Cervical Cancer Screening

Women's Preventive Services Initiative
Evidence Review Update
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CURRENT WPSI RECOMMENDATION

Clinical Recommendations (2016)[1]

The Women's Preventive Services Initiative recommends cervical cancer screening for average-risk women aged 21 to 65 years. For women aged 21 to 29 years, the Women's Preventive Services Initiative recommends cervical cancer screening using cervical cytology (Pap test) every 3 years. Cotesting with cytology and human papillomavirus testing is not recommended for women younger than 30 years. Women aged 30 to 65 years should be screened with cytology and human papillomavirus testing every 5 years or cytology alone every 3 years. Women who are at average risk should not be screened more than once every 3 years.

Implementation Considerations

The Women's Preventive Services Initiative recommends as a preventive service, cervical cancer screening for average-risk women aged 21 to 65 years. For average-risk women aged 30 to 65 years, informed shared decision-making between the patient and her clinician regarding the preferred screening strategy is recommended.

Women who have received the human papillomavirus vaccine should be screened according to the same guidelines as women who have not received the vaccine.

These recommendations are for routine screening in average-risk women and do not apply to women infected with human immunodeficiency virus, women who are immunocompromised because of another etiology (such as those who have received solid organ transplantation), women exposed to diethylstilbestrol in utero, or women treated for cervical intraepithelial neoplasia grade 2 or higher within the past 20 years. Screening strategies for high-risk women are outside the scope of these recommendations.

Cervical cancer screening is not recommended for women younger than 21 years or those older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Adequate prior negative screening is defined as documentation (or a reliable patient report) of three consecutive negative cytology results or two consecutive negative cotest results within the previous 10 years with the most recent test within the past 5 years. Cervical cancer screening is also not recommended for women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesions (eg, cervical intraepithelial neoplasia grade 2 or grade 3 or cervical cancer within the past 20 years).

INTRODUCTION

Recommendations for Cervical Cancer Screening

In addition to the WPSI recommendation, several professional organizations recommend cervical cancer screening for women at average risk for cervical cancer (**Table 1**). Current guidelines generally agree about testing intervals and approaches; however, there are some differences on the age to start screening and the age at which to consider primary high risk human papillomavirus (hrHPV) testing. Across guidelines there is consensus about when to stop screening and how to define adequate prior screening. Screening for women at high risk or with previous cervical abnormalities is addressed by other groups.[2]

Incidence and Survival

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States and the most important risk factor for cervical precancer and cancer. When persistent, HPV leads to premalignant changes that may develop into invasive cervical cancer (ICC) over time. Dysplastic changes of the cervix are defined by varying levels of cellular invasion or severity and are classified as cervical intraepithelial neoplasia (CIN) 1, 2, or 3. This terminology also corresponds to varying degrees of cytologic test result abnormalities with alternative primary definitions of low grade squamous epithelial lesion (LSIL) or high grade squamous epithelial lesion (HSIL), which encompass both CIN2 and 3, and is considered premalignant. In the presence of diagnostic uncertainty, immunohistochemical staining can be used to further categorize LSIL versus HSIL. Additional classification of CIN2+ and CIN3+ indicate CIN2 or worse, or CIN3 or worse, respectively. Precancer is defined as CIN 3+, which includes CIN 3 and adenocarcinoma in situ (AIS) and are considered precancerous lesions because they have a high risk of progressing to invasive cervical cancer if left untreated.

Cervical cancer is the 20th most frequently diagnosed cancer in the United States with most cases diagnosed between ages 35 to 44 (24.3%) and 45 to 54 (21.6%) years, with a median age of diagnosis of 50 years. According to SEER data, approximately 13,820 new cases of cervical cancer were diagnosed in 2024 comprising 0.7% of all cancers; and 4,360 deaths occurred representing 0.7% of all cancer deaths.[3,4] Incidence rates vary by age (**Table 2**) and across racial and ethnic groups (**Table 3**). Cervical cancer incidence has increased slightly among younger women, while overall age-adjusted incidence rates have been stable or have declined. Overall mortality rates have also decreased. The overall 5-year relative survival rate for cervical cancer is 67.4% and varies by stage at diagnosis.

The most common type of cervical cancer in the United States is squamous cell carcinoma, which mostly develops from cells in the cervical transformation zone. Adenocarcinoma, which develops from the mucus-producing cells of the endocervix, accounts for nearly 20% of cervical cancers in the United States. Two other less common cancer types include adenosquamous and small cell neuroendocrine carcinomas, accounting for 3 to 10% and <5% of cervical cancers, respectively.

Table 1. Cervical Cancer Screening Guidelines from Other Organizations

Patient Population	US Preventive Services Task Force (USPSTF) 2018[5]	USPSTF, 2024 (draft)[6]	American Cancer Society (ACS), 2020[7]	American Academy of Family Physicians (AAFP), 2018[8]	The American College of Obstetrics and Gynecology (ACOG), 2021[9]
<21 y	No screening	No screening	No screening	No screening	No screening
21-25 y	Cytology alone every 3y	Cytology alone every 3y	No screening	Cytology alone every 3y	Cytology alone every 3y
25-29 y	Cytology alone every 3y	Cytology alone every 3y	Preferred: primary HPV test* every 5 y Acceptable:† cotesting‡ every 5 y or cytology alone every 3y	Cytology alone every 3 y; primary HPV testing may be considered for cervical cancer screening every 3y in women ≥25y	Cytology alone every 3y preferred; cotesting women <30 y not recommended
30-65 y	Cytology alone every 3y; cotesting‡ every 5 y; primary HPV* test every 5y	Primary HPV [a] test every 5y; continued screening every 3y with cytology alone or every 5y with cotesting‡	Preferred: primary HPV[a] test every 5 y Acceptable:† cotesting‡ every 5 y or cytology alone every 3y	Cytology alone every 3y, cotesting every 5y, or hrHPV testing alone every 5y	Cytology alone every 3y; cotesting every 5y; or primary hrHPV testing every 5y
>65 y	No screening if prior adequate screening§	No screening if prior adequate screening§	No screening if prior adequate screening§	No screening if prior adequate screening§	No screening if prior adequate screening§
Prior total hysterectomy	No screening if no history of high-grade cervical dysplasia or cervical cancer	No screening if no history of CIN2+ or cervical cancer	No screening if no history of CIN 2+ or more severe diagnosis in the past 25 y or cervical cancer ever	No screening if hysterectomy is unrelated to history of CIN2+ or cervical cancer; if hysterectomy is related to a history of CIN2+ or cervical cancer, screening should continue for 20 y post hysterectomy	No screening if no history of CIN2+ or cervical cancer
Prior HPV vaccination	Follow age-specific recommendations	Follow age-specific recommendations	Follow age-specific recommendations	Follow age-specific recommendations	Follow age-specific recommendations

*Food and Drug Administration–approved test.
†Acceptable where access to primary HPV testing is not available.
‡Cotesting is cytology and hrHPV testing.
§Adequate negative prior screening is defined as 2 consecutive negative primary HPV tests, 2 negative cotests, or 3 negative cytology tests within the last 10 y, and the most recent in the past 3–5 y.
Abbreviations: CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; hrHPV = high risk human papillomavirus; y = years.

Table 2. SEER 5-Year Age-Adjusted Cervical Cancer Incidence and Mortality Rates (2017-2021) by Age, All Races and Ethnicities, All Stages[4]

Age, years	Incidence rate per 100,000	Incidence trend (2010-2020)	Mortality rate per 100,000	Mortality trend (2010-2020)
All ages	7.6	Decrease	2.2	Decrease 0.7% per year
<50	6.3	No change	1.2	No change
50-64	12.2	Decrease	4.4	Decrease
>65	10.1	Decrease	5.3	Decrease

Table 3. SEER 5-Year Age-Adjusted Cervical Cancer Incidence (2018-2020) and Mortality Rates by Race and Ethnicity, All Ages, All Stages[4]

Race and ethnicity	Incidence rate per 100,000	Incidence trend (2010-2020)	Mortality rate per 100,000	Mortality trend (2010-2020)
All races	7.6	Decrease	2.2	Decrease
Hispanic (any race)	9.8	Decrease	2.4	Decrease
Non-Hispanic American Indian/ Alaska Native	9.2	Increase	3.0	Increase
Non-Hispanic Asian/ Pacific Islander	6.1	No change	1.6	No change
Non-Hispanic Black	8.7	Decrease	3.2	Decrease
Non-Hispanic White	6.9	No change	2.1	Increase

Despite practice guidelines and established clinical algorithms, screening and follow-up rates for cervical cancer indicate incomplete capture of eligible women and variation across socio-demographic groups (**Tables 4 and 5).**[10,11]

Table 4. Proportion of Women Up to Date with Screening by Race and Ethnicity, 2021[10]

Race and ethnicity	Screening Rate, %*
All groups	72.4
Hispanic (any race)	67.9
Non-Hispanic Black	71.6
Non-Hispanic White	75.7

*The percentage of women having a Pap test within the past 3 years for all women aged 21 to 65 years; or having a Pap test, with or without an HPV test, in the past 5 years for women aged 30 to 65 years; or having an HPV test alone in the past 5 years for women aged 30 to 65 years.

Table 5. Proportion of Women Up to Date with Screening by Age, 2021*,[11]

Age	Screening Rate, %*
All ages	75.5%
21-30	67.8%
31-40	82.3%
41-50	78.0%
51-65	73.5%

*Percentage of U.S. women age-eligible for screening who were up to date with cervical cancer screening, by age — United States, 2021.

Based on statistical models, age-adjusted rates for new female cervical cancer cases have been stable from 2013 to 2022 (**Figures 1 and 2**). Age-adjusted death rates have been falling

on average 0.7% each year over 2014 to 2023. Overall, the 5-year survival rate for cervical cancer is 72.7% but varies by stage (**Table 6**).[12]

Figure 1. Age-Adjusted Incidence Rates, 2000-2021[3]
By Race and Ethnicity, Delay-adjusted SEER Incidence Rate, All Ages, All Stages

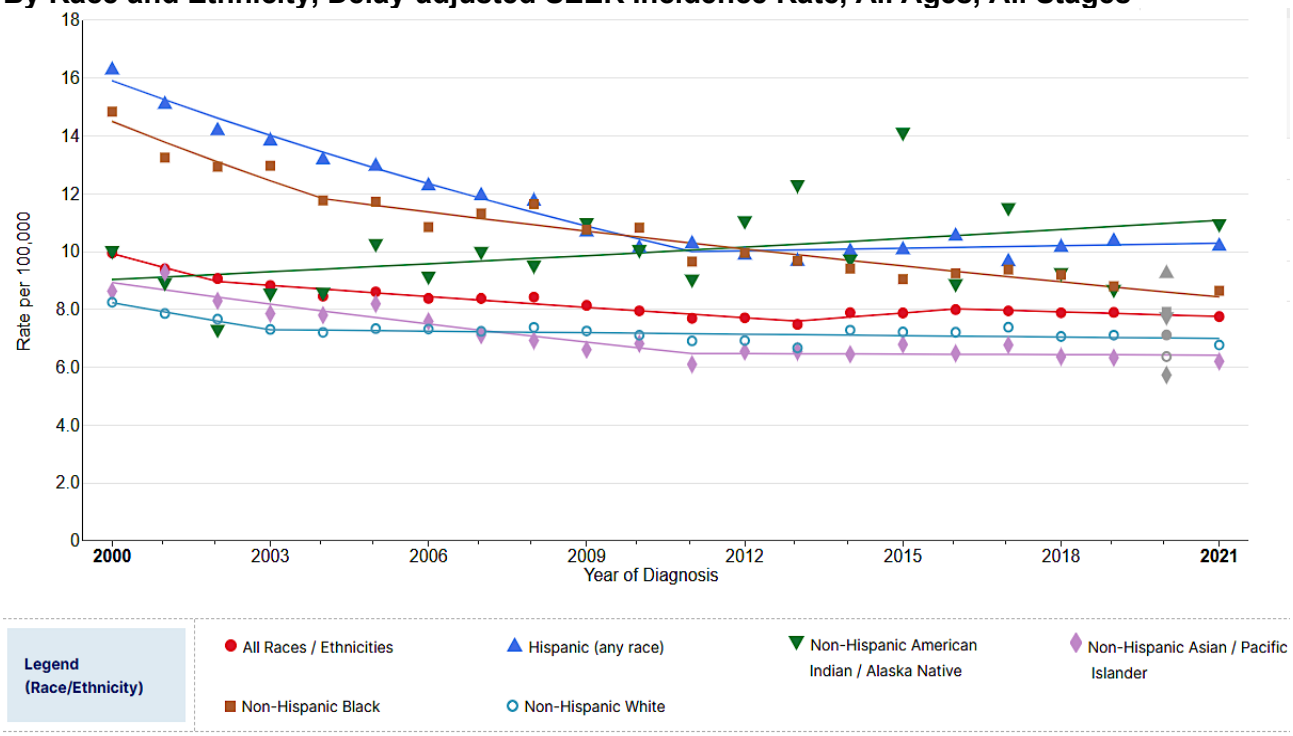
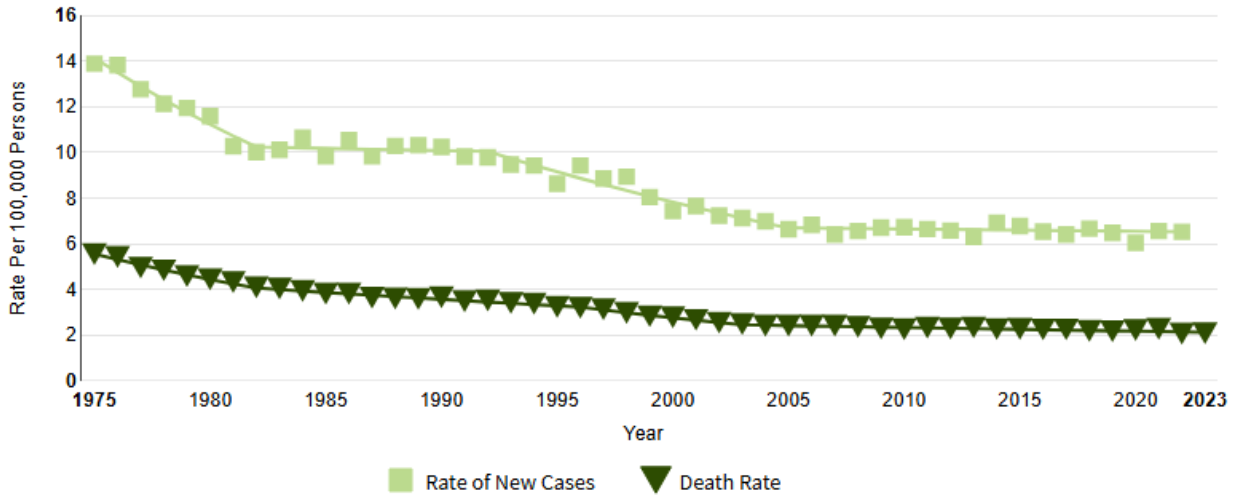


Figure 2. Overall New Cases, Deaths and 5-year Relative Survival[4]



New cases come from SEER 8. Deaths from U.S Mortality data.
All races, females, age-adjusted rates.

Table 6. Stage Distribution of SEER Incidence Cases, 2013-2021 by Age and Stage[13]

	Percent of Cases, %				5-year Survival Rate, %
Stage	**Age <50**	**50-64**	**>=65**	**All Ages**	**All Ages**
Localized	52.5	33.5	23.9	40.9	91.4
Regional	31.5	39.9	41.5	36.1	63.3
Distant	9.7	20.0	23.8	15.7	20.8

Risk Factors, Screening, Diagnosis, and Treatment

The most important risk factor for cervical cancer is persistent hrHPV infection. Increased risk for acquiring hrHPV is associated with not being vaccinated for HPV, having multiple sexual partners, sexual activity before age 18 years, or having one or more high risk sexual partners (e.g., partner with HPV infection, partner with multiple sexual partners). Women with HIV infection, compromised immune systems, previous treatment for cervical cancer or other high grade pre-cancerous lesions, or those with a history of in utero diethylstilbestrol exposure are also considered high risk.[14] Women in these high-risk groups follow different screening recommendations than average risk women. Previous abnormal cervical lesions, such as LSIL/CIN1, or precancerous lesions such as HSIL/CIN2 or 3, among others, increase risk for subsequent cervical cancer and may require more frequent monitoring. While several other risk factors have been identified, they have less effect on cancer risk and include tobacco smoking, co-infection with chlamydia or herpes simplex virus, long term use of oral contraception, and dietary deficiencies, among others.[15]

Screening for cervical cancer can reduce cervical cancer morbidity and mortality by identifying cancer at an earlier stage than it would have presented clinically. Screening for cervical cancer involves testing for high-risk HPV (hrHPV) and cytology-based screening (Pap test). Screening is the standard of care in the United States and is covered under the prevention services mandate of the Patient Protection and Affordable Care Act.[16] However, screening is only effective if subsequent steps in the clinical pathway are also completed including follow-up testing, diagnosis, treatment, and surveillance. Timely evaluation and initiation of cancer treatment improves clinical outcomes, including survival.

Recommendations for testing are primarily age based and may include primary hrHPV testing, cytology alone, or cotesting with hrHPV and cytology. Identification of abnormal screening results requires follow-up using surveillance and/or treatment, with protocols varying depending on the severity of the abnormal result. A positive hrHPV test indicates that high-risk HPV was detected and either follow-up testing or colposcopy and biopsy are required. Clinical algorithms are also dependent on age and severity of identified lesions, and may lead to increased detection rates, higher rates of treatment, or additional harms. Abnormal cytology indicates the presence of abnormal cervical cells and may require colposcopy and biopsy. Treatment primarily involves removal of abnormal tissue (excisional or ablative therapy). Precancerous lesions are treated with less invasive procedures than treatment for cancer.

An abnormality detected with routine screening is usually followed by additional evaluation with reflexive hrHPV testing, if not already completed, and then followed by colposcopy or biopsy,

when appropriate, to establish the pathologic diagnosis. The American Society for Colposcopy and Cervical Pathology (ASCCP) issued risk-based management consensus guidelines for abnormal cervical cancer screening across 19 national organizations for management of abnormal screening.[14] The guidance recommends colposcopy for any combination of history and current test results that correspond to a 4 percent or greater probability of finding CIN3+, or precancer. Once cervical cancer is identified, treatment regimens are highly individualized based on clinical status, cancer stage, tumor biomarkers, clinical subtype, and personal preferences.

While cervical cancer screening is intended to benefit patients, it may result in harms including higher rates of unnecessary treatment and biopsy; overdiagnosis and overtreatment; biopsy and colposcopy rates; anxiety, distress, stigma, and other psychological harms; impact on sexual health; procedural related harms (i.e., pain and discomfort). Overdiagnosis describes the situation where screening detects cancers unlikely to impact health outcomes. Overtreatment describes the harms caused by treatment that result from overdiagnosis.

HPV Vaccination

Vaccination with the high-risk HPV vaccine is effective at reducing hrHPV infection, cervical dysplasia, and cervical cancer at both the individual and population levels. The Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for both boys and girls beginning at age 11 or 12 years (and as young as age 9 years), given the highest effectiveness prior to hrHPV exposure.[17] HPV vaccination is also recommended beginning at age 9 years by the American Academy of Pediatrics,[18] American Academy of Family Physicians, and American Cancer Society. Overall uptake for HPV vaccines in the U.S has been slow and remains relatively low (58.6%)[19] with differences in uptake based on geography, race/ethnicity, and other factors,[20] with all groups well below the healthy people 2030 target of 80% vaccination rate (**Table 7**).

From 2008-2011, the ACIP recommendation was restricted to a 3-dose series for females only. From 2011-2016, the recommendation was expanded to include both males and females using a 3-dose series. Beginning in 2016, ACIP recommended a 2-dose series to males and females beginning their vaccination series before 15 years of age and a 3-dose series if started after age 15 years up to age 26. Recently recommendations have expanded vaccine eligibility to those aged 27 to 45 years who may decide to get vaccinated after considering their risks for new HPV infections. Recent data indicate a correlation between lower rates of cervical pre-cancers and HPV vaccination. During 2008 to 2022, cervical precancer incidence decreased 79% and higher-grade precancer incidence decreased 80% among screened women aged 20 to 24 years, the age group most likely to have been vaccinated.[21]

Table 7. HPV vaccination rates, 2022

Group	Vaccination rate, %*
All sexes	58.6
Male	56.6
Female	60.7
All races	58.6
Non-Hispanic White	55.8
Non-Hispanic Black	61.4
Hispanic	61.3
Other/Multi-race	60.8

*Vaccination rate based on the percentage of adolescents aged 13-15 years who had received 2 or 3 doses of the human papillomavirus (HPV) vaccine as recommended at time of immunization

EVIDENCE REVIEW UPDATE

WPSI 2016 Evidence Update[22]

The 2016 WPSI update focused on optimal:

- Ages to begin and discontinue regular cervical cancer screening.
- Benefits and harms of different screening strategies for women at any age.
- Screening intervals for women screened at any age.

Evidence from several trials, observational studies, and data analyses on cervical cancer screening that were conducted for the USPSTF in 2012[23] was summarized for the WPSI.

Results related to screening **benefits** included:[22,23]

- Similar or greater detection of CIN2/3+ and cancer for co-testing versus cytology in women aged 30 to 65 years based on systematic reviews, meta-analysis of RCTs, and observational studies.
- No advantage to screening prior to age 21 years, with women in this age group experiencing the largest number of false positive test results and the lowest number of expected cancer cases based on modeling studies of ages to begin and discontinue screening. With each successive year that screening was delayed beyond age 21 years, the number of false positive test results declined and expected cancer cases increased. In modeling studies, screening every 5 years from age 21 years was associated with a difference in cancer mortality of 2.4 per 1000 women and cancer incidence of 10.2 per 1000 women compared with screening every year.
- Limited evidence regarding the benefits of screening women older than age 65 years was included in the 2012 USPSTF review consistent with prior reviews. The age to stop screening was not systematically addressed by the 2012 USPSTF review. The USPSTF used epidemiological data and modeling studies to inform their recommendation.
- Fewer colposcopies (575 vs. 1083 per 1000), cancer cases (7.44 vs. 8.50 per 1000), and cancer deaths (1.35 vs. 1.55 per 1000) were associated with cytology screening every 3 years from age 21 years with cytology every 3 years prior to age 30 and then co-testing every 5 years compared to other regimens based on modeling studies evaluating benefits of screening.
- Diagnostic accuracy studies that found 1-time HPV testing was more sensitive, but less specific than cytology, with HPV testing sensitivity ranging from 86% to 97% for CIN3+ outcomes and 63% to 98% for CIN2+ outcomes versus 46% to 50% and 38% to 65%, respectively for cytology. Specificity for these outcomes was 3 to 5 percentage points lower using HPV testing compared with cytology.

Results related to screening **harms** included an analysis of screening outcomes:

- Studies addressing harms reported screening test performance (ie, false-negative and false-positive results), procedures conducted to evaluate positive screening test results (ie, colposcopy and biopsy), and potential psychological harms (eg, quality of life,

anxiety or distress, partner discord). Overall, screening with primary hrHPV or cotesting was associated with more false-positive results and higher colposcopy rates.

- Limited evidence suggested that positive hrHPV test results may be associated with greater psychological harm than abnormal cytology results. None of the included studies reported on harms occurring from the screening test, diagnostic testing, or treatments and no studies reported on the psychological effects of primary hrHPV screening.
- Assessment of harms from trial data was limited because women with positive HPV results or atypical cells of undetermined significance (ASCUS) on cytology were immediately referred to colposcopy, resulting in more colposcopies among women screened with the more sensitive HPV test compared with cytology (5.8% vs. 2.5%).
- Determination of harms was generally limited by incomplete reporting, use of different screening strategies in different rounds of the trial (e.g., cytology alone was done in both arms of round 2), and differing referral criteria.
- In women younger than 30 or 35 years, results were similar to those in older women, but they had higher rates of colposcopy referrals after HPV testing.
- The influence of screening interval and strategy on potential harms of missed cancer cases or possible overdetection could not be directly ascertained from available evidence because of lack of within–trial interval comparisons and variability of protocols across studies.

In addition, a systematic review of observational studies indicated that overdiagnosis, anxiety, pain, and additional procedures may cause harm, however, their effects on individual women are difficult to estimate and vary widely.[23]

USPSTF 2024 Systematic Review Update

A draft systematic review was conducted in 2024 to update the USPSTF recommendation on cervical cancer screening. The review addressed the comparative benefits and harms of high - risk HPV (hrHPV) based screening strategies and the test accuracy and uptake of self-collected hrHPV samples. Eligible studies included those included from prior USPSTF reviews[23,24] and new studies published through April 11, 2024. The target population for screening included asymptomatic individuals with a cervix at average risk for cervical cancer (including those who are pregnant) without HIV or other risk factors that are associated with high risk for cervical cancer. Studies evaluated hrHPV screening as either the hrHPV test with or without cytology triage (primary hrHPV screening) or in combination with cytology (co-testing).

For key questions on effectiveness, eligible studies included RCTs and nonrandomized studies of interventions (NRSI) with concurrent comparison groups that compared different screening strategies and compared health outcomes (e.g., cervical cancer mortality, quality of life) or intermediate outcomes (e.g., risk of advanced cancer). Inclusion criteria were expanded for studies identifying potential screening harms, which considered single-group cohort studies. Contextual questions were addressed using available relevant information. Microsimulation models were commissioned as part of the USPSTF update from the Cancer Intervention and

Surveillance Modeling Network (CISNET) Cervical Working Group. Additional details of the systematic review update methodology are described in the full report.[6]

The USPSTF evidence review included three key questions (KQ) relevant to the WPSI recommendation listed below. In addition, each key question also assessed differences between specific patient populations. The USPSTF evidence review also included a contextual question (CQ) relevant to the WPSI recommendation that was not systematically reviewed.

KQ1. What is the comparative effectiveness of different cervical cancer screening strategies (i.e., test, mode of collection, and interval of testing) on precancer detection, cancer incidence, morbidity, or mortality?
KQ2. What is the test accuracy of and uptake of self-collected high-risk HPV samples?
KQ3. What are the comparative harms of different cervical cancer screening strategies (i.e., test, mode of collection, and interval of testing)?
CQ1. What is the comparative test accuracy of high-risk HPV tests used in U.S.-based clinical practice?

Results of the USPSTF systematic review for key questions are summarized using evidence grades defined in **Table 8**. Evidence addressing the key questions is described in **Table 9**. A summary of the contextual question is described in **Table 10**.

Table 8. Overall Rating of the Strength of Evidence

Grade	Interpretation
High	Very confident that the estimate of effect lies close to the true effect; evidence has few or no deficiencies; findings are stable
Moderate	Moderately confident that the estimate of effect lies close to the true effect; evidence has some deficiencies; findings are likely to be stable
Low	Limited confidence that the estimate of effect lies close to the true effect; evidence has major and/or numerous deficiencies; additional evidence is needed to make conclusions
Insufficient	No evidence, unable to estimate an effect, or no confidence in the estimate

Table 9. USPSTF Summary of Evidence for Key Questions

Key Question	Screening Strategy	Outcome; Number of Studies (k) and participants (N)	Summary of Outcomes	Strength of Evidence
KQ1. Screening Effective-ness	Primary HPV (+/- cytology triage) vs. cytology	CIN3+ K=8 N=637,241	Ages 25-69 y: *Round 1,* CIN3+: pooled RR 1.80 (95% CI, 1.38 to 2.36), I^2=90.4%, 6 RCTs and 2 NRSIs *Round 2* (exit, 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	**Moderate** for increased detection of precancer, ages 25-65 y
		ICC K=6 N=569,097	Ages 25-69 y: *Round 1:* 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	**Insufficient** for detection of ICC, ages 25-69 y
	Primary HPV with cytology triage vs. usual care	CIN3+ K=1 N=44,579	Ages 65-69 y: *Round 1:* RR 11.1 (95% CI, 4.81 to 25.5)	**Low** for detection of precancer with one round of screening, ages 65-69 y
		ICC K=1 N=44,579	Ages 65-69 y: *Round 1:* RR 2.98 (95% CI, 0.75 to 11.9)	**Insufficient** for detection of ICC, ages 65-69 y
	Self-collected primary HPV vs. clinician collected	CIN3+ K=1 N=13,925	Ages 30-60 y: *Round 1:* No difference in detection of CIN3+	**Low** for no difference in detection of precancer
		ICC K=1 N=13,925	Ages 30-60 y: *Round 1:* No difference in detection of CIN3+	**Insufficient** for detection of ICC
	Co-testing vs. cytology	CIN3+ K=7 N=122,316	Ages 20-64 y: *Round 1:* pooled RR 1.13 (95% CI, 0.98 to 1.30), I^2=0%, 4 RCTs *Round 2* (exit): pooled RR 0.67 (95% CI, 0.53 to 0.83), I^2=0%, 4 RCTs NRSI results consistent with RCT findings	**Moderate** for increased detection of precancer

Key Question	Screening Strategy	Outcome; Number of Studies (k) and participants (N)	Summary of Outcomes	Strength of Evidence
		ICC k=4 N=77,142	Ages 20-64 y: *Round 1:* RR 0.42 (95% CI, 0.11 to 1.55) and RR 2.01 (95% CI, 0.76 to 5.34)	**Low** for reduction in ICC
KQ2. Test Agreement, Accuracy, and Uptake	Self-collected vs. clinician-collected hrHPV	Test agreement, HPV k=14 N=9,095	Ages 20-73 y: Positive agreement, pooled: 0.87 (95% CI, 0.83 to 0.91), I^2=62.3%, 14 studies Negative agreement, pooled: 0.96 (95% CI, 0.95 to 0.98), I^2=94.1%, 14 studies	**Moderate** for adequate test agreement
		Test accuracy k=6 N=513,952	Ages 18-65 y: *CIN2+* Relative sensitivity: 0.91 (95% CI, 0.88 to 0.96) to 0.97 (95% CI, 0.91, to 1.03), 3 studies Relative specificity: 0.98 (95% CI, 0.95 to 1.00) to 1.02 (95% CI, 1.01 to 1.02), 3 studies *CIN3+* Relative sensitivity: 0.94 (95% CI, 0.90 to 0.97) to 0.99 (95% CI, 0.92 to 1.07), 3 studies Relative specificity: 0.98 (95% CI, 0.95 to 1.00) to 1.02 (95% CI, 1.02 to 1.02), 3 studies	**Moderate** for adequate test accuracy
		Test uptake k=42 N=386,080	Ages 21-69 y: Most studies increased the proportion of screening with self-sample versus usual care/clinic screening (40/42 studies, absolute difference 2 to 56%)	**Moderate** for increased uptake, ages 21-69 y
KQ3. Comparative harms of screening strategies	Primary HPV (+/- cytology triage) vs. cytology	Burden of testing: colposcopy, false + rate k=8 N=637,241	Ages 25-65 y: *Round 1:* 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%, 7 studies	**Moderate** for increased burden of testing

Key Question	Screening Strategy	Outcome; Number of Studies (k) and participants (N)	Summary of Outcomes	Strength of Evidence
		False negative, ICC k=4 N=363,064	Ages 25-65 y: *Round 1:* No statistically significant difference	**Insufficient** for false negative rate for ICC
		Psychological harms k=1 N=2000	Ages 34-69 y: No difference in depression and anxiety measured by PHQ-4 at 4 to 24 months	**Low** for no psychological harm
	Primary HPV with cytology triage vs. usual care	Burden of testing: colposcopy k=1 N=44,579	Ages 65-69 y: *Round 1:* 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	**Low** for no difference in burden of testing
	Self-collected primary HPV vs. clinician	Burden of testing: colposcopy and false + rate k=1 N=13,925	Ages 30-60 y: *Round 1:* No difference in false positive rate between collection methods	**Low** for no difference in detection
		False negative, ICC k=1 N=13,925	Ages 30-60 y: No missed ICC in either arm	**Insufficient** for false negative rate for ICC
	Co-testing vs. cytology	Burden of testing: colposcopy and false + rate k=2 N=69,684	Ages 20-64 y: *Round 1:* 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%	**Moderate** for increased burden of testing

Key Question	Screening Strategy	Outcome; Number of Studies (k) and participants (N)	Summary of Outcomes	Strength of Evidence
		False negative, ICC k=2 N=52,632	Ages 30-60 y: *Round 1:* 3 missed cancers in both trials combined (in the cytology group only) with no statistically significant differences.	**Insufficient** for false negative rate for ICC
		Psychological harms k=1 N=2,473	Ages 20-64 y: No difference in measures of distress or anxiety at 2 weeks	**Low** for no psychological harm

Abbreviations: CIN = cervical intraepithelial neoplasia; HPV, hrHPV = high risk human papilloma virus; ICC = invasive cervical cancer; NA = not applicable

Table 10. USPSTF Summary for Contextual Question

Contextual question	Conclusion
What is the test accuracy of hrHPV tests used in U.S based clinical practice?	• 8 FDA-approved hrHPV assays in U.S. as of 2023: Digene Hybrid Capture 2 (HC2), Cervista HPV HR, Cervista HPV 16/18, Aptima HPV, Aptima HPV 16, 18/45, Cobas HPV, Onclarity HPV, and Alinity. • Relative accuracy for CIN2+ detection: 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. • Comparative detection rates from Danish Horizon substudy demonstrated relative detection of CIN3+ and CIN2+ were equivalent for HC2, Cobas, and Aptima.

Abbreviations: CIN = cervical intraepithelial neoplasia; CQ = contextual question; HPV = human papilloma virus; hrHPV = high risk human papilloma virus; PCR = polymerase chain reaction

Conclusions

- Primary hrHPV based screening increases detection of precancer vs. cytology-based screening. There are lower rates of precancer with subsequent screening and small incremental benefit in CIN3+ detection.
- Self-collected vaginal hrHPV has similar test accuracy for precancer vs. clinician collected (similar proportions screening positive) and can increase the uptake of screening.
- Harms of screening include an increased burden of testing, false positive results in younger women, and harms of treatment (procedure related).
- Differences by population characteristics have not been adequately studied.

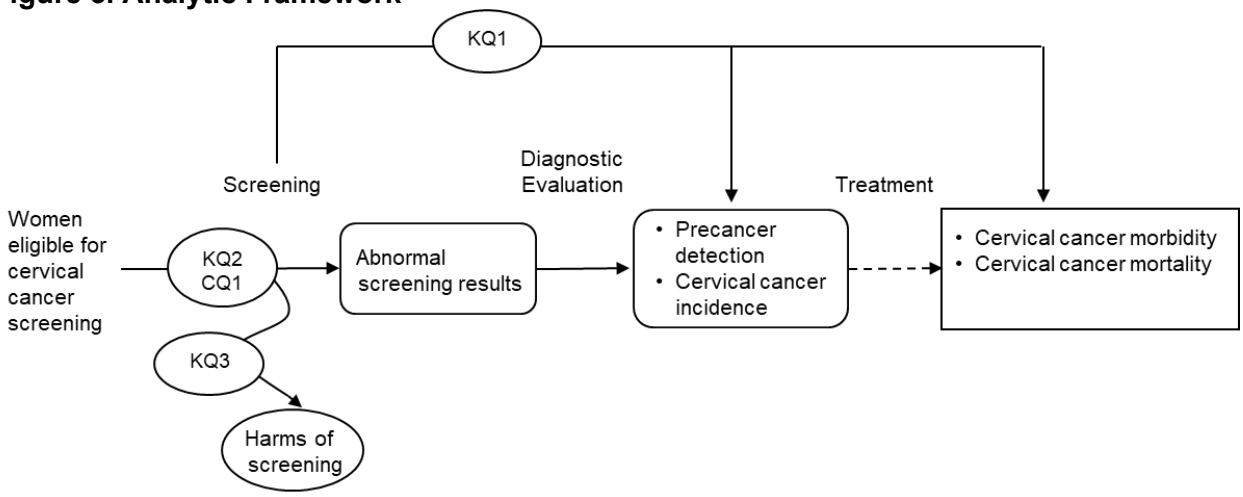
WPSI 2025 Evidence Review Update

Methods

The evidence review update for the WPSI focused on identifying research that could change the current recommendation, particularly related to optimal cervical cancer screening approaches; screening intervals; and screening tests and strategies. It is primarily based on evidence reviews conducted for the USPSTF including the 2024 draft report summarized above.[6]

Analytic Framework: The WPSI analytic framework adapts the USPSTF three key questions (KQ) and one contextual question (CQ) to the diagram below that outlines the patient population, interventions, outcomes, and links (**Figure 3**).

Figure 3. Analytic Framework



Population: Adult females ages 21 and older, including those who are pregnant, at average risk for cervical cancer, who are eligible for routine cervical cancer screening. Average risk applies to all asymptomatic women with a cervix, regardless of their sexual history. High risk populations include women who have been diagnosed with a high-grade precancerous cervical lesion or cervical cancer, in utero exposure to diethylstilbestrol, concurrent HIV infection, or with a compromised immune system, and should receive individualized follow-up. Diagnosis or surveillance beyond routine screening is outside the scope of this recommendation. Additional eligibility criteria are described in **Appendix A**.

Literature surveillance: The USPSTF conducts ongoing literature surveillance searches of published studies relevant to their recommendations to track developments in the field. Updated searches for the WPSI update were conducted through September 2024. LitWatch reports issued through February 12, 2025 were also reviewed to determine whether studies relevant to cervical cancer screening have been published since the 2024 USPSTF draft review. The WPSI did not review contextual questions or consider models as part of this update. Additional details of the contextual question reviewed for the USPSTF 2024 draft are available in the draft appendix of the USPSTF report.[6]

Summary of Relevant Studies Published since August 2022

Key Questions: 14 studies identified from searches and LitWatch met criteria for KQ2 and KQ3 on test accuracy, collection methods, and harms of screening. These are described in **Table 11** and detailed in **Appendix B**. Additional relevant studies did not meet inclusion criteria for key questions.

Table 11. Summary of Relevant Studies Addressing KQs Identified from Searches

Component	KQ1: Detection	KQ2: Accuracy	KQ3: Harms
Age to start or stop screening	No studies	No studies	No studies
Screening interval	No studies	No studies	No studies
Self-collection vs. clinician collection	1 study reported positivity rates.[25]	Good agreement across 7 studies, with no differences between self- or clinician-collected samples.[26-32]	1 study reported low rates of harms (0.7%)[32]
Screening strategy	3 studies reported detection.[25,33-35]	No studies	6 studies reported on some harm, either false positives, colposcopy referral rates, or burden of follow-up.[33-38]

Abbreviations: KQ = key question; vs. = versus

CONCLUSIONS

Recent updates of evidence related to cervical cancer screening demonstrate that primary hrHPV based screening increases detection of precancer compared with cytology-based screening. This testing approach also results in lower rates of precancer (CIN3+) with subsequent screening based on studies of first and second rounds of screening, with a small incremental benefit in precancer detection for hrHPV screening as the primary approach in women aged 30 to 65 years. Self-collected vaginal hrHPV screening demonstrated similar test accuracy for precancer when compared with clinician-collected samples, resulting in similar proportions of patients screening positive. Self-collected screening may also increase the uptake of cervical cancer screening.

Evidence updates are consistent with prior findings that the harms associated with cervical cancer screening include an increased burden of testing, false positive results in younger women, and procedure related harms of treatment resulting from overtesting and overdiagnosis, particularly in younger age groups.

While evidence on the benefits and harms of cervical cancer screening supports the effectiveness of hrHPV- based screening and cytology-based strategies, most studies limited the reported outcomes to a single round of screening and may have limited application to inform evidence on screening programs. Importantly, most comparative screening studies were conducted in countries with organized screening programs, while one large population cohort study was conducted in a U.S health setting with an organized screening program, representing a diverse group of patients. Additionally, many studies of both screening and self-collection included participants without prior HPV vaccination, did not report vaccine history, or did not stratify results by HPV vaccination status. Future studies that stratify results by HPV vaccine status could inform newer approaches to screening. For example, the most recent recommendation by the American Cancer Society includes screening initiation starting at age 25 based on the lower prevalence of hrHPV and precancer in younger age cohorts resulting from HPV vaccination.[7] While epidemiologic studies support a growing trend on the impact of HPV vaccination on hrHPV prevalence,[21] additional trial data could provide more robust evidence to support optimal ages to start screening.

Population data demonstrates an overall decline in cervical cancer incidence and mortality. However, differences remain for specific populations who are disproportionately affected by cervical cancer. Lack of screening uptake or follow-up, late-stage diagnosis, and delayed access to care impact cervical cancer incidence, follow-up, cancer progression, and mortality. Patient navigation is one strategy demonstrating an important impact on improving access to cervical cancer screening and follow-up.[39,40] Newer screening strategies, including self-collection, can also reduce barriers to care, while consideration of coverage for the entire screening pathway may facilitate more widespread access and consistent follow-up, particularly in unscreened populations or among those who are underscreened.[41]

WPSI updates to the 2024 USPSTF draft recommendation primarily focus on the use of primary hrHPV screening for women aged 30 to 65 years as the preferred screening method based on trials of effectiveness and support the use of self-collected hrHPV screening to improve the uptake of screening in clinical settings. Newer evidence informs the use of primary hrHPV screening as the preferred screening method in women aged 30 to 65 years when available, and the accuracy of self-collected vaginal samples to increase screening uptake.

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Appendix A. Inclusion and Exclusion Criteria for WPSI Update

Category	Inclusion	Exclusion
Aim	**All KQs:** Studies targeting cervical cancer screening	**KQs 1, 2, 3:** Use of HPV or cytology testing for posttreatment surveillance or other purposes
Populations	**All KQs:** Women with a cervix (any age), including those 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)	**All KQs:** Surveillance studies exclusively in individuals with HIV, in utero exposure to diethylstrilbestrol, or with previous treatment for cervical cancer or high-grade pre-cancerous lesions
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 Screening intervals: any interval of screening **KQ 2:** Self-collected hrHPV sample	**All KQs:** Non hrHPV screening strategies; non-FDA approved tests
Comparisons	**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	**All KQs:** 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); screening adherence **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)	**All KQs:** Other outcomes not listed, including cost
Setting	**All KQs:** Primary care settings and clinical settings resulting from referrals from 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 with clinical supervision	**All KQs:** Other non-primary care relevant or primary care referable setting; settings and countries not categorized as "Very High" on the Human Development Index
Study Design	**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)	**All KQ:** Other study designs; modeling studies **KQ 2:** Diagnostic test accuracy studies without a reference standard
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)	
Study Quality	Studies with low or moderate risk of bias according to U.S. Preventive Services Task Force quality criteria	High risk of bias studies

*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: FDA = U.S. Food and Drug Administration; KQ = Key Question.

Appendix B. Included Studies for WPSI Update

Author, Year	Study Objective	Intervention	Reference Standard	Results Summary
Key Question 1: Screening effectiveness				
Nonboe, 2024[33]	To analyze screening outcomes in Danish HPV-vaccinated women in a routine screening program after the first screening test at age 23.	Cytology with HPV triage	Histologic CIN2+/CIN3+	Among Cyt+/HPV+ women, 4.4 (95% CI 3.9-5.2) women followed up per detected CIN2+ case. For Cyt-/HPV+ women, 22.8 (95% CI 13.3-59.3) women followed up per detected CIN2+ case.
Partanen, 2024[34]	To compare cytology and HPV-based screening in the colposcopy referrals and detection rates of cervical lesions.	HPV-based primary screening vs. cytology-based screening	Histologic CIN2+	HPV-based screening vs. cytology: detection rates for CIN2+ were higher in Finland (RR 2.37, 95% CI: 2.13-2.63) and Norway (RR 1.66, 95% CI: 1.57-1.75), with no significant difference in Sweden (RR 1.03, 95% CI: 0.99-1.07) HPV-based screening: Number of colposcopies needed per CIN2+ case was higher in Finland (RR 1.63, 95% CI: 1.54-1.72) and Norway (RR 1.18, 95% CI: 1.14-1.22) but not significantly different in Sweden (RR 0.98, 95% CI: 0.95-1.00)
Vink, 2024[25]	To assess the effect of HPV self-sampling on cervical cancer screening participation in both urban and rural settings in Saskatchewan, Canada.	Self-collected HPV testing	Healthcare provider-collected samples	Positivity rates; handout responders (n=52) vs. mailout responders (n=28): Other hrHPV: 23.1% vs. 14.3%; p=0.40 HPV 16: 7.7% vs. 3.6%; p=0.65 HPV 18: 3.9% vs. 0.0%; p=0.54 Any HPV: 30.8% vs. 14.3%; p=0.17
Yu, 2024[35]	To assess the effectiveness of high-risk human papillomavirus (HR-HPV) primary testing for cervical cancer screening in China's rural areas.	Primary hrHPV testing, hrHPV genotyping (HPV-16/18 and 12 other genotypes)	Colposcopy with biopsy	hrHPV testing showed significantly lower risk of CIN2/3+ vs. cytology alone at 36-month follow-up: RR 0.4; 95% CI: 0.3-0.4 HPV 16 positivity showed highest risk of CIN2/3+ detection: RR 85.4; 95% CI: 72.3-100.8 Cumulative incidence of CIN3+ in HSIL cytology increased from 28.6% if HPV was negative to 56.1% in hrHPV-positive women
Key Question 2: Test accuracy, uptake and adherence of self-collected samples				
Chan, 2023[26]	To evaluate the concordance of HPV results between the self-collected and clinician-collected samples using different HPV assays.	Self-collected HPV testing (isothermal amplification)	BD OnclarityTM HPV assay (PCR-based)	Self-Sentis HPV concordance with Clinician-Sentis HPV: 89.8%, kappa=0.769 Clinician-Onclarity; 84.4%, kappa=0.643
Gibert, 2023[27]	To establish the diagnostic validity of HPV in vaginal self-samples and the acceptance of self-collection.	Self-Collected HPV Sampling	Clinician-Collected Samples	Sensitivity and Specificity Viba-Brush®: 65.0% (95% CI: 40.8-84.6%), and 84.6% (95% CI: 65.1-95.6%) Mía by XytoTest®: 55.0% (95% CI: 31.5-76.9%), and 84.6% (95% CI: 65.1-95.6%) Moderate concordance for cytology (κ 0.41-0.51) Very good concordance for HPV (κ 0.73-0.86) 91.7% of women found self-sampling advantageous

Author, Year	Study Objective	Intervention	Reference Standard	Results Summary
Giubbi, 2024[28]	To evaluate the analytical performance and stability of self-collected vaginal samples vs. professionally collected cervical samples for hrHPV detection.	Self-collected HPV with non-alcohol-based media	PCR-based ThinPrep	Clinician-collected hrHPV detection concordance Self-collected swabs suspended in eNat®: 91.2%, k=0.821 MSwab®: 91.4%, k=0.798
Kittisiam, 2024[29]	To compare self-sampling HPV-DNA and clinician-sampling HPV-mRNA to detect hrHPV and high-grade cervical lesions.	Self-collected HPV-DNA vs. clinician-collected HPV-mRNA	Colposcopy with biopsy	Self-collected HPV-DNA vs. clinician-collected HPV-mRNA Concordance: 86.8% (95% CI, 0.599-0.746), kappa=0.670, p<0.001 Sensitivity to detect CIN2+: 91.8% (95% CI: 85.4%-96.0%) vs. 90.2% (95% CI: 83.6%-94.9%) NPV: 91.9% (95% CI: 85.6%-96.0%) vs. 91.7% (95% CI: 86.0%-95.7%)
McGill, 2024[30]	To compare the adequacy, agreement, and acceptability of Papanicolaou testing (cytology) for cervical cancer screening using self-collected samples vs. physician-collected samples in Grenada in the Caribbean.	Self-collected HPV vaginal sampling	Physician-collected cytology	Self-collected samples were adequate and concordant with physician-collected samples: (Cohen's kappa = 0.662, 95% CI, 0.411, 0.913). High-risk HPV genotypes found (HPV 45, 53) differed from commonly reported types (16, 18)
Qi, 2024[31]	To evaluate the performance of self-collected vaginal swabs for HPV detection.	Self-collected vaginal HPV swabs	Provider-collected cervical samples	Self-collected vaginal vs. provider-collected cervical samples: Total agreement: 90.3% Positive percentage agreement: 84.2%
Yang, 2024[32]	To evaluate the reliability and acceptability of a self-sampling Kit for collecting vaginal samples for HPV typing vs. physician collected.	Self-collected HPV testing (HygeiaTouch Self Sampling Kit)	Physician-collected cervical specimens	Self-collected vs. physician-collected specimens Agreement: 88% (95% CI, 86.2-89.9), k=0.75 Sensitivity for CIN2+ detection: 83.9% vs. 88.5% Specificity: 48.1% vs. 49.8% Relative accuracy: 0.96 (95% CI, 0.90-1.03)
Key Question 3: Comparative harms of screening strategies				
Dun, 2024[36]	To assess the clinical values of extended HPV genotyping in triage of high-risk HPV-positive women, focusing on the trade-off between cervical precancer detections and colposcopy referrals.	Extended HPV genotyping triage strategies vs. HPV16/18 with cytology triage	Histological confirmation (CIN2+, CIN3+)	Reduced colposcopy referrals with HPV16/18/58/33/31 genotyping vs. standard triage: 6.85% vs. 7.35%, p=0.001
Dura, 2024[37]	To determine the regional prevalence of HPV with genotypic subclassification and to evaluate the efficacy of HPV testing in cervical screening.	Primary HPV screening (HR-HPV DNA test)	Colposcopic biopsy	Increased colposcopy referrals with HPV primary testing vs. cytology

Author, Year	Study Objective	Intervention	Reference Standard	Results Summary
Granados, 2024[38]	To evaluate the clinical performance of Aptima messenger RNA HPV testing in cervical cancer screening with a 9-year follow-up.	mRNA HPV Testing (Aptima)	Histologic CIN2+/CIN3+	False-positive rates for CIN2+ were 12.0% lower with AHPV vs. cytology
Nonboe, 2024[33]	To analyze screening outcomes in Danish HPV-vaccinated women in a routine screening program after the first screening test at age 23.	HPV testing with cytology triage	Histologic CIN2+/CIN3+	Burden of follow-up per CIN2+ case detected: 4.4 women followed up per CIN2+ case for Cyt+/HPV+ women; 22.8 women followed up per CIN2+ case for Cyt-/HPV+ women
Partanen, 2024[34]	To compare cytology and HPV-based screening in the colposcopy referrals and detection rates of cervical lesions.	HPV-based primary screening vs. cytology-based screening	Histologic CIN2+	Significantly higher colposcopy rates with HPV testing in Finland (RR 3.87, 95% CI: 3.67-4.08) and Norway (RR 1.46, 95% CI: 1.41-1.50), but lower in Sweden (RR 0.76, 95% CI: 0.74-0.78)
Yang, 2024[32]	To evaluate the reliability and acceptability of the HygeiaTouch Self Sampling Kit for Women in collecting vaginal samples for HPV typing, comparing the results with samples collected by physicians.	Self-collected HPV testing (HygeiaTouch Self Sampling Kit)	Physician-collected cervical specimens	Low rate of adverse events: 0.7%, 9/1210 participants High satisfaction: >90%
Yu, 2024[35]	To assess the effectiveness of high-risk human papillomavirus (HR-HPV) primary testing for cervical cancer screening in China's rural areas.	Primary hrHPV testing, hrHPV genotyping (HPV-16/18 and 12 other genotypes)	Colposcopy with biopsy	False-positive rate observed; unnecessary colposcopies in HPV-positive/cytology-negative women

Abbreviations: AHPV = Aptima HPV; CI = confidence interval; CIN = cervical intraepithelial neoplasia; CIN2+ = cervical intraepithelial neoplasia grade 2 or higher; CIN3+ = cervical intraepithelial neoplasia grade 3 or higher; Cyt+ = cytology positive; Cyt- = cytology negative; DNA = deoxyribonucleic acid; DS = dual staining; FDA = Food and Drug Administration; HPV = human papillomavirus; HR = high-risk; hrHPV = high-risk human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL+ = low-grade squamous intraepithelial lesion or higher; mRNA = messenger ribonucleic acid; NPV = negative predictive value; p16 = protein p16; PAP = Papanicolaou test; PCR = polymerase chain reaction; PPV = positive predictive value; RR = relative risk; vs. = versus