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Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing: A Draft Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted this systematic review to support the U.S. Preventive Services Task Force in updating its recommendation on screening for cervical cancer. Our review addresses the comparative benefits and harms of high-risk HPV (hrHPV) based screening strategies, as well as the test accuracy and uptake of self-collected hrHPV samples.

Data Sources: We re-evaluated all studies from our prior review and performed a comprehensive search for new literature to locate relevant studies for all key questions through April 11, 2024, using database searches of MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Clinical Trials, as well as existing systematic reviews, and experts.

Study Selection: We reviewed 6,419 abstracts and 316 articles against prespecified inclusion criteria. Eligible studies included English-language studies conducted in asymptomatic or unselected individuals with a cervix. We required studies to evaluate hrHPV screening as either the hrHPV test with or without cytology triage (primary hrHPV screening) or in combination with cytology (co-testing). For comparative benefits and harms of screening, we included randomized controlled trials (RCTs) or non-randomized studies of interventions (NRSIs) with a concurrent control; for accuracy, we included diagnostic accuracy studies using a reference standard; and for screening uptake, we included randomized participation trials.

Data Analysis: We conducted dual independent critical appraisal of all included studies and extracted all important study details and outcomes from fair- or good-quality studies. We narratively synthesized results by key question and screening strategy or test. When appropriate, we conducted meta-analyses using the restricted maximum likelihood model or, for accuracy studies, a bivariate model. We graded the overall strength of evidence as high, moderate, low, or insufficient based on criteria adapted from the Evidence-based Practice Center Program.

Results: We included 81 fair- to good-quality studies reported in 118 publications: 19 studies reporting benefits or harms of hrHPV-based screening strategies, 22 studies reporting test agreement or accuracy of self-collected hrHPV tests, and 42 participation trials reporting uptake of self-collected hrHPV tests. One RCT contributed to both diagnostic accuracy and uptake.

Comparative Benefits (Key Question 1)
Results for cervical intraepithelial neoplasia (CIN)3+ detection were generally consistent despite heterogenous screening strategies and followup protocols for abnormal testing. Eight studies (6 RCTs and 2 NRSIs, n=637,241) evaluating primary hrHPV screening strategies demonstrated that primary hrHPV screening with or without cytology triage can detect more CIN3+ in one round of screening compared to cytology with or without hrHPV triage in participants aged 25 to 64 years (RR 1.80 [95% CI, 1.38 to 2.36]; I^2=90.4%). Absolute differences in detection of CIN3+ ranged from 2 more CIN3+ cases detected per 10,000 to 75 more CIN3+ cases detected per 10,000. Only two RCTs (n=67,298) evaluated a second round of screening. The estimates of the RR for detection of CIN3+ at round two were 0.44 (95% CI, 0.25 to 0.58) and 0.22 (95% CI 0.08 to 0.58). Absolute differences were seven fewer cases of CIN3+ detected per 10,000 and 32 fewer CIN3+ detected per 10,000. One additional NRSI (n=44,579) evaluating a single primary hrHPV with cytology triage versus usual care in participants aged 65 to 69 years who were not

up to date on screening demonstrated that a one- time catch-up screening test can detect additional CIN3+ (RR 11.1 [95% CI, 4.81, 25.5]). The absolute difference in detection of CIN3+ was 21 more CIN3+ cases detected per 10,000. Likewise, four RCTs (n=122,316) evaluating co-testing versus cytology demonstrated that co-testing can detect more CIN3+ in one round of screening compared to cytology with or without hrHPV triage in participants aged 20 to 64 years, although results were not statistically significant (RR 1.13 [95% CI, 0.98 to 1.30]; I^2=0%). Absolute differences ranged from 6 fewer CIN3+ cases detected per 10,000 to 27 more CIN3+ cases detected per 10,000. All four RCTs included a second or exit round of screening demonstrating a reduction in precancer at the subsequent round (RR 0.67 [95% CI, 0.53 to 0.83]; I^2=0%) (absolute difference range: three fewer CIN3+ cases detected per 10,000 to 22 fewer CIN3+ cases detected per 10,000). One trial (IMPROVE, n=13,925) evaluating self-collected versus clinician-collected primary hrHPV screening demonstrated no differences in the detection of CIN3+ between the two arms.

Test Agreement, Accuracy, and Uptake (Key Question 2)
Fourteen studies (n=9,905) reported the agreement between self-collected vaginal and clinician-collected hrHPV samples, and six studies (n=513,952) reported the absolute or relative test accuracy of self-collected HPV samples to detect CIN2+ or CIN3+. Positive and negative agreement between self-collected vaginal and clinician-collected cervical samples was high, with similar proportions screening positive. The pooled absolute sensitivity of self-collected samples to detect CIN2+ was 0.86 (95% CI, 0.78 to 0.93; I^2=80.3%) and the pooled absolute specificity was 0.81 (95% CI, 0.71 to 0.91; I^2=99.7%). The relative accuracy of self-collected vaginal samples to detect CIN2+ compared with the accuracy of clinician-collected samples was also high (relative sensitivity 0.94 to 0.99; relative specificity 0.98 to 1.02). Forty of the 42 participation trials (n=386,080) demonstrated that offering self-collected vaginal hrHPV tests increased the proportion of participants completing cervical cancer screening; the absolute increase in screening uptake ranged from 2 to 63 percent. Effects appeared to be larger among persons who were not up to date with cervical cancer screening recommendations from traditionally underscreened groups.

Comparative Harms (Key Question 3)
Fourteen comparative studies with concurrent controls comparing hrHPV screening strategies reported burden of testing (e.g., colposcopy, false positive) and false negative rates (FPR, FNR), or psychological harms. No studies reported downstream harms of testing or treatment of cervical lesions. In six RCTs (n=563,818), primary hrHPV screening was associated with at least a 23 percent increase in colposcopy compared with cytology (RR 1.23 [95% CI, 1.16 to 1.31] to 3.05 [95% CI, 2.75 to 3.38]). The absolute difference in the proportion of screened individuals referred to or receiving colposcopy between arms ranged from 0.1 to 5.1 percent. One NRSI (n=44,579) evaluating catch up screening in women aged 65 to 69 years demonstrated no significant difference in colposcopy per CIN2+ detected from a single primary hrHPV with cytology triage versus usual care (11.6 [95% CI, 0.85, 15.8] versus 10.1 [95% CI, 5.4, 18.8], respectively). In seven studies (n=616,796), the pooled estimate for the relative increase in FPR in the primary hrHPV screening arm versus the cytology arm was 2.20 (95% CI, 1.51 to 3.21; I^2=99.6%). The absolute difference in FPR between the two arms ranged from 0.4 to 5.6 percent. In two studies (n=161,228) with lower test positivity, a lower use of colposcopies, and/or lower FPR was likely due to a more conservative protocol, in which a higher-grade cytology threshold

was used to refer to colposcopy. Likewise, in two trials (n=69,684), co-testing increased colposcopies compared with cytology (RR 1.30 [95% CI, 1.15 to 1.46] and RR 3.31 [95% CI, 3.06 to 3.59]). The absolute difference in colposcopies between arms was 1.6 and 7.6 percent. In three trials (n=107,560), the pooled estimate for the relative increase in FPR in the co-testing arm versus the cytology arm was 2.46 (95% CI, 1.70 to 3.57; I^2=98.2%). The absolute difference in FPR between the two arms ranged from 3.3 to 9.0 percent. Three primary hrHPV RCTs and one co-testing RCT demonstrated a greater difference in colposcopies and/or FPR in participants aged 30 or 35 years or younger compared to those aged 30 or 35 years or older. Based on one RCT (n=13,925), there is no difference in FPR between self- and clinician-collected hrHPV samples used in primary hrHPV screening. Only two comparative studies reported distress, anxiety, or depression outcomes. Both studies (n=3,481) demonstrated no difference in distress, anxiety, or depression between hrHPV-based (primary hrHPV or co-testing) compared to cytology-based screening at up to 24 months.

Limitations: None of the comparative studies evaluated primary hrHPV versus co-testing strategies. None of the included studies were designed to evaluate the comparative effectiveness of screening on cervical cancer morbidity or mortality given the rarity of these outcomes in high-income countries with organized screening programs. Few studies were adequately designed to evaluate the comparative effectiveness on the reduction of cervical cancer incidence as most studies were limited to a single round of screening. Included studies were predominantly or exclusively in women not vaccinated for HPV. There are few well designed studies that evaluated the diagnostic accuracy of using self-collected vaginal hrHPV to detect CIN3+. Many of the meta-analyses have very high statistical heterogeneity and meaningful meta-regression was not possible due to the small number of studies. However, we believe the high statistical heterogeneity largely reflects the clinical heterogeneity of protocols across studies or high precision due to large samples. Comparative studies evaluating hrHPV versus cytology-based screening strategies largely do not represent vaccinated cohorts or follow-up protocols currently recommended in the United States.

Conclusions: Well-conducted comparative studies demonstrate that a single round of high-risk HPV based screening can increase detection of precancer compared to cytology-based screening strategies, resulting in a lower rate of precancer at a subsequent round. However, the absolute incremental benefit in detection of CIN3+ comes at the expense of a higher burden of testing. The comparative benefit and burden of testing between strategies in women vaccinated for HPV cannot be observed from current trials. Self-collected vaginal hrHPV samples can have similar test accuracy for precancer compared to clinician-collected cervical hrHPV samples and can increase receipt of cervical cancer screening.

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Chapter 1. Introduction

Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to update the 2018 A recommendations for screening for cervical cancer in women age 21 to 65, and D recommendations against screening in persons with a cervix older than 65 years who have had adequate prior screening, those younger than 21 years, and those without a cervix who do not have a history or cervical cancer or high grade precancerous cervical lesions.[1]

Condition Background

Condition Definition

Cervical cancer is a malignant tumor that arises within the narrow portion of the lower uterus that connects to the vagina.[2] The two most common types of cervical cancers are squamous cell carcinoma and adenocarcinoma. Most cervical cancers are squamous cell carcinoma, and often arise in the transformation zone of the cervix.[3] Adenocarcinoma, which develops from the mucus-producing cells that line the inner part of the cervix (i.e., endocervix), accounts for roughly 20 percent of all cervical cancers in the United States.[4, 5] Less commonly, cervical carcinomas are adenosquamous (~3%-10%) and small cell neuroendocrine carcinomas (<5%).[6]

Invasive cervical cancer (ICC) develops over time and is preceded by premalignant changes to the cervix. Cervical intraepithelial neoplasia (CIN) are dysplastic changes of the cervix, which are identified at varying levels of severity: CIN1, CIN2, and CIN3.[7] CIN2 and CIN3 are considered premalignant lesions. 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). CIN3+ includes adenocarcinoma in situ (AIS), which is a premalignant precursor to cervical cancer adenocarcinoma. Recommended changes to this terminology were proposed in 2012, which most notably included an alternative primary definition of low grade squamous epithelial lesion (LSIL) or high grade squamous epithelial lesion (HSIL).[8] Specifically, CIN1 is considered LSIL, CIN3 is considered HSIL, and CIN2 is also considered HSIL but with the qualification that there is a reduced diagnostic certainty involving this subclassification. Further, p16 immunohistochemical staining can be used to categorize CIN2 as LSIL versus HSIL when diagnostic uncertainty is present.

Prevalence and Burden

Over the last 50 years, screening programs have notably reduced the incidence and mortality rates for cervical cancer in the United States. The cumulative age-adjusted incidence from 2016 to 2020 was 7.7 cases per 100,000 women per year; the age-adjusted mortality rate over the 2016 to 2020 time period was 2.2 deaths per 100,000 women per year.[9] There will be an estimated 13,960 new cases of cervical cancer (accounting for 0.7% of all new cancer diagnoses) and 4,310 deaths in 2023.[9] The incident rate of new diagnoses has remained stable from 2010 to 2019,

whereas the mortality rate has shown a decline over time, with age-adjusted mortality rates falling an average of 0.7 percent each year during 2011 to 2020 (**Figure 1**). Cervical cancer is most commonly found in women aged 35 to 64 years (64.9% of cases), with the median age of women diagnosed being 50 years. A smaller proportion of cervical cancer deaths, however, occurs in that same age group (57.8%) (**Figure 2**). Only 0.5 percent of cervical cancer cases occur in women aged 20 to 24 years. More than 20 percent of cervical cancer cases are diagnosed in women aged 65 years and over.[10] Further, women aged 65 years or older account for a disproportionate number of cervical cancer deaths, at 37 percent (**Figure 2**).

Data from the Surveillance, Epidemiology, and End Results (SEER) Program continue to show racial and ethnic disparities in the rates of cervical cancer incidence and mortality (**Appendix G**). When looking across all racial and ethnic groups, non-Hispanic Black (8.8 cases per 100,000 persons), Hispanic (9.8 cases per 100,000 persons), and non-Hispanic American Indian/Alaska Native women (8.8 cases per 100,000 persons) continue to have higher incidence rates of cervical cancer compared with non-Hispanic White (6.9 cases per 100,000 persons) and non-Hispanic Asian/Pacific Islander women (6.1 cases per 100,000 women) (**Figure 3**).[9] The disparities in cervical cancer mortality also show that non-Hispanic Black women have the highest mortality rates (3.3 deaths per 100,000 persons), followed by non-Hispanic Native American/Alaska Native women (2.9 deaths per 100,000 persons), and Hispanic women (2.5 deaths per 100,000 persons). The mortality rate among non-Hispanic White women is lowest, at 2.0 deaths per 100,000 persons.[9] The racial and ethnic disparities in the mortality of cervical cancer are estimated to be higher when accounting for the prevalence of hysterectomy. From 2000-2012, White women had a hysterectomy-corrected cervical cancer mortality rate of 4.7 deaths per 100,000 whereas Black women had a mortality rate of 10.1 deaths per 100,000, resulting in a mortality rate ratio of 2.2 (95% CI, 2.0 to 2.3).[11]

Etiology and Natural History

HPV is the most common sexually transmitted infection in the United States.[12] A high proportion of sexually active women who have not been vaccinated for HPV (~80%) will become infected with HPV at some point in their lifetime.[13] The 12 most common hrHPV genotypes associated with cervical cancer include: 16, 18, 58, 33, 45, 31, 52, 35, 59, 39, 51, and 56, with HPV types 16 and 18 accounting for approximately 70 percent of cervical cancers.[14-16] Overall, more than 90 percent of newly acquired HPV infections, including hrHPV types, naturally resolve within two years and clearance or remission generally occurs around 6 months after infection.[17] Around 5 percent of hrHPV infections persist after 2 years, and persistent infection with hrHPV is responsible for more than 90 percent of CIN and ICC.[18-21] In addition, reactivation of hrHPV infections occur as well, with reappearance rates of up to 15 percent by 5 years.[22] Based on data from the 2015 to 2016 National Health and Nutrition Examination Surveys (NHANES), the estimated prevalence of hrHPV among women in the United States aged 18 to 24 years is 30.3 percent, 25.3 percent among those aged 25-29 years, but falls to 15.3 to 17.1 percent among those aged 30 to 59 years (**Figure 4, Appendix A**).

Persistent hrHPV infection can result in precancerous changes which may regress or progress to cancer. Regression and progression rates correlate with increasing severity of CIN. A 2021 systematic review and meta-analysis summarized 89 studies published between 1973 and 2020

on regression, persistence, and progression rates of conservatively managed CIN.[23] Definitions of regression, persistence, and progression were based on individual included studies. CIN outcomes were preferably diagnosed via histology, and if not available, cytologic outcomes were accepted. Followup ranged from 6 months to 54 months or longer. Overall, regression was most common for CIN1 (60% regressed, 25% persisted, and 0.03% progressed to cervical cancer). For CIN2, 55 percent regressed, 23 percent persisted, and 0.3 percent progressed to cervical cancer. For CIN3, 28 percent regressed, 67 percent persisted, and 2 percent progressed to cervical cancer.[23] In addition, progression of CIN is strongly influenced by hrHPV genotype, with worse outcomes associated with HPV 16.[24]

Risk Factors

Persistent infection with hrHPV is the most important risk factor for cervical precancers and ICC.[17] The risk of acquiring hrHPV increases with not being vaccinated for HPV, increasing number of sexual partners, becoming sexually active at an early age (<18 years), or having one partner who is considered high risk (e.g., HPV infection, many sexual partners).[25] Other weaker risk associations with cervical cancer include tobacco smoking, the long-term use of oral contraceptives, high parity, young age (<20 years) at first full-term pregnancy, infection with *Chlamydia trachomatis* or Herpes Simplex virus, and a diet deficient in fruits and vegetables.[25, 26] Women with HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, or previous treatment for cervical cancer or a high-grade pre-cancerous lesion are at the highest risk for cervical cancer.[27]

Disparities in cervical cancer incidence and mortality also exist by race and ethnicity, socioeconomic status (SES), insurance status, and geographic location (**Appendix B, Contextual Question 3**). Black and Hispanic/Latina women have both higher cervical cancer incidence and higher mortality compared with White women.[28] The higher incidence rates observed among Hispanic/Latina and American Indian/Alaska Native (AI/AN) women are thought to primarily be the result of lower cervical cancer screening rates and lower rates of followup after abnormal findings on screening in these populations.[29] The disparity in incidence and mortality observed for Black women, however, is more complex, as disparities persist even when screening uptake is similar between Black and White women. The reasons for Black women experiencing a higher burden of disease are the result of structural, socioeconomic, and environmental factors that impact their health in various ways, including through inequitable access to robust and equitable medical care; for example, Black women who have low socioeconomic status or who lack health insurance have been found to have the lowest rates of followup after abnormal findings on cervical cancer screening.[29, 30] Overall, women with lower socioeconomic status have higher rates of cervical cancer mortality.[29, 31, 32] Geographical disparities have also been observed, with women living in Southern states reporting higher rates of cervical cancer than women in other geographic regions of the United States.[33, 34] Additionally, cervical cancer incidence and mortality rates are higher in rural and nonmetropolitan areas than in metropolitan areas.[35, 36] This further highlights the importance of medical resources in communities as a driver of cervical cancer screening and disease outcomes. Other barriers to screening and followup include challenges obtaining affordable health care, healthcare systems that are challenging to navigate, a lack of available convenient office hours, distrust in the health care system due to past experiences, language barriers, and lack of access to

providers with shared cultural backgrounds or cultural understanding (**Appendix B, Contextual Question 4**).[29, 37-41]

Screening

Because cervical cancer tends to develop slowly and is preceded by precancerous changes of the cervix, screening may detect these changes (i.e., CIN) before cancer occurs. Screening for cancerous or precancerous changes of the cervix in developed countries utilizes two main types of tests: cytology-based screening and hrHPV testing. Cytology and hrHPV tests can be used as standalone screening methods, but in the United States most commonly are used together (i.e., co-testing) or sequentially (i.e., for triage of positive test with another method).

Cytology-based screening can be done by the conventional methods known as the Pap test (scraping cells from the cervix and fixing them on a glass slide) or using liquid-based cytology (LBC), in which the cervical cells are suspended in a liquid fixative, collected by filtration, and transferred onto a monolayer for microscopic evaluation. Compared with conventional cytology, LBC has been shown to have a similar or higher sensitivity for the detection of CIN2+ and CIN3+, a similar or lower specificity and positive predictive value, and a lower proportion of unsatisfactory slides.[42] Cervical cytology was the standard screening test, as the effectiveness of cytology for cervical cancer screening is well established.[42] The terminology for reporting the spectrum of cervical cytologic abnormalities derives from the 2014 Bethesda Workshop and is displayed in **Table 1**.[43, 44] The term ASC-US+ is used to indicate ASC-US or worse cytology, LSIL+ to indicate LSIL cytology or worse, and HSIL+ to indicate HSIL cytology or worse. Cervical cytology results are not diagnostic of neoplasia or cancer; biopsy and histologic confirmation are required for diagnosis.

HrHPV testing may be used for primary screening (with reflex cytology), co-testing with cytology, and followup testing of positive cytology results (with reflex hrHPV). A variety of tests can be used to detect hrHPV, several of which are approved by the FDA for use in the United States (**Figure 5**). These tests vary in their methods or platforms and included genotypes of hrHPV detected. Hybrid Capture 2 (HC2), which can include low risk as well as high risk genotypes, is the most widely evaluated hrHPV test in population-based screening RCTs. However, testing for low-risk genotypes is not recommended for cervical cancer screening. Additionally, HC2 is the only FDA approved test that cannot report genotypes 16 and 18 separately. To date, three HPV assays have been approved for primary hrHPV testing—Alinity m, Cobas, and Onclarity. In addition, Cobas and Onclarity have expanded FDA approval for self-collection in clinic. Self-collected vaginal hrHPV samples may also be used in clinical practice through other regulatory pathways. Self-collected samples, in clinic or at home, for hrHPV could improve screening rates among the unscreened or underscreened as it reduces the barriers to cervical cancer screening (e.g., discomfort, inconvenience, access to clinic visit).[45] However, positive hrHPV self-collected samples require a followup in-office speculum exam to collect cytology.[46]

The screening strategy (e.g., screening test[s] used, intervals of screening) and the protocols for followup of abnormal screening results will influence the magnitude of both the benefits and harms of cervical cancer screening. Clinical trials and modeling studies demonstrate that

cytology alone is less sensitive for detecting CIN2 and CIN3 compared to hrHPV screening; however, hrHPV screening strategies result in more colposcopies.[47, 48]

Depending on the initial screening test used, followup may include triage or subsequent testing with cytology or hrHPV testing, identification of the specific hrHPV genotypes, use of biomarkers (e.g., immunostaining of abnormal cytology for p16 and Ki67) and colposcopy (i.e., visualization of the cervix under magnification) with biopsy. Protocols that result in early or more frequent use of cervical colposcopy, a diagnostic test used to evaluate dysplasia, and biopsy lead to higher CIN detection rates but reduce opportunities for low-grade CIN to regress without intervention, and therefore may lead to higher rates of unnecessary treatment with potential for associated harms. In 2019, the American Society for Colposcopy and Cervical Pathology (ASCCP) issued risk-based management consensus guidelines across 19 national organizations for abnormal cervical cancer screening, such that colposcopy is recommended for any combination of history and current test results yielding a 4 percent or greater probability of finding CIN3+.[27] This updated guidance decreases the number of needed colposcopies compared to prior guidelines[49] by deferring colposcopy on those at low risk for whom colposcopy was previously recommended (e.g., hrHPV positive with ASC-US preceded by hrHPV negative screening). In general, these guidelines recommend more frequent surveillance, colposcopy, and treatment for individuals at progressively higher risk; those at lower risk can defer colposcopy, undergo followup at longer surveillance intervals, and, when at sufficiently low risk, return to routine screening. These guidelines also specify that when primary hrHPV screening is used, reflex cytology on the same specimen should be conducted for all positive hrHPV tests regardless of genotype. Some additional guidance is given using hrHPV type for estimating risk, however the guideline does not mention the use of extended genotyping beyond hrHPV 16/18. The guideline recommends the use of immunostaining for p16 only in the context of cervical biopsy specimens.

Current Clinical Practice in the United States and Recent Recommendations

High-risk HPV vaccination is effective at reducing individual and population level infection with hrHPV, cervical dysplasia, and cervical cancer.[50-53] Routine vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) for both sexes starting at age 11 or 12 years (with option to start at age 9 years) as it is most effective when administered before exposure to hrHPV.[54] Additionally, both the American Academy of Pediatrics[55] and American Cancer Society (ACS) recommend HPV vaccination starting at age 9 years.[56] Although the uptake of HPV vaccination in the United States had been slow, there has been a steady increase in coverage among adolescents since its introduction in 2006 for females and 2011 for males (**Figure 6**).[57] Initially, a quadrivalent vaccine was introduced in 2006 targeting HPV types 6, 11, 16, and 18. In 2009, a bivalent vaccine was introduced targeting only HPV types 16 and 18. Since 2016, however, the only HPV vaccine distributed in the United States is a nonavalent vaccine (targeting HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58). Data from the 2022 National Immunization Survey-Teen, which included 16,043 adolescents aged 13 to 17 years, showed that 76.0 percent of adolescents had coverage with at least 1 dose of the HPV vaccine.[58] Data also suggest geographic variation in the uptake of vaccination,[59] and that Black (76.6%),

Hispanic/Latino (77.9%), and other or multiple-race (75.5%) persons have higher rates of uptake of at least 1 dose of the HPV vaccine than White persons (70.1%).[58]

Although cervical cancer screening is relatively common in the United States, most screening is opportunistic and not part of organized screening programs (e.g., lacking population-based registries, regular invitations to screening, systems for followup). For this reason and others related to uneven access to preventive health care, a sizeable proportion of the eligible population is not routinely screened (**Appendix B, Contextual Question 3**). In 2021, 27.6 percent of women aged 21 to 65 years were not up to date with recommended cervical cancer screening.[60] These rates varied by race and ethnicity, education and poverty. The highest proportions of unscreened women had less than a high school education (41.6% unscreened), were Hispanic/Latina (32.1% unscreened) women, and were below 200 percent of the federal poverty level (36.7% unscreened).[60] Among women diagnosed with ICC, less than half had received a Pap test in the 5 years before diagnosis even though they had the opportunity to be screened.[61]

As noted above, reasons for not being screened include a lack of access to health care (e.g., lack of insurance) and social and individual factors (e.g., discomfort with the examination, cultural or religious beliefs, socioeconomic status limiting resources needed to access care, or lack of understanding for need to be screened) (**Appendix B, Contextual Questions 3 & 4**). Another population currently being underscreened is transgender men with a cervix. In one U.S.-based study, only 64.3 percent of transgender men were up to date with screening recommendations compared to 73.5 percent of cisgender women.[62] Other underscreened populations of note include persons who are incarcerated[63, 64] and those who have immigrated.[65-67] Self-collection of hrHPV samples may help reduce disparities in underscreened populations, such as those with access to care barriers, cultural variations in willingness to have a speculum exam, sexual and gender minority individuals including transgender men with a cervix, individuals with disabilities who may not tolerate a speculum exam, and those who have experienced sexual trauma.

Within the last 20 years, LBC tests have replaced conventional cytology as the primary test method in many cervical cancer screening programs.[68] In the United States from 2013 to 2019 among commercially insured women age 30 to 64 years old, the use of cytology alone decreased (from 55.6% to 30.4%) and the use of co-testing increased (from 43.8% to 68.2%).[69] The use of primary hrHPV testing was very low in this time period (1.4% in 2019). While the rate of co-testing increased similarly for metropolitan and non-metropolitan areas, the use of cytology alone remained higher in 2019 for non-metropolitan areas. The same study found the use of cytology alone was highest in the South and lowest in the West.[69] Further, a registry-based study[70] conducted in New Mexico found that in 2019, 84.3 percent of cervical cancer screening among women 30-64 years was conducted with co-testing (up from 5.6% in 2008). These data also demonstrated the continued inappropriate screening in women younger than age 21 years: 8.7 to 13.6 percent of women below age 21 years old received cervical cancer screening.[69]

Existing guidelines are generally in agreement about intervals for testing (every 3 years with cytology alone or every 5 years with hrHPV alone or co-testing) (**Table 2**). However, there are differences between guidelines on the age to start screening: whether age 21 or age 25 years. In addition, there are differences on the age at which hrHPV testing should be considered as an

alternative to cytology: whether age 25 or age 30 years. Last, existing guidelines agree to stop screening at age 65 years if the individual has been adequately screened prior to this age. Consistent with ASCCP, guidelines from the ACS define adequate prior screening as two consecutive negative HPV tests, or two consecutive negative co-testing results, or three consecutive negative cytology results within the past 10 years before stopping screening, with the most recent test occurring within the recommended interval for the test used.[71] However, 20.9 percent of cervical cancer cases in the U.S. are diagnosed at age 65 years or older (**Figure 2**). Without organized screening programs, many age 65 years and older may not be adequately screened. Additionally, older women who are up to date on screening recommendations may also develop ICC.[72]

Previous USPSTF Recommendations

In 1996, the USPSTF first recommended cervical cancer screening in women with a cervix using cytology (A recommendation).[73] In 2012, the USPSTF introduced recommendations on using hrHPV testing in combination with cytology in women ages 30 to 65 years and made explicit to start screening at age 21, recommending against screening in women younger than age 21 regardless of sexual history (D recommendation) due to the epidemiology and natural history of hrHPV and cervical cancer.[74]

In 2018, the USPSTF recommended:

- Screening every 3 years with cervical cytology alone in individuals with a cervix aged 21 to 29 years (A recommendation)
- Screening every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, or every 5 years with hrHPV testing in combination with cytology (co-testing) in individuals with a cervix aged 30 to 65 years (A recommendation)
- Against screening in individuals with a cervix older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer (D recommendation)
- Against screening in individuals with a cervix younger than 21 years (D recommendation)
- Against screening in individuals who have had a hysterectomy with removal of the cervix (D recommendation)

The first four 2018 recommendations apply to individuals who have a cervix regardless of sexual history or HPV vaccination status. The recommendations **do not** apply to individuals who have been diagnosed with cervical cancer or have a history of a high-grade precancerous lesions (i.e., CIN grade 2 or 3).

In 2018, the USPSTF found convincing evidence from the systematic review that cervical cytology alone, primary testing for hrHPV alone, or cytology and hrHPV in combination (co-testing) can detect cervical cancer and high grade precancerous cervical lesions. Based on modeling screening with cytology alone, hrHPV testing alone and co-testing all offered a reasonable balance between benefits and harms for women aged 30 to 65 years. While cytology alone appeared to be less sensitive for detection of CIN2+ and CIN3+ than hrHPV alone or in combination with cytology, it resulted in fewer harms (i.e., false positives and diagnostic

colposcopies). False positive rates were also higher among women younger than 30 years compared to older women because of the younger group's higher incidence of transient HPV infection, and thus screening in women aged 21 to 29 years should be with cytology alone. Additionally, modeling estimates found minimal differences in terms of life years gained (LYG) compared with switching to hrHPV strategies at age 30 versus 25 or 27 years, and fewer colposcopies needed (proxy for harms). Intervals of screening were primarily based on modeling which suggested similar LYG across the recommended strategies. Ages to start and stop screening were based on epidemiology and natural history of cervical cancer as well as modeling, which suggested earlier age to start or later age to stop screening in women with an adequate screening history did not result in additional benefit.

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence review in conjunction with microsimulation models from the Cancer Intervention and Surveillance Modeling Network (CISNET) Cervical Working Group[75] to update its 2018 recommendation statement on screening for cervical cancer.[1] This systematic review is an update of the 2018 review and addresses the benefits and harms associated with cervical cancer screening. In addition, this update addresses the test accuracy and uptake of self-collected hrHPV samples. The accompanying CISNET microsimulation models address how the benefits and harms of screening might vary by screening test, age to start screening, age to switch from cytology to hrHPV primary or co-testing, screening interval, and age to stop screening.[75]

Key Questions and Analytic Framework

With input from the USPSTF, we developed an Analytic Framework (**Figure 7**) and three key questions (KQs) to guide our literature search, data abstraction, and data synthesis.

Key Questions

1. What is the comparative effectiveness of different cervical cancer screening strategies (i.e., test, mode of collection, interval of testing) on precancer detection, cancer incidence, morbidity, or mortality?
    a. Does the comparative effectiveness vary by population (e.g., age, gender, race/ethnicity, HPV vaccination status)?
2. What is the test accuracy and uptake of self-collected hrHPV samples?
    a. Does the test accuracy or uptake vary by population (e.g., age, gender, race/ethnicity, HPV vaccination status)?
3. What are the comparative harms of different cervical cancer screening strategies (i.e., test, mode of collection, interval of testing)?
    a. Do the comparative harms vary by population (e.g., age, gender, race/ethnicity, HPV vaccination status)?

Data Sources and Searches

We re-evaluated all studies from the 2018 review for inclusion in the current review and performed a comprehensive search for new literature. We searched the following databases for relevant English-language literature published between January 1, 2017, and April 11, 2024: MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Clinical Trials. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**). We supplemented our searches with suggestions from experts and reference lists of previously published systematic reviews. We also searched ClinicalTrials.gov for ongoing trials and have conducted ongoing surveillance for relevant

literature for all bodies of evidence through May 24, 2024. We imported the literature from these sources directly into EndNote® X9 (Thomson Reuters, New York, NY).

Study Selection

We developed specific criteria to guide study selection (**Appendix A Table 1**). Two reviewers independently screened all records based on the titles and abstracts, using prespecified inclusion and exclusion criteria as a guide. Subsequently, at least two reviewers assessed the full text of potentially relevant studies, including all the previously included studies. Disagreements were resolved through discussion and consensus. We kept detailed records of all included and excluded studies, including the reason for exclusion. A list of included studies is available in **Appendix C** and excluded studies can be found in **Appendix D**.

Eligible studies included asymptomatic individuals with a cervix at average risk for cervical cancer (inclusive of those who are pregnant). Throughout this report, we primarily use the term "women" to refer to individuals, as this is the term used in primary studies. However, unless otherwise noted, findings apply to those with female sex at birth with a cervix, regardless of gender identity. We excluded studies exclusively in persons with HIV, with in utero exposure to diethylstilbestrol, or with previous treatment for cervical cancer or a high-grade pre-cancerous lesion. For the greatest applicability to U.S.-based practice, we included studies conducted in developed countries, as defined by "very high" development according to the 2020 United Nations Human Development Index.[76]

We required studies to evaluate hrHPV screening as either the hrHPV test with or without cytology triage (primary hrHPV screening) or in combination with cytology (co-testing). Cervical cancer screening strategies that did not include an hrHPV test (e.g., primary cytology-based screening) or used an hrHPV test for a purpose other than primary screening (i.e., cytology with hrHPV triage of abnormal cytology) were excluded. For comparators, we included any cervical cancer screening test, including cytology-based (i.e., cytology with or without hrHPV triage) or other hrHPV screening strategies.

To address the comparative benefits (KQ1) and harms (KQ3) of screening, we included randomized controlled trials (RCTs) and large nonrandomized studies of interventions (NRSIs) comparing different screening strategies (i.e., test, mode of collection, interval of testing). We also included single-group cohort studies that provide outcomes/analyses not represented in RCTs and NRSIs (e.g., analyses by HPV vaccination status) with priority placed on studies generalizable to U.S.-based clinical practices and health care settings.

To address uptake of self-collected hrHPV screening (KQ2), we included participation trials (RCTs with a primary aim of evaluating the receipt of testing) of self-collected samples versus clinician-collected samples. To address test accuracy of self-collected hrHPV screening (KQ2), we included diagnostic accuracy studies of self-collected vaginal and urine samples using any hrHPV assay. Test accuracy studies were required to use clinician-collected cervical hrHPV samples as a reference standard and/or longitudinal followup for histological outcomes. We excluded studies whose design was subject to a high risk of bias, including those that did not apply a reference standard to at least a random subset of screen-negative people (verification

bias) or did not conduct longitudinal followup. We also excluded studies without an adequate representation of a full spectrum of patients (spectrum bias), such as studies conducted only in individuals referred for colposcopy or case-control studies.

For KQ1, studies had to report at least one of the following outcomes: CIN2+, CIN3+, ICC, all-cause or cervical cancer mortality, or quality of life. Our review prioritized CIN3+ outcomes over CIN2+ outcomes because CIN regression rates are higher for CIN2 lesions, and the risk of developing ICC is considerably lower for CIN2 than for CIN3. For KQ2, test accuracy studies had to report (or provide the data to calculate) sensitivity and specificity for the detection of hrHPV, CIN2+, or CIN3+. For KQ3, studies had to report direct harms of the hrHPV screening itself, screening inaccuracy, or downstream harms from subsequent diagnostic or treatment procedures, which included: rates of false-positive or false-negative screening tests; biopsy and/or colposcopy rates and related procedural harms; adverse effects on sexual health; or psychological harms (e.g., labeling, stigma, distress, depression, and anxiety).

Quality Assessment

We quality rated all studies for potential risks of bias that may impact the reported effects and assigned each study a quality rating of "good," "fair," or "poor." For RCT and NRSI evidence, we applied signaling questions from the Cochrane Risk of Bias (RoB 2) tool[77] and the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[78] respectively, along with design-specific criteria outlined by the USPSTF.[79] For screening accuracy evidence (KQ 2), two independent reviewers assessed each study using USPSTF-design specific criteria[79] and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2.[80] **Appendix A Table 2** lists the criteria applied for each study design. Two independent reviewers rated each study, including studies that were identified from the 2018 review. Discordant quality ratings were reviewed and discussed; a third reviewer adjudicated as needed.

Studies with a single "fatal flaw" (e.g., attrition >40%, differential attrition >20%) or multiple important limitations that could invalidate the results were rated as poor-quality and excluded. Studies rated as good-quality met all or most of the criteria for the study design (e.g., adequate randomization methods); quality ratings were downgraded if studies did not meet most of the study design–specific criteria but did not have a fatal flaw that could invalidate the results. Studies included in previous reviews were re-evaluated and not necessarily given the same quality ratings.

Data Abstraction

One reviewer extracted key elements of included studies into standardized abstraction forms in DistillerSR. A second reviewer checked the data for accuracy.

For screening comparative benefits and harms studies (KQs 1 and 3), we abstracted general characteristics about the study (e.g., study design, study period, country), clinical and sociodemographic characteristics of the population (e.g., inclusion criteria, age, race and ethnicity, baseline clinical characteristics), and screening test or strategy details (e.g., assay,

mode of collection, interval of screening, followup protocols). For outcomes, we abstracted, or calculated when possible *a priori* outcomes by screening round. Mortality data that were reported only as part of the trial's CONSORT flow diagram were not abstracted.

For screening agreement and accuracy studies (KQ 2), we abstracted details about each study's characteristics (e.g., country, target population, number of participants screened); population characteristics (e.g., notable inclusion criteria, age, race and ethnicity, screening history); index test and hrHPV assay details (e.g., manufacturer, collection); reference standard details; and diagnostic outcomes for given cutoffs (i.e., contingency table, sensitivity, specificity, positive and negative predictive values). For screening uptake trials (KQ2), we abstracted general characteristics about the study (e.g., target population, country, n randomized); characteristics of the population (e.g., age, race and ethnicity, screening history); type of offered screening (e.g., self-collected vaginal sample, participant choice, standard clinical screening); proportion that completed the screening with a self-collected sample; as well as screening completion through any method.

Data Synthesis and Analysis

We synthesized findings using text, tables, and figures; where possible we conducted quantitative syntheses with meta-analysis. We used Stata 16.1 (StataCorp LLC, College Station, TX). All significance testing was 2-sided, and results were considered statistically significant if the p-value was 0.05 or less. For all meta-analysis, we assessed the presence of statistical heterogeneity among the studies using the I^2 statistic.

For comparative screening studies (KQ1, KQ3), we organized our syntheses by comparisons (i.e., primary hrHPV testing, co-testing), and study design (i.e., RCT, comparative NRSI, single-arm cohort studies) by screening round. For meta-analysis of these studies, we used the restricted maximum likelihood model. For dichotomous outcomes, we used study-reported adjusted risk ratios (RRs) if available and calculated unadjusted RRs if adjusted results were not reported. Results from included studies were generally based on a "number of women screened" denominator, rather than intention-to-treat calculations using all women randomized, because in most cases, this is what was reported.

We grouped harms into burden of screening (test positivity, colposcopies, false positive rate [FPR]), missed cancers (false negative rate [FNR]), and psychological harms. The definition of test positive was defined as a test result that would lead to a clinical action, based on the study protocol, such as colposcopy or more intensive followup (e.g., retest in 12 months). When possible, we reported referral to colposcopy as a proportion of individuals screened; however, in some instances only receipt of colposcopy (colposcopy attendance) was reported. Two studies which reported both the referral and receipt of colposcopy found the two estimates to be similar, therefore we combined these two different measures of colposcopies (i.e., preferred referral to colposcopy and if not reported accepted receipt of colposcopy). The FPR was defined as the proportion of participants without CIN2+ who had positive screening findings, as CIN2+ lesions would necessitate treatment or active surveillance if detected. The FNR was defined as the proportion of participants with ICC who had negative screening findings.

For the test accuracy of self-collected hrHPV samples (KQ2), we organized our syntheses by the reference standard or comparison test (i.e., colposcopy with clinical followup or clinician-collected hrHPV sample). For meta-analysis of accuracy studies, data from 2-by-2 contingency tables were analyzed using a bivariate model, which modeled sensitivity and specificity simultaneously. For studies reporting agreement between a self-collected hrHPV sample and a clinician-collected hrHPV sample, we modeled positive agreement and negative agreement simultaneously. Positive agreement is defined as the proportion of women who tested positive for hrHPV with both the self- and clinician-collected samples (also referred to as analytic sensitivity or virological sensitivity). Negative agreement is defined as the proportion of women who tested negative on both the self- and clinician-collected samples (also referred to as analytic specificity or virological specificity). If there were not enough studies to use the bivariate model or the contingency table numbers were not available, sensitivity and specificity were modeled separately.

For RCTs reporting uptake of self-collected hrHPV sample protocols (KQ2), we organized our results by the target population (i.e., all eligible for screening, underscreened). When multiple comparison groups were included, our analysis was restricted to the comparison group most similar to standard clinical care. We report the proportion of women who either returned their self-collected hrHPV sample or were screened through standard clinical practice. We defined uptake of initial screening as completed self-collected hrHPV or clinic-based cervical cancer screening (hrHPV, co-testing, or cytology alone); and uptake of full screening as the proportion of those who completed initial screening as well as subsequent recommended confirmatory (e.g., repeat clinician-collected hrHPV test) or triage testing (e.g., followup cytology for positive hrHPV). Additionally, a difference in the proportion screened in both groups was calculated.

For all KQs, when reported, we evaluated differences by age, race/ethnicity, screening history, and HPV vaccination status.

Grading the Strength of the Body of Evidence

We graded the strength of the overall body of evidence for each key question. We adapted the Evidence-based Practice Center approach,[81] which is based on a system developed by the Grading of Recommendations Assessment,[82] Development and Evaluation (GRADE) Working Group. Our method explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). We did not address the fifth domain—directness—as it is implied in the structure of the key questions (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as precise, imprecise, or not applicable (e.g., no evidence). The body of evidence limitations field highlights important restrictions in answering the overall KQ (e.g., suspected reporting bias, lack of replication of interventions, nonreporting of outcomes).

We graded the overall strength of evidence as high, moderate, low, or insufficient.[81] These grades reflect our level of confidence in the estimate of effect (direction and magnitude) for benefit or harm—equating to our judgement as to how much the evidence reflects a true effect, our assessment of the level of deficiencies in the body of evidence, and our belief in the stability of the findings. The strength of evidence grade does not reflect the actual magnitude of the effect (e.g., a "small" effect, "low" sensitivity).

"High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. "Moderate" suggests moderate confidence that the evidence reflects the true effect, and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect, and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. We developed our overall strength of evidence grade based on consensus discussion involving at least two reviewers.

Contextual Questions

In addition to the systematically reviewed questions (KQ1-3), we also addressed contextual questions (CQs) to aid with the broader interpretation of the evidence (**Appendix B**). Contextual questions are important considerations that may not be readily answerable from the KQ evidence or RCT literature. Five CQs were prespecified in our Research Plan:

1. What is the comparative test accuracy of hrHPV tests used in U.S.-based clinical practice?
2. How can extended genotyping and use of biomarkers (e.g., DNA methylation testing, immunostaining for p16/Ki67) for abnormal hrHPV or cytology reduce burden of testing and diagnostic procedures?
3. What are the social risk factors (e.g., race, racism, SES, insurance status, geography) or other risk factors (e.g., history of sexual trauma, smoking, vaccination status) that contribute to inequities in cervical cancer incidence and health outcomes?
4. What are barriers and implementation considerations (e.g., health system, clinician, patient) to screening and followup testing?
5. Are there effective interventions or strategies to improve screening rates and followup to abnormal screening results?

Evidence for CQs was identified based on literature retrieved for the systematic search for KQs as well as targeted searches and scanning bibliographies of relevant articles. A best evidence approach was used to identify most recent, applicable, and robust evidence. We primarily used existing systematic reviews and large well conducted studies applicable to the United States. For CQ1 on the comparative test accuracy of hrHPV tests, we focused on FDA-approved hrHPV assays. Likewise, for CQ2 on followup testing after abnormal screening (hrHPV-positive or ASC-US/LSIL on cytology), we focused on examining FDA-approved assays for extended genotyping and immunostaining for p16/ki-67 (dual staining). For CQ3, we focused on identifying social and individual risk factors that are associated with inequities in cervical cancer

incidence and mortality. For CQ4, we focused on summarizing personal and structural (including systems-level) barriers for cervical cancer screening, with attention to hrHPV-based screening, and followup testing. For CQ5, we focused on healthcare-based strategies to improve screening and subsequent followup.

Expert Review and Public Comment

A draft Research Plan was posted on the USPSTF website for public comment from October 28 to November 30, 2021. In response to public comment, the USPSTF included studies recruiting pregnant persons and added a contextual question addressing extended genotyping and use of biomarkers following abnormal hrHPV or cytology. In addition, contextual question and inclusion criteria text were revised for clarity. The USPSTF made no other substantive changes that altered the scope of the review. This draft was peer reviewed by seven invited experts and USPSTF federal partners.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis. AHRQ staff provided oversight for the project, coordinated systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Included Studies

We screened 6,419 abstracts and 316 full text articles for inclusion (**Appendix A Figure 1**). We included 81 studies reported in 118 publications (**Appendix C**). An overview of the included studies in our review and the number of analyzed participants by key question is shown in **Figure 8**.

For KQ1, we included 11 fair- to good-quality population-based RCTs[83-92] in 30 publications[83-112]; of these comparative trials, seven evaluated primary hrHPV screening, and four[85, 90-111, 113, 114] evaluated co-testing versus cytology. In addition, we included seven NRSIs: two comparative studies evaluating primary hrHPV screening,[115, 116] one comparative study of a one-time primary hrHPV screening in older women,[117] one study with longer-term observational follow-up of a primary hrHPV screening RCTs,[118] two studies with longer-term observational followup of co-testing RCTs,[119] and one single-arm cohort study in the United States evaluating co-testing.[120] Three of the primary hrHPV RCTs[83, 84, 86] and five NRSIs[115-117] were new since the 2018 USPSTF recommendation.

For KQ2, we included 22 studies examining the accuracy of self-collected hrHPV tests[86, 121-141]: 19 for vaginal self-collection and three for urine collection. Additionally, we included 42 RCTs reporting participants' uptake of screening conducted with self-collected hrHPV tests versus usual care, most conducted among participants underscreened for cervical cancer.[86, 142-182] As the accuracy and uptake of self-collected hrHPV tests was a new KQ, all studies were newly identified since the 2018 USPSTF recommendation.

For KQ3, we included all the KQ1 studies and their long-term followup as well as two studies that specifically evaluated potential psychological harms between hrHPV- versus cytology-based screenings. One substudy from the Nygard 2022 RCT evaluated primary hrHPV screening, and the other substudy from ARTISTIC evaluated co-testing. Three of the primary hrHPV RCTs,[83, 84, 86] and two NRSIs[115, 116] one long-term followup of an RCT,[183] as well as one substudy reporting psychological harms,[184] were new since the 2018 USPSTF recommendation.

Several identified studies were excluded for quality. For KQ1 and KQ3 on benefits and harms, we excluded two comparative studies and three single-arm cohort studies for high risk of bias due to very high attrition (**Appendix D, Appendix A Figure 2**). Three of these poor-quality studies were included in the systematic review supporting the 2018 USPSTF recommendation.[185-187] In addition, several studies that only compared CIN3+ or ICC by screening test results (e.g., hrHPV-positive versus hrHPV-negative) were excluded as they did not report the comparative benefit or harms between different screening strategies. For KQ2, we excluded three test accuracy studies for high risk of bias due to selection bias, verification bias, and/or high attrition. In addition, we excluded two proof of concept studies evaluating urine hrHPV tests. For KQ3, we excluded several studies that only compared psychological harms by hrHPV test result, as they did not report comparative harms between different screening strategies.

KQ1. What Is the Comparative Effectiveness of Different Cervical Cancer Screening Strategies on Precancer Detection, Cancer Incidence, Morbidity, or Mortality?

Summary of Findings

In total, we included 18 fair- to good-quality studies evaluating hrHPV screening strategies (i.e., primary hrHPV screening or co-testing versus cytology) (**Table 3**). Studies were limited to evaluating a maximum of two rounds of screening, and most studies were limited to evaluating a single round of screening. Even in trials with two rounds of screening, most often the second round was an exit round in which both arms received the same screening test. We found no studies directly comparing primary hrHPV screening versus co-testing.

Most of the studies reported the comparative detection of precancer or ICC outcomes between screening strategies, rather than the comparative effectiveness of screening strategies on the reduction of ICC, cervical cancer morbidity or mortality. Only one study with longer-term observational follow-up on a trial evaluating primary hrHPV reported cervical cancer mortality; however, this study had significant attrition at 15 years and was not adequately powered to detect a difference in mortality. Although eight comparative studies reported ICC outcomes, there was only one trial that reported ICC detection after two rounds of screening. This trial demonstrated a statistically significant reduction of ICC with co-testing compared to cytology at a second round of screening (n=39,310 at round 2). Five studies (n=564,102) demonstrated a possible trend for increased detection of ICC in a single round of screening with primary hrHPV with or without cytology triage compared to cytology with or without hrHPV triage (RR 1.27 [95% CI, 0.86 to 1.88]). However, the absolute difference between hrHPV and cytology strategies were small and not appreciably different between arms (absolute difference range: 1 fewer ICC case detected per 10,000 to 5 more ICC cases detected per 10,000 in 5 studies). Studies were all conducted in countries with organized cervical cancer screening programs with relatively low incidence of ICC.

Results for CIN3+ detection were generally consistent despite heterogenous screening strategies (e.g., type of hrHPV test, presence of triage with a reflexive test, interval of screening) and followup protocols for abnormal testing. Eight studies (6 RCTs and 2 NRSIs, n=637,241) evaluating primary hrHPV screening strategies demonstrated that primary hrHPV screening with or without cytology triage can detect more CIN3+ in one round of screening compared to cytology with or without hrHPV triage in participants aged 25 to 64 years (RR 1.80 [95% CI, 1.38 to 2.36], I^2=90.4%). Absolute differences in detection of CIN3+ ranged from 2 more CIN3+ cases detected per 10,000 to 75 more CIN3+ cases detected per 10,000 in eight studies. Only two RCTs (n=67,298) evaluated a second round of screening. The estimates of the RR for detection of CIN3+ at round 2 were 0.44 (95% CI, 0.25 to 0.58) and 0.22 (95% CI 0.08 to 0.58). Absolute differences were 7 fewer cases of CIN3+ detected per 10,000 and 32 fewer CIN3+ detected per 10,000. Results for CIN2+ detection were concordant with results for CIN3+ detection. One additional NRSI (n=44,579) evaluating a single primary hrHPV with cytology triage versus usual care in participants aged 65 to 69 years who were not up to date on screening demonstrated that a

one- time catch-up screening test can detect additional CIN3+ (RR 11.1 [95% CI, 4.81, 25.5]). The absolute difference in detection of CIN3+ was 21 more CIN3+ cases detected per 10,000.

Likewise, four RCTs (n=122,316) evaluating co-testing versus cytology demonstrated that co-testing can detect more CIN3+ in one round of screening compared to cytology with or without hrHPV triage in participants aged 20 to 64 years, although results were not statistically significant (RR 1.13 [95% CI, 0.98 to 1.30], I^2=0%). Absolute differences in detection of CIN3+ ranged from 6 fewer CIN3+ cases detected per 10,000 to 27 more CIN3+ cases detected per 10,000. Results for CIN2+ outcomes were similar and statistically significant. All four RCTs included a second or exit round of screening demonstrating a reduction in precancer at the subsequent round (RR 0.67 [95% CI, 0.53 to 0.83], I^2=0%) (absolute difference range: 3 to 22 fewer CIN3+ cases detected per 10,000). One noncomparative NRSI (n=331,818) conducted in the United States evaluating co-testing reported absolute numbers of CIN3+ detected similar to the included RCTs.

All of the included studies evaluated DNA hrHPV assays, most commonly HC2, Cobas, and a general primer GP5/6-mediated PCR enzyme immunoassay (GP5+/6+ PCR). One trial (n=13,925) evaluating self-collected versus clinician-collected primary hrHPV screening demonstrated no differences in the detection of CIN3+ or CIN2+ between the two arms. Only HPV FOCAL (n=18,948) was designed to evaluate the comparative effectiveness between two different screening intervals (2 vs. 4 years), however, these results are not yet available.

The relative effects of increased detection of precancer at the first round and subsequent decreased detection of precancer at the second or exit round compared to cytology with or without hrHPV triage was similar across age strata. Few studies reported other sociodemographic characteristics (e.g., race/ethnicity, SES), screening history, or HPV immunization status on study participants. Based on the recruitment dates of included studies, only a few studies could have included vaccinated participants.

Description of Included Studies

In total, we included 11 fair-to-good population based RCTs[83-92] in 30 publications[83-114] from countries with cervical cancer screening programs (**Table 3, Figure 9**). Seven[83, 84, 86-89, 91] of these comparative trials evaluated primary hrHPV screening, and four[85, 90-92] evaluated co-testing versus cytology. In addition, we included three comparative NRSIs evaluating primary hrHPV screening,[115-117] one study with longer-term observational follow-up of primary hrHPV screening which preserved initial randomization,[118] two studies[119, 188] with longer-term observational followup of co-testing RCTs which preserved initial randomization, and one single-arm cohort study in the United States evaluating co-testing.[120] Three of the primary hrHPV RCTs[83, 84, 86] and three comparative NRSIs[115-117] were new since the 2018 USPSTF recommendation.

Risk of Bias

Although the RCTs and comparative NRSIs were generally well conducted (i.e., fair- to good-quality) population-based comparative screening studies, most reported results for only those who were screened (i.e., per protocol versus ITT analyses) (**Appendix A Figures 2 & 3**).

Followup after randomization to screening arms ranged from 65 to near 100 percent, and adequate adherence to followup protocols was assumed but generally not reported. Fair, as opposed to good, quality studies generally had higher attrition (i.e., greater than 20%), differential attrition between groups, possible contamination between arms, and/or possible concerns with randomization (i.e., lack of randomization, method of randomization, differences in baseline characteristics between groups). Studies reporting longer-term observational follow-up of included RCTs preserved initial randomization, however, were limited by attrition or selective followup (i.e., only persons with hrHPV negative testing).

Primary hrHPV

Trial Screening Strategies

All primary hrHPV screening trials evaluated hrHPV with or without triage versus cytology with or without triage (**Table 4**). Only one trial, NTCC Phase II, evaluated hrHPV screening without triage. And one trial, COMPASS, evaluated hrHPV with LBC or dual staining of p16 and Ki67 (dual stain) triage. Of the 11 included RCTs, three compared hrHPV versus cytology alone: COMPASS (n=4995),[88] Leinonen (n=132,194),[89] and NTCC Phase II (n=49,196).[91] Another three trials compared hrHPV versus cytology with hrHPV triage if cytology was abnormal: Nygard 2022 (n=157,447),[83] Elfstrom 2021 (n=18,948),[84] and HPV FOCAL (n=18,948).[87] One trial, the IMPROVE Study (n=13,925) compared self-collected hrHPV versus clinician-collected hrHPV, both arms with LBC triage.[86]

Trial Screening Protocols

The hrHPV assays used in the trials included Cobas (k=3[83, 84, 88]), HC2 (k=4[87-89, 91]), and GP5+/6+ PCR (k=1[86]). No studies used mRNA-based hrHPV assays. Cytology could be either LBC (i.e., ThinPrep) or conventional cytology (CC). Protocols following a positive hrHPV test varied (**Table 4**), from direct referral to colposcopy if hrHPV-positive (NTCC Phase II), to direct referral to colposcopy if hrHPV 16 or 18 positive and other hrHPV type positive with abnormal cytology or dual stain (COMPASS), to referral to colposcopy only if reflex cytology abnormal. Typically, abnormal cytology was defined as ASC-US or higher-grade cytology; however, Leinonen 2012 used a LSIL or higher-grade cytology threshold. Protocols for following abnormal cytology in the comparison arm could include reflex hrHPV, requiring either abnormal cytology (e.g., ASC-US or higher-grade cytology) and abnormal hrHPV testing or higher-grade cytology alone (e.g., LSIL or higher-grade cytology) for referral to colposcopy. In some of the participating centers in NTCC Phase II, persons with ASC-US or higher-grade cytology were referred to colposcopy.

Only NTCC Phase II[91] and HPV FOCAL[87] had two rounds of screening, and the second round of screening was an exit round in which both arms received the same screening strategy (i.e., cytology only and co-testing, respectively) in order to examine the effect of the initial randomized screening strategy. The second round of screening (exit round) was at 2 years (HPV FOCAL) and 3.5 years (NTCC Phase II) after the first round.

Trial Participant Characteristics

Screened women were generally 25 to 65 years of age, with three trials limiting participants to women aged older than 30 or 35 years (**Table 5**). Mean age was reported in seven trials and ranged from 35[90] to 50[83] years. Four trials specified that pregnant women were excluded. We identified no trials specifically recruiting pregnant women. Only HPV FOCAL,[87] conducted in Canada, reported race or ethnicity; 76 percent of women were of European origin, 14 percent were of Chinese ethnicity, 8 percent were of other Asian ethnicity, and 3 percent were of aboriginal ethnicity. HPV FOCAL[87] was also the only trial to report HPV vaccination status; only 0.6 percent of women self-reported the receipt of any doses of the HPV vaccine. Given the trial recruitment dates, only a few trials could have included women with prior HPV vaccination (**Figure 10**). In the COMPASS trial,[88] 22 percent of enrolled women were younger than age 33 years (and therefore would have been offered HPV vaccination in Australia); trial investigators estimated that 70 percent would be vaccinated in that age group. None of the trials reported screening history or percent underscreened or unscreened, however all trials were conducted in countries with cervical cancer screening programs.

NRSI Screening Strategies

We also included two comparative NRSIs[115, 116] with contemporaneous controls evaluating primary hrHPV with cytology triage versus cytology with or without hrHPV triage (**Table 4**). One NRSI, Veijalainen 2019 (n=33,375), compared hrHPV versus cytology alone.[116] And one NRSI , HPV SCREEN DENMARK (n=40,048) compared hrHPV versus cytology with hrHPV triage if the cytology was abnormal.[115]

Additionally, we included one longer-term observational follow-up study of the RCT by Leinonen (n=101,947)[118] comparing primary hrHPV versus cytology alone. One or two rounds of primary hrHPV screening was followed by one to two rounds of cytology versus cytology alone. This study reported follow-up at 15 years after the initial round of screening.

We included an additional comparative NRSI with contemporaneous controls (n=44,579) in Denmark (Tranberg 2023) evaluating primary hrHPV with LBC triage versus usual care in women aged 65 to 69 years old who were not up to date with cervical cancer screening.[117] Usual care consisted of opportunistic cervical cancer screening or case-finding (e.g., testing for vaginal bleeding).

NRSI Screening Protocols

Protocols used in the NRSIs were similar to those used in the RCTs (**Table 4**). Studies used HC2, Cobas, and Abbott RealTime hrHPV assays. The two Danish studies, HPV SCREEN DENMARK[115] and Tranberg 2023[117] had direct referral to colposcopy with hrHPV 16 or 18 positive and reflex cytology for other hrHPV genotypes, with referral to colposcopy with abnormal cytology. Additionally, Tranberg 2023 offered women the option for self-collected vaginal hrHPV samples. Women with a hrHPV positive self-sample were recommended to have cytology followup by their general practitioner within 30 days. Similar to the Leinonen 2012 RCT, Veijalainen 2019[116] had a more conservative protocol for referral to colposcopy requiring hrHPV-positive with LSIL or higher-grade cytology. Referral to colposcopy in the cytology

comparison arm required LSIL/HSIL or higher-grade cytology. NRSIs were generally limited to a single round of screening. In the longer-term observational follow-up study of the Leinonen RCT,[118] only 43 percent of participants received two rounds of primary hrHPV screening because Helsinki, the largest municipality in Finland, decided not to continue with the trial protocol after the first round of screening.

NRSI Participant Characteristics

The populations evaluated for HPV SCREEN DENMARK[115] and Veijalainen 2019[116] were similar to the RCTs. Screened women were generally 30 or 35 to 60 years of age. The mean age of screened women was 44 and 50 years (**Table 5**). These two NRSIs did not report other participant characteristics such as race or ethnicity, HPV vaccination status, or prior screening history. Tranberg 2023[117] evaluated catch up screening in women aged 65 to 69 years old who had no record of cervical cytology sample or screening invitation in the preceding 5.5 years or more, and no record of a hrHPV exit test at age 60 to 64 years. The median age of screened women was 68 years. Seventy-seven percent of screened women had been screened two or more times while age 50 to 64 years, while 24 percent of women had been screened no more than once while age 50 to 64 years.

Detailed Results for Primary HrHPV Screening

Given the rarity of morbidity or mortality from cervical cancer with screening, trials were not designed to assess these outcomes. As such, we synthesized results for the most reported outcomes (i.e., detection of CIN2+ and CIN3+) as well as ICC. Given the rarity of ICC and higher likelihood of progression of CIN3+ than CIN2+ to ICC, we prioritized CIN3+ outcomes.

ICC

In general, RCTs and NRSIs had low rates of ICC and not all RCTs reported on ICC cases. Four trials and two NRSIs evaluating primary hrHPV versus LBC reported ICC (**Appendix E Table 1**). All these studies only evaluated one round of screening, and therefore were not designed to show a reduction in ICC in subsequent rounds of screening. In five studies (3 RCTs and 2 NRSIs), the pooled estimate of the relative risk (RR) for detection of ICC with primary hrHPV versus cytology with or without hrHPV triage after a single round of screening was 1.27 (95% CI, 0.86 to 1.88; I^2=51.3%) (**Figure 11**). The total number of ICC cases in those five studies ranged from 8 to 114, resulting in absolute differences in detection of ICC that were small (absolute difference range: one fewer ICC cases detected per 10,000 to five more ICC cases detected per 10,000 in 5 studies). Pooling only the three RCTs resulted in a similar pooled estimate (RR 1.19 [95% CI, 0.74 to 1.93]; I^2=65.3%) (**Figure 11**).

In one longer-term observational follow-up study of the Leinonen RCT evaluating one or two rounds of primary hrHPV screening versus cytology alone, there was no difference in ICC (IRR 1.08 [95% CI, 0.85 to 1.37])[118] or cervical cancer mortality (IRR 1.00 [95% CI, 0.61 to 1.64]) at a median of 15 years of follow-up (**Appendix E Table 1**). In a total of 3.5 million person-years of followup there were only 139 ICC and 32 cervical cancer deaths in the primary hrHPV arm and 129 ICC and 32 cervical cancer deaths in the cytology arm.

In addition, Tranberg 2023[117] demonstrated a RR of 2.98 (95% CI, 0.75 to 11.9) for the detection of ICC with a single catch-up screening in underscreened women aged 65 to 69 years compared to usual care. The absolute difference was 2 per 10,000 more ICC detected with catch-up screening, although results were not statistically significant (**Appendix E Table 1**).

CIN3+ and CIN2+

In the six RCTs (n analyzed=563,818) and two NRSIs (n=73,423) that compared primary hrHPV screening versus cytology with or without hrHPV triage, primary hrHPV screening identified more CIN3+ with a single round of screening (**Figure 12, Appendix E Table 1**). In eight studies, the pooled estimate of the RR for detection of CIN3+ with primary hrHPV versus cytology with or without hrHPV triage after a single round of screening was 1.80 (95% CI, 1.38 to 2.36; I^2=90.4%) (**Figure 12**). Absolute differences in detection of CIN3+ ranged from 2 more CIN3+ cases detected per 10,000 to 75 more CIN3+ cases detected per 10,000 in 8 studies. The pooled estimate of the RR for the detection of CIN3+ for the six RCTs alone was similar to the overall pooled estimate inclusive of NRSIs (RR 1.70 [95% CI, 1.22 to 2.37; I^2=91.6%) (**Figure 12**). The overall pooled estimate of the RR across the eight comparative studies for the detection of CIN2+ after a single round of screening was 1.92 (95% CI, 1.50 to 2.47; I^2=94.6%) (**Figure 13**). In eight studies, absolute differences in detection of CIN2+ ranged from 11 to 114 more cases detected per 10,000. Likewise, the RR for detection of CIN2+ for the six RCTs alone was 1.84 (95% CI, 1.33 to 2.54; I^2=96.1%) (**Figure 13**). Effect sizes for the detection of CIN3+ and CIN2+ between studies comparing primary hrHPV screening to cytology alone versus cytology with hrHPV triage were similar (**Appendix F**). High statistical heterogeneity in the pooled analyses for the detection of CIN3+ and CIN2+ was primarily due the two largest RCTs—a Swedish RCT by Elfstrom and colleagues and the Norwegian RCT by Nygard and colleagues—and NTCC Phase II, which evaluated hrHPV screening alone (without cytology triage for positive hrHPV tests). The two largest RCTs reported point estimates for detection with very high precision (i.e., narrow 95% confidence intervals that did not overlap with the pooled estimate). The RCT by Elfstrom and colleagues did not show a difference in the detection of CIN3+ between primary hrHPV screening with cytology triage compared with cytology with hrHPV triage; although it did demonstrate increased detection of CIN2+ in the primary hrHPV screening arm compared with cytology screening arm. NTCC Phase II referred all hrHPV-positive women directly to colposcopy. The smallest trial, COMPASS (n=4,995), evaluated primary hrHPV screening with two different reflexive tests (LBC versus dual stain) compared to LBC. Preliminary results with 18 months of followup suggest no difference in detection of CIN3+ and CIN2+ between the two triage tests, however the relatively small sample sizes of each arm resulted in large imprecision of effect sizes.

Only two RCTs (n=68,144) reported more than one round of screening, NTCC Phase II and HPV FOCAL.[87, 91] Both trials showed a decrease in CIN3+ and CIN2+ detection in the primary hrHPV screening arm compared to cytology with or without hrHPV triage at the second and exit round of screening (**Figures 12 and 13**). The estimates of the RR for detection of CIN3+ at round 2 were 0.42 (95% CI, 0.25 to 0.70) and 0.22 (95% CI 0.08, 0.58) (**Figure 12**). Absolute differences were 7 fewer cases of CIN3+ detected per 10,000 and 32 fewer CIN3+ detected per 10,000. The estimate for detection of CIN2+ at round 2 was similar, RR 0.47 (95% CI 0.33, 0.66) and 0.32 (95% CI, 0.17 to 0.61) (**Figure 13**). Absolute differences were 11 and 56 fewer CIN2+ cases detected per 10,000. NTCC Phase II, which evaluated primary hrHPV screening

versus CC alone used CC in both arms for the exit round, while HPV FOCAL, which evaluated primary hrHPV screening versus LBC with reflex to LBC used co-testing in both arms for the exit round. There was no difference between screening strategies in the cumulative detection of CIN3+ or CIN2+ in these two rounds for both NTCC Phase II and HPV FOCAL; however, the cumulative detection does not reflect two rounds of primary hrHPV screening versus cytology with or without hrHPV triage due to the change in screening strategy in the exit round (round two). The high statistical heterogeneity in the pooled analyses for the cumulative detection may be due to different primary hrHPV strategies (and protocols) evaluated in HPV FOCAL (hrHPV with LBC triage) versus NTCC Phase II (hrHPV alone).

One additional NRSI[117] (n=44,579) evaluating a single catch-up screening compared to usual care in underscreened women aged 65 to 69 years can detect additional CIN3+ (RR 11.1 [95% CI, 4.81 to 25.5]) and CIN2+ (RR 11.9 [95% CI, 6.2 to 23.1]). The absolute difference in detection was 21 more CIN3+ cases detected per 10,000 and 36 more CIN2+ cases detected per 10,000 (**Appendix E Table 1**).

Variation by Test, Mode of Collection, and Screening Intervals

All of the included studies used DNA hrHPV testing. Although studies used different DNA hrHPV assays, we did not observe any differences in precancerous detection attributable to different assays (e.g., HC2 versus COBAS).

The IMPROVE study in the Netherlands (n=13,925) compared self-collected hrHPV versus clinician-collected hrHPV. In the self-collected sample arm, positive hrHPV results required a followup pelvic exam for LBC. There were no statistically significant differences in the detection of CIN3+and CIN2+ between the self- and clinician-collected sample arms.

The included studies are not adequate to address the impact of different screening intervals on the detection of ICC, CIN3+, or CIN2+. Only two primary hrHPV screening RCTs evaluated more than one screening round, and second rounds in these trials were exit rounds using screening strategies other than primary hrHPV screening. Only HPV FOCAL directly compared different screening intervals (i.e., 2-year interval of primary hrHPV or cytology alone versus 4-year interval of primary hrHPV) and the findings of the comparison of different screening intervals have not yet been published.

Variation by Population

All the included RCTs and NRSIs reported results by age bands, although these groups varied in reporting 5- to 10-year bands with different cut offs (**Appendix E Table 2**). Five RCTs comparing primary hrHPV with or without cytology triage versus cytology with or without hrHPV triage generally demonstrated higher detection of CIN3+ and CIN2+ in younger age bands (<30, 34 or 35 years) compared to older age bands (30, 34 or 35+ years). However, there was no evidence of effect modification by age (i.e., differences in relative detection between the primary hrHPV screening arms versus the cytology arms across age strata [with 95% CI overlapping]). Two comparative NRSIs evaluating primary hrHPV with cytology triage versus cytology with or without hrHPV triage reported different age bands, however results were generally concordant with trial findings of no effect modification by age in the detection of

CIN3+ or CIN2+ between screening strategies. No studies included women younger than 25 years of age. One large RCT, Nygard 2022,[83] included women up to 69 years. For the subgroup of women aged 65-69 years (n=15,324), hrHPV screening compared with cytology screening identified more women with CIN3+ (RR 1.7 [95% CI, 1.0 to 3.2]) and CIN2+ (RR 2.3 [95% CI, 1.3 to 4.1]). One study, Tranberg 2023,[117] exclusively studied underscreened women aged 65 to 69 years and demonstrated that a single catch-up screening compared to usual care can detect additional CIN3+ (RR 11.1 [95% CI, 4.81 to 25.5]) and CIN2+ (RR 11.9 [95% CI, 6.2 to 23.1]).

The IMPROVE study (n=13,925) comparing self-collected hrHPV versus clinician collected-hrHPV found no appreciable differences in test positivity or the detection of CIN3+ or CIN2+ with one round of screening between the two different test collection methods in any of the age bands (**Appendix E Table 2**). In women aged 34 to 38 years, the self-collected arm identified more CIN3+ than the clinician-collected, however, the number of cases were few and imprecision was quite large (RR 5.08 [95% CI, 1.51 to 17.09]).

Only Tranberg 2023[117] reported results stratified by screening history. Women were categorized as insufficiently screened if they had not more than one cervical cytology sample or categorized as sufficiently screened if two or more cervical samples at age 50 to 64 years. In women who received catch-up screening with primary hrHPV testing, the percentage of CIN2+ detected were higher in insufficiently screened women (1.4% [95% CI, 0.5, 2.9]) compared to women who were sufficiently screened (0.6% [95% CI, 0.4, 0.8%]), however results were not statistically significantly different. No additional studies reported results by prior screening history and all studies were conducted in countries with cervical cancer screening programs. Further, no studies reported results by vaccination status and based on the dates of included studies and ages of participants (or cohorts), we conclude that few, if any, were vaccinated for hrHPV. Additionally, no included studies reported results by SES, race or ethnicity, gender identity and/or use of exogenous hormones.

Co-Testing

Trial Screening Strategies

Four trials evaluating co-testing (i.e., hrHPV and cytology versus cytology alone) were included: (**Table 6**): POBASCAM (n=42,105),[92] ARTISTIC (n=24,510),[85] Swedescreen (n=12,527),[90] and NTCC Phase I (n=45,174).[91]

Trial Screening Protocols

The hrHPV assays used in the co-testing trials included HC2 (k=2[85, 91]) and GP5+/6+ PCR (k=2[90, 92]). No trials used mRNA-based hrHPV assays. Cytology was either LBC (i.e., ThinPrep) or conventional cytology (CC). Protocols for following abnormal co-testing varied widely and ranged from direct referral to colposcopy if hrHPV-positive and 35+ years (NTCC Phase I), two sequential hrHPV-positive results (repeat test at 1 or 2 years), to LSIL or higher-grade cytology regardless of hrHPV results. The cytology threshold for direct referral to colposcopy also varied across trials, however the cytology threshold in the comparison arm was the same as the co-testing arm. In those trials with higher-grade cytology thresholds, repeat testing was at 6 to 12 months for cytology not meeting threshold for direct referral to colposcopy (**Table 6**). Only

ARTISTIC[85] had three rounds of screening and the third round was an exit round in which both arms received the same screening strategy (i.e., cytology only). The other three trials[90-92] had two rounds of screening, in which the second round was the exit round in which both arms received the same screening strategy. The interval between screening rounds ranged from 3 to 5 years.

Trial Participant Characteristics

The age of women screened ranged from 20 to 64 years, although Swedescreen [90] was quite restrictive (age 32 to 38 years) (**Table 7**). The mean age in NTCC Phase I and POBASCAM was 41 and 40 years, respectively, while the mean age in Swedescreen was 35 years. NTCC Phase I[91] specified that pregnant women were excluded. Other participant characteristics such as race or ethnicity, history of HPV vaccination, and screening history were not reported. However, all trials were conducted in Western European countries with organized cervical cancer screening programs, prior to HPV vaccination in the European Union (2008) (**Figure 10**).

NRSI Screening Strategies, Protocols, and Population Characteristics

We also included three NRSIs evaluating co-testing (**Table 6**). Two[119, 188] of these NRSIs were longer-term observational followup of the Swedescreen and POBASCAM RCTs (see above).[90, 188] The longer-term observational followup study of POBASCAM was limited to a subgroup of women who had negative hrHPV testing at the second round of screening with co-testing or cytology (with blinded hrHPV). Screening during the 10-year followup of Swedescreen was not reported. However, we assume that women in both groups continued to get screened per usual care in Sweden at that time, which included primarily cytology-based screening, as hrHPV screening was not routinely done until after 2015. Followup screening during the 19-year followup of POBASCAM included cotesting in both arms at round two, cytology in both arms at round three, and primary hrHPV or cytology at round four.

The other study[120] was a single arm cohort study conducted in a large integrated managed care organization in the United States, Kaiser Permanente Northern California, (n=331,818) evaluating co-testing (using HC2 and LBC) in women aged 30 and older. Although this study did not include a comparison cohort, because it was the only study conducted in the United States meeting quality criteria, it is included in this review. This study included two rounds of screening with a 3-year interval between screening rounds; however, it did not report the first round of screening results separately, and the second round of screening results (abstracted but not discussed) are in a selected group of women whose first round of screening was normal. About half of the women of the health system from which this cohort was sampled self-reported their race/ethnicity. Among these women, 62 percent were White, 12 percent were Asian/Pacific Islander, 12 percent were Hispanic, and 8 percent were Black. Persons with LSIL+ or hrHPV-positive with ASC-US or higher-grade cytology were referred to colposcopy.

Detailed Results for Co-Testing

ICC

Similar to the primary hrHPV screening trials, RCTs evaluating co-testing had low rates of ICC and not all trials reported on ICC cases. While three trials reported ICC, only POBASCAM[92]

reported ICC at the second round of screening (n=39,310) (**Appendix E Table 3, Figure 14**). This RCT in the Netherlands showed a statistically significant greater number of ICC cases detected in the co-testing arm compared to the CC arm and a subsequent fewer number of ICC cases detected in the co-testing arm compared to the CC arm in the second (exit) round (0.02% of 19,579 women versus 0.07% of 19,731 women, respectively) (**Figure 14**). The Kaiser Permanente Northern California single-arm cohort study by Katki and colleagues had similar absolute numbers of ICC detected with a cumulative two rounds of co-testing (0.03% of 331,818 women) as ARTISTIC, with a cumulative two rounds of screening (0.04% of 18,386 women) (**Appendix E Table 3**).

CIN3+ and CIN2+

All four co-testing RCTs[85, 90-92] had at least two rounds of screening. Overall, the four RCTs[85, 90-92] (n=122,316) demonstrated that co-testing identified a greater number CIN3+ cases (**Figure 15**), as well as CIN2+ (**Figure 16**) in the first round of screening and subsequently fewer number of CIN3+ and CIN2+ cases in the second (exit) round of screening using the same screening strategy in both arms (**Appendix E Table 3**). The pooled estimate of the RR for detection of CIN3+ after a single round of screening was 1.13 (95% CI, 0.98 to 1.30; I^2=0%) for co-testing versus cytology alone and 0.67 (95% CI, 0.53 to 0.83; I^2=0%) for co-testing versus cytology in the exit round (**Figure 15**). Absolute differences in detection of CIN3+ at round 1 ranged from 6 fewer CIN3+ cases detected per 10,000 to 27 more CIN3+ cases detected per 10,000 at round 1 and 3 to 22 fewer CIN3+ cases detected per 10,000 at the exit round. Likewise, the pooled estimate of the RR for the detection of CIN2+ after a single round of screening was 1.39 (95% CI, 1.12 to 1.74; I^2=75.1%) for co-testing versus cytology and 0.73 (95% CI, 0.57 to 0.92; I^2=35.4%) for co-testing versus cytology in the exit round (**Figure 16**). The absolute differences in detection of CIN2+ at round 1 ranged from 27 to 109 more cases detected per 10,000. There was no difference between screening strategies in the cumulative detection of CIN3+ or CIN2+ (**Figures 15 and 16**); however, only ARTISTIC[85] which had a third (exit) round reported cumulative results for screening rounds one and two evaluating co-testing versus cytology. ARTISTIC[85] (n=24,510) reported a slightly higher number of cases of CIN3+ and CIN2+ in cumulative rounds comparing co-testing to cytology versus cumulative rounds with an exit round in which both arms received LBC screening (269 versus 262 CIN3+ cases and 541 versus 518 CIN2+ cases). In the third (exit) round, both arms were screening with LBC and there were no differences in the detection of CIN3+ or CIN2+, however the 95% CI were quite wide given large attrition resulting in a much smaller n analyzed (n=8,873) (**Appendix E Table 3**). High statistical heterogeneity in pooled analyses for the detection of CIN3+ and CIN2+ in round one and cumulative rounds is due to NTCC Phase I.[91] This trial had higher test positivity as well as a more permissive referral to colposcopy (i.e., all persons aged 35+ years with positive hrHPV test) compared to other studies, resulting in greater detection of precancer (**Appendix E Table 3**).

One NRSI by Elfstrom and colleagues[119] (n=12,062) reported long-term observational followup of Swedescreen for up to 13 years using a national Swedish registry (**Appendix E Table 3**). Similar to the findings of the cumulative round (round one and exit round) of Swedescreen,[90] observational followup at 3, 5, 8, and 10 years showed no difference in the detection of CIN3+ or CIN2+ in women originally randomized to co-testing versus CC (**Appendix E Table 3**). One NRSI by Inturrisi and colleagues[188] (n=18,448) reported long-term observational followup of

POBASCAM for up to 14 years after the second round of screening in hrHPV negative women. Women originally randomized to the co-testing arm had lower CIN3+ at 14 years followup, however results were not statistically significant (RR 0.62 [95% CI, 0.37 to 1.04]). Results for similar for detection of CIN2+ (RR 0.78 [95% CI, 0.56 to 1.08]) (**Appendix E Table 3**). The absolute difference in detection was 16 fewer CIN3+ cases detected per 10,000 and 20 fewer CIN2+ cases detected per 10,000, although results were not statistically significantly different (**Appendix E Table 3**). The Kaiser Permanente Northern California single arm cohort study[120] using co-testing for cervical cancer screening reported similar absolute numbers of CIN3+ and CIN2+ detected as POBASCAM and NTCC Phase I, which suggests trial findings are likely applicable to at least some U.S.-based settings (**Appendix E Table 3**).

Variation by Test, Mode of Collection, and Screening Intervals

All included RCTs used DNA hrHPV testing, clinician-collected hrHPV, and cytology samples. No included studies directly compared different screening intervals. The interval between rounds one and two of screening in the co-testing trials ranged from 3 to 5 years, however the clinical heterogeneity across trials prohibits making any conclusions regarding the comparative effectiveness of different screening intervals.

Variation by Population

Only two included RCTs evaluating co-testing, ARTISTIC and NTCC Phase I, reported results by age, however different age bands were used (**Appendix E Table 4**).[85, 91] Similar to the primary hrHPV trials, co-testing RCTs demonstrated a higher detection of CIN3+ or CIN2+ in younger age bands (<30 or 35 years) compared to older age bands (30 or 35+ years). However, there was no evidence of effect modification by age (i.e., differences in relative detection between the co-testing arms versus the cytology arms across age strata [with 95% CI overlapping]). ARTISTIC (n=24,510) included women younger than the age of 25 years, however, results are not reported by ages 20-24 and 25-29 years.[85] Likewise, ARTISTIC does not report results separately for women aged 60+ years.

No comparative co-testing studies reported results by prior screening history, and RCTs were conducted in countries with cervical cancer screening programs. One non-comparative NRSI in the United States was conducted in a large managed care organization with organized cervical cancer screening.[120] Likewise, no comparative studies reported results by vaccination status and based on the dates of the studies and ages of participants (or cohort), we conclude that no individuals in the co-testing trials or NRSI were vaccinated for hrHPV. Additionally, no included studies reported results by SES, race or ethnicity, gender identity, and/or use of exogenous hormones.

KQ2. What Is the Test Accuracy and Uptake of Self-Collected hrHPV Samples?

Summary of Findings

We included 14 studies[122-129, 131, 133, 137, 139] that reported the agreement between self-collected vaginal and clinician-collected hrHPV samples (**Table 8**). We included three studies[130, 132, 138] that reported the agreement between urine and clinician-collected cervical HPV samples (low- and high-risk HPV). We identified six studies[86, 121, 124, 134-136] that reported the absolute or relative test accuracy of self-collected vaginal hrHPV samples to detect CIN2+ or CIN3+.

Positive and negative agreement between self-collected vaginal and clinician-collected cervical samples was high, with similar proportions screening positive. The pooled absolute sensitivity of self-collected samples to detect CIN2+ was 0.86 (95% CI, 0.78 to 0.93; I^2=80.3%) and the pooled absolute specificity was 0.81 (95% CI, 0.71 to 0.91; I^2=99.7%). The relative accuracy of self-collected vaginal samples to detect CIN2+ compared with the accuracy of clinician-collected samples was also high (relative sensitivity 0.94 to 0.99; relative specificity 0.98 to 1.02). Three studies reported high agreement between urine and clinician-collected HPV samples, albeit with two of the three studies reporting high test positivity. All but one test agreement study and all test accuracy studies used DNA-based assays. There was minimal information on variation in test agreement or accuracy by population characteristics; however, one study indicated that for women aged 30 years or older specificity was higher to detect low- and high-grade disease when compared with women aged 20 to 29 years.

We also included 42 primary hrHPV screening participation RCTs of self-collected vaginal hrHPV test (or choice of a self-collected hrHPV test) compared with usual care (i.e., clinician-collected cervical sample for hrHPV, cytology, or both). In the vast majority of trials (40 of 42 trials), offering self-collected vaginal hrHPV tests increased the proportion of participants completing cervical cancer screening; the absolute increase in screening uptake ranged from 2 to 63 percent. Despite some attrition of persons not returning for followup testing after a positive self-collected hrHPV test, self-sampling still increased full screening uptake when compared to clinician-collected screening. Effects appeared to be larger among nonresponders from traditionally underscreened groups, but these results could be confounded by study design and co-interventions. We did not find any consistent variation in uptake by other population characteristics (age, race/ethnicity, SES, screening history).

Test Agreement

Study Characteristics

We included 14 studies[122-129, 131, 133, 137, 139] that reported the agreement between self-collected vaginal hrHPV and clinician-collected hrHPV samples. We included three studies[130, 132, 138] that reported the agreement between urine HPV samples and clinician-collected cervical samples (**Tables 8-10**). Most of the studies recruited all participants eligible for screening (k=14); two studies[129, 133] recruited all participants eligible for screening from traditionally underscreened

groups, and one study[128] recruited only underscreened participants from a traditionally underscreened group. While most studies recruited populations described as women, one study[129] specifically recruited participants who were assigned a female sex at birth and who had a masculine spectrum gender identity. Five studies were conducted in the United States, and the other studies were conducted in Asia, Western Europe, and South America. The study sample size ranged from 35 to 5,318 participants, but most studies screened less than 900 women (k=15).

Studies recruited a wide range of ages, from as young as 18 years[130] to as old as 85 years.[138] Mean age was reported in 13 studies and ranged from 27 years to 50 years (**Tables 8 and 9**). Race or ethnicity was reported in only four studies, all of which were conducted in the United States. Two studies[129, 141] recruited primarily White participants (74.7% and 88.6%), one study[128] had larger proportions of Black (25.7%) and Hispanic participants (25.7%), and one study[126] recruited mostly Black participants (76.8%). Four studies[127-129, 137] reported previous screening history; one reported a median of 5 years since the last Pap test (range 4-20 years), two reported that 54 to 60 percent of women had their last Pap test within the previous 2 years, and one[137] reported 98 percent had ever had cervical cancer screening.

HPV Sample Characteristics

Fourteen studies had participants collect vaginal samples and three studies had participants collect urine samples (**Table 10**). Samples were usually collected in the clinic, but two studies[126, 141] had participants collect their own sample at home, and another study[131] offered the option of home or clinic collection. The brand name of the self-collected hrHPV kit was not always reported, but eleven studies reported either a name of the collection device (Eve Medical HerSwab, Home Smear Set, FLO-QSWab, Viba brush, Evalyn Brush, Vitroveil), or only the manufacturer of the collection device (QIAGEN, Digene). The HPV assays used to detect hrHPV in self-collected vaginal samples included Cobas, HC2, HPV Selfy, Aptima, Vitro HPV, and Roche Real-Time High-Risk HPV. Two of the assays used on urine samples—Anyplex II HPV28 and NuclisSENS easy MAG—included multiple low- as well as high-risk HPV genotypes (**Figure 17**). The third assay used on urine samples included only high-risk genotypes (PANA RealTyper).

The comparison hrHPV sample was from a cervical sample taken in a clinical setting by a trained clinician, such as a nurse practitioner, physician, or midwife. The clinician collected samples using a brush (k=10) or swab (k=4). The most common named brush was the Rovers Cervex-Brush (k=3) and the Cytobrush Plus (k=2). More often, the name and manufacturer of the collection device were not reported (k=8). In three studies[126, 130, 141] very minimal information was reported on the collection methods; these studies did not report the type of collection device used. Both the self-collected and clinician-collected samples were tested for hrHPV using the same HPV assay.

Risk of Bias

Sixteen of the test agreement studies were fair-quality and a single study was rated good-quality. The risk of bias for the fair-quality studies was primarily from possible introduction of selection bias and loss of participants from the analysis (**Appendix A Figure 4**).

Detailed Results

Overall, agreement between a self-collected vaginal sample and a clinician-collected cervical sample to detect hrHPV was high (k=14) (**Appendix E Table 5**). For individual studies, the proportion of participants testing positive for hrHPV was similar for both the self-collected and clinician-collected samples. There was substantial variation in test positivity, however, between studies. The percent testing positive via self-collected hrHPV samples ranged from 4.1 to 31.9, and the percent with a positive clinician-collected sample ranged from 5.0 to 27.7. The study[133] with the highest test positivity for both self- and clinician-collected samples recruited women from temporary residential programs. The pooled positive agreement was 0.87 (95% CI, 0.83 to 0.91; I^2=62.3%) and the pooled negative agreement was 0.96 (95% CI, 0.95 to 0.98; I^2=94.1%) (**Figure 18**). Positive agreement from individual studies ranged from 0.71[129] to 1.00[126] with eleven studies[122-127, 131, 133, 137] reporting positive agreement of 0.80 or higher. Negative agreement was high, with individual study estimates ranging from 0.88[133] to 1.00[137] and eleven studies[122-125, 127, 129, 131, 137, 139] reporting negative agreement of 0.95 or higher. Four studies[125, 126] additionally reported agreement between self- and clinician-collected samples for only hrHPV types 16 or 18. Positive and negative agreement for these hrHPV types was consistent with the agreement for all hrHPV types. The positive and negative agreement between self- and clinician-collected tests did not appear to vary by test positivity. Most studies compared a single round of screening, although one study[124] reported the agreement for two rounds of screening. There did not appear to be a difference in agreement between studies with one round of screening and the single study with two rounds.

Three studies[130, 132, 138] reported the agreement between urine and clinician-collected cervical samples (**Appendix E Table 5**). The test positivity was much higher for two of the studies, at 42.9 and 48.4 percent for urine samples and 50.0 and 55.6 percent for clinician-collected cervical samples. The high test positivity in one study[132] is likely due to the inclusion of low-risk HPV types. In the other study,[130] the high test positivity is not explained by the inclusion of low-risk HPV, but may be due to higher underlying prevalence of HPV in South America. The third study[138] was within the range of the studies examining self-collected vaginal samples with 12.4 percent test positive on both the urine test and clinician-collected cervical sample. Positive agreement for the detection of hrHPV in two studies ranged from 0.73 (95% CI, 0.54 to 0.86) to 0.83 (95% CI, 0.78 to 0.87) and negative agreement ranged from 0.95 (95% CI, 0.91 to 0.97) to 0.96 (95% CI, 0.92 to 0.98). For the detection of low-risk HPV and hrHPV, positive agreement was 0.82 (95% CI, 0.74 to 0.88) and negative agreement was 0.96 (95% CI, 0.91 to 0.98).

Variation by Population Characteristics

No studies reported variation in test agreement by population characteristics, such as age, race/ethnicity, SES, and vaccination status. Two studies, however, recruited participants from groups traditionally underscreened for cervical cancer: women from temporary residential programs[133] and trans masculine individuals with a cervix.[129] Additionally, one study[128] recruited low-income, underscreened women. All three of the studies recruiting those traditionally underscreened for cervical cancer reported positive and negative agreement consistent with the results of the other studies recruiting all individuals eligible for screening (i.e., overlapping 95% CIs). Notably, the study recruiting transmasculine individuals (n=131)[129] reported a positive agreement of 0.71 (95% CI, 0.48 to 0.89) and a negative agreement of 0.98 (95% CI, 0.94 to

1.00). These results are consistent with the overall findings for test agreement as the confidence intervals from this study overlapped with the confidence intervals of the pooled positive and negative agreement.

Variation by Test and Assay Characteristics

We identified no differences in test agreement due to test and assay characteristics. We were unable to determine if there was any variation in agreement due to the vaginal collection device. The collection methods were often sparsely reported (5 agreement studies reported no information on the collection device); when the collection device name was reported, the variation prohibited us from drawing any conclusions (8 different collection devices reported in 11 agreement studies). There did not appear to be any variation in test agreement by the HPV assay used, despite the inclusion of low-risk HPV types in one urine study.[132] Cobas (target-amplification DNA-based assay) and Hybrid Capture 2 (signal-amplification DNA-based assay) were the most common HPV assays and there was no statistically significant difference in the positive agreement between studies using those assays, at 0.88 (95% CI, 0.83 to 0.92) and 0.83 (95% CI, 0.74 to 0.92), respectively. Similarly, negative agreement was nearly identical between studies using Cobas and Hybrid Capture 2, at 0.97 (95% CI, 0.95 to 0.99) and 0.94 (95% CI, 0.94 to 0.99), respectively. We included only one study using Aptima, an mRNA-based assay; therefore, we were unable to determine differences in test agreement between mRNA- and DNA-based assays. However, the one study[128] using an mRNA assay had some of the lowest reported agreement values, with a positive agreement of 0.73 (95% CI, 0.52 to 0.87) and a negative agreement of 0.92 (95% CI, 0.87 to 0.95).

Test Accuracy

Study Characteristics

We identified six studies that reported the absolute or relative accuracy of self-collected hrHPV samples to detect CIN2+ or CIN3+: five of the six studies[86, 124, 134-136] reported the absolute accuracy to detect CIN2+ or CIN3+ and three of the six studies[86, 121, 124] reported the relative accuracy of self-collected hrHPV samples versus clinician-collected samples (**Table 11**). All six accuracy studies recruited any participants presenting for routine cervical cancer screening. One study was conducted in the United States, and the other five studies were conducted in Western Europe (k=4) or Central America (k=1). The study sample size ranged from 920 women to 487,015 women, but five of the studies screened fewer than 14,000 women.

Mean age was reported in five studies and ranged from 22 years to 46 years (**Table 11**). Four studies[124, 134-136] recruited participants as young as 18 or 20 years and four studies[86, 121, 124, 136] allowed participants aged up to 59-65 years. One study[135] taking place in Costa Rica recruited only women 18 to 25 years of age as part of an HPV vaccine trial. Only the study[134] conducted in the United States reported race and ethnicity, with predominantly White (73.8%), nonHispanic (95.8%) participants. One study[121] taking place in the Netherlands reported prior screening history. In this study, 69.4 to 92.3 percent of eligible women had attended a previous round of screening, with higher proportions of previous screening attendance for women who chose clinician-collected screening and the lowest proportions for women who opted for self-sampling.

HPV Sample Characteristics

All six studies had participants collect vaginal samples in the clinic (k=4) or at the participants' homes (k=2) (**Table 12**). Two studies reported that participants used the Evalyn Brush for their self-sample collection, one study reported the use of a cotton swab from the Digene kit; the four remaining studies did not report a kit or brush name. All studies used hrHPV DNA based assays, including HC2 (k=2), Cobas (k=2), GP5/6 (k=1), and SPF_{10}-DEIA/ $HPVLiPA_{25}$ (k=1).

There was substantial variation in the methods used to determine participants with the disease status of CIN2+ and CIN3+ (i.e., reference standard) (**Table 12**). While all studies referred women to colposcopy based on positive screening results, only two studies additionally referred a random sample of participants with negative screening results. Of these two studies, one[134] adjusted their accuracy for verification bias and the other study[136] determined that the three screening tests did not miss many cases and no adjustment was made. Two additional studies[86, 121] followed screen-positive participants for 14 to 17 months to determine if they had a relevant diagnosis and searched national registries if data were missing. Both of these studies made adjustments to the sensitivity and specificity to account for verification bias. The remaining two studies[124, 135] reported longer clinical followup, from 3 years to over 5 years.

Risk of Bias

All six of the test accuracy studies were fair quality. Risk of bias was primarily from possible introduction of selection bias, verification bias (as described above), and loss of participants from the analysis (**Appendix A Figure 4**).

Detailed Results

Five studies reported the accuracy of self-collected vaginal hrHPV samples to detect CIN2+; two studies also reported the accuracy to detect CIN3+ (**Appendix E Table 6**). The proportion screening positive varied widely, from 7.4 percent to 33.1 percent. The proportion of participants with CIN2+ was generally 3 percent or lower, but in one study[134]was as high as 7.8 percent. The pooled sensitivity of self-collected samples to detect CIN2+ was 0.86 (95% CI, 0.78 to 0.93; I^2=80.3%) and the pooled specificity was 0.81 (95% CI, 0.71 to 0.91; I^2=99.7%) (**Figure 19**). The high statistical heterogeneity is partly due to the high degree of precision around estimates from individual studies (particularly for specificity), as well as the heterogeneity of reference standards across studies. Individual estimates for sensitivity to detect CIN2+ ranged from 0.74 (95% CI, 0.66 to 0.81) to 0.93 (95% CI, 0.88 to 0.98) and individual estimates for specificity ranged from 0.69 (95% CI, 0.68 to 0.71) to 0.94 (95% CI, 0.94 to 0.95). The two studies that referred a random sample of screen-negative women to colposcopy reported sensitivity of 0.85 (95% CI, 0.76 to 0.94) and 0.81 (95% CI, 0.60 to 0.92) and specificity of 0.73 (95% CI, 0.67 to 0.79) and 0.82 (95% CI, 0.80 to 0.85). The study[135] with the lowest sensitivity and specificity estimated analyzed incident cases—only cases of CIN2+ that were identified more than 6 months after the participant self-collected their hrHPV test. The sensitivity of clinician-collected hrHPV ranged from 0.72 (95% CI, 0.64 to 0.80) to 1.0 (95% CI, 0.85 to 1.0) and the specificity ranged from 0.71 (95% CI, 0.70 to 0.72) to 0.94 (95% CI, 0.94 to 0.95) in four[86, 134-136] of the five studies reporting absolute accuracy for self-collected hrHPV samples.

Two studies reported the accuracy of self-collected vaginal hrHPV samples to detect CIN3+ (**Figure 19, Appendix E Table 6**). The proportion with CIN3+ detected in one round in these two studies was similar, at 1.0 and 1.8 percent. The individual estimates for sensitivity were both 0.95 with similar 95% confidence intervals (95% CI, 0.89 to 1.00 and 95% CI, 0.88 to 0.98). Individual estimates of specificity were 0.85 (95% CI, 0.84 to 0.86) and 0.94 (95% CI, 0.93 to 0.94). In one study,[86] the test performance of clinician-collected hrHPV samples was not statistically significantly different than that of self-collected hrHPV samples, with a sensitivity of 0.96 (95% CI, 0.91 to 1.0) and a specificity of 0.94 (95% CI, 0.93 to 0.94) to detect CIN3+.

One study[124] additionally reported the accuracy of detecting CIN2+ and CIN3+ for two rounds of screening as well as the accuracy of detecting only hrHPV types 16 and 18 (**Appendix E Table 6**). Two rounds of screening did not significantly change the sensitivity and resulted in no changes to specificity for the detection of CIN2+ and CIN3+. The sensitivity of hrHPV types 16/18 to detect CIN2+ and CIN3+ was lower than the sensitivity of all hrHPV types, (0.64 [95% CI, 0.53 to 0.74] to detect CIN3+).

Three studies[86, 121, 124] reported the relative accuracy of self-collected vaginal hrHPV samples to detect CIN2+ and CIN3+ versus a clinician-collected cervical sample (n=505,557) (**Appendix E Table 7**). In two studies, 7.4 percent of women screened positive via self-collected samples whereas 7.2 percent and 9.3 percent screened positive for hrHPV using a clinician-collected cervical sample. The third study screened women for two rounds. The cumulative test positivity was higher, at 16.8 percent for self-collected and 15.2 percent for clinician-collected hrHPV samples. For one round of screening, the proportion of participants diagnosed with CIN2+ was 1.5 percent and 1.7 percent and the proportion diagnosed with CIN3+ was 0.8 percent and 1.0 percent. For two rounds of screening,[124] the cumulative proportion of participants with CIN2+ was 4.0 percent and the proportion with CIN3+ was 2.2 percent. The relative sensitivity to detect CIN2+ ranged from 0.91 (95% CI, 0.88 to 0.96) to 0.97 (95% CI, 0.91 to 1.03); the relative specificity ranged from 0.98 (95% CI, 0.95 to 1.00) to 1.02 (95% CI, 1.01 to 1.02) (**Appendix E Table 7, Figure 20**). For the detection of CIN3+, the relative sensitivity ranged from 0.94 (95% CI, 0.90 to 0.97) to 0.99 (95% CI, 0.92 to 1.07) and the relative specificity ranged from 0.98 (95% CI, 0.97 to 0.98) to 1.02 (95% CI, 1.02 to 1.02) (**Appendix E Table 7, Figure 20**).

Variation by Population Characteristics

One study[136] (n=920) reported variation in accuracy by age. For both low-grade and high-grade disease (CIN 1 and CIN2/3+), specificity was higher for women aged 30 years or older versus those aged 20-29 years, while sensitivity was similar for both age groups. Variation by other population characteristics—such as race/ethnicity, SES, and vaccination—was not reported by any studies.

Variation by Test and Assay Characteristics

We were unable to determine if there was variation in test accuracy by test characteristics or the HPV assay used, due to the limited number of studies. However, all of the included studies used DNA-, as opposed to mRNA-based assays.

Uptake of Self-Collected hrHPV Screening

Study Characteristics

We included 42 trials[86, 142-181] randomizing participants to primary hrHPV screening using a self-collected vaginal hrHPV test (or offered the choice of a self-collected hrHPV test) compared to a usual care group (i.e., clinician collected cervical sample for hrHPV, cytology, or both). Most studies (k=36) recruited persons who were not up to date with cervical cancer screening recommendations (nonresponders) (**Figure 21, Table 13**). A subset of these studies (k=9) specifically recruited nonresponders from groups who are traditionally underscreened, based on characteristics such as SES, race/ethnicity, or immigration status. Two trials did not limit their recruitment to nonresponders but recruited all persons eligible for screening from traditionally underscreened groups. Five trials were conducted with population-based screening samples. Only eight trials took place in the United States (**Figure 22**) and seven of these U.S.-based trials recruited only nonresponders or those eligible for screening from traditionally underscreened groups. The other trials took place in Western Europe (k=31) or among indigenous populations in Australasia, New Zealand, and Canada (k=3).

Most trials did not report many characteristics of the participants recruited, often only reporting their age. Mean age was reported in 23 trials and ranged from 40 to 56 years. Participants eligible for screening were usually between 30 and 60 or 65 years of age, but nine trials included women under 30 years of age and 11 trials[142, 143, 148, 153, 161-165, 176, 177] recruited participants up to 70 years of age. The number of women randomized and meeting inclusion criteria varied widely, from a sample size of 48 participants in a pilot study[182] recruited from federally qualified heath centers in rural Pennsylvania to a study[157] with a sample of 35,354 participants who were not up to date with the cervical cancer screening program in Belgium. Thirteen trials had a randomized sample of over 10,000 participants.

Only 11 trials reported racial and ethnic groups for randomized participants (**Table 13**). Two studies from Australasia reported that 30-60 percent of participants identified as Maori, with one additionally reporting 35 percent Pacific and 35 percent Asian participants. A study[162] conducted in Canada recruited 100 percent First Nations participants. A study conducted in the United Kingdom reported 57 percent White, 17 percent Black, and 16 percent Asian participants. The remaining six studies were conducted in the United States and reported varying race/ethnicity. Two studies[152, 181] recruiting from the same care delivery system in Washington State enrolled primarily White participants (71% to 77%) followed by 10 to 13 percent Asian participants. One study in rural Pennsylvania recruited 83 percent non-Hispanic White participants.[182] One study[177] conducted in Minnesota recruited only Somali immigrants. Another study[156] recruited women specifically from three ethnic neighborhoods in Florida who identified as Hispanic (59%), Haitian (35%), or non-Haitian Black (6%). A study[166] conducted in Louisiana reported that 80 percent of their randomized participants were Black. The last U.S.-based study recruited underscreened women with a low-income background in North Carolina and reported that 46 percent of their participants were Black, 39 percent White, and 8 percent Latina/Hispanic.

Nineteen trials reported additional details regarding the screening history of the randomized participants (**Table 13**). There was a wide range in the proportion of women who had never been

screened or did not have screening results on record, from 3 to 78 percent (k=14). SES was not commonly reported, but lower SES appeared to be correlated with underscreening.

Intervention Characteristics

The majority of trials (k=33) had an intervention arm where women were directly mailed a self-collected vaginal hrHPV test to complete at home ("direct mail" arm). Nine trials had an intervention arm where women were given a choice to come to the clinic for usual cervical cancer screening procedures or offered a self-collected vaginal hrHPV test ("choice" arm). Six trials invited women to order or receive a self-collected vaginal hrHPV test ("opt-in" arm), four trials provided the self-collected test in person ("outreach" arm), and one trial invited participants to complete a self-collected test at the clinic ("clinic self-sample" arm).

The comparator arms were usual care clinic-based screening, through clinician-collected cytology, hrHPV, or both. There was some variation across trials in the level of outreach to participants in the comparator arm. The comparator arm often received a reminder to schedule a clinical appointment (k=15), although in some cases no intervention or reminder was offered by the study (k=6).

Risk of Bias

Eight trials[142, 143, 145, 152, 154, 156, 158, 164, 180] were rated as good-quality and the remainder were fair (**Appendix A Figure 4**). Since we were only interested in the outcome of uptake for these trials, the main source of bias was due to the randomization process. While most times the randomization procedures were adequate, in many cases we were unable to determine if the randomization process resulted in similar groups, since very few characteristics were reported in these trials. Many studies were also limited by post-randomization exclusions, as trials were designed to randomize participants to their intervention before contact was made. This may result in differences in patient characteristics between randomized arms.

Detailed Results

Uptake of Initial Screening

All eligible for screening. Five trials[86, 144, 147, 159, 181] taking place in Sweden (k=3), the Netherlands (k=1), and the US (k=1) recruited population-based samples of women eligible for cervical cancer screening (n=113,489). These trials all randomized women to a direct mail self-collected vaginal hrHPV test or usual care. One trial[181] additionally randomized women to an opt-in group, although screening uptake was lower in this arm when compared to a direct mail arm. From the arms randomized to the mailed self-collected test, 31.8 to 93.3 percent returned the test (**Figure 23, Appendix E Table 8**). In two trials, an additional 4.3 and 17.4 percent of the group randomized to the self-collected test were screened with usual clinical screening methods. In the usual care arm, 26.0 to 76.9 percent completed screening. In four of the trials, 8 to 22 percent more women completed screening through any method when mailed a self-administered hrHPV test when compared to usual screening procedures (**Figure 24**), but in one trial[144] a higher proportion of women were screened using usual clinic procedures when compared with a mailed self-collected hrHPV test (37.8% v. 47.5%). The authors suggested that the lower uptake

in the self-sample group may have been due to a reluctance to switch to a new screening method. The study also did not send any reminders to the self-sample group and the authors hypothesized that a reminder would have increased compliance. Two of the trials[147, 159] reporting higher uptake among the self-sample groups did send reminders as part of their intervention.

Nonresponders or traditionally underscreened. The majority of the included trials recruited all eligible women who were overdue for their cervical cancer screening (k=36); nine trials[143, 146, 148, 149, 156, 176, 177, 180] specifically recruited nonresponders from traditionally underscreened groups (**Figure 25, Appendix E Table 8**). For all studies, the proportion of participants completing screening in the direct mail self-sample intervention arm was consistently higher when compared to usual care, although completion rates varied widely, from 10.2 to 94.3 percent in the mailed self-collected test arms and from 1.7 to 92.7 percent in the usual care arm. The difference in proportion screened between mailed self-sample and usual care ranged from 2 to 63 percent. In nine studies[142, 143, 150, 154, 155, 157, 158, 160, 172] with more than one intervention arm, a direct mail self-collected test resulted in a higher proportion of women screened when compared with other interventions (e.g., opt-in or choice), with the exception of one study[155] in which offering the participant a choice of screening options resulted in higher screening completion than a direct mail self-collected test or usual care.

Two additional trials recruited all women eligible for screening, but from traditionally underscreened groups (**Figure 23**). One study[162] from Canada recruited participants from First Nations communities and used an outreach intervention. The second study[166] used a direct-mail intervention in the United States and recruited participants from medically underserved neighborhoods in New Orleans and from a breast and cervical cancer screening program providing screening for low-income, uninsured women. When compared to usual care, both the Canadian and U.S. trials reported greater uptake of the self-collected hrHPV test (an increase of 23% and 8%, respectively).

Variation by consent prior to randomization. Participation trials either randomized participants prior to consent (k=32) or after consent (k=10) to participate. Randomization after consent to participate may yield optimistic screening uptake. In stratified analyses, the nine trials that asked for their consent to participate before they were randomized generally demonstrated greater differences in screening uptake (range 2% to 63%), compared to the 32 trials with the preferred study design (range -6% to 29%) (**Appendix F Figure 4**).

Uptake of Full Screening

All eligible for screening. Five trials[86, 144, 147, 159, 166] recruiting all women eligible for screening reported the proportion of women with adherence to full screening (i.e., initial screening with confirmatory or reflexive testing) (**Appendix E Table 8**). Two trials[147, 159] required a second self-collected HPV test after the initial test was positive and the other three trials[86, 144, 166] asked participants to followup with clinician-collected samples for HPV and/or cytology. Full screening uptake was very high for the four trials[86, 144, 147, 159] that recruited all women eligible for screening from general population samples. Of the women who completed their initial self-collection, the proportion who adhered to full screening ranged from 95.4 to 99.8 percent of women (**Figure 26**). The difference between the intervention and control groups in full screening

uptake ranged from 8 to 16 percent more uptake for the intervention group in three trials and 11 percent less uptake for the intervention arm in one trial.[144]

Four trials recruiting all women eligible for screening[86, 144, 147, 159] reported the proportion of women completing followup testing after a positive self-administered hrHPV test. Uptake of followup testing after a positive self-collected hrHPV test was high for all four trials, ranging from 88.6 to 97.7 percent (**Figure 27**).

One U.S.-based trial[166] recruited all women eligible for screening, but from a traditionally underscreened group, reported much lower uptake of full screening (70.8%) and no difference in full screening uptake between groups. This trial, previously described, recruited low-income, uninsured women from medically underserved neighborhoods in New Orleans. Regardless of the results from the self-collected hrHPV test, women in this trial were asked to return to the clinic for clinician-collected co-testing.

Nonresponders. Twenty-six trials[143, 145-147, 149, 150, 152-154, 157, 161, 163, 164, 167, 169-176, 178-181] reported to the uptake of full screening (**Appendix E Table 8**). Five of these trials[143, 146, 149, 176, 180] recruited women who were nonresponders from traditionally underscreened groups. After a positive self-collected HPV test, women were typically asked to attend a clinic appointment for clinician collected Pap and HPV testing. Less often, women with positive self-collected HPV tests were referred directly to colposcopy (6 trials[143, 149, 153, 161, 170, 172]). Uptake of full screening was generally high, ranging from 95.3% to 100% in the 21 trials that recruited nonresponders from the general population (**Figure 26**). The difference in full screening uptake ranged from 5 to 27 percent more for the intervention group in 19 trials and 3 percent less uptake in the intervention group in one trial.[161] For the five trials recruiting nonresponders from tradtitionally underscreened groups, full screening uptake ranged from 74.8 to 100.0 percent; the difference in full screening uptake ranged from 3 to 35 percent more uptake in the intervention compared with the control group. The trial[146] with the lowest screening uptake (74.8%) recruited participants with socioeconomic difficulties—most often newly arrived migrants (73% of participants were undocumented). However, this study reported 32 percent more uptake of full screening in the intervention group compared with the control.

Twenty-four trials[142, 143, 145, 146, 149, 150, 152, 153, 157, 161, 163, 164, 167, 169-176, 178, 179] reported the proportion of women completing followup testing after a positive self-administered hrHPV test. Four of these trials[143, 146, 149, 176] recruited women who were nonresponders from traditionally underscreened groups. Uptake of followup testing among those with a positive self-administered hrHPV test ranged from 59.4 percent to 100.00 percent in the 20 trials that recruited nonresponders from the general population (**Figure 27**). For the four trials recruiting nonresponders from traditionally underscreened groups, uptake of followup testing had a wider range, from 29.2 percent to 100 percent. The variation was not consistently explained by the stage of randomization, population recruited, or the intervention delivered; but these factors likely all contribute to the observed variation.

Variation by Population Characteristics

We found variation in self-sampling participation by age, SES, screening history, and race/ethnicity. Age was examined most often (k=16), but findings showed either similar

participation in self-sampling for all age groups,[145, 146, 167, 173, 175, 180, 189] higher participation for younger women,[158, 164, 168, 170] or higher participation for older women.[144, 151, 157, 163, 176] Participation rates in the self-collected group did not vary by SES in six studies.[146, 151, 164, 167, 180, 189] There was no consistent relationship between screening history and participation in self-collected hrHPV samples among nine studies that examined screening history subgroups. [145, 151, 158, 164, 167, 170, 173, 180, 189] Four trials reported participation rates stratified by race or ethnicity with mixed findings.[145, 148, 180, 189] One study[148] reported higher participation among Maori women in the study versus non-Maori women, another[145] reported higher rates of self-sampling among White and Black participants compared with Asian and Other/multiple race. The third[180] and fourth[189] studies both reported no differences by race/ethnicity.

Despite no consistent patterns seen across included studies, one large RCT (n=19,734) conducted in the United States among nonresponders demonstrated effect modification by screening history.[152, 189] The RR for screening uptake was 2.78 for cytology 10 years prior, 1.69 to 1.86 for cytology 5 to 10 years prior, and 1.29 to 1.37 for cytology less than 5 years prior (p for interaction 0.005 for all comparisons). However, the absolute differences varied little by screening history (8.1% for cytology 10 years prior, 9.0 to 11.0% 5 to 10 years prior, and 7.8 to 10.6% for cytology less than 5 years prior). Analyses by age, race, ethnicity, and SES indicated no statistically significant modification of the relative or absolute intervention effects.

KQ3. What Are the Comparative Harms of Different Cervical Cancer Screening Strategies?

Summary of Findings

In total, we identified 13 fair- to good-quality comparative studies with concurrent controls comparing hrHPV screening strategies (i.e., primary hrHPV screening versus cytology and co-testing versus cytology) that reported burden of testing or harms of screening, and one fair quality NRSI comparing catch up screening using primary hrHPV screening versus usual care in women aged 65 to 69 years old. Studies were generally limited to a single round of screening and no studies directly compared primary hrHPV screening versus co-testing. Studies varied in protocols to followup abnormal screening and generally differed from current recommended clinical practice in the United States. Studies were all conducted in countries with organized cervical cancer screening programs with relatively low incidence of ICC and the overall number of missed cancers in either arm was very low. None of these studies reported downstream harms of testing or treatment of cervical lesions. Additionally, we found no comparative studies with concurrent controls explicitly evaluating overdetection (i.e., CIN lesions that do not progress to cancer).

All of the primary hrHPV screening strategies resulted in an increased risk of positive tests compared to the cytology arm (RR 1.10 [95% CI, 1.02 to 1.19] to 2.99 [95% CI, 2.74 to 3.26]). In six studies, primary hrHPV screening was associated with at least a 23 percent increase in colposcopy compared with cytology (RR 1.23 [95% CI, 1.16 to 1.31] to 3.05 [95% CI, 2.75 to 3.38]). The absolute difference in the proportion of screened individuals referred to or receiving colposcopy between arms ranged from 0.1 to 5.1 percent. One longer-term observational follow-

up study of a primary hrHPV trial demonstrated that colposcopy referral rates decreased after initial rounds of primary hrHPV screening. One NRSI (n=44,579) evaluating a single round of catch up screening in women aged 65 to 69 years demonstrated no significant difference in the number of colposcopies per CIN2+ detected using primary hrHPV with cytology triage versus usual care (11.6 [95% CI, 0.85, 15.8] versus 10.1 [95% CI, 5.4, 18.8], respectively). In seven studies (n=616,796), the pooled estimate for the relative increase in FPR in the primary hrHPV screening arm versus the cytology arm was 2.20 (95% CI, 1.51 to 3.21; I^2=99.6%). The absolute difference in FPR between the two arms ranged from 0.4 to 5.6 percent. In two studies (n=161,228) with lower test positivity, a lower use of colposcopies, and/or lower FPR was likely due to a more conservative protocol, in which a higher-grade cytology threshold was used to refer to colposcopy.

Likewise, three RCTs (n=109,789) evaluating co-testing resulted in an increased risk of positive tests compared to the cytology arm. In two trials (n=69,684), co-testing increased colposcopies compared with cytology (RR 1.30 [95% CI, 1.15 to 1.46] and RR 3.31 [95% CI, 3.06 to 3.59]). The absolute difference in colposcopies between arms was 1.6 and 7.6 percent. In three trials (n=107,560), the pooled estimate for the relative increase in FPR in the co-testing arm versus the cytology arm was 2.46 (95% CI, 1.70 to 3.57). The absolute difference in FPR between the two arms ranged from 3.3 to 9.0 percent.

Only two studies reported distress, anxiety, or depression outcomes. Both studies (n=3,481) demonstrated no difference in distress, anxiety, or depression between hrHPV-based (primary hrHPV or co-testing) compared to cytology-based screening at 2 weeks or 4 to 24 months.

Based on one RCT (n=13,925), there is no difference in FPR between self- and clinician-collected hrHPV samples used in primary hrHPV screening. Test positivity, colposcopies and FPR for primary hrHPV screening and co-testing were higher in participants aged 30 or 35 years or younger compared to those aged 30 or 35 years or older. Additionally, three primary hrHPV RCTs and one co-testing RCT demonstrate a greater difference in colposcopies and/or FPR in younger compared to older age bands. From included studies, we are unable to make any conclusions on differences in harms based on screening intervals or by participant characteristics other than age.

Description of Included Studies

In total, we included 11 fair-to-good quality population-based RCTs,[83-92, 115, 116] two fair-quality[116, 117] and one good-quality[115] comparative NRSIs from countries with cervical cancer screening programs, and one study[183] reporting longer-term observational followup from an included RCT (**Table 3**). Seven RCTs,[83, 84, 86-89, 91] three NRSIs,[115-117] and one longer-term observational followup of an included RCT[183] evaluated primary hrHPV screening; four RCTs evaluated co-testing versus cytology.[85, 90-92] In addition, we included two subsamples from included RCTs that specifically evaluated potential psychological harms between hrHPV- versus cytology-based screenings.[83, 114] One study[83] evaluated primary hrHPV screening, and the other study evaluated co-testing.[114]

All comparative RCTs and NRSIs were included for KQ1. Therefore, their study characteristics and risk of bias have been previously described (see **KQ1 Study Characteristics**). One NRSI was a longer-term observational study using data from the FOCAL-DECADE cohort, a longitudinal study of participants from the HPV FOCAL RCT.[183] This study compared colposcopy referral rates of trial participants who received one to two rounds of hrHPV-based screening followed by cytology-based screening every two to three years (n=15,744) compared to a contemporary cohort from a screening registry who were trial eligible but did not participate in HPV FOCAL (n=1,140,745) and thus screened with conventional cytology alone.

Primary hrHPV

Trial Screening Strategies

Trial screening strategies among studies included for KQ3 varied in their approach. Three of the included RCTs compared hrHPV versus cytology alone: COMPASS (n=4995),[88] Leinonen 2012 (n=132,194),[89] and NTCC Phase II (n=49,196).[91] Three trials compared hrHPV versus cytology with hrHPV triage if cytology was abnormal: Nygard 2022[83] (n=157,447), Elfstrom 2021 (n=201,038),[84] and HPV FOCAL (n=18,948).[87] One NRSI[116] compared hrHPV versus cytology alone (n=33,375), whereas the other included NRSI[115] (n=40,048) compared hrHPV versus cytology with hrHPV triage if cytology was abnormal. And one trial (n=13,925) compared self-collected hrHPV versus clinician-collected hrHPV, both arms with LBC triage.[86]

Trial Screening Protocols

Protocols following a positive hrHPV test varied widely and generally differed from current recommended clinical practice in the United States (**Table 4**). Protocols ranged from direct referral to colposcopy if hrHPV-positive (NTCC Phase II), to direct referral to colposcopy if hrHPV 16 or 18 positive and other hrHPV type positive with abnormal cytology (COMPASS, HPV SCREEN DENMARK) or dual stain (COMPASS), to referral to colposcopy only if reflex cytology abnormal. Typically, abnormal cytology was defined as ASC-US or higher-grade cytology; however, the two Finnish studies by Leinonen and colleagues[89] and Veijalainen and colleagues[116] used a LSIL or higher-grade cytology threshold. Testing protocols for following abnormal cytology in the comparison arm could include reflex hrHPV, requiring either abnormal cytology (e.g., ASC-US or higher-grade cytology) and abnormal hrHPV testing or higher-grade cytology alone (e.g., LSIL or higher-grade cytology) for referral to colposcopy. In some of the participating centers in NTCC Phase II, persons with ASC-US or higher-grade cytology were referred to colposcopy.

Only NTCC Phase II[91] and HPV FOCAL[87] had two rounds of screening, and the second round of screening was an exit round in which both arms received the same screening strategy (i.e., cytology only and co-testing, respectively) in order to examine the effect of the initial randomized screening strategy. The exit round (round 2) was at 2 years (HPV FOCAL) and 3.5 years (NTCC Phase II) after the first round.

We also included an additional publication[184] reporting comparative psychological harms from the Norwegian implementation RCT by Nygard and colleagues.[83] In this substudy (n=2000), participants aged 34 to 69 years received a structured questionnaire 4 to 24 months after

receiving their cervical cancer screening results. This questionnaire included the Patient Health Questionnaire-4 (PHQ-4) to measure depression and anxiety. Fifty-one percent of questionnaires were returned, equivalent in both the co-testing and cytology arms.

Detailed Results for Primary hrHPV

To capture comparative harms between screening strategies, our review was broadly inclusive of harms of the screening test itself, screening inaccuracy (i.e., false positive and false negative results), overdetection of precursor lesions that may regress, and downstream harms from diagnostic procedures or treatment of cervical cancer lesions. However, no studies had adequate power to detect uncommon harms from subsequent diagnostic or treatment harms. And we did not identify any comparative studies that directly addressed overdetection of CIN lesions. For more detail on both of these issues, see the **Discussion**. Therefore, in this section we report burden of testing (i.e., test positivity, colposcopy referrals, and FPR), false negative rate (i.e., missed cancers), and psychological harms. Test positivity was defined as test findings that would lead to clinical action based on the study protocol (e.g., referral to colposcopy or more intensive followup). The false positive rate was defined as the proportion of individuals without detection of CIN2+ who had positive screening; the false negative rate was defined as the proportion of individuals with ICC who had negative screening. Psychological harms that were reported included potentially increased anxiety, depression, and distress, and potential decreases in sexual satisfaction. We did not identify any comparative studies of different screening strategies that reported labeling, stigma, partner discord, or quality of life. All results for primary hrHPV comparative studies were limited to a single round of screening.

Burden of Testing

Seven studies[83, 84, 87, 89, 91, 115, 116] (5 RCTs, 2 NRSIs) reported the proportion of participants with positive tests (n=627,905). All the primary hrHPV screening strategies resulted in an increased risk of positive tests compared to the cytology arm (RR 1.10 [95% CI, 1.02 to 1.19] to 2.99 [95% CI, 2.74 to 3.26]; range in absolute difference between IG and CG: 0.8 to 5.9%) (**Figure 28, Appendix E Table 1**). Being test-positive was defined as a test result that would lead to a clinical action, based on the trial protocol. Specifically, test findings that would lead to a clinical action, based on the study protocol, such as colposcopy or more intensive followup (e.g., retest in 6 months), were defined as test positive. Thus, in some trials, the test positivity rate in the intervention group was simply the rate of hrHPV test positivity, whereas in others it was the rate of hrHPV-positive plus abnormal cytology. Both the Finnish studies by Leinonen and colleagues[89] and by Veijalainen and colleagues[116] used a higher-grade cytology threshold, likely accounting for the lower test positivity in the hrHPV with cytology triage arms. Likewise, in eight studies[83, 84, 87-89, 91, 115, 116] (n=637,241), the referral or receipt of colposcopies ranged from 1.2 to 7.9 percent in the primary hrHPV arm. In six studies,[83, 84, 87, 91, 115, 116] primary hrHPV screening was statistically significantly associated with at least a 23 percent increase in colposcopy compared with cytology (RR 1.23 [95% CI, 1.16 to 1.31] to 3.05 [95% CI, 2.75 to 3.38]) (**Figure 28, Appendix E Table 1**). In two studies,[88, 89] the referral or receipt of colposcopy was not statistically significantly different between arms. In all eight studies, the absolute difference in colposcopies between arms ranged from 0.1 to 5.1 percent. One longer-term observational follow-up study of HPV FOCAL demonstrated that colposcopy referral rates between the trial arm that received two rounds of hrHPV-based screening (n=9540)[183] compared

to the non-trial participant group screened with cytology alone (n=1,140,745) at median of 14 years after the initial round of screening was higher, 6.2 percent versus 4.7 percent, respectively (RR 1.32 [95% CI, 1.22 to 1.42]) (**Appendix E Table 1**).

One additional NRSI (n=44,579)[117] evaluating catch up screening in women aged 65 to 69 years demonstrated no significant difference in the number of colposcopies per CIN3+ or CIN2+ detected from a single primary hrHPV with cytology triage versus usual care (i.e., opportunistic screening or case-finding). The number of colposcopies per CIN3+ was 19.6 (95% CI, 13.2 to 29.2) versus 15.8 (95% CI, 7.4 to 34.0), respectively. The number of colposcopies per CIN2+ was 11.6 (95% CI, 0.85 to 15.8) versus 10.1 (95% CI, 5.4 to 18.8), respectively (**Appendix E Table 1**).

We were able to calculate the FPR in seven studies (5 RCTs and 2 NRSIs).[83, 84, 87, 89, 91, 115, 116] The FPR was defined as the proportion of participants without CIN2+ who had positive screening findings, as CIN2+ lesions would necessitate treatment or active surveillance if detected. The pooled estimate for the relative increase in the FPR in the primary hrHPV screening arms versus the comparator cytology arms was 2.20 (95% CI, 1.51 to 3.21; I^2=99.6%) (**Figure 28, Appendix E Table 1**). The very high statistical heterogeneity is due to the precise estimates of FPR in each study and the two outlier Finnish studies,[89, 116] which employed a more conservative protocol for referral to colposcopy. The FPR in the primary hrHPV screening arm ranged from 4.8 to 7.9 percent (**Figure 28, Appendix E Table 1**). The absolute difference in FPR between the two arms ranged from 0.4 to 5.6 percent.

One RCT,[86] the IMPROVE study (n=13,925), comparing self- versus clinician-collected hrHPV with LBC triage, found no differences in FPR between the two different collection methods (**Appendix E Table 1**).

Missed Cancers

We were able to calculate the false negative rate in five studies (3 RCTs and 2 NRSIs).[83, 86, 89, 115, 116] The FNR was defined as the proportion of participants with ICC at the first round of screening who had negative screening findings. The FNR in the intervention group ranged from 0 to 29.4 percent and in the comparison group, from 0 to 22.2 percent (**Appendix E Table 1**). Due to the rarity of missed ICC, as well as low number of overall ICC in these trials, FNR estimates are very imprecise. Only three studies reported that the screening strategies missed cancers (**Appendix E Table 1**).[83, 89, 115] In these three studies, the total number of missed cancers ranged from two to 11 cancers. There were no statistically significant differences in missed cancers between the primary hrHPV screening and cytology arms, as the 95% CI for the risk difference between the two arms included zero. All results were limited to a single round of screening.

Psychological Harms

One study[184] (n=2000) using a subsample of participants from the Norwegian trial by Nygard and colleagues[83] found no differences in self-reported measures of depression and anxiety between participants who received primary hrHPV with cytology triage versus cytology with hrHPV triage screening 4 to 24 months after receiving their test results (**Appendix E Table 9**).

Variation by Test, Mode of Collection, or Screening Intervals

Due to the heterogeneity of tests and protocols evaluated, we are unable to draw any conclusions regarding comparative harms by the different assays used. In one RCT evaluating self- versus clinician-collected hrHPV samples, there does not appear to be any difference in test positivity or FPR between the two collection methods.[86] Harms reported were primarily limited to a single round of screening, with only two primary hrHPV trials including more than one round of screening. As noted in KQ1, only HPV FOCAL[87] directly compared different screening intervals and the findings of the comparison of different screening intervals have not yet been published.

Variation by Population

Studies used different age bands, reporting 5- to 10-year bands with different cut-offs (**Appendix E Table 2**). Three RCTs evaluating primary hrHPV screening demonstrated higher hrHPV test positivity at round one in younger age bands (<34/35 years) compared to older age bands (34/35+ years), consistent with epidemiology and distribution of hrHPV by age. Three trials[88, 89, 91] reported higher referral or receipt of colposcopy in younger age bands (<34/35 years) compared to older age bands (34/35+ years). Two of these trials[89, 91] also reported a greater difference in colposcopy between the primary hrHPV versus cytology arms in the younger compared to older age bands. The third trial—COMPASS[88]—did not show a difference, but this could be due to it being smaller in size and underpowered. Three trials also showed a higher FPR in younger age bands (<34/35 years) compared to older age bands (34/35+ years).[84, 86, 91] Two of these trials also reported greater differences in FPR between the primary hrHPV versus cytology arms, in younger compared to older age bands.[84, 91]

The IMPROVE study[86] (n=13,925) comparing self-collected hrHPV versus clinician collected-hrHPV also reported higher test positivity in younger age bands (age 29-33 and 34-38 years) compared to older age bands (age 39-43, 44-48, 49-53, 54-58, and 59-61 years), but no appreciable differences in test positivity between the two different test collection methods in any of the age bands were found (**Appendix E Table 2**).

As noted in KQ1, no studies included women aged younger than 25 years. Restrictive age inclusion criteria, age bands reported, and few older women in the RCTs and NRSIs limit any conclusions specific to women aged 60 years or older. Additionally, no studies reported results by prior screening history, vaccination status, SES, race or ethnicity, gender identity and/or use of exogenous hormones.

Co-Testing

Trial Screening Strategies

All four co-testing trials evaluating hrHPV and cytology versus cytology alone reported harms (**Table 6**): POBASCAM (n=42,105),[92] ARTISTIC (n=24,510),[85] Swedescreen (n=12,527),[92] and NTCC Phase I (n=45,174).[91]

Trial Screening Protocols

Protocols for following abnormal co-testing varied widely. Thresholds for direct referral to colposcopy ranged from hrHPV-positive and 35 years or older, two sequential hrHPV-positive results (repeat test at 1 or 2 years), to LSIL or higher-grade cytology regardless of hrHPV results. The cytology threshold for direct referral to colposcopy also varied across trials, however the cytology threshold in the comparison arm was the same as the co-testing arm. In those trials with higher-grade cytology thresholds, repeat testing was at 6 to 12 months for cytology not meeting the threshold for direct referral to colposcopy (**Table 6**). Only ARTISTIC[85] had three rounds of screening, and the third round was an exit round in which both arms received the same screening strategy (i.e., cytology only). The other three trials[90-92] had two rounds of screening, in which the second round was the exit round where both arms received the same screening strategy. The interval between screening rounds ranged from 3 to 5 years.

We also included an additional publication[114] reporting comparative psychological harms from the co-testing trial ARTISTIC.[85] In this substudy (n=3582), women aged 20 to 64 years received questionnaires approximately 2 weeks after receiving their cervical cancer screening results. Questionnaires included the General Health Questionnaire (GHQ-28) to measure psychological distress, the Sexual Rating Scale (SRS) to measure sexual satisfaction, and the Spielberger State-Trait Anxiety Inventory (STAI) to measure anxiety. Seventy percent of questionnaires were returned, equivalent in both the co-testing and cytology arms.

Detailed Results for Co-Testing

Burden of Testing

Three of the four co-testing trials reported the percentage of participants screening positive in both arms. Similar to findings from trials of primary hrHPV screening, co-testing was associated with an increased risk of positive tests compared to the cytology arm (RR 1.70 [95% CI, 1.59 to 1.83] to RR 3.27 [95% CI, 3.04 to 3.53]) (**Figure 29, Appendix E Table 3**). Being test-positive was defined as a test result that would lead to a clinical action, based on the trial protocol. Only two trials, ARTISTIC[85] and NTCC Phase I,[91] reported referral to or receipt of colposcopy, with referral to colposcopy found to be higher in the co-testing versus cytology arms (RR 1.30 [95% CI, 1.15 to 1.46] and RR 3.31 [95% CI, 3.06 to 3.59]) (**Figure 29, Appendix E Table 3**). NTCC Phase I had more than a three-fold increase in colposcopies due to a low threshold for referral (i.e., participants 35 years or older and hrHPV-positive or participants with ASC-US or higher-grade cytology) (**Figure 29, Appendix E Table 3**). The referral to or the receipt of colposcopy was 6.8 percent (ARTISTIC) and 10.9 percent (NTCC Phase I) with the absolute difference in colposcopies between arms being 1.6 percent (ARTISTIC) and 7.6 percent (NTCC Phase I) (**Figure 29, Appendix E Table 3**).

We were able to calculate the FPR for three RCTs (**Figure 29, Appendix E Table 3**).[85, 91, 92] The FPR was defined as the proportion of participants without CIN2+ who had positive screening findings, as CIN2+ lesions would necessitate treatment or active surveillance if detected. The pooled estimate for the relative increase in the FPR in the co-testing arm versus the comparator cytology arm at round one was RR 2.46 (95% CI, 1.70 to 3.57; I^2=98.2%) (**Figure 29**). The very high statistical heterogeneity is due to the precise estimates of FPR in each trial, as well as

NTCC Phase I having a larger difference in FPR between the two arms, again likely due to the more liberal protocol for referral to colposcopy. The absolute difference in FPR between the two arms ranged from 3.3 to 9.0 percent.

Missed Cancers

While three co-testing trials reported the number of missed cancers, only two reported that the screening strategies did not detect all cancers (**Appendix E Table 3**). There were only three missed cancers in both POBASCAM[92] and Swedescreen[92] combined, and these were limited to the cytology arms. The risk difference of missed cancers between arms was not statistically significant.

Psychological Harms

One study[114] (n=2,473) using a subsample of participants from the ARTISTIC trial[85] found no differences in self-reported measures of distress or anxiety between participants who received co-testing versus cytology screening approximately 2 weeks after receiving their test results (**Appendix E Table 10**). Participants in the co-testing arm did report a lower sexual satisfaction than women in the cytology arm; however, the mean adjusted difference between the two groups was -2.40 (95% CI, -4.70 to -0.09) on a 100-point scale.

Variation by Test, Mode of Collection, and Screening Intervals

Due to the heterogeneity of tests and protocols evaluated, we are unable to draw any conclusions regarding comparative harms by the different assays or intervals used. All included studies for KQ3 evaluated clinician collected samples.

Variation by Population

Only two included RCTs evaluating co-testing, ARTISTIC and NTCC Phase I,[85, 91] reported results by age, however they used different age bands (**Appendix E Table 4**). These trials demonstrated higher test positivity with co-testing in younger age bands (<30 or 35 years) compared to older age bands (30 or 35+ years). Only NTCC Phase I reported colposcopy referral and FPR by age. Referrals to colposcopy were similar in the younger age (<35 years) versus the older age band (35+ years); however, the FPR was notably higher in the younger versus older age band. Likewise, NTCC Phase I also reported greater differences in the FPR between co-testing and cytology arms in the younger compared to older age bands.

As noted in KQ1, results were not stratified for participants aged 20 to 24 years versus 25+ years. Restrictive age inclusion criteria, age bands reported, and few older women in the trials limit any conclusions specific to women age 60+ years. No studies reported results by prior screening history, vaccination status, SES, race or ethnicity, gender identity and/or use of exogenous hormones.

Chapter 4. Discussion

To support the USPSTF in updating its 2018 recommendation, we focused on evidence addressing the comparative benefits and harms of hrHPV based screening strategies, as well as the test accuracy and uptake of self-collected hrHPV samples compared to clinician-collected hrHPV samples. Given the evolution of evidence-based cervical cancer screening recommendations and current clinical practice, we considered the evidence base for cytology-based screening (including its effectiveness, harms, and test accuracy) and the evidence not to screen before age 21 years to be foundational, and therefore these two issues are not addressed in our review.

Since the 2018 USPSTF recommendation, there have been six new comparative studies of primary hrHPV screening with or without cytology triage versus cytology with or without hrHPV screening, one new study of primary hrHPV catch-up screening in women age 65 to 69 years, no new comparative studies evaluating co-testing strategies, and no studies evaluating primary hrHPV versus co-testing screening strategies. New in this review, we also systematically reviewed the evidence for test accuracy (20 studies) and uptake (41 RCTs) of self-collected hrHPV sampling.

Summary of Included and Other Relevant Evidence

Comparative Benefits (KQ1) and Harms (KQ3) of Primary hrHPV and Co-Testing Screening Strategies

Given the rarity of morbidity and mortality from ICC, we relied on the detection of cancer and precancer, namely CIN3+, to capture the benefits of screening. While we reported on the detection of CIN2+ as a benefit as well, we recognize that many CIN2 lesions appear to regress[23] and therefore identification of CIN2 may also represent a potential harm due to overdetection and overtreatment. To capture potential harms, we primarily relied on the burden of testing (e.g., colposcopies, false positives) and false negatives, as we did not identify studies meeting our inclusion criteria reporting overdetection, overtreatment, and harms due to invasive procedures. We also reported comparative psychological harms, which were included in the systematic review to support the 2018 USPSTF recommendation.

Cancer and Precancer

Overall, we found insufficient evidence for primary hrHPV screening and low strength of evidence for co-testing strategies reducing ICC compared to cytology strategies, as most studies were limited to a single round of screening (**Table 14**). Additionally, pooled analyses for the detection of ICC at round one showed no difference between hrHPV-based versus cytology-based strategies, however, there was a high level of imprecision due to the low incidence of ICC in the trials. POBASCAM—the only trial to report ICC at a second round of screening (n=39,310)—showed a statistically significant reduction in ICC in the co-testing arm compared to the cytology arm at round two. A 2014 individual participant data meta-analyses (IPD MA) by Ronco and colleagues[190] of four European co-testing RCTs (Swedescreen, POBASCAM,

ARTISTIC, and NTCC Phase I) and one primary hrHPV RCT (NTCC Phase II) included a total of 176,464 women with 1,214,415 person-years of followup; authors reported 107 cases of ICC in a median followup period of 6.5 years. In this IPD MA, ICC was found to be similar between hrHPV- versus cytology-based screening during the first 2.5 years of followup (rate ratio 0.79, [95% CI, 0.46 to 1.36]), but was significantly lower after 2.5 years (0.45 [95% CI, 0.25 to 0.81]). At 8 years of followup, the cumulative detection of ICC was 47 per 100,000 in the hrHPV-screened women compared with 94 per 100,000 women in the control groups (rate ratio 0.60 [95% CI, 0.40 to 0.89]). In a U.S.-based cohort study from Kaiser Permanente Northern California,[191] which did not meet our inclusion criteria, in 210,557 women screened with co-testing every 3 years from 2003/4 until 2012, ICC decreased from 20.4 to 9.6 per 100,000 women. There was no change noted in adenocarcinoma detected, remaining 4 to 5 per 100,000 women screened.

Despite the heterogeneity of protocols, screening intervals, and study designs across included studies, we found moderate strength of evidence that both primary hrHPV screening (6 RCTs, 2 NRSIs) and co-testing (4 RCTs) can detect more CIN3+ than cytology-based screening after a single round of screening and reduce CIN3+ at a subsequent round of screening (**Table 14**). In participants aged 25 to 64 years, the absolute difference ranged from two to 75 more CIN3+ cases detected per 10,000 in eight primary hrHPV screening studies. In two trials with a second round of screening, the absolute difference was seven and 32 fewer CIN3+ detected per 10,000 at the exit round. In participants aged 20 to 64 years, the absolute difference ranged from six fewer CIN3+ cases to 27 more CIN3+ cases detected per 10,000 in four co-testing trials. All four co-testing trials included a second or exit round of screening with an absolute difference ranging from three to 22 fewer CIN3+ cases per 10,000 at the second round.

We also found low strength of evidence from a single NRSI that one round of self- or clinician-collected primary hrHPV screening can detect more CIN3+ in women aged 65 to 69 years who were not up to date on cervical cancer screening (**Table 14**). The absolute difference between the catch-up primary hrHPV screening and usual care groups was 21 more CIN3+ cases detected per 10,000.

Burden of Testing

The increased detection of precancer with hrHPV-based strategies was at the expense of a greater burden of testing, however protocols for referral to colposcopy in included studies differed from recommended clinical practice in the United States (see Applicability and Implementation of Evidence: Protocol considerations). Nonetheless, we found moderate strength of evidence that both primary hrHPV screening (6 RCTs, 2 NRSIs) and co-testing (3 RCTs) results in up to a three-fold increase in test positivity and referral or receipt of colposcopy compared to cytology-based screening in a single round of screening (**Table 14**). The absolute difference in test positivity ranged from 0.8 to 9.1 percent; the difference in colposcopy ranged from 0.1 to 7.6 percent. However, based on longer-term observational follow-up, colposcopy referral rates for hrHPV-based screening decline after initial screening rounds. False positive rates, defined as the proportion of women without CIN2+ who had positive screening, were also over two-fold greater in hrHPV-based screening. The absolute difference in FPR ranged from 0.4 to 9.0 percent. More conservative protocols for referral to colposcopy (e.g., the use of a higher-grade cytology threshold in cytology triage of hrHPV-positive women) resulted in fewer colposcopies

and false positives compared with more permissive protocols (e.g., direct referral to colposcopy if hrHPV was positive) without apparent significant differences in CIN3+ detection.

In general, the burden of testing was higher in participants aged 30 or 35 years and younger compared to those aged 30 or 35 years and older. Additionally, three primary hrHPV RCTs and one co-testing RCT demonstrated larger differences in colposcopies and false positives in the younger versus older age grouping.

In the 2014 IPD meta-analysis by Ronco and colleagues mentioned above,[190] which obtained additional data from these co-testing trials, overall biopsy rates were similar in the co-testing and cytology arms. However, in NTCC Phase I and II, biopsy rates were twice as high in the hrHPV arm compared to cytology alone. In the hrHPV arm, hrHPV-positive women were referred directly to colposcopy without cytology triage, unlike the other trials. This IPD MA did not report colposcopy rates. Additionally, we did not identify RCT or non-randomized studies reporting colposcopy rates over multiple rounds of screening.

We found low strength of evidence from a single NRSI that catch up screening using self- or clinician-collected primary hrHPV testing versus usual care did not increase the number of colposcopies per CIN2+ detected in in women aged 65 to 69 years who were not up to date on cervical cancer screening (**Table 14**). The number of colposcopies needed to detect a case of CIN2+ in the primary hrHPV screening group was 11.6 (95% CI, 0.85 to 15.8).

Missed Cancers

The false-negative rate was defined as the proportion of women with ICC who had negative screening results. We found insufficient evidence to judge the comparative harms of FNR or missed cancers between screening strategies, as most studies were limited to a single round and the overall number of missed cancers in either arm, when reported, was very low (**Table 14**). The number of missed cancer cases ranged from 0 to 11 in both arms combined. Given the rarity of ICC, trials and even large NRSIs comparing strategies may be insufficient to inform the risk of missed cancers. In the 2014 IPD MA discussed previously,[190] rates of ICC after a negative test were lower in the pooled hrHPV arm (12 cases) compared to the cytology-only arm (35 cases) (RR, 0.30 [95% CI, 0.15 to 0.60]).

Approximately 5.5 to 11 percent of all cervical cancers are reported to be hrHPV-negative.[192, 193] However, this estimate includes both false negative and true negative results. False negative results due to insensitivity or specimen inadequacy can be mitigated by rescreening. True negative results can be due to tumors with loss of hrHPV expression or truly hrHPV-independent cancers. Most hrHPV independent cancers are thought to be cervical adenocarcinoma, which are often diagnosed at a later stage and have worse prognosis than SCC. For cervical adenocarcinoma, the hrHPV negativity rate is approximately 15 to 38 percent.[193] However, it is also important to note that cytology can miss adenocarcinomas and AIS, which at least in part explains the increase in both relative and absolute incidence of adenocarcinomas over time.[5] Adenocarcinoma and AIS can be localized deep in the endocervical canal and therefore more easily missed with usual cytology sampling. Older age and certain rare pathological types (i.e., gastric, clear cell, serious and mesonephric) have been associated with lower hrHPV positivity. hrHPV-negative cancers can also be other types of cancer (e.g., endometrial carcinoma)

misdiagnosed as primary cervical cancer.[193] However, regardless of the reasons, hrHPV negative cervical cancers have a worse prognosis that hrHPV positive cancers.[193] A 2023 meta-analysis found that across 36 studies (n=9,169 cancers)[192] patients with cervical cancer testing positive for hrHPV had 41 percent lower mortality compared with those testing negative for hrHPV and that positive hrHPV testing was more commonly associated with SCC histology, lower stage cancer or smaller tumor size.[192]

Psychological Harms

Based on two comparative studies (n=3,481), we found low strength of evidence that hrHPV-based screening does not incur greater anxiety or depression than cytology-based screening in the immediate (2 week) or longer term (up to 24 months) (**Table 14**). A 2021 systematic review by McBride and colleagues, not meeting our inclusion criteria, found that women testing hrHPV-positive regardless of cytology results had higher short-term (≤2 months) (6 studies) but not long-term (>2 months) (4 studies) anxiety than those with normal results.[194] This review also included 10 qualitative studies and found that women who were anxious often had a poor understanding of HPV, their results, or received their results by letter. Qualitative studies confirmed that anxiety regarding hrHPV results did not generally persist over time. And not surprisingly, this review found that women testing hrHPV-positive generally had greater psychological distress (general and sexual) compared to women with normal results in both the short- and longer-term (6 studies). Therefore, psychological distress may be magnified using screening strategies yielding greater false positive hrHPV testing.

Overdetection

We found no studies directly addressing overdetection of precancer that may not progress that met our inclusion criteria. One study by Loopik and colleagues,[195] excluded from our review due to the use of a historical comparator, compared overdetection (defined in the study as CIN1 or less severe histology) in the Dutch cervical cancer screening program before and after the implementation of primary hrHPV screening in 2017, which replaced cytology-based screening. Referral to colposcopy and overdetection increased by 70 and 143 percent respectively, following the implementation of primary hrHPV screening. Referral to colposcopy rose from 2.5 to 4.2 percent, and the cases of CIN1 or less severe histology rose from 61.1 to 148.7 cases per 10,000 screened. The protocol for referral to colposcopy for abnormal cytology was HSIL+ and co-testing at 6 months for ASC-US/LSIL; the protocol for abnormal hrHPV was referral to colposcopy if ASC-US+ and retesting at 6 months if cytology was normal. The rates of overtreatment, however, did not change post-implementation.

Diagnostic and Treatment Harms

The studies included in our review did not report harms of colposcopy. Colposcopy with biopsy can miss high-grade lesions and ICC.[196] Additional studies not meeting our inclusion criteria have found that the false negative rate of colposcopy, which can range from 13 to 69 percent, primarily depends on the expertise of the colposcopist and the number of biopsies taken. The procedural risks of colposcopy with biopsy are generally quite low but can include bleeding and infection. More commonly, individuals experience discomfort or pain during the procedure, and cramping from biopsies may persist for 24 hours.[196]

Our review did not address the harms due to the treatment of CIN2+ lesions. While treatment methods vary, excisional procedures (primarily loop electrosurgical excision procedure [LEEP]) are preferred over ablation in the United States. Major complications during cervical excision procedures are rare, but can include intraoperative bleeding, uterine perforation, postoperative bleeding, and infection.[197] Later complications include cervical stenosis, second-trimester pregnancy loss, and preterm birth.[198] A large population-based study conducted in Norway (n=545,243),[199] not included in our review, found that prior LEEP treatment of CIN was associated with a greater risk of pregnancy loss between 16 and 22 weeks (0.4% versus 0.2% in untreated women). Further, a Cochrane review,[200] not meeting our inclusion criteria, found that compared with untreated patients, treatment for CIN was associated with increased risk of preterm birth (RR 1.75 [95% CI, 1.57 to 1.96]), preterm premature rupture of membranes (RR 2.36 [95% CI, 1.76 to 3.17]), neonatal intensive care unit admission (RR 1.45 [95% CI, 1.16 to 1.18]), and perinatal mortality (RR 1.51 [95% CI, 1.13 to 2.03]), although the quality of evidence was low.

Self-Collected hrHPV Samples (KQ2)

In a new addition since the 2018 USPSTF recommendation, we reviewed the relative detection of precancer and cancer (KQ1), relative harms (KQ3), test agreement and accuracy and uptake of self-collected vaginal or urine hrHPV samples versus clinician-collected cervical hrHPV samples (KQ2).

Based on the IMPROVE RCT (n=13,925), we found low strength of evidence for no difference in benefits or burden of testing between self- versus clinician-collected primary hrHPV strategies in a single round of screening (**Table 14**). This trial found no differences in CIN3+ detection or false positives between self- versus clinician-collected primary hrHPV screening at a single round. However, this evidence for relative equivalence of the two collection methods is bolstered by the large evidence base and moderate strength of evidence that self-collected vaginal samples have adequate test agreement (14 studies) and test accuracy (5 studies) when compared to clinician-collected samples (**Table 14**). Positive and negative agreement using the same hrHPV assay between self-collected vaginal and clinician-collected cervical samples was high, with similar proportions screening positive. In three studies reporting the relative test accuracy between self- and clinician-collected hrHPV testing using DNA-based assays, the sensitivity may be slightly lower for the detection of both CIN2+ (0.91 [95% CI, 0.88 to 0.96] to 0.97 [95% CI, 0.91 to 1.03]) and CIN3+ (0.94 [95% CI, 0.90 to 0.97] to 0.99 [95% CI, 0.92 to 1.07]). However, the specificity was the same for either CIN2+ or CIN3+. In contrast, a 2022 systematic review by Arbyn and colleagues,[201] found the relative sensitivity between self- and clinician-collected hrHPV testing using an mRNA assay (Aptima) to detect CIN2+ was 0.84 [95% CI, 0.74 to 0.96]) and was 0.64 (95% CI, 0.43 to 0.93) for CIN3+. The relative specificity (0.96 [95% CI, 0.91 to 1.01]) was similar the relative specificity for DNA assays in our review. Another 2022 systematic review by Arbyn and colleagues also found that the overall test agreement between self- and clinician-collected hrHPV samples was higher for target amplification-based DNA (e.g., Cobas) compared to signal amplification-based DNA (e.g., HC2, Cervista) or mRNA (i.e., Aptima) assays.[202]

Based on three studies, we found low strength of evidence for adequate test agreement for urine hrHPV samples compared to clinician-collected cervical samples (**Table 14**). High test positivity in these studies may have been due to including low risk HPV genotypes and/or underlying prevalence of HPV in the population studied. High test positivity would lead to a greater burden of followup testing. However, we found no studies examining the test accuracy of urine compared to cervical hrHPV testing.

Last, we also found moderate strength of evidence that using self-collected hrHPV tests at home or offering patients a choice of collection methods increases uptake of primary hrHPV cervical cancer screening (**Table 14**). In 40 of the 42 trials, self-collected hrHPV testing increased the proportion of participants completing cervical cancer screening by 2 to 63 percent. Effects appeared to be larger in persons who were underscreened and from traditionally underscreened populations. Nonetheless, in four studies, self-collection testing resulted in increased uptake in unselected populations as well.

Applicability and Implementation of Evidence

Although there are many trials and well conducted comparative NRSIs evaluating hrHPV-based screening strategies versus cytology-based screening strategies, most of the comparative studies are limited to a single round of screening. Even in those with a second round of screening, most often the second round was an exit round using the same screening strategy in both arms, and therefore these do not provide insight into the differential effects (both positive and negative) of a program of screening using an hrHPV- versus cytology-based strategy. This is true, as well, for the single comparative trial on self-collected versus clinician-collected hrHPV samples, and participation trials evaluating the uptake of self-collected versus clinician-collected hrHPV based screening. Therefore, we have limited evidence on programs of screening. However, decision analyses can, in part, address this limited evidence on multiple rounds of screening, as well as help with understanding the balance between the relatively small differences in the absolute detection of CIN3+ and differences in the burden of testing for hrHPV-based versus cytology-based screening. This review is accompanied by collaborative microsimulation decision analyses by the CISNET Cervical Working Group.[75]

In addition to limitations of the primary evidence on the net benefit of a program of cervical cancer screening, there are several other considerations to take into account when applying this group's findings specifically to cervical cancer screening in the United States. Decision analyses can also be helpful in addressing some of the following considerations.

Population Considerations

None of the comparative studies that met our inclusion criteria for KQ1 were conducted in the United States, and all were conducted in countries with organized screening programs. We included one large noncomparative cohort study of co-testing every 3 years in Kaiser Permanente Northern California which had similar absolute numbers of CIN3+ detected compared to the included co-testing RCTs. The population in this study also had racial and ethnic diversity, representative of that region of the United States. However, even though this cohort study was conducted in the United States, it still took place in a setting with an organized

screening program. Two large single-arm cohort studies of primary hrHPV screening in the United States—the ATHENA study[204] (n=47,208) and the IMPACT trial[205] (n=34,807)—were also representative of the United States population at large, although were excluded from our review (**Appendix D**). In these two cohorts, the hrHPV test positivity was higher (12.6% and 15.1%, respectively) compared to NTCC Phase II (7.9%), despite both having a similar mean age of participants. In addition, the detection of CIN3+ was also higher in these two U.S.-based single-arm cohort studies (1.0% and 0.8%) compared to NTCC Phase II (0.4%). In one analysis using data from the National Breast and Cervical Cancer Early Detection Program and the Kaiser Permanente Northern California cohort, co-testing resulted in many more additional tests and colposcopies compared to primary hrHPV screening, particularly in setting with low prevalence of CIN3+ and among hrHPV negative individuals returning for repeat screening.[203]

Additionally, most of the comparative studies that met our inclusion criteria for KQ1, including all of the co-testing trials, were conducted among participants without prior HPV vaccination. Even in the few primary hrHPV trials that could have included participants with prior vaccination, only a small proportion of participants could have been fully vaccinated. Nonrandomized studies conducted in the United States,[204] Canada,[205] Scotland,[206] and Norway[207] have all reported a significant reduction in CIN2+ for women who received an HPV vaccination as adolescents or teenagers. A 2019 systematic review of over 60 million individuals across 14 high income countries demonstrated HPV vaccination programs have been associated with substantial decrease in hrHPV 16/18 infections and CIN2+ in women, regardless of individual receipt of vaccination after 5 to 8 years.[50] Therefore, the absolute number of precancer and cancer detected, as well as the burden of testing, will be lower in vaccinated individuals, as well as vaccine eligible cohorts. Additionally, the positive predictive value (PPV) of cytology for CIN2+ is lower in vaccinated individuals compared to unvaccinated individuals.[208, 209] Both the reduction in CIN2+ and lower PPV of cytology (increased risk of false positive) in vaccinated compared to unvaccinated individuals may warrant screening guidelines stratified by HPV vaccination status.

Studies addressing the accuracy of self-collected versus clinician-collected hrHPV samples for KQ2 generally did not report vaccination history. One study[124] conducted in the United Kingdom, however, reported that 66 percent of women 23 years of age or younger had been vaccinated with at least two doses of the bivalent HPV vaccine. Vaccination status could affect the sensitivity and specificity of hrHPV testing for precancer by altering the patient spectrum,[210] although it should not affect the relative test accuracy between self- and clinician-collected samples.

Lastly, studies addressing the uptake of self-collected versus clinician-collected hrHPV samples for KQ2 were generally from mailed self-collected samples in women who had not responded to prior cervical cancer screening invitations or were from traditionally underscreened populations. Only a few of these uptake studies were conducted in the United States.

hrHPV Assays and Collection Methods

The most commonly evaluated FDA-approved hrHPV assays in our included studies were HC2 and Cobas. Two overlapping systematic reviews in 2021 and 2022 by Arbyn and colleagues

examined the accuracy and relative accuracy of different hrHPV assays (**Appendix B, Contextual Question 1**).[201, 211] Based on these two reviews, Alinity m, Cervista, Cobas, and Onclarity assays all had similar accuracy to detect CIN2+ when compared to HC2 or GP5+/6+ PCR. However, Aptima (the only FDA-approved mRNA assay) had slightly higher specificity for the detection of CIN2+.[211] The sensitivity of Aptima to detect CIN2+ may be slightly lower, however, the relative sensitivity was not statistically significantly different. And the cross-sectional and longitudinal sensitivity of Aptima for the detection of CIN3+ was similar to other FDA-approved hrHPV assays.[201] Using a test with higher specificity with equivalent sensitivity would result in fewer colposcopies and false positives with equivalent detection of precancers.

Only the most recently FDA-approved hrHPV assays—Cobas, Onclarity, and Alinity m— have been approved for primary hrHPV testing, as opposed to approval for only co-testing or triage of cytology indications. Due to the lack of widespread availability of FDA-approved assays explicity approved for the indication of primary hrHPV testing, some remain concerned about the implementation of primary hrHPV screening in the United States. Additionally, Alinity m, Cobas, Aptima, and Cervista can do partial genotyping for hrHPV 16/18 (plus hrHPV 45 for Aptima and Alinity m), if desired. Although the clinical role of extended genotyping in cervical cancer screening is still being evaluated, Onclarity is the only FDA-approved test to individually identify and report genotype results beyond hrHPV 16/18 (**Appendix B, Contextual Question 2**).

Self-Collection

In test agreement and test accuracy studies (KQ2), self-collected hrHPV vaginal samples were either collected at the clinic or at home; however, the majority of studies had women self-collect samples at the clinic. Studies used different hrHPV assays, swabs, and storage methods. As of July 2024, the FDA has approved expanded indications for the self-collection of vaginal swabs in office for two hrHPV assays.[212-214] In the absence of FDA approval for specific indications, the lab running the hrHPV assay must validate the assay for self-collection (collection device and assay together) per the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations.

In participation trials (KQ2), women who screened positive for hrHPV on self-collection were often asked to obtain cytology with or without a second hrHPV sample, and thus required an in-clinic visit and pelvic exam. In some trials, women were referred directly to colposcopy. The adherence to followup triage testing was ranged widely in our included studies. Nonetheless, even accounting for the suboptimal uptake of subsequent triage testing, full screening uptake was still higher in the self-sampled compared to clinician-sampled arm.

Test agreement, test accuracy and adherence studies included participants who ranged widely in age, without any consistent observed differences of adherence by age. We did not hypothesize any differences in test accuracy by age, and only one accuracy study reported sensitivity and specificity by age.

Ages to Start/Stop and Switch to hrHPV Screening

Existing evidence-based guidelines differ on the optimal age to start screening: at age 21 or age 25 years (**Table 2**). In 2020, the ACS recommended that cervical cancer screening start at age 25 years.[215] This decision was in part due to the fact that the prevalence of hrHPV and precancer have dropped in women in their 20s due to HPV vaccination during childhood and adolescence, affecting the balance of benefits and harms in this age group. Several nonrandomized studies demonstrate lower risk of CIN2+ and hrHPV infection among vaccinated compared with unvaccinated individuals, particularly when vaccination occurs before the age of 15 years.[215] Epidemiologic studies demonstrate a declining trend in the detection of CIN2+ and hrHPV infection in young women during the period following the introduction of HPV vaccination. Additionally, from 2012 to 2016, rates of new cervical cancer cases among women aged 20 to 24 years were much lower than rates among women aged 25 to 29 years (0.8% versus 4% of all new cases, respectively).[215] A study by Gage and colleagues[216] using data from the New Mexico HPV Pap Registry from 2007 to 2011 (n=456,519) and Kaiser Permanente Northern California cohorts from 2003 to 2013 (n=1,313,128) examined the longitudinal risk of CIN3+. They found that for women aged 21 to 24 years, the 5-year risk for CIN3+ was 1.98 percent (95% CI, 1.83 to 2.14) in the New Mexico cohort and 0.69 percent (95% CI, 0.62 to 0.76) in the Kaiser Permanente Northern California cohort. For women aged 25 to 29 years, the 5-year risk was 1.70 percent (95% CI, 1.58 to 1.84) and 1.23 percent (95% CI, 1.09 to 1.39), respectively. Last, none of the primary hrHPV comparative screening studies included women younger than 25 years.

Guidelines differ about the age at which hrHPV-based screening should be considered as an alternative to cytology (**Table 2**). Due to the high prevalence of transient hrHPV infections in women younger than the age of 30 years that are likely to resolve spontaneously,[217] the USPSTF recommended hrHPV-based screening strategies with longer intervals of screening starting at age 30 years. Consistent with the distribution of hrHPV infections (**Figure 4**), hrHPV test positivity was greater in women younger than 30 or 35 years, compared with women 30 or 35 years and older. Comparative screening studies demonstrate higher detection of CIN3+ in younger women compared to older women. The burden of testing as measured by colposcopies or FPR was also higher in younger versus older women using hrHPV screening strategies compared with cytology-based strategies; and the difference in the burden of testing between screening strategies was greater in younger women versus older women. However, included studies were comprised overwhelmingly, and sometimes exclusively, of unvaccinated women.

Guidelines agree on stopping cervical cancer screening in women with adequate prior screening, which ASCCP defines as three consecutive negative cytology results or two consecutive negative co-testing results within 10 years before stopping screening, with the most recent test occurring within 5 years. However, subgroup analyses from one large RCT, Nygard 2022, demonstrated that a single round of primary hrHPV screening resulted in an increased detection of precancer and a trend for increased detection of ICC compared to cytology-based screening, in participants aged 65 to 69 years. Furthermore, in the absence of organized screening programs, assessment of screening history relies on the clinician's ability to determine adequacy of screening which can be complicated by disjointed medical records, changing screening guidelines over time, and patients who may be unaware of their own screening history.[218] Based on national employer insurance administrative data from women enrolled between 2016 and 2018, approximately two-

thirds of women aged 64 to 66 years failed to qualify for exiting screening or did not have adequate data to determine adequacy of prior screening.[219] The included comparative NRSI in Denmark demonstrated a benefit in CIN3+, and possibly ICC, detection using self- or clinician-collected primary hrHPV screening in women age 65 to 69 years old who had no record of cytology or screening invitation in the preceding 5.5 years or more, and no record of a hrHPV exit test at age 60 to 64 years compared to usual care which consisted of opportunistic screening or case-finding. In the Kaiser Permanente Northern California cohort, three-quarters of patients who developed cervical cancer after age 65 had not been adequately screened prior to diagnosis.[220]

Intervals of Screening

Only one included study, POBASCAM, evaluated a 5-year interval between co-testing screening rounds, concordant with the intervals recommended by the USPSTF in 2018. Further, only the HPV FOCAL study directly compared screening outcomes of hrHPV testing at different screening intervals (2 versus 4 years) and the final results of this trial have not yet been published. All other included studies screened at 2- or 3-year intervals. In general, CIN3+ rates were low, with a decrease in CIN3+ detection in the second round of screening, which supports screening no more frequently than every 3 to 5 years. Observational followup from included co-testing trials (ARTISTIC, Swedescreen, POBASCAM) found similar levels of cumulative risks of CIN3+ at 5 to 10 years after hrHPV negative screening as they found at 3 years after negative cytology screening; this implies that extending rescreening intervals up to 10 years may be reasonable.[113, 119, 221] Observational followup from POBASCAM found that women with hrHPV negative testing at the second round of screening had higher long-term risk of CIN3+ if they had positive hrHPV screening in the first round compared to women with negative hrHPV screening at the first round.[188] During 14 years of followup, the CIN3+ risk in hrHPV negative women with a previous hrHPV positive test was 2.36 percent (95% CI, 1.20 to 4.63) versus women with a previous negative HPV test was 0.43 percent (95% CI, 0.33 to 0.57). The CIN3+ risk was not influenced by the previous cytology result. These findings support risk-based screening intervals that incorporate the results from the current and previous round of hrHPV screening.

In an analysis from the Kaiser Permanente Northern California cohort, the cumulative risk of CIN3+ at 5 years after negative primary hrHPV or co-testing was lower than the 3-year risk after negative cytology,[222] consistent with findings from co-testing trials in Western Europe. Additional analyses from this cohort also support risk-based screening intervals and suggest that extended intervals may also be warranted with repeated negative screenings as subsequent rates of CIN3+ are low with repeated hrHPV negative tests (e.g., 1.8 per 10,000 person-years following four consecutive negative screens).[223] Similarly, in another analysis from the FOCAL DECADE cohort compared with the British Columbia Cancer Cervix Screening Program, the cumulative risk of CIN3+ at 10 years after negative primary hrHPV testing was similar to the 3-year risk after negative cytology.[224]

Protocol Considerations

Among the included comparative screening studies, there was substantial variation in the screening strategies evaluated (e.g., hrHPV with or without cytology triage, co-testing versus

cytology with or without hrHPV triage, assays used, collection method, conventional versus LBC, ages included, intervals between screening rounds) as well followup protocols used (i.e., threshold for referral to colposcopy versus earlier repeat testing, interval between surveillance for abnormal screening not meeting criteria for referral to colposcopy). This clinical heterogeneity likely accounts for much of the statistical heterogeneity in most quantitative analyses presented in this review. However, despite the high statistical heterogeneity in pooled analyses, overall findings were generally consistent among trials in the direction of effect. Variation in protocols appeared to be more influential for clinically important differences in colposcopy use and false positive rates than detection of precancer.

Additional Triage Strategies

Risk-based management strategies recommended by ASCCP, as well as triage strategies in place of or in addition to cytology triage of positive hrHPV testing are intended, in part, to reduce the colposcopy burden, false positives, and overdetection. Although many different triage tests have been studied to date, only dual stain and extended genotyping (beyond hrHPV 16/18) have FDA-approved assays for use in the United States (**Appendix B, Contextual Question 2**). Although dual stain appears to be more sensitive than cytology (with a threshold of ASC-US+) for the detection of CIN2+ in women who are positive for hrHPV, it is not more specific and therefore may not result in fewer colposcopies.[225] However, in one U.S.-based cohort study, hrHPV-positive women (n=1549) with a negative dual stain had a low risk of CIN2+ and CIN3+ for 5 years.[226] Dual stain negative women had a risk of precancer equivalent to having hrHPV positive testing with normal cytology for repeating testing at one year (based on hrHPV-positive with normal cytology) at 3 years. Thus, the authors concluded that the surveillance interval could be extended to 3 years for hrHPV-positive women with negative dual stain.[226] When published, the final results from the COMPASS trial, which randomized participants to primary hrHPV screening with triage (using LBC or dual stain) versus LBC, will help inform the value of dual stain triage in cervical cancer screening and the potential of reducing burden of testing without a meaningful clinical reduction in the detection of CIN3+.

Because different hrHPV genotypes carry different risk for CIN3+, stratification of management by genotype using extended genotyping could reduce the burden of testing by assigning women at the highest risk to colposcopy while designating those at lower risk to retesting at shortened intervals. Using 9258 archived samples from the NCI-Kaiser Permanente Northern California HPV Persistence and Progression (PaP) cohort, Schiffman and colleagues stratified hrHPV genotype risk profiles based on the likelihood of patients developing CIN3+ within 3 years.[227] In this study, there were four different risk profiles using combinations of the nine typing channels offered by Onclarity: (1) hrHPV 16, (2) else hrHPV 18/45 (in the absence of hrHPV16), (3) else hrHPV 33/58/31/52, (4) else hrHPV 51/35/39/68/56/59/66. Based on risk of developing CIN3+, persons with normal cytology with any hrHPV genotype other than hrHPV 16 could be managed with repeat testing in 1 year (benchmarked using risk equivalents based on cytology thresholds for referral to colposcopy). Also, persons with normal and low-grade cytologic abnormalities and only hrHPV 51/35/39/68/56/59/66 could be managed with repeat testing in 1 year. However, in 2021 the IARC noted that while extended genotyping could decrease unnecessary testing and treatment, more evidence is needed.[225] Furthermore, it is unclear what impact HPV vaccination has on the performance and role of extended genotyping, as studies to date were conducted in mostly unvaccinated women.

Colposcopy Referral Thresholds

A 2022 systematic review and network meta-analysis by Teresawa and colleagues evaluating the sensitivity and specificity of various cervical cancer screening protocols included 27 studies (n=185,269).[228] This meta-analysis found that the cross-sectional test accuracy for CIN2+ using a threshold of ASC-US or hrHPV positive results was the most sensitive but least specific, while a threshold of ASC-US and hrHPV positive was the most specific but least sensitive. Authors noted that the guideline-recommended thresholds of LSIL, hrHPV positive with ASC-US, or hrHPV 16/18 positive or other hrHPV positive with ASC-US were not as sensitive but more specific than using a threshold of hrHPV positive alone. Similarly, these proposed algorithms appeared equally specific but more sensitive than a threshold of ASC-US alone, although authors note that definitive conclusions could not be made due to limited comparative data.

In 2019, the ASCCP issued new risk-based management consensus guidelines for abnormal cervical cancer screening, such that colposcopy is recommended for any combination of history and current test results yielding a 4 percent or greater probability of finding CIN3+.[27] In general, these guidelines recommend more frequent surveillance, colposcopy, and treatment for individuals at progressively higher risk. Those at lower risk can defer colposcopy, undergo followup at longer surveillance intervals, and when at sufficiently low risk, return to routine screening. Thresholds used to refer to colposcopy used in included studies differed from ASCPP guidance which were designed to minimize colposcopies among individuals at low risk of CIN3+. For example, ASCCP guidance suggests hrHPV positive ASC-US/LSIL with prior negative hrHPV testing can be surveilled, persons screened only with cytology do not benefit from risk-based strategies that mitigate burden of colposcopies. Therefore, estimates for burden of testing from included studies may overestimate the number of colposcopies and overdetection resultant from screening with hrHPV based strategies. Four of the primary hrHPV screening studies used a threshold of ASC-US for referral to colposcopy for hrHPV positive women. Although none of the studies appeared to take screening history into account, initial screening results of hrHPV positive and ASC-US have a CIN3+ risk of 4.5 percent and would therefore be referred to immediate colposcopy per the ASCCP guidance.[27] The co-testing trials primarily used ASC-US or LSIL as a threshold for referral to colposcopy regardless of hrHPV positivity, with persons not meeting the cytologic threshold for referral to colposcopy but who were hrHPV positive to repeat screening at 6 to 12 months. Per ASCCP guidance, hrHPV-positive and ASC-US or LSIL cytology with unknown previous screening history and hrHPV-positive with normal cytology occurring at two consecutive screens (1 year interval) would meet the 4 percent risk threshold. However, hrHPV-negative and LSIL or ASC-US cytology with unknown previous screening history would fall under the risk threshold for referral to immediate colopscopy.[27] This management guidance was based on analyses from the Kaiser Permanente Northern California cohort[229, 230] and the 4 percent threshold was then validated by other study populations with more diverse sociodemographic data, including the New Mexico HPV Pap Registry, CDC's National Breast and Cervical Cancer Early Detection Program, and Onclarity trials.[231]

Long-term observational followup from ARTISTIC demonstrated that about three-quarters of women with hrHPV infection and normal cytology clear their infections within about 3 years with only a 1.5 percent risk of CIN3+ within this time frame.[221] Based on this observation, authors suggest that annual repeat testing for hrHPV-positive women and referral to colposcopy after 2 years if repeat testing is positive may be "unnecessarily cautious."

Health Equity

Inequities in Cervical Cancer Incidence and Mortality

While the overall cervical cancer incidence and mortality is low in the United States, with most recent age-adjusted rates estimated at 7.7 cases and 2.2 deaths per 100,000 women per year, [9] significant inequities exist by race and ethnicity, SES, insurance status, and geographic location (**Appendix B, Contextual Question 3**). Black, Latina, Hispanic/Latina, and AI/AN women are disproportionately affected by cervical cancer.[9, 29, 39, 232] For example, Black and Hispanic/Latina and have a higher risk of cervical cancer incidence (30% and 51%, respectively) and mortality (60% and 20%, respectively) compared with White women.[28] These disparities are even greater for Black women when using hysterectomy-adjusted data.[11] There is consistent evidence that low-SES, particularly lower income and education levels, are associated with cervical cancer incidence, late-stage diagnoses, and mortality.[29, 31, 32] Relatedly, women who are uninsured or have public health Insurance have a lower likelihood of screening and are at higher risk for cervical cancer progression than women with private or military insurance.[29, 35, 233] Women living in rural areas are disproportionately burdened by cervical cancer, experiencing 15 percent and 13 percent higher incidence and mortality rates, respectively, compared to women living in metropolitan areas.[35] Furthermore, women living in the Southern region of the United States have the highest incidence mortality rates of cervical cancer compared to women living in other regions.[33, 34]

Disparities in Screening and Followup Care

Inequities in cervical cancer incidence, late-stage disease, and mortality are influenced by complex and interrelated factors which increase the risk for developing cervical cancer and limit access to screening and high-quality health care (**Appendix B, Contextual Question 3**). For example, research indicates that poor survival rates in Black women is multifactorial, including a greater probability of diagnoses at advanced stages, limited access to or delays in treatment therapies, and intersectionality with other risk factors and barriers.[29, 30] Women with low-SES are less likely to be up to date with cervical cancer screening recommendations, attend followup appointments, and access treatment services compared to women with high-SES.[32, 34, 234] Black women who have low socioeconomic status or who lack health insurance have been found to have the lowest rates of followup after abnormal findings on cervical cancer screening.[29, 30] Further, women living in rural communities are less likely to complete cervical cancer screenings and experience higher rates of late-stage diagnoses than women living in metropolitan areas.[34-36, 235, 236] In addition, women with disabilities, particularly sensory, physical, and multiple disabilities are less likely to receive recommended cervical cancer screening compared to women without disabilities.[237, 238] Recent reviews suggest that sexual and gender minorities, particularly lesbian and bisexual women as well as transgender men who retain their cervix, are also less likely to be screened for cervical cancer and may be at greater risk for malignancy compared to heterosexual and cisgender women.[37, 239-241] Additionally, transgender men may have more inadequate cytology results due to cytomorphologic changes associated with androgen therapy. Androgenic effects on the genital tract may also result in more painful or uncomfortable speculum exams due to epithelial atrophy.

Personal and structural barriers to cervical cancer screening and followup care are well described (**Appendix B, Contextual Question 4**). Personal barriers can include the lack of trust in health providers and systems; anxiety over the procedure, fear of finding cancer, and stigma around sexually transmitted infections or reproductive health problems; history sexual trauma; and health literacy. The most often cited structural barrier to screening, and especially followup care, is cost (even in insured populations) and other financial barriers (e.g., inability to take time off work, obtaining affordable health care). Other key barriers include difficulty with transportation, navigating the health system (including language barriers), access to providers or medical facilities, access to providers with shared cultural backgrounds or culturally/sexual and gender minority sensitive care, access to timely care, and access to quality care.[29, 37-41]

Interventions to Improve Screening and Followup to Abnormal Screening

Perhaps the most impactful and immediate way to reduce cervical cancer morbidity and mortality in the United States is through improving the uptake of screening and followup care for abnormal screening. In addition to the previously described inequities in screening and followup care, it is estimated that approximately half of new cases of cervical cancer in the United States are in underscreened or unscreened persons.[242] Even a single screening may have a meaningful impact on cancer incidence and mortality. An analysis from the Kaiser Permanente Northern California cohort of over a million women demonstrated that approximately two-thirds of women found to have cancer over 10 years of followup were detected by the first screening with co-testing.[223] Similarly, approximately three-fourths of women with CIN3+ over 15 years of followup were hrHPV-positive at baseline in this study.

Cervical cancer cases diagnosed in women aged 65 years and over are primarily due to underscreening.[10] Given absence of organized screening program in most of the United States, data suggest that a sizeable proportion of women around age 65 years would not meet criteria to exit screening.[219] In this review, a comparative NRSI demonstrated a benefit in CIN3+, and possibly ICC, detection using self- or clinician-collected primary hrHPV screening in women age 65 to 69 years old who were not up to date on screening recommendations compared to usual care which consisted of opportunistic screening or case-finding.[117]

Offering screening with in-clinic or home self-collected hrHPV samples (as opposed to clinician-collected) can address many of the personal and structural barriers described above. In this review, self-collected vaginal samples for hrHPV had adequate sensitivity and specificity for the detection of precancer compared to clinician-collected cervical samples. And home self-collection or offering the choice of self-collection consistently increased receipt of screening in underscreened, as well as unselected, populations. A 2023 systematic review by Costa and colleagues[243] found that send-to-all strategies were most effective in increasing completion of screening compared to a control, but any invitation strategy to self-collected hrHPV improved screening uptake.

Many different interventions and implementation strategies to increase screening and followup for abnormal screening (e.g., different outreach and reminder strategies, use of patient

navigators, use of community health workers, and offering transportation assistance for appointments) have been evaluated (**Appendix B, Contextual Question 5**).[244] In 2022, the Community Preventive Services Task Force (CPSTF) recommended using patient navigation systems for historically disadvantaged racial and ethnic populations and people with lower incomes to increase screening uptake based on strong evidence.[245] Patient navigation systems, typically provided by the health system, are multicomponent interventions, and can include a variety of elements, such as patient reminders, assistance with appointment scheduling, transportation help, and programs to help reduce out-of-pocket costs.[245]

In 2019, the CPSTF examined the effectiveness of interventions using community health workers to increase screening uptake and found that these interventions are both helpful and cost-effective.[246] Community health workers are often included in patient navigation systems and help to increase the community demand for screening using education and client reminders. They also help to improve community access to screening by reducing existing barriers (e.g., providing language translation, childcare). A 2016 systematic review for the CPSTF found that the largest screening increases were found among interventions that combined approaches among the three strategies of increasing community demand (e.g., incentives, reminders, group education), increasing community access (e.g., interventions to reduce cost, providing appointment scheduling assistance, providing childcare/transportation/translation services), and increasing provider delivery (e.g., provider incentives, provider assessments/feedback).[247] While these more complex interventions require coordination of healthcare systems and community settings, results show that these multicomponent strategies result in notably higher receipt of screening as well as followup testing/procedures.[245-247]

Limitations of Our Approach

Our systematic review focused on evidence from comparative studies with concurrent controls, or diagnostic accuracy studies, in countries with similar economic development and health care resources to the United States. As such, we excluded studies from countries with active research in cervical cancer screening, for example China and India. We also excluded studies not published in English. Nonetheless, to our knowledge, the addition of studies in other countries, those with historical controls, or non-English language studies would not have substantively changed our assessment of the strength of evidence for systematically reviewed evidence, nor improved the applicability of this evidence to US-based practice.

We did not conduct a systematic review of the effectiveness of cytology-based screening approaches, the comparative accuracy of CC versus LBC, the comparative accuracy of different hrHPV assays, or the comparative accuracy of different triage strategies for abnormal hrHPV testing (e.g., dual stain, extended genotyping). The effectiveness of cytology-based screening was considered foundational evidence based on ecological studies, therefore our review focused on the comparative effectiveness of hrHPV-based strategies compared to cytology-based strategies. The comparative accuracy of the different FDA-approved hrHPV assays are addressed as a contextual question using primarily existing systematic reviews. Likewise, the comparative accuracy and ability of different triage strategies to reduce burden of testing is addressed as a contextual question.

Many of the meta-analyses presented in this review have high statistical heterogeneity and meaningful meta regression was not possible due to the small number of studies. However, we believe the high statistical heterogeneity largely reflects the clinical heterogeneity across studies (e.g., differences in protocols) or high precision due to large samples (e.g., specificity). Because results were generally consistent across studies, we chose to present pooled effects. However, we suggest using 95% CIs and the ranges in absolute effects presented alongside pooled estimates when trying to understand the magnitude of effects, test agreement, or test accuracy.

Limitations of the Literature and Future Research Needs

There are several RCTs and well conducted NRSIs on evaluating hrHPV screening strategies compared to cytology-based screening strategies. However, none are adequately powered to evaluate the reduction in morbidity or morality of ICC, nor the incidence of ICC. Further, none are conducted in the United States or in settings without national screening programs. Large single arm cohort studies of primary hrHPV screening in the United States suggest higher test positivity and CIN3+ detection in U.S.-based settings without organized screening programs. Additionally, none of the included studies are adequate to understand the incremental benefit or harm in HPV vaccinated cohorts.

Epidemiologic studies demonstrate decreases in hrHPV infections and precancer in vaccinated women, as well as cohorts eligible for vaccination, therefore it is likely that the magnitude of benefits and harms in these populations would differ from that seen in included studies. Included studies used different screening assays and followup protocols, which differ from currently used assays and colposcopy referral thresholds. Most included studies were limited to a single round of screening. Further, those that reported results from two or more rounds of screening used the second round as an exit round, receiving the same screening strategy in both arms.

Two primary hrHPV screening trials—the Swedish trial by Elfstrom and colleagues and COMPASS—have not yet published their final results (**Appendix G**). The Swedish trial's estimated completion date is end of 2031, therefore we anticipate results will be available for subsequent rounds of screening. COMPASS also evaluated cytology triage versus dual stain triage of hrHPV- positive women and includes younger women who have been vaccinated. One ongoing trial in Denmark evaluating screening every 6 years in women offered HPV vaccination in childhood and adolescents is expected to be completed by end of 2025.[251]

We identified no studies that empirically evaluated the age to start screening at age 21 versus 25 years or later. There is a trial in Sweden currently recruiting that will evaluate primary hrHPV screening versus cytology in participants ages 23 to 29 years, however, the trial will not be completed until end of 2038.[252] We included preliminary results from one comparative study in Denmark in women aged 65 to 69 years comparing clinician-collected hrHPV to self-collected hrHPV, or to usual care (i.e., opportunistic screening) that is scheduled to be completed at the end of 2025.[117] Lastly, none of the comparative studies evaluated primary hrHPV versus co-testing strategies. We are not aware of, nor do we anticipate, any future trials addressing this evidence gap. Given the rarity of ICC, the natural history of hrHPV infection progressing to ICC, the current age of vaccinated cohorts, and the changing nature of recommended intervals, triage testing, and referral and management thresholds, we believe decision analyses with updated

inputs relevant to current United States screening cohorts are the most helpful right now in understanding the balance of benefits and harms of a program of screening. Additionally, decision analyses play an integral role in understanding appropriate ages to start or switch to screening with hrHPV given that the cohort of women in now in their 20s have been offered HPV vaccination in their childhood and adolescence.

Given the increased burden of testing with hrHPV screening strategies, studies comparing different triage strategies of hrHPV-positive women, using cytology, dual stain, extended genotyping, and/or DNA methylation on both specificity (to decrease burden of screening) and sensitivity for detection of CIN3+ is helpful. Additionally, decision analyses using tailored screening approaches, extending intervals of screening for sequentially negative hrHPV-screened women may also be helpful. Due to the rarity of hrHPV-negative adenocarcinoma, comparative studies are not likely to clarify the impact of hrHPV screening on the incidence, stage at diagnosis, morbidity, and mortality from adenocarcinoma in general.

Current FDA approval for self-collection is limited to in clinic testing. However, self-collected hrHPV screening for use in clinic or at home can be made available through CLIA, an alternate regulatory process. The included studies for self-collection are largely limited to a single round of screening and designed primarily to inform uptake of screening. One trial (n=20,000) in Japan evaluating self-collected hrHPV screening includes precancer and cancer detection and is expected to be completed in the Spring of 2025.[253] While the adherence to followup visits for cytology triage of women who are hrHPV-positive is high in participation trials, additional studies to understand the applicability of these findings outside of a trial setting and in the United States would be helpful.

There are few diagnostic accuracy studies on the relative detection of CIN3+ for self-collected vaginal samples, therefore additional studies using commonly used hrHPV assays in the United States are needed. Studies evaluating optimal collection methods (e.g., instructions, swab, storage) and dissemination methods (e.g., outreach, mailed versus in the clinic) for self-collection would be helpful for widespread implementation of self-collected hrHPV screening. Urine hrHPV tests may be an option in the future, as they likely would result in even greater gains in uptake of screening than self-collected vaginal samples; however diagnostic accuracy studies for the detection of CIN3+ are needed to understand how they compare to cervical and vaginal samples. We are aware of at least one additional study underway that will evaluate the diagnostic accuracy of urinary, as well as vaginal, hrHPV testing.[248]

Drivers of observed health inequities, as well as evidence around barriers to screening, followup colposcopy, and quality treatment are largely understood. Therefore, the gaps are primarily in policy and practice, as opposed to evidence gaps. Data on cervical cancer, precancer, and hrHPV infections in sexual and gender minority populations, as well as disaggregated data by specific racial, ethnic, and immigrant populations, will be helpful in implementing known effective interventions to increase the uptake of screening and followup.

Conclusions

Well-conducted comparative studies demonstrate that a single round of hrHPV-based screening can increase the detection of precancer compared to cytology-based screening strategies, which results in a lower rate of precancer at a subsequent round. However, the absolute incremental benefit in detection of CIN3+ for a single round is small and comes at the expense of a higher burden of testing. The comparative benefit and burden of testing between strategies in women vaccinated for HPV cannot be observed from current trials. Self-collected vaginal hrHPV samples using DNA-based assays can have similar test accuracy for precancer compared to clinician-collected cervical hrHPV samples and increase receipt of cervical cancer screening. The largest reduction in cervical cancer incidence, morbidity and mortality in the United States will be from increasing cervical cancer screening in persons who are unscreened or underscreened, as well as assuring timely and quality followup care.

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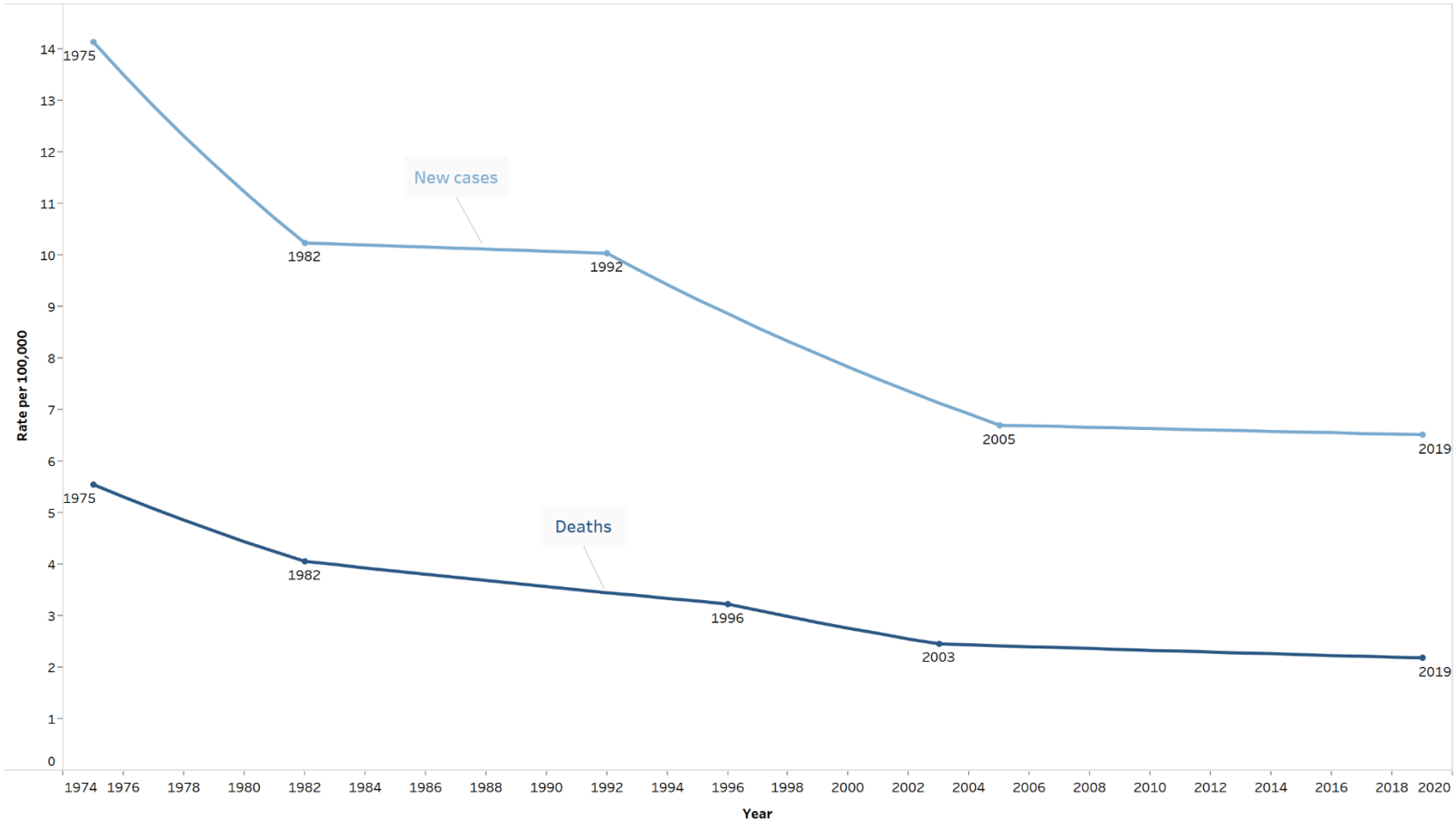
Figure 1. Incidence and Death Rate for Cervical Cancer Over Time[9]



Note: Figure is displaying age-adjusted trend lines.

Figure 2. Proportion of New Cervical Cancer Cases and Cervical Cancer Deaths by Age, SEER 2016–2020[9]

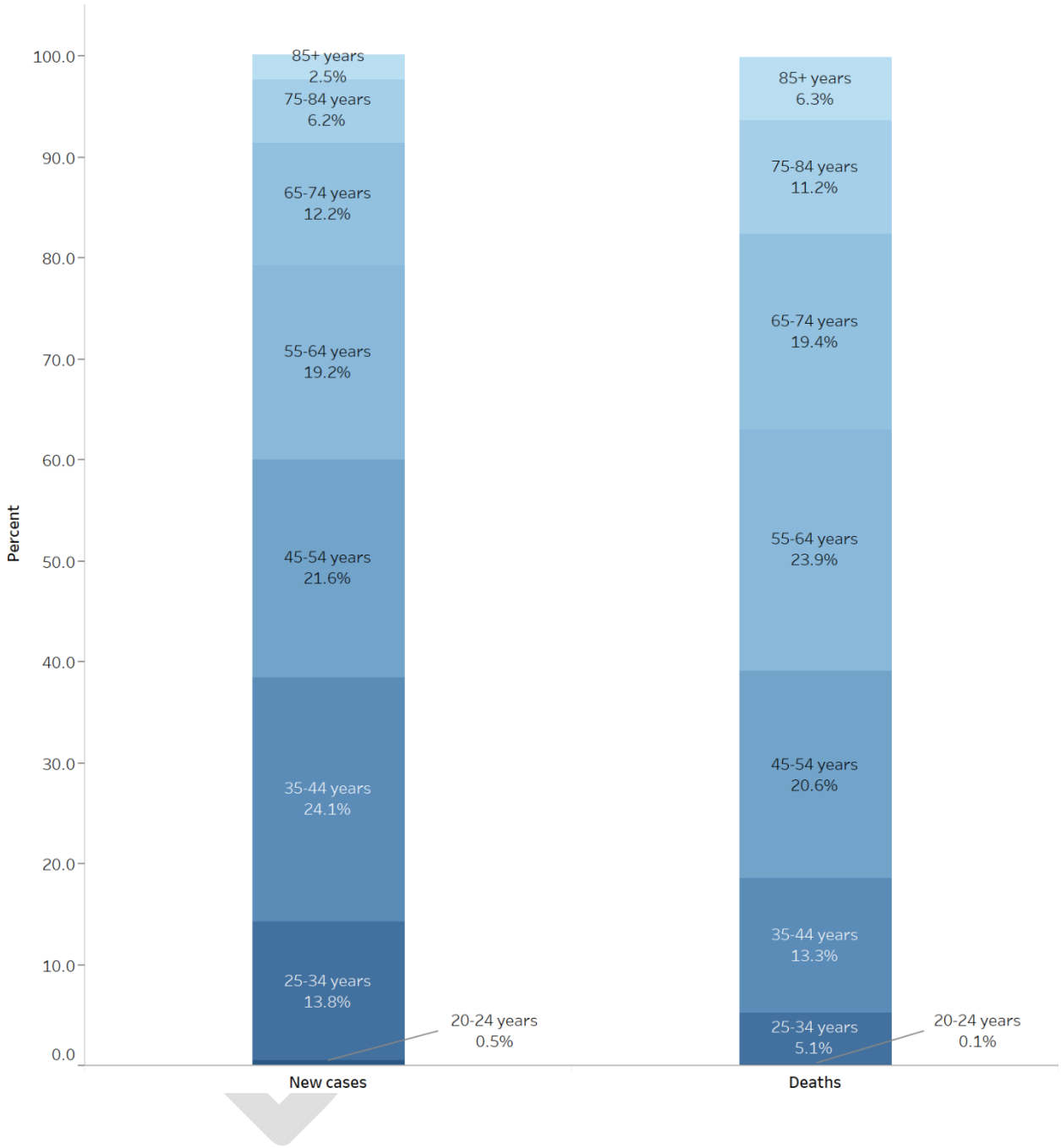
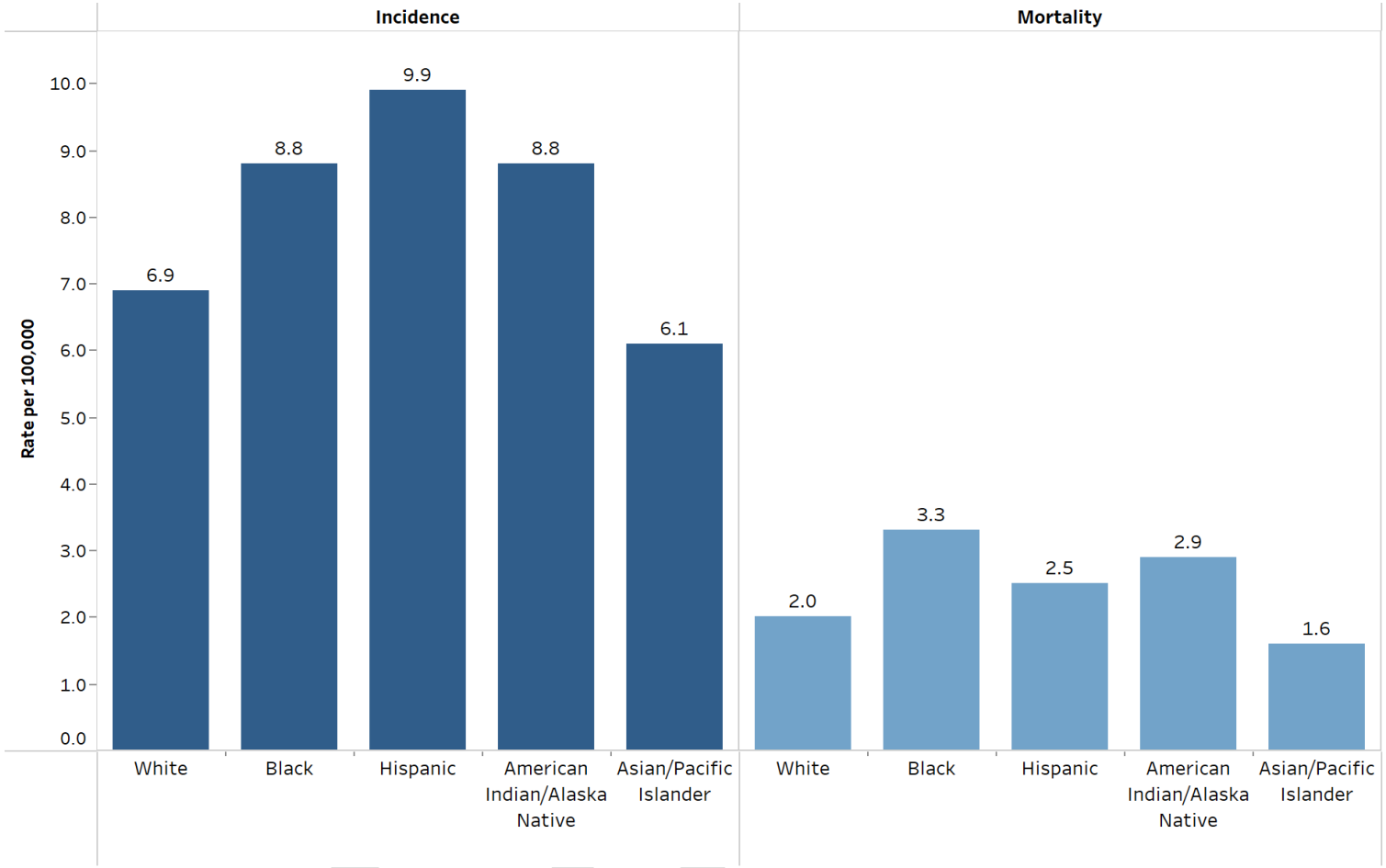


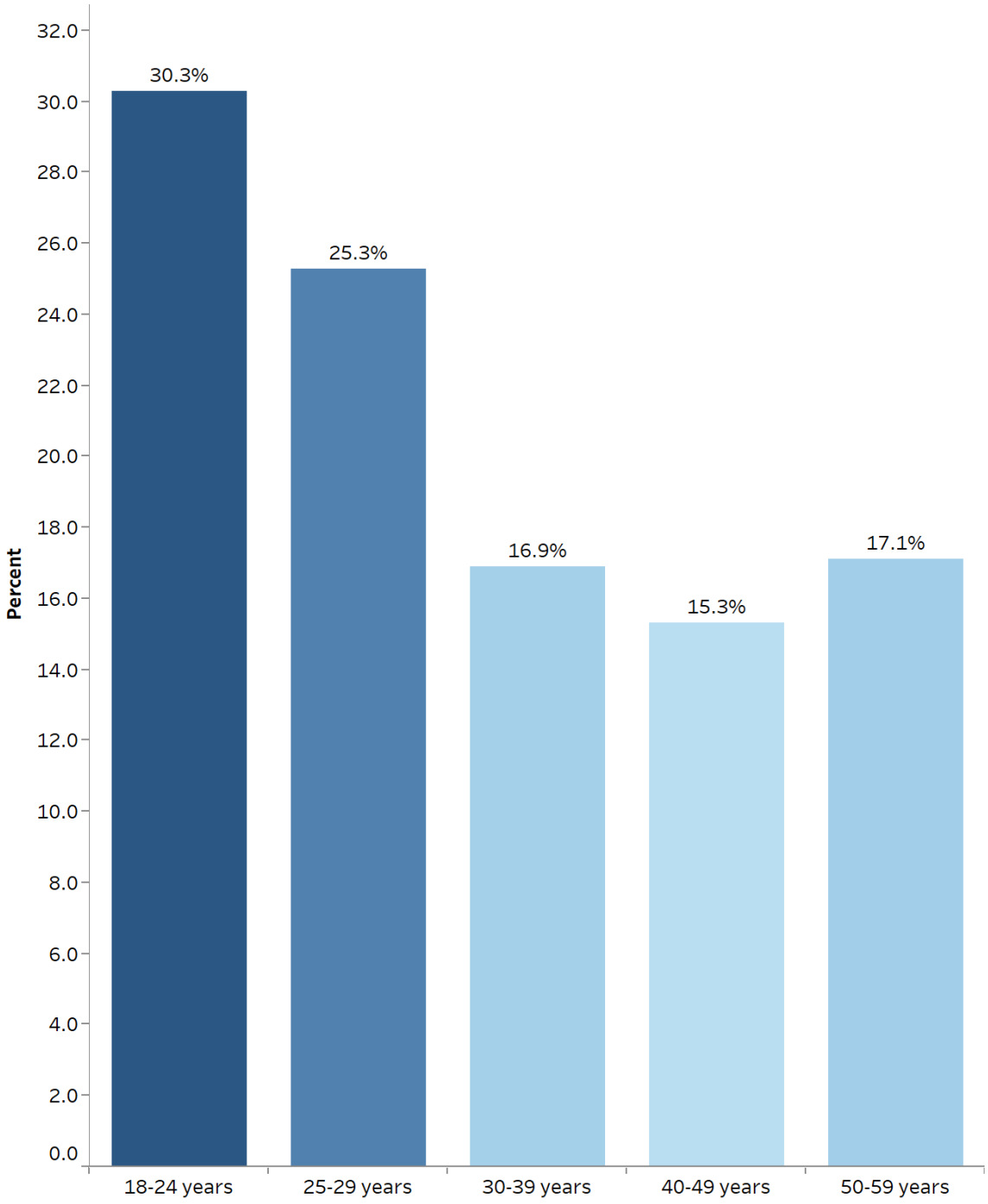
Figure 3. Rate of Cervical Cancer Incidence and Mortality by Race/Ethnicity,* SEER 2016–2020[9]



* Terms for categorizations used by SEER; all are nonHispanic if "Hispanic" not indicated.

Note: Darker shading indicates higher rates. Rates are age-adjusted.

Figure 4. Prevalence of hrHPV by Age



Source: 2015-2016 NHANES. See Appendix A for analysis methods.

Abbreviations: hrHPV = high-risk human papillomavirus.

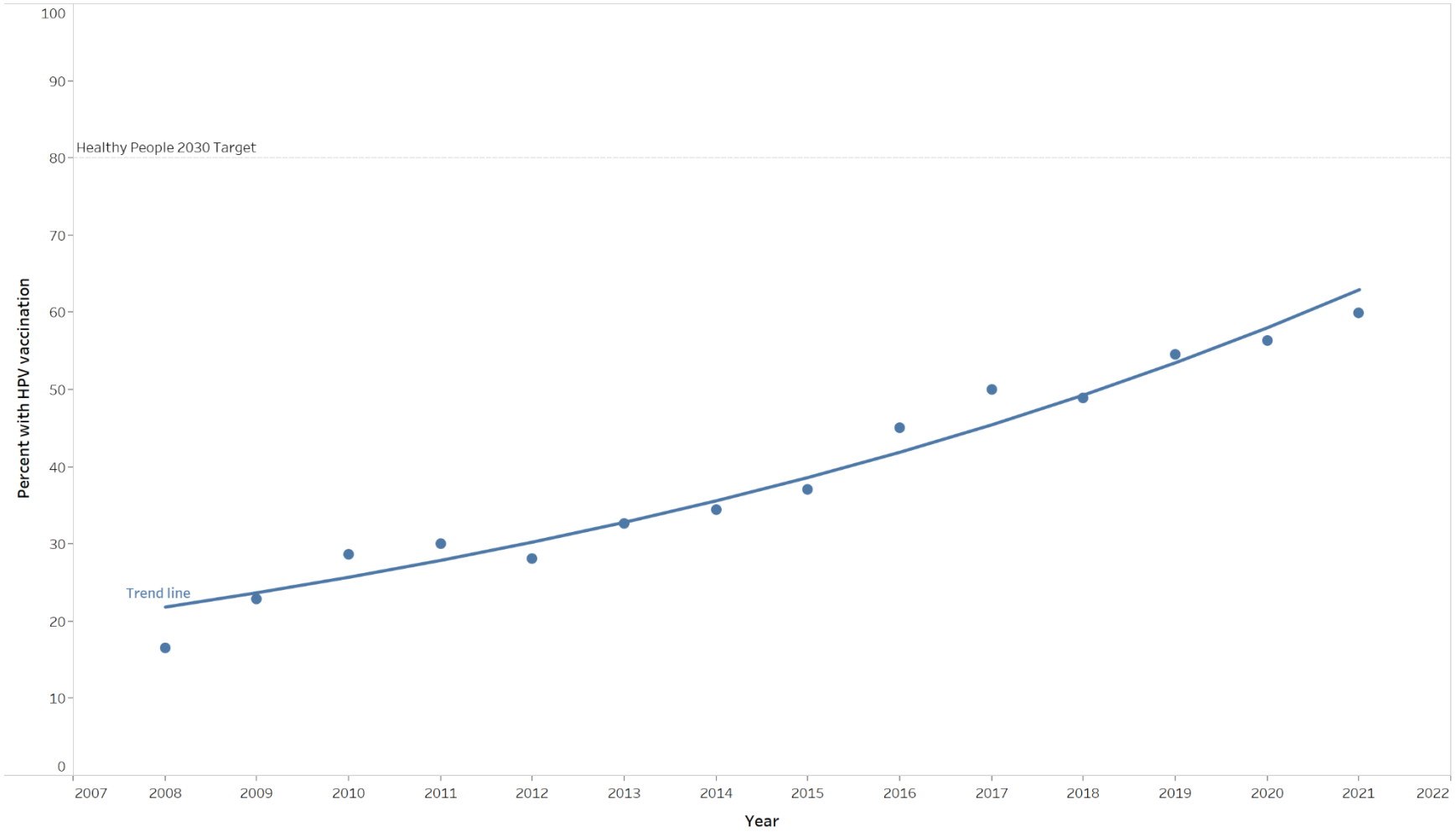
Figure 5. FDA-Approved HPV Assays

Testing Type	Target	Test Name	Manufacturer	FDA Approval Date	High-risk HPV types‡													
					16	18	31	33	35	39	45	51	52	56	58	59	66	68
Primary, reflex, or cotest	DNA	Alinity m High Risk HPV Assay	Abbott	2023	×	×	×	×	×	×	×	×	×	×	×	×	×	×
		OnClarity HPV Test*	Becton Dickinson	2018	×	×	×	×	×	×	×	×	×	×	×	×	×	×
		Cobas HPV Test*	Roche	2014	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Reflex or cotest	DNA	Cervista HPV HR**†	Hologic	2009	×	×	×	×	×	×	×	×	×	×	×	×	×	×
		Cervista HPV 16/18 (used alongside Cervista HR)	Hologic	2009	×	×												
		Digene Hybrid Capture 2 Assay (HC2)**	Qiagen	2000	×	×	×	×	×	×	×	×	×	×	×	×		×
	mRNA	Aptima HPV Assay**	Hologic	2011	×	×	×	×	×	×	×	×	×	×	×	×	×	×
		Aptima HPV 16, 18/45 Assay (used alongside Aptima HPV Assay)	Hologic	2011	×	×					×							

* FDA expanded indication for self-collection using vaginal swabs
** Reported as a pooled result
† Cervista assay is no longer sold in the U.S. or Canada
‡ Low-risk genotypes not recommended for cervical cancer screening

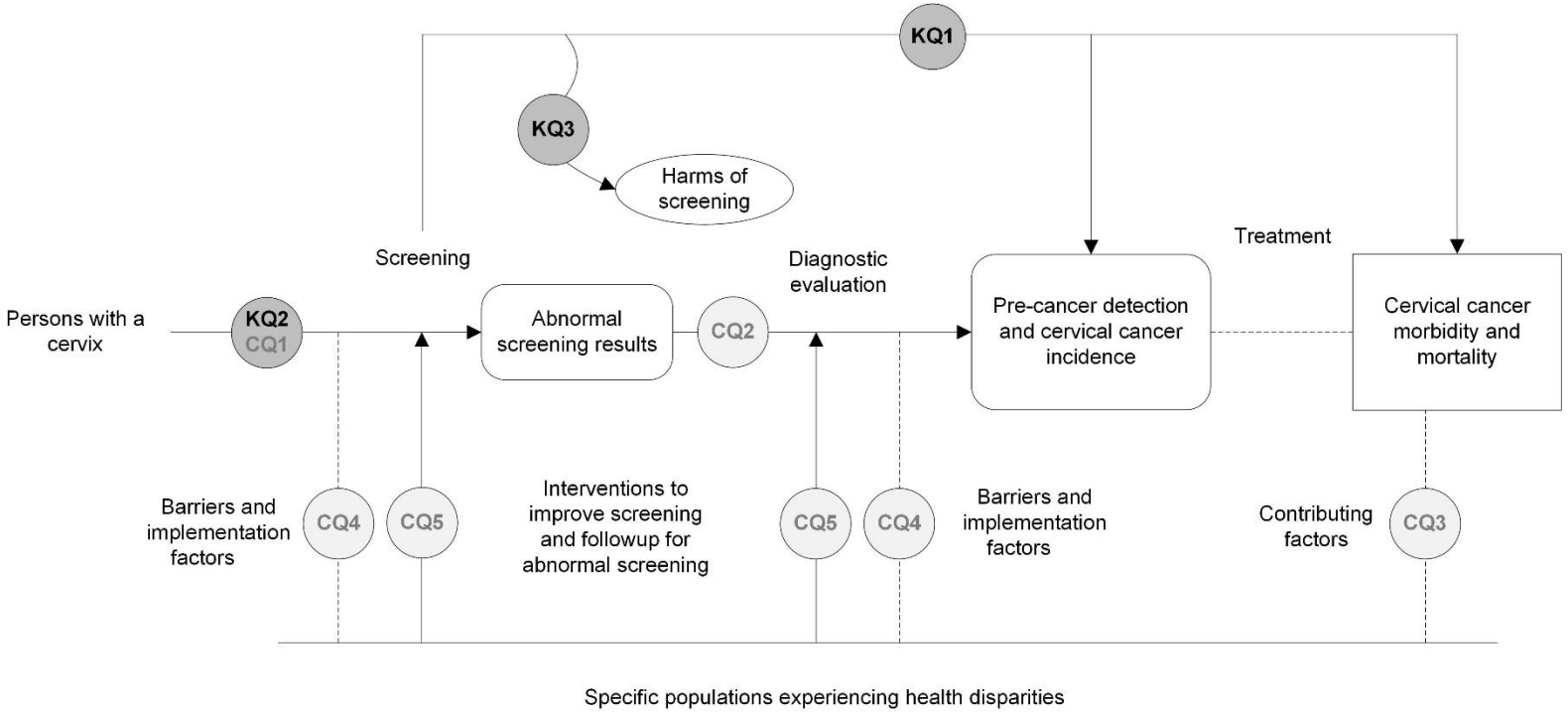
Abbreviations: FDA = U.S. Food and Drug Administration; HPV = human papillomavirus.

Figure 6. Adolescent Females 13–15 years With at Least 2 Doses of HPV Vaccine



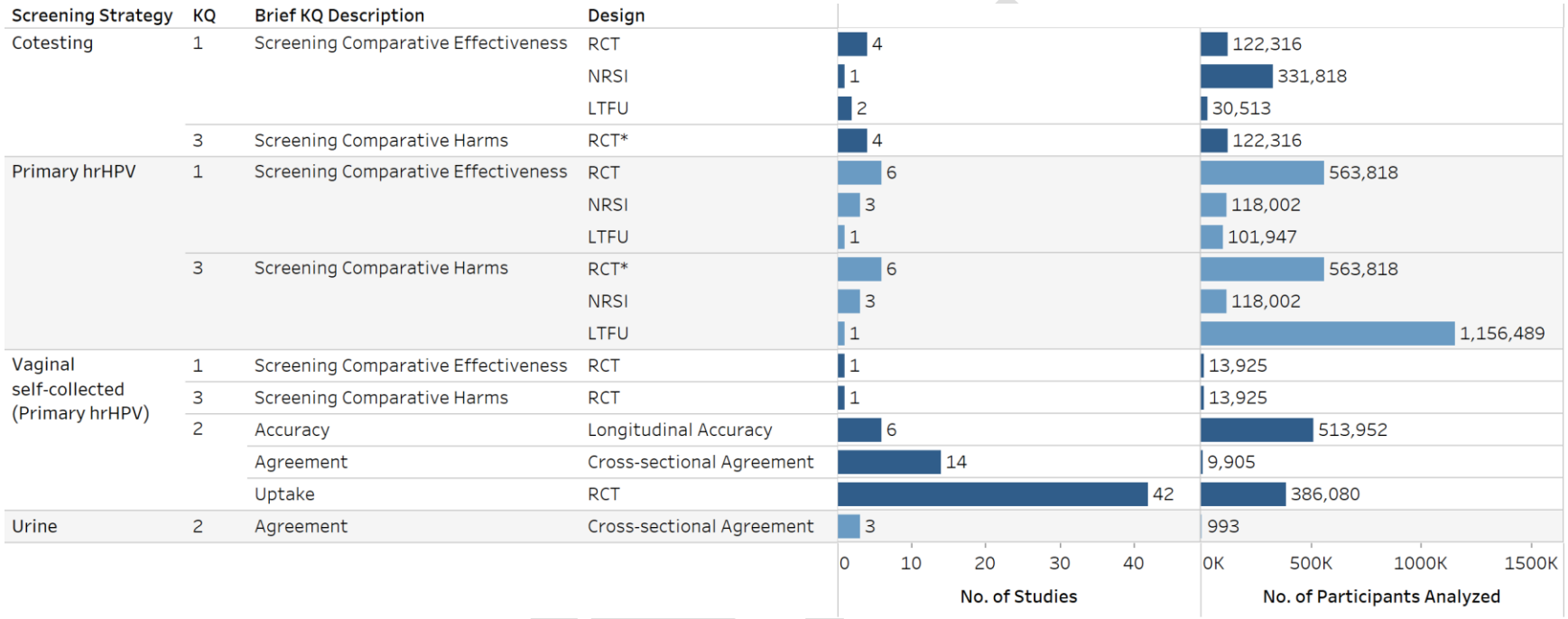
Abbreviations: HPV = human papillomavirus.

Figure 7. Analytic Framework



Abbreviations: CQ = contextual question; KQ = key question.

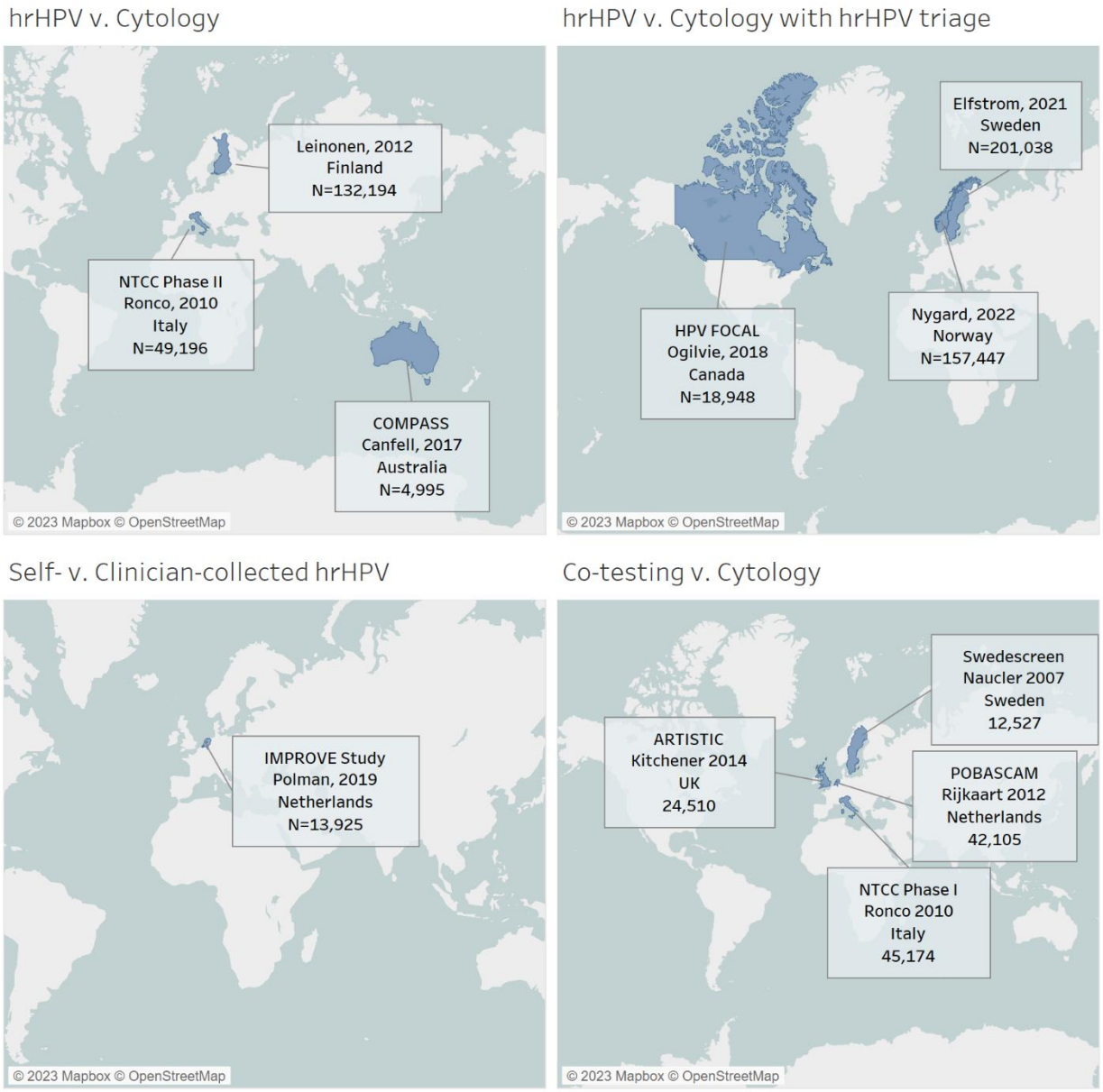
Figure 8. Included Studies and n Analyzed by Key Question



* Inclusive of 2 sub-samples for psychological harms

Abbreviations: KQ = key question; NRSI = nonrandomized study of interventions; No. = number; RCT = randomized controlled trial.

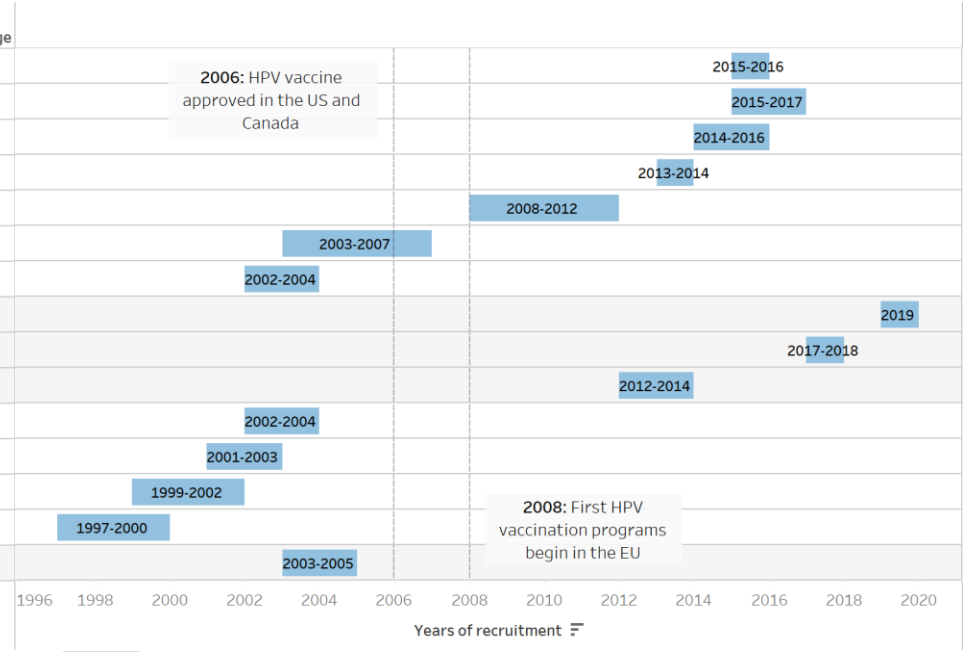
Figure 9. KQ1 and KQ3 Trials, Grouped by Comparison



Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program; UK = United Kingdom.

Figure 10. KQ1 and KQ3: Study Recruitment Years

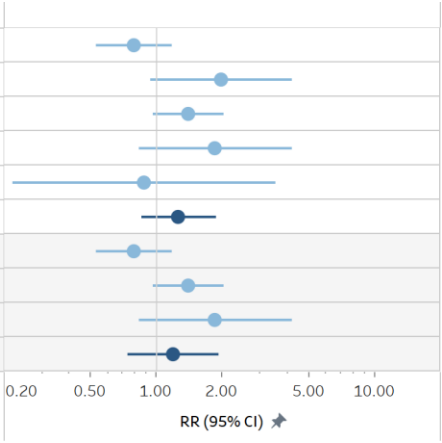
Screening strategy	Design	Author Year	Study Name	Country	Age Range
Primary HPV	RCT	Polman, 2019	IMPROVE Study	Netherlands	29-61
		Nygard, 2022		Norway	34-69
		Elfstrom, 2021		Sweden	30-64
		Canfell, 2017	COMPASS	Australia	25-64
		Ogilvie, 2018	HPV FOCAL	Canada	25-65
		Leinonen, 2012		Finland	25-65
		Ronco, 2010	NTCC Phase II	Italy	25-60
	NRSI	Tranberg, 2023		Denmark	65-69
		Thomsen, 2020	HPV SCREEN DENMARK	Denmark	30-59
		Veijalainen, 2018		Finland	35-60
Cotesting	RCT	Ronco, 2010	NTCC Phase I	Italy	25-60
		Kitchener, 2009	ARTISTIC	UK	20-64
		Rijkaart, 2012	POBASCAM	Netherlands	29-56
		Naucler, 2007	SWEDESCREEN	Sweden	32-38
	NRSI (single arm)	Katki, 2011	KPNC	US	30+



Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; HPV = human papillomavirus; NRSI = nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program; US = United States.

Figure 11. KQ1: Primary hrHPV Screening Strategies, ICC

Round	Group	Author, year	Study name	Design	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
1	RCTs and NRSIs	Elfstrom, 2021		RCT	hrHPV+LBC triage	LBC+hrHPV triage	46/110197 (0)	48/90841 (.1)	0.79 (0.53, 1.18)
		Thomsen, 2021	HPV SCREEN DENMARK	NRSI	hrHPV+LBC triage	LBC+hrHPV triage	16/16067 (.1)	12/23981 (.1)	1.99 (0.94, 4.21)
		Nygard, 2022		RCT	hrHPV+LBC triage	LBC+hrHPV triage	66/77207 (.1)	48/80240 (.1)	1.4 (0.97, 2.03)
		Leinonen, 2012		RCT	hrHPV+CC triage	CC	17/66410 (0)	9/65784 (0)	1.87 (0.83, 4.2)
		Veijalainen, 2019		NRSI	hrHPV+CC triage	CC	4/17770 (0)	4/15605 (0)	0.88 (0.22, 3.51)
		Total							1.27 (0.86, 1.88)
	RCTs only	Elfstrom, 2021		RCT	hrHPV+LBC triage	LBC+hrHPV triage	46/110197 (0)	48/90841 (.1)	0.79 (0.53, 1.18)
		Nygard, 2022		RCT	hrHPV+LBC triage	LBC+hrHPV triage	66/77207 (.1)	48/80240 (.1)	1.4 (0.97, 2.03)
		Leinonen, 2012		RCT	hrHPV+CC triage	CC	17/66410 (0)	9/65784 (0)	1.87 (0.83, 4.2)
		Total							1.19 (0.74, 1.93)

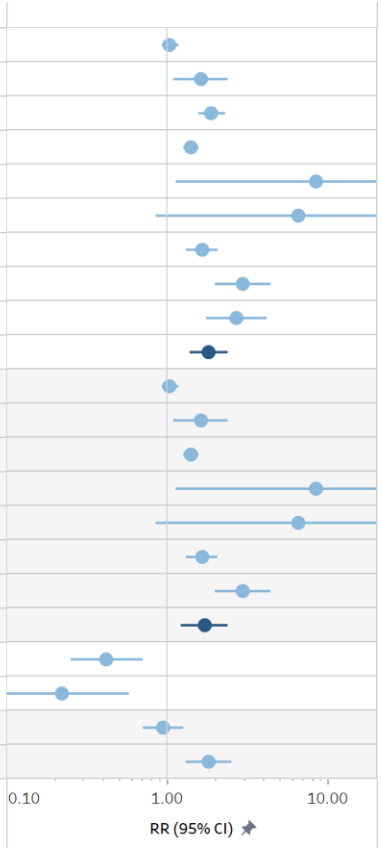


Note: Random effects REML model. I^2=51.3 for RCTs and NRSIs; I^2=65.3% for RCTs only.

Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; hrHPV = high-risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; n = number; NRSI= nonrandomized study of interventions; RCT = randomized controlled trial; RR = relative risk.

Figure 12. KQ1: Primary hrHPV Screening Strategies, CIN3+

Round	Group	Author, year	Study name	Design	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
1	RCTs and NRSIs	Elfstrom, 2021		RCT	hrHPV+LBC triage	LBC+hrHPV triage	655/110197 (.6)	524/90841 (.6)	1.03 (0.92, 1.16)
		Ogilvie, 2018	HPV FOCAL	RCT	hrHPV+LBC triage	LBC+hrHPV triage	67/9540 (.7)	41/9408 (.4)	1.61 (1.09, 2.37)
		Thomsen, 2021	HPV SCREEN DENMARK	NRSI	hrHPV+LBC triage	LBC+hrHPV triage	238/16067 (1.5)	188/23981 (.8)	1.88 (1.56, 2.27)
		Nygard, 2022		RCT	hrHPV+LBC triage	LBC+hrHPV triage	991/77207 (1.3)	711/80240 (.9)	1.4 (1.26, 1.55)
		Canfell, 2017	COMPASS	RCT	hrHPV+DS triage	LBC	17/2008 (.8)	1/995 (.1)	8.42 (1.12, 63.2)
					hrHPV+LBC triage	LBC	13/1992 (.7)	1/995 (.1)	6.49 (0.85, 49.6)
		Leinonen, 2012		RCT	hrHPV+CC triage	CC	195/66410 (.3)	118/65784 (.2)	1.64 (1.3, 2.06)
		Ronco, 2010	NTCC Phase II	RCT	hrHPV	CC	97/24661 (.4)	33/24535 (.1)	2.92 (1.97, 4.34)
		Veijalainen, 2019		NRSI	hrHPV+CC triage	CC	83/17770 (.5)	27/15605 (.2)	2.7 (1.75, 4.17)
		Total							1.80 (1.38, 2.36)
	RCTs only	Elfstrom, 2021		RCT	hrHPV+LBC triage	LBC+hrHPV triage	655/110197 (.6)	524/90841 (.6)	1.03 (0.92, 1.16)
		Ogilvie, 2018	HPV FOCAL	RCT	hrHPV+LBC triage	LBC+hrHPV triage	67/9540 (.7)	41/9408 (.4)	1.61 (1.09, 2.37)
		Nygard, 2022		RCT	hrHPV+LBC triage	LBC+hrHPV triage	991/77207 (1.3)	711/80240 (.9)	1.4 (1.26, 1.55)
		Canfell, 2017	COMPASS	RCT	hrHPV+DS triage	LBC	17/2008 (.8)	1/995 (.1)	8.42 (1.12, 63.2)
					hrHPV+LBC triage	LBC	13/1992 (.7)	1/995 (.1)	6.49 (0.85, 49.6)
		Leinonen, 2012		RCT	hrHPV+CC triage	CC	195/66410 (.3)	118/65784 (.2)	1.64 (1.3, 2.06)
		Ronco, 2010	NTCC Phase II	RCT	hrHPV	CC	97/24661 (.4)	33/24535 (.1)	2.92 (1.97, 4.34)
		Total							1.7 (1.22, 2.37)
2	RCTs only	Ogilvie, 2018	HPV FOCAL	RCT	Cotesting	Cotesting	22/9540 (.2)	52/9408 (.6)	0.42 (0.25, 0.7)
		Ronco, 2010	NTCC Phase II	RCT	CC	CC	5/23978 (0)	23/24372 (.1)	0.22 (0.08, 0.58)
1 + 2	RCTs only	Ogilvie, 2018	HPV FOCAL	RCT	hrHPV with LBC triage, Co..	LBC with hrHPV triage, Co..	89/9540 (.9)	93/9408 (1)	0.94 (0.71, 1.25)
		Ronco, 2010	NTCC Phase II	RCT	hrHPV/CC	CC	102/24661 (.4)	56/24535 (.2)	1.81 (1.31, 2.51)

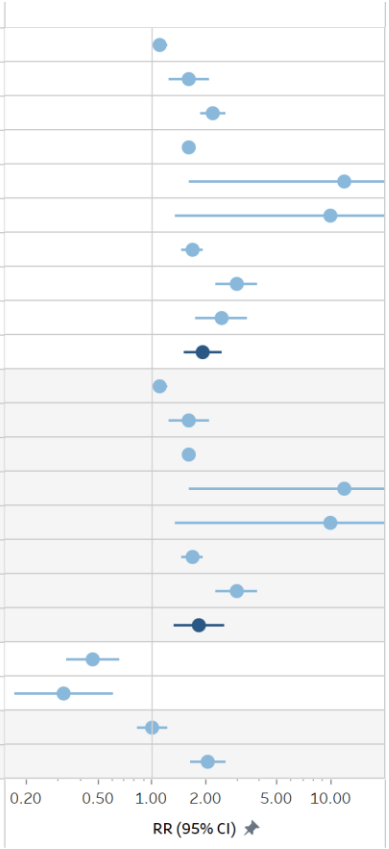


Note: Random effects REML model. I^2=90.4% for RCTs and NRSIs; I^2=91.6% for RCTs only.

Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; DS = dual stain; HPV FOCAL = Human Papillomavirus for Cervical Cancer Screening Trial; hrHPV = high-risk human papillomavirus; IG = intervention group; LBC = liquid-based cytology; n = number; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; RCT = randomized controlled trial; RR = relative risk.

Figure 13. KQ1: Primary hrHPV Screening Strategies, CIN2+

Round	Group	Author, year	Study name	Design	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
1	RCTs and NRSIs	Elfstrom, 2021		RCT	hrHPV+LBC triage	LBC+hrHPV triage	1140/110197 (1)	844/90841 (.9)	1.11 (1.02, 1.22)
		Ogilvie, 2018	HPV FOCAL	RCT	hrHPV+LBC triage	LBC+hrHPV triage	147/9540 (1.5)	90/9408 (1)	1.61 (1.24, 2.09)
		Thomsen, 2021	HPV SCREEN DENMARK	NRSI	hrHPV+LBC triage	LBC+hrHPV triage	348/16067 (2.2)	236/23981 (1)	2.19 (1.86, 2.58)
		Nygard, 2022		RCT	hrHPV+LBC triage	LBC+hrHPV triage	1263/77207 (1.6)	822/80240 (1)	1.6 (1.5, 1.7)
		Canfell, 2017	COMPASS	RCT	hrHPV+DS triage	LBC	24/2008 (1.2)	1/995 (.1)	11.89 (1.61, 87.8)
					hrHPV+LBC triage	LBC	20/1992 (1)	1/995 (.1)	9.99 (1.34, 74.3)
		Leinonen, 2012		RCT	hrHPV+CC triage	CC	540/66410 (.8)	319/65784 (.5)	1.68 (1.46, 1.92)
		Ronco, 2010	NTCC Phase II	RCT	hrHPV	CC	218/24661 (.9)	73/24535 (.3)	2.97 (1.28, 3.87)
		Veijalainen, 2019		NRSI	hrHPV+CC triage	CC	134/17770 (.8)	48/15605 (.3)	2.45 (1.76, 3.41)
		Total							1.92 (1.5, 2.47)
	RCTs only	Elfstrom, 2021		RCT	hrHPV+LBC triage	LBC+hrHPV triage	1140/110197 (1)	844/90841 (.9)	1.11 (1.02, 1.22)
		Ogilvie, 2018	HPV FOCAL	RCT	hrHPV+LBC triage	LBC+hrHPV triage	147/9540 (1.5)	90/9408 (1)	1.61 (1.24, 2.09)
		Nygard, 2022		RCT	hrHPV+LBC triage	LBC+hrHPV triage	1263/77207 (1.6)	822/80240 (1)	1.6 (1.5, 1.7)
		Canfell, 2017	COMPASS	RCT	hrHPV+DS triage	LBC	24/2008 (1.2)	1/995 (.1)	11.89 (1.61, 87.8)
					hrHPV+LBC triage	LBC	20/1992 (1)	1/995 (.1)	9.99 (1.34, 74.3)
		Leinonen, 2012		RCT	hrHPV+CC triage	CC	540/66410 (.8)	319/65784 (.5)	1.68 (1.46, 1.92)
		Ronco, 2010	NTCC Phase II	RCT	hrHPV	CC	218/24661 (.9)	73/24535 (.3)	2.97 (1.28, 3.87)
		Total							1.84 (1.33, 2.54)
2	RCTs only	Ogilvie, 2018	HPV FOCAL	RCT	Cotesting	Cotesting	48/9540 (.5)	100/9408 (1.1)	0.47 (0.33, 0.66)
		Ronco, 2010	NTCC Phase II	RCT	CC	CC	12/23978 (.1)	38/24372 (.2)	0.32 (0.17, 0.61)
1 + 2	RCTs only	Ogilvie, 2018	HPV FOCAL	RCT	hrHPV+LBC triage/Cotest	LBC+hrHPV triage/Cotest	195/9540 (2)	190/9408 (2)	1.01 (0.83, 1.23)
		Ronco, 2010	NTCC Phase II	RCT	hrHPV/CC	CC	230/24661 (.9)	111/24535 (.5)	2.06 (1.64, 2.58)

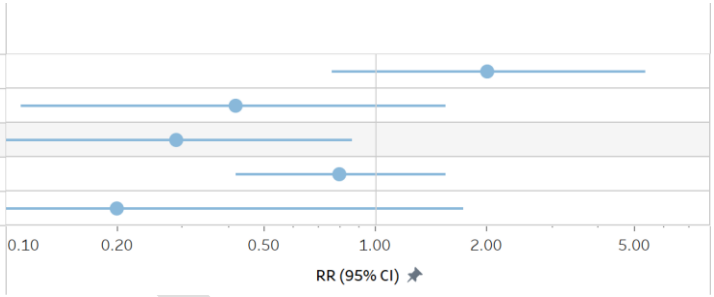


Note: Random effects REML model. I^2=94.6% for RCTs and NRSIs; I^2=96.1% for RCTs only.

Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; DS = dual stain; hrHPV = high risk human papillomavirus; IG = intervention group; KQ = key question; LBC = liquid-based cytology; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; RCT = randomized controlled trial; RR = relative risk.

Figure 14. KQ1: Co-Testing Screening Strategies, ICC

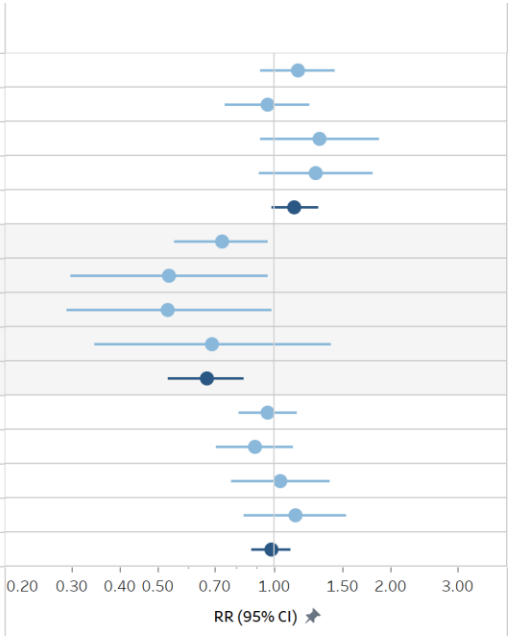
Round	Group	Author, year	Study name	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
1	RCTs only	Rijkaart, 2012	POBASCAM	Cotesting	CC	12/19999 (.1)	6/20106 (.03)	2.01 (0.76, 5.34)
		Kitchener, 2014	ARTISTIC	Cotesting	LBC	5/18386 (.03)	4/6124 (.1)	0.42 (0.11, 1.55)
2	RCTs only	Rijkaart, 2012	POBASCAM	Cotesting	Cotesting	4/19579 (.02)	14/19731 (.1)	0.29 (0.10, 0.86)
1 + 2	RCTs only	Rijkaart, 2012	POBASCAM	Cotesting	CC/Cotesting	16/19999 (.1)	20/20106 (.1)	0.80 (0.42, 1.54)
		Naucler, 2007	Swedescreen	Cotesting/CC	CC	1/6257 (.01)	5/6270 (.1)	0.20 (0.02, 1.72)



Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CC = conventional cytology; CG = control group; CI = confidence interval; ICC = invasive cervical cancer; IG = intervention group; KQ = key question; LBC = liquid-based cytology; POBASCAM = Population Based Screening Study Amsterdam Program; RCT = randomized controlled trial; RR = relative risk.

Figure 15. KQ1: Co-Testing Screening Strategies, CIN3+

Round	Group	Author, year	Study name	Design	Years of LTFU	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
1	RCTs only	Rijkaart, 2012	POBASCAM	RCT		Cotesting	CC	171/19999 (.9)	150/20106 (.7)	1.15 (0.92, 1.43)
		Kitchener, 2014	ARTISTIC	RCT		Cotesting	LBC	233/18386 (1.3)	81/6124 (1.3)	0.96 (0.75, 1.23)
		Naucler, 2007	Swedescreen	RCT		Cotesting	CC	72/6257 (1.2)	55/6270 (.9)	1.31 (0.92, 1.87)
		Ronco, 2010	NTCC Phase I	RCT		Cotesting	CC	75/22708 (.3)	58/22466 (.3)	1.28 (0.91, 1.80)
		Total								1.13 (0.98, 1.30)
2	RCTs only	Rijkaart, 2012	POBASCAM	RCT		Cotesting	Cotesting	88/19579 (.4)	122/19731 (.6)	0.73 (0.55, 0.96)
		Kitchener, 2014	ARTISTIC	RCT		LBC	LBC	29/11676 (.2)	18/3866 (.5)	0.53 (0.30, 0.96)
		Naucler, 2007	Swedescreen	RCT		CC	CC	16/6257 (.3)	30/6270 (.5)	0.53 (0.29, 0.98)
		Ronco, 2010	NTCC Phase I	RCT		CC	CC	13/22093 (.1)	19/22330 (.1)	0.69 (0.34, 1.40)
		Total								0.67 (0.53, 0.83)
1 + 2	RCTs only	Rijkaart, 2012	POBASCAM	RCT		Cotesting	CC/Cotesting	259/19999 (1.3)	272/20106 (1.4)	0.96 (0.81, 1.14)
		Kitchener, 2014	ARTISTIC	RCT		Cotesting/LBC	LBC	262/18386 (1.4)	98/6124 (1.6)	0.89 (0.71, 1.12)
		Naucler, 2007	Swedescreen	RCT		Cotesting/CC	CC	88/6257 (1.4)	85/6270 (1.4)	1.04 (0.77, 1.39)
		Ronco, 2010	NTCC Phase I	RCT		Cotesting/CC	CC	88/22708 (.4)	77/22466 (.3)	1.13 (0.83, 1.53)
		Total								0.98 (0.87, 1.10)

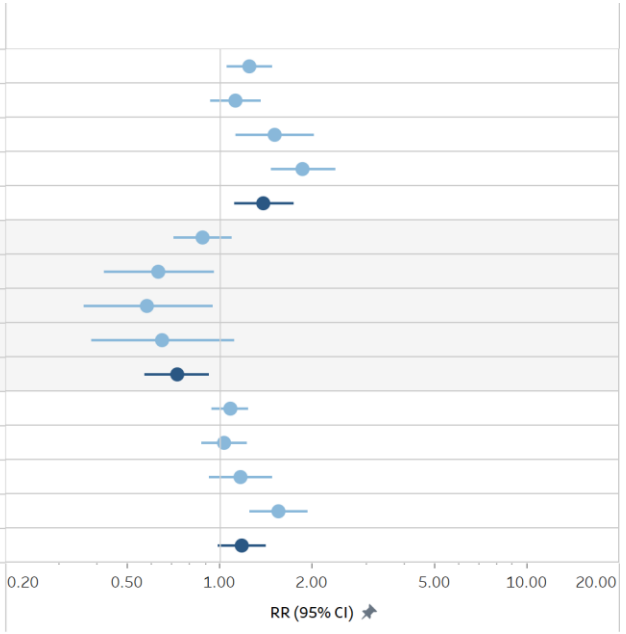


Note: Random-effects REML model. I^2=0% for round 1; I^2=0% for round 2; I^2=0% for round 1+2 (cumulative).

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; IG = intervention group; KQ = key question; LBC = liquid-based cytology; LTFU = long-term followup; POBASCAM = Population Based Screening Study Amsterdam Program; NTCC = New Technologies for Cervical Cancer Screening; RCT = randomized controlled trial; RR = relative risk.

Figure 16. KQ1: Co-Testing Screening Strategies, CIN2+

Round	Group	Author, year	Study name	Design	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
1	RCTs only	Rijkaart, 2012	POBASCAM	RCT	Cotesting	CC	267/19999 (1.3)	215/20106 (1.1)	1.25 (1.05, 1.49)
		Kitchener, 2009	ARTISTIC	RCT	Cotesting	LBC	453/18386 (2.5)	134/6124 (2.2)	1.13 (1.93, 1.36)
		Naucler, 2007	SWEDESCREEN	RCT	Cotesting	CC	144/6257 (2.3)	76/6270 (1.2)	1.51 (1.13, 2.02)
		Ronco, 2010	NTCC Phase I	RCT	Cotesting	CC	187/22708 (.8)	99/22466 (.4)	1.87 (1.47, 2.38)
		Total							1.39 (1.12, 1.74)
2	RCTs only	Rijkaart, 2012	POBASCAM	RCT	Cotesting	Cotesting	160/19579 (.8)	184/19731 (.9)	0.88 (2.71, 1.09)
		Kitchener, 2009	ARTISTIC	RCT	LBC	LBC	65/11676 (.6)	34/3866 (.9)	0.63 (2.42, 0.96)
		Naucler, 2007	SWEDESCREEN	RCT	CC	CC	25/6257 (.4)	43/6270 (.7)	0.58 (2.36, 0.95)
		Ronco, 2010	NTCC Phase I	Cotesting	CC	CC	22/22093 (.1)	34/22330 (.2)	0.65 (2.38, 1.12)
		Total							0.73 (0.57, 0.92)
1+2	RCTs only	Rijkaart, 2012	POBASCAM	Cotesting	Cotesting	CC	427/19999 (2.1)	399/20106 (2)	1.08 (0.94, 1.24)
		Kitchener, 2009	ARTISTIC	Cotesting	Cotesting	LBC	518/18386 (2.8)	167/6124 (2.7)	1.03 (0.87, 1.23)
		Naucler, 2007	SWEDESCREEN	Cotesting	Cotesting	CC	139/6257 (2.2)	119/6270 (1.9)	1.17 (0.92, 1.49)
		Ronco, 2010	NTCC Phase I	Cotesting	Cotesting	CC	209/22708 (.9)	133/22466 (.6)	1.55 (1.25, 1.93)
		Total		Cotesting					1.18 (0.99, 1.41)



Note: Random-effects REML model. I^2=75.1% for round 1; I^2=35.4% for round 2; I^2=71.5% for round 1 + 2 (cumulative).

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; IG = intervention group; KQ = key question; LBC = liquid-based cytology; LTFU = long-term followup; POBASCAM = Population Based Screening Study Amsterdam Program; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; RCT = Randomized controlled trial; RR = relative risk.

Figure 17. KQ2: HPV Assays in Test Accuracy/Agreement Studies

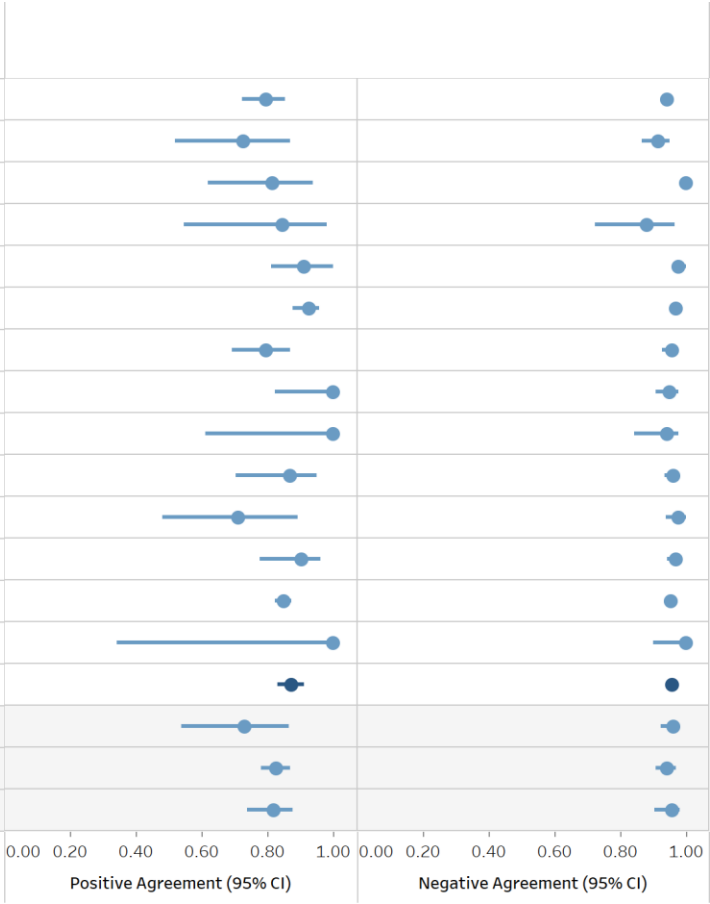
		High-risk HPV types													Low-risk HPV types																			
HPV assay	Author Year	16	18	31	33	35	39	45	51	52	56	58	59	66	68	6	11	26	34	40	42	43	44	53	54	55	57	61	69	70	73	82	83	84
Cobas 4800 System	Eamratsameekool, 2023	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
	Inturrisi, 2021	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
	Ketelaars, 2017	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
	McLarty, 2019	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
	Satake, 2020	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
	Stanczuk, 2021	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
Hybrid capture 2	Balasubramanian, 2010	X	X	X	X	X	X	X	X	X	X	X	X		X																			
	Harvey, 2016	X	X	X	X	X	X	X	X	X	X	X	X		X																			
	Nutthachote, 2019	X	X	X	X	X	X	X	X	X	X	X	X		X																			
	Reisner, 2018	X	X	X	X	X	X	X	X	X	X	X	X		X																			
	Szarewski, 2007	X	X	X	X	X	X	X	X	X	X	X	X		X																			
Aptima HPV assay	Des Marais, 2018	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
GP5/6 PCR enzyme immunoassay	Polman, 2019	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
HPV Selfy	Avian, 2022	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
Roche Real-Time High-Risk HPV	Ilardo, 2022	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
	Wong, 2024	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
SPF10-DEIA HPVLiPA25 (PCR)	Porras, 2015	X	X	X	X	X	X	X	X	X	X	X	X																					
Vitro HPV	Lopez Castro, 2024	X	X	X	X	X	X	X	X	X	X	X	X	X	X																			
Anyplex II HPV28	Hagihara, 2016	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X			X	X	X	X	X		
NuclisSENS easy MAG	Vergara, 2018	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
PANA RealTyper	Kim, 2022	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																	

* While Hybrid capture 2 can also identify low-risk HPV types, the studies using Hybrid capture 2 assays noted that they were looking for high-risk types only.

Abbreviations: HPV = human papillomavirus; KQ = key question; NR = not reported; PCR = polymerase chain reaction.

Figure 18. KQ2: Test Agreement of Self-Collected and Clinician-Collected hrHPV

Screening test	Condition	Author Year	Total n	Screening positive, %	Condition, %	Positive agreement (95% CI)	Negative agreement (95% CI)
Self-collected vaginal HPV	hrHPV	Avian, 2022	910	17.0	15.6	0.80 (0.72, 0.85)	0.95 (0.93, 0.96)
		Des Marais, 2018	193	15.5	11.4	0.73 (0.52, 0.87)	0.92 (0.87, 0.95)
		Eamratsameekool, 2023	535	4.1	5.0	0.82 (0.62, 0.94)	1.00 (0.99, 1.00)
		Harvey, 2016	47	31.9	27.7	0.85 (0.55, 0.98)	0.88 (0.73, 0.97)
		Ilardo, 2022	157	20.4	21.0	0.91 (0.81, 1.00)	0.98 (0.96, 1.00)
		Ketelaars, 2017	2049	10.0	8.0	0.93 (0.88, 0.96)	0.97 (0.96, 0.98)
		Lim, 2022	300	20.0	21.0	0.79 (0.69, 0.87)	0.96 (0.93, 0.98)
		Lopez Castro, 2024	185	14.1	9.7	1.00 (0.82, 1.00)	0.95 (0.91, 0.98)
		McLarty, 2019	58	15.5	10.3	1.00 (0.61, 1.00)	0.94 (0.84, 0.98)
		Nutthachote, 2019	400	10.0	7.5	0.87 (0.70, 0.95)	0.96 (0.94, 0.98)
		Reisner, 2018	131	13.0	16.0	0.71 (0.48, 0.89)	0.98 (0.94, 1.00)
		Satake, 2020	300	14.7	13.7	0.90 (0.77, 0.96)	0.97 (0.95, 0.99)
		Stanczuk, 2021	4605	16.8	15.2	0.85 (0.82, 0.87)	0.95 (0.95, 0.96)
		Wong, 2024	35	5.7	5.7	1.00 (0.34, 1.00)	1.00 (0.90, 1.00)
		Total				0.87 (0.83, 0.91)	0.96 (0.95, 0.98)
Urine	hrHPV	Kim, 2022	210	12.4	12.4	0.73 (0.54, 0.86)	0.96 (0.92, 0.98)
		Vergara, 2018	543	48.4	55.6	0.83 (0.78, 0.87)	0.95 (0.91, 0.97)
	HPV	Hagihara, 2016	240	42.9	50.0	0.82 (0.74, 0.88)	0.96 (0.91, 0.98)

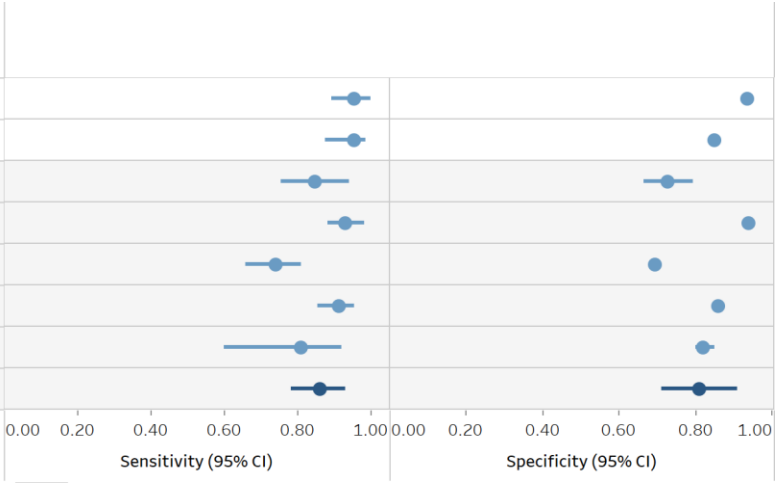


Note: I^2=62.3% for positive agreement, I^2=94.1% for negative agreement

Abbreviations: CI = confidence interval; hrHPV = high risk human papillomavirus; KQ = key question.

Figure 19. KQ2: Test Accuracy of Self-Collected hrHPV Test

Condition	Author Year	Total n	Screening positive, %	Condition, %	Sensitivity (95% CI)	Specificity (95% CI)
CIN3+	Polman, 2019	7643	7.4	1.0	0.95 (0.89, 1.00)	0.94 (0.93, 0.94)
	Stanczuk, 2021	4617		1.8	0.95 (0.88, 0.98)	0.85 (0.84, 0.86)
CIN2+	Balasubramanian, 2010	1665	33.1	7.8	0.85 (0.76, 0.94)	0.73 (0.67, 0.79)
	Polman, 2019	7643	7.4	1.5	0.93 (0.88, 0.98)	0.94 (0.94, 0.95)
	Porras, 2015	5109	31.8	2.7	0.74 (0.66, 0.81)	0.69 (0.68, 0.71)
	Stanczuk, 2021	4617		3.3	0.91 (0.86, 0.95)	0.86 (0.85, 0.87)
	Szarewski, 2007	920	19.2	2.3	0.81 (0.60, 0.92)	0.82 (0.80, 0.85)
	Total				0.86 (0.78, 0.93)	0.81 (0.71, 0.91)

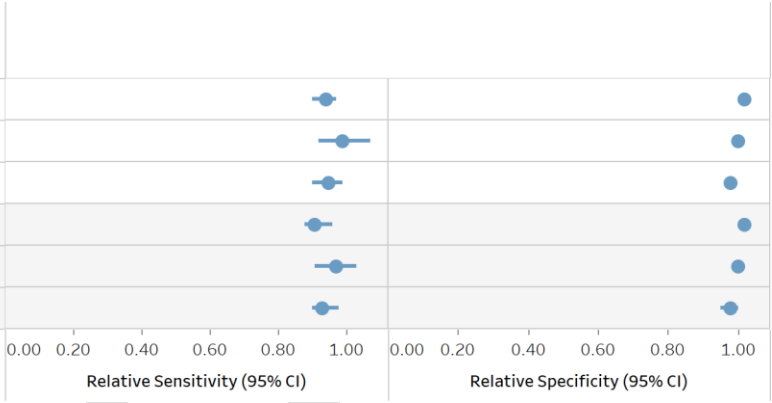


Note: I^2=80.3% for sensitivity; I^2=99.7% for specificity

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; KQ = key question.

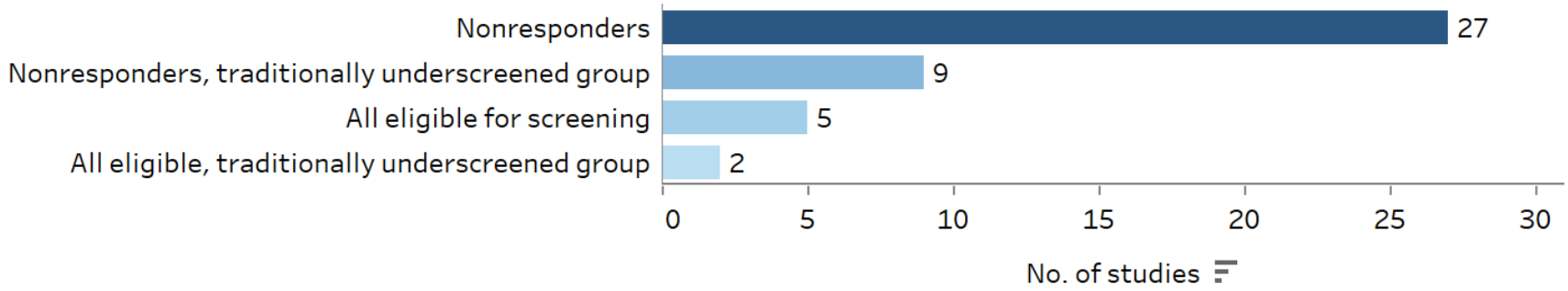
Figure 20. KQ2: Relative Test Accuracy of Self-Collected hrHPV Test

Condition	Author Year	Total n	Screening positive, %	Condition, %	Sensitivity (95% CI)	Specificity (95% CI)
CIN3+	Inturrisi, 2021	487015	7.4 (self), 9.3 (clinic)		0.94 (0.90, 0.97)	1.02 (1.02, 1.02)
	Polman, 2019	13925	7.4 (self), 7.2 (clinic)	1.0	0.99 (0.92, 1.07)	1.00 (0.99, 1.01)
	Stanczuk, 2021	4617		2.2	0.95 (0.90, 0.99)	0.98 (0.97, 0.98)
CIN2+	Inturrisi, 2021	487015	7.4 (self), 9.3 (clinic)		0.91 (0.88, 0.96)	1.02 (1.01, 1.02)
	Polman, 2019	13925	7.4 (self), 7.2 (clinic)	1.5	0.97 (0.91, 1.03)	1.00 (0.99, 1.01)
	Stanczuk, 2021	4617		4.0	0.93 (0.90, 0.98)	0.98 (0.95, 1.00)



Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; KQ = key question.

Figure 21. KQ2 Uptake: Target Population* of Included Studies

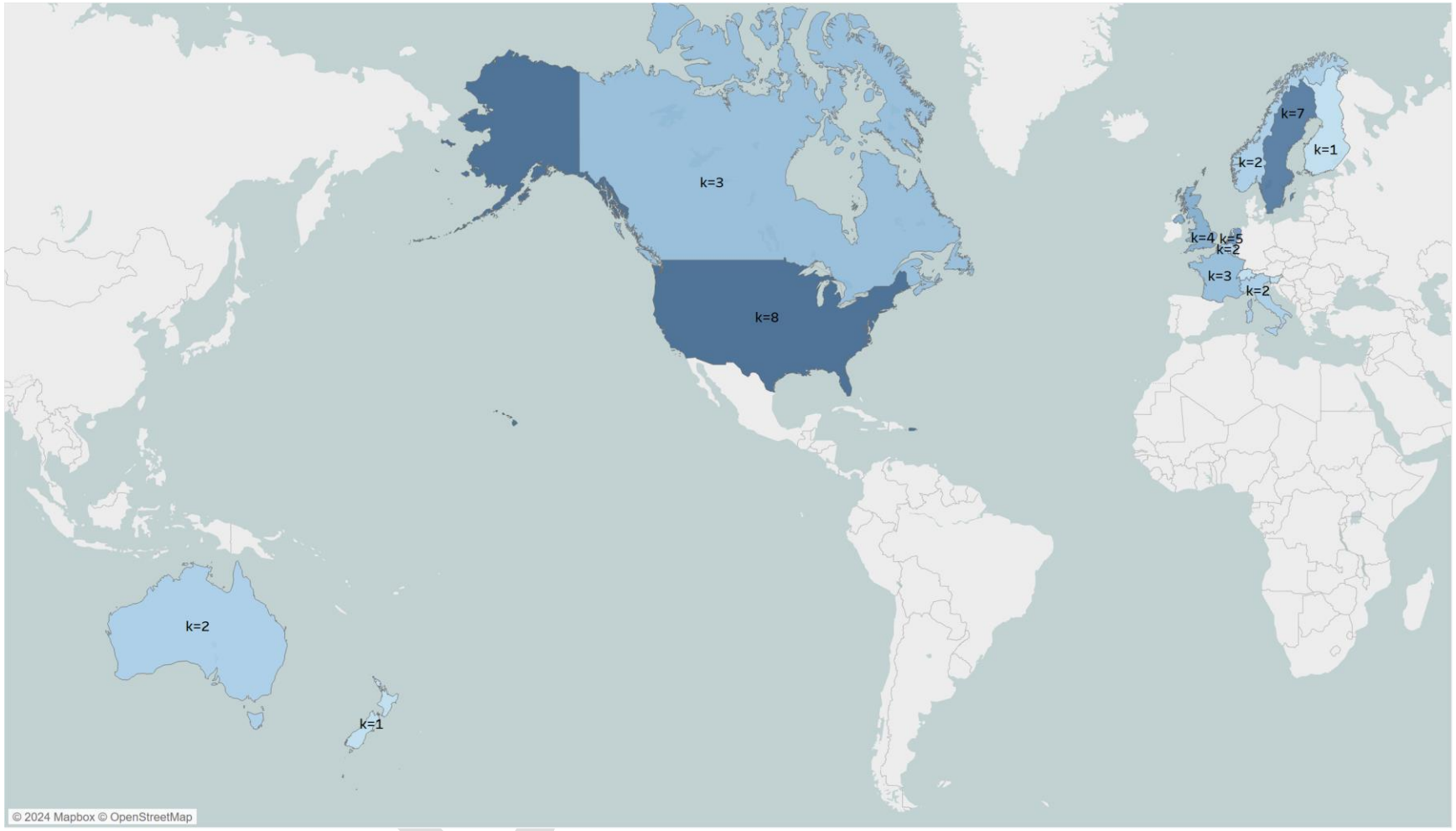


* One study[181] reported results stratified by screening history and is counted here among the nonresponders and all eligible for screening.

Note: Darker color indicates more studies

Abbreviations: KQ = key question; No. = number; Nonresponders = not up to date with recommended cervical cancer screening.

Figure 22. KQ2 Uptake: Location of Included Studies

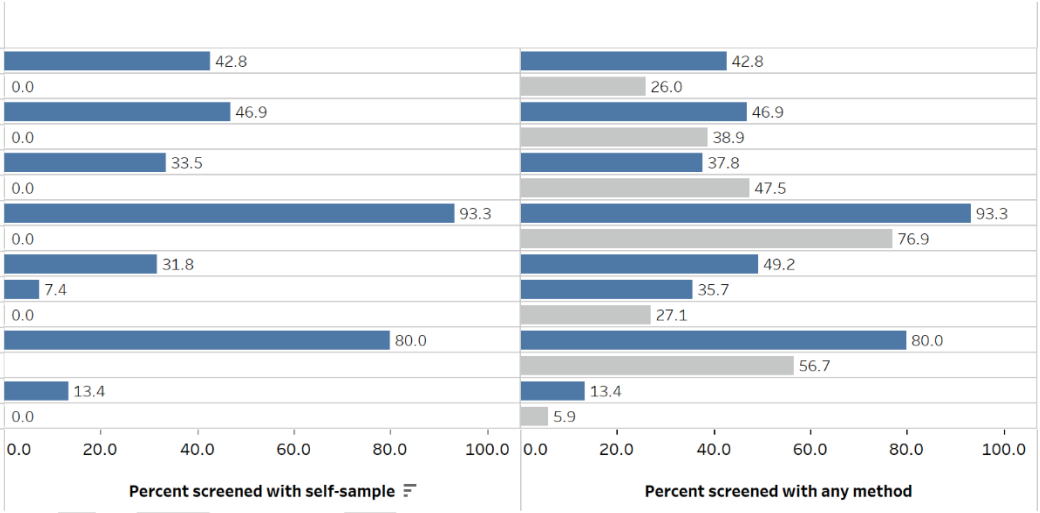


Note: Darker color indicates more studies

Abbreviations: k = number of studies; KQ = key question.

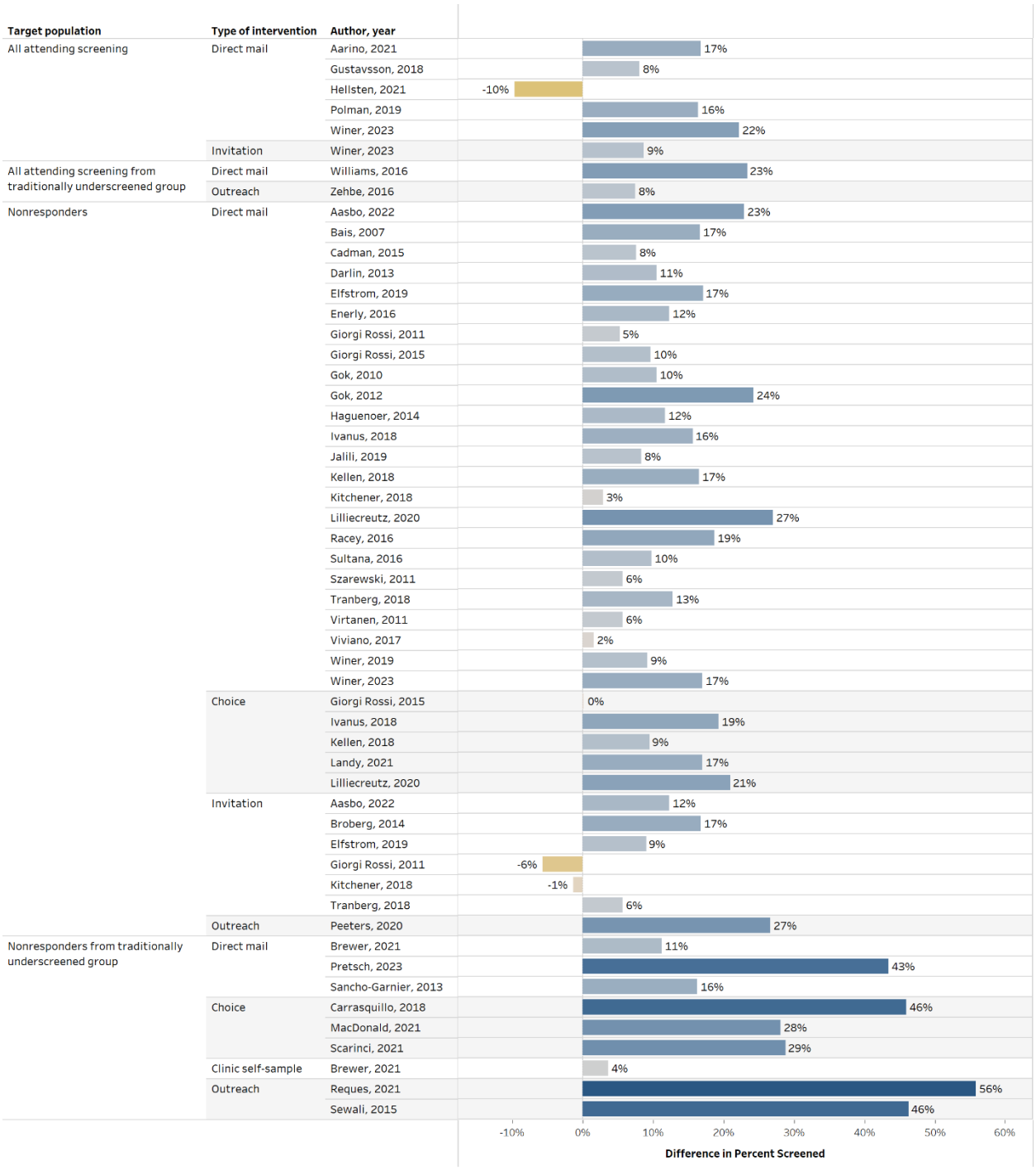
Figure 23. KQ2 Uptake: Uptake of Cervical Cancer Screening Among Studies Recruiting All Participants Eligible for Screening

Target population	Author, year	Arm	Type of Screening	n analyzed	Percent screened with self-sample	Percent screened with any method
All eligible for screening	Aarino, 2021	IG1	Direct mail	5,767	42.8	42.8
		CG	Usual care (+/- reminder)	5,846	0.0	26.0
	Gustavsson, 2018	IG1	Direct mail	17,046	46.9	46.9
		CG	Usual care (+/- reminder)	16,364	0.0	38.9
	Hellsten, 2021	IG1	Direct mail	14,765	33.5	37.8
		CG	Usual care (+/- reminder)	14,839	0.0	47.5
	Polman, 2019	IG1	Direct mail	8,193	93.3	93.3
		CG	Usual care (+/- reminder)	8,168	0.0	76.9
	Winer, 2023	IG1	Direct mail	2,897	31.8	49.2
		IG2	Invitation	7,462	7.4	35.7
		CG	Usual care (+/- reminder)	12,142	0.0	27.1
All eligible, traditionally underscreened group	Williams, 2016	IG1	Direct mail	60	80.0	80.0
		CG	Usual care (+/- reminder)	60		56.7
	Zehbe, 2016	IG1	Outreach	404	13.4	13.4
		CG	Usual care (+/- reminder)	598	0.0	5.9



Abbreviations: CG = control group; IG = intervention group; KQ = key question.

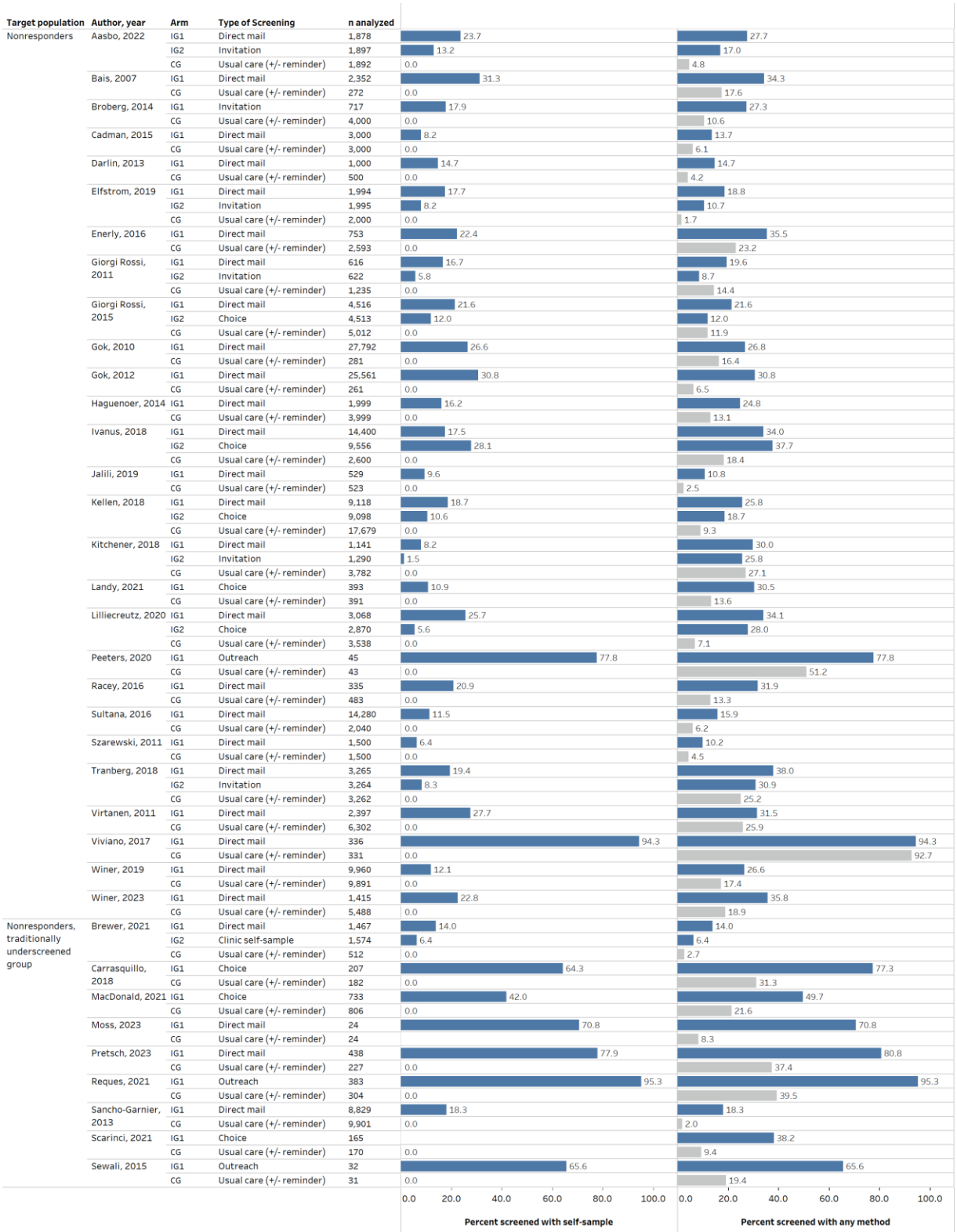
Figure 24. KQ2 Uptake: Difference Between IG and CG in Percent Screened With Any Method



Note: Darker shading indicates higher percent.

Abbreviations: CG = control group; IG = intervention group; KQ = key question; Nonresponders = not up to date with recommended cervical cancer screening.

Figure 25. KQ2 Uptake: Uptake of Cervical Cancer Screening Among Studies Recruiting All Participants Who Are Not Up to Date With Cervical Cancer Screening



Abbreviations: CG = control group; IG = intervention group; KQ = key question; Nonresponders = not up to date with recommended cervical cancer screening.

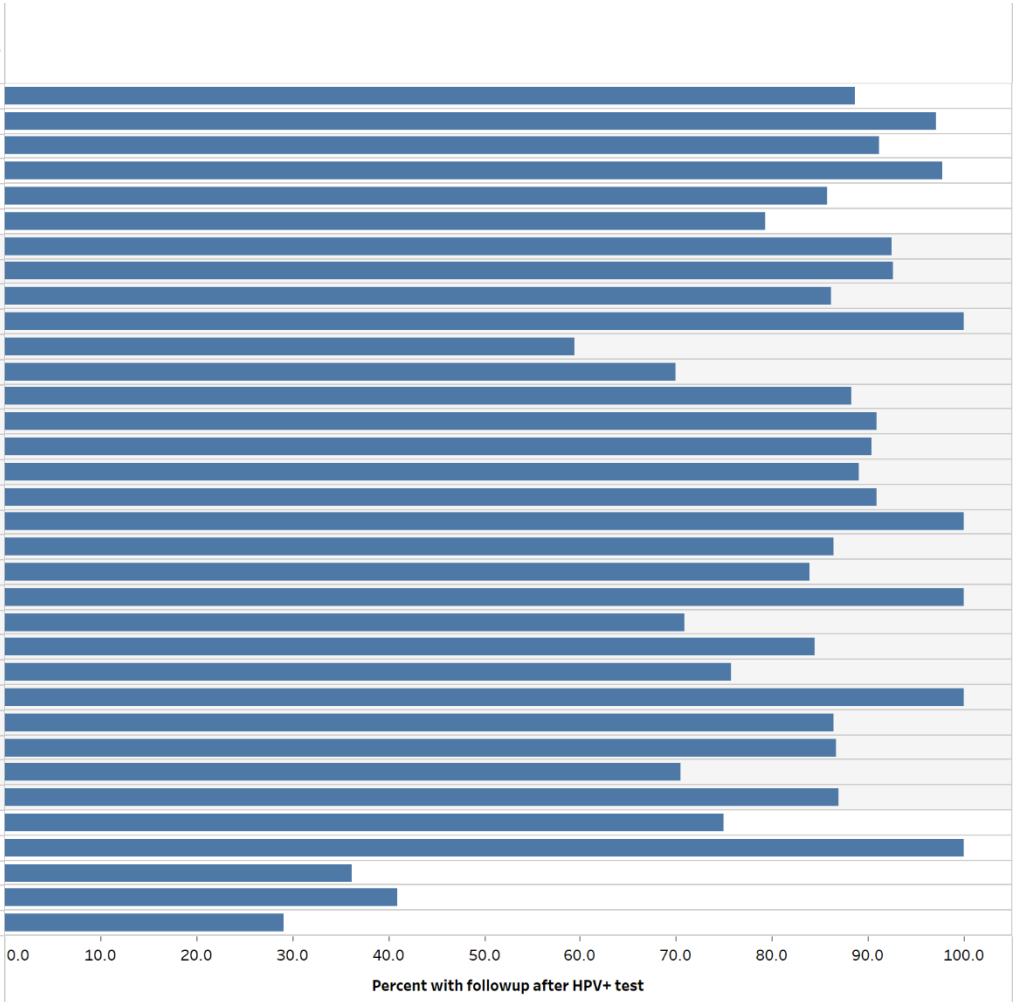
Figure 26. KQ2 Uptake: Uptake of Full Screening

Target population	Author, year	Type of Screening	Percent with full screening uptake
All eligible for screening	Aarino, 2021	Direct mail	99.6
	Gustavsson, 2018	Direct mail	99.8
	Hellsten, 2021	Direct mail	95.4
	Polman, 2019	Direct mail	99.8
	Winer, 2023	Direct mail	99.2
		Invitation	99.5
All eligible, traditionally underscreened group	Williams, 2016	Direct mail	70.8
Nonresponders	Aasbo, 2022	Direct mail	99.2
		Invitation	99.4
	Bais, 2007	Direct mail	97.9
	Broberg, 2014	Invitation	100.0
	Cadman, 2015	Direct mail	96.6
	Darlin, 2013	Direct mail	98.0
	Elfstrom, 2019	Direct mail	100.0
		Invitation	100.0
	Enerly, 2016	Direct mail	98.5
	Giorgi Rossi, 2011	Direct mail	98.3
	Gok, 2010	Direct mail	99.0
	Gok, 2012	Direct mail	99.1
	Haguenoer, 2014	Direct mail	98.6
	Jalili, 2019	Direct mail	100.0
	Kellen, 2018	Direct mail	98.8
		Choice	99.4
	Landy, 2021	Choice	100.0
	Lilliecreutz, 2020	Direct mail	100.0
		Choice	100.0
	Sultana, 2016	Direct mail	98.5
	Szarewski, 2011	Direct mail	100.0
	Virtanen, 2011	Direct mail	98.5
	Viviano, 2017	Direct mail	95.3
	Winer, 2019	Direct mail	98.9
	Winer, 2023	Direct mail	99.4
Nonresponders, traditionally underscreened group	Brewer, 2021	Direct mail	99.0
		Clinic self-sample	98.0
	Pretsch, 2023	Direct mail	89.5
	Reques, 2021	Outreach	74.8
	Sancho-Garnier, 2013	Direct mail	89.6
	Scarinci, 2021	Choice	100.0

Abbreviations: Nonresponders = not up to date with recommended cervical cancer screening.

Figure 27. KQ2 Uptake: Proportion Completing Clinical Followup Testing of Those With Positive hrHPV Test in the Intervention Groups

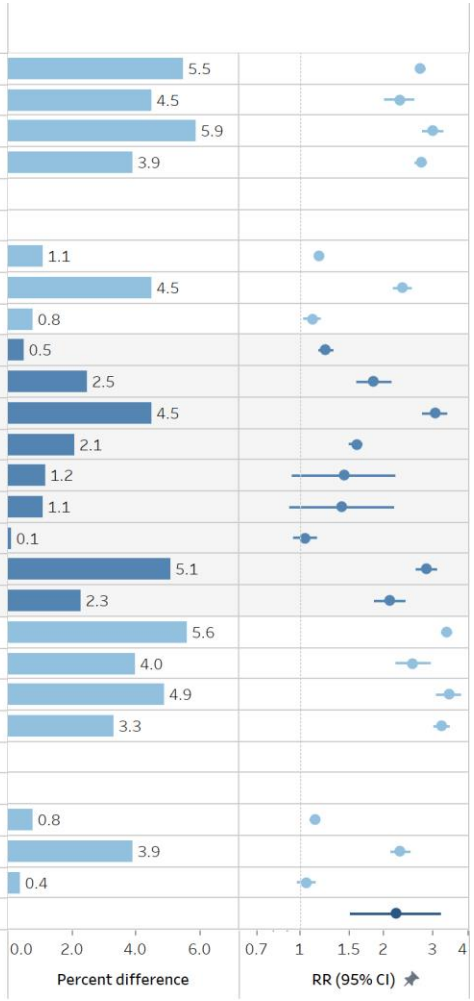
Target population	Author, year	Type of Screening	Percent with followup after HPV+ test
All eligible for screening	Aarino, 2021	Direct mail	88.6
	Gustavsson, 2018	Direct mail	97.1
	Hellsten, 2021	Direct mail	91.2
	Polman, 2019	Direct mail	97.7
	Winer, 2023	Direct mail	85.7
		Invitation	79.4
Nonresponders	Aasbo, 2022	Direct mail	92.5
		Invitation	92.6
	Bais, 2007	Direct mail	86.2
	Broberg, 2014	Invitation	100.0
	Cadman, 2015	Direct mail	59.4
	Darlin, 2013	Direct mail	70.0
	Enerly, 2016	Direct mail	88.2
	Giorgi Rossi, 2011	Direct mail	90.9
	Gok, 2010	Direct mail	90.4
	Gok, 2012	Direct mail	89.1
	Haguenoer, 2014	Direct mail	90.9
	Jalili, 2019	Direct mail	100.0
	Kellen, 2018	Choice	86.5
		Direct mail	83.9
	Landy, 2021	Choice	100.0
	Lilliecreutz, 2020	Choice	70.8
		Direct mail	84.5
	Sultana, 2016	Direct mail	75.7
	Szarewski, 2011	Direct mail	100.0
	Virtanen, 2011	Direct mail	86.4
	Viviano, 2017	Direct mail	86.7
	Winer, 2019	Direct mail	70.4
	Winer, 2023	Direct mail	87.0
Nonresponders, traditionally underscreened group	Brewer, 2021	Clinic self-sample	75.0
		Direct mail	100.0
	Reques, 2021	Outreach	36.2
	Sancho-Garnier, 2013	Direct mail	41.0
	Scarinci, 2021	Choice	29.2



Abbreviations: Nonresponders = not up to date with recommended cervical cancer screening.

Figure 28. KQ3: Primary hrHPV Screening Strategies, Burden of Testing

Outcome	Author, Year	Study Name	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
Screening test positive	Elfstrom, 2021		hrHPV with LBC triage	LBC with hrHPV triage	9712/110197 (8.8)	2955/90841 (3.3)	2.71 (2.60, 2.82)
	Ogilvie, 2018	HPV FOCAL	hrHPV with LBC triage	LBC with hrHPV triage	771/9540 (8.1)	334/9408 (3.6)	2.28 (2.01, 2.58)
	Thomsen, 2021	HPV SCREEN DENMARK	hrHPV with LBC triage	LBC with hrHPV triage	1433/16067 (8.9)	716/23981 (3)	2.99 (2.74, 3.26)
	Nygard, 2022		hrHPV with LBC triage	LBC with hrHPV triage	4784/77207 (6.2)	1834/80240 (2.3)	2.71 (2.57, 2.86)
	Canfell, 2017	COMPASS	hrHPV with DS triage	LBC			
			hrHPV with LBC triage	LBC			
	Leinonen, 2012		hrHPV with CC triage	CC	4971/62106 (8)	4506/65747 (6.9)	1.17 (1.12, 1.21)
	Ronco, 2010	NTCC Phase II	hrHPV	CC	1936/24661 (7.9)	825/24535 (3.4)	2.33 (2.16, 2.53)
	Veijalainen, 2019		hrHPV with CC triage	CC	1455/17770 (8.2)	1160/15605 (7.4)	1.10 (1.02, 1.19)
Colposcopy referral/ attendance	Elfstrom, 2021		hrHPV with LBC triage	LBC with hrHPV triage	2489/110197 (2.3)	1663/90841 (1.8)	1.23 (1.16, 1.31)
	Ogilvie, 2018	HPV FOCAL	hrHPV with LBC triage	LBC with hrHPV triage	522/9540 (5.5)	280/9408 (3)	1.84 (1.59, 2.12)
	Thomsen, 2021	HPV SCREEN DENMARK	hrHPV with LBC triage	LBC with hrHPV triage	1057/16067 (6.6)	515/23981 (2.1)	3.05 (2.75, 3.38)
	Nygard, 2022		hrHPV with LBC triage	LBC with hrHPV triage	4305/77207 (5.6)	2845/80240 (3.5)	1.60 (1.50, 1.68)
	Canfell, 2017	COMPASS	hrHPV with DS triage	LBC	78/2008 (3.9)	27/995 (2.7)	1.43 (0.93, 2.2)
			hrHPV with LBC triage	LBC	76/1992 (3.8)	27/995 (2.7)	1.41 (0.91, 2.17)
	Leinonen, 2012		hrHPV with CC triage	CC	796/66410 (1.2)	755/65784 (1.1)	1.04 (0.95, 1.15)
	Ronco, 2010	NTCC Phase II	hrHPV	CC	1936/24661 (7.9)	679/24535 (2.8)	2.84 (2.60, 3.09)
	Veijalainen, 2019		hrHPV with CC triage	CC	779/17770 (4.4)	326/15605 (2.1)	2.10 (1.85, 2.38)
False positive rate for CIN2+	Elfstrom, 2021		hrHPV with LBC triage	LBC with hrHPV triage	8572/109057 (7.9)	2111/89997 (2.3)	3.35 (3.20, 3.51)
	Ogilvie, 2018	HPV FOCAL	hrHPV with LBC triage	LBC with hrHPV triage	624/9393 (6.6)	244/9318 (2.6)	2.54 (2.19, 2.93)
	Thomsen, 2021	HPV SCREEN DENMARK	hrHPV with LBC triage	LBC with hrHPV triage	1085/15719 (6.9)	480/23745 (2)	3.41 (3.07, 3.79)
	Nygard, 2022		hrHPV with LBC triage	LBC with hrHPV triage	3588/75512 (4.8)	1103/74944 (1.5)	3.23 (3.02, 3.45)
	Canfell, 2017	COMPASS	hrHPV with DS triage	LBC			
			hrHPV with LBC triage	LBC			
	Leinonen, 2012		hrHPV with CC triage	CC	4450/61585 (7.2)	4187/65428 (6.4)	1.13 (1.08, 1.18)
	Ronco, 2010	NTCC Phase II	hrHPV	CC	1718/24443 (7)	752/24462 (3.1)	2.29 (2.10, 2.49)
	Veijalainen, 2019		hrHPV with CC triage	CC	1321/17636 (7.5)	1112/15557 (7.1)	1.05 (0.97, 1.13)
	Total						2.20 (1.51, 3.21)

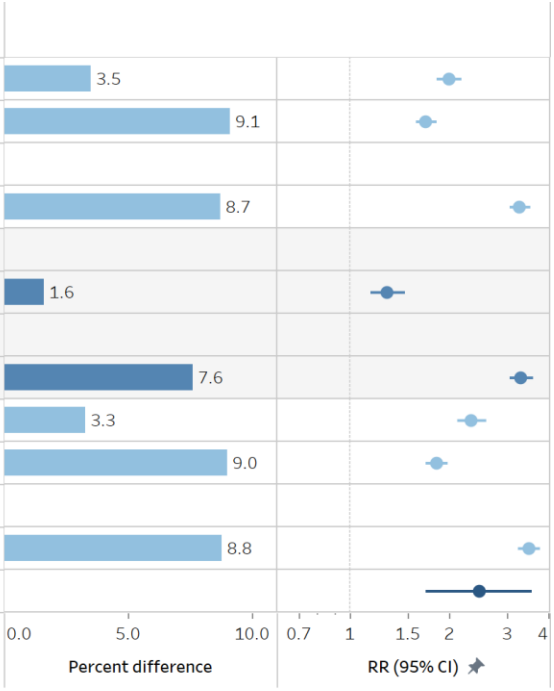


Note: Random-effects REML model for false positive rate. I^2=99.6%.

Abbreviations: CC = conventional cytology; hrHPV = high risk human papillomavirus; KQ = key question; LBC = liquid-based cytology; NTCC = New Technologies for Cervical Cancer Screening.

Figure 29. KQ3: Co-Testing Screening Strategies, Burden of Testing

Outcome	Author, Year	Study Name	Screening strategy	Comparison	IG n/n (%)	CG n/n (%)	RR (95% CI)
Screening test positive	Rijkaart, 2012	POBASCAM	Cotesting	CC	1406/19999 (7)	706/20106 (3.5)	2.00 (1.83, 2.19)
	Kitchener, 2014	ARTISTIC	Cotesting	LBC	4019/18386 (21.9)	786/6124 (12.8)	1.70 (1.59, 1.83)
	Naucler, 2007	Swedescreen	Cotesting	CC		150/6270 (2.4)	
	Ronco, 2010	NTCC Phase I	Cotesting	CC	2830/22708 (12.5)	855/22466 (3.8)	3.27 (3.04, 3.53)
Colposcopy referral/ attendance	Rijkaart, 2012	POBASCAM	Cotesting	CC			
	Kitchener, 2014	ARTISTIC	Cotesting	LBC	1247/18386 (6.8)	320/6124 (5.2)	1.30 (1.15, 1.46)
	Naucler, 2007	Swedescreen	Cotesting	CC			
	Ronco, 2010	NTCC Phase I	Cotesting	CC	2470/22708 (10.9)	738/22466 (3.3)	3.31 (3.06, 3.59)
False positive rate for CIN2+	Rijkaart, 2012	POBASCAM	Cotesting	CC	1139/19732 (5.8)	491/19891 (2.5)	2.34 (2.11, 2.59)
	Kitchener, 2014	ARTISTIC	Cotesting	LBC	3566/17933 (19.9)	652/5990 (10.9)	1.83 (1.69, 1.98)
	Naucler, 2007	Swedescreen	Cotesting	CC		74/6194 (1.2)	
	Ronco, 2010	NTCC Phase I	Cotesting	CC	2702/22042 (12.3)	771/21972 (3.5)	3.49 (3.23, 3.78)
	Total						2.46 (1.70, 3.57)



Note: Random-effects REML model for false positive rate; I^2=98.2%.

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CC = conventional cytology; CG = control group; CI = confidence Interval; CIN = cervical intraepithelial neoplasia; IG = Intervention group; KQ = key question; LBC = liquid-based cytology; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program; RR = relative risk.

Table 1. Cytology Test Result Categories, Bethesda System[43, 44]

Acronym	Description
ASC-US	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells – cannot exclude HSIL
LSIL	Low-grade Squamous Intraepithelial Lesion
HSIL	High-grade Squamous Intraepithelial Lesion; Includes moderate and severe dysplasia
AGC	Atypical Glandular Cells (specify endocervical or not otherwise specified [NOS])
---	Atypical Glandular Cells, favor neoplastic (specify endocervical or not otherwise specified [NOS])
AIS	Endocervical Adenocarcinoma In Situ
ADC	Adenocarcinoma
SCC	Squamous Cell Carcinoma

Table 2. Recent Cervical Cancer Screening Recommendations of Other Organizations, Sorted by Year

Organization	Year	Recommendation Statement
American College of Obstetrics and Gynecologists (ACOG)[249]	2021	• Screening should begin at 21 years and women ages 21−29 should be tested every 3 years with cytology alone. • Co-testing in women <30 is not recommended. • Women ages 30−65 should receive any of the following: co-testing with cytology and hrHPV testing every 5 years, FDA-approved primary hrHPV testing every 5 years, or cytology alone every 3 years. • Screening of individuals who have had a hysterectomy with the removal of the cervix and have no history of CIN2+ or cervical cancer is not recommended.
National Health Service (NHS)[250, 251]	2021	• All women and people with a cervix ages of 25−64 should go for regular cervical screening with primary HPV with cytology triage when invited. • Individuals aged 25−49 should be screened every 3 years. • Individuals aged 50−64 should be screened every 5 years. • Individuals aged 65 should be screened only if a recent test was abnormal. • Screening of individuals <25 years or individuals who have had a total hysterectomy is not recommended.
World Health Organization (WHO)[252]	2021	• Use either of the following strategies for cervical cancer prevention among the general population of women: 1.) hrHPV DNA detection in a screen-and-treat approach starting at age 30 years with regular screening every 5−10 years; 2.) hrHPV DNA detection in a screen, triage and treat approach starting at age 30 years with regular screening every 5−10 years.
The American Cancer Society (ACS)[215]	2020	• Individuals with a cervix should initiate cervical cancer screening at age 25 years and undergo primary hrHPV testing every 5 years through age 65 years (preferred); if primary hrHPV testing is not available, then individuals aged 25 to 65 years should be screened with co-testing every 5 years or cytology alone every 3 years (acceptable). • Individuals aged >65 years who have no history of CIN2+ within the past 25 years, and who have documented adequate negative prior screening in the prior 10 years, discontinue all cervical cancer screening. • Followup for individuals who screen positive for hrHPV and/or cytology should be in accordance with the 2019 American Society for Colposcopy and Cervical Pathology risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. • Individuals should not be screened more frequently than the recommended interval for the test used and should not be screened annually at any age by any method. • Individuals without a cervix and without a history of CIN2 or a more severe diagnosis in the previous 25 years or cervical cancer should not be screened.
American Academy of Family Physicians (AAFP)[253]	2018	• Cervical cancer screening in women aged <21 years leads to more harms than benefits and does not reduce cervical cancer incidence or mortality • Average-risk women 21−29 years of age should be screened every three years with cytology alone every five years with primary hrHPV testing, or every five year with co-testing. • Average-risk women 30−65 years of age should be screened every three years with cytology alone or every five years with a combination of cytology and hrHPV testing. • Cervical cancer screening should be discontinued in women ≥65 years with an adequate history of negative screening results. • Annual cervical cancer screening is not recommended for average-risk women of any age. • Women with a hysterectomy unrelated to cancer should not be screened for cervical cancer. • Women with a hysterectomy related to a history of cervical precancer (CIN2+) or cervical cancer should be screened for cervical cancer for 20 years after the hysterectomy. • Primary HPV testing may be considered for cervical cancer screening every three years in women ≥25 years.

Abbreviations: CIN = cervical intraepithelial neoplasia; FDA = Food & Drug Administration; hrHPV = high-risk human papillomavirus.

Table 3. KQ1 and KQ3: Summary Study and Population Characteristics

	Primary hrHPV No. of Studies (%)	Co-testing No. of Studies (%)
Design		
RCT	7 (70.0)	4 (80.0)
NRSI	3 (30.0)	1 (20.0)
Long-term followup from included RCT*	2 (NA)	2 (NA)
Quality		
Good	3 (30.0)	2 (40.0)
Fair	7 (70.0)	3 (60.0)
Country		
US	0 (0)	1 (20.0)
Europe	10 (100)	4 (80.0)
Population		
Population-based	9 (90.0)	4 (80.0)
Population-based + Primary care	1 (10.0)	0 (0)
Health System	0 (0)	1 (20.0)
Screening era		
Prior to HPV vaccination	3 (30.0)**	5 (100.0)
After HPV vaccination	7 (70.0)	0 (0)
Eligibility start age		
20	0 (0)	1 (20.0)
25	4 (40.0)	1 (20.0)
29/30	3 (30.0)	2 (40.0)
32/34/35	2 (20.0)	1 (20.0)
65	1 (10.0)	0 (0)
Eligibility end age		
38	0 (0)	1 (20.0)
56	0 (0)	1 (20.0)
59/60	4 (40.0)	1 (20.0)
64/65	4 (40.0)	1 (20.0)
69	2 (20.0)	0 (0)
NR	0 (0)	1 (20.0)
N analyzed		
<50,000	7 (70.0)	4 (80.0)
132,000-202,000	3 (30.0)	1 (20.0)
Screening comparison		
LBC with hrHPV triage	4 (40.0)	0 (0)
LBC	1 (10.0)	1 (20.0)
CC	3 (30.0)	4 (80.0)
NA	0 (0)	0 (0)
hrHPV with LBC triage (clinician-collected)	1 (10.0)	0 (0)
Usual care	1 (1.0)	
HPV Assay		
Cobas 4800	5† (45.4)	0 (0)
HC2	4† (36.4)	3 (60.0)
GP5+/6+ PCR	1 (9.1)	2 (40.0)
Abbott RealTime	1 (9.1)	0 (0)

* These studies include long-term followup from included RCTs and primarily included the same patient samples. These studies are not included further for the characteristics in this table.
† Not mutually exclusive; the COMPASS trial used both HC2 and Cobas.
** A recent NRSI[117] was counted as taking place prior to HPV vaccination since they recruited only participants aged 65-69 years.

Abbreviations: CC = conventional cytology; HC2 = Hybrid Capture 2; KQ = key question; LBC = liquid-based cytology; NA = not applicable; No. = number; NRSI= nonrandomized study of interventions; PCR = polymerase chain reaction; RCT = randomized controlled trial.

Table 4. KQ1 and KQ3: Screening Characteristics for RCTs and NRSIs, Primary hrHPV Strategies

Study design	Study name Author, year	Screening strategy	Comparison	HPV assay	Criteria for immediate colposcopy referral	Comparison criteria for immediate colposcopy referral	Number of screening rounds	Screening interval, years
RCT	Nygard, 2022[83]	hrHPV with LBC triage	LBC with hrHPV triage	Cobas 4800	HPV+ and ASC-US+	High-grade lesions (≥HSIL, ASC-H, AGC) ASC-US/LSIL+ or HPV+ x2*	1	NA
	Elfstrom, 2021[84]	hrHPV with LBC triage	LBC with hrHPV triage	Cobas 4800	HPV+ and ASC-US+	High-grade lesions (HSIL+, ASC-H, AGC) ASC-US and HPV+	1	NA
	IMPROVE Study Polman, 2019[86]	self-HPV with LBC triage	hrHPV with LBC triage	GP5/6	HPV+ and ASC-US+	ASC-US+ and HPV+	1	NA
	HPV FOCAL Ogilvie, 2018[87]	hrHPV with LBC triage	LBC with hrHPV triage	HC2	HPV+ and ASC-US+	ASC-US and HPV+ LSIL+	2	4
	COMPASS Canfell, 2017[88]	hrHPV with LBC triage	LBC	HC2 and Cobas 4800	HPV 16/18+ Other HPV+ and ASC-H/HSIL+	ASC-H/HSIL+	1	NA
		hrHPV with DS triage†	LBC	HC2 and Cobas 4800	HPV 16/18+ Other HPV+ and DS+	ASC-H/HSIL+	1	NA
	Leinonen, 2012[89]	hrHPV with CC triage	CC	HC2	HPV+ and LSIL+‡	LSIL+‡	1	NA
	NTCC Phase II Ronco, 2010[91]	hrHPV	CC	HC2	HPV+	ASC-US+ (7 centers) LSIL+ (2 centers)	2	3.5

Table 4. KQ1 and KQ3: Screening Characteristics for RCTs and NRSIs, Primary hrHPV Strategies

Study design	Study name Author, year	Screening strategy	Comparison	HPV assay	Criteria for immediate colposcopy referral	Comparison criteria for immediate colposcopy referral	Number of screening rounds	Screening interval, years
NRSI	HPV SCREEN DENMARK Thomsen, 2021[115]	hrHPV with LBC triage	LBC with hrHPV triage	Cobas 4800	HPV 16/18+ Other HPV+ and ASC-US+	HSIL+, ASC-H, AGC ASC-US/LSIL and HPV+ ASC-US/LSIL x2§	1	NA
	Veijalainen, 2019[116]	hrHPV with CC triage	CC	Abbott RealTime	HPV+ and LSIL+	LSIL+	1	NA
	Tranberg, 2023[117]	hrHPV with LBC triage	Usual care	Cobas 4800	HPV 16/18+ Other HPV+ and ASC-US+	NA	1	NA
LTFU	HPV FOCAL and FOCAL DECADE (LTFU) Gottschlich, 2023[183]	hrHPV with LBC triage	CC	HC2	HPV+ and ASC-US+	ASC-US and HPV+ LSIL+	2	4
	Leinonen, 2012 (LTFU) Vahteristo, 2024[118]	hrHPV with CC triage	CC	HC2	HPV+ and LSIL+‡	LSIL+‡	1	NA

* Women who were HPV+ with ASC-US or LSIL were tested again in 6-12 mo. If the subsequent test was HPV+ or LSIL+ they were referred to colposcopy.
† DS with CINtec PLUS
‡ LSIL+ or Pap classes III to V
§ Women who were HPV- with LSIL were tested again 12 months later. If the subsequent test was ASC-US+ they were referred to colposcopy

Abbreviations: AGC = atypical glandular cells; ASC-H = atypical squamous cells – cannot exclude HSIL; ASC-US = atypical squamous cells of undetermined significance; CC = conventional cytology; DS = dual stain; HC2 = Hybrid Capture 2; hrHPV = high risk human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; KQ = key question; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; LTFU = long-term followup; NA = not applicable; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; RCT = randomized controlled trial.

Table 5. KQ1 and KQ3: Study and Population Characteristics for RCTs and NRSIs, Primary hrHPV Strategies

Study design	Study name Author, year	Country	Recruitment setting	Recruitment years	Brief population description	N randomized	N analyzed	Mean age
RCT	Nygard, 2022[83]	Norway	Population-based	2015-2017	Women aged 34-69 years	302,295	157,447	50
	Elfstrom, 2021[84]	Sweden	Population-based	2014-2016	Women aged 30-64 years	395,725	201,038	45
	HPV FOCAL Ogilvie, 2018[87]	Canada	Population-based	2008-2012	Women aged 25-65 years, not HIV-positive or receiving immunosuppressive therapy, without history of CIN2+ in past 5 years	19,009	18,948	45
	COMPASS Canfell, 2017[88]	Australia	Population-based, Primary care clinic	2013-2014	Women aged 25-64 years, not pregnant	5,006	4,995	NR
	Leinonen, 2012[89]	Finland	Population-based	2003-2007	Women aged 25-65 years	203,425	132,194	NR
	NTCC Phase II Ronco, 2010[91]	Italy	Population-based	2002-2004	Women aged 25-60 years, not pregnant, without history of CIN2+ in past 5 years	49,196	49,196	41
	IMPROVE Study Polman, 2019[86]	Netherlands	Population-based	2015-2016	Women aged 30-60 years, not pregnant or childbirth <6 months ago	16,410	13,925	46
NRSI	HPV SCREEN DENMARK Thomsen, 2021[115]	Denmark	Population-based	2017-2018	Women aged 30-59 years	40,048	40,048	44
	Veijalainen, 2019[116]	Finland	Population-based	2012-2014	Women aged 35-60 years	46,708	33,375	50
	Tranberg, 2023[117]	Denmark	Population-based	2019	Women aged 65-69 years with no record of cytology in previous 5.5 years and no HPV exit test	45,237	44,579	68
LTFU	HPV FOCAL and FOCAL-DECADE (LTFU) Gottschlich, 2023[183]	Canada	Population-based	2008-2012	Participants from HPV FOCAL HPV-based screening arms (women aged 25-65 years, not HIV-positive or receiving immunosuppressive therapy, without history of CIN2+ in past 5 years) and a comparison cohort mirroring trial inclusion	1,156,489	1,156,489	NR

Table 5. KQ1 and KQ3: Study and Population Characteristics for RCTs and NRSIs, Primary hrHPV Strategies

Study design	Study name Author, year	Country	Recruitment setting	Recruitment years	Brief population description	N randomized	N analyzed	Mean age
	Leinonen, 2012 (LTFU) Vahteristo, 2024[118]	Finland	Population-based	2003-2007	Participants from Leinonen, 2012 (women aged 25-65 years)	101,947	101,947	NR

Abbreviations: CIN = cervical intraepithelial neoplasia; hrHPV = high risk human papillomavirus; KQ = key question; LTFU = long-term followup; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; RCT = randomized controlled trial.

Table 6. KQ1 and KQ3: Screening Characteristics for RCTs and NRSIs, Co-Testing Screening Strategies

Study design	Author, year	Screening strategy	Comparison	HPV assay	Criteria for immediate colposcopy referral	Comparison criteria for immediate colposcopy referral	Number of screening rounds	Screening interval, years
RCT	ARTISTIC Kitchener, 2014[85]	Co-testing	LBC*	HC2	LSIL+† HPV+ x2‡	LSIL+§	3	3
	Swedescreen Naucler, 2007[90]	Co-testing	CC	GP5+/6+ PCR	ASC-US+ (Stockholm) CIN2+ (Other regions) HPV+ x2‖	ASC-US+ (Stockholm) CIN2+ (Other regions)	2	3
	NTCC Phase I Ronco, 2010[91]	Co-testing	CC	HC2	HPV+ and ≥35 years ASC-US+ HPV+ x2‖	ASC-US+ (7 centers) LSIL+ (2 centers)	2	3
	POBASCAM Rijkaart, 2012[92]	Co-testing	CC*	GP5+/6+ PCR	LSIL+	LSIL+	2	5
NRSI	Katki, 2011[120]	Co-testing	NA (single arm)	HC2	LSIL+ HPV+ and ASC-US	NA	2	3
LTFU	Swedescreen (long-term followup) Elfstrom, 2014[119]	Co-testing	CC	GP5+/6+ PCR	ASC-US+ (Stockholm) CIN2+ (Other regions) HPV+ x2‖	ASC-US+ (Stockholm) CIN2+ (Other regions)	1	NA
	POBASCAM (long-term followup) Inturrisi, 2022[188]	Co-testing	CC*	GP5+/6+ PCR	LSIL+	LSIL+	4	5

* All women received HPV testing as well as cytology, but the HPV results were concealed in the comparison group.
† For the 3rd round, ASC-US+ and HPV+ were referred to colposcopy.
‡ Age 24-35 years HPV+, repeat HPV in 2 years, if HPV+ x2, referred to colposcopy.
§ For the 3rd round, HSIL+ were referred to colposcopy.
‖ Age 24-35 years HPV+, repeat HPV in 1 years, if HPV+ x2, referred to colposcopy.

Table 6. KQ1 and KQ3: Screening Characteristics for RCTs and NRSIs, Co-Testing Screening Strategies

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASC-US = atypical squamous cells of undetermined significance; CC = conventional cytology; CIN = cervical intraepithelial neoplasia; HC2 = Hybrid Capture 2; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; KQ = key question; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; LTFU = long-term followup; NA = not applicable; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; RCT = randomized controlled trial.

Table 7. KQ1 and KQ3: Study and Population Characteristics for RCTs and NRSIs, Co-Testing Strategies

Study design	Study name Author, year	Country	Recruitment setting	Recruitment years	Brief population description	N randomized	N analyzed	Mean age
RCT	ARTISTIC Kitchener, 2014[85]	UK	Population-based	2001-2003	Women aged 20-64 years	25078	24510	NR
	Swedescreen Naucler, 2007[90]	Sweden	Population-based	1997-2000	Women aged 32-38 years	12527	12527	35
	NTCC Phase I Ronco, 2010[91]	Italy	Population-based	2002-2004	Women aged 25-60 years, not pregnant, without history of CIN in the past 5 years	45174	45174	41
	POBASCAM Rijkaart, 2012[92]	Netherlands	Population-based	1999-2002	Women aged 30-60 years, without a history of CIN in the past 2 years	44938	42105	40
NRSI	Katki, 2011[120]	US	Health system	2003-2005	Women aged 30 years and older	NA	331818	NR
LTFU	Swedescreen (long-term followup) Elfstrom, 2014[119]	Sweden	Population-based	1997-2000	Participants from Swedescreen (women aged 32-38 years)	12527	12062	NR
	POBASCAM (long-term followup) Inturrisi, 2022[188]	Netherlands	Population-based	1999-2002	Participants from POBASCAM (women aged 30-60 years, without a history of CIN in the past 2 years) with a negative HPV test result at exit round	44938	18451	45

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; CIN = cervical intraepithelial neoplasia; KQ = key question; LTFU = long-term followup; NA = not applicable; NR = not reported; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; POBASCAM = Population Based Screening Study Amsterdam Program; RCT = randomized controlled trial; UK = United Kingdom; US = United States.

Table 8. KQ2: Summary Study and Population Characteristics for Vaginal and Urine Self-Sample Studies

	Agreement/Accuracy No. of Studies (%)	**Uptake** No. of Studies (%)
Design		
RCT	0 (0)	42 (100.0)
Test agreement	14* (73.7)	0 (0)
Test accuracy	6* (31.6)	0 (0)
Randomization stage		
Prior to consent	NA	32 (76.2)
After consent	NA	10 (23.8)
Quality		
Good	1 (5.3)	10 (23.8)
Fair	18 (94.7)	32 (76.2)
Country		
US	6 (31.6)	8 (19.1)
Europe	8 (42.1)	31 (73.8)
New Zealand/Australia	0 (0)	3 (7.1)
Asia	3 (15.8)	0 (0)
Central and South America	2 (10.5)	0 (0)
Population		
All eligible	16 (84.2)	5 (11.9)
All eligible from traditionally underscreened group	2 (10.5)	2 (4.8)
Nonresponders	0 (0)	26 (61.9)
Nonresponders from traditionally underscreened group	1 (5.3)	9 (21.4)
Mean age		
20-29	3 (15.8)	0 (0)
30-39	3 (15.8)	0 (0)
40-45	5 (26.3)	9 (21.4)
46-50	4 (21.0)	8 (19.1)
51-55	0 (0)	5 (11.9)
56+	0 (0)	1 (2.4)
NR	4 (21.0)	19 (45.2)
Inclusion of those aged 65+ years		
Yes	2 (10.5)	11 (26.2)
No	17 (89.5)	31 (73.8)
N analyzed		
<8,000	17 (89.5)	26 (61.9)
≥8,000	2 (10.5)	16 (38.1)
Screening test		
Self-collected vaginal HPV	17 (89.5)	42 (100.0)
Urine	2 (10.5)	0 (0)
Self-sample collection setting		
Clinic	16 (84.2)	1 (2.4)
Home	2 (10.5)	41 (97.6)
Clinic or Home	1 (5.3)	0 (0)

* Not mutually exclusive; one study reported both agreement and accuracy.

Abbreviations: hrHPV = high risk human papillomavirus; KQ = key question; No. = number; Nonresponders = not up to date with recommended cervical cancer screening; RCT = randomized controlled trial; US = United States.

Table 9. KQ2: Study and Population Characteristics for Vaginal and Urine Sample Test Agreement Studies, Sorted by Author

Author, year	Quality	Country	Target population	N analyzed	Age range (mean)	Screening history	Race/ ethnicity	Specimen type	Collection setting	HPV Assay
Avian, 2022[122]	Good	ITA	All attending screening	889	25-64 (NR)	NR	NR	Self-collected vaginal HPV	Clinic	HPV Selfy
Des Marais, 2018[128]	Fair	US	Low SES nonresponders	193	30-63 (45)	Median time since last Pap test: 5 years (range 4–20 years)	White: 44.5 Black: 25.7 Asian: 0.5 AI/AN: 0.5 Hispanic: 25.7 Other: 3.1	Self-collected vaginal HPV	Clinic	Aptima HPV assay
Eamratsameekool, 2023[137]	Fair	THA	All attending screening	535	30-59 (50)	Previous cervical screening: 98.7%	NR	Self-collected vaginal HPV	Clinic	Cobas 4800
Harvey, 2016[133]	Fair	US	All attending screening from traditionally underscreened group	47	NR (31)	NR	NR	Self-collected vaginal HPV	Clinic	HC2
Ilardo, 2022[123]	Fair	FRA	All attending screening	157	20-73 (40)		NR	Self-collected vaginal HPV	Clinic	Roche Real-Time High-Risk HPV
Ketelaars, 2017[131]	Fair	NLD	All attending screening	2194	29-61 (43)	NR	NR	Self-collected vaginal HPV	Clinic or Home	Cobas 4800
Lim, 2022[139]	Fair	SGP	All attending screening	300	30-69 (NR)	NR	NR	Self-collected vaginal HPV	Clinic	Cobas 6800
Lopez Castro, 2024[140]	Fair	ESP	All attending screening	382	23-73 (44)	NR	NR	Self-collected vaginal HPV	Clinic	Vitro
McLarty, 2019[126]	Fair	US	All attending screening	174	21+ (49)	NR	Black 76.8	Self-collected vaginal HPV	Home	Cobas 4800
Nutthachote, 2019[127]	Fair	THA	All attending screening	400	NR (46)	Last Pap test, % Never: 26 <2 years: 60 2-5 years: 11 >5 years: 3	NR	Self-collected vaginal HPV	Clinic	HC2
Reisner, 2018[129]	Fair	US	All attending screening from traditionally	150	21-50 (27)	Last Pap test, %: ≤1 year: 36.9 >1 to ≤2 years: 17.2	White: 74.7	Self-collected vaginal HPV	Clinic	HC2

Table 9. KQ2: Study and Population Characteristics for Vaginal and Urine Sample Test Agreement Studies, Sorted by Author

Author, year	Quality	Country	Target population	N analyzed	Age range (mean)	Screening history	Race/ ethnicity	Specimen type	Collection setting	HPV Assay
			underscreened group			>2 to ≤3 years: 23.0 >3 to ≤5 years: 13.9 >5 years: 9.0	Black: 2.7 Asian: 6.0 AI/AN: 0 Hispanic: 9.3 Other: 15.3			
Satake, 2020[125]	Fair	JPN	All attending screening	300	20-59 (NR)	NR	NR	Self-collected vaginal HPV	Clinic	Cobas 4800
Stanczuk, 2021[124]	Fair	GBR	All attending screening	5318	20-59 (41)	NR	NR	Self-collected vaginal HPV	Clinic	Cobas 4800
Wong, 2024[141]	Fair	US	All attending screening	35	30-65 (NR)	NR	Non-Hispanic White: 89 Hispanic: 6 Other: 2	Self-collected vaginal HPV	Home	Roche Real-Time High-Risk HPV
Hagihara, 2016[132]	Fair	JPN	All attending screening	240	19-58 (32)	NR	NR	Urine	Clinic	Anyplex II HPV28
Kim, 2022[138]	Fair	KOR	All attending screening	210	20-85 (40)	NR	NR	Urine	Clinic	PANA RealTyper
Vergara, 2018[130]	Fair	CHL	All attending screening	543	18-64 (36)	NR	NR	Urine	Clinic	NuclisSENS easy MAG

Abbreviations: AI/AN = American Indian/Alaska Native; CHL = Chile; FRA = France; GBR = Great Britain; HC2 = Hybrid Capture 2; HPV = human papillomavirus; ITA = Italy; JPN = Japan; KQ = key question; NLD = New Zealand; NR = not reported; SES = socioeconomic status; THA = Thailand; US = United States.

Table 10. KQ2: Screening Test and Reference Standard Characteristics for Vaginal and Urine Test Agreement Studies, Sorted by Author

Author, year	Specimen type	Self-collected HPV kit or brush/swab name	Collection setting	HPV Assay
Avian, 2022[122]	Self-collected vaginal HPV	FLO-QSwab	Clinic	HPV Selfy
Des Marais, 2018[128]	Self-collected vaginal HPV	Viba brush	Home	Aptima
Eamratsameekool, 2023[137]	Self-collected vaginal HPV	--	Clinic	Cobas 4800
Harvey, 2016[133]	Self-collected vaginal HPV	--	Clinic	Hybrid capture II
Ilardo, 2022[123]	Self-collected vaginal HPV	FLO-QSwab	Clinic	Roche Real-Time
Ketelaars, 2017[131]	Self-collected vaginal HPV	Evalyn Brush	Clinic or Home	Cobas 4800
Lim, 2022[139]	Self-collected vaginal HPV	--	Clinic	Cobas 6800
Lopez Castro, 2023[140]	Self-collected vaginal HPV	Vitroveil	Clinic	Vitro HPV
McLarty, 2019[126]	Self-collected vaginal HPV	Eve Medical HerSwab	Home	Cobas 4800
Nutthachote, 2019[127]	Self-collected vaginal HPV	QIAGEN brush	Clinic	Hybrid capture II
Reisner, 2018[129]	Self-collected vaginal HPV	Puritan Medical Products swab	Clinic	Hybrid capture II
Satake, 2020[125]	Self-collected vaginal HPV	Home Smear Set	Clinic	Cobas 4800
Stanczuk, 2021[124]	Self-collected vaginal HPV	--	Clinic	Cobas 4800
Wong, 2024[141]	Self-collected vaginal HPV	--	Home	Roche Real-Time
Hagihara, 2016[132]	Urine	--	Clinic	GeneAll Ribospin vRD
Kim, 2022[138]	Urine	--	Clinic	PANA RealTyper
Vergara, 2018[130]	Urine	--	Clinic	NuclisSENS easy MAG

Abbreviations: HPV = human papillomavirus; KQ = key question.

Table 11. KQ2: Study and Population Characteristics for Vaginal Sample Test Accuracy Studies, Sorted by Author

Author, year	Quality	Country	Target population	N analyzed	Age range (mean)	Screening history	Race/ ethnicity
Balasubramanian, 2010[134]	Fair	US	All attending screening	1665	18-50 (23)	NR	White: 73.8 Hispanic: 4.2
Polman, 2019[86]	Fair	NLD	All attending screening	13925	29 to 61 (46)	NR	NR
Porras, 2015[135]	Fair	Costa Rica	All attending screening	5109	18-25 (22)	NR	NR
Stanczuk, 2021[124]	Fair	GBR	All attending screening	5318	20-59 (41)	NR	NR
Szarewski, 2007[136]	Fair	GBR	All attending screening	920	20-65 (NR)	NR	NR
Inturrisi, 2021[121]	Fair	NLD	All attending screening	487015	30-60 (47)	Attending the previous round: Self-collection 69.4% (HPV+) 73.6% (HPV-) Clinician-collection 88.0% (HPV+) 92.3% (HPV-)	NR

Abbreviations: GBR = Great Britain; HPV = human papillomavirus; KQ = key question; NLD = New Zealand; NR = not reported; US = United States.

Table 12. KQ2: Screening Test and Reference Standard Characteristics for Vaginal Sample Test Accuracy Studies, Sorted by Author

Author, year	Screener	Collection setting	HPV Assay	Reference standard
Balasubramanian, 2010[134]	Self-collected vaginal HPV	Clinic	Hybrid capture 2	Women with positive/abnormal screening test results and a subset of women with negative screening test results were triaged to colposcopy. Corrected for verification bias.
Inturrisi, 2021[121]	Self-collected vaginal HPV	Home	Cobas 4800	Histological results from a nationwide network and registry of histo- and cytopathology. Followup was collected for a minimum of 17 months. Underscreened women were not included as screening non-attendance is a risk factor for CIN3+. Estimates of clinical sensitivity were from the tail of the distribution of cycle threshold scores in women with CIN3+.
Polman, 2019[86]	Self-collected vaginal HPV	Home	GP5/6 PCR enzyme immunoassay	Followup cytology, colposcopy, and histology in HPV-positive women were collected directly from pathology laboratories and gynecologists. A nationwide network and registry of histo- and cytopathology was consulted to complete cytology and histology when missing. Followup was collected for a minimum of 14 months. Adjusted data were obtained by imputing the expected number of CIN2+ and CIN3+ in HPV-positive women without histology or two-times normal cytology, based on their cytology and colposcopy results.
Porras, 2015[135]	Self-collected vaginal HPV	Clinic	SPF10-LiPA25	Histologically confirmed CIN2+, based on colposcopic referral after yearly (or six-monthly) cytology. Case patients were considered as having incident CIN2+ if the diagnosis occurred at or after the first annual followup visit (CIN2+ diagnosed prior to the first annual followup visit was categorized as prevalent CIN2+). Followup visits for incident CIN2+ occurred for 3 years.
Stanczuk, 2021[124]	Self-collected vaginal HPV	Clinic	Cobas 4800	The longitudinal sensitivity includes all CIN2/3+ detected at baseline and during the whole study period including the second screening round. Sixty-nine months was the longest time between the baseline test and diagnosis of an HG lesion. The computation of the longitudinal specificity was based on women who showed no evidence of previous CIN2+ (≤CIN1) who had normal LBC in at least two screening rounds.
Szarewski, 2007[136]	Self-collected vaginal HPV	Clinic	Hybrid capture 2	Women with either an abnormal cervical smear or a positive HPV test result were offered colposcopy, with biopsy as appropriate as the reference test. In addition, a randomly selected 5% sample of women who tested negative on all three tests were asked to attend for colposcopy, to ascertain whether any disease could be missed by all the tests. Not adjusted for verification bias, but only 1/16 women had low-grade CIN on biopsy.

Abbreviations: CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; KQ = key question; LBC = liquid-based cytology; PCR = polymerase chain reaction.

Table 13. KQ2 Uptake: Study and Population Characteristics for Self-Collected Vaginal Primary hrHPV Screening, Sorted by Author

Target population	Author, year	Quality	Country	N randomized*	Mean age	Age groups†	Race/Ethnicity†	Screening history†
All attending screening	Aarino, 2021 Aarnio, 2021 #1718}	Fair	Sweden	11613	42	30-60: 100%	NR	NR
	Gustavsson, 2018[159]	Fair	Sweden	33410	40	30-39: 49.6% 40-49: 50.4	NR	NR
	Hellsten, 2021[144]	Fair	Sweden	29604	NR	NR	NR	NR
	Polman, 2019[86]	Fair	Netherlands	16361	46	29-33: 9.7% 34-38: 11.5 39-43: 13.6 44-48: 18.2 49-53: 15.1 54-58: 17.8 59-61: 14.1	NR	NR
	Winer, 2023[181]	Good	US	22501	46	30-34: 18.3% 35-39: 15.2 40-44: 13.9 45-49: 13.2 50-54: 13.2 55-59: 13.4 60-64: 12.8	White: 71.3% Asian: 13.4 Black or AA: 5.6 Hawaiian/PI: 1.5 NA/AN: 0.7 More than 1 race: 3.6 Other: 3.9 Hispanic ethnicity: 8.4% Non-Hispanic: 91.6	Not overdue: 61.0% <3 years overdue: 15.9 3+ years overdue: 11.5 No prior screen: 11.7
All attending screening from traditionally underscreened group	Williams, 2016[166]	Fair	US	120	NR	21-29: 14% 30-49: 30 50-64: 56	African American: 80% White: 13 Refused: 7	Last pap test >12 months to <3 years: 83% 3 to <5 years: 6 5 years +: 8 Refused to answer: 3
	Zehbe, 2016[162]	Fair	Canada	1002	NR	25-69: 100%	First Nations: 100%	NR
Nonresponders	Aasbo, 2022[142]	Good	Norway	5667	54	36-45: 23.3% 46-55: 26.8 56-65: 34.6 66-69: 15.3	NR	Time since last screening: 10-15 years: 31.5% >15 years: 34.4 Never: 34.1

Table 13. KQ2 Uptake: Study and Population Characteristics for Self-Collected Vaginal Primary hrHPV Screening, Sorted by Author

Target population	Author, year	Quality	Country	N randomized*	Mean age	Age groups†	Race/Ethnicity†	Screening history†
	Bais, 2007[169]	Fair	Netherlands	2624	NR	30-50: 100%	NR	NR
	Broberg, 2014[170]	Fair	Sweden	4800	47	30-40: 30% 41-51: 34 52-61: 36	NR	Pap history None: 40% >10 years: 36 6-10 years: 25
	Cadman, 2015[167]	Fair	UK	6000	40	25-29: 20.0% 30-34: 17.3 35-39: 12.6 40-44: 13.0 50-54: 12.8 55-59: 8.3 60-65: 3.8	NR	Time from last cytology to date of invitation No previous cytology: 36.8% >10 years: 16.1 5-10 years: 26.2 3-5 years: 18.9 0-3 years: 2.0 Mean number of months from last cytology test: 92.9
	Darlin, 2013[171]	Fair	Sweden	1500	51	NR	NR	NR
	Elfstrom, 2019[154]	Good	Sweden	5989	48	33-50: 59.5% 51-60: 40.5	NR	Time since last smear obtained in organized screening, years 0-0.5: 0.5% 10-15: 2.3 >15: 19.5 No smears on record: 77.7
	Enerly, 2016[163]	Fair	Norway	3346	NR	26-34: 33.8% 35-49: 37.8 50-69: 28.4	NR	NR
	Giorgi Rossi, 2011[172]	Fair	Italy	2473	NR	35-65: 100%	NR	NR
	Giorgi Rossi, 2015[168]	Fair	Italy	14041	48	<39: 23.7% 40-49: 37.5 50-59: 29.8 60+: 10.8	NR	NR
	Gok, 2010[173]	Fair	Netherlands	27163	NR	NR	NR	NR
	Gok, 2012[174]	Fair	Netherlands	25822	NR	29-33: 16.3% 34-38: 19.1 39-43: 16.3	NR	NR

Table 13. KQ2 Uptake: Study and Population Characteristics for Self-Collected Vaginal Primary hrHPV Screening, Sorted by Author

Target population	Author, year	Quality	Country	N randomized*	Mean age	Age groups†	Race/Ethnicity†	Screening history†
						44-48: 14.7 49-53: 12.3 54-58: 8.9 59-63: 10.4		
	Haguenoer, 2014[175]	Fair	France	5998	51	30-49: 50% 50-65: 50	NR	NR
	Ivanus, 2018[155]	Fair	Slovenia	26556	50	30-64: 100%	NR	NR
	Jalili, 2019[153]	Fair	Canada	1052	52	30-39: 7.4% 40-49: 27.7 50-59: 41.0 60-69: 23.9		
	Kellen, 2018[157]	Fair	Belgium	35354	NR	30-34: 7.8% 35-39: 8.9 40-44: 8.1 45-49: 9.2 50-54: 10.5 55-59: 12.6 60-64: 19.3	NR	NR
	Kitchener, 2018[160]	Fair	UK	6213	NR	NR	NR	NR
	Landy, 2021[145]	Good	UK	784	NR	50-54: 33.4% 55-59: 36.5 60-64: 30.1	White: 57.0% Black: 17.3 Asian: 15.7 Mixed/other/ unknown: 9.9	Time since last screening test, % Late (6-<10 years): 68.4 Very late (10-15 years): 31.6
	Lilliecreutz, 2020[150]	Fair	Sweden	9410	NR	30-64: 100%	NR	NR
	Peeters, 2020[151]	Fair	Belgium	88	NR	25-34: 9% 35-44: 20 45-54: 28 55-64: 42		Time interval since last Pap smear 3 years: 18% 4+ years: 82
	Racey, 2016[165]	Fair	Canada	818	NR	30-70: 100%	NR	NR
	Sultana, 2016[164]	Good	Australia	16320	NR	30-39: 29.9% 40-49: 25.9 50-59: 20.3 60-69: 23.9	NR	Never screened: 50% Under screened: 50
	Szarewski, 2011[178]	Fair	UK	3000	48	<35: 5.7%	NR	NR
	Tranberg, 2018[158]	Good	Netherlands	9791	NR	30-39: 38% 40-49: 41 50-64: 21	NR	Unscreened: 18% Underscreened: 25 Regularly screened: 57

Table 13. KQ2 Uptake: Study and Population Characteristics for Self-Collected Vaginal Primary hrHPV Screening, Sorted by Author

Target population	Author, year	Quality	Country	N randomized*	Mean age	Age groups†	Race/Ethnicity†	Screening history†
	Virtanen, 2011[179]	Fair	Finland	8699	NR	30-60: 100%	NR	NR
	Viviano, 2017[161]	Fair	Switzerland	667	42	25-69: 100%	NR	Previous CC screening Yes: 81.7% No: 18.3
	Winer, 2019[152]	Good	US	19851	50.1	30-34: 8.1% 35-39: 9.4 40-44: 12.0 45-49: 13.9 50-54: 17.2 55-59: 19.6 60-64: 19.7	Non-Hispanic: 94.8% Hispanic: 5.2 Unknown: 6.6 White: 76.8% Asian: 9.6 Black/AA: 4.7 NH/PI: 1.5 AI/AN: 1.6 >1 race: 3.1 Other: 2.6 Unknown: 6.7	Time since last Pap test, years (by length of enrollment in health plan) Enrolled 3.4 to <5 years No test: 68.4% >3.4 to <5: 31.7 Enrolled 5 to <10 years No test: 34.5% >3.4 to <5: 48.5 5 to <10: 17.0 Enrolled 10+ years No test: 15.0% >3.4 to <5: 48.8 5 to <10: 25.6 10+: 10.8
	Winer, 2023[181]	Good	US	6903	46	30-34: 18.3% 35-39: 15.2 40-44: 13.9 45-49: 13.2 50-54: 13.2 55-59: 13.4 60-64: 12.8	White: 71.3% Asian: 13.4 Black or AA: 5.6 Hawaiian/PI: 1.5 NA/AN: 0.7 More than 1 race: 3.6 Other: 3.9 Hispanic ethnicity: 8.4% Non-Hispanic: 91.6	Not overdue: 61.0% <3 years overdue: 15.9 3+ years overdue: 11.5 No prior screen: 11.7
Nonresponders from traditionally underscreened group	Brewer, 2021[143]	Good	New Zealand	3553	44	30-39: 38.1% 40-49: 26.9 50-59: 21.4 60-69: 13.7	Maori: 30.2% Pacific: 35.2 Asian: 34.6	Previous screening history Never screened: 44.0% Under screened: 56.0

Table 13. KQ2 Uptake: Study and Population Characteristics for Self-Collected Vaginal Primary hrHPV Screening, Sorted by Author

Target population	Author, year	Quality	Country	N randomized*	Mean age	Age groups†	Race/Ethnicity†	Screening history†
	Carrasquillo, 2018[156]	Good	US	389	48	30-65: 100%	Hispanic: 59.1% Haitian: 34.9 Black non-Haitian: 6.0	Ever had a Pap smear: 83.2%
	MacDonald, 2021[148]	Fair	Australia	1539	42	25-29: 19% 30-39: 26 40-49: 22 50-59: 23 60-69: 11	Maori: 60%	Time since last screen, %: 4-5 years: 32 6-10 years: 28 >10 years: 16 Never screened: 24
	Moss, 2023[182]	Fair	US	48	56	50-65: 100%	Non-Hispanic White: 83.3% Non-Hispanic African-American or Black: 4.2 Multiracial: 12.5	NR
	Pretsch, 2023[180]	Good	US	697	42	25-34: 31% 35-44: 26 >45: 43	Black non-Latina or non-Hispanic, %: 46 White non-Latina or non-Hispanic: 39 Latina or Hispanic: 8 Other (AI/AN, NH/PI, Asian, other ethnicities): 6	Median time since last cervical cancer screening, years: 5 Not sure, but >4 years ago: 8% Never screened: 4
	Reques, 2021[146]	Fair	France	687	41	<40: 50.4% 40+: 49.6	NR	Screening test completion (%): 57.2
	Sancho-Garnier, 2013[176]	Fair	France	18730	NR	35-39: 23.6% 40-44: 22.6 45-49: 19.0 50-54: 15.2 55-59: 11.8 60-64: 6.1 65-69: 1.7	NR	NR
	Scarinci, 2021[176]	Fair	US	335	43	NR	NR	Last pap test 4 years ago: 38.2% 5 years ago: 16.8 >5 years ago: 40.6

Table 13. KQ2 Uptake: Study and Population Characteristics for Self-Collected Vaginal Primary hrHPV Screening, Sorted by Author

Target population	Author, year	Quality	Country	N randomized*	Mean age	Age groups†	Race/Ethnicity†	Screening history†
								Never: 2.7 Don't know/Unsure: 1.8
	Sewali, 2015[177]	Fair	US	63	55	25-70: 100%	Somali origin: 100%	Last Pap test 3.5 years: 34.9% 5-10 years: 9.5 >10 years: 4.8 Never: 50.8

* N randomized, eligible, and offered the intervention

Abbreviations: AA = African American; AI/AN = American Indian/Alaska Native; KQ = key question; NH/PI = Native Hawaiian/Pacific Islander; NR = not reported; UK = United Kingdom; US = United States.

Table 14. Summary of Evidence

Key question	Screening strategy (Comparator)	Outcome	No. of included studies and individuals	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
1. What is the comparative effectiveness of different cervical cancer screening strategies?	Primary HPV with or without cytology triage (Cytology with or without HPV triage)	CIN3+	K=8 (6 RCTs, 2 NRSIs) N analyzed =637,241	Age 25-69 <u>Round 1:</u> CIN3+: Pooled RR 1.80 (95% CI, 1.38 to 2.36), I^2=90.4%, 6 RCTs and 2 NRSIs <u>Round 2 (exit):</u> CIN3+: RR 0.22 (0.08 to 0.58) and RR 0.42 (95% CI, 0.25 to 0.70), 2 RCTs NRSI results consistent with RCT findings	Consistent Precise	Mostly per protocol analyses Variable protocols and length of f/u Only 2 studies with more than one round (exit round)	Moderate for increased detection of precancer	Absolute differences between screening strategies were small Studies in countries with organized screening programs Most studies without women with HPV vaccination
		ICC	K=6 (4 RCTs, 2 NRSIs, 1 LTFU*) N analyzed =569,097	Age 25-69 <u>Round 1:</u> ICC: Pooled RR 1.27 (95% CI, 0.86 to 1.88), I^2=51.3%, 3 RCTs and 2 NRSIs NRSI results consistent with RCT findings	Consistent Imprecise	Mostly per protocol analyses Variable protocols and length of f/u Low incidence of ICC	Insufficient	Studies in countries with organized screening programs Most studies without women with HPV vaccination
	Primary HPV with cytology triage (usual care)	CIN3+	K=1 (1 NRSI) N analyzed =44,579	Age 65-69 <u>Round 1:</u> CIN3+: RR 11.1 (95% CI, 4.81 to 25.5)	NA	One study Limited to a single round	Low for increased detection of precancer	Study conducted in Denmark in older women not up to date with screening recommendations
		ICC	K=1 (1 NRSI) N analyzed =44,579	Age 65-69 <u>Round 1:</u> RR 2.98 (95% CI, 0.75 to 11.9)	NA	One study Limited to a single round	Insufficient	Study conducted in Denmark in older women not up to date with screening recommendations
	Self-collected primary HPV	CIN3+	K=1 (1 RCT)	Age 30-60 <u>Round 1:</u>	NA	One study	Low for no difference in detection	Conducted in the Netherlands

Table 14. Summary of Evidence

Key question	Screening strategy (Comparator)	Outcome	No. of included studies and individuals	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
	(clinician-collected primary HPV)		N analyzed =13,925	No difference in the detection of CIN3+ between arms			of precancer	Possible effect modification by age
		ICC	K=1 (1 RCT) N analyzed =13,925	Age 30-60 <u>Round 1:</u> No difference in the detection of ICC between arms	NA	One study Low incidence of ICC	Insufficient	
	Co-testing (cytology)	CIN3+	K=7 (4 RCTs, 1 NRSIs, 2 LTFU*) N analyzed =122,316	Age 20-64 <u>Round 1:</u> CIN3+: Pooled RR 1.13 (95% CI, 0.98 to 1.30), I^2=0%, 4 RCTs <u>Round 2 (exit):</u> CIN3+: Pooled RR 0.67 (95% CI, 0.53 to 0.83), I^2=0%, 4 RCTs NRSI results were consistent with RCT findings	Consistent Precise	Variable protocols and length of f/u	Moderate for increased detection of precancer	Absolute differences were small Studies in countries or health care settings with organized screening programs All trials among women unvaccinated for HPV
		ICC	K=4 (3 RCTs, 1 NRSI, 1 LTFU*) N analyzed =77,142	Age 20-64 <u>Round 1:</u> RR 0.42 (95% CI, 0.11 to 1.55) and RR 2.01 (95% CI, 0.76 to 5.34) POBASCAM with lower detection of ICC in the exit round (RR 0.29 [95% CI, 0.10 to 0.86]).	Inconsistent Imprecise	Low incidence of ICC	Low for reduction in ICC	Studies in countries or health care settings with organized screening programs All trials among women unvaccinated for HPV
2. What is the test accuracy of	Self-collected HPV	Test Agreement	K=14 (14 test agreement studies)	Age 20-73 <u>HPV:</u>	Consistent Precise	Variable HPV assays	Moderate for adequate	Most studies with in-clinic collection of self-samples

Table 14. Summary of Evidence

Key question	Screening strategy (Comparator)	Outcome	No. of included studies and individuals	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
and adherence to self-collected HPV samples?	(clinician-collected HPV)		N analyzed =9,905	Pooled positive agreement: 0.87 (95% CI, 0.83 to 0.91), I^2=62.3% Pooled negative agreement: 0.96 (95% CI, 0.95 to 0.98), I^2=94.1%		Primarily estimates for single round	test agreement	
		Test Accuracy	K=6 (6 test accuracy studies) N analyzed =513,952	Age 18-65 <u>CIN2+:</u> Relative sensitivity: 0.91 (95% CI, 0.88 to 0.96) to 0.97 (95% CI, 0.91, to 1.03), k=3 Relative specificity: 0.98 (95% CI, 0.95 to 1.00) to 1.02 (95% CI, 1.01 to 1.02), k=3 <u>CIN3+:</u> Relative sensitivity: 0.94 (95% CI, 0.90 to 0.97) to 0.99 (95% CI, 0.92 to 1.07), k=3 Relative specificity: 0.98 (95% CI, 0.95 to 1.00) to 1.02 (95% CI, 1.02 to 1.02), k=3	Consistent Precise	Variable HPV assays Primarily estimates for single round study accounts for majority of participants Few studies reported accuracy to detect CIN3+	Moderate for adequate test accuracy	All studies used DNA-based HPV assays
		Uptake	K=42 (RCTs) N analyzed =386,080	Age 21-69 Most studies increased proportion of screening with self-sample versus usual care/clinic screening (40/42 studies, absolute difference 2 to 56 percent)	Consistent Imprecise	Higher uptake when consent obtained prior to randomization. Variable delivery and reminders Estimates for single round	Moderate for increased uptake	Few studies in the US Few studies in unselected populations Primarily mailed self-collected sampling, not in-clinic self-sampling High proportion of full screening uptake

Table 14. Summary of Evidence

Key question	Screening strategy (Comparator)	Outcome	No. of included studies and individuals	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
								after completing initial HPV screening
3. What are the comparative harms of different cervical cancer screening strategies?	Primary HPV with or without cytology triage (cytology with or without HPV triage)	Burden of testing (colposcopy and false positive rate)	Colposcopy: K=8 (6 RCT, 2 NRSI, 1 LTFU*) N analyzed =637,241 FPR: K=7 (5 RCT, 2 NRSI) N analyzed =616,796	Age 25-65 <u>Round 1:</u> Referral/receipt of colposcopy: RR 1.04 (95% CI, 0.95 to 1.15) to 3.05 (95% CI, 2.75 to 3.38) FPR for CIN2+: RR 2.20 (1.51 to 3.21), I^2=99.6%, k=7	Consistent Imprecise	Variable protocols (more conservative protocols with lower burden of testing) Limited to a single round	Moderate for increased burden of testing	Protocols for followup of abnormal screening not consistent with current ASCCP guidance Effect modification by age with greater differences in younger participants (<34/35 years)
		False negative rate for ICC	K=4 (2 RCT, 2 NRSI) N=363,064	Age 25-65 <u>Round 1:</u> No statistically significant difference between arms	Consistent Imprecise	Low incidence of ICC Lack of adequate folllowup Limited to a single round	Insufficient	Studies in countries with organized screening programs
		Psychological harms	K=1 (RCT) N analyzed =2000	Age 34-69 No difference in depression and anxiety measured by PHQ-4 at 4 to 24 months	NA	One study Limited to a single round	Low for no psychological harm	Study conducted in Norway in unvaccinated women
	Primary HPV with cytology triage	Burden of testing (colposcopy)	K=1 (NRSI) N analyzed =44,579	Age 65-69 <u>Round 1:</u>	NA	One study Limited to a single round	Low for no difference in burden of testing	Study conducted in Denmark in older women not up to date

Table 14. Summary of Evidence

Key question	Screening strategy (Comparator)	Outcome	No. of included studies and individuals	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
	(usual care)			Colposcopy per CIN2+ case: 11.6 (95% CI, 0.85 to 15.8) with catch-up screening versus 10.1 (95% CI, 5.1 to 18.8) with usual care				with screening recommendations
	Self-collected primary HPV (clinician-collected primary HPV)	Burden of testing (colposcopy and false positive rate)	K=1 (RCT) N analyzed =13,925	Age 30-60 <u>Round 1:</u> No difference in FPR between collection methods	NA	One study Limited to a single round	Low for no difference in burden of testing	Study conducted in the Netherlands
		False Negative rate for ICC	K=1 N analyzed =13,925	Age 30-60 No missed ICC in either arm	NA	Low incidence of ICC	Insufficient	NA
	Co-testing (cytology)	Burden of testing (colposcopy, and false positive rate for CIN2+)	K=2 (2 RCT) N analyzed =69,684 [colpo] K=3 (3 RCT) N analyzed =107,560 [FPR]	Age 20-64 <u>Round 1:</u> Referral/receipt of colposcopy: RR 1.30 (95% CI, 1.15 to 1.46) and 3.31 (95% CI, 3.06 to 3.59) FPR for CIN2+: 2.46 (1.70, 3.57), I^2=98.2%	Consistent Imprecise	Variable protocols Limited to a single round	Moderate for increased burden of testing	Protocols for followup of abnormal screening not consistent with current ASCCP guidance Effect modification by age with greater differences in FPR in younger participants (<35 years)
		False negative rate for ICC	K=2 (RCT) N analyzed =52,632	Age 30-60 <u>Round 1:</u> There were only 3 missed cancers in both POBASCAM and Swedescreen combined (in the cytology group only) with no statistically significant risk differences.	Consistent Imprecise	Low incidence of ICC	Insufficient	Studies in countries with organized screening programs

Table 14. Summary of Evidence

Key question	Screening strategy (Comparator)	Outcome	No. of included studies and individuals	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
		Psychological harms	K=1 (RCT) N analyzed =2,473	Age 20-64 At 2 weeks, no difference in measures of distress or anxiety	NA	One study Limited to a single round with 2 week followup	Low for no psychological harm	Study conducted in UK in unvaccinated women

* LTFU studies are long-term observational followup from an included RCT. The patient sample is not unique compared with the RCTs and is not included in the N analyzed.

Abbreviations: ARTISTIC = A Randomised Trial in Screening to Improve Cytology; ASCCP = American Society for Colposcopy and Cervical Pathology; CI = confidence Interval; CIN = cervical intraepithelial neoplasia; FDA = Food & Drug Administration; FPR = false positive rate; F/u = followup; HC2 = Hybrid Capture 2; HPV = human papillomavirus; hrHPV = high risk human papillomavirus; ICC = Invasive cervical cancer; K = Number of studies; LTFU = long-term followup; NA = Not applicable; NRSI= nonrandomized study of interventions; NTCC = New Technologies for Cervical Cancer Screening; PHQ = Patient Health Questionnaire; POBASCAM = Population Based Screening Study Amsterdam Program; RCT = randomized controlled trial; RR = relative risk; US = United States.

Appendix A. Detailed Methods

Literature Search Strategies for Primary Literature

Bridge 2024 – Date delivered 4/11/2024
Bridge 2023 – Date delivered 9/5/2023
Original search – Date delivered 9/6/2022

Sources Searched: database and platform
MEDLINE via Ovid
Cochrane Central Register of Controlled Clinical Trials via Wiley
PsycInfo via Ovid

Modified search filters used from search filters:
Chris Cooper, Jo Varley-Campbell and Patrice Carter, Established search filters may miss studies when identifying randomized controlled trials, Journal of Clinical Epidemiology, 2019-08-01, Volume 112, Pages 12-19
Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. Journal of the Medical Library Association 2006; 94: 130-136. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1435857/
Box 3.d Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format from: Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook
Tudor Car L, Li L, Smith H, Atun R. Cochrane review: Search strategies to identify observational studies in MEDLINE and EMBASE. J Evid Based Med. 2019;12(3):225–226. doi:10.1111/jebm.12358
Waffenschmidt S, Navarro-Ruan T, Hobson N, Hausner E, Sauerland S, Haynes RB. Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. Res Synth Methods. 2020 Sep;11(5):617-626. doi: 10.1002/jrsm.1425. Epub 2020 Jun 25. PMID: 32472632.

Justification for Limits (what studies/papers):
This search strategy was adapted from the search in the 2017 review.

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword

Appendix A. Detailed Methods

MEDLINE

Ovid MEDLINE(R) ALL <1946 to September 02, 2022>

1 Papillomavirus Infections/di [Diagnosis] 6748
2 Papillomaviridae/cy, ip [Cytology, Isolation & Purification] 9854
3 exp Alphapapillomavirus/ip [Isolation & Purification] 2744
4 Human papillomavirus 16/ip [Isolation & Purification] 1475
5 Human papillomavirus 18/ip [Isolation & Purification] 685
6 DNA Probes, HPV/ 1071
7 Human Papillomavirus DNA Tests/ 568
8 ((hpv$ or hrhpv) adj5 (test$ or detect$ or screen$ or smear$ or assay$ or cytology or rescreen$ or cotest$)).ti,ab,kf. 17798
9 (papillomavir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$ or cytology or rescreen$ or cotest$)).ti,ab,kf. 6992
10 ((papilloma vir$ or papiloma vir$) adj5 (test$ or detect$ or screen$ or smear$ or assay$ or cytology or rescreen$ or cotest$)).ti,ab,kf. 839
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 [Hpv diagnosis/detection/tests] 26977
12 Papillomavirus Infections/ 31336
13 Papillomaviridae/ 27578
14 exp Alphapapillomavirus/ 9763
15 Human papillomavirus 16/ 5516
16 Human papillomavirus 18/ 2236
17 Human papillomavirus 31/ 106
18 papillomavir$.ti,ab,kf. 45684
19 (papilloma vir$ or papiloma vir$).ti,ab,kf. 8477
20 (hpv$ or hrhpv).ti,ab,kf. 51207
21 or/12-20 68899
22 Mass screening/ 114418
23 Early detection of cancer/ 34807
24 Vaginal smears/ 22762
25 Papanicolaou Test/ 7104
26 "Diagnostic Techniques, Obstetrical and Gynecological"/ 481
27 Cytological Techniques/ 11055
28 Histocytological Preparation Techniques/ 1595
29 Cytodiagnosis/ 17166
30 (test$ or detect$ or screen$ or smear$ or assay$ or cytology or rescreen$ or cotest$).ti. 1170742
31 diagnostic self evaluation/ 4036
32 Self-Examination/ 1211
33 self-testing/ 339
34 (self-exam$ or self administer$ or self collect$ or self sampl$ or home).ti,ab,kf. 310476
35 or/22-34 1552652
36 21 and 35 [hpv screening] 14630
37 Hybrid Capture.ti,ab. 1956
38 HC2.ti,ab. 938
39 hc 2.ti,ab. 236
40 hcII.ti,ab. 376
41 hc II.ti,ab. 261

42 cobas.ti,ab. 3570
43 APTIMA.ti,ab. 530
44 Cervista.ti,ab. 76
45 digene.ti,ab. 429
46 amplicor.ti,ab. 1513
47 Onclarity .ti,ab. 56
48 polymerase chain reaction/ 248884
49 (Papanicolaou or Pap test or Pap smear or cervical smear or cervical screening or smear test or vaginal smear).ti,ab,kf. 17799
50 Reverse Transcriptase Polymerase Chain Reaction/ 154302
51 polymerase chain reaction$.ti. 19848
52 pcr.ti. 49275
53 linear array.ti,ab. 3373
54 or/37-53 442367
55 21 and 54 [specific tests AND hpv] 12314
56 11 or 36 or 55 31607
57 limit 56 to (systematic reviews pre 2019 or systematic reviews) 896
58 (clinical trial or adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or equivalence trial or pragmatic clinical trial or Meta-Analysis).pt. 1091312
59 clinical trials as topic/ or adaptive clinical trials as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or non-randomized controlled trials as topic/ or randomized controlled trials as topic/ or equivalence trials as topic/ or intention to treat analysis/ or pragmatic clinical trials as topic/ or meta-analysis as topic/ 383578
60 control groups/ or double-blind method/ or single-blind method/ or random allocation/ or placebos/ 323055
61 (random$ or placebo or phase iii or phase 3).ti,ab. 1458765
62 (RCT or sham or dummy or single blind$ or double blind$ or allocated or allocation or triple blind$ or treble blind$).ti,ab. 427470
63 ((control$ or clinical) adj3 (study or studies or trial$ or group$)).ti,ab. 1767806
64 (Nonrandom$ or non random$ or non-random$ or quasi-random$ or quasirandom$).ti,ab. 50874
65 ((open label or open-label) adj5 (study or studies or trial$)).ti,ab. 41978
66 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab. 10421
67 (pragmatic study or pragmatic studies).ti,ab. 531
68 ((pragmatic or practical) adj3 trial$).ti,ab. 5281
69 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial$)).ti,ab. 10805
70 (metaanaly$ or meta analy$).ti,ab. 244756
71 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ 2389894
72 longitudinal.ti,ab. 299968
73 (follow up or followup).ti,ab. 1151966
74 (prospective$ or retrospective$).ti,ab. 1684926
75 (comparison group$ or matched comparison).ti,ab. 22956
76 observational.ti,ab. 238094
77 population$.ti,ab. 2022560
78 Registries/ 105634

79 (registr$ or register$).ti,ab. 505299
80 cohort.ti,ab. 710293
81 pool$.ti,ab. 263423
82 or/58-81 7870796
83 56 and 82 14721
84 "Sensitivity and Specificity"/ 365801
85 "Predictive Value of Tests"/ 221399
86 ROC Curve/ 69460
87 Receiver operat$.ti,ab. 114255
88 ROC curve$.ti,ab. 48553
89 sensitivit$.ti,ab. 944667
90 specificit$.ti,ab. 554748
91 predictive value.ti,ab. 108157
92 accuracy.ti,ab. 501028
93 False Negative Reactions/ 18295
94 False Positive Reactions/ 28576
95 Diagnostic Errors/ 39422
96 "Reproducibility of Results"/ 449161
97 Reference Values/ 163522
98 Reference Standards/ 45423
99 Observer Variation/ 44725
100 Psychometrics/ 85767
101 Psychometric$.ti,ab. 56298
102 false positive$.ti,ab. 65763
103 false negative$.ti,ab. 37175
104 miss rate$.ti,ab. 622
105 error rate$.ti,ab. 16951
106 evaluation study/ 261715
107 or/84-106 2771729
108 56 and 107 6673
109 57 or 83 or 108 18093
110 Cervix Uteri/ or Uterine Cervical Neoplasms/ or Cervical Intraepithelial Neoplasia/ or Papanicolaou Test/ or exp Uterine Cervical Diseases/ or Urine Specimen Collection/ or (cervic$ or cervix or genital$ or vagina$ or vulva$ or pap test or pap smear or Papanicolaou or smear test or urine).ti,ab,kf. 748630
111 109 and 110 13747
112 111 not (animals/ not humans/) 13719
113 (201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).dt,da,ez. 9202880
114 112 and 113 4968
115 limit 114 to english language 4794
116 remove duplicates from 115 4775

Appendix A. Detailed Methods

Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via Wiley

Date Run: 07/09/2022 04:41:07

ID	Search	Hits
#1	hpv*:ti,ab,kw near (test* or detect* or screen* or smear* or assay* or cytology or rescreen* or cotest*):ti,ab,kw	1309
#2	papillomavir*:ti,ab,kw near (test* or detect* or screen* or smear* or assay* or cytology or rescreen* or cotest*):ti,ab,kw	549
#3	(papilloma* next vir*):ti,ab,kw near (test* or detect* or screen* or smear* or assay* or cytology or rescreen* or cotest*):ti,ab,kw	52
#4	(papiloma* next vir*):ti,ab,kw near (test* or detect* or screen* or smear* or assay* or cytology or rescreen* or cotest*):ti,ab,kw	2
#5	#1 or #2 or #3 or #4	1432
#6	"hybrid capture":ti,ab,kw	138
#7	(HC2 or "HC 2" or HCII or "HC II"):ti,ab,kw	119
#8	cobas:ti,ab,kw	574
#9	APTIMA:ti,ab,kw	38
#10	Cervista:ti,ab,kw	7
#11	digene:ti,ab,kw	39
#12	amplicor:ti,ab,kw	177
#13	Onclarity :ti,ab,kw	2
#14	pcr:ti,ab,kw	14664
#15	(polymerase next chain next reaction*):ti,ab,kw	10092
#16	"linear array":ti,ab,kw	188
#17	(Papanicolaou or Pap test or Pap smear or cervical smear or cervical screening or smear test or vaginal smear):ti,ab,kw	4132
#18	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	23547
#19	(hpv* or papillomavir* or (papilloma next vir*) or (papiloma next vir*)):ti,ab,kw	3954
#20	#18 and #19	1249
#21	#5 or #20 with Cochrane Library publication date from Jul 2016 to present, in Trials	1144
#22	(cervic* or cervix or genital* or vagina* or vulva* or "pap test" or "pap smear" or Papanicolaou or "smear test" or urine):ti,ab,kw	93822
#23	#21 AND #22	959
#24	#23 NOT (conference:pt or (clinicaltrials or trialsearch):so)	484
#25	#23 AND (conference:pt or (clinicaltrials or trialsearch):so)	475

PsycInfo via Ovid

APA PsycInfo <1806 to October Week 2 2022>

1	human papillomavirus/	1630
2	testing/	9320
3	Cancer Screening/	5328
4	Screening/	10025
5	exp Screening Tests/	8570
6	disease screening/	1206
7	"self-examination (medical)"/	502
8	2 or 3 or 4 or 5 or 6 or 7	33510
9	1 and 8	188
10	(hpv$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab,id.	438

11 (papillomavir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab,id. 174
12 (papilloma vir$ adj5 (test$ or detect$ or screen$ or smear$ or assay$)).ti,ab,id. 21
13 ((hpv$ or papillomavir$ or papilloma vir$) adj5 (self-exam$ or self administer$ or self collect$ or self sampl$ or home)).ti,ab,id. 69
14 or/9-13 563
15 limit 14 to (english language and yr="2017 -Current") 201

Appendix A. Detailed Methods

Methods to Determine hrHPV Prevalence by Age

The data used to determine the prevalence of HPV by age groups came from the 2015-2016 National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention.

Our analysis includes all females aged 18 to 59 years who submitted hrHPV vaginal swabs. Of the 2064 females who completed a vaginal swab, 1834 (88.7%) had results that could be interpreted as positive or negative (i.e., were not inadequate or missing). The swabs were analyzed for hrHPV using Roche Cobas assay, which determines only the presence or absence of hrHPV.

Laboratory (Human Papillomavirus (HPV) DNA - Vaginal Swab: Roche Cobas High-Risk) and demographics (Demographic Variables and Sample Weights) datasets used for the analysis can be found here:

https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2015

Statistical analyses were conducted using Stata 16.1 (StataCorp LLC, College Station, TX). Variance estimates were calculated by using a Taylor series linearization. All estimates were weighted using the 2015-2016 medical examination weights.

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Included	Excluded
Aim	**KQs 1, 2, 3:** Studies targeting cervical cancer screening	**KQs 1, 2, 3:** Use of HPV or cytology testing for posttreatment surveillance or other purposes
Population	**KQs 1, 2, 3:** Persons who have a cervix (any age), including persons at increased risk for cervical cancer or morbidity/mortality from cervical cancer (e.g., by race/ethnicity, income/SES, insurance, geography, history of sexual trauma, smoking history, HPV vaccination status)	**KQs 1, 2, 3:** • Surveillance studies exclusively in persons with HIV, with in utero exposure to diethylstrilbestrol, or with previous treatment for cervical cancer or a high-grade pre-cancerous lesion
Interventions	**KQs 1, 3:** • Test: any test strategy using hrHPV assay* with or without cytology • Specimen type: cervical, vaginal, urine • Mode of collection: Self- or clinician-collected hrHPV samples • Intervals of testing: any interval of screening **KQ 2:** • Self-collected hrHPV sample	**KQs 1, 2, 3:** Non hrHPV screening strategies
Comparators	**KQs 1, 3:** Any alternate test (including cytology only) and/or assay, mode of collection or interval of testing **KQ 2:** • Clinician-collected hrHPV sample • Reference standard	**KQs 1, 2, 3:** no screening
Outcomes	• KQ 1: • Pre-cancerous lesions (i.e., CIN2+, CIN3+) • Invasive cervical cancer (squamous cell carcinoma or adenocarcinoma) • Mortality (all-cause or cervical cancer) • Quality of life or other cancer related morbidity • KQ 2: • Test accuracy (e.g., sensitivity, specificity, false positive, false negative) • Adherence to screening • KQ 3: • Rates of false-positive and false-negative screening test results • Lack of adherence to screening • Rates of colposcopy and/or biopsy and related procedural harms • Adverse effects on sexual health • Psychological harms (e.g., stigma, labeling, partner discord, depression/anxiety)	
Study Designs	**KQs 1, 3:** • Individual patient data meta-analyses and systematic reviews • Randomized, controlled trials; controlled clinical trials • Nonrandomized studies (NRS) with unbiased selection and contemporaneous controls **KQ 2:** • Diagnostic test accuracy studies • Participation trials (for adherence only)	**KQs 1, 3:** • Quasi-experimental studies (e.g., pre-post studies) • NRS with historical controls • Case reports • Case series • Narrative reviews • Editorials **KQ 2:** Diagnostic test accuracy studies without a reference standard

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Included	Excluded
Setting	**KQs 1, 2, 3:** Primary care (e.g., internal medicine, family medicine, obstetrics/gynecology), other settings generalizable to primary care (e.g., university-based health clinics, mobile clinics, sexually transmitted infection clinics, family planning clinics) or any setting for self-collection of samples	
Country	**KQs 1, 2, 3:** Countries with cervical cancer screening programs comparable to those of the United States and categorized as "Very High" or equivalent on the 2020 Human Development Index (as defined by the United Nations Development Programme)	**KQs 1, 2, 3:** Countries not categorized as "Very High" on the Human Development Index or not applicable to U.S. clinical settings or populations
Language	**KQs 1, 2, 3:** English only	**KQs 1, 2, 3:** Non-English publications
Quality	**KQs 1, 2, 3:** Fair- or good-quality, according to USPSTF design-specific criteria	**KQs 1, 2, 3:** Poor-quality, according to USPSTF design-specific criteria

*HPV tests approved by the U.S. Food and Drug Administration include: the Hybrid Capture 2 High-Risk HPV DNA Test (Qiagen, Hilden, Germany); cobas HPV Test (Roche Molecular Systems, Inc., Pleasanton, CA); APTIMA® HPV and HPV 16, 18/45 Assays (Hologic, Inc., Madison, WI); Cervista™ HPV 16/18 and Cervista™ HR HPV (Hologic, Inc., Madison, WI); and Onclarity HPV™ (Becton Dickinson, Franklin Lakes, NJ)

Abbreviations: CIN = cervical intraepithelial neoplasia; HIV = human immunodeficiency virus; HPV = human papilloma virus; hr = high risk; KQ = Key question; SES = socioeconomic status; U.S. = United States

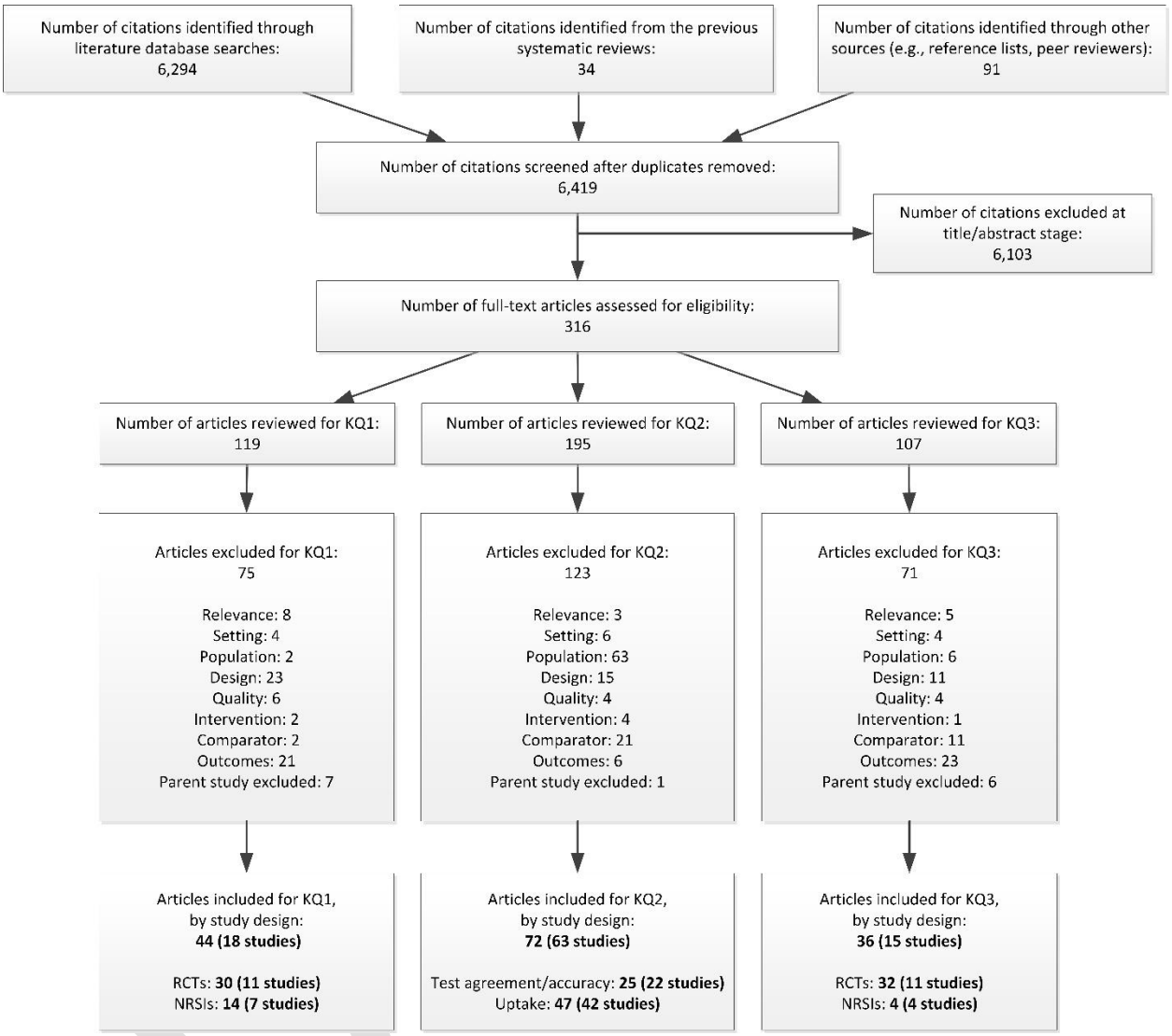
Appendix A Table 2. Study Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
Adapted Risk of Bias Assessment (ROBINS-I)[1]	**Bias due to confounding** • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias in classifying interventions** • Intervention groups are clearly defined • Information used to define intervention groups was recorded at the start of the intervention • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias due to deviations from intended interventions** • No deviations from intended intervention • Important co-interventions are balanced across intervention groups • Analysis adjusts for deviations from intended intervention that could have affected outcomes **Bias from missing data** • Outcome data are available for all, or nearly all, participants • Proportion of participants and reasons for missing data are similar across groups • Appropriate statistical methods used to account for missing data or there was evidence that results were robust to the presence data **Bias in measurement of outcomes** • Blinding of participants • Blinding of outcome assessors • Methods of outcome assessment are comparable across intervention groups • No systematic errors in measurement of the outcome related to intervention received **Bias in reporting results selectively** No evidence that the measures, analyses, or subgroup analyses are selectively reported
Diagnostic accuracy studies, adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II instrument[2]	**Patient Selection** • Was a consecutive or random sample of patients enrolled? • Did the study avoid inappropriate exclusions? **Index Test** • Were the index test results interpreted without knowledge of the reference standard results? • If a threshold was used, was it prespecified or was a range of values presented? **Reference Standard** • Is the reference standard likely to correctly classify the target condition? • Were the reference standard results interpreted without knowledge of the index test? • Were staff trained in the use of the reference standard? • Was fidelity of the reference standard monitored or reported? **Flow and Timing** • Was there an appropriate interval between the index test and reference standard? • Did all patients receive a reference standard? • Did all patients receive the same reference standard? ○ Were all patients included in the analysis?

Appendix A Table 2. Study Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
Randomized clinical trials, adapted from U.S. Preventive Services Task Force Manual[3]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

Appendix A Figure 1. Literature Flow Diagram



Abbreviations: KQ = key question; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial

Appendix A Figure 2. Quality Rating of Screening RCTs (KQ1), by Domain

Quality	Author	Domain				
		Intervention deviations	Missing data	Outcome measurement	Randomization process/confounding	Selective reporting
Good	Canfell, 2017	✓	✓	✓	✓	✓
	Naucler, 2007	✓	✓	✓	✓	✓
	Ogilvie, 2018	✓	✓	✓	✓	✓
	Rijkaart, 2012	✓	✓	✓	✓	✓
	Ronco, 2010	✓	✓	✓	✓	✓
Fair	Elfstrom, 2021	✓	✓	✓	△	✓
	Kitchener, 2014	✓	△	✓	✓	✓
	Leinonen, 2012	△	△	✓	✓	✓
	Nygard, 2022	△	△	✓	△	✓
	Polman, 2019	✓	△	✓	✓	✓
Poor	Lamin, 2017	✓	✗	✓	△	✓

Risk of Bias Legend
✗ High
✓ Low
△ Moderate

Appendix A Figure 3. Quality Rating of NRSIs (KQ1 and KQ3), by Domain

Quality	Author	Domain						
		Confounding	Selection Bias	Classification of Interventions	Deviations for Intended Interventions	Measurement of Outcomes	Missing Data	Selective Reporting
Good	Thomsen, 2021	✓	✓	✓	✓	✓	✓	✓
Fair	Andreassen, 2019 (KQ3 only)	✓	✓	✓	✓	✓	▲	✓
	Elfstrom, 2014	▲	✓	▲	✓	✓	✓	✓
	Gottschlich, 2023 (KQ3 only)	▲	✓	✓	✓	✓	○	✓
	Inturrisi, 2022	✓	▲	✓	✓	✓	✓	✓
	Katki, 2011	○	✓	✓	✓	✓	▲	✓
	Maissi, 2005 (KQ3 only)	▲	✓	✓	✓	✓	▲	✓
	Tranberg, 2023	✓	✓	✓	✓	✓	▲	✓
	Vahteristo, 7709	✓	✓	✓	▲	✓	✓	✓
	Veijalainen, 2019	✓	✓	✓	✓	✓	▲	✓
Poor	Aitken, 2023	✗	✓	✓	✓	✓	✗	✓
	Bennett, 2021	▲	✓	✓	✓	✓	✗	✗
	Horn, 2019	○	✓	✓	✓	✓	✗	✓
	Ibanez, 2014	○	✓	✓	✓	✓	✗	✓
	Wright, 2015	○	✓	✓	✓	✓	✗	✓

Risk of Bias Legend
✗ High
✓ Low
▲ Moderate
○ Unclear

Appendix A Figure 4. Quality Rating of Agreement and Accuracy Studies, by Domain

Quality	Outcome	Author	Domain			
			Patient selection	Index test	Reference standard	Patient flow
Good	Agreement	Avian, 2022	✓	✓	✓	✓
Fair	Agreement	Des Marais, 2018	△	✓	✓	△
		Eamratsameekool, 2023	△	✓	✓	✓
		Hagihara, 2016	△	✓	✓	△
		Harvey, 2016	△	✓	✓	△
		Ilardo, 2022	△	✓	✓	△
		Ketelaars, 2017	✓	✓	✓	△
		Kim, 2022	△	✓	✓	△
		Lim, 2022	△	✓	✓	△
		Lopez Castro, 2024	△	✓	✓	✓
		McLarty, 2019	△	✓	✓	△
		Nutthachote, 2019	△	✓	✓	△
		Reisner, 2018	△	✓	✓	✓
		Satake, 2020	△	✓	✓	△
		Vergara, 2018	△	✓	✓	△
		Wong, 2024	△	✓	✓	△
	Accuracy	Balasubramanian, 2010	△	✓	✓	△
		Inturrisi, 2021	△	✓	✓	✓
		Polman, 2019	✓	✓	✓	✗
		Porras, 2015	△	✓	✓	△
		Szarewski, 2007	△	✓	✓	△
	Agreement and Accuracy	Stanczuk, 2021	✓	✓	✓	△
Poor	Agreement	Naseri, 2022	✗	✓	✓	△
	Accuracy	Auvinen, 2022	△	✓	✓	✗
	Agreement and Accuracy	Dannecker, 2004	△	✓	✓	✗

Risk of Bias
✗ High
△ Medium
✓ Low

Appendix A Figure 5. Quality Rating of Uptake RCTs, by Domain

Quality	Author	Domain				
		Intervention deviations	Missing data	Outcome measurement	Randomization process/ confounding	Selective reporting
Good	Aasbo, 2022	✓	✓	✓	✓	✓
	Brewer, 2021	✓	✓	✓	✓	✓
	Canfell, 2017	✓	✓	✓	✓	✓
	Carrasquillo, 2018	✓	✓	✓	✓	✓
	Elfstrom, 2019	✓	✓	✓	✓	✓
	Landy, 2022	✓	✓	✓	✓	✓
	Naucler, 2007	✓	✓	✓	✓	✓
	Ogilvie, 2018	✓	✓	✓	✓	✓
	Polman, 2019	✓	✓	✓	✓	✓
	Pretsch, 2023	✓	✓	✓	✓	✓
	Rijkaart, 2012	✓	✓	✓	✓	✓
	Ronco, 2010	✓	✓	✓	✓	✓
	Sultana, 2016	✓	✓	✓	✓	✓
	Tranberg, 2018	✓	✓	✓	✓	✓
	Winer, 2019	✓	✓	✓	✓	✓
	Winer, 2023	✓	✓	✓	✓	✓
Fair	Aarnio, 201	✓	△	✓	△	✓
	Bais, 2007	✓	△	✓	△	✓
	Broberg, 2014	✓	△	✓	✓	✓
	Cadman, 2015	✓	✓	✓	△	✓
	Darlin, 2013	✓	✓	✓	△	✓
	Elfstrom, 2021	✓	✓	✓	△	✓
	Enerly, 2016	✓	✓	✓	△	✓
	Giorgi Rossi, 2011	✓	✓	✓	△	✓
	Giorgi Rossi, 2015	✓	✓	✓	△	✓
	Gok, 2010	✓	✓	✓	△	✓
	Gok, 2012	✓	✓	✓	△	✓
	Gustavsson, 2018	✓	△	✓	✓	✓
	Haguenoer, 2014	✓	△	✓	△	✓
	Hellsten, 2021	✓	✓	✓	△	✓
	Ivanus, 2018	✓	△	✓	✓	✓
	Jalili, 2019	✓	✓	✓	△	✓
	Kellen, 2018	✓	✓	✓	△	✓
	Kitchener, 2014	✓	△	✓	✓	✓
	Kitchener, 2018	✓	✓	✓	△	✓
	Leinonen, 2012	△	△	✓	✓	✓
	Lilliecreutz, 2020	✓	△	✓	△	✓
	MacDonald, 2021	✓	✓	✓	△	✓
	Moss, 2024	✓	✓	✓	△	✓
	Peeters, 2020	✓	△	✓	△	✓
	Racey, 2016	✓	✓	✓	△	✓
	Reques, 2021	✓	✓	✓	△	✓
	Sancho-Garnier, 2013	✓	✓	✓	△	✓
	Scarinci, 2021	✓	✓	✓	△	✓
	Sewali, 2015	✓	✓	✓	✓	✓
	Szarewski, 2011	✓	✓	✓	△	✓
	Virtanen, 2011	✓	✓	✓	△	✓
	Viviano, 2017	✓	△	✓	✓	✓
	Williams, 2016	✓	△	✓	△	✓
	Zehbe, 2016	✓	✓	✓	△	✓
Poor	Wikstrom, 2011	△	✓	✓	△	✓

Risk of Bias Legend
✓ Low
△ Moderate

Contextual Question 1. What is the comparative test accuracy of hrHPV tests used in U.S.-based clinical practice?

As of 2023, eight hrHPV assays are currently FDA-approved for use in the United States: Digene Hybrid Capture 2 (HC2); Cervista HPV HR, as well as Cervista HPV 16/18 to be used alongside of Cervista H; Aptima HPV, as well as Aptima HPV 16, 18/45 to be used alongside Aptima HPV; Cobas HPV; Onclarity HPV; and Alinity m (**Appendix B Table 1**). HC2 can include low-risk HPV genotypes, however, low risk genotypes are not recommended for cervical cancer screening. Cervista is no longer sold in the United States or Canada. The Cobas, Onclarity, and Alinity m assays have been FDA-approved specifically for the use of primary hrHPV screening. The primary hrHPV screening comparative effectiveness studies (KQ1) used HC2, Cobas, Abbott RealTime hrHPV (not FDA approved), and GP5/6-mediated PCR enzyme immunoassay (GP5+/6+ PCR) assays. Aptima (the only mRNA assay) is commonly used in the United States, in part due to the manufacturer Hologic also makes the most commonly used LBC test (ThinPrep).

Based on 2021 systematic review by Arbyn and colleagues, which conducted a meta-analysis of the relative accuracy of index hrHPV assays to detect CIN2+ versus comparator assays (HC2 or GP5+/6+ PCR), FDA approved assays generally had similar relative accuracy; however Aptima, which is an mRNA as opposed to DNA assay, had slightly higher specificity, with no statistically significant difference in sensitivity, compared to HC2 or GP5+/6+ PCR (**Appendix B Table 1**).[4]

A 2022 systematic review by Arbyn and colleagues demonstrated that Aptima had similar cross-sectional sensitivity for CIN3+, as CIN2+, when compared to DNA hrHPV assays.[5] The relative sensitivity for CIN3+ (k=5) was 0.98 (95% CI, 0.95 to 1.01). This review also identified three studies for which longitudinal sensitivity could be assessed.[6-8] In these three studies, the sensitivity for the cumulative detection of CIN3+ was not statistically significantly different between assays at 4 or 5 years of followup. In the HPV FOCAL trial, the cumulative detection rate of CIN3+ among women who tested negative at baseline with Aptima versus HC2 was similar at up to 10 years of followup.[9]

In a sub-sample (n=2869) from the Danish Horizon study, the relative detection of CIN3+ and CIN2+ were equivalent for HC2, Cobas, and Aptima; however, Aptima had lower test positivity, colposcopies, and false positives (**Appendix B Table 2**).[10]

A 2019 systematic review by Macedo and colleagues that compared the accuracy of mRNA versus DNA hrHPV testing in women with low-grade cytologic abnormalities (i.e., hrHPV triage of cytology screening), found no significant difference (k=9) in sensitivity between Aptima versus HC2 in women with ASC-US (91.7% [95% CI, 88.3 to 94.4] and 94.8% [95% CI, 91.9 to 96.9], respectively) for CIN2+, and a higher specificity for Aptima (56.4% [95% CI, 54.1 to 58.7] and 45.5% [95% CI, 43.2 to 47.9]).[11] The same patterns in sensitivity and specificity were observed for the detection of CIN3+. Another study, the Onclarity trial (n=33,858), found that Onclarity had no significant difference in sensitivity compared to HC2 (85.7% [95% CI, 77.8 to 91.1]) versus 82.9% [95% CI, 74.5 to 88.9], respectively) or specificity compared to HC2 (64.1% [95% CI, 61.6 to 66.5] versus 61.4% [95% CI, 58.9 to 63.9]), respectively) for the

detection of CIN2+ in women with ASC-US.[12] Likewise, the same patterns in sensitivity and specificity were observed for the detection of CIN3+.

Contextual Question 2. How can extended genotyping and use of biomarkers (e.g., DNA methylation testing, immunostaining for p16/Ki67) for abnormal hrHPV or cytology reduce burden of testing and diagnostic procedures?

Triage tests in place of or in addition to reflexive cytology (for positive hrHPV) or reflexive hrHPV (for abnormal cytology) may reduce the burden of testing for positive cervical cancer screening without decreasing the ability to detect precancer or cancer (i.e., increase specificity without lowering sensitivity). Many new technologies have been studied, including: immunostaining for p16, Ki-67, and other proteins; extended hrHPV genotyping; DNA viral load; DNA methylation markers; DNA ploidy analysis; and mRNA markers other than oncogenes E6/E7.

The 2019 ASCCP Risk based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors did not recommend the use of additional triage tests but did state 'guidelines must allow updates to incorporate new test methods as they are validated…" Immunostaining for p16 is only discussed in the context of assisting the interpretation of histology (hematoxylin and eosin [H&E] slides).[13] Although the ASCCP guidelines mention partial genotyping (hrHPV 16/18), they do not mention extended genotyping. The 2021 IARC Handbook on Cervical Cancer Screening mentions dual staining for p16/Ki-67 (dual stain) as a triage strategy, but notes that extended genotyping and testing for DNA methylation could decrease unnecessary treatment, although more evidence is needed.[14] A separate 2021 review on options for triage in hrHPV-based cervical cancer screening by Leeson and colleagues confirmed that the evidence supports triage of hrHPV-positive testing with any two of the following tests: cytology, HPV partial genotyping, or dual stain.[15] Leeson and colleagues also concluded that DNA methylation may be an acceptable option in the future, but the current evidence is insufficient to support a recommendation for or against its use. None of these three reports mention the utility of extended genotyping for the triage of abnormal hrHPV testing with or without cytology.

Dual Stain

Dual staining for overexpression of p16 and ki67 proteins on cytology can be used for triage of borderline cytology or of hrHPV positive tests. As of 2023, the only FDA-approved test for dual stain is CINtec PLUS.

For triage of abnormal cytology (ASC-US+)

Based on a 2019 systematic review by Peeters and colleagues, dual stain compared to hrHPV testing was less sensitive but more specific for triage of ASC-US or LSIL to detect CIN2+.[16] Therefore, use of dual stain would decrease the burden of testing but at the risk of missing precancers if used in place of hrHPV triage of abnormal cytology (**Appendix B Table 3**).

For triage of hrHPV-positive women

In the 2021 IARC Handbook, for triage of hrHPV-positive women, dual stain was more sensitive than reflex cytology at a threshold of ASC-US+, but the difference in sensitivity was only statistically significant for the detection of CIN2+ (relative sensitivity 1.12 [95% CI, 1.01 to 1.25]), and not for the detection of CIN3+.[14] For hrHPV-positive women, dual stain compared to

partial genotyping hrHPV 16/18 was more sensitive to detect CIN2+. In neither comparison was dual stain more specific than cytology or hrHPV 16/18, and therefore it did not result in fewer colposcopies (**Appendix B Table 4**).

In ATHENA, a large US-based multicenter cervical cancer screening NRSI, the relative sensitivity and 1-specificity for CIN3+ of hrHPV 16/18 positive or 12 other hrHPV positive and dual stain positive versus hrHPV 16/18 positive or other hrHPV positive and ASC-US+ was 1.11 (95% CI, 1.04 to 1.19) and 1.04 (95% CI, 0.99 to 1.09), respectively.[17] Triage for other than 16/18 genotypes positive with cytology resulted in more colposcopies per CIN3+ detected than dual stain (7.3 versus 6.9 colposcopies per CIN3+ detected, respectively). See Table below under 'Extended genotyping'.

In NTCC Phase II, although the referral to colposcopy was initially slightly higher in hrHPV-positive women for dual stain as compared to cytology triage, the overall referral to colposcopy was not different in the two groups after hrHPV retesting at 1 year for hrHPV positive women with normal triage testing (women who continued to be positive hrHPV at 1 year were referred to colposcopy).[18] Additionally, in this trial hrHPV positive women with negative dual stain (CINtec PLUS) or negative E6/E7 mRNA (Aptima) had about twice the probability of clearing infection within 12 months.[19]

One cohort study based in a large integrated managed care organization in the United States found that in hrHPV positive women (n=1549), dual stain negative women had a low risk of CIN2+ and CIN3+ (below the threshold for colposcopy referral based on hrHPV positive with ASCUS+) for 5 years.[20] Dual stain negative women had a risk of precancer for repeating testing at 1 year (based on hrHPV positive with normal cytology) at 3 years, and thus authors concluded that the surveillance interval could be extended to 3 years for hrHPV positive women with negative dual stain.[20]

The COMPASS trial, which randomized participants to primary hrHPV screening with LBC or dual stain triage versus LBC, has not yet published its final results.

Extended genotyping

Specific HPV genotypes are definitively associated with risk of cervical cancer and thus called high risk; of these hrHPV genotypes, hrHPV 16/18 come with greater risk of cervical cancer and therefore are sometimes managed differently than other hrHPV genotypes.[14] However, extended genotyping (beyond partial genotyping including hrHPV 16/18) for triage of abnormal hrHPV testing has not been recommended in national or international guidance to date. As of 2023, the only FDA-approved test for extended genotyping is Onclarity . Onclarity has nine typing channels: hrHPV 16, hrHPV 18, hrHPV 31, hrHPV 45, hrHPV 51, hrHPV 52, hrHPV 33/58, hrHPV 35/39/68 and hrHPV 56/59/66.

A 2020 systematic review by Bonde and colleagues (16 studies), found that regardless of cytology, hrHPV 16 consistently carries the highest risk for CIN3+ (risk ranging from 15% to 35%) at baseline and with longitudinal followup, regardless of age or cytology result.[21] Additionally, hrHPV 31, 18, and 33 carried intermediate-high risk for CIN+ (risk ranging from 8% to 20%). Meanwhile, hrHPV 52, 58, and 45 carried moderate risk and hrHPV 35, 39, 51, 56,

59, 66, and 68 consistently had the lowest risk for CIN3+.[21] These results were similar to the Onclarity HPV trial, a large study representative of the US population, except that in this study, risk associated with genotype 45 was low, not moderate.[22, 23] However, at least in one cohort, hrHPV 45 was associated with a greater proportion of adenocarcinoma.[24] Stratification of management by hrHPV genotype may reduce burden of colposcopy by assigning women at highest risk to colposcopy, while designating those with lower risk to retesting at shortened intervals, for example.

Using 9258 archived samples from the NCI-Kaiser Permanente Northern California HPV Persistence and Progression (PaP) cohort, Schiffman and colleagues stratified hrHPV genotype risk profiles based on the likelihood of patients developing CIN3+ within 3 years (**Appendix B Table 5**).[24] In this study, there were four risk profiles: hrHPV 16, else hrHPV 18/45 (in the absence of hrHPV16), else hrHPV 33/58/31/52, else hrHPV 51/35/39/68/56/59/66. Based on risk of developing CIN3+, persons with normal cytology with any hrHPV genotype other than hrHPV 16 could be managed with repeat testing in 1 year. Also, persons with only hrHPV 51/35/39/68/56/59/66 could be managed with repeat testing in 1 year with normal and low-grade cytologic abnormalities. Proposed management thresholds were benchmarked using US guidelines for cytology management and their risk equivalents.

Among 734 hrHPV positive samples from the Canadian Cervical Cancer Screening Trial (CCCaST), hrHPV 16/31 had greater sensitivity for CIN3+ compared to hrHPV 16/18 (65.2 [95% CI, 49.8, 78.6] and 58.7 [95% CI, 43.2, 73.0], respectively).[25] The increased sensitivity was at a tradeoff of a somewhat lower specificity in hrHPV 16/31 compared to hrHPV 16/18 (76.9 [95% CI, 73.2, 80.3] and 81.6 [95% CI, 78.2, 84.7], respectively).[25] These differences held true for detection of CIN2+ as well. However, differences in sensitivity and specificity between the two triage strategies were not statistically significant.

In ATHENA, a large U.S.-based multicenter cervical cancer screening study, the sensitivity for CIN3+ was higher for using other genotypes, specifically hrHPV 16/18 plus 31,33, 45, 52 plus or minus 58, but with greater colposcopies per CIN3+ detected (**Appendix B Table 6**).[17]

However, it is unclear what impact HPV vaccination has on the performance of extended, or partial, genotyping as studies to date were conducted in mostly unvaccinated women.

DNA methylation

Aberrant DNA methylation may help to distinguish non-progressive hrHPV infections from those that will progress to cervical cancer, and may thus be used as a triage strategy in hrHPV positive women. DNA methylation has been studied in the context of human (e.g., *CADM1*, *MAL*, and *miR-124-2* in different combinations, and of *PAX-1*, *SOX-1*, *POU4F3*, and *FAM19A4*, alone or in combination with *miR-124-2*) and viral (e.g., early [E2] as well as late [L1 and L2] coding regions) genes. As of 2023, we identified no FDA-approved tests for HPV DNA methylation; therefore we only present a summary contained in the 2021 IARC Handbook here.

Overall, the sensitivity and specificity of DNA methylation tests in human genes vary widely depending on the gene of interest, the CpG targets of the gene, thresholds used to define methylation positivity, and the study design.[14] PROHTECT-3, a non-inferiority RCT of self-collected hrHPV samples, found that DNA methylation testing *MAL*, and *miR-124-2* (n=515)

was non-inferior to cytology (n=505) for the detection of CIN2+ in hrHPV positive women.[26] In a study of long-term observational followup of 1040 hrHPV positive women in POBASCAM, a negative *FAM19A4*/*miR-124-2* test was associated with a lower risk of cervical cancer over 14 years compared with normal cytology (risk ratio 0.71 [95% CI, 0.16 to 1.40).[27]

Likewise, the sensitivity and specificity of DNA methylation tests in viral genes varies due to hrHPV genotype and CpG sites targeted. In a 2019 systematic review by Kelly and colleagues evaluating DNA methylation of the E2, L1 and/or L2 coding regions of hrHPV 16 in women positive for hrHPV 16, the pooled sensitivity and specificity for CIN2+ was 754 percent (95% CI, 57 to 85) and 73 percent (95% CI, 66 to 79), respectively.[28]

Contextual Question 3. What are the social risk factors (e.g., race, racism, SES, insurance status, geography) or other risk factors (e.g., history of sexual trauma, smoking, vaccination status) that contribute to inequities in cervical cancer incidence and health outcomes?

Despite advances in the prevention and treatment of cervical cancer, marginalized and medically underserved populations are disproportionately affected by cervical cancer incidence, late-stage diagnoses, and mortality.[29, 30] These inequities are influenced by complex and interrelated factors, which limit access to screening and receipt of high-quality health care. Although discussed separately for this CQ, these factors are not mutually exclusive, and the presence of multiple factors may heighten cervical cancer risk and burden.

Social risk factors

Sociodemographic factors associated with inequities in cervical cancer morbidity and mortality include race and ethnicity, nativity, disability, sexual orientation and gender identity, socioeconomic status (SES), insurance status, and geographic location. Historically disadvantaged racial and ethnic groups, specifically Black, Hispanic/Latina, and AI/AN women, continue to be disproportionately affected by cervical cancer.[31-35] For example, Hispanic/Latina and Black women have a higher risk of cervical cancer incidence (51% and 30%, respectively) and mortality (20% and 60%, respectively) compared with White women.[35] Further, a 2023 analysis[32] of Surveillance, Epidemiology, and End Results (SEER) registry data from 2005 to 2018 showed that while Black women were less likely to be diagnosed with adenocarcinoma, they experienced the highest mortality rates and lowest 5-year relative survival rates for both regional and distant adenocarcinoma, compared with other racial and ethnic groups. Research indicates that poor survival rates in Black women are multifactorial, including greater probability of diagnoses at advanced stages, limited access to or delays in treatment therapies, and intersectionality with other risk factors and barriers (see below).[33, 36]

In addition to racial and ethnic disparities, women born outside of the United States have a lower likelihood of receiving recommended cervical cancer screening than women born in the United States.[37] For instance, an analysis of combined data from the 2005, 2008, 2010, 2013, and 2015 National Health Interview Surveys (n=11,791) revealed that foreign-born women aged 18 years and older were more than twice as likely to have never received cervical cytology screening compared to women born in the United States (18.6% vs 6.8%, respectively).[37] Moreover, women with pre-existing disabilities are at increased risk of developing cervical cancer compared to women without disabilities.[38] Studies have shown that women with disabilities, especially those with sensory, physical, and multiple disabilities, are less likely to receive recommended cervical cancer screening than women without disabilities.[38-40] Further, women with disabilities face numerous social, economic, and structural barriers when trying to access care, leading to observed disparities in receipt of cervical cancer screening as well as higher incidence rates of cancer compared to women without disabilities.[38-40] Although data from cancer surveillance programs is limited, recent reviews suggest that sexual and gender minorities (SGM), particularly lesbian and bisexual women as well as transgender men who retain their cervix, are less likely to receive cervical cancer screenings and may be at greater risk for malignancy compared to heterosexual and cisgender women.[41-44] For example, a 2022 analysis of Behavioral Risk Factor Surveillance System (BRFSS) data showed that transgender men were 58

percent less likely to be up-to date with cervical cancer screening recommendations compared to cisgender women.[33, 45] Results also showed that transgender men were less likely to have a primary care physician than cisgender women.[38]

Along with underscreening, increased cervical cancer burden among historically disadvantaged racial and ethnic populations, foreign-born women as well as SGM is considered to be the result of lower rates of followup after abnormal findings and lack of access to or receipt of treatment, leading to later stage diagnoses, mortality, and lower quality of life. Underutilization of healthcare services among disadvantaged populations is attributed to several intersecting barriers, including: challenges to obtaining affordable health care; distrust in the health care system due to past experiences; fear of discrimination and stigma from healthcare and insurance providers; language barriers; perception of cervical cancer risk; lack of knowledge and awareness regarding HPV and cervical cancer; lack of understanding for need to be screened; limited access related to transportation, parking, building, and examination room designs; lack of access to LGBTQ+-competent care; and reduced access to providers with shared cultural backgrounds or cultural understanding (**see Contextual Question 4**).[33, 34, 37, 39, 40, 44-49]

There is consistent evidence that low SES, particularly lower income and education levels, are associated with cervical cancer incidence, late-stage diagnoses, and mortality.[29, 33, 50] A recent population-based study[51] found that women residing in the lowest-SES neighborhoods of New York City were 73 percent more likely to develop cervical cancer than women living in the highest-SES neighborhoods. Women with low SES are less likely to be screened for cervical cancer, attend followup appointments, and access treatment services compared to women with high SES.[30, 50, 52] For example, the National Health Interview Survey estimates that among women aged 21 to 65 years,[53] 76 percent of women whose income was above 200 percent of the federal poverty level (FPL) were up-to-date with cervical cancer screening, compared with 63 percent of women whose income was less than 200 percent of FPL. Similarly, 77 percent of women with an education beyond high school were up-to-date with screening, compared with 58 percent of women with less than a high school education.[53] Relatedly, women who are uninsured or have public health insurance have a lower likelihood of screening and are at higher risk for cervical cancer progression than women with private or military insurance.[33, 54, 55] A recent analysis of 23,492 women aged 21 to 64 years diagnosed with cervical cancer between 2007 and 2016[54] showed that women without insurance or with Medicaid were less likely to be diagnosed with early-stage cervical cancer than women with private insurance (41.1% versus 57.8%, respectively).

Women living in rural areas are disproportionately burdened by cervical cancer, experiencing 15 percent and 13 percent higher incidence and mortality rates, respectively, compared to women living in metropolitan areas.[55] In addition, women living in rural communities are less likely to complete cervical cancer screenings and experience higher rates of late-stage diagnoses than women living in metropolitan areas.[30, 55-58] Furthermore, women living in the Southern region of the United States have the highest incidence (8.5 per 100,000) and mortality (2.7 per 100,000) rates of cervical cancer compared to women living in other regions in the United States.[30, 59] Potential contributors to these inequities in rural and Southern areas include infrequency of patient visits due to distance, transportation difficulties, lower provider density, high rates of

provider turnover, lack of healthcare facilities, longer clinic wait times, and lack of high-quality medical care (**See Contextual Question 4**).[44, 55, 56]

Other risk factors

Additional individual and modifiable risk factors that contribute to inequities in cervical cancer prevention and treatment include smoking, risky sexual behavior (e.g., multiple concurrent partners), history of sexual trauma, malnutrition, and HIV infection.[33, 55, 60, 61] For instance, smoking tobacco is a significant risk factor for the persistence of hrHPV infections and the development of CIN and ICC.[62, 63] Women who smoke are twice as likely to get cervical cancer compared to women who do not smoke.[64] Moreover, prevalence of cigarette smoking is higher among historically disadvantaged racial and ethnic groups, uninsured women, and women with low-SES.[60] Additionally, women with a history of sexual trauma are at increased risk of cervical dysplasia and ICC.[65, 66] History of childhood abuse, particularly among low SES women, is associated with lower likelihood of cervical cancer screening, greater risky sexual behavior, higher perceived stress, and history of smoking, further exacerbating cervical cancer risk.[65] Lastly, HPV vaccination status has also been identified as a risk factor for cervical cancer. A 2021 modelling study[67] found that unvaccinated women were two times (bivalent vaccine for females and males) to nine times (nonvalent vaccine for females-only) more likely to develop cervical cancer than vaccinated women. Evidence has shown that uninsured women as well as Asian, Black, and Hispanic/Latina women are less likely to be vaccinated for HPV compared with insured women and White women.[68]

Contextual Question 4. What are barriers and implementation considerations (e.g., for the health system, clinician, or patient) to screening and followup testing?

Barriers to cervical cancer screening are important to consider because they are often directly related to the disparities observed in screening uptake and followup testing.[44, 69, 70] Overall compliance with cervical cancer screening recommendations is reported to be 72 percent of women aged 21 to 65 years being up to date with their screening in 2021.[53] This high rate of compliance differs, however, by the factors discussed in **Contextual Question 3**. Screening uptake is one aspect of the treatment pathway, with compliance with followup testing being another crucial element to consider. A recent study (n=28,706) examined the time-to-colposcopy after an abnormal cervical cancer screening test using 2010 – 2018 data from the MultilEvel opTimization of the ceRvIcal Cancer Screening process in diverse Settings & populations (METRICS) Research Center, which is part of the Population-based Research to Optimize the Screening Process (PROSPR II) consortium.[71] Researchers found that among patients aged 21-65 years with an abnormal test result, 57 percent received a colposcopy within 3 months, 70 percent within 6 months, and 75 percent received a colposcopy within 12 months. Results varied, however, by severity of the abnormal test result (women with higher-grade abnormalities had greater compliance than those with lower-grade findings), age (older women were less compliant than younger), and healthcare system norms.[71] A systematic review published in 2023 found mixed results among these factors.[72] Overall, these findings highlight opportunities for implementation strategies that focus on possible personal and structural barriers.

When considering barriers to cervical cancer screening and followup testing, researchers have often divided them into broad categories of personal barriers and structural (including system-level) barriers.[69, 70, 72, 73] Personal barriers are felt by and within the control of the individual, such as avoiding screening or followup testing out of fear of finding cancer, embarrassment about the screening procedure, and lack of understanding of the importance of the screening or followup procedures. Structural and system-level barriers are issues that impact the individual, but are typically not within their control, such as the cost of screening/followup procedures, scheduling systems that are challenging to navigate, not being able to take time away from work to attend the screening/followup appointment, a lack of followup with patients who need rescreening or additional procedures scheduled, and patients not having access to affordable childcare that enables them to go to the appointment.[69, 73] Understanding both personal, structural and system-level barriers during the implementation of a screening and followup program is key if it is to be successful in increasing the uptake of cervical cancer screening and subsequent followup testing.

While personal barriers are often in the sphere of influence of the individual patient, these items are important to consider during implementation because they strongly influence patient behavior. Among the Black community for example, individuals have expressed a lower level of trust in medical providers and the health system than other racial and/or ethnic groups due to a complicated history with the medical establishment.[44] This can be seen in the reduced rate of cervical cancer screening in this population, and Black women have noted these feelings specifically as influencing their screening behaviors and avoidance of screening. Relatedly, perceived stigmatization by healthcare providers is a barrier to screening reported by transgender men and individuals in the LGBQ+ community.[41, 44, 70] In addition, among transgender

individuals, vaginal and cervical atrophy resulting from testosterone therapy can make the speculum exam associated with cervical cancer screening uncomfortable and something to be avoided. These issues along with challenges to gender identity and anxiety around privacy in these populations act as barriers to completing screening and followup.[41, 44] The high prevalence of sexual trauma among women and transgender men and how this may result in screening avoidance should be considered as well.[41, 44]

The fear of finding cancer as the result of screening, as well as a lack of urgency around less severe findings, are notable barriers that are commonly reported as a reason for avoiding screening and not receiving recommended followup testing. In a survey of 433 uninsured and low-income women, 53 percent reported the fear of finding cancer as the main reason that they have avoided screening.[69] Further, a qualitative study of under- and never-screened women reported fear of the results as a major theme that emerged when talking with these individuals.[74] In terms of followup testing, it has been reported that the severity of the results impacts the urgency felt by the individual to receive recommended followup diagnostic testing, with women with low-grade abnormalities being less likely to receive colposcopy than women with high-grade abnormalities.[71] Anxiety about the screening/followup procedure and embarrassment with cervical screening, especially with a male physician, are commonly reported barriers, especially among individuals belonging to religiously conservative populations.[44, 69, 70, 75, 76] Other important personal barriers include a lack of awareness about the need for screening/followup testing, limited health literacy, fear of the stigma of being diagnosed with a reproductive health problem that can be perceived as being caused by promiscuous behavior, and language barriers.[44, 69, 70, 72, 75]

Structural barriers to screening and followup testing are wide-reaching and encompass many situations encountered throughout an individual's life. The cost of screening and related procedures is a major barrier to completing screening and followup testing. In the survey study (n=433) noted above, 62 percent of respondents indicated that cost was the most important barrier to screening for them.[69] Although the cost of screening is covered by the Affordable Care Act as a preventive service, this may not apply to health plans that were in place prior to its passage in 2010, and coverage of subsequent procedures needed based on the results of screening may not be covered by insurance.[77] A study published in 2022 found that the out-of-pocket costs that women face have increased sharply over time and were notable.[78] Specifically, individuals undergoing a colposcopy without further procedures paid an average of $112, while those who had cells taken for further examination paid an average of $155. If further procedures were needed, individuals could face hundreds of dollars more in costs. By 2019, if additional care beyond a biopsy was needed, a total bill of nearly $1,000 could be expected. Many underscreened groups, including low-income, un- and under-insured, and immigrant populations note that financial barriers related to the cost of screening and followup are important in influencing their screening choices.[44, 70, 73, 75, 76]

The inability to take time off from work to attend appointments and the difficulty in finding affordable childcare so that women can complete cervical cancer screening and necessary followup are significant barriers that should be considered in the implementation of a screening program.[44, 70, 75] Additionally, transportation challenges, difficulty in navigating the healthcare system to make appointments, and a lack of access to providers (especially among rural patients) or available clinic hours that are convenient are notable challenges that can be remedied by creative implementation strategies.[44, 69, 70, 75, 79] Among some healthcare systems there is not a

robust system in place providing screening reminders to patients or followup scheduling assistance if rescreening or additional procedures are needed. This can contribute to underscreening and reduced followup of screened patients, especially among populations who might already have reduced health literacy.[44, 70, 72, 80] Other barriers experienced among individuals living in rural areas, which are an important underscreened group, include a high rate of turnover among providers, a lack of medical facilities, extended wait times for appointments due to a low number of providers, and a reduced availability of quality healthcare.[44, 70, 79]

Contextual Question 5. Are there effective interventions or strategies to improve screening rates and followup to abnormal screening results?

Improving screening rates and receipt of needed followup testing/procedures among underscreened women is crucial in reducing the incidence of cervical cancer.[44, 76] With that goal in mind, a variety of screening strategies and implementation programs have been designed explicitly to achieve this goal. The most promising strategy of recent years appears to be making self-collected hrHPV tests available to women, either through direct mailing of the test kits or offering them as part of an office visit.[44, 81, 82] The availability of self-screening tests is important because this mode of testing helps to address many of the barriers described in **Contextual Question 4**. Specifically, the feelings of embarrassment and fear of stigma associated with the traditional screening procedure, as well as the logistical and access barriers (e.g., inability to find child care/transportation/time off to attend an in-person appointment, lack of medical facilities or providers in rural areas).[44, 73] This systematic review, as well as a recent meta-analysis by Arbyn and colleagues of 55 accuracy studies and 25 participation trials, found that the test accuracy of self-collected vaginal samples was on par with clinician-collected cervical samples.[81] The review by Arbyn and colleagues also found that directly mailing the tests for women to complete at home and return via the mail was more effective in increasing completion of screening than inviting women to come into a clinician's office to complete the self-collected sample or sending them reminder letters to come in for conventional screening. Further, strategies in which individuals had to request the self-collection test kits themselves, or "opt-in," were found to be similarly effective in increasing compliance with screening compared to strategies involving invitation letters to come in to complete a self-collected sample.[81] These findings are concurrent with other recent publications which show that offering self-collected hrHPV testing increases screening uptake over traditional screening outreach.[76, 82-85]

In addition to offering the option for self-collected hrHPV vaginal samples, over the past decade researchers have evaluated the effectiveness of other implementation strategies with mixed, but mostly positive results. These have included sending personalized letters with or without cervical cancer risk information, telephone calls to remind or assist women with making screening and followup appointments, using patient navigation systems, using community or lay health workers to educate women about screening, text message reminders/education campaigns, and offering assistance with transportation to attend appointments.[44, 76, 86-90] Overall, the majority of these strategies had a positive impact on screening uptake and followup testing, although some were not found to be significantly more effective than usual care.

The Community Preventive Services Task Force (CPSTF) has recently evaluated the effectiveness of the related implementation strategies of patient navigation systems, interventions engaging community health workers, and multicomponent interventions in increasing cervical cancer screening.[89, 91, 92] These interventions are overlapping, with the recommendation on using patient navigation systems being the most recent. In 2022, the CPSTF recommended using patient navigation systems for historically disadvantaged racial and ethnic populations and people with lower incomes to improve screening uptake based on strong evidence.[89] These navigation services are typically provided through existing health systems and aim to assist patients in overcoming existing barriers to screening and associated followup. Patient navigation systems are considered multicomponent interventions, and can include a variety of elements, such as patient reminders, assistance with appointment scheduling, transportation help, and

programs to help reduce out-of-pocket costs.[89] Multicomponent interventions are an implementation approach to screening that combine two or more strategies for the purpose of increasing effectiveness, and aim to tackle multiple barriers to screening at the same time.[91] In their review, the CPSTF found that patient navigation services help to advance health equity, improve health, and reduce cancer-related disparities among these targeted groups.

Prior to this recommendation, in 2019, the CPSTF examined the effectiveness of interventions using community health workers to increase screening uptake and found that these interventions are both helpful and cost-effective.[92] These types interventions are often included in patient navigation systems and help to increase the community demand for screening using education and client reminders. They also help to improve community access to screening by reducing existing barriers (e.g., providing language translation, childcare). Relatedly, the CPSTF evaluated the effectiveness of multicomponent interventions, which both patient navigation systems and interventions using community health workers are, in increasing cervical cancer screening uptake, and recommended this approach in 2017 based on strong evidence.[91] In their review, they found that the largest screening increases were found among interventions that combined approaches among the three strategies of increasing community demand (e.g., incentives, reminders, group education), increasing community access (e.g., interventions to reduce cost, providing appointment scheduling assistance, providing childcare/transportation/translation services), and increasing provider delivery (e.g., provider incentives, provider assessments/feedback). These types of interventions are often more complex and can require the coordination of healthcare systems and community settings, but results show that the effort results in notably higher screening uptake and compliance with followup testing/procedures among targeted populations.[89, 91, 92]

Appendix B Table 1. Relative Sensitivity and Specificity of FDA Approved hrHPV Assays for the Detection of CIN2+[4]

Index assay	Studies (k)	Relative sensitivity for CIN2+ (95% CI)	Relative specificity for CIN2+ (95% CI)
Cervista	2	0.98 (0.95 to 1.01)	1.01 (0.98 to 1.04)
Aptima	8	0.97 (0.95 to 1.00)	1.03 (1.02 to 1.05)
Cobas	5	1.00 (0.98 to 1.03)	1.00 (0.99 to 1.01)
Onclarity	4	1.00 (0.97 to 1.03)	1.00 (0.98 to 1.01)
Alinity	1	1.05 (1.00 to 1.10)	1.01 (0.99 to 1.02)

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; FDA = U.S. Food and Drug Administration; hrHPV = high-risk human papilloma virus; k = number of studies

Appendix B Table 2. Detection of Precancer and Burden of Testing of FDA Approved hrHPV Assays[10]

Assay	Test positive	Detection of CIN2+	Detection of CIN3+	Colposcopy	False positive rate
HC2	11.7%	1.6%	1.2%	4.1%	10.1%
Cobas	16.2%	1.7%	1.3%	4.5%	14.5%
Aptima	9.4%	1.6%	1.2%	3.4%	7.8%

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; FDA = U.S. Food and Drug Administration; HC2 = Hybrid Capture-2; hrHPV = high-risk human papilloma virus

Appendix B Table 3. Sensitivity and Specificity of Triage Tests for the Detection of CIN2+ in Women With Abnormal Cytology[16]

Triage test	Triage group	Studies (k)	Sensitivity (95% CI)	Specificity (95% CI)
hrHPV DNA test	ASC-US	25	93 (91 to 95)	45 (38 to 53)
	LSIL	25	95 (94 to 96)	27 (23 to 33)
Dual stain	ASC-US	13	84 (77 to 89)	77 (70 to 82)
	LSIL	18	86 (82 to 89)	66 (59 to 72)
P16 only	ASCUS	17	82 (76 to 87)	71 (65 to 76)
	LSIL	15	83 (76 to 88)	62 (52 to 71)

Abbreviations: ASC-US = Atypical Squamous Cells of Undetermined Significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; DNA = deoxyribonucleic acid; hrHPV = high-risk human papilloma virus; k = number of studies; LSIL = Low-grade Squamous Intraepithelial Lesion

Appendix B Table 4. Sensitivity and Specificity of Triage Tests for the Detection of CIN2+ in hrHPV-Positive Women[14]

Triage test	Studies (k)	Sensitivity (95% CI)	Specificity (95% CI)	Colposcopy referral (IQR or range)
Cytology, ASC-US+	39	71.5 (65.2 to 77.1)	74.7 (69.2 to 79.5)	33.8 (28.9 to 43.8)
Dual stain	5	80.8 (74.5 to 85.8)	69.0 (61.1 to 75.9)	36.5 (29.4 to 46.0)
hrHPV 16/18	16	52.9 (50.2 to 55.7)	74.9 (70.3 to 79.0)	30.7 (20.2 to 34.3)
hrHPV 16/18, other genotype+ if ASC-US+	12	82.6 (79.2 to 85.5)	55.4 (48.2 to 62.4)	53.5 (44.6 to 68.8)

Abbreviations: ASC-US = Atypical Squamous Cells of Undetermined Significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papilloma virus; IQR = interquartile range; k = number of studies; LSIL = Low-grade Squamous Intraepithelial Lesion

Appendix B Table 5. 18-Month and 3-Year Risk of CIN3+ by hrHPV Types, Cytology, and Proposed Management[24]

hrHPV risk profile	Cytology	% Test positive	18mo risk (95%CI)	3y risk (95%CI)	Management
hrHPV 16	LSIL/ASC-US	7.8	15.1 (14.6 to 15.6)	17.9 (16.2 to 19.5)	Colposcopy
	normal	6.6	10.7 (9.1 to 12.4)	13.8 (11.9 to 15.6)	Colposcopy
else hrHPV 18/45	LSIL/ASC-US	3.4	6.0 (5.7 to 6.4)	7.1 (5.6 to 8.6)	Colposcopy
	normal	4.8	3.3 (2.3 to 4.2)	4.4 (3.2 to 5.6)	1y vs colposcopy
else hrHPV 33/58/31/52	LSIL/ASC-US	11.5	5.4 (5.1 to 5.8)	5.7 (5.0 to 6.4)	Colposcopy
	normal	11.9	2.9 (1.8 to 3.9)	4.0 (3.2 to 4.7)	1y
else hrHPV 51/35/39/68/56/59/66	LSIL/ASC-US	15.2	1.5 (1.4 to 1.6)	2.0 (1.7 to 2.4)	1y
	normal	18.1	0.8 (0.0 to 1.6)	1.2 (6.2 to 8.7)	1y

Abbreviations: ASC-US = Atypical Squamous Cells of Undetermined Significance; CI = confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papilloma virus; IQR = interquartile range; k = number of studies; LSIL = Low-grade Squamous Intraepithelial Lesion; mo = months; vs = versus; y = year

Appendix B Table 6. Sensitivity and Specificity (Compared to hrHPV 16/18+ or Other hrHPV and ASC-US+ Threshold) for CIN3+, and Colposcopies per CIN3+ Detected for Different Extended Genotyping Triage Strategies[17]

Triage strategy	Sensitivity	Specificity	Colposcopies per CIN3+
16/18+, 12 other+ and ASC-US+	77.2	61.6	7.3
16/18/31/33/45/52/58+	88.3	45.0	8.9
16/18/31/33/45/52+	86.6	49.7	8.4
16/18+, 12 other genotype+ if dual stain+	86.0	60.1	6.9
16/18/31/33/35+	76.0	58.7	7.9
14 genotypes hrHPV+ if dual stain+	73.7	76.3	5.1
16/18/31/33+	72.5	64.2	7.3

Abbreviations: ASC-US = Atypical Squamous Cells of Undetermined Significance; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papilloma virus

Included studies List, by Key Question and Study Design

Ancillary publication(s) indented under primary article

Key Question 1 – Trials

1. Canfell K, Caruana M, Gebski V, et al. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial. PLoS Med. 2017;14(9):e1002388. PMID: 28926579. https://dx.doi.org/10.1371/journal.pmed.1002388
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Key Question 2 – Test Agreement and Accuracy

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Key Question 3 – Trials

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    c. 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(11):765-74. PMID: 16757701. https://dx.doi.org/10.1093/jnci/djj209
11. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Phase II: Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010;11(3):249-57. PMID: 20089449. https://dx.doi.org/10.1016/S1470-2045(09)70360-2

Key Question 3 – Nonrandomized Studies

1. Gottschlich, A, Gondara, L, et al. Colposcopy referral rates post-introduction of primary screening with human papillomavirus testing: evidence from a large British Columbia cohort study. Lancet Regional Health. Americas. 26:100598. 2023. PMID: 37786399. https://dx.doi.org/10.1016/j.lana.2023.100598
2. Thomsen LT, Kjaer SK, Munk C, et al. Benefits and potential harms of human papillomavirus (HPV)-based cervical cancer screening: A real-world comparison of HPV testing versus cytology. Acta Obstetricia et Gynecologica Scandinavica. 2021;100(3):394-402. PMID: 33566361. https://dx.doi.org/10.1111/aogs.14121
3. Tranberg M, Petersen LK, Hammer A, et al. Value of a catch-up HPV test in women aged 65 and above: A Danish population-based nonrandomized intervention study. PLoS Med. 2023;20(7):e1004253. PMID: 37410699. https://dx.doi.org/10.1371/journal.pmed.1004253
4. Veijalainen O, Kares S, Kujala P, et al. Implementation of HPV-based cervical cancer screening in an organised regional screening programme: 3 years of experience. Cytopathology. 2019;30(2):150-6. PMID: 30421573. https://dx.doi.org/10.1111/cyt.12652

Appendix D. Excluded Studies List

Reason for Exclusion*
E1. Aim/relevant
E2. Setting (Not a very high HDI country)
E3. Population
E3a. Exclusively HIV, in utero exposure diethylstilbestrol, previous treatment for cervical cancer or a high-grade precancerous lesion
E3b. Population not representative of population screening (e.g., patients referred to colposcopy, those with positive cytology results, followup from previous treatment for an abnormality)
E4. Study design
E4a. Pre-post, case studies, narrative reviews, editorials (KQ1/3)
E4b. No reference standard, case control, non-randomized (KQ2)
E4c. Followup not adequate for screen negatives
E4d. Study not designed for screening effectiveness
E5. Study quality
E6. Intervention
E6a. Non-hrHPV screening strategies
E6b. Not a commercially available test (proof of concept)
E7. Comparator (no screening [KQ1/3]; wrong reference standard [KQ2])
E8. Outcomes (no relevant outcomes or unable to calculate accuracy)
E9. Primary article excluded
E10. Single arm cohorts not adding new outcomes/analyses to comparative studies

*Assigned at full-text phase

1. Agorastos, T, Chatzistamatiou, K, et al. Primary screening for cervical cancer based on high-risk human papillomavirus (HPV) detection and HPV 16 and HPV 18 genotyping, in comparison to cytology. PLoS One. 10(3): e0119755. 2015. PMID: 25793281. https://dx.doi.org/10.1371/journal.pone.0119755 **KQ1E10**
2. Aiko, KY, Yoko, M, et al. Accuracy of self-collected human papillomavirus samples from Japanese women with abnormal cervical cytology. Journal of Obstetrics & Gynaecology Research. 43(4): 710-717. 2017. PMID: 28418208. https://dx.doi.org/10.1111/jog.13258 **KQ2E3b; KQ3E3b**
3. Aitken CA, Inturrisi F, Kaljouw S, et al. Sociodemographic Characteristics and Screening Outcomes of Women Preferring Self-Sampling in the Dutch Cervical Cancer Screening Programme: A Population-Based Study. Cancer Epidemiology, Biomarkers & Prevention. 2023;32(2):183-92. PMID: 36099416. https://dx.doi.org/10.1158/1055-9965.EPI-22-0712 KQ1E5**; KQ3E5**
4. Aitken, CA, van Agt, HME, et al. Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. BMC Med. 17(1): 228. 2019. PMID: 31829241. https://dx.doi.org/10.1186/s12916-019-1460-0 **KQ1E4a**
5. Alameda, F, Bellosillo, B, et al. Human papillomavirus detection in urine samples: an alternative screening method. J Low Genit Tract Dis. 11(1): 5-7. 2007. PMID: 17194943. https://dx.doi.org/10.1097/01.lgt.0000230204.65742.e4 **KQ2E6b**
6. Alay, I, Kaya, C, et al. The effect of being diagnosed with human papillomavirus infection on women's sexual lives. J Med Virol. 92(8): 1290-1297. 2020. PMID: 31696950. https://dx.doi.org/10.1002/jmv.25623 **KQ1E3b; KQ3E3b**

7. Al-Kalbani, M, Price, J, et al. Does Cervical Screening in Young Women Aged 20-25 Years Lead to Unnecessary and Harmful Interventions?. Asian Pacific Journal of Cancer Prevention: Apjcp. 16(15): 6557-9. 2015. PMID: 26434874. **KQ1E1**
8. Andersen, B, Njor, SH, et al. HrHPV testing vs liquid-based cytology in cervical cancer screening among women aged 50 and older: a prospective study. Int J Gynecol Cancer. 30(11): 1678-1683. 2020. PMID: 33037107. https://dx.doi.org/10.1136/ijgc-2020-001457 **KQ1E10; KQ3E10**
9. Aranda Flores, CE, Gomez Gutierrez, G, et al. Self-collected versus clinician-collected cervical samples for the detection of HPV infections by 14-type DNA and 7-type mRNA tests. BMC Infect Dis. 21(1): 504. 2021. PMID: 34058992. https://dx.doi.org/10.1186/s12879-021-06189-2 **KQ2E2**
10. Arbyn, M, de Sanjose, S, et al. HPV-based cervical cancer screening, including self-sampling, versus screening with cytology in Argentina. The Lancet Global Health. 7(6): e688-e689. 2019. PMID: 31097266. https://dx.doi.org/10.1016/S2214-109X(19)30067-1 **KQ2E4b**
11. Arbyn, M, Peeters, E, et al. VALHUDES: A protocol for validation of human papillomavirus assays and collection devices for HPV testing on self-samples and urine samples. J Clin Virol. 107(): 52-56. 2018. PMID: 30195193. https://dx.doi.org/10.1016/j.jcv.2018.08.006 **KQ2E9**
12. Arrossi, S, Paolino, M, et al. Programmatic human papillomavirus testing in cervical cancer prevention in the Jujuy Demonstration Project in Argentina: a population-based, before-and-after retrospective cohort study. The Lancet Global Health. 7(6): e772-e783. 2019. PMID: 31097279. https://dx.doi.org/10.1016/S2214-109X(19)30048-8 **KQ1E10**
13. Asciutto, KC, Ernstson, A, et al. Self-sampling with HPV mRNA analyses from vagina and urine compared with cervical samples. J Clin Virol. 101(): 69-73. 2018. PMID: 29433016. https://dx.doi.org/10.1016/j.jcv.2018.02.002 **KQ2E3b**
14. Asciutto, KC, Henningsson, AJ, et al. Vaginal and Urine Self-sampling Compared to Cervical Sampling for HPV-testing with the Cobas 4800 HPV Test. Anticancer Res. 37(8): 4183-4187. 2017. PMID: 28739704. **KQ2E3b**
15. Auvinen, E, Nieminen, P, et al. Human papillomavirus self-sampling with mRNA testing benefits routine screening. Int J Cancer. 18(): 18. 2022. PMID: 35716139. https://dx.doi.org/10.1002/ijc.34170 **KQ2E5**
16. Baldauf, JJ, Fender, M, et al. Cervical morbidity in Alsace, France: results from a regional organized cervical cancer screening program. Eur J Cancer Prev. 28(1): 33-39. 2019. PMID: 29135538. https://dx.doi.org/10.1097/CEJ.0000000000000415 **KQ1E6; KQ3E6**
17. Bennett, KF, Waller, J, et al. Psychosexual distress following routine primary human papillomavirus testing: a longitudinal evaluation within the English Cervical Screening Programme. BJOG: An International Journal of Obstetrics & Gynaecology. 128(4): 745-754. 2021. PMID: 32783300. https://dx.doi.org/10.1111/1471-0528.16460 **KQ1E8; KQ3E5**
18. Bergengren, L, Kaliff, M, et al. Comparison between professional sampling and self-sampling for HPV-based cervical cancer screening among postmenopausal women. Int J Gynaecol Obstet. 142(3): 359-364. 2018. PMID: 29856071. https://dx.doi.org/10.1002/ijgo.12538 **KQ2E3b**
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20. Bik, EM, Bird, SW, et al. A novel sequencing-based vaginal health assay combining self-sampling, HPV detection and genotyping, STI detection, and vaginal microbiome analysis. PLoS ONE [Electronic Resource]. 14(5): e0215945. 2019. PMID: 31042762. https://dx.doi.org/10.1371/journal.pone.0215945 **KQ2E7**
21. Blake, DA, Crosbie, EJ, et al. Urinary HPV testing may offer hope for cervical screening non-attenders. BJOG: An International Journal of Obstetrics & Gynaecology. 124(9): 1364. 2017. PMID: 28391626. https://dx.doi.org/10.1111/1471-0528.14683 **KQ2E4a**
22. Bokan, T, Ivanus, U, et al. Long term results of follow-up after HPV self-sampling with devices Qvintip and HerSwab in women non-attending cervical screening programme. Radiol Oncol. 55(2): 187-195. 2021. PMID: 33764704. https://dx.doi.org/10.2478/raon-2021-0001 **KQ2E3b**
23. Bottari, F, Igidbashian, S, et al. HPV self-sampling in CIN2+ detection: sensitivity and specificity of different RLU cut-off of HC2 in specimens from 786 women. J Clin Pathol. 70(4): 327-330. 2017. PMID: 27672216. https://dx.doi.org/10.1136/jclinpath-2016-204044 **KQ2E3b**
24. Boyard, J, Caille, A, et al. A Home-Mailed Versus General Practitioner-Delivered Vaginal Self-Sampling Kit for Cervical Cancer Screening: A Cluster Randomized Controlled Trial with a Cost-Effectiveness Analysis. Journal of Women's Health. 13(): 13. 2022. PMID: 35834620. https://dx.doi.org/10.1089/jwh.2021.0597 **KQ2E7**
25. Buchegger, K, Viscarra, T, et al. Detection and genotyping of human papillomavirus virus (HPV): a comparative analysis of clinical performance in cervical and urine samples in Chilean women. Int J Clin Exp Pathol. 11(11): 5413-5421. 2018. PMID: 31949624. **KQ2E3b**
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28. Carozzi, F, Burroni, E, et al. Implementation of a centralized HPV-based cervical cancer screening programme in Tuscany: First round results and comparison with the foregoing Pap-based screening programme. J Med Screen. 29(2): 110-122. 2022. PMID: 35038279. https://dx.doi.org/10.1177/09691413211067922 **KQ1E10; KQ3E10**
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31. Catarino, R, Vassilakos, P, et al. Randomized Comparison of Two Vaginal Self-Sampling Methods for Human Papillomavirus Detection: dry Swab versus FTA Cartridge. PLoS One. 10(12) (no pagination): . 2015. PMID: CN-01198669. 10.1371/journal.pone.0143644 **KQ2E3b**

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33. Chatzistamatiou, Kimon, Vrekoussis, Thomas, et al. Acceptability of self-sampling for human papillomavirus-based cervical cancer screening. Journal of Women's Health. 29(11): 1447-1456. 2020. PMID: . https://dx.doi.org/10.1089/jwh.2019.8258 **KQ2E4b**
34. Chen, Q, Du, H, et al. Evaluation of novel assays for the detection of human papilloma virus in self-collected samples for cervical cancer screening. Genet Mol Res. 15(2): 24. 2016. PMID: 27420961. https://dx.doi.org/10.4238/gmr.15027896 **KQ2E3b; KQ3E3b**
35. Chernesky, M, Jang, D, et al. Evaluation of a new APTIMA specimen collection and transportation kit for high-risk human papillomavirus E6/E7 messenger RNA in cervical and vaginal samples. Sex Transm Dis. 41(6): 365-8. 2014. PMID: 24825332. https://dx.doi.org/10.1097/OLQ.0000000000000125 **KQ2E3b**
36. Chiappetta, C, Lendaro, E, et al. Primary HPV test screening in cervical cancer: a two-year experience of a single screening center in Latina (Italy). Eur J Gynaecol Oncol. 36(5): 569-73. 2015. PMID: 26513885. **KQ1E4a; KQ3E4a**
37. Cho, HW, Hong, JH, et al. Performance and Diagnostic Accuracy of Human Papillomavirus Testing on Self-Collected Urine and Vaginal Samples in a Referral Population. Cancer Research & Treatment. 53(3): 829-836. 2021. PMID: 33421987. https://dx.doi.org/10.4143/crt.2020.1165 **KQ2E3b**
38. Cho, HW, Ouh, YT, et al. Comparison of urine, self-collected vaginal swab, and cervical swab samples for detecting human papillomavirus (HPV) with Roche Cobas HPV, Anyplex II HPV, and RealTime HR-S HPV assay. J Virol Methods. 269(): 77-82. 2019. PMID: 30998958. https://dx.doi.org/10.1016/j.jviromet.2019.04.012 **KQ2E3b**
39. Choi, YS, Jin, H, et al. Usefulness Analysis of Urine Samples for Early Screening of Human Papilloma Virus Infection. Journal of Cancer Prevention. 24(4): 240-244. 2019. PMID: 31950024. https://dx.doi.org/10.15430/JCP.2019.24.4.240 **KQ2E7**
40. Chou, HH, Yang, CY, et al. Consistency in human papillomavirus type detection between self-collected vaginal specimens and physician-sampled cervical specimens. J Med Virol. 96(3): e29426. 2024. PMID: 38420851. https://dx.doi.org/10.1002/jmv.29426 **KQ2E4b**
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44. Das S, Wentzensen N, Sawaya GF, et al. Primary human papillomavirus testing versus CO-testing: clinical outcomes in populations with different disease prevalence. J Natl Cancer Inst. 2024. PMID: 38830048. https://dx.doi.org/10.1093/jnci/djae117 **KQ1E4; KQ1E4**

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47. Dijkstra, MG, Heideman, DA, et al. Brush-based self-sampling in combination with GP5+/6+-PCR-based hrHPV testing: high concordance with physician-taken cervical scrapes for HPV genotyping and detection of high-grade CIN. J Clin Virol. 54(2): 147-51. 2012. PMID: 22445557. https://dx.doi.org/10.1016/j.jcv.2012.02.022 **KQ2E3b**
48. Du, H, Duan, X, et al. An evaluation of solid versus liquid transport media for high-risk HPV detection and cervical cancer screening on self-collected specimens. Infectious Agents & Cancer [Electronic Resource]. 15(1): 72. 2020. PMID: 33292341. https://dx.doi.org/10.1186/s13027-020-00333-4 **KQ2E2**
49. Elfstrom, M, Gray, PG, et al. Cervical cancer screening improvements with self-sampling during the COVID-19 pandemic. Elife. 12(): 12. 2023. PMID: 38085566. https://dx.doi.org/10.7554/eLife.80905 **KQ2E4b**
50. El-Zein, M, Bouten, S, et al. Predictive Value of HPV Testing in Self-collected and Clinician-Collected Samples Compared with Cytology in Detecting High-grade Cervical Lesions. Cancer Epidemiol Biomarkers Prevent. 28(7): 1134-1140. 2019. PMID: 31015201. https://dx.doi.org/10.1158/1055-9965.EPI-18-1338 **KQ2E3b**
51. El-Zein, M, Bouten, S, et al. Validation of a new HPV self-sampling device for cervical cancer screening: The Cervical and Self-Sample In Screening (CASSIS) study. Gynecol Oncol. 149(3): 491-497. 2018. PMID: 29678360. https://dx.doi.org/10.1016/j.ygyno.2018.04.004 **KQ2E3b**
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54. Ertik, FC, Kampers, J, et al. CoCoss-Trial: Concurrent Comparison of Self-Sampling Devices for HPV-Detection. International Journal of Environmental Research & Public Health [Electronic Resource]. 18(19): 02. 2021. PMID: 34639688. https://dx.doi.org/10.3390/ijerph181910388 **KQ2E3b**
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56. Feldstein O, Gali-Zamir H, Schejter E, et al. High-risk HPV testing vs liquid-based cytology for cervical cancer screening among 25- to 30-year-old women: A historical cohort study. Acta Obstetricia et Gynecologica Scandinavica. 2023;102(2):226-33. PMID: 36478537. https://dx.doi.org/10.1111/aogs.14482 **KQ1E4a; KQ3E4a**

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58. Fielding, S, Rothnie, K, et al. Psychosocial morbidity in women with abnormal cervical cytology managed by cytological surveillance or initial colposcopy: longitudinal analysis from the TOMBOLA randomised trial. Psychooncology. 26(4): 476-483. 2017. PMID: 27297097. https://dx.doi.org/10.1002/pon.4163 **KQ3E1**
59. Fujita, M, Nagashima, K, et al. Implementation of a self-sampling HPV test for non-responders to cervical cancer screening in Japan: secondary analysis of the ACCESS trial. Sci Rep. 12(1): 14531. 2022. PMID: 36008554. https://dx.doi.org/10.1038/s41598-022-18800-w **KQ2E7**
60. Fujita M, Nagashima K, Shimazu M, et al. Acceptability of self-sampling human papillomavirus test for cervical cancer screening in Japan: A questionnaire survey in the ACCESS trial. PLoS ONE [Electronic Resource]. 2023;18(6):e0286909. PMID: 37289798. https://dx.doi.org/10.1371/journal.pone.0286909 **KQ2E7**
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65. Goldstein, Z, Martinson, T, et al. Improved Rates of Cervical Cancer Screening Among Transmasculine Patients Through Self-Collected Swabs for High-Risk Human Papillomavirus DNA Testing. Transgender Health. 5(1): 10-17. 2020. PMID: 32322684. https://dx.doi.org/10.1089/trgh.2019.0019 **KQ2E7**
66. Gustavsson, I, Sanner, K, et al. Type-specific detection of high-risk human papillomavirus (HPV) in self-sampled cervicovaginal cells applied to FTA elute cartridge. J Clin Virol. 51(4): 255-8. 2011. PMID: 21632283. https://dx.doi.org/10.1016/j.jcv.2011.05.006 **KQ2E3b**
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71. Hermansson, RS, Olovsson, M, et al. Elderly women's experiences of self-sampling for HPV testing. BMC Cancer. 20(1): 473. 2020. PMID: 32456679. https://dx.doi.org/10.1186/s12885-020-06977-0 **KQ2E1**
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Appendix E Table 1. KQ1 and KQ3: Results From RCTs and NRSIs, Primary hrHPV Screening Strategies

Study design	Author, year Study name	Rand screening strategy	Round	Screening strategy	Comparison	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
RCT	Nygard, 2022[93]	hrHPV with LBC triage v. LBC with hrHPV triage	1	hrHPV with LBC triage	LBC with hrHPV triage	Screening test positive	4784/77207 (6.2)	1834/80240 (2.3)	2.71 (2.57, 2.86)
						Colposcopy attendance	4305/77207 (5.6)	2845/80240 (3.5)	1.60 (1.50, 1.68)
						CIN2+	1263/77207 (1.6)	822/80240 (1)	1.60 (1.50, 1.70)
						CIN3+	991/77207 (1.3)	711/80240 (0.9)	1.40 (1.30, 1.60)
						ICC	66/77207 (0.08)	48/80240 (0.06)	1.40 (0.97, 2.03)
						FPR for CIN2+	3588/75512 (4.8)	1103/74944 (1.5)	3.23 (3.02, 3.45)
						FNR for ICC	5/63 (7.9)	6/47 (12.8)	--
	Elfstrom, 2021[94]	hrHPV with LBC triage v. LBC with hrHPV triage	1	hrHPV with LBC triage	LBC with hrHPV triage	Screening test positive	9712/110197 (8.8)	2955/90841 (3.3)	2.71 (2.60, 2.82)
						Colposcopy attendance	2489/110197 (2.3)	1663/90841 (1.8)	1.23 (1.16, 1.31)
						CIN2+	1140/110197 (1)	844/90841 (0.9)	1.11 (1.02, 1.22)
						CIN3+	655/110197 (0.6)	524/90841 (0.6)	1.03 (0.92, 1.16)
						ICC	46/110197 (0.04)	48/90841 (0.1)	0.79 (0.53, 1.18)
						FPR for CIN2+	8572/109057 (7.9)	2111/89997 (2.3)	3.35 (3.20, 3.51)
	Polman, 2019[95]	self-HPV with LBC triage v. hrHPV with LBC triage	1	self-HPV with LBC triage	hrHPV with LBC triage	Screening test positive	569/7643 (7.4)	451/6282 (7.2)	1.04 (0.92, 1.17)
						CIN2+	111/7643 (1.5)	92/6282 (1.5)	0.99 (0.75, 1.31)
						CIN3+	73/7643 (1.0)	45/6282 (0.7)	1.33 (0.92, 1.93)
						ICC	3/7643 (0.04)	2/6282 (0.03)	1.23 (0.21, 7.38)
						FPR for CIN2+	458/7532 (6.1)	359/6190 (5.8)	1.05 (0.92, 1.2)
						FNR for ICC	0/3 (0)	0/2 (0)	--
	Ogilvie, 2018[96] HPV FOCAL	hrHPV with LBC triage v. LBC with hrHPV triage	1	hrHPV with LBC triage	LBC with hrHPV triage	Screening test positive	771/9540 (8.1)	334/9408 (3.6)	2.28 (2.01, 2.58)
						Colposcopy referral	544/9540 (5.7)	290/9408 (3.1)	1.85 (1.61, 2.13)
						Colposcopy attendance	522/9540 (5.5)	280/9408 (3)	1.84 (1.59, 2.12)
						CIN2+	147/9540 (1.5)	90/9408 (1)	1.61 (1.24, 2.09)
						CIN3+	67/9540 (0.7)	41/9408 (0.4)	1.61 (1.09, 2.37)
						FPR for CIN2+	624/9393 (6.6)	244/9318 (2.6)	2.54 (2.19, 2.93)

Appendix E Table 1. KQ1 and KQ3: Results From RCTs and NRSIs, Primary hrHPV Screening Strategies

Study design	Author, year Study name	Rand screening strategy	Round	Screening strategy	Comparison	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
			2 (exit)	Cotesting	Cotesting	Screening test positive	469/8296 (5.7)	513/8078 (6.4)	0.89 (0.79, 1.01)
						CIN2+	48/9540 (0.5)	100/9408 (1.1)	0.47 (0.34, 0.67)
						CIN3+	22/9540 (0.2)	52/9408 (0.6)	0.42 (0.25, 0.69)
			Cumulative (1 and 2 [exit])	hrHPV with LBC triage (round 1) Cotesting (round 2)	LBC with hrHPV triage (round 1) Cotesting (round 2)	CIN2+	195/9540 (2)	190/9408 (2)	1.01 (0.83, 1.23)
						CIN3+	89/9540 (0.9)	93/9408 (1)	0.94 (0.71, 1.26)
	Canfell, 2017[97] COMPASS	hrHPV with LBC or DS triage v. LBC	1	hrHPV with LBC triage	LBC	Colposcopy referral	76/1992 (3.8)	27/995 (2.7)	1.41 (0.91, 2.17)
						CIN2+	20/1992 (1)	1/995 (0.1)	9.99 (1.34, 74.3)
						CIN3+	13/1992 (0.7)	1/995 (0.1)	6.49 (0.85, 49.6)
						ICC	0/1992 (0)	0/995 (0)	NA
				hrHPV with DS triage	LBC	Colposcopy referral	78/2008 (3.9)	27/995 (2.7)	1.43 (0.93, 2.20)
						CIN2+	24/2008 (1.2)	1/995 (0.1)	11.9 (1.61, 87.8)
						CIN3+	17/2008 (0.8)	1/995 (0.1)	8.42 (1.12, 63.2)
						ICC	0/2008 (0)	0/995 (0)	NA
	Leinonen, 2012[98]	hrHPV with CC triage v. CC	1	hrHPV with CC triage	CC	Screening test positive	4971/62106 (8)	4506/65747 (6.9)	1.17 (1.12, 1.21)
						Colposcopy referral	796/66410 (1.2)	755/65784 (1.1)	1.04 (0.95, 1.15)
						CIN2+	540/66410 (0.8)	319/65784 (0.5)	1.68 (1.46, 1.92)
						CIN3+	195/66410 (0.3)	118/65784 (0.2)	1.64 (1.30, 2.06)
						ICC	17/66410 (0.03)	9/65784 (0.01)	1.87 (0.83, 4.20)
						FPR for CIN2+	4450/61585 (7.2)	4187/65428 (6.4)	1.13 (1.08, 1.18)
						FNR for ICC	5/17 (29.4)	2/9 (22.2)	--
	Ronco, 2010[99] NTCC Phase II	hrHPV v. CC	1	hrHPV	CC	Screening test positive	1936/24661 (7.9)	825/24535 (3.4)	2.33 (2.16, 2.53)
						Colposcopy referral	1936/24661 (7.9)	679/24535 (2.8)	2.84 (2.60, 3.09)
						CIN2+	218/24661 (0.9)	73/24535 (0.3)	2.97 (2.28, 3.87)
						CIN3+	97/24661 (0.4)	33/24535 (0.1)	2.92 (1.97, 4.34)
						FPR for CIN2+	1718/24443 (7)	752/24462 (3.1)	2.29 (2.10, 2.49)

Appendix E Table 1. KQ1 and KQ3: Results From RCTs and NRSIs, Primary hrHPV Screening Strategies

Study design	Author, year Study name	Rand screening strategy	Round	Screening strategy	Comparison	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
			2 (exit)	CC	CC	CIN2+	12/23978 (0.1)	38/24372 (0.2)	0.32 (0.17, 0.61)
						CIN3+	5/23978 (0.02)	23/24372 (0.1)	0.22 (0.08, 0.58)
			Cumulative (1 and 2)	hrHPV (round 1) CC (round 2)	CC	CIN2+	230/24661 (0.9)	111/24535 (0.5)	2.06 (1.64, 2.58)
						CIN3+	102/24661 (0.4)	56/24535 (0.2)	1.81 (1.31, 2.51)
NRSI	Thomsen, 2021[100] HPV SCREEN DENMARK	hrHPV with LBC triage v. LBC with hrHPV triage	1	hrHPV with LBC triage	LBC with hrHPV triage	Screening test positive	1433/16067 (8.9)	716/23981 (3)	2.99 (2.74, 3.26)
						Colposcopy referral	1057/16067 (6.6)	515/23981 (2.1)	3.05 (2.75, 3.38)
						CIN2+	348/16067 (2.2)	236/23981 (1.0)	2.19 (1.86, 2.59)
						CIN3+	238/16067 (1.5)	188/23981 (0.8)	1.88 (1.56, 2.28)
						ICC	16/16067 (0.1)	12/23981 (0.1)	1.99 (0.94, 4.21)
						FPR for CIN2+	1085/15719 (6.9)	480/23745 (2)	3.41 (3.07, 3.79)
						FNR for ICC	0/16 (0)	2/14 (14.3)	--
	Veijalainen, 2019[101]	hrHPV with CC triage v. CC	1	hrHPV with CC triage	CC	Screening test positive	1455/17770 (8.2)	1160/15605 (7.4)	1.10 (1.02, 1.19)
						Colposcopy referral	795/17770 (4.5)	352/15605 (2.3)	1.98 (1.75, 2.24)
						Colposcopy attendance	779/17770 (4.4)	326/15605 (2.1)	2.10 (1.85, 2.38)
						CIN2+	134/17770 (0.8)	48/15605 (0.3)	2.45 (1.76, 3.41)
						CIN3+	83/17770 (0.5)	27/15605 (0.2)	2.70 (1.75, 4.17)
						ICC	4/17770 (0.02)	4/15605 (0.02)	0.88 (0.22, 3.51)
						FPR for CIN2+	1321/17636 (7.5)	1112/15557 (7.1)	1.05 (0.97, 1.13)
						FNR for ICC	0/4 (0)	0/4 (0)	--
	Tranberg, 2023[102]	hrHPV with LBC triage v. Usual care	1	hrHPV with LBC triage (catch-up HPV)	Usual care	CIN2+	44/11192 (0.4)	11/33387 (0.03)	11.9 (6.2, 23.1)
						CIN3+	26/11192 (0.2)	7/33387 (0.02)	11.1 (4.81, 25.5)
						ICC	4/11192 (0.04)	4/33387 (0.01)	2.98 (0.75, 11.9)
						Colposcopies per CIN2+ case	Number (95% CI): 11.6 (0.85, 15.8)	Number (95% CI): 10.1 (5.4, 18.8)	Comparison between IG and CG, p=0.69
						Colposcopies per CIN3+ case	Number (95% CI): 19.6 (13.2, 29.2)	Number (95% CI): 15.8 (7.4, 34.0)	Comparison between IG and CG, p=0.62

Appendix E Table 1. KQ1 and KQ3: Results From RCTs and NRSIs, Primary hrHPV Screening Strategies

Study design	Author, year Study name	Rand screening strategy	Round	Screening strategy	Comparison	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
LTFU	Vahteristo, 2024[103] Leinonen, 2012 LTFU[98]	hrHPV with CC triage v. CC	1-2 rounds of hrHPV followed by 1-2 rounds of cytology (15 years after round 1)	hrHPV with CC triage	CC	ICC	139/50,997	129/50,950	IRR: 1.08 (0.85, 1.37)
						Cervical cancer mortality	32/50,997	32/50,950	IRR: 1.00 (0.61, 1.64)
	Gottschlich, 2023[104] HPV FOCAL LTFU and HPV-DECADE	hrHPV with LBC triage (round 1), cotesting (round 2) v. CC	1 round of hrHPV testing, exit round of cotesting, followed by CC every 2-3 years (14 years after round 1)	hrHPV (with LBC triage or cotesting)	CC	Colposcopy referral	589/9540 (6.2)	53,470/1,140,745 (4.7)	1.32 (1.22, 1.42)
		hrHPV with LBC triage (round 1) v. CC	1 round of hrHPV testing, followed by CC every 2-3 years (14 years after round 1)	hrHPV with LBC triage	CC	Colposcopy referral	299/6204 (4.8)	53,470/1,140,745 (4.7)	1.03 (0.92, 1.15)

Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; DS = dual-stained; FNR = false negative rate; FPR = false positive rate; HPV = human papilloma virus; HPV FOCAL = Human Papillomavirus For Cervical Cancer screening trial; hr = high-risk; ICC = invasive cervical cancer; IG = intervention group; LBC = liquid-based cytology; N = number of participants; NA = not applicable; NRSI = non-randomized studies of interventions; NTCC = New Technologies for Cervical Cancer Screening trial; Rand = randomized; RCT = randomized controlled trial; RR = relative risk; v = versus

Appendix E Table 2. KQ1 and KQ3: Results From Primary hrHPV Screening Strategies, by Age Groups

Author, year Study name	Rand screening strategy	Round	IG strategy	CG strategy	Outcome	Age group, years	IG n/n (%)	CG n/n (%)	RR (95% CI)
Nygard, 2022[93]	hrHPV with LBC triage v. LBC with hrHPV triage	1	hrHPV with LBC triage	LBC	Colposcopy attendance	34-39	1090/14847 (7.3)	733/15123 (4.8)	1.50 (1.40, 1.50)
						40-44	857/12361 (6.9)	533/12804 (4.2)	1.70 (1.50, 1.90)
						45-49	705/12565 (5.6)	450/13033 (3.5)	1.60 (1.40, 1.80)
						50-54	531/11133 (4.8)	356/11737 (3)	1.60 (1.40, 1.80)
						55-59	441/10029 (4.4)	324/1341 (24.2)	1.40 (1.20, 1.60)
						60-64	359/8775 (4.1)	263/9375 (2.8)	1.50 (1.20, 1.70)
						65-69	322/7497 (4.3)	186/7827 (2.4)	1.80 (1.50, 2.10)
					CIN2+	34-39	492/14847 (3.3)	332/15123 (2.2)	1.50 (1.30, 1.70)
						40-44	307/12361 (2.5)	196/12804 (1.5)	1.60 (1.40, 1.90)
						45-49	196/12565 (1.6)	136/13033 (1)	1.50 (1.20, 1.90)
						50-5	109/11133 (1)	67/11737 (0.6)	1.70 (1.30, 2.30)
						55-59	71/10029 (0.7)	45/10341 (0.4)	1.60 (1.10, 2.40)
						60-64	48/8775 (0.5)	28/9375 (0.3)	1.80 (1.20, 2.90)
						65-69	40/7497 (0.5)	18/7827 (0.2)	2.30 (1.30, 4.10)
					CIN3+	34-39	397/14847 (2.7)	293/15123 (1.9)	1.40 (1.20, 1.60)
						40-44	245/12361 (2)	168/12804 (1.3)	1.50 (1.20, 1.80)
						45-49	152/12565 (1.2)	120/13033 (0.9)	1.30 (1.00, 1.70)
						50-54	82/11133 (0.7)	52/11737 (0.4)	1.70 (1.20, 2.40)
						55-59	52/10029 (0.5)	37/10341 (0.4)	1.40 (1.00, 2.20)
						60-64	32/8775 (0.4)	23/9375 (0.2)	1.50 (0.90, 2.50)
						65-69	31/7497 (0.4)	18/7827 (0.2)	1.70 (1.00, 3.20)
					ICC	34-39	23/14847 (0.2)	11/15123 (0.1)	2.1 (1.0, 4.4)
						40-44	13/12361 (0.1)	10/12804 (0.1)	1.3 (0.6, 3.0)
						45-49	11/12565 (0.1)	12/13033 (0.1)	1.0 (0.4, 2.0)
						50-54	9/11133 (0.1)	7/11737 (0.1)	1.4 (0.5, 3.4)
						55-59	3/10029 (0.03)	4/10341 (0.04)	0.8 (0.2, 3.5)
						60-64	2/8775 (0.02)	2/9375 (0.02)	1.1 (0.2, 7.6)
						65-69	5/7497 (0.1)	2/7827 (0.03)	2.6 (0.5, 13.5)
Elfstrom, 2021[94]	hrHPV with LBC triage v.	1	hrHPV with LBC triage	LBC with hrHPV triage	Screening test positive	30-34	2796/16411 (17)	819/16162 (5.1)	3.36 (3.12, 3.62)
						35-39	1741/16411 (10.6)	574/16112 (3.6)	2.98 (2.72, 3.26)
						40-44	1488/17728 (8.4)	518/16688 (3.1)	2.70 (2.45, 2.98)
						45-49	1223/16253 (7.5)	497/15928 (3.1)	2.41 (2.18, 2.67)

Appendix E Table 2. KQ1 and KQ3: Results From Primary hrHPV Screening Strategies, by Age Groups

Author, year Study name	Rand screening strategy	Round	IG strategy	CG strategy	Outcome	Age group, years	IG n/n (%)	CG n/n (%)	RR (95% CI)
	LBC with hrHPV triage					50-54	1058/17628 (6)	253/9497 (2.7)	2.25 (1.97, 2.58)
						55-59	767/13484 (5.7)	156/8780 (1.8)	3.20 (2.70, 3.79)
						60-64	639/12115 (5.3)	138/7674 (1.8)	2.93 (2.45, 3.52)
					CIN2+	30-34	404/16411 (2.5)	332/16162 (2.1)	1.20 (1.04, 1.38)
						35-39	255/16578 (1.5)	190/16112 (1.2)	1.30 (1.08, 1.57)
						40-44	207/17728 (1.2)	147/16688 (.9)	1.33 (1.07, 1.64)
						45-49	119/16253 (0.7)	98/15928 (.6)	1.19 (0.91, 1.55)
						50-54	68/17628 (0.4)	30/9497 (.3)	1.22 (0.80, 1.88)
						55-59	47/13484 (0.3)	25/8780 (.3)	1.22 (0.75, 1.99)
						60-64	40/12115 (0.3)	22/7674 (.3)	1.15 (0.69, 1.94)
					FPR for CIN2+	30-34	2392/16007 (14.9)	487/15830 (3.1)	4.86 (4.42, 5.34)
						35-39	1486/16323 (9.1)	384/15922 (2.4)	3.77 (3.38, 4.21)
						40-44	1281/17521 (7.3)	371/16541 (2.2)	3.26 (2.91, 3.65)
						45-49	1104/16134 (6.8)	399/15830 (2.5)	2.71 (2.43, 3.04)
						50-54	990/17560 (5.6)	223/9467 (2.4)	2.39 (2.07, 2.76)
						55-59	720/13437 (5.4)	131/8755 (1.5)	3.58 (2.98, 4.31)
						60-64	599/12075 (5)	116/7652 (1.5)	3.27 (2.69, 3.98)
Polman, 2019[95] IMPROVE Study	self-HPV with LBC triage v. hrHPV with LBC triage	1	self-HPV with LBC triage	hrHPV with LBC triage	Screening test positive	29-33	129/745 (17.3)	98/600 (16.3)	1.06 (0.83, 1.35)
						34-38	96/888 (10.8)	75/712 (10.5)	1.03 (0.77, 1.37)
						39-43	68/1055 (6.4)	58/839 (6.9)	0.93 (0.66, 1.31)
						44-48	82/1394 (5.9)	74/1149 (6.4)	0.91 (0.67, 1.24)
						49-53	82/1154 (7.1)	65/957 (6.8)	1.05 (0.76, 1.43)
						54-58	69/1333 (5.2)	56/1143 (4.9)	1.06 (0.75, 1.49)
						59-61	43/1074 (4)	25/882 (2.8)	1.41 (0.87, 2.29)
					CIN2+	29-33	34/745 (4.6)	33/600 (5.5)	0.83 (0.52, 1.32)
						34-38	26/888 (2.9)	12/712 (1.7)	1.74 (0.88, 3.42)
						39-43	17/1055 (1.6)	14/839 (1.7)	0.97 (0.48, 1.95)
						44-48	14/1394 (1)	9/1149 (0.8)	1.28 (0.56, 2.95)
						49-53	11/1154 (1)	17/957 (1.8)	0.54 (0.25, 1.14)
						54-58	6/1333 (0.5)	5/1143 (0.4)	1.03 (0.31, 3.36)
						59-61	3/1074 (0.3)	2/882 (0.2)	1.23 (0.21, 7.36)
					CIN3+	29-33	22/745 (3)	19/600 (3.2)	0.93 (0.51, 1.71)
						34-38	19/888 (2.1)	3/712 (0.4)	5.08 (1.51, 17.09)
						39-43	13/1055 (1.2)	7/839 (0.8)	1.48 (0.59, 3.69)

Appendix E Table 2. KQ1 and KQ3: Results From Primary hrHPV Screening Strategies, by Age Groups

Author, year Study name	Rand screening strategy	Round	IG strategy	CG strategy	Outcome	Age group, years	IG n/n (%)	CG n/n (%)	RR (95% CI)
						44-48	7/1394 (0.5)	5/1149 (0.4)	1.15 (0.37, 3.63)
						49-53	9/1154 (0.8)	6/957 (0.6)	1.24 (0.44, 3.48)
						54-58	2/1333 (0.2)	4/1143 (0.3)	0.43 (0.08, 2.34)
						59-61	1/1074 (0.1)	1/882 (0.1)	0.82 (0.05, 13.11)
					FPR for CIN2+	29-33	95/711 (13.4)	65/567 (11.5)	1.17 (0.87, 1.57)
						34-38	70/862 (8.1)	63/700 (9)	0.90 (0.65, 1.25)
						39-43	51/1038 (4.9)	44/825 (5.3)	0.92 (0.62, 1.36)
						44-48	68/1380 (4.9)	65/1140 (5.7)	0.86 (0.62, 1.20)
						49-53	71/1143 (6.2)	48/940 (5.1)	1.22 (0.85, 1.74)
						54-58	63/1327 (4.7)	51/1138 (4.5)	1.06 (0.74, 1.52)
						59-61	40/1071 (3.7)	23/880 (2.6)	1.43 (0.86, 2.37)
Ogilvie, 2018[96] HPV FOCAL	hrHPV with LBC triage v. LBC with hrHPV triage	1	hrHPV with LBC triage	LBC with hrHPV triage	CIN2+	25-29	45/826 (5.4)	26/828 (3.1)	1.73 (1.08, 2.78)
						30-65	102/8714 (1.2)	64/8580 (0.7)	1.57 (1.15, 2.14)
					CIN3+	25-29	20/826 (2.4)	14/828 (1.7)	1.43 (0.73, 2.82)
						30-65	47/8714 (0.5)	27/8580 (0.3)	1.71 (1.07, 2.74)
		2 (exit)	Cotesting	Cotesting	CIN2+	25-29	14/826 (1.7)	27/828 (3.3)	0.52 (0.27, 0.98)
						30-65	34/8714 (0.4)	73/8580 (0.9)	0.46 (0.31, 0.69)
					CIN3+	25-29	6/826 (0.7)	15/828 (1.8)	0.40 (0.16, 1.02)
						30-65	16/8714 (0.2)	37/8580 (0.4)	0.43 (0.24, 0.76)
		Cumulative (1 and 2 [exit])	hrHPV with LBC triage (round 1) Cotesting (round 2)	LBC with hrHPV triage (round 1) Cotesting (round 2)	CIN2+	25-29	59/826 (7.1)	53/828 (6.4)	1.11 (0.78, 1.60)
						30-65	136/8714 (1.6)	137/8580 (1.6)	0.98 (0.77, 1.24)
					CIN3+	25-29	26/826 (3.1)	29/828 (3.5)	0.90 (0.53, 1.51)
						30-65	63/8714 (0.7)	64/8580 (0.7)	0.97 (0.69, 1.37)
Canfell, 2017[97] COMPASS	hrHPV with LBC triage or hrHPV with DS triage v. LBC	1	hrHPV with LBC triage	LBC	Colposcopy referral	25-33	34/418 (8.1)	10/211 (4.7)	1.72 (0.86, 3.41)
						34-64	41/1574 (2.6)	17/784 (2.2)	1.20 (0.69, 2.10)
					CIN2+	25-33	11/418 (2.6)	1/211 (0.5)	5.55 (0.72, 42.72)
						34-64	9/1574 (0.6)	.5/784 (0.1)	8.97 (0.52, 154.46)
					CIN3+	25-33	9/418 (2.2)	1/211 (0.5)	4.54 (0.58, 35.62)
						34-64	9/1574 (0.6)	.5/784 (0.1)	8.97 (0.52, 154.46)
			hrHPV with DS triage	LBC	Colposcopy referral	25-33	40/449 (8.9)	10/211 (4.7)	1.88 (0.96, 3.69)
						34-64	39/1559 (2.5)	17/784 (2.2)	1.15 (0.66, 2.03)
					CIN2+	25-33	13/449 (2.9)	1/211 (0.5)	6.11 (0.80, 46.39)

Appendix E Table 2. KQ1 and KQ3: Results From Primary hrHPV Screening Strategies, by Age Groups

Author, year Study name	Rand screening strategy	Round	IG strategy	CG strategy	Outcome	Age group, years	IG n/n (%)	CG n/n (%)	RR (95% CI)
						34-64	11/1559 (0.7)	.5/784 (0.1)	11.06 (0.65, 188.01)
					CIN3+	25-33	9/449 (2)	1/211 (0.5)	4.23 (0.54, 33.17)
						34-64	8/1559 (0.5)	.5/784 (0.1)	8.05 (0.46, 139.92)
Leinonen, 2012[98]	hrHPV with CC triage v. CC	1	hrHPV with CC triage	CC	Colposcopy referral	25-34	290/11191 (2.6)	211/11071 (1.9)	1.36 (1.14, 1.62)
						35-65	506/55219 (0.9)	544/54713 (1)	0.92 (0.82, 1.04)
					CIN2+	25-34	218/11191 (1.9)	119/11071 (1.1)	1.81 (1.45, 2.26)
						35-65	322/55219 (0.6)	200/54713 (0.4)	1.60 (1.34, 1.90)
					CIN3+	25-34	63/11191 (0.6)	34/11071 (0.3)	1.83 (1.21, 2.78)
						35-65	132/55219 (0.2)	84/54713 (0.2)	1.56 (1.18, 2.05)
					ICC	25-34	1/11191 (0.01)	2/11071 (0.02)	0.49 (0.04, 5.45)
						35-65	16/55219 (0.03)	7/54713 (0.01)	2.26 (0.93, 5.50)
Ronco, 2010[99] NTCC Phase II	hrHPV v. CC	1	hrHPV	CC	Screening test positive	25-34	907/6937 (13.1)	270/6788 (4)	3.29 (2.88, 3.75)
						35-60	1029/17724 (5.8)	555/17747 (3.1)	1.86 (1.68, 2.05)
					Colposcopy referral	25-34	907/6937 (13.1)	244/6788 (3.6)	3.64 (3.17, 4.17)
						35-60	1029/17724 (5.8)	435/17747 (2.5)	2.37 (2.12, 2.64)
					CIN2+	25-34	116/6937 (1.7)	25/6788 (0.4)	4.54 (2.95, 6.99)
						35-60	102/17724 (0.6)	48/17747 (.3)	2.13 (1.51, 3.00)
					CIN3+	25-34	45/6937 (0.6)	11/6788 (0.2)	4.00 (2.07, 7.73)
						35-60	52/17724 (0.3)	22/17747 (0.1)	2.37 (1.44, 3.89)
					FPR for CIN2+	25-34	791/6821 (11.6)	245/6763 (3.6)	3.20 (2.78, 3.68)
						35-60	927/17622 (5.3)	507/17699 (2.9)	1.84 (1.65, 2.04)
		2	CC	CC	CIN2+	25-34	7/6577 (0.1)	18/6714 (0.3)	0.40 (0.17, 0.95)
						35-60	5/17401 (0.03)	20/17658 (0.1)	0.25 (0.10, 0.68)
					CIN3+	25-34	2/6577 (0.03)	10/6714 (0.1)	0.20 (0.04, 0.93)
						35-60	3/17401 (0.02)	13/17658 (0.1)	0.23 (0.07, 0.82)
		Cumulative (1 and 2)	hrHPV (round 1) CC (round 2)	CC	CIN2+	25-34	123/6937 (1.8)	43/6788 (0.6)	2.80 (1.98, 3.95)
						35-60	107/17724 (0.6)	68/17747 (0.4)	1.58 (1.16, 2.13)
					CIN3+	25-34	47/6937 (0.7)	21/6788 (0.3)	2.19 (1.31, 3.66)
						35-60	55/17724 (0.3)	35/17747 (0.2)	1.57 (1.03, 2.40)
Thomsen, 2021[100]	hrHPV with LBC triage v.	1	hrHPV with LBC triage	LBC with hrHPV triage	Colposcopy referral	30-39	479/5349 (9)	254/8023 (3.2)	2.83 (2.45, 3.29)
						40-49	405/6831 (5.9)	188/9896 (1.9)	3.12 (2.63, 3.70)
						50-59	173/3887 (4.5)	73/6062 (1.2)	3.64 (2.79, 4.80)
					CIN2+	30-39	191/5349 (3.6)	134/8023 (1.7)	2.15 (1.73, 2.67)

Appendix E Table 2. KQ1 and KQ3: Results From Primary hrHPV Screening Strategies, by Age Groups

Author, year Study name	Rand screening strategy	Round	IG strategy	CG strategy	Outcome	Age group, years	IG n/n (%)	CG n/n (%)	RR (95% CI)
HPV SCREEN DENMARK	LBC with hrHPV triage					40-49	124/6831 (1.8)	74/9896 (0.7)	2.42 (1.82, 3.24)
						50-59	33/3887 (0.8)	28/6062 (0.5)	1.81 (1.09, 3.00)
					CIN3+	30-39	141/5349 (2.6)	114/8023 (1.4)	1.86 (1.46, 2.38)
						40-49	75/6831 (1.1)	52/9896 (0.5)	2.08 (1.47, 2.97)
						50-59	22/3887 (0.6)	22/6062 (0.4)	1.52 (0.84, 2.74)
Veijalainen, 2019[101]	hrHPV with CC triage v. CC	1	hrHPV with CC triage	CC	CIN2+	35	41/2847 (1.4)	15/2383 (0.6)	2.29 (1.27, 4.12)
						40	26/2318 (1.1)	15/2519 (0.6)	1.88 (1.00, 3.55)
						45	22/2836 (0.8)	8/2638 (0.3)	2.56 (1.14, 5.74)
						50	20/3236 (0.6)	5/2793 (0.2)	3.45 (1.30, 9.19)
						55	12/3219 (0.4)	3/2540 (0.1)	3.16 (0.89, 11.2)
						60	13/3314 (0.4)	2/2732 (0.1)	5.36 (1.21, 23.7)
					CIN3+	35	28/2847 (1.0)	10/2383 (0.4)	2.34 (1.14, 4.81)
						40	16/2318 (0.7)	9/2519 (0.4)	1.93 (0.86, 4.36)
						45	12/2836 (0.4)	3/2638 (0.1)	3.72 (1.05, 13.2)
						50	15/3236 (0.5)	4/2793 (0.1)	3.24 (1.08, 9.74)
						55	6/3219 (0.2)	0/2540 (0)	9.47 (0.53, 169)
						60	6/3314 (0.2)	1/2732 (0)	4.95 (0.60, 41.1)
Tranberg, 2023[102]	hrHPV with LBC triage v. Usual care	1	hrHPV with LBC triage (catch-up HPV)	Usual care	CIN2+	65-67	12/4262 (0.3)	5/11589 (0.04)	6.53 (2.30, 18.5)
						68-69	32/6930 (0.5)	6/21798 (0.03)	16.8 (7.02, 40.1)

Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; DS = dual-stained; FPR = false positive rate; HPV = human papilloma virus; HPV FOCAL = Human Papillomavirus For Cervical Cancer screening trial; hr = high-risk; ICC = invasive cervical cancer; IG = intervention group; LBC = liquid-based cytology; N = number of participants; NTCC = New Technologies for Cervical Cancer Screening trial; RR = relative risk; v = versus

Appendix E Table 3. KQ1 and KQ3: Results From RCTs and NRSIs, Cotesting Screening Strategies

Design	Author, year Study name	Randomized screening strategy	Round	IG strategy	CG strategy	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
RCT	Kitchener, 2014[105] ARTISTIC	Cotesting v. LBC	1	Cotesting	LBC	Screening test positive	4019/18386 (21.9)	786/6124 (12.8)	1.70 (1.59, 1.83)
						Colposcopy attendance	1247/18386 (6.8)	320/6124 (5.2)	1.30 (1.15, 1.46)
						CIN2+	453/18386 (2.5)	134/6124 (2.2)	1.13 (0.93, 1.36)
						CIN3+	233/18386 (1.3)	81/6124 (1.3)	0.96 (0.75, 1.23)
						ICC	5/18386 (0)	4/6124 (.1)	0.42 (0.11, 1.55)
						FPR for CIN2+	3566/17933 (19.9)	652/5990 (10.9)	1.83 (1.69, 1.98)
						FNR for ICC	0/5 (0)	0/4 (0)	--
			2 (exit)	LBC	LBC	Screening test positive	575/11676 (4.9)	210/3866 (5.4)	0.91 (0.78, 1.06)
						CIN2+	65/11676 (.6)	34/3866 (.9)	0.63 (0.42, 0.96)
						CIN3+	29/11676 (.2)	18/3866 (.5)	0.53 (0.30, 0.96)
						FPR for CIN2+	510/11611 (4.4)	176/3832 (4.6)	0.96 (0.81, 1.13)
			Cumulative (1 and 2 [exit])	Cotesting (round 1) LBC (round 2)	LBC	CIN2+	518/18386 (2.8)	167/6124 (2.7)	1.03 (0.87, 1.23)
						CIN3+	262/18386 (1.4)	98/6124 (1.6)	0.89 (0.71, 1.12)
			2	Cotesting	LBC	Screening test positive	1258/11862 (10.6)	210/3928 (5.3)	1.98 (1.72, 2.29)
						Colposcopy attendance	284/10716 (2.7)	74/3514 (2.1)	1.26 (0.98, 1.62)
						CIN2+	88/11862 (.7)	35/3928 (.9)	0.83 (0.56, 1.23)
						CIN3+	36/11862 (.3)	17/3928 (.4)	0.70 (0.39, 1.25)
						ICC	3/10716 (0)	0/3514 (0)	(,)
						FPR for CIN2+	1189/11774 (10.1)	178/3893 (4.6)	2.21 (1.89, 2.57)
						FNR for ICC	0/3 (0)	0/0 (0)	--
			Cumulative (1 and 2)	Cotesting	LBC	CIN2+	541/18386 (2.9)	169/6124 (2.8)	1.07 (0.90, 1.26)
						CIN3+	269/18386 (1.5)	98/6124 (1.6)	0.91 (0.73, 1.15)
						ICC	8/18386 (0)	4/6124 (.1)	0.67 (0.20, 2.21)
			3 (exit)	LBC	LBC	Screening test positive	799/6665 (12)	102/2208 (4.6)	2.60 (2.12, 3.17)
						CIN2+	51/6665 (0.8)	15/2208 (0.7)	1.13 (0.63, 2.00)
						CIN3+	23/6665 (0.3)	8/2208 (0.4)	0.95 (0.43, 2.13)

Appendix E Table 3. KQ1 and KQ3: Results From RCTs and NRSIs, Cotesting Screening Strategies

Design	Author, year Study name	Randomized screening strategy	Round	IG strategy	CG strategy	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
						FPR for CIN2+	748/6614 (11.3)	87/2193 (4)	2.85 (2.30, 3.54)
			Cumulative (1 and 2 and 3 [exit])	Cotesting (round 1, 2) LBC (round 3)	LBC	CIN2+	592/18386 (3.2)	184/6124 (3)	1.07 (0.91, 1.26)
						CIN3+	292/18386 (1.6)	106/6124 (1.7)	0.92 (0.74, 1.14)
	Naucler, 2007[106] Swedescreen	Cotesting v. CC	1	Cotesting	CC	Screening test positive	NR	150/6270 (2.4)	NR
						CIN2+	144/6257 (2.3)	76/6270 (1.2)	1.51 (1.13, 2.02)
						CIN3+	72/6257 (1.2)	55/6270 (0.9)	1.31 (0.92, 1.87)
						FPR for CIN2+	NR	74/6194 (1.2)	NR
						FNR for ICC	0/1 (0)	2/5 (40.0)	--
			2 (exit)	CC	CC	CIN2+	25/6257 (0.4)	43/6270 (0.7)	0.58 (0.36, 0.96)
						CIN3+	16/6257 (0.3)	30/6270 (0.5)	0.53 (0.29, 0.98)
			Cumulative (1 and 2 [exit])	Cotesting (round 1) CC (round 2)	CC	CIN2+	139/6257 (2.2)	119/6270 (1.9)	1.17 (0.92, 1.49)
						CIN3+	88/6257 (1.4)	85/6270 (1.4)	1.04 (0.77, 1.39)
						ICC	1/6257 (0.02)	5/6270 (0.1)	0.20 (0.02, 1.72)
	Ronco, 2010[99] NTCC Phase I	Cotesting v. CC	1	Cotesting	CC	Screening test positive	2830/22708 (12.5)	855/22466 (3.8)	3.27 (3.04, 3.53)
						Colposcopy referral	2470/22708 (10.9)	738/22466 (3.3)	3.31 (3.06, 3.59)
						CIN2+	187/22708 (0.8)	99/22466 (0.4)	1.87 (1.47, 2.38)
						CIN3+	75/22708 (0.3)	58/22466 (0.3)	1.28 (0.91, 1.80)
						FPR for CIN2+	2702/22042 (12.3)	771/21972 (3.5)	3.49 (3.23, 3.78)
			2 (exit)	CC	CC	CIN2+	22/22093 (0.1)	34/22330 (0.2)	0.65 (0.38, 1.12)
						CIN3+	13/22093 (0.1)	19/22330 (0.1)	0.69 (0.34, 1.40)
			Cumulative (1 and 2 [exit])	Cotesting (round 1) CC (round 2)	CC	CIN2+	209/22708 (0.9)	133/22466 (0.6)	1.55 (1.25, 1.93)
						CIN3+	88/22708 (0.4)	77/22466 (0.3)	1.13 (0.83, 1.53)
	Rijkaart, 2012[107] POBASCAM	Cotesting v.	1	Cotesting	CC	Screening test positive	1406/19999 (7)	706/20106 (3.5)	2.00 (1.83, 2.19)
						CIN2+	267/19999 (1.3)	215/20106 (1.1)	1.25 (1.05, 1.50)
						CIN3+	171/19999 (0.9)	150/20106 (0.7)	1.15 (0.92, 1.43)

Appendix E Table 3. KQ1 and KQ3: Results From RCTs and NRSIs, Cotesting Screening Strategies

Design	Author, year Study name	Randomized screening strategy	Round	IG strategy	CG strategy	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
		CC				ICC	12/19999 (0.1)	6/20106 (0)	2.01 (0.76, 5.36)
						FPR for CIN2+	1139/19732 (5.8)	491/19891 (2.5)	2.34 (2.11, 2.59)
						FNR for ICC	0/12 (0)	1/6 (16.7)	--
			2 (exit)	Cotesting	Cotesting	Screening test positive	742/19579 (3.8)	774/19731 (3.9)	0.97 (0.88, 1.07)
						CIN2+	160/19579 (0.8)	184/19731 (0.9)	0.88 (0.71, 1.08)
						CIN3+	88/19579 (0.4)	122/19731 (0.6)	0.73 (0.55, 0.96)
						ICC	4/19579 (0)	14/19731 (0.1)	0.29 (0.10, 0.87)
						FPR for CIN2	582/19419 (3.0)	590/19547 (3.0)	0.99 (0.89, 1.11)
						FNR for ICC	0/4 (0)	0/14 (0)	--
			Cumulative (1 and 2 [exit])	Cotesting	CC (round 1) Cotesting (round 2)	CIN2+	427/19999 (2.1)	399/20106 (2)	1.08 (0.94, 1.24)
						CIN3+	259/19999 (1.3)	272/20106 (1.4)	0.96 (0.81, 1.14)
						ICC	16/19999 (0.1)	20/20106 (0.1)	0.80 (0.42, 1.55)
NRSI	Katki, 2011[108] Kaiser	Cotesting (single arm)	2	Cotesting	NA	CIN2+	346/195975 (0.2)	NA	NA
						CIN3+	102/195975 (0.1)	NA	NA
						ICC	13/195975 (0.01)	NA	NA
			Cumulative (1 and 2)	Cotesting	NA	CIN2+	2310/331818 (0.7)	NA	NA
						CIN3+	834/331818 (0.3)	NA	NA
						ICC	87/331818 (0.03)	NA	NA
LTFU	Elfstrom, 2014[109] Swedescreen (LTFU)	Cotesting v. CC	1 (3-year fu)	NA	NA	CIN2+	91/6028 (1.5)	86/6034 (1.4)	1.06 (0.79, 1.42)
						CIN3+	52/6028 (0.9)	51/6034 (0.8)	1.02 (0.69, 1.50)
			1 (5-year fu)	NA	NA	CIN2+	126/6028 (2.1)	111/6034 (1.8)	1.14 (0.88, 1.46)
						CIN3+	76/6028 (1.3)	67/6034 (1.1)	1.14 (0.82, 1.57)
			1 (8-year fu)	NA	NA	CIN2+	157/6028 (2.6)	146/6034 (2.4)	1.08 (0.86, 1.34)
						CIN3+	93/6028 (1.5)	94/6034 (1.6)	0.99 (0.75, 1.32)
			1 (10-year fu)	NA	NA	CIN2+	175/6028 (2.9)	164/6034 (2.7)	1.07 (0.87, 1.32)
						CIN3+	107/6028 (1.8)	99/6034 (1.6)	1.08 (0.83, 1.42)
	Inturrisi, 2022[110]	Cotesting		Cotesting (1)	Cytology (1)	CIN2+	65/9293 (0.7)	82/9155 (0.9)	0.78 (0.56, 1.08)
						CIN3+	24/9293 (0.3)	38/9155 (0.4)	0.62 (0.37, 1.04)

Appendix E Table 3. KQ1 and KQ3: Results From RCTs and NRSIs, Cotesting Screening Strategies

Design	Author, year Study name	Randomized screening strategy	Round	IG strategy	CG strategy	Outcome	IG n/n (%)	CG n/n (%)	RR (95% CI)
	POBASCAM (LTFU)	v. CC	4 (14 year fu after round 2)	Cotesting (2) Cytology (3) Primary HPV or cytology (4)	Cotesting (2) Cytology (3) Primary HPV or cytology (4)	ICC	2/9293 (0.02)	3/9155 (0.03)	0.66 (0.11, 3.93)

Abbreviations: ARTISTIC = A Randomized Trial In Screening To Improve Cytology; CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; FNR = false negative rate; FPR = false positive rate; FU = followup; HPV = human papilloma virus; hr = high-risk; ICC = invasive cervical cancer; IG = intervention group; LBC = liquid-based cytology; LTFU = long-term followup; n = number of participants; NA = not applicable; NRSI = non-randomized studies of interventions; NTCC = New Technologies for Cervical Cancer Screening trial; POBASCAM = Population Based Screening Study Amsterdam; Rand = randomized; RCT = randomized controlled trial; RR = relative risk; v = versus

Appendix E Table 4. KQ1 and KQ3: Results From Cotesting Screening Strategies, by Age Groups

Author, year Study name	Randomized screening strategy	Round	IG strategy	CG strategy	Outcome	Age group, years	IG n/n (%)	CG n/n (%)	RR (95% CI)
Kitchener, 2014[105] ARTISTIC	Cotesting v. LBC	1	Cotesting	LBC	Screening test positive	20-29	1554/3879 (40.1)	278/1287 (21.6)	1.85 (1.66, 2.07)
						30-65	2465/14507 (17)	508/4837 (10.5)	1.62 (1.48, 1.77)
					CIN2+	20-29	236/3879 (6.1)	73/1287 (5.7)	1.07 (0.83, 1.38)
						30-65	217/14507 (1.5)	60/4837 (1.2)	1.21 (0.91, 1.60)
					CIN3+	20-29	117/3879 (3)	42/1287 (3.3)	0.92 (0.65, 1.31)
						30-65	116/14507 (0.8)	38/4837 (0.8)	1.02 (0.71, 1.47)
					ICC	20-29	0/3879 (0)	1/1287 (0.1)	0.17 (0.01, 4.94)
						30-65	5/14507 (0.03)	3/4837 (0.1)	0.56 (0.13, 2.32)
		2	Cotesting	LBC	ICC	20-29	1/1679 (0.1)	0/549 (0)	0.65 (0.02, 19.5)
						30-65	2/9037 (0)	0/2965 (0)	1.31 (0.06, 29.1)
		Cumulative (1 and 2)	Cotesting	LBC	ICC	20-29	1/3879 (0.03)	1/1287 (0.1)	0.33 (0.02, 5.30)
						30-65	7/14507 (0.05)	3/4837 (0.1)	0.78 (0.20, 3.01)
Ronco, 2010[99] NTCC Phase I	Cotesting v. CC	1	Cotesting	CC	Screening test positive	25-34	1047/6002 (17.4)	261/5808 (4.5)	3.88 (3.41, 4.42)
						35-60	1783/16706 (10.7)	594/16658 (3.6)	2.99 (2.73, 3.28)
					CIN2+	25-34	78/6002 (1.3)	38/5808 (0.7)	1.99 (1.35, 2.92)
						35-60	109/16706 (0.7)	61/16658 (0.4)	1.78 (1.30, 2.44)
					CIN3+	25-34	23/6002 (0.4)	25/5808 (0.4)	0.89 (0.51, 1.57)
						35-60	52/16706 (0.3)	33/16658 (0.2)	1.57 (1.02, 2.43)
					Colposcopy referral	25-34	697/6002 (11.6)	237/5808 (4.1)	2.85 (2.47, 3.28)
						35-60	1773/16706 (10.6)	501/16658 (3)	3.53 (3.20, 3.89)
					FPR for CIN2+	25-34	998/4980 (20)	228/5775 (3.9)	5.08 (4.42, 5.83)
						35-60	1704/16335 (10.4)	543/16607 (3.3)	3.19 (2.90, 3.51)
		2	CC	CC	CIN2+	25-34	11/5761 (0.2)	15/5769 (0.3)	0.73 (0.34, 1.60)
						35-60	11/16332 (0.1)	19/16561 (0.1)	0.59 (0.28, 1.24)
					CIN3+	25-34	8/5761 (0.1)	8/5769 (0.1)	1.00 (0.38, 2.67)
						35-60	5/16332 (0.03)	11/16561 (0.1)	0.46 (0.16, 1.33)
		Cumulative (1 and 2)	Cotesting (round 1) CC (round 2)	CC	CIN2+	25-34	89/6002 (1.5)	53/5808 (0.9)	1.63 (1.16, 2.28)
						35-60	120/16706 (0.7)	80/16658 (0.5)	1.50 (1.13, 1.98)
					CIN3+	25-34	31/6002 (0.5)	33/5808 (0.6)	0.91 (0.56, 1.48)
						35-60	57/16706 (0.3)	44/16658 (0.3)	1.30 (0.87, 1.91)

Abbreviations: ARTISTIC = A Randomized Trial In Screening To Improve Cytology; CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; FPR = false positive rate; ICC = invasive cervical cancer; IG = intervention group; LBC = liquid-based cytology; n = number of participants; NTCC = New Technologies for Cervical Cancer Screening trial; RR = relative risk; v = versus

Appendix E Table 5. KQ2: Test Agreement of Self-Collected Vaginal and Clinician-Collected Cervical Samples

Screener	Author, year	Condition	Round	N analyzed	Test positive with self-sample, %	Test positive with clinician sample, %	Positive agreement (95% CI)	Negative agreement (95% CI)
Self-collected vaginal HPV	Avian, 2022[111]	hrHPV	1	910	17.0	15.6	0.80 (0.72, 0.85)	0.95 (0.93, 0.96)
	Des Marais, 2018[112]	hrHPV	1	193	15.5	11.4	0.73 (0.52, 0.87)	0.92 (0.87, 0.95)
	Eamratsameekool, 2023[113]	hrHPV	1	535	4.1	5.0	0.82 (0.62, 0.94)	1.00 (0.99, 1.00)
	Harvey, 2016[114]	hrHPV	1	47	31.9	27.7	0.85 (0.55, 0.98)	0.88 (0.73, 0.97)
	Ilardo, 2022[115]	hrHPV	1	157	20.4	21.0	0.91 (0.81, 1.00)	0.98 (0.96, 1.00)
	Ketelaars, 2017[116]	hrHPV	1	2049	10.0	8.0	0.93 (0.88, 0.96)	0.97 (0.96, 0.98)
	Lim, 2022[117]	hrHPV	1	300	20.0	21.0	0.79 (0.69, 0.87)	0.96 (0.93, 0.98)
	Lopez Castro, 2024[118]	hrHPV	1	185	14.1	9.7	1.0 (0.82, 1.0)	0.95 (0.91, 0.98)
	McLarty, 2019[119]	hrHPV	1	58	15.5	10.3	1.00 (0.61, 1.00)	0.94 (0.84, 0.98)
		HPV 16	1	58	1.7	1.7	1.00 (0.21, 1.00)	1.00 (0.94, 1.00)
		HPV 18	1	58	0	0	--	1.00 (0.94, 1.00)
		HPV non-16/18	1	58	15.5	12.1	0.86 (0.49, 0.97)	0.94 (0.84, 0.98)
	Nutthachote, 2019[120]	hrHPV	1	400	10.0	7.5	0.87 (0.70, 0.95)	0.96 (0.94, 0.98)
	Reisner, 2018[121]	hrHPV	1	131	13.0	16.0	0.71 (0.48, 0.89)	0.98 (0.94, 1.00)
	Satake, 2020[122]	hrHPV	1	300	14.7	13.7	0.90 (0.77, 0.96)	0.97 (0.95, 0.99)
		HPV 16/18	1	300	2.3	2.3	0.86 (0.49, 0.97)	1.00 (0.98, 1.00)
	Stanczuk, 2021[123]	hrHPV	1 + 2	4605	16.8	15.2	0.85 (0.82, 0.87)	0.95 (0.95, 0.96)
	Wong, 2024[124]	hrHPV	1	35	5.7	5.7	1.0 (0.34, 1.0)	1.0 (0.90, 1.0)
Urine	Hagihara, 2016[125]	HPV	1	240	42.9	50.0	0.82 (0.74, 0.88)	0.96 (0.91, 0.98)
	Kim, 2022[126]	hrHPV	1	210	12.4	12.4	0.73 (0.54, 0.86)	0.96 (0.92, 0.98)
	Vergara, 2018[127]	hrHPV	1	543	48.4	55.6	0.83 (0.78, 0.87)	0.95 (0.91, 0.97)

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus; hr = high risk; KQ = Key Question; N = number of participants

Appendix E Table 6. KQ2: Test Accuracy of Self-Collected Vaginal HPV

Condition	Author, year	Round	HPV types for positivity	N analyzed	Screened positive, %	Condition positive, %	Sensitivity (95% CI)	Specificity (95% CI)
CIN2+	Polman, 2019[95]	1	hrHPV	7643	7.4	1.5	0.93 (0.88, 0.98)	0.94 (0.94, 0.95)
	Balasubramanian, 2010[128]	1	hrHPV	1665	33.1	7.8	0.85 (0.76, 0.94)	0.73 (0.67, 0.79)
	Porras, 2015[129]	1	hrHPV	5109	31.8	2.7	0.74 (0.66, 0.81)	0.69 (0.68, 0.71)
	Szarewski, 2007[130]	1	hrHPV	920	19.2	2.3	0.81 (0.60, 0.92)	0.82 (0.80, 0.85)
	Stanczuk, 2021[123]	1	hrHPV	4617	NR	3.3	0.91 (0.86, 0.95)	0.86 (0.85, 0.87)
		2	hrHPV	4617	NR	0.7	0.88 (0.82, 0.92)	0.86 (0.85, 0.87)
		1	HPV 16/18	4617	NR	3.3	0.60 (0.52, 0.68)	0.96 (0.96, 0.97)
		2	HPV 16/18	4617	NR	0.7	0.55 (0.48, 0.63)	0.96 (0.96, 0.97)
CIN3+	Polman, 2019[95]	1	hrHPV	7643	7.4	1.0	0.95 (0.89, 1.00)	0.94 (0.93, 0.94)
	Stanczuk, 2021[123]	1	hrHPV	4617	NR	1.8	0.95 (0.88, 0.98)	0.85 (0.84, 0.86)
		2	hrHPV	4617	NR	0.4	0.93 (0.86, 0.97)	0.85 (0.84, 0.86)
		1	HPV 16/18	4617	NR	1.8	0.64 (0.53, 0.74)	0.96 (0.95, 0.96)
		2	HPV 16/18	4617	NR	0.4	0.59 (0.49, 0.68)	0.95 (0.95, 0.96)

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus; hr = high risk; KQ = Key Question; n = number of participants; NR = not reported

Appendix E Table 7. KQ2: Relative Test Accuracy of Self-Collected Vaginal HPV Tests

Condition	Author, year	Rounds	N analyzed	Screened positive with self-sample, %	Screened positive with clinician sample, %	Condition positive, %	Relative sensitivity (95% CI)	Relative specificity (95% CI)
CIN2+	Inturrisi, 2021[131]	1	487015	7.4	9.3	1.7	0.91 (0.88, 0.96)	1.02 (1.01, 1.02)
	Polman, 2019[95]	1	13925	7.4	7.2	1.5	0.97 (0.91, 1.03)	1.00 (0.99, 1.01)
	Stanczuk, 2021[123]	1 + 2	4617	16.8	15.2	4.0	0.93 (0.90, 0.98)	0.98 (0.95,1.00)
CIN3+	Inturrisi, 2021[131]	1	487015	7.4	9.3	1.0	0.94 (0.90, 0.97)	1.02 (1.02, 1.02)
	Polman, 2019[95]	1	13925	7.4	7.2	0.8	0.99 (0.92, 1.07)	1.00 (0.99, 1.01)
	Stanczuk, 2021[123]	1 + 2	4617	16.8	15.2	2.2	0.95 (0.90, 0.99)	0.98 (0.97, 0.98)

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus; KQ = Key Question; n = number of participants

Appendix E Table 8. KQ2 Uptake: Number of Participants Completing Cervical Cancer Screening

Target population	Author, year	Arm	Type	Followup, months	n analyzed	n screened with self-sample	n screened using any method
All attending screening	Aarino, 2021[132]	IG1	Mailed vaginal self-sample	NR	5767	2556	2556
		CG	Mail reminder (invite to clinical screening)	NR	5846	0	1548
	Gustavsson, 2018[133]	IG1	Mailed vaginal self-sample	12	17046	7997	7997
		CG	Offered standard clinical screening	12	16364	0	6364
	Hellsten, 2021[134]	IG1	Mailed vaginal self-sample	2	14765	4943	5581
		CG	Offered standard clinical screening	2	14839	0	7042
	Polman, 2019[95]	IG1	Mailed vaginal self-sample	NR	8193	7643	7643
		CG	Offered standard clinical screening	NR	8168	0	6282
	Winer, 2023[135]	IG1	Mailed vaginal self-sample	6	2897	920	1426
		IG2	Invited to vaginal self-sample	6	7462	554	2665
		CG	Offered standard clinical screening	6	12142	0	3286
All attending screening from traditionally underscreened group	Williams, 2016[136]	IG1	Mailed vaginal self-sample	NR	60	48	48
		CG	Offered standard clinical screening	NR	60	34	34
	Zehbe, 2016[137]	IG1	Invited to vaginal self-sample	3	404	54	54
		CG	Offered standard clinical screening	3	598	0	35
Nonresponders	Aasbo, 2022[83]	IG1	Mailed vaginal self-sample	6	1878	445	520
		IG2	Invited to vaginal self-sample	6	1897	250	323
		CG	Mail reminder (invite to clinical screening)	6	1892	0	90
	Bais, 2007[138]	IG1	Mailed vaginal self-sample	6	2352	736	806
		CG	Mail reminder (invite to clinical screening)	6	272	0	48
	Broberg, 2014[139]	IG1	Invited to vaginal self-sample	13	717	128	196
		CG	Offered standard clinical screening	13	4000	0	422
	Cadman, 2015[140]	IG1	Mailed vaginal self-sample	3	3000	247	411
		CG	Mail reminder (invite to clinical screening)	3	3000	0	183
	Darlin, 2013[141]	IG1	Mailed vaginal self-sample	NR	1000	147	147
		CG	Invited to clinical screening	NR	500	0	21
	Elfstrom, 2019[142]	IG1	Mailed vaginal self-sample	3	1994	352	374
		IG2	Invited to vaginal self-sample	3	1995	163	213
		CG	Mail reminder (invite to clinical screening)	3	2000	0	34
	Enerly, 2016[143]	IG1	Mailed vaginal self-sample	NR	753	169	267
		CG	Offered standard clinical screening	NR	2593	0	601
	Giorgi Rossi, 2011[144]	IG1	Mailed vaginal self-sample	3	616	103	121
		IG2	Invited to vaginal self-sample	3	622	36	54

Appendix E Table 8. KQ2 Uptake: Number of Participants Completing Cervical Cancer Screening

Target population	Author, year	Arm	Type	Followup, months	n analyzed	n screened with self-sample	n screened using any method
		CG	Offered standard clinical screening	3	1235	0	178
	Giorgi Rossi, 2015[145]	IG1	Mailed vaginal self-sample	3	4516	974	974
		IG2	Choice	3	4513	540	540
		CG	Standard recall letter	3	5012	0	598
	Gok, 2010[146]	IG1	Mailed vaginal self-sample	NR	27792	7404	7455
		CG	Mail reminder (invite to clinical screening)	NR	281	0	46
	Gok, 2012[147]	IG1	Mailed vaginal self-sample	18	25561	7870	7870
		CG	Mail reminder (invite to clinical screening)	18	261	0	17
	Haguenoer, 2014[148]	IG1	Mailed vaginal self-sample	12	1999	324	496
		CG	No intervention	12	3999	0	524
	Ivanus, 2018[149]	IG2	Choice	12	9556	2684	3598
		IG1	Mailed vaginal self-sample	12	14400	2524	4896
		CG	Mail reminder (invite to clinical screening)	12	2600	0	478
	Jalili, 2019[150]	IG1	Mailed vaginal self-sample	6	529	51	57
		CG	No intervention	6	523	0	13
	Kellen, 2018[151]	IG1	Mailed vaginal self-sample	12	9118	1707	2356
		IG2	Choice	12	9098	965	1705
		CG	No intervention or reminder	12	17679	0	1640
	Kitchener, 2018[152]	IG1	Mailed vaginal self-sample	12	1141	93	342
		IG2	Invited to vaginal self-sample	12	1290	19	333
		CG	No intervention	12	3782	1	1026
	Landy, 2021[153]	IG1	Non-speculum choice	12	393	43	120
		CG	Offered standard clinical screening	12	391	0	53
	Lilliecreutz, 2020[154]	IG1	Mailed vaginal self-sample	6	3068	788	1047
		IG2	Choice	6	2870	161	803
		CG	No intervention	6	3538	0	250
	Peeters, 2020[155]	IG1	Provided vaginal self-sample	NR	45	35	35
		CG	Offered standard clinical screening	NR	43	0	22
	Racey, 2016[156]	IG1	Mailed vaginal self-sample	10	335	70	107
		CG	No intervention	10	483	0	64
	Sultana, 2016[157]	IG1	Mailed vaginal self-sample	6	14280	1649	2270
		CG	Mail reminder (invite to clinical screening)	6	2040	0	126
	Szarewski, 2011[158]	IG1	Mailed vaginal self-sample	6	1500	96	153
		CG	Mail reminder (invite to clinical screening)	6	1500	0	68
	Tranberg, 2018[159]	IG1	Mailed vaginal self-sample	6	3265	635	1242

Appendix E Table 8. KQ2 Uptake: Number of Participants Completing Cervical Cancer Screening

Target population	Author, year	Arm	Type	Followup, months	n analyzed	n screened with self-sample	n screened using any method
		IG2	Invited to vaginal self-sample	6	3264	270	1009
		CG	Mail reminder (invite to clinical screening)	6	3262	0	823
	Virtanen, 2011[160]	IG1	Mailed vaginal self-sample	NR	2397	663	756
		CG	Mail reminder (invite to clinical screening)	NR	6302	0	1631
	Viviano, 2017[161]	IG1	Mailed vaginal self-sample	NR	336	317	317
		CG	Mail reminder (invite to clinical screening)	NR	331	0	307
	Winer, 2019[82]	IG1	Mailed vaginal self-sample	6	9960	1206	2646
		CG	Invited to clinical screening	6	9891	0	1719
	Winer, 2023[135]	IG1	Mailed vaginal self-sample	6	1415	322	507
		CG	Invited to clinical screening	6	5488	0	1036
Nonresponders from traditionally underscreened group	Brewer, 2021[162]	IG1	Mailed vaginal self-sample	3	1467	205	205
		IG2	Clinic self-sample	3	1574	100	100
		CG	Offered standard clinical screening	3	512	0	14
	Carrasquillo, 2018[163]	IG1	Choice	6	207	133	160
		CG	Referral for screening	6	182	0	57
	MacDonald, 2020[164]	IG1	Choice	NR	733	308	364
		CG	Offered standard clinical screening	NR	806	0	174
	Moss, 2024[165]	IG1	Mailed vaginal self-sample	2	24	17	17
		CG	Invited to clinical screening	2	24	0	2
	Pretsch, 2023[166]	IG1	Mailed vaginal self-sample	6	461	341	354
		CG	Offered standard clinical screening	6	236	0	85
	Reques, 2021[167]	IG1	Provided vaginal self-sample	NR	383	365	365
		CG	Referral for screening	NR	304	0	120
	Sancho-Garnier, 2013[168]	IG1	Mailed vaginal self-sample	NR	8829	1613	1613
		CG	Mail reminder (invite to clinical screening)	NR	9901	0	199
	Scarinci, 2021[169]	IG1	Choice	1	165	NR	63
		CG	Offered standard clinical screening	1	170	0	16
	Sewali, 2015[170]	IG1	Provided vaginal self-sample	3	32	21	21
		CG	Referral for screening	3	31	0	6

Abbreviations: CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus; IG = intervention group; KQ = Key Question; n = number of participants; NR = not reported

Appendix E Table 9. KQ3: Psychological Harms, Dichotomous Outcomes

Comparison	Author, year Study name	Design	Followup	Outcome	Instrument	IG n/n (%)	CG n/n (%)	RR (95% CI)
Cotesting (IG) v. LBC (CG)	Kitchener, 2014[105] ARTISTIC	RCT	2 weeks	Anxiety (state)	STAI-STATE	717/1872 (38.3)	223/593 (37.6)	1.02 (0.90, 1.15)
hrHPV with LBC triage (IG) v. LBC with hrHPV triage (CG)	Andreassen, 2019[171] Nygard RCT	NRSI	4-24 months	Anxiety and depression Mild v. normal	PHQ-4	97/443 (21.9)	107/470 (22.8)	0.96 (0.70, 1.31)
				Anxiety and depression Moderate/severe v. normal	PHQ-4	27/373 (7.2)	26/389 (6.7)	1.14 (0.65, 2.02)

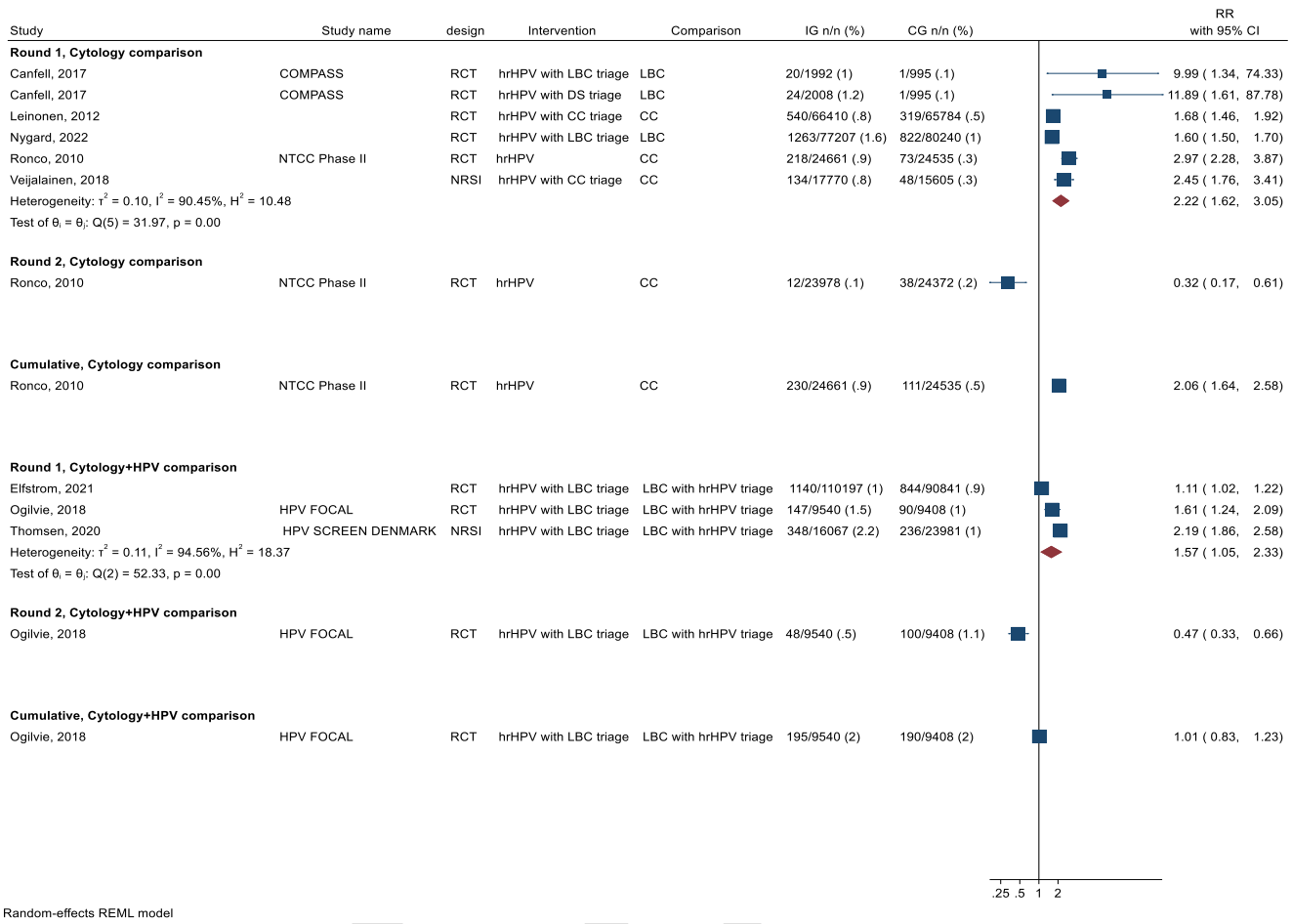
Abbreviations: ARTISTIC = A Randomized Trial In Screening To Improve Cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; hrHPV = high-risk human papilloma virus; IG = intervention group; KQ = Key Question; LBC = liquid based cytology; n = number of participants; PHQ-4 = Patient Health Questionaire-4; RCT = randomized controlled trial; RR = relative risk; STAI = State-Trait Anxiety Inventory

Appendix E Table 10. KQ3: Psychological Harms, Continuous Outcomes

Comparison	Author, year Study name	FU, wks	Outcome	Instrument	IG n analyzed	CG n analyzed	IG mean (SD)	CG mean (SD)	Adjusted mean difference (95% CI)
Cotesting (IG) v. LBC (CG)	Kitchener, 2014[105] ARTISTIC	2	Anxiety (state)	STAI-STATE (low scores indicate better outcome)	1875	594	38.10 (12.64)	38.27 (12.61)	-0.31 (-1.27, 1.13)
			Anxiety (trait)	STAI-TRAIT (low scores indicate better outcome)	1877	596	40.12 (11.40)	40.13 (11.49)	-0.10 (-1.27, 1.13)
			Psychological distress	GHQ-28 (1-28; low scores indicate better outcome)	1872	593	4.26 (5.73)	4.18 (5.71)	-0.01 (-0.65, 0.60)
			Sexual satisfaction	Sexual Rating Scale (0-100; high scores indicate better outcome)	1520	483	53.32 (23.02)	54.90 (23.00)	-2.40 (-4.70, -0.09)

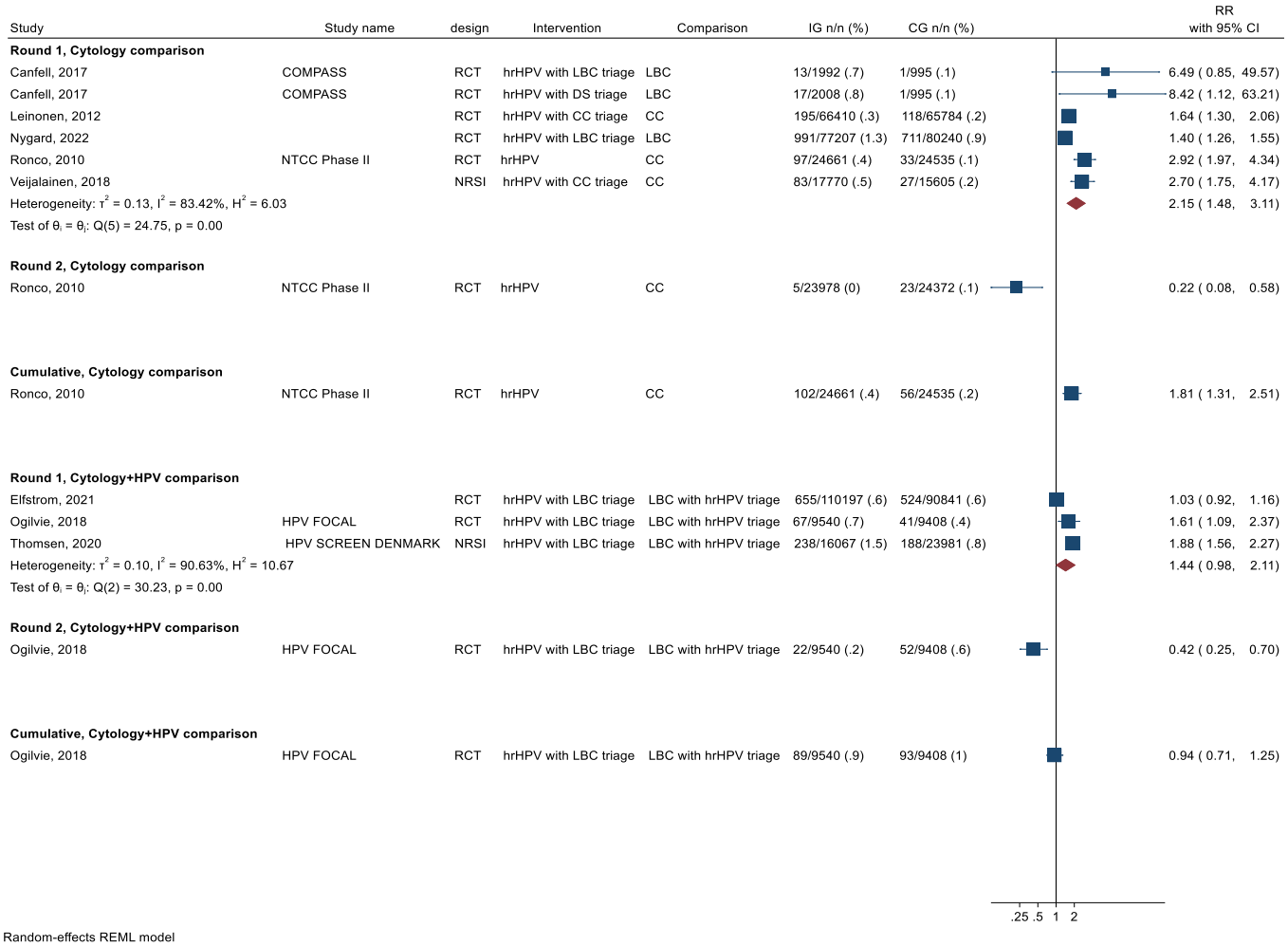
Abbreviations: ARTISTIC = A Randomized Trial In Screening To Improve Cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; FU = followup; GHQ-28 = General Health Questionaire-28; IG = intervention group; KQ = Key Question; LBC = liquid based cytology; n = number of participants; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; STAI = State-Trait Anxiety Inventory

Appendix F Figure 1. Analysis Stratified by Comparison, Primary HPV Trials, CIN2+



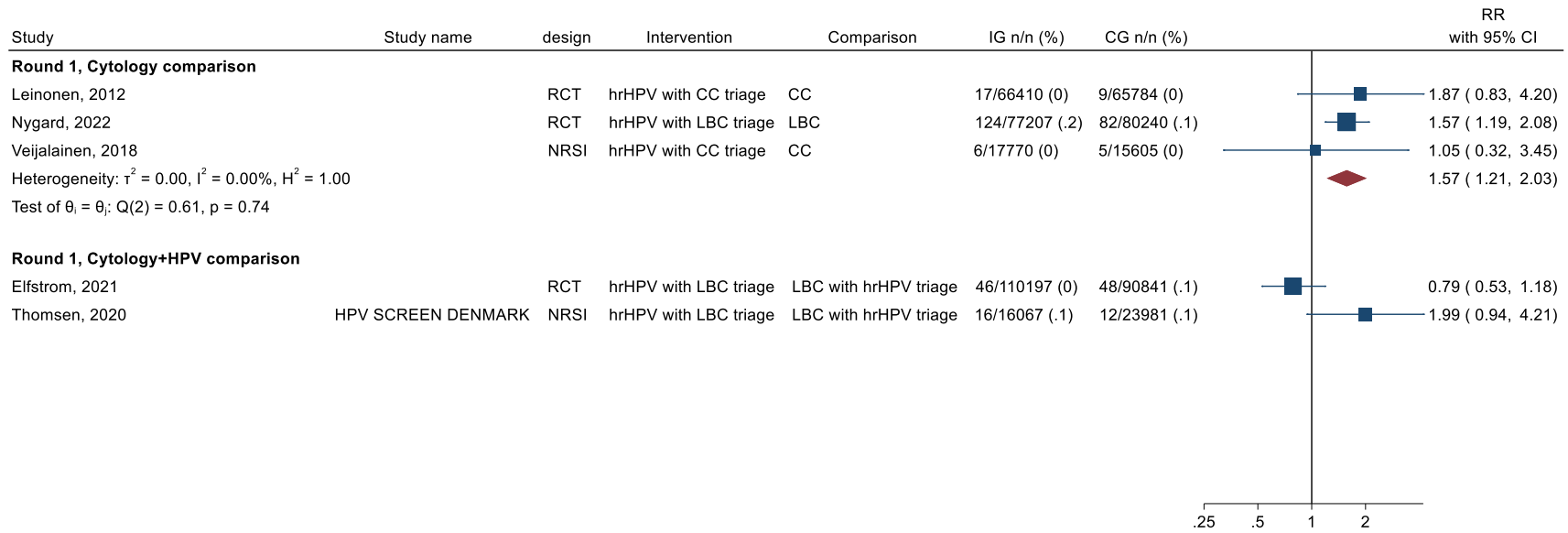
Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; DS = dual-stained; HPV = human papilloma virus; HPV FOCAL = Human Papillomavirus For Cervical Cancer screening trial; hr = high-risk; IG = intervention group; LBC = liquid-based cytology; n = number of participants; NRSI = non-randomized studies of interventions; NTCC = New Technologies for Cervical Cancer Screening trial; RCT = randomized controlled trial; RR = relative risk

Appendix F Figure 2. Analysis Stratified by Comparison, Primary HPV Trials, CIN3+



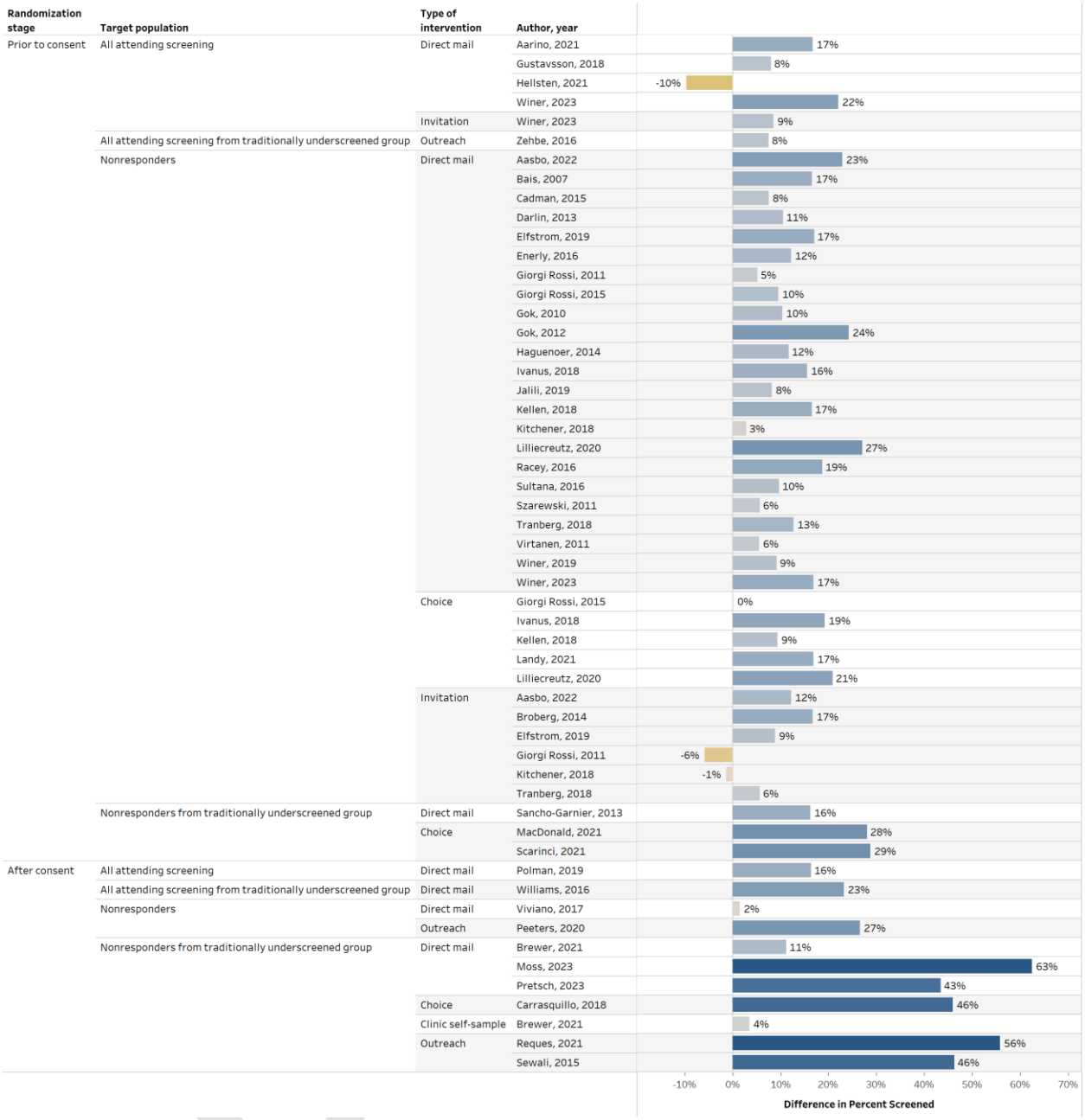
Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; DS = dual-stained; HPV = human papilloma virus; HPV FOCAL = Human Papillomavirus For Cervical Cancer screening trial; hr = high-risk; IG = intervention group; LBC = liquid-based cytology; n = number of participants; NRSI = non-randomized studies of interventions; NTCC = New Technologies for Cervical Cancer Screening trial; RCT = randomized controlled trial; RR = relative risk

Appendix F Figure 3. Analysis Stratified by Comparison, Primary HPV Trials, ICC



Abbreviations: CC = conventional cytology; CG = control group; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus; hr = high-risk; ICC = invasive cervical cancer; IG = intervention group; LBC = liquid-based cytology; n = number of participants; NRSI = non-randomized studies of interventions; RCT = randomized controlled trial; RR = relative risk

Appendix F Figure 4. KQ2 Uptake: Difference Between IG and CG in Percent Screened With Any Method Stratified by Stage of Randomization



Appendix G Table 1. Ongoing Studies

Relevant KQ	Trial Identifier	Study Name	Country	N	Aim	Relevant Outcome	Status 2023
KQs 1, 3	NCT04185389	Evaluation of CIN2+ Rates up to 120 Months After 48-Month Co-Testing (Long Term Follow up of HPV FOCAL Participants)	CAN	1,710	Assess the long-term effectiveness and safety of primary HPV testing for cervical cancer screening. A cohort of participants from the original FOCAL study will be asked to see their health care provider to submit another cervical sample for cytology and HPV testing. This will permit evaluation of long-term safety and effectiveness of primary HPV testing up to ten years after a participant's first screening in the FOCAL study and comparison of primary HPV testing to HPV and cytology co-testing.	CIN2+	Preliminary results included in review Estimated completion date: December 2024
	NCT02328872	Compass - Randomized Controlled Trial of 5-yearly Cervical Screening With Primary HPV Testing Versus Cervical Screening With 2.5-yearly Liquid Based Cytology Testing, in HPV-Unvaccinated and HPV-Vaccinated Women in Australia	AUS	76,181	Evaluate and compare the performance of image-read cytology versus primary HPV screening in both vaccinated and unvaccinated women.	CIN3+	Preliminary results included in review Estimated completion date: March 2027
	NCT01511328	Randomized Implementation of Primary HPV Testing in the Organized Screening for Cervical Cancer in Stockholm	SWE	270,000	Evaluate whether implementation of primary human papillomavirus (HPV) screening improves the cervical cancer screening program in terms of better cancer protection and better cost efficiency.	CIN2+	Preliminary results included in review Estimated completion date: December 2031

Appendix G Table 1. Ongoing Studies

Relevant KQ	Trial Identifier	Study Name	Country	N	Aim	Relevant Outcome	Status 2023
	NCT04111835	HPV Testing In Polish POpulation-based Cervical Cancer Screening Program. (HIPPOPROJECT)	POL	33,000	Assess the performance of hrHPV molecular testing vs conventional exfoliative cytology/LBC before its implementation in Poland.	CIN2+; CIN3+; ICC; colposcopy referral or receipt	Active, not recruiting Estimated completion date: September 2023
	jRCT1030200276	Accelerating Cervical Cancer Elimination by Self-Sampling test (ACCESS)	JPN	20,000	Compare the effectiveness of screening using the self-sampling HPV test with that of routine screening concerning screening uptake and precancer detection.	CIN2+; CIN3+; ICC; adverse events	Active, not recruiting Estimated completion date: March 2025
	NCT03049553	Trial23 - A Method Study on the Use of Primary HPV-testing With Cytology Triage in Women Offered HPV-vaccination as Girls	DNK	7,000	Evaluate if primary screening with HPV-testing and LBC triage every 6 years in women offered HPV-vaccination as girls would provide at least the same protection as the present screening, measured by cumulative number of cervical intraepithelial neoplasia (CIN). This screening scheme would allow HPV-negative women to benefit from a prolonged screening interval and thereby reduce the burden of screening for HPV-vaccinated birth cohorts.	CIN 2+; CIN3+; colposcopy referral or receipt	Active, not recruiting Estimated completion date: December 2025
	NCT04114968	Reducing the Burden of Cervical Cancer Among Older Women by Expanding the Screening Age and Offering HPV Self-sampling	DNK	20,000	Evaluate the effect and feasibility of expanding the target population in the Danish cervical cancer screening program to include women aged 65 to 69 years. The study also evaluates if HPV self-sampling constitutes an appropriate screening method among older women.	Cervical cancer; mortality; screening participation	Preliminary results included in review Estimated completion date: December 2025

Appendix G Table 1. Ongoing Studies

Relevant KQ	Trial Identifier	Study Name	Country	N	Aim	Relevant Outcome	Status 2023
	NCT05229679	Evaluation of Organized Human Papilloma Virus (HPV) Screening of 23-29-year-old Women	SWE	180,000	Determine whether organized screening with primary HPV analysis provide higher cancer protection in the age group 23-29 years compared to primary cytology.	Cervical cancer	Recruiting Estimated completion date: December 2038
KQ2	NCT05065853	Urinary and Vaginal HPV Testing as a Novel Cervical Cancer Screening Tool: a Diagnostic Test Accuracy Study	DNK	330	Test the hypotheses: 1) urinary HPV testing is non-inferior to HPV testing on clinician-collected cervical samples for detection of high-grade cervical pre-cancer, 2) Vaginal HPV testing is non-inferior to HPV testing on clinician-collected cervical samples for detection of high-grade cervical pre-cancer and 3) DNA methylation testing is suitable as a colposcopy triage test among women with HPV-positive urine and/or vaginal samples to prevent unnecessary colposcopies and overtreatment of women without clinically meaningful HPV infections.	Diagnostic accuracy	Not yet recruiting Estimated completion date: December 2023
	NCT05243888	A Randomised Controlled Trial Assessing the Efficacy of Strategies Involving Self-sampling to Reach Women Not Participating in Regular Cervical Cancer Screening	FRA	15,000	Evaluate the efficacy of two experimental invitation strategies (offer of urine or vaginal self-sampling kits) to reach under-screened populations and compare them with the current invitation strategy in rural departments (low medical density and low participation rate) in France.	Screening participation; screen test positivity	Recruiting Estimated completion date: February 2025
	NCT04557423	Evidence-Based Approach to Empower Asian American Women in Cervical Cancer Screening	US	800	Compare rates of providing a self-collected sample vs. obtaining clinic-based screening among 800 Asian American women. It is hypothesized that the proportion of women in the HPV self-sampling program who provide a self-collected sample will be higher than the proportion of women in the clinic-based program who obtain clinic-based screening.	Screening participation	Recruiting Estimated completion date: April 2026

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