Annals of Internal Medicine | Review

# Liquid-Based Cytology and Human Papillomavirus Testing to Screen for Cervical Cancer: A Systematic Review for the U.S. Preventive Services Task Force

Evelyn P. Whitlock, MD, MPH; Kimberly K. Vesco, MD, MPH; Michelle Eder, PhD; Jennifer S. Lin, MD, MCR; Caitlyn A. Senger, MPH; and Brittany U. Burda, MPH

**Background:** Screening programs using conventional cytology have successfully reduced cervical cancer, but newer tests might enhance screening.

**Purpose:** To systematically review the evidence on liquid-based cytology (LBC) and high-risk human papillomavirus (HPV) screening for U.S. Preventive Services Task Force use in updating its 2003 recommendation.

**Data Sources:** MEDLINE, Cochrane Central Register of Controlled Trials, and PsycINFO from January 2000 through September 2010.

**Study Selection:** Two independent reviewers selected fair- to good-quality English-language studies that compared LBC or HPV-enhanced primary screening with conventional cytology in countries with developed population-based screening for cervical cancer.

**Data Extraction:** At least 2 independent reviewers critically appraised and rated the quality of studies and used standardized abstraction forms to extract data about test performance for detecting cervical intraepithelial neoplasia (CIN) and cancer and screening-related harms.

**Data Synthesis:** On the basis of 4 fair- to good-quality studies (141 566 participants), LBC had equivalent sensitivity and specificity to conventional cytology. Six fair- to good-quality diagnostic accuracy studies showed that 1-time HPV screening was more sensitive than cytology for detecting CIN3+/CIN2+ but was less specific. On the basis of 2 fair- to good-quality randomized, controlled trials (RCTs) (120 533 participants), primary HPV screening detected more cases of CIN3 or cancer in women older than 30 years. Four fair- to good-quality diagnostic accuracy studies and 4 fair- to good-quality RCTs showed mixed results of cotesting (HPV plus cytology) in women aged 30 years or older compared with cytology alone, with no clear advantage over primary HPV screening. Incomplete reporting of results for all screening rounds, including detection of disease and colposcopies, limits our ability to determine the net benefit of HPV-enhanced testing strategies.

**Limitation:** Resources were insufficient to gather unpublished data, short-term trial data showed possible ascertainment bias, and most RCTs used protocols that differed from current U.S. practice.

**Conclusion:** Evidence supports the use of LBC or conventional cytology for cervical cancer screening, but more complete evidence is needed before HPV-enhanced primary screening is widely adopted for women aged 30 years or older.

**Primary Funding Source:** Agency for Healthcare Research and Quality.

*Ann Intern Med.* 2011;155:687-697. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 18 October 2011.

Cervical cancer screening programs that use conventional cytology every 1 to 5 years have demonstrated reductions in both cervical cancer incidence and mortality over time (1). Conventional cytology, however, is imperfectly sensitive and labor-intensive, leading to keen interest in new screening technologies serving as alternatives or adjuncts (2). Liquid-based cytology (LBC) offers potentially improved test specimen collection that can support cotesting (HPV plus cytology), but its effect on screening test performance remains uncertain (2). Other, newer technologies have been spurred by the scientific establishment of the causal role of various high-risk human papillomavirus (HPV) types in cancer of the cervix and other tissues (3).

Currently, 3 tests for high-risk HPV—Digene Hybrid Capture 2 (Qiagen, Germantown, Maryland), Cobas 4800 HPV (Roche Diagnostics, Indianapolis, Indiana), and Cervista HR HPV (Hologic, Bedford, Massachusetts)—are approved by the U.S. Food and Drug Administration (FDA) for patients with atypical squamous cells of undetermined significance (ASC-US) on cytology to determine referral for colposcopy, and for cotesting women aged 30 years or older as a risk assessment or patient management tool (4, 5). A fourth test, Amplicor HPV (Roche Diagnostics), is awaiting FDA approval (6).

Benefits from screening rely primarily on histologic diagnosis and treatment of cervical intraepithelial neoplasia (CIN) (7) during the long preclinical period typical of cervical cancer (8, 9). Although there are varying levels of CIN (1, 2, and 3), CIN3 is considered the only truly precancerous lesion because it includes carcinoma in situ (10, 11) and is more likely to progress to invasive cervical cancer (12). Although CIN2 is the usual treatment threshold, it is heterogeneous, equivocal in cancer potential, and more likely to regress than CIN3 (10, 11). Histologic diagnoses (CIN or cancer) are made from a biopsy specimen taken during colposcopy. In the United

*See also:*

**Print**
Editors' Notes . . . . . 688
Related article . . . . . 698

**Web-Only**
Appendix Table
CME quiz (preview on page I-27)
Conversion of graphics into slides

***Context***

Several techniques may be used to screen for cervical cancer.

***Contribution***

This systematic review focused on screening for women aged 30 years or older. Liquid-based cytology and conventional cytology had similar sensitivity and specificity for detecting cervical intraepithelial neoplasia. One-time human papillomavirus (HPV) testing was more sensitive but less specific than cytology. The overall harms and costs of work-up for false-positive HPV test results were unclear.

***Implication***

Liquid-based and conventional cytology seem interchangeable for cervical cancer screening. Substituting a strategy of HPV screening (with or without cytology triage for positive test results) seems promising but needs evaluation in long-term, large trials.

*—The Editors*

States, the cytologic threshold for immediate colposcopy referral is generally a low-grade squamous intraepithelial lesion (13). For abnormal screening test results that do not meet the immediate referral threshold, retesting at shorter intervals is recommended; colposcopy referral should be triggered for persistent or progressively abnormal results on retesting (13, 14).

In 2003, the U.S. Preventive Services Task Force (USPSTF) recommended cervical cancer screening in sexually active women with a cervix (grade A recommendation), but concluded that the evidence was insufficient to recommend for or against the routine use of LBC or HPV testing as alternatives or adjuncts to cytology screening. In support of its updated recommendation, the USPSTF commissioned a targeted systematic review (15) and a separate modeling exercise comparing the benefits and harms of various screening strategies (16). We summarize the evidence from our full report here and in our companion paper (17). This article addresses the following questions:

1. To what extent does LBC improve sensitivity, specificity, and diagnostic yield and reduce indeterminate results and inadequate samples compared with conventional cervical cytology?
2. What are the harms of LBC?
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 in women aged 30 years or older?
4. What are the harms of using HPV testing as a screening test, either alone or in combination with cytology, in women aged 30 years or older?

## METHODS

We followed a standard protocol; search, selection, assessment, and synthesis methods, with evidence tables, which are detailed in our full report (15). This article summarizes the evidence about primary HPV screening in women aged 30 years or older. The full report also details the evidence for HPV screening in younger women and for HPV triage of ASC-US or low-grade squamous intraepithelial lesions on cytology (15).

### Data Sources

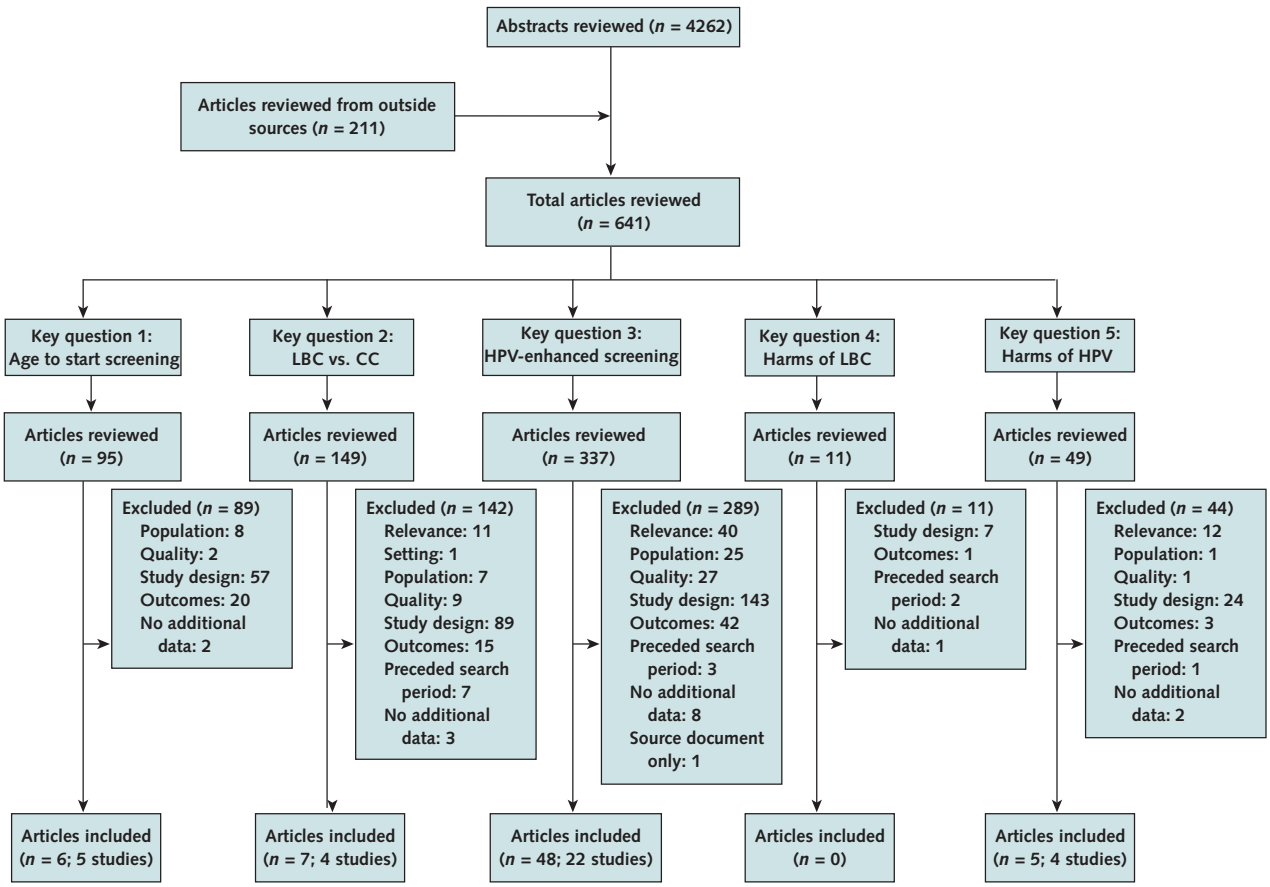
We initially searched for systematic reviews, meta-analyses, and evidence-based guidelines on cervical cancer screening listed in the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, PubMed, and the Health Technology Assessment Database from 2000 through 2007. Two systematic reviews addressing LBC screening (18, 19) were used to identify primary studies before 2003. No systematic reviews on HPV testing that met our inclusion criteria were identified. We considered all studies in the previous USPSTF review (20) and conducted literature searches from 2003 through September 2010 by using MEDLINE, the Cochrane Central Register of Controlled Trials, and PsycINFO.

We conducted a targeted search for any studies related to the trials included in our review (published from September 2010 to 3 August 2011 in PubMed) to ensure that all relevant studies were captured in our previous literature searches. In addition, selected experts in the field were queried on 8 August 2011 to identify relevant publications. We found 9 additional studies including no additional reports from trials included the review: 4 contextually relevant (21, 22) or unrelated (23, 24) reports from previously identified cohorts, 1 performance study of a new HPV test (25), 2 unrelated reports from trial authors (26, 27), and 2 public health reports (28, 29). None added primary results to our key questions, but most added to our discussion (21–23, 26, 27).

### Study Selection

We evaluated 4262 abstracts and 641 full-text articles (**Figure**). Two reviewers evaluated abstracts and articles against prespecified inclusion criteria. Discrepancies were resolved by consensus. We included fair- to good-quality studies that provided evidence regarding test performance for detection of CIN2+ (CIN2, CIN3, or cancer) or CIN3+ (CIN3 or cancer), as well as harms. Included studies met design-specific quality standards that minimized the effect of verification bias and were conducted in routine screening populations in countries with developed population-based screening for cervical cancer. For question 3, we evaluated the evidence regarding the use of HPV testing in screening scenarios: primary screening with HPV testing alone, primary HPV testing with cytology triage of positive HPV (reflex cytology), primary HPV plus cytology screening (cotesting), and cytology testing with HPV triage of ASC-US or low-grade squamous intraepithelial lesion on cytology (reflex HPV). Cytology with reflex HPV is covered in our full report (15).

*Figure.* **Summary of evidence search and selection.**




CC = conventional cytology; HPV = human papillomavirus; LBC = liquid-based cytology.

### Data Extraction and Quality Assessment

At least 2 investigators critically appraised and independently rated the quality of all eligible studies by using criteria based on the USPSTF methods, supplemented by the National Institute for Health and Clinical Excellence criteria for quality of systematic reviews and the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool (30–32). Good-quality studies generally met all design-specific criteria, whereas fair-quality studies did not meet all the criteria but had no fatal flaws in study design. Poor-quality studies had substantial flaws or lack of reporting that implied bias affecting interpretation of study results and were therefore excluded after agreement among reviewers. One investigator abstracted data from included studies into evidence tables, and a second reviewer verified these data.

### Data Synthesis and Analysis

We performed qualitative data synthesis because heterogeneity in the samples, study designs, screening protocols, and instruments did not allow for quantitative synthesis. We synthesized results from diagnostic accuracy studies (to evaluate 1-time test performance) separately from randomized, controlled trials (RCTs). For RCTs of HPV screening, we report results for each round of screening, as well as cumulative results. In these RCTs, results were generally reported for women screened (rather than an intention-to-screen analysis). For consistency, we report the results for women screened (denominator) unless otherwise noted. We also synthesize results for both CIN2+ and CIN3+, even though many CIN2 lesions will regress.

### Role of the Funding Source

The Agency for Healthcare Research and Quality funded this work, provided project oversight, and assisted with internal and external review of the draft evidence synthesis, but had no role in the design, conduct, or reporting of the review. The authors worked with 8 USPSTF members, who helped set the review scope and provided input into methodological issues during the conduct of the review.

## RESULTS

### Benefits and Harms of LBC Compared With Conventional Cytology

We identified 1 fair- and 1 good-quality RCT (33, 34) comprising 134 162 women exclusively or predominately

*Table 1.* **Results of Liquid-Based Cytology Studies**

| Study, Year (Reference); Country; USPSTF Quality Rating | Sample Size, *n*; Ages Recruited, *y* | Cytology Cutoff | Sensitivity/Relative Detection Ratio (95% CI)* | |
|---|---|---|---|---|
| | | | LBC | CC |
| | | | Detection of CIN3+ | |
| NETHCON trial, 2009 (34); the Netherlands; good | 88 988; 30–60 | ASC-US+ | 1.05 (0.86–1.29) (adjusted) | |
| | | LSIL+ | NR | |
| NTCC trial, 2007 (33); Italy; fair | 45 174; 25–60 | ASC-US+ | 0.84 (0.56–1.25) | |
| | | LSIL+ | 0.72 (0.46–1.13) | |
| Taylor et al, 2006 (35); South Africa; fair | 5647; 35–65 | ASC-US+ | 75.8 (57.7–88.9) | 87.9 (71.8–96.6) |
| | | LSIL+ | 66.7 (48.2–82.0) | 72.7 (54.5–86.7) |
| | | | Detection of CIN2+ | |
| NETHCON trial, 2009 (34); the Netherlands; good | 88 988; 30–60 | ASC-US+ | 1.00 (0.84–1.20) (adjusted) | |
| | | LSIL+ | NR | |
| NTCC trial, 2007 (33); Italy; fair | 45 174; 25–60 | ASC-US+ | 1.11 (0.81–1.52)† | |
| | | LSIL+ | 1.03 (0.74–1.43) | |
| Taylor et al, 2006 (35); South Africa; fair | 5647; 35–65 | ASC-US+ | 70.6 (58.3–81.0) | 83.6 (71.2–92.2) |
| | | LSIL+ | 60.3 (47.7–71.9) | 69.1 (55.2–80.9) |
| Coste et al, 2003 (36); France; fair | 1757; 23–46 | ASC-US+ | 87.5 (73.2–95.8) | 87.8 (73.8–95.9) |
| | | LSIL+ | 80.0 (64.4–90.9) | 73.2 (57.1–85.8) |

ASC-US = atypical squamous cells of undetermined significance; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; NA = not applicable; NETHCON = Netherlands ThinPrep Versus Conventional Cytology; NR = not reported; NTCC = New Technologies for Cervical Cancer; USPSTF = U.S. Preventive Services Task Force.
* Relative detection ratio, relative positive predictive value, and relative false-positive proportion for randomized, controlled trials.
† Restricted to centers with ASC-US+ referral criteria.

aged 30 to 60 years. These trials compared relative detection of CIN3+ and CIN2+ and relative positive predictive value after a single screening with LBC or conventional cytology. We identified 2 fair-quality observational studies (35, 36) of 7404 similarly aged women that reported absolute sensitivity and specificity of both tests in primary care–applicable settings (**Table 1**).

On the basis of these studies, LBC and conventional cytology did not differ substantially in relative detection or absolute sensitivity or specificity for detection of CIN2+/CIN3+ at any cytologic threshold (**Table 1**). Although the fair-quality NTCC (New Technologies for Cervical Cancer Screening) trial reported lower relative positive predictive value for LBC than for conventional cytology (33), its findings are inconsistent with the good-quality NETHCON (Netherlands ThinPrep Versus Conventional Cytology) trial (34) and with both observational studies (35, 36). The limitations of the NTCC trial, including the newness of LBC reading in many centers and lack of blinding, could have influenced these results. In terms of specimen adequacy, most of the evidence indicated a lower proportion of unsatisfactory slides for LBC than for conventional cytology (0.4% vs. 1.1% in NETHCON; 2.6% vs. 4.1% in NTCC). Technical issues probably explain disparate findings in smaller observational studies (15). Although we found no studies that directly addressed harms of LBC testing, we would not expect to find differential patient effects because LBC differs from conventional cytology primarily in specimen preparation and handling (37, 38).

### Benefit and Harms of HPV Testing in Women Aged 30 Years or Older as an Alternative or Adjunct to Conventional Cytology Screening

We included 6 diagnostic accuracy studies, 6 RCTs of comparative effectiveness, and 4 studies on psychological harms of HPV screening. The volume (and quality) of evidence varied among 3 HPV screening strategies (**Tables 2** and **3** and **Appendix Table**, available at www.annals.org) (39–51). For primary HPV screening compared with cytology, we found 1 RCT (NTCC phase 2; 49 196 participants) (39) and 6 diagnostic accuracy studies (comprising 37 431 participants) (36, 40–44). For HPV screening followed by cytology triage compared with cytology alone, we found 1 Finnish RCT (71 337 participants) (45). For HPV and cytology cotesting, we found 4 RCTs (NTCC phase 1, POBASCAM [Population Based Screening Study Amsterdam Program], Swedescreen, and ARTISTIC [A Randomised Trial in Screening to Improve Cytology]; comprising 127 149 participants) (46–49) and 4 diagnostic accuracy studies (comprising 21 739 participants) (36, 41–43).

Studies of HPV-enhanced primary cervical cancer screening primarily evaluated Hybrid Capture 2, whereas a few used polymerase chain reaction testing. We report results for women aged 30 years or older to reflect the age bracket for FDA-approved use of Hybrid Capture 2 as an adjunct to cytology (4, 5) and the reduced prevalence of high-risk HPV in women as they age (17, 52). For results in younger women, please see our full report (15).

*Table 1*—Continued

| Specificity (95% CI) | | Positive Predictive Value (95% CI)* | | False-Positive Rate (95% CI)* | |
|---|---|---|---|---|---|
| LBC | CC | LBC | CC | LBC | CC |
| **Detection of CIN3+** | | | | | |
| NA | | 1.17 (0.99–1.39) | | 0.89 (0.82–0.98) | |
| NA | | 1.17 (1.01–1.36) | | NR | |
| NA | | 0.42 (0.29–0.62) | | 1.93 (1.72–2.21) | |
| NA | | 0.40 (0.26–0.62) | | 1.72 (1.42–2.07) | |
| 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) |
| 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) |
| **Detection of CIN2+** | | | | | |
| NA | | 1.09 (0.95–1.25) | | 0.90 (0.82–0.99) | |
| NA | | 1.04 (0.93–1.15) | | NR | |
| NA | | 0.65 (0.49–0.88)† | | 1.97 (1.75–2.21) | |
| NA | | 0.58 (0.43–0.78) | | 1.80 (1.48–2.19) | |
| 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) |
| 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) |
| 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) |
| 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) |

### *Primary HPV Screening Alone Compared With Cytology Alone*

In 6 fair- or good-quality diagnostic accuracy studies, 1-time HPV testing was more sensitive but less specific than cytology. For CIN3+ outcomes, point estimates for sensitivity ranged from 86% to 97% for HPV testing versus 46% to 50% for cytology at a colposcopy referral threshold of ASC-US. For CIN2+ outcomes, sensitivity ranged from 63% to 98% for HPV testing versus 38% to 65% for cytology (**Table 2**). However, specificity for CIN2+ and CIN3+ was consistently 3 to 5 percentage points lower for HPV testing than for cytology (**Table 2**).

In phase 2 of the NTCC, a fair-quality Italian RCT comparing Hybrid Capture 2 HPV screening with cytology in 35 471 women aged 35 to 60 years, about twice as many cases of CIN3+ were detected in the HPV testing group after a single round, with relatively fewer cases detected in the second screening round (relative detection ratio, 0.23 [95% CI, 0.07 to 0.82]) (**Table 3**) (39). After the second screening round (using cytology only in both groups) and a median of 3.5 years of follow-up from baseline, the cumulative relative detection of CIN3+ still increased in the HPV testing group (1.57 [CI, 1.03 to 2.40]). Because women with a positive HPV result or ASC-US on cytology were immediately referred for colposcopy, many baseline colposcopies were done overall but many more were done in the HPV testing group than in the cytology group (5.8% vs. 2.5%).

Trial investigators pooled cumulative cases of invasive cancer from the primary Hybrid Capture 2 screening strategy (NTCC phase 2) (39) with the Hybrid Capture 2–cytology cotesting strategy (NTCC phase 1) (46), citing insignificant statistical heterogeneity between the trials. Pooled results suggested decreased cumulative cases of invasive cancer after HPV screening, compared with cytology (6 vs. 15; $P = 0.052$) in women aged 35 years or older. These findings are preliminary because these cancer outcomes were based on pooling noncomparable screening strategies and also did not reflect similar opportunities for diagnosis in both strategies. More valid studies would ensure or control for similar delivery of colposcopy or provide longer follow-up with registry linkages to allow disease ascertainment outside the screening program.

Phase 2 of NTCC referred many women for colposcopy who would instead have been retested in the United States. The **Appendix Table** details other interpretation and quality issues with NTCC phase 2. Determination of benefits and burdens or harms of HPV testing and cytology screening is impossible because neither cumulative colposcopy results nor cumulative relative positive predictive value over both screening rounds were reported.

### *Primary HPV Screening Followed by Cytology Triage Compared With Cytology Alone*

A large, fair-quality Finnish trial (59 757 women aged 35 to 65 years) compared primary Hybrid Capture 2 screening (with cytology triage for positive HPV test results) with cytology screening alone (45). Women with minimally abnormal results had repeated testing recommended. After a single screening round, Hybrid Capture 2 testing with cytology triage compared with cytology alone increased relative CIN2+ detection (1.36 [CI, 0.98 to

*Table 2.* **Absolute Test Performance of Primary Screening With HPV Testing Alone and Combination HPV and Cytology Screening in Developed Countries in Women Aged 30 Years or Older**

| Study, Year (Reference); USPSTF Quality Rating | Sample Size, *n* | Sensitivity (95% CI) | | | Specificity (95% CI) | | |
|---|---|---|---|---|---|---|---|
| | | HC2 | Cytology: ASC-US+ | HC2 and Cytology | HC2 | Cytology: ASC-US+ | HC2 and Cytology |
| | | Detection of CIN3+ | | | | | |
| Petry et al, 2003 (41); fair | 7908 | 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)* |
| Kulasingam et al, 2002 (43); good | 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)† |
| | | Detection of CIN2+ | | | | | |
| Bigras and de Marval, 2005 (44); fair | 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 |
| Cárdenas-Turanzas et al, 2008 (40); fair | 1850 | 69 (41–89) | 44 (20–70) | NR | 93 (91–95) | 94 (92–95) | NR |
| Coste et al, 2003 (36)‖; good | 3080 | 96 (88–100) | 65 (50–80) | 76 (59–93)‡ | 85 (83–87) | 98 (98–99) | 97 (97–98)‡ |
| Kulasingam et al, 2002 (43); good | 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)† |
| Mayrand et al, 2007 (42); fair | 9977 | 97.4 (NR) | 56.4 (NR) | 100 (NR)§ | 94.3 (NR) | 97.3 (NR) | 92.5 (NR)§ |
| Petry et al, 2003 (41); fair | 7908 | 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) |

ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2 (Qiagen, Germantown, Maryland); HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; NR = not reported; Pap = Papanicolaou; USPSTF = U.S. Preventive Services Task Force.

* HC2 and cytology reported as positive on either test with cytology threshold of PapIIw+ (equivalent to ASC-US+) for CIN2+ and PapIII+ for CIN3+.

† HC2 and cytology reported as ASC-US+ and high-risk HPV+.

‡ HC2 and cytology reported as HSIL+ or relative light units/cut-off value ratio >1.0 if ASC-US or atypical glandular cells of undetermined significance.

§ HC2 and cytology reported as Pap test result of ASC-US+ or HPV ≥1 pg HPV DNA/mL.

‖ Data were not stratified by age; the study included women aged >18 y; the average age was 33.3 y.

1.89]); effects on relative detection of CIN3+ were less clear because of the small sample size and wide CIs (1.38 [CI, 0.81 to 2.36]) (**Table 3**). Colposcopy referrals were modest in women older than 35 years and similar between HPV screening (0.9%) and cytology alone (1.0%); however, these probably include only immediate colposcopy referrals, because retesting was recommended for slightly more women who received HPV testing than who received cytology (7.2% vs. 6.6%). Extended follow-up (mean, 3.3 years; maximum, 5.0 years) with linkage to registry data in 38 670 screened women aged 30 to 60 years found significantly increased relative detection of CIN3+ (and cancer) after a single round of HPV screening (1.77 [CI, 1.16 to 2.74]) (51). Among women with positive results in either group, most were retested to confirm abnormalities before colposcopy referral. Women with negative results on initial HPV testing tended toward a lower cumulative 5-year CIN3+ rate than women with negative results on initial cytology, although the CI for this estimate was wide (0.28 [CI, 0.04 to 1.17]) (data not shown).

In the Finnish trial, issues with interpretation and quality primarily reflect its incomplete reporting and implementation to date and the attributes of a pragmatic trial. As with many other trials, data for cumulative colposcopies, adherence to colposcopy, and retesting referrals for the entire first screening round are not yet reported. A second screening round at 3 years is planned. As more data from this trial are reported, differences with practice in the United States will also need to be considered.

### *Combination HPV and Cytology Screening (Cotesting) Compared With Cytology Alone*

Four diagnostic accuracy studies (comprising 21 739 participants) reported the absolute test performance of HPV–cytology cotesting (**Table 2**). Two studies reporting sensitivity and specificity for Hybrid Capture 2–cytology cotesting among 17 885 women aged 30 to 60 years (36, 41) used a positive result from either test so that all HPV-positive patients met the threshold. For the detection of CIN3+/CIN2+, Hybrid Capture 2 testing plus cytology (either test positive) was more sensitive but less specific than cytology alone (**Table 2**). The combination of Hybrid Capture 2 plus cytology did not differ in performance from Hybrid Capture 2 alone. Two smaller studies (36, 43), comprising 3852 participants, reported positive cotesting

results only if results of both tests were positive, unless a relatively high cytology threshold (that is, high-grade squamous intraepithelial lesion) was met, similar to some cotesting trials. Wide CIs limit sensitivity comparisons, although specificity with this type of cotesting was clearly better than that of Hybrid Capture 2 alone (**Table 2**).

Four large, fair-quality RCTs (46–49)—NTCC phase 1, POBASCAM, Swedescreen, and ARTISTIC (comprising 82 390 participants)—compared cotesting with cytology screening alone in European women aged 30 to 64 years (**Table 3**). Cumulative CIN3+ detection was the same between cotesting and cytology alone after 2 screening rounds in all 4 RCTs, even though most cotesting trials also reported differences in round-specific relative CIN detection (**Table 3**). Cumulative invasive cancer detection was similar or slightly higher for cytology alone than for cotesting in 3 trials (46, 47, 49). However, ARTISTIC (48) had the opposite result: More cases of cancer were found after 2 screening rounds in the cotesting group (8 total), compared with cytology (4 total). Mixed round-specific and cumulative results among the trials may reflect between-trial differences in colposcopy referral and retesting protocols, as well as incomplete reporting of results.

***Table 3.*** **Results From Randomized, Controlled Trials of HPV Screening Strategies in Cervical Cancer Screening in Women 30 Years or Older**

| Variable | Screening Round | Study (Reference) | | | | | |
|---|---|---|---|---|---|---|---|
| | | NTCC Phase 2 (39) | Finnish Trial (45, 51)‡‡ | NTCC Phase 1 (46) | POBASCAM (47) | Swedescreen (49, 50) | ARTISTIC (48) |
| Participants randomly assigned and screened (all ages), *n* | – | 49 196 | 71 337 | 45 174 | 44 938 | 12 527 | 24 510 |
| Ages recruited, *y* | – | 25–60 | 25–65 | 25–60 | 30–56 | 32–38 | 20–64 |
| Screened women aged ≥30 y, *n* | – | 35 471 (35–60 y) | 59 757 (35–65 y) | 33 364 (35–60 y) | 17 155 (30–56 y) | 12 527 (32–38 y) | 19 344 (30–64 y) |
| Test positivity, *n (%)* | Baseline | IG: 1029 (5.8)<br>CG: 555 (3.1)*,<br>182 (1.0)† | NR | IG: 1789 (10.7)<br>CG: 594 (3.6)*,<br>212 (1.3)† | NR | NR | NR |
| | 1 | NR | IG: 1645 (5.5)‖,<br>258 (0.9)¶<br>CG: 293 (1.0) | NR | IG: 56 (0.7)<br>CG: 54 (0.6) | IG: 146 (2.3)‡<br>CG: 150 (2.4) | 248 (1.3)§ |
| | 2 | NR | NA | NR | IG: 38 (0.6)<br>CG: 50 (0.7) | NR | IG: 47 (0.40)**<br>CG: 16 (0.41)** |
| | Cumulative | NR | NA | NR | IG: 94 (1.1)<br>CG: 104 (1.2) | NR | IG: 405 (2.2)**<br>CG: 121 (2.0)** |
| Colposcopy referrals, *n (%)* | Baseline | IG: 1029 (5.8)<br>CG: 435 (2.5) | NR | IG: 1773 (10.6)<br>CG: 498 (3.0) | NR | NR | NR |
| | 1 | NR | IG: 258 (0.9)<br>CG: 293 (1.0) | NR | IG: 201 (2.3)<br>CG: 115 (1.3)†† | NR | IG: 707 (4.9)<br>CG: 197 (4.1) |
| | 2 | NR | NA | NR | IG: 87 (1.3)<br>CG: 129 (1.9)†† | NR | IG: 160 (NR)<br>CG: 42 (NR) |
| | Cumulative | NR | NA | NR | IG: 288 (3.4)<br>CG: 244 (2.8) | NR | IG: 867 (6.0)<br>CG: 239 (4.9) |
| Absolute detection for CIN3+, *n (%)* | Baseline | NR | NR | NR | NR | NR | NR |
| | 1 | IG: 52 (0.29)<br>CG: 22 (0.12) | IG: 32 (0.11)<br>CG: 23 (0.08) | IG: 52 (0.31)<br>CG: 33 (0.20) | IG: 68 (0.79)<br>CG: 40 (0.47) | IG: 72 (1.15)<br>CG: 55 (0.88) | IG: 116 (0.80)<br>CG: 38 (0.79) |
| | 2 | IG: 3 (0.02)<br>CG: 13 (0.07) | NR | IG: 5 (0.03)<br>CG: 11 (0.07) | IG: 24 (0.35)<br>CG: 54 (0.79) | IG: 16 (0.26)<br>CG: 30 (0.48) | IG: 29 (0.25)**<br>CG: 18 (0.47)** |
| | Cumulative | IG: 55 (0.31)<br>CG: 35 (0.20) | NR | IG: 57 (0.34)<br>CG: 44 (0.26) | IG: 92 (1.07)<br>CG: 94 (1.10) | IG: 88 (1.41)<br>CG: 85 (1.36) | IG: 262 (1.51)**<br>CG: 98 (1.77)** |
| Relative detection ratio for CIN3+ (95% CI) | Baseline | NR | NR | NR | NR | NR | NR |
| | 1 | 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) |
| | 2 | 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)**†† |
| | Cumulative | 1.57 (1.03–2.54)†† | 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+ (95% CI) | Baseline | NR | NR | NR | NR | NR | NR |
| | 1 | 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) |
| | 2 | 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)**†† |
| | Cumulative | 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)** |

ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = atypical squamous cells of undetermined significance; CG = control group; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; IG = intervention group; LSIL = low-grade squamous intraepithelial lesion; NA = not applicable; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program.

* Colposcopy referral threshold varied by site: ASC-US+ (7 sites).

† Colposcopy referral threshold varied by site: LSIL+ (2 sites).

‡ Colposcopy referral threshold (ASC-US+ or HSIL+): only ASC-US+ reported.

§ Colposcopy referral threshold (HSIL+) pooled across both groups.

‖ Colposcopy referral criteria (HPV+ and LSIL+): HPV+ results.

¶ Colposcopy referral criteria (HPV+ and LSIL+): LSIL+ results.

** All age data reported ($n$ = 15 542); incomplete second-round follow-up.

†† Statistically significant.

‡‡ Finnish trial extended 5-y follow-up data for a subset of the screened population ($n$ = 38 670); absolute detection for CIN3+, IG: 59 (0.30%), CG: 23 (0.17%); relative detection ratio for CIN3+, 1.77 (CI, 1.16–2.74).

Only 1 trial, NTCC phase 1 (46), found a relative increase in any cumulative CIN measure after cotesting. This test, however, used a lower threshold for immediate colposcopy than the other trials. Women aged 35 years or older were referred for colposcopy with either a cytology threshold of ASC-US or a positive HPV result regardless of cytology. This strategy increased detection of both CIN2+ and CIN3+ after 1 screening round and cumulative CIN2+ detection overall (RR, 1.50 [CI, 1.13 to 1.98]) compared with cytology alone; however, it did not substantially decrease cases of CIN3+ in the second round or affect cumulative CIN3+ detection. More cases of invasive cancer occurred in the cytology-only group than in the cotesting group (10 vs. 2). On the basis of indirect comparisons between NTCC phases 1 and 2, cotesting offers no additional CIN3+ detection above primary HPV screening alone but may yield more false-positive results.

In the other 3 trials, high-grade squamous intraepithelial lesion was the referral threshold for colposcopy, with colposcopy referral for HPV-positive results only after repeated testing revealed persistent HPV positivity or abnormal cytology (47–49). These trials have not completely reported second-round detection outcomes for a substantial proportion of trial participants (47), the complete follow-up period (49), or both (48). Data from a third screening round reported in 2011 from ARTISTIC do not correct all of these reporting deficiencies but provide 6-year cumulative rates of CIN2+ and CIN3+ development by baseline screening test results (53).

Only 2 trials (47, 48) have reported cumulative colposcopies. These were slightly higher in the cotesting group than in the cytology group of POBASCAM (3.4% vs. 2.8%), although both groups received HPV testing with polymerase chain reaction in the second round. For women aged 30 to 64 years, cumulative colposcopy referrals after 2 screening rounds in ARTISTIC were 6.0% in the cotesting group compared with 4.9% in the LBC-only group (48). However, ARTISTIC varied somewhat from other trials in several round-specific findings, so the relative colposcopy requirement between groups is probably not applicable to trials with different protocols and CIN detection results. Although the interpretation and quality issues vary between cotesting trials, reporting on colposcopy referrals, adherence, referrals for retesting, CIN treatments, and related harms was insufficient across all trials. Cotesting trials also generally represent approaches to managing abnormal screening results that differ from current U.S. recommendations.

### *Harms of HPV Testing*

Human papillomavirus testing could increase harms relative to cytology by increasing the number of unnecessary colposcopies and downstream consequences related to diagnosis and treatment. These concerns cannot be completely addressed due to incomplete reporting, but are considered further elsewhere (9, 21). To evaluate the potential psychological effects of HPV testing, we found 4 fair-quality observational studies (54–57) that used mailed questionnaires to examine the immediate and short-term effects of HPV testing in 4104 women in the United Kingdom or Australia. Levels of immediate anxiety and distress were increased in women who tested positive for HPV compared with those who tested negative. These differences, however, were resolved by 6-month follow-up. Data on other psychosocial outcomes and longer-term follow-up were sparse.

## DISCUSSION

Substantial new evidence has become available since the previous USPSTF review and recommendation and continues to accrue. Large RCTs clearly establish that for cytology-based screening, LBC does not differ from conventional cytology 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 conducting cytology screening.

Numerous studies have confirmed that HPV testing is more sensitive than cytology, but with a tradeoff in terms of reduced specificity. Thus, although HPV-enhanced screening strategies offer a potential cancer prevention benefit compared with cytology alone, test performance studies alone are insufficient to justify substituting HPV testing for cytology (58). Diagnostic work-up for false-positive results and diagnosis of regressive or nonprogressive histologic predisease could result in harms from unnecessary procedures or overtreatment. Understanding the tradeoff from reduced specificity is critical, particularly given the relatively low incidence of cervical cancer and the established practice of repeated cervical cancer screening (17). Thus, experts agree that large, pragmatic, comparative RCTs of repeated screening rounds are necessary, with increasing emphasis on the need to confirm the effect not just on surrogates (such as CIN) but also on cancer incidence and mortality (27).

On the basis of large RCTs, primary HPV screening seems very promising, particularly when coupled with reflex cytology to triage positive results before colposcopy. Screening with HPV testing enhances the detection of CIN3+ compared with cytology alone but also increases CIN2+ detection and immediate colposcopy referrals. All CIN lesions, even CIN3, have some potential for overdiagnosis and therefore potential harms (26). Thus, the net effect of primary HPV screening needs to be determined through the completion of ongoing trials and more detailed reporting of potential harms and benefits from completed trials. An ongoing trial in Canada will also provide new evidence that directly compares primary HPV screening and cytology triage with cytology screening and HPV triage in a protocol more similar to U.S. practice

than the European trials (59); a collaborative pooling of European trial results is also expected (60).

The FDA has already approved screening with cytology plus HPV testing (cotesting) in women aged 30 years or older (4, 5). Our report found that cotesting was much more sensitive than cytology alone but may represent a strategy that adds little when compared with primary HPV screening. On the basis of test performance data and indirect comparisons between trials, 1-time HPV–cytology cotesting was very similar to HPV testing alone for the detection of CIN2+ or CIN3+, with similar (or slightly reduced) specificity. However, incomplete reporting complicates the interpretation of cotesting trials, because most lack cumulative outcome reporting for their entire study populations, and all lack data on cumulative colposcopies and related harms. A large observational study (61) conducted in the United States (331 818 participants) reported high clinician and patient acceptance of cotesting in women aged 30 years or older, with rescreening deferred until 3 years after negative results in an HMO setting. The cumulative 5-year incidence of CIN3 and cervical cancer from this cotested cohort suggests that primary HPV testing, particularly if followed by cytology triage, would efficiently detect more cases of CIN3+ and cancer, particularly adenocarcinoma (78% vs. 15%), than cytology alone, with a very high negative predictive value for cancer after negative HPV test results (21). Data on the proportion of cumulative cases of cancer among HPV-negative/Papanicolaou-positive women and their relative stages at diagnosis would clarify any safety tradeoffs in moving away from cotesting.

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. As discussed in our full report, mounting evidence suggests that the cumulative risk for CIN3+ is very low for 5 or more years in women after negative results on HPV testing (15, 22, 47, 49, 51, 53, 62–64). Risk-stratifying approaches, whereby the rescreening interval is prolonged on the basis of initial screening results, have not been directly incorporated into trials to date, and safety data on prolonged screening intervals in low-risk women based on baseline HPV testing (with or without cytology) seem promising but are still accruing. Such an approach could potentially reduce screening demands for many women; for example, in cotesting trials, 78% to 93% of tested women had negative results on both tests initially (15). Besides safety, feasibility or acceptability may affect adoption of a risk-stratified policy on cervical cancer screening because primary care physicians may not currently be extending the screening interval to 3 years after negative cotesting results (65). For women with positive as well as negative results on HPV screening, ongoing research into HPV subtypes (22), HPV-related biomarkers, and other factors (such as screening history [23]), will probably advance effective and efficient risk stratification necessary for appropriately targeted screening.

The most thoroughly studied HPV test for use in cervical cancer screening or triage is Hybrid Capture 2. In the absence of adequate RCT data, those planning substitution of other types of HPV testing in cervical cancer screening programs based on these studies should carefully consider clinical test performance when directly compared with Hybrid Capture 2, evidence of test–retest and interlaboratory test reliability, other quality control issues, and cost (66).

The main limitations of our review and of this body of evidence follow. Our search may have missed smaller European studies published in national journals only. Most studies used colposcopy or biopsy as the reference standard, neither of which is 100% sensitive for detecting preinvasive disease. Trials that do not have full or complete ascertainment for undetected disease can inaccurately reflect sensitivity or true disease detection. Longer follow-up after multiple screening rounds, ideally combined with methods of creating equal probability of cervical lesion detection in all participants, gives a truer picture of the relative effect of different screening strategies on disease (67). Linking screening trial results with outside data, including registries, can help overcome possible ascertainment biases that are particularly likely to distort screening comparisons with relatively short-term results. Most trials did not report results by using an intention-to-screen analysis, in which all women in the randomized group are in the denominator of all calculations.

Finally, the data from trials involving HPV testing are reported in many publications, with updated results being published over time. Despite our efforts to search for additional data from studies with incomplete reporting, some missing data may have been available through more extensive author requests (which were beyond our resource capabilities) or could soon be published. Thus, our findings will probably need rapid updating as more data from completed and ongoing trials become available. In addition, none of the trials included the effect of HPV vaccines on screening, which will be critical in the future.

Liquid-based cytology and conventional cytology perform interchangeably in terms of newer screening technologies for cervical cancer screening. Compared with cytology, HPV testing offers a tradeoff between increased sensitivity and decreased specificity. Because cervical cancer screening is repeated over time, results from RCTs should inform a proposed change in screening approach. Substituting a strategy of primary HPV screening (with or without cytology triage) for one of cytology alone in women aged 30 years or older is appealing, but important details remain unclear, including how much early disease detection is improved, whether such a strategy would have a beneficial effect on invasive cervical cancer, and what other effects it would have in terms of burden and diagnosis- and treatment-related harms.

From the Oregon Evidence-based Practice Center, Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon.

**Acknowledgment:** The authors thank Daphne Plaut, MLS, for conducting the literature searches; Kevin Lutz, MFA, for editorial support; and Rebecca Holmes, MD, MS, and Sarah Zuber, MSW, for assistance in conducting the evidence review. They also thank the Agency for Healthcare Research and Quality and the USPSTF and Marc Arbyn, MD,

MSc, DrTMH; Walter Kinney, MD; Mary Mitchell; Alan G. Waxman, MD, MPH; and Diana Petitti, MD, MPH, for their contribution to this evidence review.

**Grant Support:** This review was conducted by the Oregon Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (contract HHS-290-2007-10057-I, task order 3).

**Potential Conflicts of Interest:** Drs. Whitlock, Vesco, Eder, and Lin and Ms. Senger: *Grant (money to institution):* Agency for Healthcare Research and Quality; *Support for travel to meetings for the study or other purposes (money to institution):* Agency for Healthcare Research and Quality; *Payment for writing or reviewing the manuscript (money to institution):* Agency for Healthcare Research and Quality. Drs. Whitlock, Eder, and Lin and Ms. Senger: *Provision of writing assistance, medicines, equipment, or administrative support (money to institution):* Agency for Healthcare Research and Quality. Ms. Senger: *Support for travel to meetings for the study or other purposes (money to institution):* National Institutes of Health. Ms. Burda: *Grant (money to institution):* Agency for Healthcare Research and Quality; *Support for travel to meetings for the study or other purposes (money to institution):* Agency for Healthcare Research and Quality; *Consultancy:* Oregon Health & Science University. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1382.

**Requests for Single Reprints:** Reprints are available from the Agency for Healthcare Research and Quality Web site (www.preventiveservices.ahrq.gov).

Current author addresses and author contributions are available at www.annals.org.

## References

1. **International Agency for Research on Cancer.** Cervix Cancer Screening. IARC Handbook of Cancer Prevention, vol. 10. Lyon, France: IARC Pr; 2005.
2. **Arbyn M, Antilla A, Jordan J, Ronco G, Schenck U, Segnan N, et al.** European Guidelines for Quality Assurance in Cervical Cancer Screening. 2nd ed. Luxembourg: Office for Official Publications of the European Communities; 2008.
3. **Trottier H, Franco EL.** The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24 Suppl 1:S1-15. [PMID: 16406226]
4. **Center for Devices and Radiological Health.** Approval Letter: Digene Hybrid Capture 2 High-Risk HPV DNA Test-P890064/S009. Rockville, MD: U.S. Food and Drug Administration; 2003. Accessed at www.accessdata.fda.gov/cdrh_docs/pdf/p890064s009a.pdf on 25 September 2011.
5. **Center for Devices and Radiological Health.** Summary of Safety and Effectiveness Data. Rockville, MD: U.S. Food and Drug Administration; 2002. Accessed at www.accessdata.fda.gov/cdrh_docs/pdf/p890064s009b.pdf on 25 September 2011.
6. **Arney A, Bennett KM.** Molecular diagnostics of human papillomavirus. Lab Med. 2010;41:523-30.
7. **American College of Obstetricians and Gynecologists.** ACOG Practice Bulletin No. 99: management of abnormal cervical cytology and histology. Obstet Gynecol. 2008;112:1419-44. [PMID: 19037054]
8. **Östör AG.** Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993;12:186-92. [PMID: 8463044]
9. **Richart RM.** Cervical intraepithelial neoplasia. Pathol Annu. 1973;8:301-28. [PMID: 4583016]
10. **Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S.** Human papillomavirus and cervical cancer. Lancet. 2007;370:890-907. [PMID: 17826171]
11. **Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference.** 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. J Low Genit Tract Dis. 2007;11:223-39. [PMID: 17917567]
12. **McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al.** Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9:425-34. [PMID: 18407790]
13. **Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference.** 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol. 2007;197:346-55. [PMID: 17904957]
14. **ACOG Committee on Practice Bulletins—Gynecology.** ACOG Practice Bulletin no. 109: Cervical cytology screening. Obstet Gynecol. 2009;114:1409-20. [PMID: 20134296]
15. **Vesco KK, Whitlock EP, Eder M, Lin J, Burda BU, Senger CA, et al.** Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Report no. 86. AHRQ Publication no. 11-05156-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
16. **Kulasingam S, Havrilesky L, Ghebre R, and 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.
17. **Vesco KK, Whitlock EP, Eder M, Burda BU, Senger CA, Lutz K.** Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155:698-705.
18. **Medical Services Advisory Committee.** Liquid Based Cytology for Cervical Screening. MSAC Reference 12a. Canberra, Australia: Australia Department of Health and Aging; 2002.
19. **Noorani HZ, Brown A, Skidmore B, Stuart GCE.** Liquid-based cytology and human papillomavirus testing in cervical cancer screening. Technology Report no. 40. Ottawa: Canadian Coordinating Office of Health Technology Assessment; 2003.
20. **Hartmann KE, Hall SA, Nanda K, Boggess JF, Zolnoun D.** Screening for Cervical Cancer. Systematic Review no. 25. Rockville, MD: Agency for Healthcare Research and Quality; 2002.
21. **Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, 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;12:663-72. [PMID: 21684207]
22. **Schiffman M, Glass AG, Wentzensen N, Rush BB, Castle PE, Scott DR, 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;20:1398-409. [PMID: 21602310]
23. **Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Schiffman M, et al.** Variable risk of cervical precancer and cancer after a human papillomavirus-positive test. Obstet Gynecol. 2011;117:650-6. [PMID: 21343769]
24. **Littell RD, Kinney W, Fetterman B, Cox JT, Shaber R, Poitras N, 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;15:54-9. [PMID: 21192178]
25. **Castle PE, Gutierrez EC, Leitch SV, Maus CE, McMillian RA, Nussbaumer WA, et al.** Evaluation of a new DNA test for detection of carcinogenic human papillomavirus. J Clin Microbiol. 2011;49:3029-32. [PMID: 21632892]
26. **Kotaniemi-Talonen L, Malila N, Anttila A, Nieminen P, Hakama M.** Intensified screening among high risk women within the organised screening programme for cervical cancer in Finland. Acta Oncol. 2011;50:106-11. [PMID: 20560860]
27. **Anttila A, Pokhrel A, Kotaniemi-Talonen L, Hakama M, Malila N, Nieminen P.** Cervical cancer patterns with automation-assisted and conventional cytological screening: a randomized study. Int J Cancer. 2011;128:1204-12. [PMID: 20848590]
28. **Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, et al.** Worldwide burden of cervical cancer in 2008. Ann Oncol. 2011. [PMID: 21471563]
29. **Franceschi S, Denny L, Irwin KL, Jeronimo J, Lopalco PL, Monsonego J, et al.** Eurogin 2010 roadmap on cervical cancer prevention. Int J Cancer. 2011;128:2765-74. [PMID: 21207409]
30. **Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al; Methods Work Group, Third US Preventive Services Task Force.** Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]
31. **National Institute for Health and Clinical Excellence.** The Guidelines Manual. London: National Institute for Health and Clinical Excellence; 2006.

32. **Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J.** 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. [PMID: 14606960]
33. **Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, 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. [PMID: 17517761]
34. **Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A, et al.** Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. JAMA. 2009;302:1757-64. [PMID: 19861667]
35. **Taylor S, Kuhn L, Dupree W, Denny L, De Souza M, Wright TC Jr.** Direct comparison of liquid-based and conventional cytology in a South African screening trial. Int J Cancer. 2006;118:957-62. [PMID: 16152600]
36. **Coste J, Cochand-Priollet B, de Cremoux P, Le Galès C, Cartier I, Molinié V, et al; French Society of Clinical Cytology Study Group.** Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. BMJ. 2003;326:733. [PMID: 12676841]
37. **Hologic.** ThinPrep Pap Test Quick Reference Guide: Endocervical Brush/Spatula Protocol. Marlborough, MA: Hologic; 2004. Accessed at www.thinprep.com/pdfs/pap_quick_reference.pdf on 25 September 2011.
38. **TriPath Imaging.** SurePath Technology Is Changing Cervical Cancer Screening for the Better. Burlington, NC: TriPath Imaging; 2004. Accessed at www.nlma.nf.ca/documents/health_promotion/health_promotion_8.pdf on 25 September 2011.
39. **Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al; New Technologies for Cervical Cancer screening (NTCC) Working Group.** Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010;11:249-57. [PMID: 20089449]
40. **Cárdenas-Turanzas M, Nogueras-Gonzalez GM, Scheurer ME, Adler-Storthz K, Benedet JL, Beck JR, et al.** The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. Cancer Epidemiol Biomarkers Prev. 2008;17:2865-71. [PMID: 18843032]
41. **Petry KU, Menton S, Menton M, van Loenen-Frosch F, de Carvalho Gomes H, Holz B, 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;88:1570-7. [PMID: 12771924]
42. **Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al; Canadian Cervical Cancer Screening Trial Study Group.** Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med. 2007;357:1579-88. [PMID: 17942871]
43. **Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al.** Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. JAMA. 2002;288:1749-57. [PMID: 12365959]
44. **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;93:575-81. [PMID: 16136031]
45. **Leinonen M, Nieminen P, Kotaniemi-Talonen L, Malila N, Tarkkanen J, Laurila P, et al.** Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. J Natl Cancer Inst. 2009;101:1612-23. [PMID: 19903804]
46. **Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al; New Technologies for Cervical Cancer Working Group.** 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;98:765-74. [PMID: 16757701]
47. **Bulkmans NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, 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;370:1764-72. [PMID: 17919718]
48. **Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al.** HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol. 2009;10:672-82. [PMID: 19540162]
49. **Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al.** Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. 2007;357:1589-97. [PMID: 17942872]
50. **Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, 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. [PMID: 19141778]
51. **Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J, 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. [PMID: 20423964]
52. **Datta SD, Koutsky LA, Ratelle S, Unger ER, Shlay J, McClain T, 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. [PMID: 18378945]
53. **Kitchener HC, Gilham C, Sargent A, Bailey A, Albrow R, Roberts C, 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. [PMID: 21334200]
54. **McCaffery K, Waller J, Forrest S, Cadman L, Szarewski A, Wardle J.** Testing positive for human papillomavirus in routine cervical screening: examination of psychosocial impact. BJOG. 2004;111:1437-43. [PMID: 15663132]
55. **Kitchener HC, Fletcher I, Roberts C, Wheeler P, Almonte M, Maguire P.** The psychosocial impact of human papillomavirus testing in primary cervical screening-a study within a randomized trial. Int J Gynecol Cancer. 2008;18:743-8. [PMID: 17944916]
56. **McCaffery KJ, Irwig L, Turner R, Chan SF, Macaskill P, Lewicka M, et al.** Psychosocial outcomes of three triage methods for the management of borderline abnormal cervical smears: an open randomised trial. BMJ. 2010;340:b4491. [PMID: 20179125]
57. **Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A.** 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. [PMID: 15166066]
58. **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;144:850-5. [PMID: 16754927]
59. **Ogilvie GS, van Niekerk DJ, Krajden M, Martin RE, Ehlen TG, Ceballos K, 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. [PMID: 20334685]
60. **Arbyn M, Rebolj M, De Kok IM, Fender M, Becker N, O'Reilly M, et al.** The challenges of organising cervical screening programmes in the 15 old member states of the European Union. Eur J Cancer. 2009;45:2671-8. [PMID: 19695867]
61. **Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE.** Human papillomavirus testing in the prevention of cervical cancer. J Natl Cancer Inst. 2011;103:368-83. [PMID: 21282563]
62. **Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, et al; Joint European Cohort Study.** Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ. 2008;337:a1754. [PMID: 18852164]
63. **Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, 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. [PMID: 12509400]
64. **Kjaer S, Høgdall E, Frederiksen K, Munk C, van den Brule A, Svare E, 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;66:10630-6. [PMID: 17062559]
65. **Saraiya M, Berkowitz Z, Yabroff KR, Wideroff L, Kobrin S, Benard V.** Cervical cancer screening with both human papillomavirus and Papanicolaou testing vs Papanicolaou testing alone: what screening intervals are physicians recommending? Arch Intern Med. 2010;170:977-85. [PMID: 20548011]
66. **Kinney W, Stoler MH, Castle PE.** Special commentary: patient safety and the next generation of HPV DNA tests. Am J Clin Pathol. 2010;134:193-9. [PMID: 20660320]
67. **Stoler MH, Vichnin MD, Ferenczy A, Ferris DG, Perez G, Paavonen J, et al; FUTURE I, II and III Investigators.** The accuracy of colposcopic biopsy: analyses from the placebo arm of the Gardasil clinical trials. Int J Cancer. 2011;128:1354-62. [PMID: 20506504]

**Current Author Addresses:** Drs. Whitlock, Vesco, Eder, Lin, and Senger and Ms. Burda: Center for Health Research, Kaiser Permanente Northwest, 3800 North Interstate Avenue, Portland, OR 97227.

**Author Contributions:** Conception and design: E.P. Whitlock, K.K. Vesco.
Analysis and interpretation of the data: E.P. Whitlock, K.K. Vesco, M. Eder, J.S. Lin.
Drafting of the article: E.P. Whitlock, K.K. Vesco, M. Eder, C.A. Senger.
Critical revision of the article for important intellectual content: E.P. Whitlock, K.K. Vesco, J.S. Lin, C.A. Senger.
Final approval of the article: E.P. Whitlock, K.K. Vesco, M. Eder, J.S. Lin.
Obtaining of funding: E.P. Whitlock.
Administrative, technical, or logistic support: C.A. Senger, B.U. Burda.
Collection and assembly of data: K.K. Vesco, M. Eder, J.S. Lin, C.A. Senger, B.U. Burda.

## *Appendix Table.* Characteristics of Randomized, Controlled Trials of HPV Screening Strategies for Cervical Cancer Screening

| Variable | Study (Reference) | | | | | |
|---|---|---|---|---|---|---|
| | NTCC Phase 2 (39) | Finnish Trial (45, 51) | NTCC Phase 1 (46) | POBASCAM (47) | Swedescreen (49, 50) | ARTISTIC (48) |
| Total randomized and screened, *n* | 49 196 | 71 337 | 45 174 | 44 938 | 12 527 | 24 510 |
| Ages recruited, *y* | 25–60 | 25–65 | 25–60 | 30–56 | 32–38 | 20–64 |
| Older women, *n* | 35 471 | 59 757 | 33 364 | 44 938 | 12 527 | 19 344 |
| Number of screening rounds | 2 | 1 | 2 | 2 | 2 | 2 |
| Round interval, *y* | 3 | 2–4 | 3 | 5 | 3 | 3 |
| Follow-up, *y* | 3.5* | Mean, 3.3 | 3.5* | 6.5† | Mean, 4.1‡ | 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 |
| Round 2 | CC vs. CC | NA | CC vs. CC | PCR + CC vs. PCR + CC | PCR + CC vs. CC | HC2 + LBC vs. LBC |
| Treatment threshold | CIN2+ | CIN1+/CIN2+‖ | CIN2+ | NR | High-grade CIN | CIN2+ |
| Treatment | NR | LEEP | NR | NR | Conization, loop excision | Excision, ablation¶ |
| USPSTF quality rating | Fair | Fair | Fair | Fair | Fair | Fair |
| Quality and interpretation issues | Participants were not blinded.<br>Cytology may be relatively poor if laboratory standards among the 14 that performed the analyses differ.<br>Colposcopists and local histologists were not blinded to HPV results, but there was blinded central review of diagnosis.<br>Community colposcopy was repeated if normal but "clearly abnormal cytology"; no biopsies were done in negative colposcopy.<br>Nonadherent women in round 1 were not invited to round 2 (2.8% in IG vs. 0.7% in CG).<br>Different tests in round 1 and round 2: HC2 vs. CC in round 1, CC vs. CC in round 2.<br>Does not exclude women with CIN2+ in round 1 from round 2.<br>Cytology referral threshold differed by site. | Single screening round, but extended 5-y follow-up.<br>Cytologist, colposcopists, and pathologists were not blinded to HPV results; community colposcopy; no biopsies were done in normal colposcopy.<br>Randomization scheme was not reported.<br>Eligibility (other than age) was not clear. | Cytology may be relatively poor if community standards are not good, especially for LBC (14 laboratories); blinded to HPV.<br>Colposcopists and histologists were not blinded to HPV results.<br>Community colposcopy was repeated if normal but "clearly abnormal cytology"; no clear biopsies done in negative colposcopy.<br>Nonadherent women in round 1 were not invited to round 2 (2.7% in IG vs. 0.6% in CG).<br>Different tests in round 1 and round 2: HC2 vs. CC in round 1, CC vs. CC in round 2.<br>Does not exclude women with CIN2+ in round 1 from round 2.<br>Cytology referral threshold differed by site. | Round 2 results for two thirds of the sample were still not reported.<br>Blinding was reported for cytology and HPV results but not for participants or histology.<br>5-y interval between rounds (3 in most trials).<br>59% of participants had not completed 6.5 y of follow-up at the time of analysis.<br>For both round 1 and round 2, data were reported only for those completing all 6.5 y of follow-up.<br>In round 2, all women received both HPV screening and CC. | Cytology reading was not described; patients were unblinded to HPV at year 3 owing to high CIN2+/3+ in those who were HPV-positive.<br>Round 2 follow-up is limited to 1 y; does not include retesting results.<br>Number of women with incomplete follow-up was not quantified.<br>Round 2 occurs outside study, with registry data only.<br>Referral threshold differed by site (about one half ASC-US+, one half HSIL+). | Colposcopists were aware of HPV+/cytology− results.<br>No biopsies in negative colposcopy.<br>Round 2 data ignored CIN2+ histology after normal cytology to make diagnostic criteria the same in both groups—reduces impact of retesting (HPV+/cytology−).<br>Interval between round 1 and round 2 ranged from 26 to 54 mo.<br>Excludes women with CIN2+ from subsequent rounds.<br>Incomplete round 2 follow-up (34% not attending round 2 at time of analysis).<br>Maximum follow-up from baseline of 7 y; mean follow-up NR.<br>Histology follow-up in round 2 after screening shortened (<30 mo) for 29%. |

ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = atypical squamous cells of undetermined significance; CC = conventional cytology; CG =control group; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2 (Qiagen, Germantown, Maryland); HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; IG =intervention group; LBC = liquid-based cytology; LEEP = loop electrosurgical excision procedure; NA = not applicable; NR = not reported; NTCC = New Technologies for Cervical Cancer Screening; PCR = polymerase chain reaction; POBASCAM = Population Based Screening Study Amsterdam Program; USPSTF = U.S. Preventive Services Task Force.

* NTCC phase 1 and NTCC phase 2, maximum follow-up after invitation to round 2 reported.

† Follow-up among a subset of the population.

‡ Median follow-up years between enrollment and colposcopy.

§ Maximum follow-up reported.

‖ Treatment method varied by date and age.

¶ Treatment method varied by site.