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Cervical Cancer Screening Guideline

Last guideline approval: January 2024

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Guideline Scope

This guideline focuses on recommendations for screening for cervical cancer in asymptomatic patients who were born with a cervix, including those at average as well as increased risk. Patients may be at increased risk of cervical cancer due to a compromised immune system, HIV, in utero exposure to diethylstilbestrol, or previous treatment of a high-grade precancerous lesion or cervical cancer, vulvar cancer, or vaginal cancer.

For the management of Pap test (cytology) and high-risk human papillomavirus (hrHPV) test results and follow-up colposcopy results, the recommendations of the 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors have been adopted. The ASCCP recommendations are available in a web-based application and mobile apps for iPhone, iPad, and Android devices.

Eligible population/terminology note: All patients born with a cervix, including transgender men, are included in the target population for this guideline. The terms *patient* and *individual* should be understood to include everyone eligible for cervical cancer screening under this definition. Ensure that the cervix is still present and not congenitally absent or surgically removed, as cervical cancer screening Health Maintenance does not populate for our transgender male patients after their sex has been changed in KP HealthConnect. For more about screening recommendations for transgender patients, see page 2 of the Hamman-Fields Gender Health Primary Care Reference Tool.

Major Changes as of January 2024

- Self-collected primary hrHPV screening is an acceptable cervical cancer screening method for **average-risk patients,** as it has a similar sensitivity and specificity as clinician-collected samples and increases the uptake of cervical cancer screening when the collection kit is mailed directly to patients' homes.

- Self-collected primary hrHPV screening is not recommended for cervical cancer screening in **high-risk patients** due to insufficient evidence in this population.

Prevention

Cervical cancer prevention measures include regular screening and reducing the risk of human papillomavirus (HPV) infection through condom use and HPV vaccination. In the presence of HPV infection, cigarette smoking is thought to be associated with a significantly increased risk of squamous cell carcinoma, and tobacco cessation is an important aspect of decreasing risk of cervical dysplasia (ACOG 2009).

- HPV vaccination is recommended for all individuals aged 9–26 years for the prevention of HPV-related diseases. See the Immunization Schedules and Talking Points for HPV Vaccination.
- HPV vaccination may be appropriate for adults aged 27–45. Use shared decision-making SmartPhrase **.SDMHPVVACCINE27TO45**. See patient handout.
- Tobacco cessation is recommended for all individuals. See the KPWA Tobacco and Nicotine Cessation Guideline.

Screening

Virtually all cervical cancers are caused by HPV infections, with just two types—16 and 18—responsible for approximately 70% of all cases. Other high-risk genotypes (such as 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are also included in the hrHPV test.

Screening recommendations for average-risk populations

Primary hrHPV screening is the **preferred** screening option for patients **aged 30–64** and should be repeated every 5 years. A reflex Pap test (cytology) is done when hrHPV results are positive. Primary hrHPV screening is as effective as co-testing, with fewer false positives and fewer unnecessary follow-up procedures. Primary hrHPV screening is more efficient and cost-effective than co-testing and simplifies outreach, result interpretation, and follow-up of abnormal results. See Provider Talking Points.

Self-collect hrHPV: a new option for cervical cancer screening

KPWA now offers average-risk patients aged 30–64 who are on a 5-year HPV screening track the option of using self-swab testing to collect samples. The self-collection may be done either at home—with a testing kit that is mailed to eligible members—or in clinic. Patients who receive a result that is positive or inconclusive will need in-clinic follow-up. See this huddle card for more information.

The Pap test (cytology) is the **preferred** screening option for patients **aged 21 through 29** and should be repeated every 3 years. The Pap test is also an alternative screening option for women aged 30 and older. For patients aged 25 and older, a reflex hrHPV test is performed when Pap results are ASC-US (atypical squamous cells of undetermined significance).

Co-testing (with both Pap [cytology] and hrHPV tests) is an **alternative** screening option for patients **aged 30–64** and should be repeated every 5 years. Co-testing is **not** recommended for patients under age 30; while there is a high prevalence of HPV in this population, there is a lower risk of cervical dysplasia, as the infection is most likely to clear on its own and not develop into cervical cancer.

Who to screen

- All patients with a cervix aged 21 through 64 years should be screened regardless of whether they have ever been sexually active.
- Patients who are immunized against HPV should be screened by the same regimen as non-immunized patients.

Table 1. Recommendations for routine cervical cancer screening for patients at average risk

Eligible population	Test(s)	Frequency
Average-risk patients aged 21 through 29 years (See Notes that follow this table.)	Pap test (cytology)	Every 3 years
Average-risk patients aged 30 through 64 years	***Preferred*** Primary hrHPV screening (Self-collect or clinician-collected)	Every 5 years
	Alternative Co-testing (Pap test [cytology] plus hrHPV test)	Every 5 years
	Alternative Pap test (cytology)	Every 3 years

***Notes:* Patients under age 30**

- **Screening test selection:** While the American Cancer Society recommends primary hrHPV screening in average-risk patients starting at age 25, the KPWA guideline team has not adopted these recommendations. There is a high prevalence of HPV in this population, but also a lower risk of cervical dysplasia, as the infection is most likely to clear on its own and not develop into cervical cancer. With the KPWA recommendation of Pap test (cytology) every 3 years with reflex hrHPV testing for ASC-US, fewer patients in this age group will have unnecessary anxiety and procedures than if they were screened with primary hrHPV.
- **New patients who have previously been screened with primary hrHPV:** For patients younger than 30 years who have previously received primary hrHPV screening, this does not technically satisfy current health maintenance reminders, which will flag showing that the patient is due for Pap testing (cytology). However, some external organizations including the American Cancer Society do consider primary HPV screening acceptable starting at age 25, so some patients aged 25–29 may have received primary HPV testing

(without Pap). In this case, if the HPV results were negative, the primary care provider needs to manually satisfy the cervical cancer screening Health Maintenance without resetting the interval. If HPV results were positive, then follow up per ASCCP guidelines.

Who *not* to screen

Patients younger than 21 years: Screening is not recommended for patients younger than 21 years regardless of age at onset of sexual activity, as it may lead to unnecessary and harmful evaluation and treatment in individuals at very low risk of cervical cancer. Findings from observational studies suggest that high-risk HPV infections and cytologic abnormalities are common and transient in patients younger than 21. In addition, CIN 3+ is much less common in the younger cohort. Sexually active patients younger than 21 should be counseled regarding safe sex and contraception, tested for sexually transmitted infections, and offered the HPV vaccine if they haven't yet received it.

Patients aged 65 and older: Screening is generally not recommended for patients aged 65 and older. There is adequate evidence that screening with Pap tests (cytology) in individuals aged 65 and older who have had adequate prior screening and are not otherwise at high risk provides little to no benefit. Adequate prior screening is defined as three or more documented, consecutive, and technically satisfactory normal/negative Pap tests, or two consecutive negative co-tests, with the most recent test occurring within the past 5 years and no abnormal/positive Pap tests within the last 10 years. Patients who have had any abnormal Pap tests in the past 10 years should continue screening.

Patients who have had a hysterectomy that included the removal of the cervix with no prior history of CIN: Screening for cervical cancer is not recommended in women who have had a hysterectomy that included removal of the cervix and **no prior history of CIN**.

Screening recommendations for high-risk populations

All high-risk patients:

- Continue screening ***at least* 25 years**, or as long as patient is in good health. Use shared decision-making about when to discontinue.
- Primary hrHPV screening for high-risk patients must be collected by a provider. Self-collect hrHPV is not recommended in this population.

Table 2. Recommendations for cervical cancer screening for patients at high risk

Patient History	Screening Recommendations
Either of previous 2 hrHPV tests or Pap (cytology) results were abnormal.	Follow 2019 ASCCP app/webtool recommendations.
Recent colposcopy/LEEP/ablation procedure.	Follow 2019 ASCCP app/webtool recommendations.
CIN 2/CIN3/AIS/high-grade dysplasia. [1]	Primary hrHPV (clinician collected) or co-testing every 3 years.
Immunosuppressed patients • HIV-positive status • Solid organ or bone marrow transplant • Inflammatory bowel disease (ulcerative colitis and Crohn's disease) **or** systemic lupus erythematosus **or** rheumatoid arthritis **and** on immunosuppressant treatment (see Table 3). [2]	• Start screening within 1 year of first penetrative intercourse or at age 21 years, whichever comes first. • Screen with Pap test (cytology) annually for 3 years, then every 3 years until age 30. • At age 30, screen with co-testing (not primary hrHPV screening) every 3 years.
Exposed to diethylsylbestrol (DES) in utero. (All patients in this group were born prior to 1971, when DES was banned.)	Annual Pap test (cytology) with 4-quadrant vaginal cytology. Collect cervical sample as usual, and use spatula to sample the upper one-third of the vagina in all 4 quadrants. All specimens can go in the same pap vial.
History of cervical or vaginal cancer.	Annual primary hrHPV (clinician-collected) or co-testing.
History of vulvar cancer.	Refer to OB/GYN.

[1] Based on pathology (not cytology) report, may be reported as HSIL.
[2] Patients who have inflammatory bowel disease, rheumatoid arthritis, or lupus but are **not** on immunosuppressant medications are not considered to be at high risk of cervical cancer. Screen these patients per the recommendations for average-risk patients in Table 1.

Table 3. Immunosuppressants and immunosuppressive treatments		
Calcineurin inhibitors ▪ Tacrolimus ▪ Cyclosporine Cytotoxic agents ▪ Mycophenolate ▪ Azathrioprine ▪ Leflunomide ▪ Chlorambucil ▪ Cyclophosphamide ▪ Mercaptopurine ▪ Methotrexate ▪ Platinum compounds ▪ Fluorouracil ▪ Dactinomycin	mTOR inhibitors ▪ Sirolimus ▪ Everolimus Steroids ▪ Prednisone ▪ Prednisolone ▪ Budesonide ▪ Desamethasone Monoclonal antibodies ▪ Galiximabs ▪ Daclizumab ▪ Muromonab	Biologics ▪ Abatacept ▪ Adalimumab ▪ Anakinra ▪ Apremilast ▪ Certolizumab ▪ Etanercept ▪ Golimumab ▪ Infliximab ▪ Ixekizumab ▪ Natalizumab ▪ Rituximab ▪ Secukinumab ▪ Tocilizumab ▪ Ustekinumab ▪ Vedolizumab

Referral/E-Consult

- Refer to OB/GYN for LEEP or colposcopy if patient is HPV 16/18 positive and Pap (cytology) is HSIL or higher.
- Consider E-Consult with OB/GYN when the appropriate clinical follow-up for patients is unclear for patients at high risk or other special cases.
- For questions about using the ASCCP app or webtool, see the ASCCP app Quick Start Guide: https://www.asccp.org/quickstart

Evidence Summary

To develop the Cervical Cancer Screening Guideline, the guideline team has adapted the following recommendations from externally developed evidence-based guidelines and/or recommendations of organizations that establish community standards:

- 2019 ASCCP Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection
- 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors
- 2018 USPSTF Screening for Cervical Cancer US Preventive Services Task Force Recommendation Statement

Key questions addressed in the KPWA evidence review

Q1: What is the diagnostic accuracy of self-sampled HPV tests compared with clinician-sampled HPV tests for asymptomatic cervical cancer screening?

Q2: What is the accuracy of home-/self-collected HPV tests in high-risk patients (patients with history of CIN, immunosuppression, DES, recent colposcopy/LEEP/ablation procedure)?

A systematic review and meta-analysis (Arbyn 2018) was the principal source of the evidence. The review included 56 diagnostic studies, most of which were cross-sectional. Few studies were retrospective in design. The population consisted of participants presenting for regular cervical cancer screening, others presenting for follow-up at colposcopy clinic. Few studies included high-risk patients. The findings suggest hrHPV testing with an hrHPV assay based on PCR has comparable sensitivity (absolute) for detection of CIN2+ and CIN3+ and is slightly less specific on self- versus clinician-collected samples (sensitivity for CIN2+ 96% versus 96%; sensitivity for CIN3+ 95% versus 96%; specificity for CIN2+ 79% versus 79%; specificity for CIN3+ 86% versus 88%). The relative sensitivity and specificity showed that

hrHPV assays based on PCR were equally sensitive and slightly less specific on self- versus clinician-collected samples. The positive predictive values for CIN2+ or CIN3+ were not significantly lower for self-collected samples.

In high-risk groups, the sensitivity for the detection of CIN2+ using PCR was comparable for self- versus clinician-collected samples (100% versus 100%). The specificity was slightly lower in self-collected samples compared to clinician-collected samples (61% versus 64%).

In summary, low-quality evidence suggests that hrHPV based on PCR is similar in sensitivity for the detection of CIN2+ and CIN3+ and slightly less specific on self-collected versus clinician-collected samples.

An RCT (Polman 2019) with moderate risk of bias demonstrated that the clinical accuracy of primary HPV testing (using PCR-based assay) on self-collected samples is similar to that of physician-collected samples for the detection of CIN2+ or CIN3+.

Q3: What are the factors associated with the uptake of HPV self-sampling?

A systematic review and meta-analysis of 33 studies (Yeh 2019) indicates that HPV self-sampling is significantly associated with high cervical cancer screening uptake compared to standard screening (RR: 2.13; 95% CI, 1.89 to 2.40; I-squared: 99.34), particularly when HPV self-sampling kits are sent directly to women's homes (RR: 2.27; 95% CI, 1.89 to 2.71; I-squared: 99.27) or offered door-to-door by a health worker (RR: 2.37; 95% CI, 1.12 to 5.03; I-squared: 99.72).

Other studies (Pretsch 2023, Xiong 2023, Wong 2020, Winer 2022) suggest that other factors that increase HPV self-sampling include high income, urban settings, age, socioeconomic status, race, time since last cervical cancer screening, Medicaid coverage, and education. Screening uptake seems to be high in all subgroups, but the magnitude of the effects is different. One study (Winer 2022) reported no significant differences in relative effects by race, ethnicity, income, BMI, tobacco use (RR 1.33 to 1.48 across 5-year age groups in women aged 30–54 years versus RR 1.60 in women aged 55–59 years and RR 1.77 in women aged 60–64 years). The findings should be interpreted with caution due to the high risk of bias of the studies.

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Guideline Development Process and Team

Development process

The Cervical Cancer Screening Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

This edition of the guideline was approved for publication by the Guideline Oversight Group in January 2024.

Team

The Cervical Cancer Screening Guideline development team included representatives from the following specialties: clinical lab, family medicine, midwifery, obstetrics/gynecology, pathology, population health, and residency.

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