Follow-up adjusted mean scores (SE) **S-STAI-6** Normal: 36.8 (0.8) HPV-: 35.7 (0.8) HPV+: 36.7 (0.7) No HPV test: 36.7 (1.3) F=0.40, p=0.752 for all groups ns for HPV+ vs. HPV- **GHQ-12** Normal: 2.0 (0.2) HPV-: 2.0 (0.2) HPV+: 2.3 (0.2) No HPV test: 1.9 (0.3) F=0.81, p=0.487 for all groups ns for HPV+ vs. HPV- **Concern about test result** Normal: 2.0 (0.1) HPV-: 3.5 (0.1) HPV+: 3.8 (0.1) No HPV test: 4.4 (0.2) F=83.39, p<0.001 ns for HPV+ vs. HPV- **HRQoL (EQ-5D)** Normal: 0.86 (0.02) HPV-: 0.90 (0.02) HPV+: 0.89 (0.02) No HPV test: 0.88 (0.04) F=0.70, p=0.554	Baseline means (SE) **Perceived severity** (Two 7-point scales) Normal: 12.4 (0.1) HPV-: 12.3 (0.1) HPV+: 12.3 (0.1) No HPV test: 12.1 (0.2) F=1.13, p=0.334 **Perceived risk** (7-point scale) Normal: 3.7 (0.1) HPV-: 3.9 (0.1) HPV+: 4.4 (0.1) No HPV test: 4.1 (0.1) F=25.51, p<0.0001 **Perceived importance of HPV in the development of cervical cancer** Normal: 5.9 (0.1) HPV-: 5.9 (0.1) HPV+: 5.8 (0.1) No HPV test: 5.3 (0.3) F=3.42, p=0.017 **Unsure what HPV is** Normal: 54% HPV-: 38% HPV+: 25% No HPV test: 62% p value NR	Follow-up means (SE) **Perceived severity:** NR **Perceived risk** (7-point scale) Normal: 3.0 (0.2) HPV-: 3.3 (0.2) HPV+: 4.1 (0.1) No HPV test: 4.7 (0.3) F=14.88, p<0.001 **Perceived importance of HPV in the development of cervical cancer:** NR **Unsure what HPV is:** NR **Sexual health worries** Normal: NA HPV-: 1.0 (0.1) HPV+: 1.8 (0.1) No HPV test: 1.1 (0.1) F=30.64, p<0.001 for all groups p<.05 for HPV+ vs. HPV-	Fair	Fair Predominantly White and highly educated

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Study design	Setting	Number of patients Inclusion & exclusion criteria	Patient characteristics	Funding source
McCaffery 2004[141]	Cross sectional survey using postal questionnaire sent one week after receipt of HPV and cytology screening results At screening, all women given standard information about HPV and HPV testing; information covered sexually transmitted nature of HPV, its high prevalence, association with CIN, and potential for long periods of latency Women sent cervical smear and HPV results by post and those who tested HPV+ were sent second copy of HPV information; women with borderline or abnormal cytology, unsatisfactory smears, or positive HPV results were invited for colposcopy All psychosocial measures were taken prior to colposcopic follow up Four study groups: 1) Normal cytology, HPV- 2) Normal cytology, HPV+ 3) Abnormal/unsatisfactory cytology, HPV- 4) Abnormal/unsatisfactory cytology, HPV+ STAI assessed before screening to examine differences between HPV/cytology groups - no significant differences found	London, England National Health Service well-woman clinic Women presenting for routine screening	428 recruited 311 (73%) returned questionnaire 271 included in analysis Normal cytology, HPV-: 185 (68%) Normal cytology, HPV+: 46 (17%) Abnormal/unsatisfactory cytology, HPV-: 17 (6%) Abnormal/unsatisfactory cytology, HPV+: 23 (8%) **Inclusion:** Women presenting for routine screening **Exclusion:** Completed follow-up questionnaire after colposcopy (n=28), part of randomly selected control group of cytology and HPV negative women who were invited and attended colposcopy (n=12)	**Age** Mean age: 32 (SD 8.0, range 20-61) <30: 55% 30-34: 18% 35-39: 10% ≥40: 17% **Ethnicity** White: 90% Black: 2% Asian: 3% Other: 6% **Age left full-time education (years)** Under 16: 8% 17-18: 14% 19+: 78% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking** Yes: 32% No: 68%	Cancer Research UK

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Outcome measures	Results	Other results	Quality rating	Applicability
McCaffery 2004[141]	Short form of Spielberger State-Trait Anxiety Inventory (STAI); Cervical Screening Questionnaire (CSQ); feelings towards current, previous, and future sexual partners	**Normal cytology, HPV+ vs HPV-** STAI: F(1,267) = 39, p < 0.0001 CSQ: F(1,267) = 69, p < 0.0001 **Abnormal/unsatisfactory cytology, HPV+ vs HPV-** STAI: F(1,267) = 1.3, ns CSQ: F(1,267) = 8.8, p = 0.002 **HPV+, normal vs abnormal/unsatisfactory cytology** STAI: F(1,267) = 0.55, ns CSQ: F(1,267) = 15, p = 0.0001 **HPV-, normal vs abnormal/unsatisfactory cytology** STAI: F(1,267) = 11, p = 0.0008 CSQ: F(1,267) = 21, p < 0.0001 **Mean STAI scores (95% CI)** Normal cytology, HPV-: 29.8 (27.9-31.7) Normal cytology, HPV+: 43.5 (39.7-47.3) Abnormal/unsatisfactory cytology, HPV-: 41.1 (34.9-47.5) Abnormal/unsatisfactory cytology, HPV+: 46 (40.6-51.4) **Mean CSQ scores (95% CI)** Normal cytology, HPV-: 8.9 (8.4-9.3) Normal cytology, HPV+: 13 (12-14) Abnormal/unsatisfactory cytology, HPV-: 14 (12-15) Abnormal/unsatisfactory cytology, HPV+: 17 (16-18)	**Normal Cytology** Feelings about current partner **HPV+:** worse/much worse = 3 (8%), better/same = 33 (92%) **HPV-:** worse/much worse = 2 (1%), better/same = 160 (99%), p = 0.04 Feelings about previous partners **HPV+:** worse/much worse = 15 (33%), better/same = 230 (67%) **HPV-:** worse/much worse = 2 (1%), better/same = 167 (99%), p < 0.0001 Feelings about future partners **HPV+:** worse/much worse = 12 (27%), better/same = 32 (73%) **HPV-:** worse/much worse = 3 (2%), better/same = 173 (98%), p < 0.0001 **Abnormal/unsatisfactory cytology** Feelings about current partner **HPV+:** worse/much worse = 2 (13%), better/same = 14 (87%) **HPV-:** worse/much worse = 0 (0%), better/same = 16 (100%), ns Feelings about previous partners **HPV+:** worse/much worse = 8 (35%), better/same = 15 (65%) **HPV-:** worse/much worse = 0 (0%), better/same = 15 (100%), p = 0.01 Feelings about future partners **HPV+:** worse/much worse = 7 (32%), better/same = 15 (68%) **HPV-:** worse/much worse = 0 (0%), better/same = 15 (100%), p = 0.02	Fair	Fair Predominantly white and highly educated

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Study design	Setting	Number of patients Inclusion & exclusion criteria	Patient characteristics	Funding source	Outcome measures
Kitchener 2007[139]	Consecutive series within an RCT Women with normal or mildly abnormal cytology who had been recruited into the ARTISTIC trial were mailed a booklet of questionnaires approximately two weeks after they had received the results of their baseline cytology In the ARTISTIC trial, women presenting for routine screening were randomized 3:1 into two study groups: HPV-revealed and HPV-concealed; women in the HPV-revealed group received the results of their HPV test along with their baseline cytology results while women in the HPV-concealed group were only informed of their cytology result Initially the data was collected in face-to-face interviews; later switched to postal delivery for economic reasons; there was evidence of differences in outcome for the two modes of data collection so the face-to-face interview data were excluded from the main analysis	Manchester, England General practices in primary care within the National Cervical Screening Programme Women presenting for routine screening	3,582 sent questionnaires 2,700 HPV-revealed 882 HPV-concealed 2,508 (70.0%*) returned questionnaire 1904 (70.5%†)HPV-revealed 604 (68.5%‡)HPV-concealed **Inclusion:** Women aged 20-64 years with normal or mildly abnormal cytology test result **Exclusion:** NR *69% reported in text †70.7% reported in text ‡71.1% reported in text	**Age:** NR **Ethnicity:** NR **Education:** NR **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking:** NR	Health Technology Assessment Programme and National Health Service Research and Development	General Health Questionnaire (GHQ-28); Spielberger State-Trait Anxiety Inventory (STAI); Sexual Rating Scale (SRS)

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Results	Other results	Quality rating	Applicability
Kitchener 2007[139]	**GHQ** HPV-revealed Mean (SD) / HPV-concealed Mean (SD) / Age-adjusted mean difference (95% CI) / P HPV-/Normal smear 3.31 (5.18) 3.22 (4.80) HPV+/Normal smear 4.77 (6.21) 4.02 (5.77) 0.74 (-0.63-1.91) 0.220 HPV-/abnormal smear 4.22 (5.63) 4.29 (5.83) HPV+/abnormal smear 4.57 (5.44) 5.75 (6.50) -1.19 (-2.98-0.40) 0.121 Total 4.26 (5.73) 4.18 (5.71) -0.01 (-0.65-0.60) 0.968 **STAI-STATE** HPV-revealed Mean (SD) / HPV-concealed Mean (SD) / Age-adjusted mean difference (95% CI) / P HPV-/Normal smear 35.85 (11.92) 36.00 (11.49) HPV+/Normal smear 38.87 (13.33) 37.10 (12.58) 1.73 (-1.27-4.53) 0.202 HPV-/abnormal smear 37.99 (12.43) 40.66 (13.57) HPV+/abnormal smear 39.77 (12.05) 39.97 (12.35) -0.25 (-3.79-3.03) 0.885 Total 38.10 (12.64) 38.27 (12.61) -0.31 (-1.27-1.13) 0.618 **STAI-TRAIT** HPV-revealed Mean (SD) / HPV-concealed Mean (SD) / Age-adjusted mean difference (95% CI) / P HPV-/Normal smear 38.84 (11.34) 39.00 (11.13) HPV+/Normal smear 40.54 (11.83) 39.39 (10.80) 1.07 (-1.30-3.41) 0.386 HPV-/abnormal smear 39.95 (11.08) 41.57 (12.43) HPV+/abnormal smear 41.28 (10.89) 40.88 (11.54) 0.36 (-2.80-3.53) 0.819 Total 40.12 (11.40) 40.13 (11.49) -0.10 (-1.27-1.13) 0.858 **SRS** HPV-revealed Mean (SD) / HPV-concealed Mean (SD) / Age-adjusted mean difference (95% CI) / P HPV-/Normal smear 51.28 (20.89) 50.81 (22.50) HPV+/Normal smear 55.32 (22.95) 61.10 (23.74) -7.28 (-12.60- -1.96) 0.007 HPV-/abnormal smear 48.73 (23.34) 50.53 (21.26) HPV+/abnormal smear 62.67 (23.00) 62.46 (22.97) 0.15 (-6.44-6.74) 0.965 Total 53.32 (23.02) 54.90 (23.00) -2.40 (-4.70- -0.09) 0.042	**Observational comparison of HPV+ with HPV- in revealed arm** **GHQ** Mean difference (95%CI) / P Normal smear 1.43 (0.75-2.10) <0.0001 Abnormal smear 0.28 (-0.76-1.24) 0.581 **STAI-STATE** Mean difference (95%CI) / P Normal smear 2.90 (1.40-4.39) <0.0001 Abnormal smear 1.56 (-0.59-3.80) 0.174 **STAI-TRAIT** Mean difference (95%CI) / P Normal smear 1.53 (0.16-2.92) 0.023 Abnormal smear 0.98 (-1.05-2.97) 0.354 **SRS** Mean difference (95%CI) / P Normal smear 1.46 (-1.34-4.27) 0.306 Abnormal smear 8.66 (4.30-13.02) <0.0001 **GHQ caseness (≥4)** Odds ratio (95%CI) / P Normal smear 1.70 (1.33-2.17) <0.0001 Abnormal smear 1.07 (0.74-1.56) 0.724	Fair	Good

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Study design	Setting	Number of patients Inclusion & exclusion criteria	Patient characteristics	Funding source	Outcome measures
McCaffery 2010[142]	Multi-center RCT of triage testing Randomized to three arms: **HPV:** HPV testing (HC2) arranged as soon as possible **IC:** Choice of HPV or repeat smear, informed by decision aid **RS:** Repeat smear 6 months after randomization **Clinical management:** HPV: followed ALTS protocol with HPV+ women referred for colposcopy and HPV- recalled for repeat smear at 12 months Repeat smear: followed Australian guidelines; those with negative or borderline results referred for second repeat smear 6 months later, those with moderate dyskaryosis or above referred to colposcopy, and those with mild dyskaryosis offered choice of colposcopy or repeat smear **Questionnaires:** Baseline questionnaire assessing psychosocial wellbeing was conducted immediately after consent, close to receipt of first abnormal smear result Follow-up questionnaires conducted at regular intervals during the 12 months after triage testing	Australia 18 urban and rural family planning clinics across the country Women attending routine cervical screening	314 women randomized **HPV:** 104 **IC:** 104 **RS:** 106 **235** (75%) included in primary analysis, 305 (97%) in sensitivity analysis **Inclusion:** Age 16-70, women with Pap smear categorized as "non-specific minor changes with or without HPV effect," equivalent to ASC-US **Exclusion:** Pregnant, unable to complete questionnaire in English, history of previous abnormal cervical smears, history of external visible genital warts in previous two years	**Age (calc):** 30+: 66% <30: 34% **Ethnicity:** NR **Education (calc):** Secondary: 34% Tertiary: 24% University: 42% **Income:** NR **HIV+:** NR **Other STIs:** NR **Smoking (calc):** Yes: 24% No: 76%	Australian National Health and Medical Research Council	**Primary:** Quality of life measured using the mental health component of the Short Form (36) Health Survey (SF-36) **Other measures:** Cognitive, emotional, and behavioral outcomes and knowledge measured using a variety of instruments and questions

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

Study ID	Results	Other results	Quality rating	Applicability
McCaffery 2010[142]	**Psychosocial outcomes at two weeks after triage** Trial arm mean score Measure / HPV / IC / RS / Overall P value / Pairwise P values SF36 mental health combined score: 44.3 / 47.0 / 46.3 / 0.35 / — STAI (anxiety)**: 11.5 / 10.5 / 10.6 / 0.25 / — CSQ (distress)**: 18.7 / 17.9 / 18.2 / 0.62 / — PEAPS-Q: infectivity**: 3.1 / 3.0 / 2.9 / 0.68 / — PEAPS-Q: relationships**: 4.7 / 4.5 / 4.3 / 0.74 / — **Psychosocial outcomes over one year*** Trial arm mean score Measure / HPV / IC / RS / Overall P value / Pairwise P values SF36 mental health combined score: 46.2 / 48.5 / 45.5 / 0.16 / — STAI (anxiety)**: 10.9 / 10.5 / 11.4 / 0.27 / — CSQ (distress)**: 16.6 / 17.5 / 18.4 / **0.01** / HPV vs. RS: **<0.01** PEAPS-Q: infectivity**: 2.7 / 2.8 / 2.5 / 0.53 / — PEAPS-Q: relationships**: 4.1 / 4.0 / 4.1 / 0.99 / — *Area under the curve analysis used to estimate average score per day for all outcomes **Higher score indicates poorer psychological outcome; for all other measures, higher score indicates better outcome	**Psychosocial outcomes at two weeks after triage** Trial arm mean score Measure / HPV / IC / RS / Overall P value / Pairwise P values Worry about getting cervical cancer**: 25% / 23% / 24% / 0.98 / — Relationship concern: worry about current, previous and future sexual partners: 9.2 / 9.4 / 9.0 / 0.39 / — **Psychosocial outcomes over one year** Trial arm mean score Measure / HPV / IC / RS / Overall P value / Pairwise P values Worry about getting cervical cancer**: 16% / 8% / 15% / 0.4 / — Relationship concern: worry about current, previous and future sexual partners: 8.7 / 9.1 / 9.0 / 0.15 / — **Higher score indicates poorer psychological outcome; for all other measures, higher score indicates better outcome	Fair	Fair Highly educated

Appendix C Table 4. Evidence Table for Harms of HPV Testing (KQ5)

ALTS-ASCUS-LSIL Triage Study; ASCUS-atypical squamous cells of undetermined significance; CSQ-Caregiver Survey Questionnaire; GHQ-12- General Health Questionnaire; HIV-human immunodeficiency virus; HPV-human papillomavirus; IC-informed choice; LBC-liquid-based cytology; NR-not reported; ns-not significant; PEAPS-Q-Psychosocial Effects of Abnormal Pap Smears Questionnaire; RS-repeat smear; SD-standard deviation; SE-standard error; S-STAI-6- Short form of Spielberger State-Trait Anxiety Inventory; STAI-state trait anxiety inventory; STI-sexually-transmitted infection;

Appendix D Table 1. Studies Excluded From the Review for KQ1

Key Question 1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?	
Reference	**Reason for exclusion***
Acladious NN, Mandal D. Cervical cytology screening for sexually-active teenagers. *International Journal of STD & AIDS.* 2000;11:648-650.	Reported outcomes do not address a key question
Baay MF, Tjalma WA, Lambrechts HA et al. Combined Pap and HPV testing in primary screening for cervical abnormalities: should HPV detection be delayed until age 35? *Eur J Cancer.* 2005;41:2704-2708.	Reported outcomes do not address a key question
Bacon J, Francoeur D, Goldfarb AF, Breech LL. Abnormal pap smears in adolescents. J Pediatr Adolesc Gynecol. 2003;16:157-166.	Editorials; letters; non-systematic reviews; opinions
Bano F, Kolhe S, Zamblera D et al. Cervical screening in under 25s: a high-risk young population. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 2008;139:86-89.	Provides prevalence data only
Barnholtz-Sloan J, Patel N, Rollison D, Kortepeter K, MacKinnon J, Giuliano A. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. Cancer Causes & Control. 2009;20:1129-1138.	Ecological study without link to screening
Benard VB, Eheman CR, Lawson HW et al. Cervical screening in the National Breast and Cervical Cancer Early Detection Program, 1995-2001. Obstetrics & Gynecology. 2004;103:564-571.	Data not stratified by age, age groupings not appropriate, or denominators not known
Bos AB, Rebolj M, Habbema JD, van Ballegooijen M. Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. Int J Cancer. 2006;119:2372-2375.	Data not stratified by age, age groupings not appropriate, or denominators not known
Bray F, Loos AH, McCarron P et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiology, Biomarkers & Prevention.* 2005;14:677-686.	Ecological study without link to screening
Bulk S, Visser O, Rozendaal L, Verheijen RH, Meijer CJ. Cervical cancer in the Netherlands 1989-1998: Decrease of squamous cell carcinoma in older women, increase of adenocarcinoma in younger women. *Int J Cancer.* 2005;113:1005-1009.	Ecological study without link to screening
Bulkmans NW, Berkhof J, Bulk S et al. High-risk HPV type-specific clearance rates in cervical screening. *Br J Cancer.* 2007;96:1419-1424.	Data not stratified by age, age groupings not appropriate, or denominators not known
Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. *Br J Cancer.* 2004;91:530-536.	Modeling study
Canfell K, Sitas F, Beral V. Cervical cancer in Australia and the United Kingdom: comparison of screening policy and uptake, and cancer incidence and mortality. *Med J Aust.* 2006;185:482-486.	Data not stratified by age, age groupings not appropriate, or denominators not known
Cecchini S, Ciatto S, Zappa M, Biggeri A. Trends in the prevalence of cervical intraepithelial neoplasia grade 3 in the district of Florence, Italy. Tumori. 1995;81:330-333.	Poor reporting
Cervical Cancer Screening Programme. Cervical Cancer Screening Programme, England: 2002-03. 1-44. 2003. England, Government Statistical Service.	Reported outcomes do not address a key question
Chan PG, Sung HY, Sawaya GF. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstet Gynecol.* 2003;102:765-773.	Ecological study without link to screening
Chan PK, Chang AR, Yu MY et al. Age distribution of human papillomavirus infection and cervical neoplasia reflects caveats of cervical screening policies. *Int J Cancer.* 2010;126:297-301.	Data not stratified by age, age groupings not appropriate, or denominators not known
Cohen D. BMA meeting: Doctors urge government to lower age limit for cervical cancer screening. BMJ. 2009;339:b2711.	Editorials; letters; non-systematic reviews; opinions
Coldman A, Phillips N, Kan L, Matisic J, Benedet L, Towers L. Risk of invasive cervical cancer after three consecutive negative Pap smears. *J Med Screen.* 2003;10:196-200.	Data not stratified by age, age groupings not appropriate, or denominators not known

Appendix D Table 1. Studies Excluded From the Review for KQ1

Key Question 1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?	
Reference	**Reason for exclusion***
Coldman A, Phillips N, Kan L, Matisic J, Benedet L, Towers L. Risk of invasive cervical cancer after Pap smears: the protective effect of multiple negatives. *J Med Screen.* 2005;12:7-11.	Data not stratified by age, age groupings not appropriate, or denominators not known
Colgan TJ, Clarke A, Hakh N, Seidenfeld A. Screening for cervical disease in mature women: strategies for improvement. *Cancer.* 2002;96:195-203.	Reported outcomes do not address a key question
Coppell K, Paul C, Cox B. An evaluation of the National Cervical Screening Programme Otago site. *N Z Med J.* 2000;113:48-51.	Reported outcomes do not address a key question
Cotton SC, Sharp L, Seth R et al. Lifestyle and socio-demographic factors associated with high-risk HPV infection in UK women. *Br J Cancer.* 2007;97:133-139.	Reported outcomes do not address a key question
Coupe VM, Berkhof J, Bulkmans NW, Snijders PJ, Meijer CJ. Age-dependent prevalence of 14 high-risk HPV types in the Netherlands: implications for prophylactic vaccination and screening. *Br J Cancer.* 2008;98:646-651.	Reported outcomes do not address a key question
Crowther S, Turner L, Magee D, Gibbons D. Role of age stratification for colposcopy referral following initial diagnosis of mild dyskaryosis. *J Clin Pathol.* 2008;61:665-668.	Reported outcomes do not address a key question
Fiander AN. Cervical screening in young women aged 20-24 years. Journal of Family Planning & Reproductive Health Care. 2008;34:19.	Editorials; letters; non-systematic reviews; opinions
Fraser A, Hellmann S, Leibovici L, Levavi H. Screening for cervical cancer--an evidence-based approach. *Eur J Gynaecol Oncol.* 2005;26:372-375.	Reported outcomes do not address a key question
Ghosh A, Rao S, Pramanik T. Is it relevant to screen women younger than 26 years for precancerous and malignant cervical lesions ?[see comment]. *Asian Pacific Journal of Cancer Prevention: Apjcp.* 2005;6:123-124.	Reported outcomes do not address a key question
Giannopoulos T, Butler-Manuel S, Tailor A, Demetriou E, Daborn L. Prevalence of high-grade CIN following mild dyskaryotic smears in different age groups.[see comment]. *Cytopathology.* 2005;16:277-280.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Guido R. Guidelines for screening and treatment of cervical disease in the adolescent. Journal of Pediatric & Adolescent Gynecology. 2004;17:303-311.	Editorials; letters; non-systematic reviews; opinions
Hall HI, Rogers JD, Weir HK, Miller DS, Uhler RJ. Breast and cervical carcinoma mortality among women in the Appalachian region of the U.S., 1976-1996. *Cancer.* 2000;89:1593-1602.	Ecological study without link to screening
Hartmann, KE, Hall, SA, Nanda, K, Boggess, JF, and Zolnoun, D. Screening for Cervical Cancer. ii-74. 2002. Agency for Healthcare Research and Quality.	Data covered in other articles
Hemminki K, Li X, Mutanen P. Age-incidence relationships and time trends in cervical cancer in Sweden. *Eur J Epidemiol.* 2001;17:323-328.	Ecological study without link to screening
Herbert A, Anshu, Gregory M, Gupta SS, Singh N. Screen-detected invasive cervical carcinoma and its clinical significance during the introduction of organized screening. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2009;116:854-859.	Data not stratified by age, age groupings not appropriate, or denominators not known
Herbert A, Holdsworth G, Kubba AA. Cervical screening: why young women should be encouraged to be screened. *Journal of Family Planning & Reproductive Health Care.* 2008;34:21-25.	Ecological study without link to screening
Howell LP, Tabnak F, Tudury AJ, Stoodt G. Role of Pap Test terminology and age in the detection of carcinoma invasive and carcinoma in situ in medically underserved California women. *Diagn Cytopathol.* 2004;30:227-234.	Data not stratified by age, age groupings not appropriate, or denominators not known
Hoyer H, Scheungraber C, Kuehne-Heid R et al. Cumulative 5-year diagnoses of CIN2, CIN3 or cervical cancer after concurrent high-risk HPV and cytology testing in a primary screening setting. *Int J Cancer.* 2005;116:136-143.	Data not stratified by age, age groupings not appropriate, or denominators not known
Insinga RP, Dasbach EJ, Elbasha EH, Liaw KL, Barr E. Incidence and duration of cervical human papillomavirus 6, 11, 16, and 18 infections in young women: an evaluation from multiple analytic perspectives. *Cancer Epidemiology, Biomarkers & Prevention.* 2007;16:709-715.	Ecological study without link to screening

Appendix D Table 1. Studies Excluded From the Review for KQ1

Key Question 1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?	
Reference	**Reason for exclusion***
Insinga RP, Dasbach EJ, Elbasha EH, Liaw KL, Barr E. Progression and regression of incident cervical HPV 6, 11, 16 and 18 infections in young women. *Infectious Agents & Cancer.* 2007;2:15.	Ecological study without link to screening
Jacobs MV, Walboomers JM, Snijders PJ et al. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. *Int J Cancer.* 2000;87:221-227.	Reported outcomes do not address a key question
Kahn JA, Hillard PJ. Cervical cytology screening and management of abnormal cytology in adolescent girls. *J Pediatr Adolesc Gynecol.* 2003;16:167-171.	Editorials; letters; non-systematic reviews; opinions
Kyndi M, Frederiksen K, Kruger KS. Cervical cancer incidence in Denmark over six decades (1943-2002). *Acta Obstet Gynecol Scand.* 2006;85:106-111.	Ecological study without link to screening
Lawson HW, Lee NC, Thames SF, Henson R, Miller DS. Cervical cancer screening among low-income women: results of a national screening program, 1991-1995. *Obstet Gynecol.* 1998;92:745-752.	Data not stratified by age, age groupings not appropriate, or denominators not known
Liu S, Semenciw R, Probert A, Mao Y. Cervical cancer in Canada: changing patterns in incidence and mortality. *International Journal of Gynecological Cancer.* 2001;11:24-31.	Ecological study without link to screening
Luke C, Nguyen AM, Heard A, Kenny B, Shorne L, Roder D. Benchmarking epidemiological characteristics of cervical cancer in advance of change in screening practice and commencement of vaccination. *Australian & New Zealand Journal of Public Health.* 2007;31:149-154.	Data not stratified by age, age groupings not appropriate, or denominators not known
Massad SL, Markwell S, Cejtin HE, Collins Y. Risk of high-grade cervical intraepithelial neoplasia among young women with abnormal screening cytology. *Journal of Lower Genital Tract Disease.* 2005;9:225-229.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Mitchell H, Medley G, Higgins V. An audit of the women who died during 1994 from cancer of the cervix in Victoria, Australia. *Aust N Z J Obstet Gynaecol.* 1996;36:73-76.	Data not stratified by age, age groupings not appropriate, or denominators not known
Monteiro DL, Trajano AJ, da Silva KS, Russomano FB. Pre-invasive cervical disease and uterine cervical cancer in Brazilian adolescents: prevalence and related factors. *Cad Saude Publica.* 2006;22:2539-2548.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. *Journal of Lower Genital Tract Disease.* 2010;14:73-80.	Editorials; letters; non-systematic reviews; opinions
Moscicki AB. HPV infections in adolescents. *Dis Markers.* 2007;23:229-234.	Editorials; letters; non-systematic reviews; opinions
Mount SL, Papillo JL. A study of 10,296 pediatric and adolescent Papanicolaou smear diagnoses in northern New England. *Pediatrics.* 1999;103:539-545.	Reported outcomes do not address a key question
Nair MS, Bhandari HM, Nordin AJ. Cervical cancer in women aged less than 25: East Kent experience. *Journal of Obstetrics & Gynaecology.* 2007;27:706-708.	Editorials; letters; non-systematic reviews; opinions
O'Mahony C, Steedman N, Yong M, Anderson ER, Finnegan V, Price L. Cervical screening by age: let's not screen women under 25 throughout the UK. *BMJ.* 2009;339:b3426.	Editorials; letters; non-systematic reviews; opinions
Omar H, Callahan P, Aggarwal S, Perkins K, Young K. Cervical pathology in West Virginia adolescents. *W V Med J.* 2000;96:408-409.	Reported outcomes do not address a key question
Partridge EE, bu-Rustum N, Campos S et al. Cervical cancer screening. *Journal of the National Comprehensive Cancer Network.* 2008;6:58-82.	Editorials; letters; non-systematic reviews; opinions

Appendix D Table 1. Studies Excluded From the Review for KQ1

Key Question 1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?	
Reference	**Reason for exclusion***
Petignat P, Faltin D, Goffin F et al. Age-related performance of human papillomavirus testing used as an adjunct to cytology for cervical carcinoma screening in a population with a low incidence of cervical carcinoma. *Cancer.* 2005;105:126-132.	Data not stratified by age, age groupings not appropriate, or denominators not known
Prussia PR, Gay GH, Bruce A. Analysis of cervico-vaginal (Papanicolaou) smears, in girls 18 years and under. *West Indian Med J.* 2002;51:37-39.	Reported outcomes do not address a key question
Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ.* 1999;318:904-908.	Ecological study without link to screening
Rieck GC, Tristram A, Hauke A, Fielder H, Fiander AN. Cervical screening in 20-24-year olds. J Med Screen. 2006;13:64-71.	Insufficient information
Rodriguez AC, Burk R, Herrero R et al. The natural history of human papillomavirus infection and cervical intraepithelial neoplasia among young women in the Guanacaste cohort shortly after initiation of sexual life. *Sex Transm Dis.* 2007;34:494-502.	Data not stratified by age, age groupings not appropriate, or denominators not known
Saleh MM, Seoud AA, Zaklama MS. Abnormal cervical smears in adolescents: a ten-year comparative study of demographic criteria and management. *Clinical & Experimental Obstetrics & Gynecology.* 2007;34:139-142.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Saleh MM, Seoud AA, Zaklama MS. Study of the demographic criteria and management of adolescents referred with abnormal cervical smears. *Journal of Obstetrics & Gynaecology.* 2007;27:824-827.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Saraiya M, Ahmed F, Krishnan S, Richards TB, Unger ER, Lawson HW. Cervical cancer incidence in a prevaccine era in the United States, 1998-2002. *Obstetrics & Gynecology.* 2007;109:t-70.	Ecological study without link to screening
Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer.* 2003;89:88-93.	Data not stratified by age, age groupings not appropriate, or denominators not known
Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ.* 1999;318:1244-1245.	Ecological study without link to screening
Sasieni P, Castanon A, Cuzick J. What is the right age for cervical cancer screening? *Women's health.* 2010;6:1-4.	Editorials; letters; non-systematic reviews; opinions
Sasieni P, Castanon A, Parkin DM. How many cervical cancers are prevented by treatment of screen-detected disease in young women? *Int J Cancer.* 2009;124:461-464.	Modeling study
Sasieni, P. and Castanon, A. Call and recall cervical screening programme: screening interval and age limits. Current Diagnostic Pathology 12, 114-126. 2006.	Editorials; letters; non-systematic reviews; opinions
Sawaya GF. Should routine screening Papanicolaou smears be done for women older than 65 years? *Arch Intern Med.* 2004;164:243-245.	Editorials; letters; non-systematic reviews; opinions
Sellors JW, Karwalajtys TL, Kaczorowski J et al. Incidence, clearance and predictors of human papillomavirus infection in women. *CMAJ Canadian Medical Association Journal.* 2003;168:421-425.	Reported outcomes do not address a key question
Sigurdsson K, Adalsteinsson S. Risk variables affecting high-grade Pap smears at second visit: effects of screening interval, year, age and low-grade smears. *Int J Cancer.* 2001;94:884-888.	Data not stratified by age, age groupings not appropriate, or denominators not known
Sigurdsson K, Sigvaldason H. Effectiveness of cervical cancer screening in Iceland, 1964-2002: a study on trends in incidence and mortality and the effect of risk factors. *Acta Obstet Gynecol Scand.* 2006;85:343-349.	Data not stratified by age, age groupings not appropriate, or denominators not known

Appendix D Table 1. Studies Excluded From the Review for KQ1

Key Question 1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?	
Reference	**Reason for exclusion***
Sigurdsson K, Sigvaldason H. Longitudinal trends in cervical cytological lesions and the effect of risk factors. A 30-year overview. *Acta Obstet Gynecol Scand.* 2006;85:350-358.	Reported outcomes do not address a key question
Sigurdsson K, Sigvaldason H. Longitudinal trends in cervical histological lesions (CIN 2-3+): a 25-year overview. *Acta Obstet Gynecol Scand.* 2006;85:359-365.	Data covered in other articles
Sigurdsson K. Trends in cervical intra-epithelial neoplasia in Iceland through 1995: evaluation of targeted age groups and screening intervals. *Acta Obstet Gynecol Scand.* 1999;78:486-492.	Reported outcomes do not address a key question
Silva CS, Souza MA, Angelo AG, Pavani R, Adad SJ, Murta EF. Increased frequency of abnormal Papanicolaou smears in adolescents. *Archives of Gynecology & Obstetrics.* 2002;266:154-156.	Reported outcomes do not address a key question
Soren K, Kharbanda EO, Chen S, Westhoff C. A 6-year experience with Pap smears in an urban adolescent practice: the scope and burden of abnormalities. *Journal of Pediatric & Adolescent Gynecology.* 2009;22:217-222.	Provides prevalence data only
Stuart G, Taylor G, Bancej CM et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *J Obstet Gynaecol Can.* 2004;26:1004-1028.	Editorials; letters; non-systematic reviews; opinions
Sykes P, Harker D, Peddie D. Findings and outcome of teenage women referred for colposcopy at Christchurch Women's Hospital, New Zealand. *N Z Med J.* 2005;118:U1350.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Syrjanen S, Shabalova I, Petrovichev N et al. Acquisition of high-risk human papillomavirus infections and pap smear abnormalities among women in the New Independent States of the Former Soviet Union. *J Clin Microbiol.* 2004;42:505-511.	Reported outcomes do not address a key question
Syrjanen S, Shabalova I, Petrovichev N et al. Age-specific incidence and clearance of high-risk human papillomavirus infections in women in the former Soviet Union. *International Journal of STD & AIDS.* 2005;16:217-223.	Reported outcomes do not address a key question
Tiews S, Steinberg W, Schneider W, Hanrath C. Determination of the diagnostic accuracy of testing for high-risk (HR) human papillomavirus (HPV) types 16, 18 and 45 in precancerous cervical lesions: preliminary data. *J Clin Virol.* 2009;46:Suppl-5.	Data not stratified by age, age groupings not appropriate, or denominators not known
Tota J, Franco EL. Effectiveness of cervical cancer screening at different ages. *Women's health.* 2009;5:613-616.	Editorials; letters; non-systematic reviews; opinions
van den Akker-van Marle ME, van Ballegooijen M, Habbema JD. Low risk of cervical cancer during a long period after negative screening in the Netherlands. *Br J Cancer.* 2003;88:1054-1057.	Data not stratified by age, age groupings not appropriate, or denominators not known
van der Aa MA, de Kok IM, Siesling S, van Ballegooijen M, Coebergh JW. Does lowering the screening age for cervical cancer in The Netherlands make sense? *Int J Cancer.* 2008;123:1403-1406.	Data not stratified by age, age groupings not appropriate, or denominators not known
Vetrano G, Lombardi G, Di LG et al. Cervical intraepithelial neoplasia: risk factors for persistence and recurrence in adolescents. *Eur J Gynaecol Oncol.* 2007;28:189-192.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Wang SS, Sherman ME, Hildesheim A, Lacey JV, Jr., Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. *Cancer.* 2004;100:1035-1044.	Ecological study without link to screening
Wise J. Age for starting cervical cancer screening in England will not be lowered. *BMJ.* 2009;338:b2583.	Editorials; letters; non-systematic reviews; opinions

Appendix D Table 1. Studies Excluded From the Review for KQ1

Key Question 1: When should cervical cancer screening begin, and does this vary by screening technology or by age, sexual history, or other patient characteristics?	
Reference	**Reason for exclusion***
Wright VC, Riopelle MA. Age at beginning of coitus versus chronologic age as a basis for Papanicolaou smear screening: an analysis of 747 cases of preinvasive disease. *Am J Obstet Gynecol.* 1984;149:824-830.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Wu S, Meng L, Wang S, Ma D. A comparison of four screening methods for cervical neoplasia. *International Journal of Gynaecology & Obstetrics.* 2005;91:189-193.	Data not stratified by age, age groupings not appropriate, or denominators not known

* See Appendix B Table 2 for more detailed exclusion criteria

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Abulafia O, Pezzullo JC, Sherer DM. Performance of ThinPrep liquid-based cervical cytology in comparison with conventionally prepared Papanicolaou smears: a quantitative survey. *Gynecol Oncol.* 2003;90:137-144.	Includes studies that do not meet design criteria
Almonte M, Ferreccio C, Winkler JL et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer.* 2007;121:796-802.	Colposcopy and/or histology only in positives
Angstetra D, Tait T, Tan J, Symonds I. Should liquid-based cytology be performed prior to colposcopy? A comparison of the accuracy, unsatisfactory rates and cost in a tertiary referral setting. *Australian & New Zealand Journal of Obstetrics & Gynaecology.* 2009;49:681-684.	Screening conducted solely in referred population or does not report routine and referred outcomes separately
Anton RC, Ramzy I, Schwartz MR, Younes P, Chakraborty S, Mody DR. Should the cytologic diagnosis of "atypical squamous cells of undetermined significance" be qualified? An assessment including comparison between conventional and liquid-based technologies. *Cancer.* 2001;93:93-99.	Reported outcomes do not address a key question
Aponte-Cipriani SL, Teplitz C, Rorat E, Savino A, Jacobs AJ. Cervical smears prepared by an automated device versus the conventional method. A comparative analysis. *Acta Cytol.* 1995;39:623-630.	Does not systematically apply reference standard
Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J. Liquid Compared With Conventional Cervical Cytology: A Systematic Review and Meta-analysis. *Obstet Gynecol.* 2008;111:167-177.	Includes studies that do not meet design criteria
Ashfaq R, Gibbons D, Vela C, Saboorian MH, Iliya F. ThinPrep Pap Test. Accuracy for glandular disease. *Acta Cytol.* 1999;43:81-85.	Does not systematically apply reference standard
Atkins KA, Jeronimo J, Stoler MH, ALTS Group. Description of patients with squamous cell carcinoma in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion triage study. *Cancer.* 2006;108:212-221.	Reported outcomes do not address a key question
Australian Health Technology Advisory Committee. Review of Automated and Semi-Automated Cervical Screening Devices. 1-86. 1998. Canberra, Commonwealth Department of Health and Family Services.	Focus on excluded screening methods
Awen C, Hathway S, Eddy W, Voskuil R, Janes C. Efficacy of ThinPrep preparation of cervical smears: a 1,000-case, investigator-sponsored study. *Diagn Cytopathol.* 1994;11:33-36.	Does not systematically apply reference standard
Bacon J, Francoeur D, Goldfarb AF, Breech LL. Abnormal pap smears in adolescents. *J Pediatr Adolesc Gynecol.* 2003;16:157-166.	Editorials, letters, non-systematic review, opinion or case-control
Bai H, Sung CJ, Steinhoff MM. ThinPrep Pap Test promotes detection of glandular lesions of the endocervix. *Diagn Cytopathol.* 2000;23:19-22.	Editorials, letters, non-systematic review, opinion or case-control
Baker JJ. Conventional and liquid-based cervicovaginal cytology: a comparison study with clinical and histologic follow-up. *Diagn Cytopathol.* 2002;27:185-188.	Physician choice of cytology
Bastian, L., Datta, S., Hasselblad, V., Hickey, J., Myers, E., and Nanda, K. Evidence Report No. 5, Summary. Evaluation of Cervical Cytology. 5. 1999. Rockville, MD, Agency for Heath Care Policy and Research.	Precedes search period
Beerman H, van-Dorst EB, Kuenen B, V, Hogendoorn PC. Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. *SO: Gynecologic oncology.* 2009;112:572-576.	Does not systematically apply reference standard
Belinson J, Qiao YL, Pretorius R et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecol Oncol.* 2001;83:439-444.	No comparison to conventional cytology
Bergeron C, Fagnani F. Performance of a new, liquid-based cervical screening technique in the clinical setting of a large French laboratory. *Acta Cytol.* 2003;47:753-761.	Colposcopy and/or histology only in positives
Bergeron C. Accuracy of thin-layer cytology in patients undergoing cervical cone biopsy. *Acta Cytol.* 2001;519-524.	Screening conducted solely in referred population or does not report routine and referred outcomes separately

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Bernstein SJ, Sanchez-Ramos L, Ndubisi B. Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: a metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy. *Am J Obstet Gynecol.* 2001;185:308-317.	Precedes search period
Biscotti CV, O'Brien DL, Gero MA, Gramlich TL, Kennedy AW, Easley KA. Thin-layer Pap test vs. conventional Pap smear. Analysis of 400 split samples. *J Reprod Med.* 2002;47:9-13.	Does not systematically apply reference standard
Bishop JW, Bigner SH, Colgan TJ et al. Multicenter masked evaluation of AutoCyte PREP thin layers with matched conventional smears. Including initial biopsy results. *Acta Cytol.* 1998;42:189-197.	Does not systematically apply reference standard
Bishop JW. Comparison of the CytoRich system with conventional cervical cytology. Preliminary data on 2,032 cases from a clinical trial site. *Acta Cytol.* 1997;41:15-23.	Does not systematically apply reference standard
Bolick DR, Hellman DJ. Laboratory implementation and efficacy assessment of the ThinPrep cervical cancer screening system. *Acta Cytol.* 1998;42:209-213.	Physician choice of cytology
Boon ME, Rijkaart DC, Ouwerkerk-Noordam E, Korporaal H. Dutch solutions for liquid-based cytology: analysis of unsatisfactory slides and HPV testing of equivocal cytology. *Diagn Cytopathol.* 2006;34:644-648.	Reported outcomes do not address a key question
Bratti MC, Rodriguez AC, Schiffman M et al. Description of a seven-year prospective study of human papillomavirus infection and cervical neoplasia among 10000 women in Guanacaste, Costa Rica. *Rev Panam Salud Publica.* 2004;15:75-89.	Reference standard not independent of screening test‡
Bur M, Knowles K, Pekow P, Corral O, Donovan J. Comparison of ThinPrep preparations with conventional cervicovaginal smears. Practical considerations. *Acta Cytol.* 1995;39:631-642.	Does not systematically apply reference standard
Canda MT, Demir N, Sezer O, Doganay L, Ortac R. Clinical results of the liquid-based cervical cytology tool, Liqui-PREP, in comparison with conventional smears for detection of squamous cell abnormalities. *Asian Pacific Journal of Cancer Prevention: Apjcp.* 2009;10:399-402.	Does not systematically apply reference standard
Carpenter AB, Davey DD. ThinPrep Pap Test: performance and biopsy follow-up in a university hospital. *Cancer.* 1999;87:105-112.	Editorials, letters, non-systematic review, opinion or case-control
Celik C, Gezginc K, Toy H, Findik S, Yilmaz O. A comparison of liquid-based cytology with conventional cytology. *International Journal of Gynaecology & Obstetrics.* 2008;100:163-166.	Colposcopy and/or histology only in positives
Cheung AN, Szeto EF, Leung BS, Khoo US, Ng AW. Liquid-based cytology and conventional cervical smears: a comparison study in an Asian screening population. *Cancer.* 2003;99:331-335.	Reported outcomes do not address a key question
Cheuvront DA, Elston RJ Bishop JW. Effect of a thin-layer preparation system on workload in a cytology laboratory. Laboratory Medicine 29, 174-179. 1998.	Does not systematically apply reference standard
Chung JH, Park EJ, Choi YD et al. Efficacy assessment of CellSlide in liquid-based gynecologic cytology. *Gynecol Oncol.* 2005;99:597-602.	Focus on excluded screening methods
Clavel C, Masure M, Bory JP et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer.* 2001;84:1616-1623.	Poor reporting
Cochand-Priollet B, Cartier I, de Cremoux P et al. Cost-effectiveness of liquid-based cytology with or without hybrid-capture II HPV test compared with conventional Pap smears: a study by the French Society of Clinical Cytology. *Diagn Cytopathol.* 2005;33:338-343.	Provides data already covered in other article
Confortini M, Bulgaresi P, Cariaggi MP et al. Comparing conventional and liquid-based smears from a consecutive series of 297 subjects referred to colposcopy assessment. *Cytopathology.* 2004;15:168-170.	Poor reporting
Confortini M, Bulgaresi P, Cariaggi MP et al. Conventional pap smear and liquid-based cervical cytology smear: comparison from the same patient. *Tumori.* 2002;88:288-290.	Screening conducted solely in referred population or does not report routine and referred outcomes separately
Corkill MM, Knapp DC, Hutchinson MLM. Improved Accuracy for Cervical Cytology with the ThinPrep Method and the Endocervical Brush-Spatula Collection Procedure. *Journal of Lower Genital Tract Disease.* 1998;2:12-16.	Does not systematically apply reference standard

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Davey E, Barratt A, Irwig L et al. Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. *Lancet.* 2006;367:122-132.	Includes studies that do not meet design criteria
Davey E, d'Assuncao J, Irwig L et al. Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study. *BMJ.* 2007;335:31.	Focus on excluded screening methods
Day SJ, Deszo EL, Freund GG. Dual sampling of the endocervix and its impact on AutoCyte Prep endocervical adequacy. *Am J Clin Pathol.* 2002;118:41-46.	Reported outcomes do not address a key question
Diaz-Rosario LA, Kabawat SE. Performance of a fluid-based, thin-layer papanicolaou smear method in the clinical setting of an independent laboratory and an outpatient screening population in New England. *Arch Pathol Lab Med.* 1999;123:817-821.	Does not systematically apply reference standard
Dupree WB, Suprun HZ, Beckwith DG, Shane JJ, Lucente V. The promise and risk of a new technology: The Lehigh Valley Hospital's experience with liquid-based cervical cytology. *Cancer.* 1998;84:202-207.	Does not systematically apply reference standard
Ferenczy A, Franco E, Arseneau J, Wright TC, Richart RM. Diagnostic performance of Hybrid Capture human papillomavirus deoxyribonucleic acid assay combined with liquid-based cytologic study. *Am J Obstet Gynecol.* 1996;175:651-656.	Reported outcomes do not address a key question
Ferenczy A, Robitaille J, Franco E, Arseneau J, Richart RM, Wright TC. Conventional cervical cytologic smears vs. ThinPrep smears. A paired comparison study on cervical cytology. *Acta Cytol.* 1996;40:1136-1142.	Screening conducted solely in referred population or does not report routine and referred outcomes separately
Ferreccio C, Bratti MC, Sherman ME et al. A comparison of single and combined visual, cytologic, and virologic tests as screening strategies in a region at high risk of cervical cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 2003;12:815-823.	Reference standard not independent of screening test
Ferris DG, Heidemann NL, Litaker MS, Crosby JH, Macfee MS. The efficacy of liquid-based cervical cytology using direct-to-vial sample collection. *J Fam Pract.* 2000;49:1005-1011.	Does not systematically apply reference standard
Fremont-Smith M, Marino J, Griffin B, Spencer L, Bolick D. Comparison of the SurePath liquid-based Papanicolaou smear with the conventional Papanicolaou smear in a multisite direct-to-vial study. *Cancer.* 2004;102:269-279.	Reported outcomes do not address a key question
Genova NJ. Evidence-based medicine--in real time. Comparing methods of cervical Ca screening. *JAAPA.* 2000;13:55-60, 63.	Editorials, letters, non-systematic review, opinion or case-control
Geyer JW, Hancock F, Carrico C, Kirkpatrick M. Preliminary evaluation of Cyto-Rich: an improved automated cytology preparation. *Diagn Cytopathol.* 1993;9:417-422.	Does not systematically apply reference standard
Girianelli VR, Thuler LC, Szklo M et al. Comparison of human papillomavirus DNA tests, liquid-based cytology and conventional cytology for the early detection of cervix uteri cancer. *Eur J Cancer Prev.* 2006;15:504-510.	Focus on excluded screening methods
Guidos BJ, Selvaggi SM. Detection of endometrial adenocarcinoma with the ThinPrep Pap test. *Diagn Cytopathol.* 2000;23:260-265.	Physician choice of cytology
Guidos BJ, Selvaggi SM. Use of the Thin Prep Pap Test in clinical practice. *Diagn Cytopathol.* 1999;20:70-73.	Physician choice of cytology
Guo M, Hu L, Martin L, Liu S, Baliga M, Hughson MD. Accuracy of liquid-based Pap tests: comparison of concurrent liquid-based tests and cervical biopsies on 782 women with previously abnormal Pap smears. *Acta Cytol.* 2005;49:132-138.	No comparison to conventional cytology
Harkness CB, Theofrastous JP, Ibrahim SN, Galvin SL, Lawrence HC. Papanicolaou and thin-layer cervical cytology with colposcopic biopsy control. A comparison. *J Reprod Med.* 2003;48:681-686.	Colposcopy and/or histology only in positives
Hartmann KE, Nanda K, Hall S, Myers E. Technologic advances for evaluation of cervical cytology: is newer better? *Obstet Gynecol Surv.* 2001;56:765-774.	Provides data already covered in other article
Hartmann, KE, Hall, SA, Nanda, K, Boggess, JF, and Zolnoun, D. Screening for Cervical Cancer. ii-74. 2002. Agency for Healthcare Research and Quality.	Provides data already covered in other article
Hatch KD, Sheets E, Kennedy A, Ferris DG, Darragh T, Twiggs L. Multicenter direct to vial evaluation of a liquid-based pap test. *J Low Genit Tract Dis.* 2004;8:308-312.	Editorials, letters, non-systematic review, opinion or case-control

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Hatch, K. D. Multi-site clinical outcome trial to evaluate performance of the ThinPrep test. Obstet Gynecol 95[4, Suppl. 1], S51. 2000.	Editorials, letters, non-systematic review, opinion or case-control
HAYES and Inc. Thin-layer pap preparations for detecting cervical cancer. 2003.	Editorials, letters, non-systematic review, opinion or case-control
Health Technology Advisory Committee. Screening for cervical cancer: recent advances. 2002.	Editorials, letters, non-systematic review, opinion or case-control
Herrero R, Schiffman MH, Bratti C et al. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. *Rev Panam Salud Publica.* 1997;1:362-375.	Reference standard not independent of screening test
Hessling JJ, Raso DS, Schiffer B, Callicott J, Jr., Husain M, Taylor D. Effectiveness of thin-layer preparations vs. conventional Pap smears in a blinded, split-sample study. Extended cytologic evaluation. *J Reprod Med.* 2001;46:880-886.	Does not systematically apply reference standard
Howell LP, Davis RL, Belk TI, Agdigos R, Lowe J. The AutoCyte preparation system for gynecologic cytology. *Acta Cytol.* 1998;42:171-177.	Does not systematically apply reference standard
Hussein T, Desai M, Tomlinson A, Kitchener HC. The comparative diagnostic accuracy of conventional and liquid-based cytology in a colposcopic setting. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2005;112:1542-1546.	Screening conducted solely in referred population or does not report routine and referred outcomes separately
Hutchinson ML, Agarwal P, Denault T, Berger B, Cibas ES. A new look at cervical cytology. ThinPrep multicenter trial results. *Acta Cytol.* 1992;36:499-504.	Does not systematically apply reference standard
Hutchinson ML, Cassin CM, Ball HG, III. The efficacy of an automated preparation device for cervical cytology. *Am J Clin Pathol.* 1991;96:300-305.	Does not systematically apply reference standard
Hutchinson ML, Zahniser DJ, Sherman ME et al. Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. *Cancer.* 1999;87:48-55.	Reference standard not independent of screening test
Inhorn SLM, Wilbur DM, Zahniser DP, Linder JM. Validation of the ThinPrep Papanicolaou Test for Cervical Cancer Diagnosis. *Journal of Lower Genital Tract Disease.* 1998;2:212.	Reported outcomes do not address a key question
Institute for Clinical Systems Improvement. Liquid-based cervical cytology. 2003.	Editorials, letters, non-systematic review, opinion or case-control
Kahn JA, Hillard PJ. Cervical cytology screening and management of abnormal cytology in adolescent girls. *J Pediatr Adolesc Gynecol.* 2003;16:167-171.	Editorials, letters, non-systematic review, opinion or case-control
Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. *Health Technol Assess.* 2004;8:iii, 1-iii,78.	Includes studies that do not meet design criteria
Kim HS, Park JS, Park JY et al. Comparison of two preparation methods for endocervical evaluation. *Acta Cytol.* 2007;51:742-748.	Screening conducted solely in referred population or does not report routine and referred outcomes separately
Kim JJ, Leung GM, Woo PP, Goldie SJ. Cost-effectiveness of organized versus opportunistic cervical cytology screening in Hong Kong. *J Public Health (Oxf).* 2004;26:130-137.	Editorials, letters, non-systematic review, opinion or case-control
Klinkhamer PJ, Meerding WJ, Rosier PF, Hanselaar AG. Liquid-based cervical cytology. *Cancer.* 2003;99:263-271.	Precedes search period
Kruger J. Randomized pilot study comparing rates of endocervical cell recovery between conventional pap smears and liquid-based cytology in a pregnant population. *Journal of Lower Genital Tract Disease.* 2003;101-103.	Does not systematically apply reference standard
Lancaster JM RSB. Evaluation of three cervical cytology screening techniques for use with liquid-based preparations. Adequacy of the endocervical component. *Gynecol Oncol.* 2001;293-294.	Focus on comparison of cytologic collection tools
Laverty CR, Farnsworth A, Thurloe JK, Grieves A, Bowditch R. Evaluation of the CytoRich slide preparation process. *Anal Quant Cytol Histol.* 1997;19:239-245.	Does not systematically apply reference standard

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Laverty CR, Thurloe JK, Redman NL, Farnsworth A. An Australian trial of ThinPrep: a new cytopreparatory technique. *Cytopathology.* 1995;6:140-148.	Does not systematically apply reference standard
Lee KR, Ashfaq R, Birdsong GG, Corkill ME, McIntosh KM, Inhorn SL. Comparison of conventional Papanicolaou smears and a fluid-based, thin-layer system for cervical cancer screening. *Obstet Gynecol.* 1997;90:278-284.	Does not systematically apply reference standard
Lerma E, Quintana MJ, Quilez M et al. Effectiveness of liquid-based cytology and papanicolaou tests in a low risk population. *Acta Cytol.* 2007;51:399-406.	Colposcopy and/or histology only in positives
Levine T. ThinPrep LBC cervical sample. *Cytopathology.* 2007;18:391.	Editorials, letters, non-systematic review, opinion or case-control
Longatto FA, Pereira SM, Di LC et al. DCS liquid-based system is more effective than conventional smears to diagnosis of cervical lesions: study in high-risk population with biopsy-based confirmation. *Gynecol Oncol.* 2005;97:497-500.	Focus on excluded screening methods
Longatto-Filho A, Maeda MY, Erzen M et al. Conventional Pap smear and liquid-based cytology as screening tools in low-resource settings in Latin America: experience of the Latin American screening study. *Acta Cytol.* 2005;49:500-506.	Colposcopy and/or histology only in positives
Luthra UK CM. Performance of monolayered cervical smears in a gynecology outpatient setting in Kuwait. *Acta Cytol.* 2002;303-310.	Does not systematically apply reference standard
Maccallini V, Angeloni C, Caraceni D et al. Comparison of the conventional cervical smear and liquid-based cytology: results of a controlled, prospective study in the Abruzzo Region of Italy. *SO: Acta Cytologica.* 2008;52:568-574.	Colposcopy and/or histology only in positives
Malle D, Pateinakis P, Chakka E, Destouni C. Experience with a thin-layer, liquid-based cervical cytologic screening method. *Acta Cytol.* 2003;47:129-134.	Does not systematically apply reference standard
Marino JF, Fremont-Smith M. Direct-to-vial experience with AutoCyte PREP in a small New England regional cytology practice. *J Reprod Med.* 2001;46:353-358.	Does not systematically apply reference standard
Masumoto N, Fujii T, Ishikawa M et al. Papanicolaou tests and molecular analyses using new fluid-based specimen collection technology in 3000 Japanese women. *Br J Cancer.* 2003;88:1883-1888.	Poor reporting
Mattosinho de Castro Ferraz Mda, Nicolau SM, Stavale JN et al. Cervical biopsy-based comparison of a new liquid-based thin-layer preparation with conventional Pap smears. *Diagn Cytopathol.* 2004;30:220-226.	Focus on excluded screening methods
McGoogan E, Reith A. Would monolayers provide more representative samples and improved preparations for cervical screening? Overview and evaluation of systems available. *Acta Cytol.* 1996;40:107-119.	Focus on comparison of cytologic collection tools
McGoogan, E. Improved adequacy rates using ThinPrep Pap test for routine cytopahtology. Cytopathology 10 (Suppl 1), 2. 1999.	Reported outcomes do not address a key question
Medical Services Advisory Committee. Liquid based cytology for cervical screening. 2002.	Includes studies that do not meet design criteria
Minge L, Fleming M, VanGeem T, Bishop JW. AutoCyte Prep system vs. conventional cervical cytology. Comparison based on 2,156 cases. *J Reprod Med.* 2000;45:179-184.	Does not systematically apply reference standard
Monsonego J, utillo-Touati A, Bergeron C et al. Liquid-based cytology for primary cervical cancer screening: a multi-centre study. *Br J Cancer.* 2001;84:360-366.	Does not systematically apply reference standard
Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. *Journal of Lower Genital Tract Disease.* 2010;14:73-80.	Editorials, letters, non-systematic review, opinion or case-control
Moseley RP, Paget S. Liquid-based cytology: is this the way forward for cervical screening? *Cytopathology.* 2002;13:71-82.	Precedes search period
Moss SM, Gray A, Legood R, and Henstock E. Evaluation of hpv/lvc: cervical screening pilot studies. First report to the Department of Health on LBC. 1-96. 2003.	Reported outcomes do not address a key question
Nanda K, McCrory DC, Myers ER et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med.* 2000;132:810-819.	Precedes search period
NHS, Quality, I. The use of liquid-based cytology for cervical screening (review). 2003.	Editorials, letters, non-systematic review, opinion or case-control

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Noorani, H. Z., Brown, A., Skidmore, B., and Stuart, G. C. E. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. 2003.	Includes studies that do not meet design criteria
Obwegeser JH BS. Does liquid-based technology really improve detection of cervical neoplasia? A prospective, randomized trial comparing the ThinPrep Pap Test with the conventional Pap Test, including follow-up of HSIL cases. *Acta Cytol.* 2001;709-714.	Colposcopy and/or histology only in positives
Pan Q, Belinson JL, Li L et al. A thin-layer, liquid-based pap test for mass screening in an area of China with a high incidence of cervical carcinoma. A cross-sectional, comparative study. *Acta Cytol.* 2003;47:45-50.	No comparison to conventional cytology
Papillo JL, Zarka MA, St John TL. Evaluation of the ThinPrep Pap test in clinical practice. A seven-month, 16,314-case experience in northern Vermont. *Acta Cytol.* 1998;42:203-208.	Does not systematically apply reference standard
Park IA, Lee SN, Chae SW, Park KH, Kim JW, Lee HP. Comparing the accuracy of ThinPrep Pap tests and conventional Papanicolaou smears on the basis of the histologic diagnosis: a clinical study of women with cervical abnormalities. *Acta Cytol.* 2001;45:525-531.	Colposcopy and/or histology only in positives
Partridge EE, bu-Rustum N, Campos S et al. Cervical cancer screening. *Journal of the National Comprehensive Cancer Network.* 2008;6:58-82.	Editorials, letters, non-systematic review, opinion or case-control
Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: a rapid and systematic review. *Health Technol Assess.* 2000;4:1-73.	Precedes search period
Pretorius RG, Kim RJ, Belinson JL, Elson P, Qiao YL. Inflation of sensitivity of cervical cancer screening tests secondary to correlated error in colposcopy. *Journal of Lower Genital Tract Disease.* 2006;10:5-9.	No comparison to conventional cytology
Ring M, Bolger N, O'Donnell M et al. Evaluation of liquid-based cytology in cervical screening of high-risk populations: a split study of colposcopy and genito-urinary medicine populations. *Cytopathology.* 2002;13:152-159.	Does not systematically apply reference standard
Roberts JM, Gurley AM, Thurloe JK, Bowditch R, Laverty CR. Evaluation of the ThinPrep Pap test as an adjunct to the conventional Pap smear. *Med J Aust.* 1997;167:466-469.	Does not systematically apply reference standard
Roberts JM, Thurloe JK, Bowditch RC et al. A three-armed trial of the ThinPrep Imaging System. *Diagn Cytopathol.* 2007;35:96-102.	Focus on excluded screening methods
Ronco G, Giorgi RP, Carozzi F et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. *The lancet oncology.* 2006;7:547-555.	Differential loss to followup and referral criteria
Rosenthal DL, Geddes S, Trimble CL, Carson KA, Alli PM. The PapSpin: a reasonable alternative to other, more expensive liquid-based Papanicolaou tests. *Cancer.* 2006;108:137-143.	Focus on excluded screening methods
Sheets EE, Constantine NM, Dinisco S, Dean B, Cibas ES. Colposcopically Directed Biopsies Provide a Basis for Comparing the Accuracy of ThinPrep and Papanicolaou Smears. *Obstetrical & Gynecological Survey.* 1995;50:659-661.	Does not systematically apply reference standard
Sherman M, Schiffman M. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst.* 2002;102-107.	Reported outcomes do not address a key question
Sherman ME, Mendoza M, Lee KR et al. Performance of liquid-based, thin-layer cervical cytology: correlation with reference diagnoses and human papillomavirus testing. *Mod Pathol.* 1998;11:837-843.	Does not systematically apply reference standard
Sherman ME, Schiffman MH, Lorincz AT et al. Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer.* 1997;81:89-97.	Reported outcomes do not address a key question
Shield PW, Nolan GR, Phillips GE, Cummings MC. Improving cervical cytology screening in a remote, high risk population. *Med J Aust.* 1999;170:255-258.	Does not systematically apply reference standard
Sprenger E, Schwarzmann P, Kirkpatrick M et al. The false negative rate in cervical cytology. Comparison of monolayers to conventional smears. *Acta Cytol.* 1996;40:81-89.	Does not systematically apply reference standard
Stevens MW, Nespolon WW, Milne AJ, Rowland R. Evaluation of the CytoRich technique for cervical smears. *Diagn Cytopathol.* 1998;18:236-242.	Does not systematically apply reference standard

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Strander B, ndersson-Ellstrom A, Milsom I, Radberg T, Ryd W. Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program : a prospective randomized study. *Cancer.* 2007;111:285-291.	Does not systematically apply reference standard
Stuart G, Taylor G, Bancej CM et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *J Obstet Gynaecol Can.* 2004;26:1004-1028.	Editorials, letters, non-systematic review, opinion or case-control
Sulik SM, Kroeger K, Schultz JK, Brown JL, Becker LA, Grant WD. Are fluid-based cytologies superior to the conventional Papanicolaou test? A systematic review. *J Fam Pract.* 2001;50:1040-1046.	Precedes search period
Syrjanen K, Derchain S, Roteli-Martins C et al. Value of conventional pap smear, liquid-based cytology, visual inspection and human papillomavirus testing as optional screening tools among Latin American women <35 and > or =35 years of age: experience from the Latin American Screening Study. *Acta Cytol.* 2008;52:641-653.	Poor reporting
Syrjanen K, Naud P, Derchain S et al. Comparing PAP smear cytology, aided visual inspection, screening colposcopy, cervicography and HPV testing as optional screening tools in Latin America. Study design and baseline data of the LAMS study. *Anticancer Res.* 2005;25:3469-3480.	Reported outcomes do not address a key question
Takahashi M, Naito M. Application of the CytoRich monolayer preparation system for cervical cytology. A prelude to automated primary screening. *Acta Cytol.* 1997;41:1785-1789.	Does not systematically apply reference standard
Tench W. Preliminary assessment of the AutoCyte PREP. Direct-to-vial performance. *J Reprod Med.* 2000;45:912-916.	Does not systematically apply reference standard
Tezuka F, Oikawa H, Shuki H, Higashiiwai H. Diagnostic efficacy and validity of the ThinPrep method in cervical cytology. *Acta Cytol.* 1996;40:513-518.	Colposcopy and/or histology only in positives
Tuncer ZS, Baaran M, Sezgin Y, Firat P, Mocan KG. Clinical results of a split sample liquid-based cytology (ThinPrep) study of 4,322 patients in a Turkish institution. *Eur J Gynaecol Oncol.* 2005;26:646-648.	Colposcopy and/or histology only in positives
Utagawa ML, Pereira SM, Makabe S et al. Pap test in a high-risk population comparison of conventional and liquid-base cytology. *Diagn Cytopathol.* 2004;31:169-172.	Focus on excluded screening methods
Vassilakos P, Cossali D, Albe X, Alonso L, Hohener R, Puget E. Efficacy of monolayer preparations for cervical cytology: emphasis on suboptimal specimens. *Acta Cytol.* 1996;40:496-500.	Reported outcomes do not address a key question
Vassilakos P, Griffin S, Megevand E, Campana A. CytoRich liquid-based cervical cytologic test. Screening results in a routine cytopathology service. *Acta Cytol.* 1998;42:198-202.	Does not systematically apply reference standard
Vassilakos P, Saurel J, Rondez R. Direct-to-vial use of the AutoCyte PREP liquid-based preparation for cervical-vaginal specimens in three European laboratories. *Acta Cytol.* 1999;43:65-68.	Does not systematically apply reference standard
Wang TY, Chen HS, Yang YC, Tsou MC. Comparison of fluid-based, thin-layer processing and conventional Papanicolaou methods for uterine cervical cytology. *J Formos Med Assoc.* 1999;98:500-505.	Does not systematically apply reference standard
Weintraub J, Morabia A. Efficacy of a liquid-based thin layer method for cervical cancer screening in a population with a low incidence of cervical cancer. *Diagn Cytopathol.* 2000;22:52-59.	Does not systematically apply reference standard
Weintraub, J. The coming revolution in cervical cytology: a pathologist's guide for the clinician. References en Gynecologie Obstetrique 5, 1-6. 1997.	Editorials, letters, non-systematic review, opinion or case-control
Wilbur DC, Cibas ES, Merritt S, James LP, Berger BM, Bonfiglio TA. ThinPrep Processor. Clinical trials demonstrate an increased detection rate of abnormal cervical cytologic specimens. *Am J Clin Pathol.* 1994;101:209-214.	Does not systematically apply reference standard
Wilbur DC, Dubeshter B, Angel C, Atkison KM. Use of thin-layer preparations for gynecologic smears with emphasis on the cytomorphology of high-grade intraepithelial lesions and carcinomas. *Diagn Cytopathol.* 1996;14:201-211.	Setting not primary care or comparable
Wilbur DC, Facik MS, Rutkowski MA, Mulford DK, Atkison KM. Clinical trials of the CytoRich specimen-preparation device for cervical cytology. Preliminary results. *Acta Cytol.* 1997;41:24-29.	Does not systematically apply reference standard

Appendix D Table 2. Studies Excluded From the Review for KQ2

Key Question 2: To what extent does liquid-based cytology improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared to conventional cervical cytology?	
Reference	**Reason for exclusion***
Yeoh GP, Chan KW, Lauder I, Lam MB. Evaluation of the ThinPrep Papanicolaou test in clinical practice: 6-month study of 16,541 cases with histological correlation in 220 cases. *Hong Kong Med J.* 1999;5:233-239.	Physician choice of cytology
Yeoh GP, Chan KW. Cell block preparation on residual ThinPrep sample. *Diagn Cytopathol.* 1999;21:427-431.	Reported outcomes do not address a key question
Zhu J, Norman I, Elfgren K et al. A comparison of liquid-based cytology and Pap smear as a screening method for cervical cancer. *Oncol Rep.* 2007;18:157-160.	Screening conducted solely in referred population or does not report routine and referred outcomes separately
Zielinski SL. Trial quickly changed management of cervical abnormalities. *J Natl Cancer Inst.* 2005;97:479-480.	Editorials, letters, non-systematic review, opinion or case-control

* See Appendix B Table 2 for more detailed exclusion criteria

‡ One example of a large study that did not meet criteria for our review is the Guanacaste study, a population-based study of over 10,000 high-risk women that compared liquid-based to conventional cytology. In this study, the final histologic diagnosis included the results of the screening tests. Additionally, the reference standard of colposcopy and biopsy was not systematically applied.

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Adam E, Kaufman RH, Berkova Z, Icenogle J, Reeves WC. Is human papillomavirus testing an effective triage method for detection of high-grade (grade 2 or 3) cervical intraepithelial neoplasia? *Am J Obstet Gynecol.* 1998;1998:1235-1244.	Included women with repeated abnormal smears or abnormal smear other than ASC
Adamopoulou M, Kalkani E, Charvalos E, Avgoustidis D, Haidopoulos D, Yapijakis C. Comparison of cytology, colposcopy, HPV typing and biomarker analysis in cervical neoplasia. *Anticancer Res.* 2009;29:3401-3409.	Included women with repeated abnormal smears or abnormal smear other than ASC
Agorastos T, Dinas K, Lloveras B et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecol Oncol.* 2005;96:714-720.	Poor reporting
Agorastos T, Sotiriadis A, Emmanouilides CJ. Effect of type-specific human papillomavirus incidence on screening performance and cost. *International Journal of Gynecological Cancer.* 2010;20:276-282.	Editorial, letter, non-systematic review, opinion, or case-control
Al-Alwan NA. Colposcopy, cervical cytology and human papillomavirus detection as screening tools for cervical cancer. *Eastern Mediterranean Health Journal.* 2001;7:100-105.	No relevant outcomes
Almonte M, Ferreccio C, Winkler JL et al. Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer.* 2007;121:796-802.	Colposcopy and/or histology only in positives
Antonishyn NA, Horsman GB, Kelln RA, Severini A. Human papillomavirus typing and viral gene expression analysis for the triage of women with abnormal results from papanicolaou test smears to colposcopy. *Archives of Pathology & Laboratory Medicine.* 2009;133:1577-1586.	Included women with repeated abnormal smears or abnormal smear other than ASC
Arbyn M, Buntinx F, Van Ranst M, Paraskevaidis E, Martin-Hirsch P, Dillner J. Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intraepithelial neoplasia. *J Natl Cancer Inst.* 2004;96:280-293.	SER includes studies that do not meet design criteria
Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. *Gynecol Oncol.* 2005;99:S7-11.	SER includes studies that do not meet design criteria
Arbyn M, Ronco G, Meijer CJ, Naucler P. Trials comparing cytology with human papillomavirus screening. *Lancet Oncology.* 2009;10:935-936.	Editorial, letter, non-systematic review, opinion, or case-control
Arbyn M, Sankaranarayanan R, Muwonge R et al. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer.* 2008;123:153-160.	SER includes studies that do not meet design criteria
Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: A summary of meta-analyses. *Vaccine.* 2006;24 Suppl 3:S78-S89.	Editorial, letter, non-systematic review, opinion, or case-control
Arbyn M., Buntinx F Van Ranst M Corinas Abrahantes J. Triage of women with atypical or low-grade cytological abnormalities of the cervix by HPV testing: systematic review and meta-analysis. IPH/EPI-REPORTS Nr.2001-019, 1-240. 2002. Brussels, Scientific Institute of Public Health.	SER includes studies that do not meet design criteria
Arbyn, M. HPV testing in triage of women with equivocal cytology. HPV Today 11, 6-7. 2007.	SER includes studies that do not meet design criteria
Arora R, Kumar A, Prusty BK, Kailash U, Batra S, Das BC. Prevalence of high-risk human papillomavirus (HR-HPV) types 16 and 18 in healthy women with cytologically negative Pap smear. *European Journal of Obstetrics, Gynecology, & Reproductive Biology.* 2005;121:104-109.	No relevant outcomes
Atkins KA, Jeronimo J, Stoler MH, ALTS Group. Description of patients with squamous cell carcinoma in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion triage study. *Cancer.* 2006;108:212-221.	No relevant outcomes
Bacon J, Francoeur D, Goldfarb AF, Breech LL. Abnormal pap smears in adolescents. *J Pediatr Adolesc Gynecol.* 2003;16:157-166.	Editorial, letter, non-systematic review, opinion, or case-control

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Bais AG, Rebolj M, Snijders PJ et al. Triage using HPV-testing in persistent borderline and mildly dyskaryotic smears: proposal for new guidelines. *Int J Cancer.* 2005;116:122-129.	No comparison to cytology
Bavin PJ, Giles JA, Deery A et al. Use of semi-quantitative PCR for human papillomavirus DNA type 16 to identify women with high grade cervical disease in a population presenting with a mildly dyskaryotic smear report. *Br J Cancer.* 1993;67:602-605.	No relevant outcomes
Belinson JL, Qiao YL, Pretorius RG et al. Shanxi Province cervical cancer screening study II: self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. *International Journal of Gynecological Cancer.* 2003;13:819-826.	Focus on excluded screening methods
Bengtsson E, Lindell M, Wikstrom I, Wilander E. Human papilloma virus tests of normal cervical smears collected prior to the development of squamous carcinoma: a pilot study. *Acta Derm Venereol.* 2009;89:516-517.	Editorial, letter, non-systematic review, opinion, or case-control
Bergeron C, Cas F, Fagnani F, iller-Lambert F, Poveda JD. Human papillomavirus testing with a liquid-based system: feasibility and comparison with reference diagnoses. *Acta Cytol.* 2006;50:16-22.	Editorial, letter, non-systematic review, opinion, or case-control
Berkhof J, Coupe VM, Bogaards JA et al. The health and economic effects of HPV DNA screening in The Netherlands. *Int J Cancer.* 2010.	Editorial, letter, non-systematic review, opinion, or case-control
Bewtra C, Xie Q, Soundararajan S, Gatalica Z, Hatcher L. Genital human papillomavirus testing by in situ hybridization in liquid atypical cytologic materials and follow-up biopsies. *Acta Cytol.* 2005;49:127-131.	Focus on excluded screening methods
Bhatla N, Mukhopadhyay A, Kriplani A et al. Evaluation of adjunctive tests for cervical cancer screening in low resource settings. *Indian J Cancer.* 2007;44:51-55.	Population not comparable to primary care
Blumenthal PD, Gaffikin L, Chirenje ZM, McGrath J, Womack S, Shah K. Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear. *International Journal of Gynaecology & Obstetrics.* 2001;72:47-53.	Population not comparable to primary care
Boardman LA, Weitzen S, Stanko C. Atypical squamous cells of undetermined significance, human papillomavirus, and cervical intraepithelial neoplasia 2 or 3 in adolescents: ASC-US, age, and high-grade cervical neoplasia. *Journal of Lower Genital Tract Disease.* 2006;10:140-145.	No relevant outcomes
Bollen LJ, Tjong AHS, van der Velden J et al. Human papillomavirus deoxyribonucleic acid detection in mildly or moderately dysplastic smears: a possible method for selecting patients for colposcopy. *Am J Obstet Gynecol.* 1997;1997:548-553.	Included women with repeated abnormal smears or abnormal smear other than ASC
Bollmann R, Bankfalvi A, Griefingholt H et al. Validity of combined cytology and human papillomavirus (HPV) genotyping with adjuvant DNA-cytometry in routine cervical screening: results from 31031 women from the Bonn-region in West Germany. *Oncol Rep.* 2005;13:915-922.	Colposcopy and/or histology only in positives
Boon ME, Rijkaart DC, Ouwerkerk-Noordam E, Korporaal H. Dutch solutions for liquid-based cytology: analysis of unsatisfactory slides and HPV testing of equivocal cytology. *Diagn Cytopathol.* 2006;34:644-648.	No relevant outcomes
Bory JP, Cucherousset J, Lorenzato M et al. Recurrent human papillomavirus infection detected with the hybrid capture II assay selects women with normal cervical smears at risk for developing high grade cervical lesions: a longitudinal study of 3,091 women. *Int J Cancer.* 2002;102:519-525.	No relevant outcomes
Bosch FX, de SS. Human papillomavirus in cervical cancer. *Curr Oncol Rep.* 2002;4:175-183.	Editorial, letter, non-systematic review, opinion, or case-control
Bozzetti M, Nonnenmacher B, Mielzinska I, I et al. Comparison between hybrid capture II and polymerase chain reaction results among women at low risk for cervical cancer. *Ann Epidemiol.* 2000;10:466.	Editorial, letter, non-systematic review, opinion, or case-control
Braganca JF, Derchain SF, Sarian LO, Messias da Silva SM, Labatte S, Zeferino LC. Aided visual inspection with acetic acid (VIA) and HPV detection as optional screening tools for cervical cancer and its precursor lesions. *Clinical & Experimental Obstetrics & Gynecology.* 2005;32:225-229.	Colposcopy and/or histology only in positives

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Bratti MC, Rodriguez AC, Schiffman M et al. Description of a seven-year prospective study of human papillomavirus infection and cervical neoplasia among 10000 women in Guanacaste, Costa Rica. *Rev Panam Salud Publica.* 2004;15:75-89.	Reference standard not independent of screening test
Bulk S, Bulkmans NW, Berkhof J et al. Risk of high-grade cervical intra-epithelial neoplasia based on cytology and high-risk HPV testing at baseline and at 6-months. *Int J Cancer.* 2007;121:361-367.	Provides no data not otherwise covered in other articles for this study
Bulkmans NW, Bulk S, Ottevanger MS et al. Implementation of human papillomavirus testing in cervical screening without a concomitant decrease in participation rate. *J Clin Pathol.* 2006;59:1218-1220.	No relevant outcomes
Bulkmans NW, Rozendaal L, Voorhorst FJ, Snijders PJ, Meijer CJ. Long-term protective effect of high-risk human papillomavirus testing in population-based cervical screening. *Br J Cancer.* 2005;92:1800-1802.	Does not systematically apply reference standard of colposcopy and/or histology
Cagle AJ, Hu SY, Sellors JW et al. Use of an expanded gold standard to estimate the accuracy of colposcopy and visual inspection with acetic acid. *Int J Cancer.* 2010;126:156-161.	Colposcopy and/or histology only in positives
Carozzi F, Bisanzi S, Sani C et al. Agreement between the AMPLICOR Human Papillomavirus Test and the Hybrid Capture 2 assay in detection of high-risk human papillomavirus and diagnosis of biopsy-confirmed high-grade cervical disease. *J Clin Microbiol.* 2007;45:364-369.	Colposcopy and/or histology only in positives
Carozzi FM, Confortini M, Cecchini S et al. Triage with human papillomavirus testing of women with cytologic abnormalities prompting referral for colposcopy assessment. *Cancer.* 2005;105:2-7.	Poor reporting
Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Five-year experience of human papillomavirus DNA and Papanicolaou test cotesting. *Obstetrics & Gynecology.* 2009;113:595-600.	No relevant outcomes
Castle PE, Gravitt PE, Solomon D, Wheeler CM, Schiffman M. Comparison of linear array and line blot assay for detection of human papillomavirus and diagnosis of cervical precancer and cancer in the atypical squamous cell of undetermined significance and low-grade squamous intraepithelial lesion triage study. *J Clin Microbiol.* 2008;46:109-117.	No comparison to cytology
Castle PE, Schiffman M, Wheeler CM, Wentzensen N, Gravitt PE. Impact of improved classification on the association of human papillomavirus with cervical precancer. *Am J Epidemiol.* 2010;171:155-163.	No comparison to cytology
Castle PE, Stoler MH, Solomon D, Schiffman M. The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *Am J Clin Pathol.* 2007;127:805-815.	No relevant outcomes
Cattani P, Zannoni GF, Ricci C et al. Clinical performance of human papillomavirus E6 and E7 mRNA testing for high-grade lesions of the cervix. *J Clin Microbiol.* 2009;47:3895-3901.	No comparison to cytology
Cibas ES, Hong X, Crum CP, Feldman S. Age-specific detection of high risk HPV DNA in cytologically normal, computer-imaged ThinPrep Pap samples. *Gynecol Oncol.* 2007;104:702-706.	Does not systematically apply reference standard of colposcopy and/or histology
Ciotti M, Sesti F, Paba P et al. Human papillomavirus (HPV) testing in the management of women with abnormal Pap smears. Experience of a colposcopy referral clinic. *Eur J Gynaecol Oncol.* 2004;25:577-584.	Poor reporting
Clavel C, Masure M, Bory JP et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer.* 2001;84:1616-1623.	Poor reporting
Clavel C, Masure M, Levert M et al. Human papillomavirus detection by the hybrid capture II assay: a reliable test to select women with normal cervical smears at risk for developing cervical lesions. *Diagn Mol Pathol.* 2000;9:145-150.	No relevant outcomes
Cochand-Priollet B, Cartier I, de Cremoux P et al. Cost-effectiveness of liquid-based cytology with or without hybrid-capture II HPV test compared with conventional Pap smears: a study by the French Society of Clinical Cytology. *Diagn Cytopathol.* 2005;33:338-343.	Provides no data not otherwise covered in other articles for this study
Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El GF. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol.* 2005;6:552-553.	Editorial, letter, non-systematic review, opinion, or case-control

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Confortini M, Giorgi RP, Barbarino P, Passarelli AM, Orzella L, Tufi MC. Screening for cervical cancer with the human papillomavirus test in an area of central Italy with no previous active cytological screening programme. *J Med Screen.* 2010;17:79-86.	Colposcopy and/or histology only in positives
Contribution of human papillomavirus testing by hybrid capture in the triage of women with repeated abnormal pap smears before colposcopy referral. *Journal of Lower Genital Tract Disease.* 2001;5:195-196.	Editorial, letter, non-systematic review, opinion, or case-control
Costa S, Sideri M, Syrjanen K et al. Combined Pap smear, cervicography and HPV DNA testing in the detection of cervical intraepithelial neoplasia and cancer. *Acta Cytol.* 2000;44:310-318.	Focus on excluded screening methods
Cotton S, Sharp L, Little J et al. The role of human papillomavirus testing in the management of women with low-grade abnormalities: multicentre randomised controlled trial. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2010;117:645-659.	No comparison to cytology
Cotton SC, Sharp L, Little J et al. Trial of management of borderline and other low-grade abnormal smears (TOMBOLA): Trial design. *Contemporary Clinical Trials.* 2006;27:449-471.	No relevant outcomes
Coupe VM, Berkhof J, Bulkmans NW, Snijders PJ, Meijer CJ. Age-dependent prevalence of 14 high-risk HPV types in the Netherlands: implications for prophylactic vaccination and screening. *Br J Cancer.* 2008;98:646-651.	No relevant outcomes
Cox JT, Lorincz AT, Schiffman MH, Sherman ME, Cullen A, Kurman RJ. Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol.* 1995;1995:946-954.	Focus on excluded screening methods
Cox JT. The development of cervical cancer and its precursors: what is the role of human papillomavirus infection? *Curr Opin Obstet Gynecol.* 2006;18 Suppl 1:s5-s13.	Editorial, letter, non-systematic review, opinion, or case-control
Cuschieri KS, Cubie HA, Whitley MW et al. Persistent high risk HPV infection associated with development of cervical neoplasia in a prospective population study. *J Clin Pathol.* 2005;58:946-950.	No relevant outcomes
Cuschieri KS, Graham C, Moore C, Cubie HA. Human Papillomavirus testing for the management of low-grade cervical abnormalities in the UK--Influence of age and testing strategy. *J Clin Virol.* 2007;38:14-18.	Does not systematically apply reference standard of colposcopy and/or histology
Cuzick J, Arbyn M, Sankaranarayanan R et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine.* 2008;26:Suppl-41.	SER includes studies that do not meet design criteria
Cuzick J, Beverley E, Ho L et al. HPV testing in primary screening of older women. *Br J Cancer.* 1999;81:554-558.	Colposcopy and/or histology only in positives
Cuzick J, Clavel C, Petry KU et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119:1095-1101.	Editorial, letter, non-systematic review, opinion, or case-control
Cuzick J, Sasieni P, Davies P et al. A systematic review of the role of human papilloma virus (HPV) testing within a cervical screening programme: summary and conclusions. *Br J Cancer.* 2000;83:561-565.	Editorial, letter, non-systematic review, opinion, or case-control
Cuzick J, Sasieni P, Davies P et al. A systematic review of the role of human papillomavirus testing within a cervical screening programme. *Health Technol Assess.* 1999;3:i-196.	Precedes search period
Cuzick J, Szarewski A, Cubie H et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet.* 2003;362:1871-1876.	Verification bias, lack of blinding, time to colpo/bx not reported‡
Cuzick J, Szarewski A, Terry G et al. Human papillomavirus testing in primary cervical screening. *Lancet.* 1995;1995:1533-1536.	Colposcopy and/or histology only in positives
Dalla Palma P, Pojer A, Girlando S. HPV triage of women with atypical squamous cells of undetermined significance: a 3-year experience in an Italian organized programme. *Cytopathology.* 2005;16:22-26.	Colposcopy and/or histology only in positives
Davies P, Arbyn M, Dillner J et al. A report on the current status of European research on the use of human papillomavirus testing for primary cervical cancer screening. *Int J Cancer.* 2006;118:791-796.	Editorial, letter, non-systematic review, opinion, or case-control

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Dawar M, Deeks S, Dobson S. Human papillomavirus vaccines launch a new era in cervical cancer prevention. *CMAJ.* 2007;2007:456-461.	Editorial, letter, non-systematic review, opinion, or case-control
De Francesco MA, Gargiulo F, Schreiber C, Ciravolo G, Salinaro F, Manca N. Comparison of the AMPLICOR human papillomavirus test and the hybrid capture 2 assay for detection of high-risk human papillomavirus in women with abnormal PAP smear. *J Virol Methods.* 2008;147:10-17.	No comparison to cytology
de OM, varez-Arguelles ME, Torrents M et al. Prevalence, evolution, and features of infection with human papillomavirus: a 15-year longitudinal study of routine screening of a women population in the north of Spain. *J Med Virol.* 2010;82:597-604.	No relevant outcomes
de Vuyst H, Claeys P, Njiru S et al. Comparison of pap smear, visual inspection with acetic acid, human papillomavirus DNA-PCR testing and cervicography. *International Journal of Gynaecology & Obstetrics.* 2005;89:120-126.	Conducted solely in referred population or does not report routine and referred population outcomes separately
de Vuyst H, Steyaert S, Van Renterghem L et al. Distribution of human papillomavirus in a family planning population in nairobi, kenya. *Sex Transm Dis.* 2003;30:137-142.	No comparison to cytology
Denny L, Kuhn L, Pollack A, Wainwright H, Wright TC, Jr. Evaluation of alternative methods of cervical cancer screening for resource-poor settings. *Cancer.* 2000;89:826-833.	Focus on excluded screening methods
Derchain SF, Sarian LO, Naud P et al. Safety of screening with Human papillomavirus testing for cervical cancer at three-year intervals in a high-risk population: experience from the LAMS study. *J Med Screen.* 2008;15:97-104.	Colposcopy and/or histology only in positives
Dillner J, Rebolj M, Birembaut P et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ.* 2008;337:a1754.	Editorial, letter, non-systematic review, opinion, or case-control
Dockter J, Schroder A, Hill C, Guzenski L, Monsonego J, Giachetti C. Clinical performance of the APTIMA HPV Assay for the detection of high-risk HPV and high-grade cervical lesions. *J Clin Virol.* 2009;45:Suppl-61.	No comparison to cytology
Dowie R, Stoykova B, Crawford D et al. Liquid-based cytology can improve efficiency of cervical smear readers: evidence from timing surveys in two NHS cytology laboratories. *Cytopathology.* 2006;17:65-72.	No relevant outcomes
Ekalaksananan T, Pientong C, Kotimanusvanij D, Kongyingyoes B, Sriamporn S, Jintakanon D. The relationship of human papillomavirus (HPV) detection to pap smear classification of cervical-scraped cells in asymptomatic women in northeast Thailand. *Journal of Obstetrics & Gynaecology Research.* 2001;27:117-124.	Colposcopy and/or histology only in positives
Eltoum IA, Chhieng DC, Roberson J, McMillon D, Partridge EE. Reflex human papilloma virus infection testing detects the same proportion of cervical intraepithelial neoplasia grade 2-3 in young versus elderly women. *Cancer.* 2005;105:194-198.	Editorial, letter, non-systematic review, opinion, or case-control
Evans MF, Adamson CS, Papillo JL, St John TL, Leiman G, Cooper K. Distribution of human papillomavirus types in ThinPrep Papanicolaou tests classified according to the Bethesda 2001 terminology and correlations with patient age and biopsy outcomes. *Cancer.* 2006;106:1054-1064.	Does not systematically apply reference standard of colposcopy and/or histology
Fait G, Daniel Y, Kupferminc MJ, Lessing JB, Niv J, Bar-Am A. Does typing of human papillomavirus assist in the triage of women with repeated low-grade, cervical cytologic abnormalities? *Gynecol Oncol.* 1998;1998:319-322.	Focus on excluded screening methods
Fait G, Kupferminc MJ, Daniel Y et al. Contribution of human papillomavirus testing by hybrid capture in the triage of women with repeated abnormal pap smears before colposcopy referral. *Gynecol Oncol.* 2000;79:177-180.	Focus on excluded screening methods
Farag R, Redline R, bdul-Karim FW. Value of combining HPV-DNA testing with follow-up Papanicolaou smear in patients with prior atypical squamous cells of undetermined significance. *Acta Cytol.* 2008;52:294-296.	Does not systematically apply reference standard of colposcopy and/or histology
Ferenczy A, Franco E, Arseneau J, Wright TC, Richart RM. Diagnostic performance of Hybrid Capture human papillomavirus deoxyribonucleic acid assay combined with liquid-based cytologic study. *Am J Obstet Gynecol.* 1996;175:651-656.	Focus on excluded screening methods
Ferreccio C, Bratti MC, Sherman ME et al. A comparison of single and combined visual, cytologic, and virologic tests as screening strategies in a region at high risk of cervical cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 2003;12:815-823.	Reference standard not independent of screening test

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Ferris DG, Schiffman M, Litaker MS. Cervicography for triage of women with mildly abnormal cervical cytology results. *Am J Obstet Gynecol.* 2001;185:939-943.	Focus on excluded screening methods
Ferris DG, Wright TC, Jr., Litaker MS et al. Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. *J Fam Pract.* 1998;1998:136-141.	No comparison to cytology
Ferris DG, Wright TC, Jr., Litaker MS et al. Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? *J Fam Pract.* 1998;1998:125-134.	No comparison to cytology
Flores Y, Bishai D, Lazcano E et al. Improving cervical cancer screening in Mexico: results from the Morelos HPV Study. *Salud Publica Mex.* 2003;45:Suppl-98.	Colposcopy and/or histology only in positives
Flores Y, Shah K, Lazcano E et al. Design and methods of the evaluation of an HPV-based cervical cancer screening strategy in Mexico: The Morelos HPV Study. *Salud Publica Mex.* 2002;44:335-344.	No relevant outcomes
Forslund O, Antonsson A, Edlund K et al. Population-based type-specific prevalence of high-risk human papillomavirus infection in middle-aged Swedish women. *J Med Virol.* 2002;66:535-541.	No relevant outcomes
Franco EL. A new generation of studies of human papillomavirus DNA testing in cervical cancer screening. *J Natl Cancer Inst.* 2009;101:1600-1601.	Editorial, letter, non-systematic review, opinion, or case-control
Franco EL. Randomized controlled trials of HPV testing and Pap cytology: toward evidence-based cervical cancer prevention. *Int J Cancer.* 2004;110:1-2.	Editorial, letter, non-systematic review, opinion, or case-control
Genova NJ. Evidence-based medicine--in real time. Comparing methods of cervical Ca screening. *JAAPA.* 2000;13:55-60, 63.	Editorial, letter, non-systematic review, opinion, or case-control
Gilbert G. HPV screening more accurate than pap (CCCaST). *SO: Journal of the National Medical Association.* 2008;100:265-266.	Editorial, letter, non-systematic review, opinion, or case-control
Giovannelli L, Capra G, Lama A et al. Atypical squamous cells of undetermined significance-favour reactive compared to atypical squamous cells of undetermined significance-favour dysplasia: association with cervical intraepithelial lesions and human papillomavirus infection. *J Clin Virol.* 2005;33:281-286.	No comparison to cytology
Girianelli VR, Thuler LC, Szklo M et al. Comparison of human papillomavirus DNA tests, liquid-based cytology and conventional cytology for the early detection of cervix uteri cancer. *Eur J Cancer Prev.* 2006;15:504-510.	Poor reporting
Goff BA, Muntz HG, Bell DA, Wertheim I, Rice LW. Human papillomavirus typing in patients with Papanicolaou smears showing squamous atypia. *Gynecol Oncol.* 1993;1993:384-388.	Focus on excluded screening methods
Gogola J, Van Dinh T, Lucci JA, III, Smith E, Hannigan EV. Human papillomavirus testing for triage in a referral population. *Journal of Lower Genital Tract Disease.* 2001;5:29-32.	Included women with repeated abnormal smears or abnormal smear other than ASC
Gonzalez-Bosquet E, Almagro MM, Mora I, Sunol M, Callejo J, Lailla JM. Prevalence of human papilloma virus infection of the uterine cervix in women with abnormal cervical cytology. *Eur J Gynaecol Oncol.* 2006;27:135-138.	Poor reporting
Gravitt PE, Schiffman M, Solomon D, Wheeler CM, Castle PE. A comparison of linear array and hybrid capture 2 for detection of carcinogenic human papillomavirus and cervical precancer in ASCUS-LSIL triage study. *Cancer Epidemiology, Biomarkers & Prevention.* 2008;17:1248-1254.	No comparison to cytology
Guido R, Schiffman M, Solomon D, Burke L. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. *Am J Obstet Gynecol.* 2003;188:1401-1405.	Focus on methods to improve followup of abnormal screening findings
Guido RS, Jeronimo J, Schiffman M, Solomon D. The distribution of neoplasia arising on the cervix: results from the ALTS trial. *Am J Obstet Gynecol.* 2005;193:1331-1337.	Does not focus on screening or harms of screening

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Guillaud M, Benedet JL, Cantor SB, Staerkel G, Follen M, MacAulay C. DNA ploidy compared with human papilloma virus testing (Hybrid Capture II) and conventional cervical cytology as a primary screening test for cervical high-grade lesions and cancer in 1555 patients with biopsy confirmation. *Cancer.* 2006;107:309-318.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Guyot A, Karim S, Kyi MS, Fox J. Evaluation of adjunctive HPV testing by Hybrid Capture II in women with minor cytological abnormalities for the diagnosis of CIN2/3 and cost comparison with colposcopy. *BMC Infectious Diseases.* 2003;3:23.	No comparison to cytology
Halfon P, Benmoura D, Khiri H et al. Comparison of the clinical performance of carcinogenic HPV typing of the Linear Array and Papillocheck HPV-screening assay. *J Clin Virol.* 2010;47:38-42.	No comparison to cytology
Halfon P, Trepo E, Antoniotti G et al. Prospective evaluation of the Hybrid Capture 2 and AMPLICOR human papillomavirus (HPV) tests for detection of 13 high-risk HPV genotypes in atypical squamous cells of uncertain significance. *J Clin Microbiol.* 2007;45:313-316.	Does not systematically apply reference standard of colposcopy and/or histology
Hall S, Lorincz A, Shah F et al. Human papillomavirus DNA detection in cervical specimens by hybrid capture: correlation with cytologic and histologic diagnoses of squamous intraepithelial lesions of the cervix. *Gynecol Oncol.* 1996;62:353-359.	Focus on excluded screening methods
Hartmann, KE, Hall, SA, Nanda, K, Boggess, JF, and Zolnoun, D. Screening for Cervical Cancer. ii-74. 2002. Agency for Healthcare Research and Quality.	Provides no data not otherwise covered in other articles for this study
HAYES and Inc. Hybrid capture HPV testing for cervical cancer. 2004.	Editorial, letter, non-systematic review, opinion, or case-control
HAYES. HPV Testing Versus Standard Cytology for Primary Screening of Cervical Cancer. 2007.	Editorial, letter, non-systematic review, opinion, or case-control
Herbert A, Best JM, Chana P et al. Human papillomavirus testing with conventional Pap smear screening in three inner London community clinics. *Journal of Family Planning & Reproductive Health Care.* 2007;33:171-176.	Colposcopy and/or histology only in positives
Herrero R, Hildesheim A, Bratti C et al. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J Natl Cancer Inst.* 2000;92:464-474.	No relevant outcomes
Herrero R, Schiffman MH, Bratti C et al. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. *Rev Panam Salud Publica.* 1997;1:362-375.	Reference standard not independent of screening test
Herrington CS, Evans MF, Hallam NF, Charnock FM, Gray W, McGee JD. Human papillomavirus status in the prediction of high-grade cervical intraepithelial neoplasia in patients with persistent low-grade cervical cytological abnormalities. *Br J Cancer.* 1995;1995:206-209.	Poor reporting
Hildesheim A, Herrero R, Castle PE et al. HPV co-factors related to the development of cervical cancer: results from a population-based study in Costa Rica. *Br J Cancer.* 2001;84:1219-1226.	No relevant outcomes
Hillemanns P, Kimmig R, Huttemann U, Dannecker C, Thaler CJ. Screening for cervical neoplasia by self-assessment for human papillomavirus DNA. *Lancet.* 1999;1999:1970.	Focus on excluded screening methods
Ho L, Terry G, Londesborough P, Cuzick J, Lorenzato F, Singer A. Human papillomavirus DNA detection in the management of women with twice mildly abnormal cytological smears. *J Med Virol.* 2003;69:118-121.	No relevant outcomes
Hovland S, Arbyn M, Lie AK et al. A comprehensive evaluation of the accuracy of cervical pre-cancer detection methods in a high-risk area in East Congo. *Br J Cancer.* 2010;102:957-965.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Howard M, Sellors JW, Lytwyn A, Roth P, Mahony JB. Combining human papillomavirus testing or cervicography with cytology to detect cervical neoplasia. *Archives of Pathology & Laboratory Medicine.* 2004;128:1257-1262.	Poor reporting

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
HPV DNA Testing in Cervical Cancer Screening: Results From Women in a High-Risk Province of Costa Rica. *Obstetrical & Gynecological Survey May 2000;55(5):284-286.* 2000;284-286.	Editorial, letter, non-systematic review, opinion, or case-control
Huang S, Erickson B, Tang N et al. Clinical performance of Abbott RealTime High Risk HPV test for detection of high-grade cervical intraepithelial neoplasia in women with abnormal cytology. *J Clin Virol.* 2009;45:Suppl-23.	Included women with repeated abnormal smears or abnormal smear other than ASC
Infantolino C, Fabris P, Infantolino D et al. Usefulness of human papilloma virus testing in the screening of cervical cancer precursor lesions: a retrospective study in 314 cases. *European Journal of Obstetrics, Gynecology, & Reproductive Biology.* 2000;93:71-75.	Editorial, letter, non-systematic review, opinion, or case-control
Inoue M, Okamura M, Hashimoto S, Tango M, Ukita T. Adoption of HPV testing as an adjunct to conventional cytology in cervical cancer screening in Japan. *Int J Gynaecol Obstet.* 2010.	Colposcopy and/or histology only in positives
Inoue M, Sakaguchi J, Sasagawa T, Tango M. The evaluation of human papillomavirus DNA testing in primary screening for cervical lesions in a large Japanese population. *International Journal of Gynecological Cancer.* 2006;16:1007-1013.	Colposcopy and/or histology only in positives
Institute for Clinical Systems Improvement. HPV DNA Testing for the Screening and Monitoring of Cervical Cancer. 2007.	Editorial, letter, non-systematic review, opinion, or case-control
Jastania R, Geddie WR, Chapman W, Boerner S. Characteristics of apparently false-negative digene hybrid capture 2 high-risk HPV DNA testing. *Am J Clin Pathol.* 2006;125:223-228.	No relevant outcomes
Juric D, Mahovlic V, Rajhvajn S et al. Liquid-based cytology--new possibilities in the diagnosis of cervical lesions. *Coll Antropol.* 2010;34:19-24.	Does not systematically apply reference standard of colposcopy and/or histology
Kahn JA, Hillard PJ. Cervical cytology screening and management of abnormal cytology in adolescent girls. *J Pediatr Adolesc Gynecol.* 2003;16:167-171.	Editorial, letter, non-systematic review, opinion, or case-control
Kahn JA, Slap GB, Bernstein DI et al. Personal meaning of human papillomavirus and Pap test results in adolescent and young adult women. *Health Psychology.* 2007;26:192-200.	No relevant outcomes
Kaufman RH, Adam E, Icenogle J et al. Relevance of human papillomavirus screening in management of cervical intraepithelial neoplasia. *Am J Obstet Gynecol.* 1997;176:87-92.	Included women with repeated abnormal smears or abnormal smear other than ASC
Kaufman RH, Adam E, Icenogle J, Reeves WC. Human papillomavirus testing as triage for atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions: sensitivity, specificity, and cost-effectiveness. *Am J Obstet Gynecol.* 1997;177:930-936.	Included women with repeated abnormal smears or abnormal smear other than ASC
Khanna N, Brooks SE, Chen TT, Simsir A, Gordon NJ, Taylor G. Human papillomavirus absence predicts normal cervical histopathologic findings with abnormal papanicolaou smears: a study of a university-based inner city population. *J Hum Virol.* 2001;4:283-287.	No comparison to cytology
Kiatpongsan S, Niruthisard S, Mutirangura A et al. Role of human papillomavirus DNA testing in management of women with atypical squamous cells of undetermined significance. *International Journal of Gynecological Cancer.* 2006;16:262-265.	No comparison to cytology
Kitchener HC, Almonte M, Wheeler P et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. *Br J Cancer.* 2006;95:56-61.	Provides no data not otherwise covered in other articles for this study
Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: A systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol.* 2007;104:232-246.	SER includes studies that do not meet design criteria
Koliopoulos G, Martin-Hirsch P, Paraskevaidis E, Arbyn M. HPV testing versus cervical cytology for screening for cancer of the uterine cervix. *Cochrane Database of Systematic Reviews.* 2006.	Editorial, letter, non-systematic review, opinion, or case-control

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Kotaniemi TL, Malila N, Nieminen P et al. Test positivity cutoff level of a high risk human papillomavirus test could be increased in routine cervical cancer screening. *SO: International journal of cancer Journal international du cancer.* 2008;123:2902-2906.	Provides no data not otherwise covered in other articles for this study
Koutsky LA, Harper DM, Breen N et al. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: Baseline data from a randomized trial. *J Natl Cancer Inst.* 2000;92:397-402.	No relevant outcomes
Kuhn L, Denny L, Pollack A, Lorincz A, Richart RM, Wright TC. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. *J Natl Cancer Inst.* 2000;92:818-825.	Colposcopy and/or histology only in positives
Kulasingam SL, Rajan R, St PY, Atwood CV, Myers ER, Franco EL. Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: a cost-effectiveness analysis. *BMC Medicine.* 2009;7:69.	Editorial, letter, non-systematic review, opinion, or case-control
Kumar K, Iyer VK, Bhatla N, Kriplani A, Verma K. Comparative evaluation of smear cytology & hybrid capture II for the diagnosis of cervical cancer. *Indian J Med Res.* 2007;126:39-44.	Population not comparable to primary care
Lazcano-Ponce E, Lorincz AT, Salmeron J et al. A pilot study of HPV DNA and cytology testing in 50,159 women in the routine Mexican Social Security Program. *Cancer Causes Control.* 2010.	Colposcopy and/or histology only in positives
Lee GY, Kim SM, Rim SY, Choi HS, Park CS, Nam JH. Human papillomavirus (HPV) genotyping by HPV DNA chip in cervical cancer and precancerous lesions. *International Journal of Gynecological Cancer.* 2005;15:81-87.	Included women with repeated abnormal smears or abnormal smear other than ASC
Lee JK, Kim MK, Song SH et al. Comparison of human papillomavirus detection and typing by hybrid capture 2, linear array, DNA chip, and cycle sequencing in cervical swab samples. *International Journal of Gynecological Cancer.* 2009;19:266-272.	Poor reporting
Lee KJ, Lee JK, Saw HS. Can human papillomavirus DNA testing substitute for cytology in the detection of high-grade cervical lesions? *Archives of Pathology & Laboratory Medicine.* 2004;128:298-302.	Included women with repeated abnormal smears or abnormal smear other than ASC
Lee NW, Kim D, Park JT, Kim A. Is the human papillomavirus test in combination with the Papanicolaou test useful for management of patients with diagnoses of atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions? *Archives of Pathology & Laboratory Medicine.* 2001;125:1453-1457.	Colposcopy and/or histology only in positives
Lepej SZ, Grgic I, Poljak M et al. Detection of human papillomavirus genotypes 16/18/45 by hybrid capture hybridisation genotyping probe in clinical specimens: the first report. *J Clin Virol.* 2007;40:171-172.	Focus on excluded screening methods
Lerma E, Quintana MJ, Quilez M et al. Effectiveness of liquid-based cytology and papanicolaou tests in a low risk population. *Acta Cytol.* 2007;51:399-406.	Colposcopy and/or histology only in positives
Li C, Wu M, Wang J et al. A population-based study on the risks of cervical lesion and human papillomavirus infection among Women in Beijing, People's Republic of China. *Cancer Epidemiol Biomarkers Prev.* 2010.	Does not systematically apply reference standard of colposcopy and/or histology
Li N, Shi JF, Franceschi S et al. Different cervical cancer screening approaches in a Chinese multicentre study. *Br J Cancer.* 2009;100:532-537.	Poor reporting, no indeterminate results provided
Li Y, Ye F, Lu WG, Zeng WJ, Wei LH, Xie X. Detection of human telomerase RNA gene in cervical cancer and precancerous lesions: comparison with cytological and human papillomavirus DNA test findings. *International Journal of Gynecological Cancer.* 2010;20:631-637.	Poor reporting
Lin CT, Tseng CJ, Lai CH, Hsueh S, Huang HJ, Law KS. High-risk HPV DNA detection by Hybrid Capture II. An adjunctive test for mildly abnormal cytologic smears in women > or = 50 years of age. *J Reprod Med.* 2000;45:345-350.	No comparison to cytology
Lin HP, Huang YY, Wu HY, Kao JT. Method for testing for human papillomavirus infection in patients with cervical intraepithelial disease. *J Clin Microbiol.* 2004;42:366-368.	Poor reporting
Lindh M, Gorander S, Andersson E, Horal P, Mattsby-Balzer I, Ryd W. Real-time Taqman PCR targeting 14 human papilloma virus types. *J Clin Virol.* 2007;40:321-324.	Focus on excluded screening methods

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Little J. Human papillomavirus testing. Effectiveness of testing for high risk HPV for triage of low grade abnormal smears is being assessed in TOMBOLA trial. *BMJ.* 2001;323:109.	Editorial, letter, non-systematic review, opinion, or case-control
Longatto-Filho A, Erzen M, Branca M et al. Human papillomavirus testing as an optional screening tool in low-resource settings of Latin America: experience from the Latin American Screening study. *International Journal of Gynecological Cancer.* 2006;16:955-962.	No comparison to cytology
Lonky NM, Felix JC, Naidu YM, Wolde-Tsadik G. Triage of atypical squamous cells of undetermined significance with hybrid capture II: colposcopy and histologic human papillomavirus correlation. *Obstetrics & Gynecology.* 2003;101:481-489.	No comparison to cytology
Lonky NM, Mahdavi A, Wolde-Tsadik G, Bajamundi K, Felix JC. Evaluation of the clinical performance of high-risk human papillomavirus testing for primary screening: a retrospective review of the Southern California Permanente Medical Group experience. *Journal of Lower Genital Tract Disease.* 2010;14:200-205.	Colposcopy and/or histology only in positives
Lorenzato F, Ho L, Terry G et al. The use of human papillomavirus typing in detection of cervical neoplasia in Recife (Brazil). *Int J Gynecol Cancer.* 2000;10:143-150.	Focus on excluded screening methods
Lorincz AT, Richart RM. Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. *Archives of Pathology & Laboratory Medicine.* 2003;127:959-968.	Editorial, letter, non-systematic review, opinion, or case-control
Luyten A, Scherbring S, Reinecke-Luthge A et al. Risk-adapted primary HPV cervical cancer screening project in Wolfsburg, Germany--experience over 3 years. *J Clin Virol.* 2009;46:Suppl-10.	Colposcopy and/or histology only in positives
Lytwyn A, Sellors JW, Mahony JB et al. Adjunctive human papillomavirus testing in the 2-year follow-up of women with low-grade cervical cytologic abnormalities: a randomized trial and economic evaluation. *Archives of Pathology & Laboratory Medicine.* 2003;127:1169-1175.	Focus on excluded screening methods
Lytwyn A, Sellors JW, Mahony JB et al. Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. HPV Effectiveness in Lowgrade Paps (HELP) Study No. 1 Group. *CMAJ.* 2000;163:701-707.	Insufficient sample size, poor reporting, inappropriate exclusions
MacDonald N, Hebert PC. Human papillomavirus vaccine: waiting for a miracle. *CMAJ.* 2007;2007:433, 435.	Editorial, letter, non-systematic review, opinion, or case-control
Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2007;56:1-24.	Does not focus on screening or harms of screening
Masumoto N, Fujii T, Ishikawa M et al. Papanicolaou tests and molecular analyses using new fluid-based specimen collection technology in 3000 Japanese women. *Br J Cancer.* 2003;88:1883-1888.	Poor reporting
Medical Services Advisory Committee. Human papillomavirus testing in women with cytological prediction of low-grade abnormality. 2002.	Precedes search period
Medical Services Advisory Committee. Human papillomavirus testing for cervical screening. 2003.	Precedes search period
Monsonego J, Pintos J, Semaille C et al. Human papillomavirus testing improves the accuracy of colposcopy in detection of cervical intraepithelial neoplasia. *International Journal of Gynecological Cancer.* 2006;16:591-598.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Morin C, Bairati I, Bouchard C et al. Managing atypical squamous cells of undetermined significance in Papanicolaou smears. *J Reprod Med.* 2001;46:799-805.	Poor reporting
Morin, C. Comparison of the hybrid capture test and polymerase chain reaction in identifying women who have an atypical squamous cell of undetermined significance Papanicolaou smear and need colposcopy. J Lower Genit Tract Disease 3, 231-238. 1999.	Focus on excluded screening methods
Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. *Journal of Lower Genital Tract Disease.* 2010;14:73-80.	Editorial, letter, non-systematic review, opinion, or case-control

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Moscicki AB, Hills N, Shiboski S et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *JAMA.* 2001;285:2995-3002.	No relevant outcomes
Moscicki AB. Cervical cytology testing in teens. *Curr Opin Obstet Gynecol.* 2005;17:471-475.	Editorial, letter, non-systematic review, opinion, or case-control
Moss S, Gray A, Legood R et al. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. *BMJ.* 2006;332:83-85.	No relevant outcomes
Mould TA, Singer A, Gallivan S. Quantitative detection of oncogenic HPV DNA using hybrid capture to triage borderline and mildly dyskaryotic Papanicolaou smears. *Eur J Gynaecol Oncol.* 2000;21:245-248.	Focus on excluded screening methods
Munoz N, Bosch FX, Castellsague X et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer.* 2004;111:278-285.	Does not focus on screening or harms of screening
Nene BM, Sankaranaryanan R, Dinshaw KD et al. Comparative efficacy of visual inspection with acetic acid, HPV testing and conventional cytology in cervical cancer screening: a randomised intervention trial in Maharashtra State, India. *Int J Cancer.* 2002;98.	Editorial, letter, non-systematic review, opinion, or case-control
Nieminen P, Vuorma S, Viikki M, Hakama M, Anttila A. Comparison of HPV test versus conventional and automation-assisted Pap screening as potential screening tools for preventing cervical cancer. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2004;111:842-848.	Colposcopy and/or histology only in positives
Nobbenhuis MA, Walboomers JM, Helmerhorst TJ et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet.* 1999;354:20-25.	No relevant outcomes
Nomelini RS, Barcelos AC, Michelin MA, Adad SJ, Murta EF. Utilization of human papillomavirus testing for cervical cancer prevention in a university hospital. *Cad Saude Publica.* 2007;23:1309-1318.	No comparison to cytology
Noorani, H. Z., Brown, A., Skidmore, B., and Stuart, G. C. E. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. 2003.	SER includes studies that do not meet design criteria
Nuovo GJ, Bartholomew D, Jung WW et al. Correlation of Pap smear, cervical biopsy, and clinical follow-up with an HPV typing microarray system. *Diagn Mol Pathol.* 2008;17:107-111.	Does not systematically apply reference standard of colposcopy and/or histology
Nyirjesy I, Billingsley FS, Forman MR. Evaluation of atypical and low-grade cervical cytology in private practice. *Obstet Gynecol.* 1998;92:601-607.	Focus on excluded screening methods
Ogilvie G, Krajden M, Maginley J et al. Feasibility of self-collection of specimens for human papillomavirus testing in hard-to-reach women. *CMAJ.* 2007;2007:480-483.	Focus on excluded screening methods
Ogilvie GS, van Niekerk DJ, Krajden M et al. A randomized controlled trial of Human Papillomavirus (HPV) testing for cervical cancer screening: trial design and preliminary results (HPV FOCAL Trial). *BMC Cancer.* 2010;10:111.	No relevant outcomes
Oh YL, Shin KJ, Han J, Kim DS. Significance of high-risk human papillomavirus detection by polymerase chain reaction in primary cervical cancer screening. *Cytopathology.* 2001;12:75-83.	Does not systematically apply reference standard of colposcopy and/or histology
Ozsaran AA, Dikmen Y, Akercan F et al. The triage of squamous cell abnormalities of cervical cytology by human papilloma virus screening. *Eur J Gynaecol Oncol.* 2003;24:535-538.	Focus on excluded screening methods
Pajtler M, Milicic-Juhas V, Milojkovic M, Topolovec Z, Curzik D, Mihaljevic I. Assessment of HPV DNA test value in management women with cytological findings of ASC-US, CIN1 and CIN2. *Coll Antropol.* 2010;34:81-86.	Does not systematically apply reference standard of colposcopy and/or histology
Pannier-Stockman C, Segard C, Bennamar S et al. Prevalence of HPV genotypes determined by PCR and DNA sequencing in cervical specimens from French women with or without abnormalities. *J Clin Virol.* 2008;42:353-360.	Does not systematically apply reference standard of colposcopy and/or histology
Paraskevaidis E, Malamou-Mitsi V, Koliopoulos G et al. Expanded cytological referral criteria for colposcopy in cervical screening: comparison with human papillomavirus testing. *Gynecol Oncol.* 2001;82:355-359.	Colposcopy and/or histology only in positives

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Partridge EE, bu-Rustum N, Campos S et al. Cervical cancer screening. *Journal of the National Comprehensive Cancer Network.* 2008;6:58-82.	Editorial, letter, non-systematic review, opinion, or case-control
Peto J, Gilham C, Deacon J et al. Cervical HPV infection and neoplasia in a large population-based prospective study: the Manchester cohort. *Br J Cancer.* 2004;91:942-953.	No relevant outcomes
Petry KU, Bohmer G, Iftner T, Flemming P, Stoll M, Schmidt RE. Human papillomavirus testing in primary screening for cervical cancer of human immunodeficiency virus-infected women, 1990-1998. *Gynecol Oncol.* 1999;1999:427-431.	Population not comparable to primary care
Petry, K. U., Menton, M., Bohmer, G., and Iftner, T. Human papillomavirus DNA-testing for primary cervical cancer screening in germany. Anticancer Research 22[1B], 482. 2002.	Editorial, letter, non-systematic review, opinion, or case-control
Plummer M, Schiffman M, Castle PE, Maucort-Boulch D, Wheeler CM, ALTS Group. A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis.* 2007;195:1582-1589.	No relevant outcomes
Powell N. Single HPV test not useful for predicting CIN2 or worse or for guiding choice of further investigations for women aged 20-59 presenting to NHS Cervical Screening Programme with borderline abnormalities or mild dyskaryosis. *Evid Based Med.* 2010.	Editorial, letter, non-systematic review, opinion, or case-control
Pretorius RG, Kim RJ, Belinson JL, Elson P, Qiao YL. Inflation of sensitivity of cervical cancer screening tests secondary to correlated error in colposcopy. *Journal of Lower Genital Tract Disease.* 2006;10:5-9.	Provides no data not otherwise covered in other articles for this study
Pretorius RG, Peterson P, Novak S, Azizi F, Sadeghi M, Lorincz AT. Comparison of two signal-amplification DNA tests for high-risk HPV as an aid to colposcopy. *J Reprod Med.* 2002;47:290-296.	No comparison to cytology
Prinsen CF, Fles R, Wijnen-Dubbers CW et al. Baseline human papillomavirus status of women with abnormal smears in cervical screening: a 5-year follow-up study in The Netherlands. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2007;114:951-957.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Proca DM, Williams JD, Rofagha S, Tranovich VL, Keyhani-Rofagha S. Improved rate of high-grade cervical intraepithelial neoplasia detection in human papillomavirus DNA hybrid capture testing. *Analytical & Quantitative Cytology & Histology.* 2007;29:264-270.	Focus on excluded screening methods
Ratnam S, Franco EL, Ferenczy A. Human papillomavirus testing for primary screening of cervical cancer precursors. *Cancer Epidemiol Biomarkers Prev.* 2000;9:945-951.	Focus on excluded screening methods
Rebello G, Hallam N, Smart G, Farquharson D, McCafferty J. Human papillomavirus testing and the management of women with mildly abnormal cervical smears: an observational study. *BMJ.* 2001;322:893-894.	Poor reporting
Reuschenbach M, Clad A, von Knebel DC et al. Performance of p16(INK4a)-cytology, HPV mRNA, and HPV DNA testing to identify high grade cervical dysplasia in women with abnormal screening results. *Gynecol Oncol.* 2010.	No comparison to cytology
Rijkaart DC, Berkhof J, van Kemenade FJ et al. Comparison of HPV and cytology triage algorithms for women with borderline or mild dyskaryosis in population-based cervical screening (VUSA-screen study). *Int J Cancer.* 2010;126:2175-2181.	Colposcopy and/or histology only in positives
Rijkaart DC, Coupe VM, van Kemenade FJ et al. Comparison of Hybrid capture 2 testing at different thresholds with cytology as primary cervical screening test. *Br J Cancer.* 2010.	Colposcopy and/or histology only in positives
Rodriguez AC, Schiffman M, Herrero R et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst.* 2010;102:315-324.	No comparison to cytology
Ronnett BM, Manos MM, Ransley JE et al. Atypical glandular cells of undetermined significance (AGUS): cytopathologic features, histopathologic results, and human papillomavirus DNA detection. *Hum Pathol.* 1999;30:816-825.	Included women with repeated abnormal smears or abnormal smear other than ASC

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Rousseau MC, Villa LL, Costa MC, Abrahamowicz M, Rohan TE, Franco E. Occurrence of cervical infection with multiple human papillomavirus types is associated with age and cytologic abnormalities. *Sex Transm Dis.* 2003;30:581-587.	No relevant outcomes
Safaeian M, Solomon D, Wacholder S, Schiffman M, Castle P. Risk of precancer and follow-up management strategies for women with human papillomavirus-negative atypical squamous cells of undetermined significance. *Obstetrics & Gynecology.* 2007;109:1325-1331.	No relevant outcomes
Salmeron J, Lazcano-Ponce E, Lorincz A et al. Comparison of HPV-based assays with Papanicolaou smears for cervical cancer screening in Morelos State, Mexico. *Cancer Causes & Control.* 2003;14:505-512.	Colposcopy and/or histology only in positives
Sandri MT, Lentati P, Benini E et al. Comparison of the Digene HC2 assay and the Roche AMPLICOR human papillomavirus (HPV) test for detection of high-risk HPV genotypes in cervical samples. *J Clin Microbiol.* 2006;44:2141-2146.	Does not systematically apply reference standard of colposcopy and/or histology
Sankaranarayanan R, Nene BM, Dinshaw KA et al. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer.* 2005;116:617-623.	Provides no data not otherwise covered in other articles for this study
Sankaranarayanan R, Thara S, Sharma A et al. Accuracy of conventional cytology: results from a multicentre screening study in India. *J Med Screen.* 2004;2004;11:77-84.	Focus on excluded screening methods
Santos AL, Derchain SF, Martins MR, Sarian LO, Martinez EZ, Syrjanen KJ. Human papillomavirus viral load in predicting high-grade CIN in women with cervical smears showing only atypical squamous cells or low-grade squamous intraepithelial lesion. *Sao Paulo Medical Journal = Revista Paulista de Medicina.* 2003;121:238-243.	Poor reporting
Sarian LO, Derchain SF, Naud P et al. Evaluation of visual inspection with acetic acid (VIA), Lugol's iodine (VILI), cervical cytology and HPV testing as cervical screening tools in Latin America. This report refers to partial results from the LAMS (Latin AMerican Screening) study. *J Med Screen.* 2005;12:142-149.	Poor reporting
Sarode VR, Werner C, Gander R et al. Reflex human papillomavirus DNA testing on residual liquid-based (TPPT) cervical samples: focus on age-stratified clinical performance. *Cancer.* 2003;99:149-155.	No comparison to cytology
Saslow D, Castle PE, Cox JT et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin.* 2007;57:7-28.	Does not focus on screening or harms of screening
Schiffman M, Herrero R, Hildesheim A et al. HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. *JAMA.* 2000;283:87-93.	Reference standard not independent of screening test
Schiffman M, Khan MJ, Solomon D et al. A study of the impact of adding HPV types to cervical cancer screening and triage tests. *J Natl Cancer Inst.* 2005;97:147-150.	Does not focus on screening or harms of screening
Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med.* 2003;127:946-949.	Editorial, letter, non-systematic review, opinion, or case-control
Schlecht NF, Platt RW, Duarte-Franco E et al. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *J Natl Cancer Inst.* 2003;95:1336-1343.	No relevant outcomes
Schledermann D, Andersen BT, Bisgaard K et al. Are adjunctive markers useful in routine cervical cancer screening? Application of p16(INK4a) and HPV-PCR on ThinPrep samples with histological follow-up. *Diagn Cytopathol.* 2008;36:453-459.	Does not systematically apply reference standard of colposcopy and/or histology
Schneede P, Hillemanns P, Ziller F et al. Evaluation of HPV testing by Hybrid Capture II for routine gynecologic screening. *Acta Obstet Gynecol Scand.* 2001;80:750-752.	No relevant outcomes
Schneider A, Hoyer H, Lotz B et al. Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. *Int J Cancer.* 2000;89:529-534.	Colposcopy and/or histology only in positives
Selvaggi SM. ASC-US and high-risk HPV testing: performance in daily clinical practice. *Diagn Cytopathol.* 2006;34:731-733.	Does not systematically apply reference standard of colposcopy and/or histology

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Sherman ME, Castle PE, Solomon D. Cervical cytology of atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H): characteristics and histologic outcomes. *Cancer.* 2006;108:298-305.	No relevant outcomes
Sherman ME, Lorincz AT, Scott DR et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst.* 2003;95:46-52.	No relevant outcomes
Sherman ME, Schiffman MH, Lorincz AT et al. Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer.* 1997;81:89-97.	Focus on excluded screening methods
Shi JF, Belinson JL, Zhao FH et al. Human papillomavirus testing for cervical cancer screening: results from a 6-year prospective study in rural China. *Am J Epidemiol.* 2009;170:708-716.	Provides no data not otherwise covered in other articles for this study
Shin EK, Lee SR, Kim MK et al. Immunocytochemical staining of p16(ink4a) protein as an adjunct test in equivocal liquid-based cytology. *Diagn Cytopathol.* 2008;36:311-316.	No comparison to cytology
Shlay JC, Dunn T, Byers T, Baron AE, Douglas JM, Jr. Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on papanicolaou smears. *Obstetrics & Gynecology.* 2000;96:410-416.	No comparison to cytology
Siddiqi A, Spataro M, McIntire H et al. Hybrid capture 2 human papillomavirus DNA testing for women with atypical squamous cells of undetermined significance Papanicolaou results in SurePath and ThinPrep specimens. *Cancer Cytopathology.* 2009;117:318-325.	Does not systematically apply reference standard of colposcopy and/or histology
Sideri M, Spinaci L, Schettino F et al. Risk factors for high-grade cervical intraepithelial neoplasia in patients with mild cytological dyskaryosis: human papillomavirus testing versus multivariate tree analysis of demographic data. *Cancer Epidemiol Biomarkers Prev.* 1998;7:237-241.	Focus on excluded screening methods
Sigurdsson K, Arnadottir T, Snorradottir M, Benediktsdottir K, Saemundsson H. Human papillomavirus (HPV) in an Icelandic population: the role of HPV DNA testing based on hybrid capture and PCR assays among women with screen-detected abnormal Pap smears. *Int J Cancer.* 1997;1997:446-452.	Editorial, letter, non-systematic review, opinion, or case-control
Silverloo I, Andrae B, Wilander E. Value of high-risk HPV-DNA testing in the triage of ASCUS. *Acta Obstet Gynecol Scand.* 2009;88:1006-1010.	Colposcopy and/or histology only in positives
Slawson DC, Bennett JH, Simon LJ, Herman JM. Should all women with cervical atypia be referred for colposcopy: a HARNET study. Harrisburgh Area Research Network. *J Fam Pract.* 1994;1994:387-392.	Focus on excluded screening methods
Snijders PJ, Hogewoning CJ, Hesselink AT et al. Determination of viral load thresholds in cervical scrapings to rule out CIN 3 in HPV 16, 18, 31 and 33-positive women with normal cytology. *Int J Cancer.* 2006;119:1102-1107.	No relevant outcomes
Sodhani P, Gupta S, Sharma JK et al. Test characteristics of various screening modalities for cervical cancer: a feasibility study to develop an alternative strategy for resource-limited settings. *Cytopathology.* 2006;17:348-352.	Poor reporting
Srodon M, Parry DH, Ronnett BM. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion: diagnostic performance, human papillomavirus testing, and follow-up results. *Cancer.* 2006;108:32-38.	Does not systematically apply reference standard of colposcopy and/or histology
Stoler MH, Castle PE, Solomon D, Schiffman M, American Society for Colposcopy and Cervical Pathology. The expanded use of HPV testing in gynecologic practice per ASCCP-guided management requires the use of well-validated assays. *Am J Clin Pathol.* 2007;127:335-337.	Editorial, letter, non-systematic review, opinion, or case-control
Stuart G, Taylor G, Bancej CM et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *J Obstet Gynaecol Can.* 2004;26:1004-1028.	Editorial, letter, non-systematic review, opinion, or case-control
Sun XW, Ferenczy A, Johnson D et al. Evaluation of the Hybrid Capture human papillomavirus deoxyribonucleic acid detection test. *Am J Obstet Gynecol.* 1995;1995:1432-1437.	Focus on excluded screening methods
Suwannarurk K, Tapanadechopol P, Pattaraarchachai J, Bhamarapravati S. Hospital-based prevalence and sensitivity of high-risk human papillomavirus in Thai urban population. *Cancer Epidemiology.* 2009;33:56-60.	Colposcopy and/or histology only in positives

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Syrjanen K, Derchain S, Roteli-Martins C et al. Value of conventional pap smear, liquid-based cytology, visual inspection and human papillomavirus testing as optional screening tools among Latin American women <35 and > or =35 years of age: experience from the Latin American Screening Study. *Acta Cytol.* 2008;52:641-653.	Poor reporting
Syrjanen K, Naud P, Derchain S et al. Comparing PAP smear cytology, aided visual inspection, screening colposcopy, cervicography and HPV testing as optional screening tools in Latin America. Study design and baseline data of the LAMS study. *Anticancer Res.* 2005;25:3469-3480.	Poor reporting
Syrjanen S, Shabalova IP, Petrovichev N et al. Human Papillomavirus Testing and Conventional Pap Smear Cytology as Optional Screening Tools of Women at Different Risks for Cervical Cancer in the Countries of the Former Soviet Union. *J Low Genit Tract Dis.* 2002;6:97-110.	Colposcopy and/or histology only in positives
Tarkkanen J, Auvinen E, Nieminen P et al. HPV DNA testing as an adjunct in the management of patients with low grade cytological lesions in Finland. *Acta Obstet Gynecol Scand.* 2007;86:367-372.	Included women with repeated abnormal smears or abnormal smear other than ASC
Terry G, Ho L, Londesborough P, Cuzick J, Mielzynska-Lohnas I, Lorincz A. Detection of high-risk HPV types by the hybrid capture 2 test. *J Med Virol.* 2001;65:155-162.	No relevant outcomes
Tiews S, Steinberg W, Schneider W, Hanrath C. Determination of the diagnostic accuracy of testing for high-risk (HR) human papillomavirus (HPV) types 16, 18 and 45 in precancerous cervical lesions: preliminary data. *J Clin Virol.* 2009;46:Suppl-5.	Does not systematically apply reference standard of colposcopy and/or histology
UK NHS National Coordinating Centre for Health Technology Assessment. A randomised trial of human papillomavirus testing in primary cervical screening - primary research project (ongoing). *UK NHS National Coordinating Centre for Health Technology Assessment.* 2002.	Editorial, letter, non-systematic review, opinion, or case-control
University of Zimbabwe/JHPIEGO Cervical Cancer Project. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. University of Zimbabwe/JHPIEGO Cervical Cancer Project. *Lancet.* 1999;1999:869-873.	Focus on excluded screening methods
Utagawa ML, Pereira SM, Makabe S et al. Pap test in a high-risk population comparison of conventional and liquid-base cytology. *Diagn Cytopathol.* 2004;31:169-172.	Focus on excluded screening methods
van den Akker-van Marie ME, van Ballegooijen M, Rozendaal L, Meijer CJ, Habbema JD. Extended duration of the detectable stage by adding HPV test in cervical cancer screening. *Br J Cancer.* 2003;89:1830-1833.	No relevant outcomes
Vassilakos P. Biopsy-based comparison of liquid-based, thin-layer preparations to conventional Pap smears. *The Journal of reproductive medicine.* 2000;11-16.	Colposcopy and/or histology only in positives
Voss JS, Kipp BR, Campion MB et al. Assessment of fluorescence in situ hybridization and hybrid capture 2 analyses of cervical cytology specimens diagnosed as low grade squamous intraepithelial lesion for the detection of high grade cervical intraepithelial neoplasia. *Analytical & Quantitative Cytology & Histology.* 2010;32:121-130.	No comparison to cytology
Vrtacnik-Bokal E, Rakar S, Jancar N, Mozina A, Poljak M. Role of human papillomavirus testing in reducing the number of surgical treatments for precancerous cervical lesions. *Eur J Gynaecol Oncol.* 2005;26:427-430.	No comparison to cytology
Wahlstrom C, Iftner T, Dillner J, Dillner L, Swedescreen Study Group. Population-based study of screening test performance indices of three human papillomavirus DNA tests. *J Med Virol.* 2007;79:1169-1175.	Conducted solely in referred population or does not report routine and referred population outcomes separately
Walker JL, Wang SS, Schiffman M, Solomon D. Predicting absolute risk of CIN3 during post-colposcopic follow-up: results from the ASCUS-LSIL Triage Study (ALTS). *Am J Obstet Gynecol.* 2006;195:341-348.	Focus on methods to improve followup of abnormal screening findings
Wensveen C, Kagie M, Veldhuizen R et al. Detection of cervical intraepithelial neoplasia in women with atypical squamous or glandular cells of undetermined significance cytology: a prospective study. *Acta Obstet Gynecol Scand.* 2003;82:883-889.	Included women with repeated abnormal smears or abnormal smear other than ASC

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Wentzensen N, Gravitt PE, Solomon D, Wheeler CM, Castle PE. A study of Amplicor human papillomavirus DNA detection in the atypical squamous cells of undetermined significance-low-grade squamous intraepithelial lesion triage study. *Cancer Epidemiology, Biomarkers & Prevention.* 2009;18:1341-1349.	No comparison to cytology
Witt A, Hudelist G, Gregor H, Kucera E, Walchetseder C, Czerwenka K. The detection of HPV DNA improves the recognition of cervical intraepithelial lesions. *Archives of Gynecology & Obstetrics.* 2003;268:29-34.	Focus on excluded screening methods
Womack SD, Chirenje ZM, Blumenthal PD et al. Evaluation of a human papillomavirus assay in cervical screening in Zimbabwe. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2000;107:33-38.	Population not comparable to primary care
Womack SD, Chirenje ZM, Gaffikin L et al. HPV-based cervical cancer screening in a population at high risk for HIV infection. *Int J Cancer.* 2000;85:206-210.	Population not comparable to primary care
Wright JD, Rader JS, Davila R et al. Human papillomavirus triage for young women with atypical squamous cells of undetermined significance. *Obstetrics & Gynecology.* 2006;107:822-829.	Editorial, letter, non-systematic review, opinion, or case-control
Wright TC, Jr. Cervical cancer screening in the 21st century: is it time to retire the PAP smear? *Clin Obstet Gynecol.* 2007;50:313-323.	Editorial, letter, non-systematic review, opinion, or case-control
Wright TC, Jr., Denny L, Kuhn L, Pollack A, Lorincz A. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. *JAMA.* 2000;283:81-86.	Colposcopy and/or histology only in positives
Wright TC, Jr., Lorincz A, Ferris DG et al. Reflex human papillomavirus deoxyribonucleic acid testing in women with abnormal Papanicolaou smears. *Am J Obstet Gynecol.* 1998;178:962-966.	No comparison to cytology
Wright TC, Sun XW, Koulos J. Comparison of management algorithms for the evaluation of women with low-grade cytologic abnormalities. *Obstet Gynecol.* 1995;1995:202-210.	Focus on excluded screening methods
Wu HH, Allen SL, Kirkpatrick JL, Elsheikh TM. Reflex high-risk human papilloma virus DNA test is useful in the triage of women with atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion. *Diagn Cytopathol.* 2006;34:707-710.	Does not systematically apply reference standard of colposcopy and/or histology
Wu S, Meng L, Wang S, Ma D. A comparison of four screening methods for cervical neoplasia. *International Journal of Gynaecology & Obstetrics.* 2005;91:189-193.	No relevant outcomes
Xiao GQ, Emanuel PO. Cervical parakeratosis/hyperkeratosis as an important cause for false negative results of Pap smear and human papillomavirus test. *Australian & New Zealand Journal of Obstetrics & Gynaecology.* 2009;49:302-306.	Does not systematically apply reference standard of colposcopy and/or histology
Yarandi F, Shojaei H, Eftekhar Z, Izadi-Mood N. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance, after six months delay: a three-year experience in an Iranian university hospital. *Australian & New Zealand Journal of Obstetrics & Gynaecology.* 2009;49:207-210.	Poor reporting
Yeoh GP, Tse MP, Chan KW, Lord L. Human papillomavirus DNA and liquid-based cervical cytology cotesting in screening and follow-up patient groups. *Acta Cytol.* 2006;50:627-631.	Does not systematically apply reference standard of colposcopy and/or histology
Yoon JH, Yoo SC, Kim WY, Chang SJ, Chang KH, Ryu HS. Role of HPV DNA testing for detection of high-grade cervical lesions in women with atypical squamous cells of undetermined significance: a prospective study in a Korean population. *Eur J Gynaecol Oncol.* 2009;30:271-274.	No comparison to cytology
You K, Liang X, Qin F, Guo Y, Geng L. High-risk human papillomavirus DNA testing and high-grade cervical intraepithelial lesions. *Australian & New Zealand Journal of Obstetrics & Gynaecology.* 2007;47:141-144.	Focus on excluded screening methods
Zappacosta R, Caraceni D, Ciccocioppo L et al. Is HPV-DNA testing a useful tool in predicting low-grade squamous intraepithelial lesion outcome? A retrospective longitudinal study. *Int J Immunopathol Pharmacol.* 2010;23:317-326.	No relevant outcomes
Zdenek, H., Lukac, J., Jabor, A., Chvalova, M., Voracek, J., and Brozkova, M. H. Human papillomavirus deoxyribonucleic acid testing in screening of high grade cervical intraepithelial neoplasia. Saudi Medical Journal 20[11], 861-864. 1999.	Poor reporting
Zhao C, Zhao S, Heider A, Austin RM. Significance of high-risk human papillomavirus DNA detection in women 50 years and older with squamous cell papanicolaou test abnormalities. *Archives of Pathology & Laboratory Medicine.* 2010;134:1130-1135.	Does not systematically apply reference standard of colposcopy and/or histology

Appendix D Table 3. Studies Excluded From the Review for KQ3

Key Question 3: What are the benefits of using HPV testing as a screening test, either alone or in combination with cytology, compared with not testing for HPV?	
Reference	**Reason for exclusion***
Zielinski GD, Snijders PJ, Rozendaal L et al. High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance. *J Pathol.* 2001;195:300-306.	No comparison to cytology
Zielinski SL. Trial quickly changed management of cervical abnormalities. *J Natl Cancer Inst.* 2005;97:479-480.	Editorial, letter, non-systematic review, opinion, or case-control
Zuna RE, Wang SS, Rosenthal DL et al. Determinants of human papillomavirus-negative, low-grade squamous intraepithelial lesions in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions triage study (ALTS). *Cancer.* 2005;105:253-262.	No relevant outcomes

* See Appendix B Table 2 for more detailed exclusion criteria

‡ A large trial that did not meet criteria for inclusion in Key Question 3 was the HPV in Addition to Routine Testing (HART) study conducted in the UK. In this study, 10,358 women who presented for screening at one of 161 family practice clinics in the UK received both an HPV test (HC2) and cytology. Women with LSIL or worse went directly to colposcopy. A 5 percent sample of women negative on both HPV tests and cytology were recalled for colposcopy, and approximately two-thirds attended. The remaining subset of women who had either ASC-US cytology, HPV positive test results, or both were randomized to cytology and HPV testing at 6 and 12 months or to immediate colposcopy. Although the authors report that the specific aims of the study were to compare HPV assays with conventional cytology in the detection rate and positive predictive value of CIN2+, the results of both tests were used to determine management of positive screening results after co-testing. Thus, the randomized portion of the HART study was not designed to determine whether there are benefits of using HPV testing alone or in combination with cytology compared to not testing for HPV but to evaluate relative merits of management strategies after co-testing or HPV with cytology triage. Results from HART might be useful to inform future modeling exercises of HPV testing (with or without cytology co-testing or triage) in women aged 30 to 35 years and older.

The HART study could potentially provide theoretical absolute test results of the sensitivity and specificity of HPV versus cytology, as they offered colposcopy to a random 5 percent subset of those who were HPV negative and cytology negative. However, there was 38 percent nonreceipt of colposcopy from that sample, yielding a nonrandom group of approximately 3 percent of women who were both HPV and cytology negative. Although none of these had CIN2+, it is a small nonrandom sample (n=283) whose results are assumed to apply to all women who tested negative on both tests (n=9173) for the purposes of test performance calculations. Relative test performance (between randomized arms) of HPV versus cytology was not available, as the randomization scheme was performed in order to determine effective management strategies (immediate colposcopy versus surveillance over 6 to 12 months) for women who were HPV positive but cytology negative or borderline at most. Given other limitations to the study, we could not be sure that this study could provide unbiased theoretical absolute test performance estimates for HPV versus cytology. The main limitation is risk of verification bias given that there was differential loss to followup for colposcopy referral among the study arms (13 to 28%). Although the authors tried to calculate test performance within strata to “adjust” for differential noncompliance, this assumes that those not lost to followup are representative of the whole sample, which was shown to not be true using data provided in Table 4 of the Cuzick article. Other issues include uncertainty as to the timeframe within which colposcopy and biopsy was provided, lack of blinding of colposcopists to cytology results (with perhaps the ability to guess HPV results), and exclusion of those with unsatisfactory cytology or incomplete cytology or HPV results (even those with colposcopy).

Appendix D Table 4. Studies Excluded From the Review for KQ4

Key Question 4: What are the harms of liquid-based cytology?	
Reference	**Reason for exclusion***
Atkins KA, Jeronimo J, Stoler MH, ALTS Group. Description of patients with squamous cell carcinoma in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion triage study. *Cancer.* 2006;108:212-221.	Reported outcomes do not address a key question
Bacon J, Francoeur D, Goldfarb AF, Breech LL. Abnormal pap smears in adolescents. *J Pediatr Adolesc Gynecol.* 2003;16:157-166.	Editorials, letters, non-systematic review, opinion or case-control
Genova NJ. Evidence-based medicine--in real time. Comparing methods of cervical Ca screening. *JAAPA.* 2000;13:55-60, 63.	Editorials, letters, non-systematic review, opinion or case-control
Hartmann, KE, Hall, SA, Nanda, K, Boggess, JF, and Zolnoun, D. Screening for Cervical Cancer. ii-74. 2002. Agency for Healthcare Research and Quality.	Provides data covered in other articles
Kahn JA, Hillard PJ. Cervical cytology screening and management of abnormal cytology in adolescent girls. *J Pediatr Adolesc Gynecol.* 2003;16:167-171.	Editorials, letters, non-systematic review, opinion or case-control
Moseley RP, Paget S. Liquid-based cytology: is this the way forward for cervical screening? *Cytopathology.* 2002;13:71-82.	Precedes search period
Noorani, H. Z., Brown, A., Skidmore, B., and Stuart, G. C. E. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. 2003.	SER includes studies that do not meet design criteria
Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K. False-negative results in screening programmes: systematic review of impact and implications. *Health Technol Assess.* 2000;4:1-120.	Precedes search period
Stuart G, Taylor G, Bancej CM et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *J Obstet Gynaecol Can.* 2004;26:1004-1028.	Editorials, letters, non-systematic review, opinion or case-control
Weintraub, J. The coming revolution in cervical cytology: a pathologist's guide for the clinician. References en Gynecologie Obstetrique 5, 1-6. 1997.	Editorials, letters, non-systematic review, opinion or case-control
Zielinski SL. Trial quickly changed management of cervical abnormalities. *J Natl Cancer Inst.* 2005;97:479-480.	Editorials, letters, non-systematic review, opinion or case-control

* See Appendix B Table 2 for more detailed exclusion criteria

Appendix D Table 5. Studies Excluded From the Review for KQ5

Key Question 5: What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?	
Reference	**Reason for exclusion***
Atkins KA, Jeronimo J, Stoler MH, ALTS Group. Description of patients with squamous cell carcinoma in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion triage study. *Cancer.* 2006;108:212-221.	Reported outcomes do not address a key question
Bacon J, Francoeur D, Goldfarb AF, Breech LL. Abnormal pap smears in adolescents. *J Pediatr Adolesc Gynecol.* 2003;16:157-166.	Editorials, letters, non-systematic review, opinion or case-control
Bell S, Porter M, Kitchener H, Fraser C, Fisher P, Mann E. Psychological response to cervical screening. *Prev Med.* 1995;24:610-616.	Does not focus on screening or harms of screening
Campion MJ, Brown JR, McCance DJ et al. Psychosexual trauma of an abnormal cervical smear. *Br J Obstet Gynaecol.* 1988;95:175-181.	Editorials, letters, non-systematic review, opinion or case-control
Castle PE, Katki HA. Benefits and risks of HPV testing in cervical cancer screening. *Lancet Oncology.* 2010;11:214-215.	Editorials, letters, non-systematic review, opinion or case-control
Clarke P, Ebel C, Catotti DN, Stewart S. The psychosocial impact of human papillomavirus infection: implications for health care providers. *Int J STD AIDS.* 1996;7:197-200.	Editorials, letters, non-systematic review, opinion or case-control
Conaglen HM, Hughes R, Conaglen JV, Morgan J. A prospective study of the psychological impact on patients of first diagnosis of human papillomavirus. *International Journal of STD & AIDS.* 2001;12:651-658.	Population not comparable to primary care
Daley EM, Perrin KM, McDermott RJ et al. The psychosocial burden of HPV: a mixed-method study of knowledge, attitudes and behaviors among HPV+ women. *Journal of Health Psychology.* 2010;15:279-290.	Editorials, letters, non-systematic review, opinion or case-control
Filiberti A, Tamburini M, Stefanon B et al. Psychological aspects of genital human papillomavirus infection: a preliminary report. *J Psychosom Obstet Gynaecol.* 1993;14:145-152.	Editorials, letters, non-systematic review, opinion or case-control
Genova NJ. Evidence-based medicine--in real time. Comparing methods of cervical Ca screening. *JAAPA.* 2000;13:55-60, 63.	Editorials, letters, non-systematic review, opinion or case-control
Graziottin A, Serafini A. HPV infection in women: psychosexual impact of genital warts and intraepithelial lesions. *Journal of Sexual Medicine.* 2009;6:633-645.	Editorials, letters, non-systematic review, opinion or case-control
Hartmann, KE, Hall, SA, Nanda, K, Boggess, JF, and Zolnoun, D. Screening for Cervical Cancer. Rockville (MD): Agency for Healthcare Research and Quality; 2002. Systematic Evidence Review Number 25.	Data covered in other articles
Howlett RI. Acceptability of HPV-DNA testing HPV vaccines and levels of HPV knowledge. *Dissertation Abstracts International: Section B: The Sciences and Engineering.* 2008;Vol.68:4420.	Does not focus on screening or harms of screening
Kahn JA, Hillard PJ. Cervical cytology screening and management of abnormal cytology in adolescent girls. *J Pediatr Adolesc Gynecol.* 2003;16:167-171.	Editorials, letters, non-systematic review, opinion or case-control
Kahn JA, Slap GB, Bernstein DI et al. Psychological, behavioral, and interpersonal impact of human papillomavirus and Pap test results. *Journal of Psychiatric Research.* 2005;14:650-659.	Editorials, letters, non-systematic review, opinion or case-control
Keller ML, von S, V, Pankratz B, Hermsen J. Self-disclosure of HPV infection to sexual partners. *West J Nurs Res.* 2000;22:285-296.	Reported outcomes do not address a key question
Kitchener HC, Almonte M, Gilham C et al. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. *Health technology assessment (Winchester, England).* 2009;13:1-150.	Data covered in other articles
Lehr, S. and Lee, M. The psychosocial and sexual trauma of a genital HPV infection. *Nurse Practitioner Forum* 1990; 1, 25-30.	Editorials, letters, non-systematic review, opinion or case-control
Linnehan MJ, Groce NE. Psychosocial and educational services for female college students with genital human papillomavirus infection. *Fam Plann Perspect.* 1999;31:137-141.	Editorials, letters, non-systematic review, opinion or case-control

Appendix D Table 5. Studies Excluded From the Review for KQ5

Key Question 5: What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?	
Reference	**Reason for exclusion***
Maggino T, Casadei D, Panontin E et al. Impact of an HPV diagnosis on the quality of life in young women. *Gynecol Oncol.* 2007;107:Suppl-9.	Quality issues: small sample size, poor reporting, >6 mos between HPV diagnosis and questionnaire in 50% of sample
Mast TC, Zhu X, muro-Mercon C, Cummings HW, Sings HL, Ferris DG. Development and psychometric properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV. *Current Medical Research & Opinion.* 2009;25:2609-2619.	Does not focus on screening or harms of screening
McCaffery K, Forrest S, Waller J, Desai M, Szarewski A, Wardle J. Attitudes towards HPV testing: a qualitative study of beliefs among Indian, Pakistani, African-Caribbean and white British women in the UK. *Br J Cancer.* 2003;88:42-46.	Editorials, letters, non-systematic review, opinion or case-control
McCaffery K, Waller J, Nazroo J, Wardle J. Social and psychological impact of HPV testing in cervical screening: a qualitative study. *Sex Transm Infect.* 2006;82:169-174.	Editorials, letters, non-systematic review, opinion or case-control
Monk BJ, Wiley DJ. Human papillomavirus infections: truth or consequences. *Cancer.* 2004;100:225-227.	Editorials, letters, non-systematic review, opinion or case-control
Newton DC, McCabe MP. Sexually transmitted infections: impact on individuals and their relationships. *Journal of Health Psychology.* 2008;13:864-869.	Does not focus on screening or harms of screening
Noorani, H. Z., Brown, A., Skidmore, B., and Stuart, G. C. E. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003. Technology report no 40.	SER includes studies that do not meet design criteria
Perrin KK, Daley EM, Naoom SF et al. Women's reactions to HPV diagnosis: insights from in-depth interviews. *Women & Health.* 2006;43:93-110.	Editorials, letters, non-systematic review, opinion or case-control
Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K. False-negative results in screening programmes: systematic review of impact and implications. *Health Technol Assess.* 2000;4:1-120.	Precedes search period
Philips Z, Johnson S, Avis M, Whynes DK. Human papillomavirus and the value of screening: young women's knowledge of cervical cancer. *Health Educ Res.* 2003;18:318-328.	Does not focus on screening or harms of screening
Pirotta M, Ung L, Stein A et al. The psychosocial burden of human papillomavirus related disease and screening interventions. *Sex Transm Infect.* 2009;85:508-513.	Does not focus on screening or harms of screening
Ramirez JE, Ramos DM, Clayton L, Kanowitz S, Moscicki AB. Genital human papillomavirus infections: knowledge, perception of risk, and actual risk in a nonclinic population of young women. *J Womens Health.* 1997;6:113-121.	Editorials, letters, non-systematic review, opinion or case-control
Reed BD, Ruffin MT, Gorenflo DW, Zazove P. The psychosexual impact of human papillomavirus cervical infections. *J Fam Pract.* 1999;48:110-116.	Editorials, letters, non-systematic review, opinion or case-control
Rosen NO, Knauper B, Di DP et al. The impact of intolerance of uncertainty on anxiety after receiving an informational intervention about HPV: A randomised controlled study. *Psychol Health.* 2009;1-17.	Does not focus on screening or harms of screening
Rosen NO, Knauper B, Page G et al. Brief research report: uncertainty-inducing and reassuring facts about HPV: a descriptive study of French Canadian women. *Health Care Women Int.* 2009;30:892-902.	Does not focus on screening or harms of screening
Rubin MM, Tripsas CK. Perceived uncertainty, coping strategies, and adaptation in women with human papillomavirus on pap smear. *Journal of Lower Genital Tract Disease.* 2010;14:81-89.	Does not focus on screening or harms of screening
Stuart G, Taylor G, Bancej CM et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *J Obstet Gynaecol Can.* 2004;26:1004-1028.	Editorials, letters, non-systematic review, opinion or case-control

Appendix D Table 5. Studies Excluded From the Review for KQ5

Key Question 5: What are the harms of using HPV testing as a screening test, either alone or in combination with cytology?	
Reference	**Reason for exclusion***
Waller J, Marlow LA, Wardle J. The association between knowledge of HPV and feelings of stigma, shame and anxiety. *Sex Transm Infect.* 2007;83:155-159.	Editorials, letters, non-systematic review, opinion or case-control
Waller J, McCaffery K, Forrest S, Szarewski A, Cadman L, Wardle J. Awareness of human papillomavirus among women attending a well woman clinic. *Sex Transm Infect.* 2003;79:320-322.	Does not focus on screening or harms of screening
Waller J, McCaffery K, Kitchener H, Nazroo J, Wardle J. Women's experiences of repeated HPV testing in the context of cervical cancer screening: a qualitative study. *Psycho-Oncology.* 2007;16:196-204.	Editorials, letters, non-systematic review, opinion or case-control
Waller J, McCaffery K, Nazroo J, Wardle J. Making sense of information about HPV in cervical screening: a qualitative study. *Br J Cancer.* 2005;92:265-270.	Reported outcomes do not address a key question
Waller J, McCaffery KJ, Forrest S, Wardle J. Human papillomavirus and cervical cancer: issues for biobehavioral and psychosocial research. *Ann Behav Med.* 2004;27:68-79.	Editorials, letters, non-systematic review, opinion or case-control
Wang KL, Jeng CJ, Yang YC et al. The psychological impact of illness among women experiencing human papillomavirus-related illness or screening interventions. *Journal of Psychosomatic Obstetrics & Gynecology.* 2010;31:16-23.	Does not focus on screening or harms of screening
Wilkinson C, Jones JM, McBride J. Anxiety caused by abnormal result of cervical smear test: a controlled trial. *BMJ.* 1990;300:440.	Does not focus on screening or harms of screening
Zielinski SL. Trial quickly changed management of cervical abnormalities. *J Natl Cancer Inst.* 2005;97:479-480.	Editorials, letters, non-systematic review, opinion or case-control

*See Appendix B Table 2 for more detailed exclusion criteria

Appendix E. Screening Benefit Considerations Illustrated by NTCC Phase II Trial[113]

The recently reported NTCC Phase II trial of primary HPV screening (compared with cytology) illustrates the tricky and complicated considerations when trying to determine screening benefit, much less net impact (screening benefit minus harms), for alternative approaches in a program of cervical cancer screening. After a single round of HPV screening, disease detection was relatively greater (2-4 times greater, depending on age and whether defined as CIN3+ or CIN2+) compared with cytology alone, although cancers were uncommon in both arms. However, colposcopies were also relatively elevated, at least 2-4 times, with a much higher burden in younger women undergoing primary HPV screening (13.1% in those under 35 vs. 5.8% in women 35 and older) and as compared to younger and older women undergoing conventional cytology (3.6% and 2.4% respectively). This trial also reported a relative decrease in CIN3+ in the HPV arm compared with cytology at the second screening round 3.5 years later which consisted of both groups receiving conventional cytology. While this finding has been interpreted as indicating preventive benefit, since the same test was used in both arms, it is unfortunate that this approach renders the trial non-informative about repeat HPV screening. Experts have suggested that reduced CIN3+ detection in subsequent screening rounds may be a surrogate measure of screening program benefit, by signaling earlier disease detection and treatment. However, CIN3+ is a combined outcome (CIN3, CIS, ICC) that includes some potentially regressive disease. And in NTCC Phase II (as with most trials to date) no impact on cancers was detected. Also, even if one accepts this trial as evidence of HPV screening benefit, net impact cannot be determined as cumulative colposcopy burden is not reported yet for this study. Colposcopy burden could conceivably be improved in the HPV screening arm relative to cytology if early treatment has prevented disease, but whether this is true and how much remains to be demonstrated. And, the potential harms from diagnosis and treatment of non-progressive disease cannot even be estimated due to incomplete reporting. Longer term follow-up and more complete reporting of all screening-related activities and results, including colposcopies, are needed to fully interpret this trial. However, this trial provides several take-away messages as presented. First, given the greatly increased colposcopy requirement and relatively diminished cancer burden in younger women, HPV screening alone in women under 35 is not promising. Second, unless future reporting confirms an ongoing reduction in CIN3+ (and ideally cervical cancers) after one-time HPV screening in older women, careful weighing of benefits with harms from additional colposcopy requirements will be necessary even for modeling an ongoing program of repeat cervical cancer screening. Finally, modeling will also need to adjust for the difference between the trial colposcopy referral threshold (ASC-US+) and US practice.

ASC-US: atypical squamous cells of undetermined significance; CIN: cervical intraepithelial neoplasia; CIS: carcinoma *in situ;* HPV: human papillomavirus; ICC: invasive cervical cancer; NTCC: New Technologies for Cervical Cancer ; US: United States

Appendix F. Ongoing and Pending Trials

Principal investigators	Location	Population	Approximate size	Investigations	Outcomes	Status as of 2010
KQ1: Age to begin screening						
KQ2: Liquid-based cytology						
KQ3: HPV testing						
Coldman*	Vancouver, BC	Routine screening Age 25-69	33,000	HPV DNA testing with cytology triage	≥CIN2 ≥CIN3 Cost analysis	Trial expected to finish March 2014
Murphy*	Toronto, ON	Routine screening Aged ≥18	1712	HPV testing alone or in combination with conventional cytology	≥CIN2 ≥CIN3 Rate of colposcopies	Trial expected to finish January 2011
Ngan*	Hong Kong	Routine screening Age 30-60	12,000	HPV cotesting with conventional cytology compared to conventional cytology alone	≥CIN2 ≥CIN3	Trial expected to finish January 2017
KQ4: Harms of liquid-based cytology						
KQ5: Harms of HPV testing						

*Available at: www.clinicaltrials.gov. Accessed September 29, 2010.

Appendix G. Recommendations of Other Groups

Organization	Age to start screening	Screening interval	Definition of high risk	Interval for high risk	Age to stop screening
American College of Obstetricians and Gynecologists, 2009[1]	Age 21	Under age 30: 2 years Age 30+ with three consecutive normal screenings: every 3 years	HIV infection Immunosuppressed Diethylstilbestrol exposure in utero Women previously treated for CIN 2, CIN 3, or cancer in the past	Annual HIV: twice in the first year of diagnosis and annually after	65 or 70 years with 3 normal screenings and no abnormalities within past 10 years. Assess risk factors annually. After total hysterectomy if no prior high-grade CIN If had CIN 2 or 3, then continue screening
American College of Preventive Medicine, Practice Guidelines Committee, 1996[2] "Although the research on which this statement was based is out of date, the position/ recommendations contained in this policy were reaffirmed by the ACPM Board of Regents on 1/31/2005 until the evidence can be reevaluated."	At onset of sexual activity or age 18 if sexual history is unknown	At least 2 initial screening tests 1 year apart; then interval lengthened at discretion of patient and doctor, but not to exceed >3 year interval	Not mentioned	Not mentioned	Age 65, if no abnormal smears
American Academy of Family Physicians, 2008[3]	Onset of sexual activity or age 18	Once a year until at least 3 normal smears After this, you should have a Pap smear at least every 3 years	Starting to have sex early (before age 20) Having had many sexual partners Being infected with an STD or having had a sex partner who has an STD Smoking Using birth control pills and/or giving birth to many children when also infected with HPV	Not mentioned	Throughout life even after menopause; discuss with physician if > 65 years

Appendix G. Recommendations of Other Groups

Organization	Age to start screening	Screening interval	Definition of high risk	Interval for high risk	Age to stop screening
Canadian Task Force on Preventive Health Care, 1994[4] Is on priority list for update	Women > age 18 who have had sexual intercourse	Two annual screens, then every three years	Early onset of sexual intercourse Many sexual partners Sexual partner with many sexual partners	More frequently than 3 years	Until age 69
American Cancer Society, 2009[5]	Three years after beginning to have vaginal intercourse, but no later than age 21 years	Testing should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test Beginning at age 30, women who have had 3 normal Pap test results in a row may get tested every 2 to 3 years with either the conventional (regular) or liquid-based Pap test or every 3 years with HPV testing	HPV Infection Smoking HIV infection/ Immunosupressed Chlamydia infection Diet (overweight, low in fruits/veggies) Oral contraceptives >2 full-term pregnancies Low SES First full-term pregnancy at <17 yrs Diethylstilbestrol (DES) Family history of cervical cancer	Yearly	Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer testing Women with a history of cervical cancer, DES exposure before birth, HIV infection, or a weakened immune system should continue to have annual screening Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer testing, unless the surgery was done as a treatment for cervical cancer or pre-cancer
Institute for Clinical Systems Improvement, 2009[6]	Three years post-onset of sexual activity or by age 21	Every 3 years after 3 consecutive normal smears over 5 years. -	Not mentioned	Not mentioned	No age recommended for screening to stop Women with total hysterectomy for benign disease and no history of CIN 2 or 3 can stop screening.
UK National Health Service Cervical Screening Programme, 2009[7]	Age 25	Age 25-49: every 3 years Age 50-65: every 5 years Age 65+: Only screen those who have not been screened since age 50 or have had recent abnormal tests	Not mentioned	Not mentioned	Age 65+: Only screen those who have not been screened since age 50 or have had recent abnormal tests

Appendix G. Recommendations of Other Groups

Organization	Age to start screening	Screening interval	Definition of high risk	Interval for high risk	Age to stop screening
Australian National Cervical Screening Program, 2009[8]	18-20 years or 1-2 yrs within first sexual intercourse whichever is later	Every 2 years		"check with your doctor"	Age 70 if two normal Pap smears in last 5 years.
New Zealand National Cervical Screening Programme, 2008[9]	Age 20 for all women who have had sexual intercourse	If first cervical smear test, or if haven't had a test for over 5 years, have a second cervical smear test at 1 year Otherwise, every three years for most women	Immunosuppressed	Annual	Age 70
European guidelines for quality assurance in cervical cancer screening, 2008[10]	Age 20 to 30 yrs	3-5-year intervals until the age of 60	Special attention should be paid to the problem of older women who have never attended screening, as they exhibit increased risk for cervical cancer.		The upper limit should not be lower than 60 years. Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous (recent) normal cytology results.

References

1. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 109: cervical cytology screening. *Obstet Gynecol*. 2009;114(6):1409-1419.
2. Hawkes AP, Kronenberger CB, MacKenzie TD, et al. Cervical cancer screening: American College of Preventive Medicine practice policy statement. *Am J Prev Med*. 1996;12(5):342-344.
3. American Academy of Family Physicians. Pap Smears. Leawood, KS: American Academy of Family Physicians; 2008. Accessed at http://familydoctor.org/online/famdocen/home/women/reproductive/gynecologic/138.html on 11 May 2011.
4. Canadian Task Force on Preventive Health Care. Screening for Cervical Cancer. Ottawa, Ontario: Canadian Task Force on Preventive Health Care; 1994. Accessed at http://www.canadiantaskforce.ca/_archive/index.html on 11 May 2011.
5. American Cancer Society Guidelines for the Early Detection of Cancer. Atlanta, GA: American Cancer Society; 2010. Accessed at http://www.cancer.org/Healthy/FindCancerEarly/CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer on 11 May 2011.
6. Institute for Clinical Systems Improvement. Health Care Guideline: Preventive Services for Adults. Bloomington, MN: Institute for Clinical Systems Improvement; 2010. Accessed at http://www.icsi.org/preventive_services_for_adults/preventive_services_for_adults_4.html on 11 May 2011.
7. NHS Cervical Screening Programme. About Cervical Screening. London: National Health Service; 2011. Accessed at http://www.cancerscreening.nhs.uk/cervical/about-cervical-screening.html on 11 May 2011.
8. Australia Department of Health and Ageing. National Cervical Screening Program. Canberra, Australia: Australia Department of Health and Ageing; 2009. Accessed at http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-about on 11 May 2011.
9. New Zealand National Cervical Screening Programme. Guidelines for Cervical Screening in New Zealand. Wellington, New Zealand: National Screening Unit, Ministry of Health; 2008. Accessed at http://www.nsu.govt.nz/files/NCSP/NCSP_Guidelines_ALL_small(1).pdf on 11 May 2011.
10. Arbyn M, Anttila A, Jordan J, et al. European Guidelines for Quality Assurance in Cervical Cancer Screening: second edition—summary document. *Ann Oncol*. 2010;21(3):448-458.

Appendix H. Cervical Cancer and HPV: Prevalence, Incidence and Mortality Rates

Country	HPV							
	Prevalence among women with normal cytology (general population) % (95% CI)	Adjusted Prevalence among women with normal cytology (general population), by region,* % (95% CI)†	Crude age-specific prevalence among women with normal cytology (general population) % (95% CI) (Estimated from Figure 24)					Prevalence of HPV types 16 and 18 among cervical cancer cases % (95% CI)
			< 25y	25-34y	35-44y	45-54y	55+y	
Canada	9.9 (9.5-10.4)	North America: 11.3 (10.6-12.1)	26 (22.5-32.5)	27.5 (22.5-34)	14 (6.3-25)	12 (4.4-24)	12.5 (5.0-25)	74.3 (67.0-80.6)
China	12.2 (11.8-12.6)	Eastern Asia: 13.6 (12.5-14.9)	9 (6-14)	10 (8-12.5)	13.5 (12-15.5)	12.5 (10-15)	10 (7.5-14)	71.0 (69.8-72.2)
England (UK)	8.9 (8.6-9.1)	Northern Europe: 7.9 (7.4-8.4)	22 (21.5-23)	14 (13.5-15)	7 (6-7.5)	6 (5-6.5)	6 (5.0-6.4)	79.1 (74.4-83.2)
Finland	7.5 (7.1-7.9)	NR	No data available	18.5 (17-20)	8.5 (7.5-9)	4.3 (3.9-5.0)	4 (3.5-5)	88.5 (85.2-91.2)
France	12.8 (12.3-13.4)	Western Europe: 8.4 (8.0-8.8)	43 (35-51)	31.5 (26.5-38.5)	19 (16-24)	21 (16-26.5)	13 (8-18.5)	75.6 (73.3-77.8)
Germany	6.3 (5.9-6.8)	Western Europe: 8.4 (8.0-8.8)	No data available					76.8 (65.1-86.1)
India	7.9 (7.5-8.2)	South-Central Asia: 7.5 (7.0-8.0)	15.5 (14-18)	14 (13-15)	14 (11-15)	14 (10-16)	14.5 (9.5-19)	82.5 (79.5-85.1)
Italy	9.0 (8.7-9.3)	Southern Europe: 6.8 (5.7-7.7)	22 (19-25)	10 (9.5-10.5)	11.5 (8.5-15)	9.5 (7-13)	9 (7-12)	72.1 (67.6-76.4)
Netherlands	3.9 (3.6-4.1)	Western Europe: 8.4 (8.0-8.8)	16.5 (5-35)	8 (7.5-9)	5 (NR)	3.5 (NR)	2.5 (NR)	87.9 (84.6-90.7)
Sweden	5.5 (4.9-6.0)	Northern Europe: 7.9 (7.4-8.4)	7 (3.5-11)	7.5 (6-8)	5 (4.5-6.5)	5.5 (1-16)	No data available	68.5 (64.7-72.2)
Switzerland	6.3 (5.9-6.7)	NR	17.1 (11.5-25.0)	7.8 (6.4-8.5)	6.4 (5.7-7.4)	5.3 (4.7-6.4)	5.7 (5.0-6.4)	78.7 (77.0-80.3)‡
United States	13.3 (13.0-13.6)	North America: 11.3 (10.6-12.1)	27 (26.5-27.5)	12 (11-12.5)	6 (5.5-6.5)	4.5 (3.5-5)	3 (2.5-3.5)	76.6 (74.3-78.8)

Appendix H. Cervical Cancer and HPV: Prevalence, Incidence and Mortality Rates

Country	Cervical Cancer											
	Crude Incidence Rate (per 100,000 women per year)	Age-standardized Incidence Rate (per 100,000 women per year)	Age-specific incidence rates (per 100,000 women per year) (Estimated from Figure 17)				Crude Mortality Rate (per 100,000 women per year)	Age-standardized Mortality Rate (per 100,000 women per year)	Age-specific mortality rates (per 100,000 women per year) (Estimated from Figure 17)			
			15-44y	45-54y	55-64y	65+y			15-44y	45-54y	55-64y	65+y
Canada	8.5	6.6	8.5	12	12	11	3.2	1.9	1	4	5.5	10
China	11.7	9.6	11	21	22	15	5.2	4.2	2	8.5	13	21.5
England (UK)	9.3	7.2	10	12	10.5	13	3.6	2.0	1	4.5	5	10
Finland	5.2	3.7	4.5	6	6	9.5	1.9	0.9	0.5	1	2.5	6
France	9.1	7.1	9	16	11.5	11	3.1	1.8	1	5	5	7
Germany	10.6	6.9	6	20	15	15.5	4.8	2.3	1	5.5	7	12.5
India	23.5	27.0	15.5	72	90	68	12.8	15.2	6	33	53	63
Italy	9.4	6.7	7.5	16.5	15	11	3.0	1.5	1	4	4	6.5
Netherlands	7.1	5.4	7	10	8	11	2.8	1.5	1	3	3.5	9.5
Sweden	9.7	7.4	10	13	13	13.5	3.8	1.8	1	4	5	11.5
Switzerland	5.7	4.0	5	7	7	10.5	1.9	0.9	0.5	1.5	2.5	6
United States	7.0	5.7	7	11	10	10	2.4	1.7	1.5	4	4.5	6

Unless otherwise specified, all data from WHO/ICO Information Center on HPV and Cervical Cancer, 2008; http://apps.who.int/hpvcentre/statistics/dynamic/ico/SummaryReportsSelect.cfm (updated September 15, 2010)

* Data from de Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet. 2007;7:453-459.

† Adjusted for region, study type, study design, publication year, sampling collection device, cell storage medium, HPV assay, primer used, study youngest age included, and study oldest age included

‡ Western Europe regional estimated used instead as specific data unavailable