

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

DRAFT COVERAGE GUIDANCE: CERVICAL CANCER SCREENING

DATE: XX/XX/XXXX

HERC COVERAGE GUIDANCE

Cervical cancer screening should be covered in women 21 to 29 years old with cytology alone, not more than every 3 years.

- HPV testing with or without cytology should not be covered

Cervical cancer screening should be covered in women 30 to 65 years old either with:

- Co-testing not more than every 5 years
- Cytology alone not more than every 3 years

Cervical cancer screening should be covered in women over 65 years old

- Until adequate screening is achieved*
- Until 20 years after regression or appropriate management of a high-grade precancerous lesion

Cervical cancer screening should not be covered for the following populations:

- Women less than age 21
- Women who have had a hysterectomy with removal of cervix for non-cervical cancer related (i.e. high grade precancerous lesion, i.e. CIN 2 or 3, or cervical cancer)
- Women over age 65 who have had adequate prior screening and are not otherwise at high risk of cervical cancer

Specific testing considerations:

- Either liquid based cytology or conventional cytology are appropriate and should be covered.
- HPV testing should not be covered for further triaging when low-grade squamous intraepithelial lesions or higher are diagnosed
- The above recommendations also apply to women who have had abnormal testing but whom are indicated to resume routine screening.**

* Adequate screening is defined as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years of the cessation of screening, with the most recent test occurring within 5 years.

** Management of abnormal cytology and HPV testing is not addressed in this coverage guidance. The United States Preventive Services Task Force refers to the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology guideline (Saslow 2012) to address management of abnormal results.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Health Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Hartmann, K.E., Hall, S.A., Nanda, K., et al. (2002). *Screening for cervical cancer* [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US). Retrieved September 18, 2012, from <http://www.ncbi.nlm.nih.gov/books/NBK42831/>

Moyer, V.A., & U.S. Preventive Services Task Force. (2012). Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, 156, 880-891.

Saslow, D., Solomon, D., Lawson, H.W., Killackey, M., Kulasingam, S.L., Cain, J., et al. (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA: A Cancer Journal for Clinicians*, 62(3), 147-172. doi: 10.3322/caac.21139. Retrieved October 8, 2012, from <http://www.ncbi.nlm.nih.gov/pubmed/22422631>

Vesco, K.K., Whitlock, E.P., Eder, M., Lin, J., Burda, B.U., Senger, C.A., et al. (2011). *Screening for cervical cancer: A systematic evidence review for the U.S. Preventive Services Task Force*. Evidence Synthesis No. 86. AHRQ Publication No. 11-05156-EF-1. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved September 18, 2012, from <http://www.ncbi.nlm.nih.gov/books/NBK66099/>

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Cervical cancer remains a significant public health issue, even though the incidence and associated mortality of cervical cancer have continued to decrease in the United States since the introduction of cervical cytology screening programs in the 1950s and 60s. In 1950, the Centers for Disease Control (CDC) – Vital Statistics of the United States reported a death rate of 10.2 per 100,000 for white women, while in 2007 the mortality rate had dropped to 2.2. Incidence varies significantly by age and race/ethnicity.

Cervical cancer does not develop suddenly and is preceded by precancerous changes of the cervix. Precancerous changes of the cervix are histologically defined as cervical intraepithelial neoplasia (CIN) and are identified at varying levels of severity: CIN1, CIN2, and CIN3. The latter includes carcinoma in situ. Progression of neoplasia to invasive cervical cancer is slow. The rate of progression of CIN3 to cancer has recently been estimated as 31.3% in 30 years.

It is well recognized that infection with oncogenic human papilloma virus (HPV) is a necessary, although not sufficient, cause of virtually all cervical cancer. While there are multiple types of HPV, types 16 and 18 alone are responsible for approximately 70% of cervical cancer cases, and HPV is present in 99.7% of cases. The progression from HPV infection to cervical cancer occurs over a series of four steps: 1) HPV transmission, 2) acute HPV infection, 3) persistent HPV infection leading to precancerous changes, and 4) invasive cervical cancer. A high proportion of sexually active women become infected with HPV, but only a small proportion of HPV infections become persistent. Among 4,504 women aged 18 years and older with a cytologic diagnosis of atypical squamous cells of uncertain significance or low-grade squamous intraepithelial lesion, 91% of prevalent HPV infections detected at enrollment cleared within 24 months. These data illustrate that HPV infections are very likely to regress, and persistence of HPV infection is more likely to occur in older women. Numerous analyses, including large cohort studies, have demonstrated that CIN not only progresses, but may also regress. Newer data suggest that CIN1 does not predict any meaningful risk of CIN3.

While it is estimated that around 80% of US women have had cervical cytology screening within the past three years, screening history varies by educational attainment, race/ethnicity, and age. While the great majority of US women have had recent cytology screening, the majority of cervical cancer cases occur in those without such a history.

With regard to screening methods, liquid-based cytology differs from conventional cytology in how the cervical specimen is sent to the cytology laboratory for evaluation. For conventional cytology, the cervical specimen is smeared onto a glass slide immediately after collection and the slide is either sprayed with or placed in fixative. For liquid-based cytology, the sample collected from the cervix is suspended in fixative, then collected by filtration on a membrane, and then transferred onto a microscope slide in a monolayer.

In recent years, high-risk HPV testing has been incorporated into screening and screening triage algorithms, as either a combined test (with cytology, co-test) to determine rescreening interval in women who are cytology negative, or as one possible triage strategy to determine colposcopy. There are many methods available for detecting HPV, including in situ hybridization, polymerase chain reaction, and Hybrid Capture (HC2) technology.

Evidence Review

US Preventive Services Task Force Clinical Considerations

Patient Population under Consideration

This recommendation statement applies to all women who have a cervix, regardless of sexual history. This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

Screening Tests

The effectiveness of cervical cancer screening observed in the United States over the past several decades is attributed to the use of conventional cytology. Current evidence indicates that there are no clinically important differences between liquid-based cytology and conventional cytology. The USPSTF realizes that the choice of cytology method may not be under the direct control of the clinician and considers cytology screening in appropriate age groups at appropriate intervals to be of substantial net benefit, regardless of method. Human papillomavirus testing with Digene Hybrid Capture 2 (HC2) (Qiagen, Germantown, Maryland) is commonly used in the United States, and both HC2 and polymerase chain reaction– based methods have been evaluated in effectiveness trials. Although alternative HPV detection methods are emerging, the clinical comparability and implications of these methods are not completely understood.

Screening Interval

Screening women aged 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms. Among women aged 30 to 65 years, HPV testing combined with cytology (co-testing) every 5 years offers a comparable balance of benefits and harms and is therefore a reasonable alternative for women in this age group who would prefer to extend the screening interval. Screening with cytology more often than every 3 years confers little additional benefit, with large increases in harms, including additional procedures and assessment and treatment of transient lesions. Treatment of lesions that would otherwise resolve on their own is harmful because it can lead to procedures with unwanted side effects, including the potential for cervical incompetence and preterm labor. Similarly, HPV testing with cytology should not be done more often than every 5 years to maintain a reasonable balance of benefits and harms similar to that seen with cytology alone every 3 years. Among women younger than 30 years, there is adequate evidence that screening with HPV testing (alone or in combination with cytology) confers little to no benefit, and that

the harms of HPV testing in this age group are moderate. Therefore, routine screening with HPV in this population is not recommended.

Maintaining the comparability of the benefits and harms of co-testing and cytology alone demands that patients, clinicians, and health care organizations adhere to currently recommended screening intervals, protocols for repeated testing, cytologic thresholds for further diagnostic testing (that is, colposcopy) and treatments, and extended surveillance as recommended by current American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP) guidelines. Women who choose co-testing to increase their screening interval (and potentially decrease testing) should be aware that positive screening results are more likely with HPV-based strategies than with cytology alone and that some women may require prolonged surveillance with additional frequent testing if they have persistently positive HPV results. Because HPV test results may be positive among women who would otherwise be advised to end screening at age 65 years on the basis of previously normal cytology results alone, the likelihood of continued testing may increase with HPV testing. The percentage of US women undergoing co-testing who will have a normal cytology test result and a positive HPV test result (and who will therefore require additional testing) ranges from 11% among women aged 30 to 34 years to 2.6% among women aged 60 to 65 years.

Triage of Women with Atypical Squamous Cells of Uncertain Significance

For the triage of women with atypical squamous cells of uncertain significance cytology to colposcopy, a single HC2 test has a higher sensitivity and similar specificity compared to single repeat cytology at a threshold of atypical squamous cells of uncertain significance for the detection of CIN2+. No additional benefit occurs when HC2 triage is combined with cytology, but this strategy increases false positives. The HC2 does not appear useful for the triage of women with low-grade squamous intraepithelial lesion cytology because such a high proportion of women will test positive. Human papilloma virus testing has few unique harms compared with cytology screening, but a positive HPV test may increase anxiety and distress, in the short-term only.

Timing of Screening

Women Younger Than Age 21 Years

Cervical cancer is rare before age 21 years. The USPSTF found little evidence to determine whether and how sexual history should affect the age at which to begin screening. Although exposure of cervical cells to sexually transmitted HPV during vaginal intercourse may lead to cervical carcinogenesis, the process has multiple steps, involves regression, and is generally not rapid. There is evidence that screening earlier than age 21 years, regardless of sexual history, would lead to more harm than benefit. The harms are greater in this younger age group because abnormal test results are likely to be transient and to resolve on their own; in addition, treatment may have an adverse effect on childbearing.

Women Older Than Age 65 Years

Clinicians and patients should base the decision to end screening on whether the patient meets the criteria for adequate prior testing and appropriate follow-up per established guidelines. The ACS/ASCCP/ASCP guidelines define adequate prior screening as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years before cessation of screening, with the most recent test occurring within 5 years. They further state that routine screening should continue for at least 20 years after spontaneous regression or appropriate management of a high-grade precancerous lesion, even if this extends screening past age 65 years. The ACS further states that screening should not resume after cessation in women older than age 65 years, even if a woman reports having a new sexual partner.

Women Older Than Age 65 Years Who Have Never Been Screened

Screening may be clinically indicated in older women for whom the adequacy of prior screening cannot be accurately accessed or documented. Women with limited access to care, minority women, and women from countries where screening is not available may be less likely to meet the criteria for adequate prior screening. The USPSTF realizes that certain considerations may support screening in women older than age 65 years who are otherwise considered high risk (such as women with a high grade precancerous lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised).

Assessment of Risk

It is well-established that HPV infection is associated with nearly all cases of cervical cancer. Other risk factors include HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer. Women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion or cervical cancer are not at risk for cervical cancer and should not be screened. Women who had their cervix removed during surgery for ovarian or endometrial cancer are not at high risk for cervical cancer and would not benefit from screening. Clinicians should confirm through review of surgical records or direct examination that the cervix was removed.

Recommendations

These recommendations apply to women who have a cervix, regardless of sexual history. These recommendations do not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

- The USPSTF recommends screening for cervical cancer in women ages 21 to 65 years with cytology (Pap smear) every 3 years or, for women ages 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. Grade: [A Recommendation](#).

- The USPSTF recommends against screening for cervical cancer in women younger than age 21 years. Grade: [D Recommendation](#).
- The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Grade: [D Recommendation](#).
- The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer. Grade: [D Recommendation](#).
- The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years. Grade: [D Recommendation](#).

Overall Summary

A reasonable age at which to initiate cervical cancer screening in women is age 21. For cytology-based screening, liquid-based cytology does not differ from conventional cytology in sensitivity, specificity, or relative CIN detection. Screening women aged 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms. Among women aged 30 to 65 years, HPV testing combined with cytology (co-testing) every 5 years offers a comparable balance of benefits and harms. Screening with cytology more often than every 3 years confers little additional benefit, with large increases in harms. Among women younger than 30 years, screening with HPV testing (alone or in combination with cytology) confers little to no benefit but has moderate harms. Treatment of lesions that would otherwise resolve on their own is harmful because it can lead to procedures with unwanted side effects, including the potential for cervical incompetence and preterm labor. For the triage of women with atypical squamous cells of uncertain significance cytology to colposcopy, a single HC2 test has a higher sensitivity and similar specificity compared to single repeat cytology, but there are no additional benefits when HC2 triage is combined with cytology. The HC2 is not useful for the triage of women with low-grade squamous intraepithelial lesion cytology. It is reasonable to discontinue routine cervical cancer screening for women older than age 65 years who have had adequate screening with negative results and who are not otherwise at high risk for cervical cancer, and for women who have undergone a hysterectomy in which the cervix was removed, unless it was performed because of cervical cancer.

PROCEDURE

Pap smear
HPV testing

DIAGNOSES

Cervical cancer screening

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
V76.2	Special screening for malignant neoplasms; cervix
V73.81	Special screening for viral and chlamydial diseases; human papilloma virus
079.4	Viral and chlamydial infection in conditions classified elsewhere; HPV
795.0	Abnormal PAP smear of cervix and cervical HPV
ICD-9 Volume 3 (Procedure Codes)	
None	
CPT Codes	
88141	Cytopathology, cervical or vaginal, requiring interpretation by physician
88142-3	Cytopathology, cervical or vaginal, collected in preservative fluid, manual screening
88147-8	Cytopathology smears, cervical or vaginal
88150-4	Cytopathology slides, cervical or vaginal
88164-7	Cytopathology slides, cervical or vaginal, Bethesda system
88174-5	Cytopathology, cervical or vaginal, collected in preservative fluid, automated screening
87620	Detection infectious agent by probe technique; HPV, direct
87621	Detection infectious agent by probe technique; HPV, amplified
HCPCS Codes	
G0123-4	Screening cytopathology, cervical or vaginal, collected in preservative fluid, automated thin-layer prep
G0141	Screening cytopathology, cervical or vaginal, requiring interpretation by physician
G0143-5	Screening cytopathology, cervical or vaginal, collected in preservative fluid, automated thin-layer prep
G0147-8	Screening cytopathology smears, cervical or vaginal

Note: Inclusion on this list does not guarantee coverage

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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