Test Specific Guidelines

Human Papillomavirus (HPV) Molecular Testing

MOL.CS.362.A
v1.0.2023

Introduction

Molecular testing for human papillomavirus-related conditions is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Human Papillomavirus (HPV), high-risk types (for example, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)	87624 G0476
Human papillomavirus (HPV), high-risk types (ie, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), male urine	0096U
Human Papillomavirus (HPV), low-risk types (for example, 6, 11, 42, 43, 44)	87623
Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed	87625
Immunohistochemistry, each additional single antibody stain procedure (eg p16)	88341
Immunohistochemistry or immunocytochemistry per specimen, initial single antibody stain procedure (eg p16)	88342
In situ hybridization (eg FISH) per specimen; initial single probe stain procedure (eg p16)	88365
In situ hybridization; each additional single probe stain procedure (eg p16)	88364
Infectious agent detection by nucleic acid (DNA or RNA), human papillomavirus (HPV) for five or more separately reported highrisk HPV types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, 68) (ie, genotyping)	0500T

Procedures addressed by this guideline	Procedure codes
PreTect HPV-Proofer' 7	0354U

What Is Human Papillomavirus?

Definition

There are more than 1000 types of Human Papillomavirus (HPV), with about 40 of them transmitted through sexual contact.[1,2]

HPV infection commonly clears on its own without treatment, but it can persist in some individuals. Persistent genital HPV infection can cause genital warts and cervical cancer.[2] Persistent oral HPV infection can cause oropharyngeal cancer (cancer of the base of the tongue or back of the throat).[1]

HPV can be classified as high risk or low-risk genotype based on the association of that virus with cancer risk. The most common high-risk HPV genotypes are 16 and 18, although several others have been identified (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Low-risk genotypes (including 6, 11, 42, 43, 44) are not associated with cancer risk.

Indications for HPV testing include cervical cancer screening and evaluation of oropharyngeal cancer.

Test Information

Introduction

Molecular testing for HPV-related conditions may include nucleic acid testing, immunohistochemistry, in-situ hybridization, or other specialized molecular studies.

Nucleic acid testing amplifies a microorganism’s DNA or RNA to directly identify specific viral strains, rather than standard microorganism detection techniques such as direct fluorescent antibody testing, rapid antigen testing, qualitative and quantitative immunoassay for identification of antigens, and single-plex PCR assays. This technology offers results in a matter of hours, rather than 2-3 days of time consuming and labor-intensive immunoassays.

In-situ hybridization (ISH) involves using synthesized single stranded DNA or RNA probes to detect the genetic material of a virus within a cell.

Immunohistochemistry (IHC) is used to determine the expression of biomarkers in tissue. Antibodies that detect specific antigens (proteins, biomarkers) are applied to the tissue and attach to their target antigen. The antibodies are tagged with a visible label that allows the pattern of distribution in the tissue to be directly visualized under a microscope.

IHC for p16 can be a good surrogate for HPV status in oropharyngeal cancers.[3,4] Cancers can be p16 positive/HPV negative, and vice versa, however.[4] For this reason, multiple test modalities may be employed.[4,5]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to molecular testing for HPV for cervical cancer screening and evaluation of oropharyngeal cancer.

American Cancer Society

In a 2020 update to the jointly published screening guideline by the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) (see below), the ACS recommended the following in regard to human papillomavirus testing:[6]

The ACS defines a primary HPV test as one that detects high-risk HPV genotypes (HPV types 16 and 18).

"The ACS recommends that individuals with a cervix initiate cervical cancer screening at age 25 y and undergo primary HPV testing every 5 y through age 65 y (preferred). If primary HPV testing is not available, individuals aged 25□65 y should be screened with cotesting (HPV testing in combination with cytology) every 5 y or cytology alone every 3 y (acceptable) (strong recommendation)."

"Cotesting or cytology testing alone are included as acceptable options for cervical cancer screening because access to primary HPV testing with a test approved by the FDA for primary screening may be limited in some settings. As the United States makes the transition to primary HPV testing, the use of cotesting or cytology alone for cervical cancer screening will be eliminated from future guidelines."

The ACS (2020) stated the following regarding routine HPV screening for purposes other than cervical cancer screening:[7]

"The FDA has only approved tests to find HPV in individuals with a cervix, where positive results can be managed with extra testing and prompt treatment if the infection causes abnormal cell growth. Although HPV tests might be used in research studies to look for HPV in other sites, there's no proven way to manage positive findings."

"Finally there's no useful test to find out a person's "HPV status," because an HPV test result can change over a period of months or years as the body fights the virus".

American Cancer Society, American Society for Colposcopy and Cervical

Pathology, and American Society for Clinical Pathology

In a jointly published screening guideline, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (2012) stated:[8]

"Women aged 30 to 65 years should be screened with cytology and HPV testing ("cotesting") every 5 years (preferred) or cytology alone every 3 years (acceptable). There is insufficient evidence to change screening intervals in this age group following a history of negative screens."

"In most clinical settings, women aged 30 years to 65 years should not be screened with HPV testing alone as an alternative to cotesting at 5-year intervals or cytology alone at 3-year intervals."

"Recommended screening practices should not change on the basis of HPV vaccination status."

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2021) released a Practice Advisory endorsing the endorsing the U.S. Preventive Services Task Force (USPSTF, 2018; see below) cervical cancer screening recommendations. The advisory stated:[9]

"The adoption of the USPSTF guidelines expands the recommended options for cervical cancer screening in average-risk individuals aged 30 years and older to include screening every 5 years with primary high-risk human papillomavirus (hrHPV) testing."

"Primary hrHPV testing uses high-risk HPV testing alone (no cytology) with a test that is approved by the U.S. Food and Drug Administration (FDA) for stand-alone screening."

"Consistent with prior guidance, screening should begin at age 21 years, and screening recommendations remain unchanged for average-risk individuals aged 21–29 years and those who are older than 65 years."

The ACOG advisory has been endorsed by the American Society for Colposcopy and Cervical Pathology (ASCCP) and the Society of Gynecologic Oncology (SGO).

American Society for Colposcopy and Cervical Pathology

In a 2019 update to the jointly published screening guideline by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology, the American Society for Clinical Pathology (ASCCP) stated:[10]

"Human papillomavirus assays that are Food and Drug Administration (FDA)-approved for screening should be used for management according to their regulatory approval in the United States. (Note: all HPV testing in this document refers to testing for high-risk HPV types only)."

"Repeat HPV testing or cotesting at 1 year is recommended for patients with minor screening abnormalities indicating HPV infection with low risk of underlying CIN 3+ (e.g., HPV-positive, low-grade cytologic abnormalities after a documented negative screening HPV test or cotest)."

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2018) endorsed the College of American Pathologists guideline on HPV testing in individuals with head and neck cancer.[5] The ASCO published endorsement included the following qualifying statements:[11]

"A small fraction of oropharyngeal tumors are not etiologically driven by HPV yet overexpress p16. Pathologists should be experienced with and have available confirmatory HPV testing."

"When oropharyngeal tumors are poorly differentiated and there is uncertainty that the carcinoma is nonsquamous, for example with neuroendocrine tumors, HPV tumor testing is warranted."

"Additional HPV testing on p16-positive cases should be performed for tumors located outside of level II or III (nonroutine testing) in the neck and/or for tumors with keratinizing morphology. ASCO qualifying statement: p16 IHC alone may not be sufficient in this scenario. Additional confirmatory testing should be performed at the discretion of the pathologists and/or clinician. ASCO recommends HPV tumor detection for unknown primary in head and neck squamous cell cancer independent of keratinizing morphology."

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC, 2021) Sexually Transmitted Diseases Treatment Guidelines recommended the following in regard to human papillomavirus testing:[12]

"No HPV test can determine which HPV infection will clear and which will progress. However, in certain circumstances, HPV tests can determine whether a woman is at increased risk for cervical cancer. These tests are not for detecting other HPV-related problems, nor are they useful in women aged <25 years or men of any age."

"The role of testing for non-oncogenic HPV types (e.g., 6 and 11) is unclear and is not recommended."

"Oncogenic high-risk HPV infection (e.g., HPV types 16 and 18) causes most cervical, penile, vulvar, vaginal, anal, and oropharyngeal cancers and precancers

(760), whereas nononcogenic, low-risk HPV infection (e.g., HPV types 6 and 11) causes genital warts and recurrent respiratory papillomatosis."

"Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. "

College of American Pathologists

The College of American Pathologists (CAP, 2018) stated the following regarding HPV testing in individuals with head and neck cancers:[5]

"Pathologists should perform HR-HPV [high risk-HPV] testing on all patients with newly diagnosed OPSCC [oropharyngeal squamous cell carcinoma], including all histologic subtypes. This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary. The strength of evidence is convincing to support this guideline statement." (Strong Recommendation)

"For oropharyngeal tissue specimens (ie, noncytology), pathologists should perform HR-HPV testing by surrogate marker p16 IHC. Additional HPV-specific testing may be done at the discretion of the pathologist and/or treating clinician, or in the context of a clinical trial." (Recommendation)

"Pathologists should not routinely perform HR-HPV testing on patients with nonoropharyngeal primary tumors of the head and neck." (Recommendation)

"Pathologists should routinely perform HR-HPV testing on patients with metastatic SCC [squamous cell carcinoma] of unknown primary in a cervical upper or mid jugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended." (Recommendation)

In its guideline, CAP described the role of HPV testing in oropharyngeal squamous cell carcinoma (OPSCC) to be primarily prognostic in nature:

"Human papillomavirus status of a primary or metastatic OPSCC may have diagnostic staging, and even therapeutic implications. Currently, however, the call for routine HPV testing reflects its standing as a powerful prognostic indicator for patients with OPSCC."

CAP also suggested that HPV testing in the OPSCC setting may serve as an aid in identifying the site of a primary neoplasm in those presenting with metastatic disease:

"Unknown primary is defined as any metastasis for which the primary site has not been clinically identified at the time the biopsy of the metastasis is performed. In this setting, HR-HPV testing may aid in determining the most likely primary site. Hence, HR-HPV status is important for patient management as it informs the clinical team where to search for the primary, or limits the likely area of primary if a definitive lesion is not identified."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) clinical practice guidelines for head and neck cancer stated the following regarding HPV testing in oropharyngeal cancer:[3]

NCCN guidelines regarding cancers of the oropharynx (base of tongue, tonsil, posterior pharyngeal wall, and soft palate) consider tumor HPV testing by p16 immunohistochemistry to be a required part of the workup as management and staging differ between HPV positive and negative tumors.

"A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by IHC is a widely available surrogate biomarker that has very good agreement with HPV status as determined by the gold standard of HPV E6/E7 mRNA expression [Jordan et al., 2012; Weinberger et al., 2006; Cantley et al., 2011]. Other tests include HPV detection through PCR and in situ hybridization (ISH) [Jordan et al., 2012; Cantley et al., 2011]."

"Due to variations in sensitivity and specificity values of testing options, multiple methods may be used in combination for HPV detection, but HPV detection through PCR and ISH may provide additional sensitivity for the former and specificity for the latter in the case of an equivocal p16 or unclear scenario [Cantley et al., 2011; Singhi et al., 2010; Thavaraj et al., 2011; Snow et al., 2010]."

"A small proportion of tumors at non-oropharyngeal sites (eg, paranasal sinus, oral cavity, larynx) are HPV-related. However, given the small proportion and lack of consistent evidence in support of prognostic significance, routine HPV testing or p16 testing or non-oropharyngeal cancers is not recommended."

U.S. Preventive Services Task Force

With regard to cervical cancer screening, the U S. Preventive Services Task Force (USPSTF, 2018) recommended the following:[13]

The USPSTF recommends screening by cervical cytology alone in women aged 21-29 years. HPV testing for screening purposes is not recommended in this age group.

With regard to screening for oral cancer, the USPSTF (2013) recommended the following:[14]

"Oropharyngeal cancer, another subset of neck and head cancer, includes human papillomavirus (HPV) as an important risk factor. The incidence and mortality rate of oral cancer has been decreasing in the United States presumably because of reduced tobacco and alcohol use. However, HPV-related oropharyngeal cancer is increasing in incidence. Oropharyngeal cancer includes lesions of the tonsil, oropharynx, and base of the tongue."

"Patients with HPV-positive oropharyngeal cancer are diagnosed an average 5 years younger and have better survival than patients with HPV-negative oral cancer [Blott et al., 1988]."

"Although there is interest in screening for oral HPV infection, medical and dental organizations do not recommend it. Currently, no screening test for oral HPV infection has been approved by the U.S. Food and Drug Administration (FDA). Evaluating the accuracy of tests that detect oral HPV infection is a potentially promising area of research."

World Health Organization

The World health Organization (WHO, 2021) guideline for screening and treatment of cervical cancer stated:[15]

"WHO recommends using HPV DNA detection as the primary screening test rather than VIA [visual inspection with acetic acid] or cytology in screening and treatment approaches among both the general population of women and women living with HIV.* [Strong recommendation, moderate-certainty evidence]"

"WHO recommends starting regular cervical cancer screening at the age of 30 years among the general population of women. [Strong recommendation, moderate-certainty evidence]"

"WHO suggests a a regular screening interval of every 5 to 10 years when using HPV DNA detection as the primary screening test among the general population of women. [Conditional recommendation, low-certainty evidence]"

Selected Relevant Publications

While there are published guidelines that recommend HPV testing to determine the origin of a cancer that has metastasized to the oropharynx or cervical lymph nodes, it has been demonstrated that as many as 41% of oropharyngeal squamous cell carcinomas will be HPV negative at time of diagnosis and that 42% of OPSCC that exhibit disease progression are HPV negative.[16,17] Hence, HPV testing may not be a reliable indicator of a cancer's site of origin.

Criteria

Introduction

Requests for molecular testing for HPV are reviewed using these criteria.

Screening for Cervical Cancer

Nucleic acid amplification testing (NAAT) for human papillomavirus high-risk genotypes (87624, 87625, G0476) is considered medically necessary for individuals with clinical indications as outlined here.

Indications for testing in asymptomatic individuals:

Screening for cervical cancer is recommended every 3 years by cervical cytology alone. HPV testing to screen for cervical cancer should not be performed in women under age 25 years.

Among women age 25 years - 65 years:

High-risk HPV testing alone may be performed every 5 years, or

High-risk HPV testing may be performed every 5 years in combination with pap smear (co-testing) for routine screening.

Women aged 25 years and older who are HPV positive but cytology negative may:

Test again by co-testing in one year, or

Be tested by HPV high-risk oncogenic subtype genotyping.

Women aged 25 years and older with cytology reported as negative and with absent or insufficient endocervical/transformation zone (EC/TZ) component and no or unknown HPV test result.

Indications for testing in symptomatic individuals:

Reflex to HPV testing for management of women with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results starting at age 21 years.

Co-testing at 1 year post cervical intraepithelial neoplasia grade 1 (CIN1) or no lesion preceded by HPV-16 or HPV-18 positivity, persistent untyped oncogenic HPV, ASC-US, and low grade squamous intraepithelial lesion (LSIL) starting at age 25 years.

For women treated for cervical intraepithelial neoplasia (CIN 2, CIN 3, or CIN 2, 3), co-testing at 12 months and 24 months is recommended.

Post-menopausal women with LSIL.

Exclusions

Medical necessity of the following methods for HPV detection has not been demonstrated and is therefore determined to be investigational and experimental.

Flow cytometry (e.g., HPV OncoTect) (CPT 88184, 88185, and/or 88187).

PreTect HPV-Proofer' 7 (CPT 0354U)

Billing and reimbursement considerations

When testing is medically necessary, the following limitations apply:

Nucleic acid amplification test (NAAT) may be performed on endocervical samples. It is typically sufficient to test one specimen. Therefore, no more than 1

unit of CPT 87624 or 87625 for human papillomavirus molecular testing may be billed for the same date of service.

More than one type of molecular test for the same organism will not be reimbursed for the same date of service. For example, nucleic acid detection of high risk subtypes HPV-16 and HPV-18 by two methodologies (CPT 87624 and 87625) cannot be billed together, and nucleic acid detection by either of these methodologies cannot be billed with a test using another molecular methodology (e.g., in situ hybridization, CPT 88365).

Genitourinary Conditions: Exclusions

HPV testing in individuals without a cervix is not currently supported in clinical practice guidelines for genitourinary disorders. In addition, there is no standard of care for managing positive results. Therefore, HPV testing for genitourinary disorders in individuals without a cervix (e.g. CPT 0096U) is considered not medically necessary.

Medical necessity of testing for low-risk (non-oncogenic) types of HPV (e.g. CPT 87623) has not been demonstrated, and is therefore determined to be investigational and experimental. This procedure code is not eligible for reimbursement for any clinical indications, including but not limited to cervical cancer screening and anogenital wart diagnosis.

Evaluation of Oropharyngeal Cancer

HPV testing is considered medically necessary when:

Member has established squamous cell carcinoma involving the oropharynx or cervical lymph nodes, AND

No p16 immunohistochemistry testing has been successfully performed for this occurrence of oropharyngeal cancer, and/or

No previous high-risk HPV testing by PCR or in situ hybridization has been successfully performed for this occurrence of oropharyngeal cancer, AND

Test result is required to determine treatment, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and reimbursement considerations

p16 immunohistochemistry, HPV in situ hybridization, and high-risk HPV genotyping are allowed once per occurrence of an oropharyngeal or cervical lymph node squamous cell carcinoma. Repeat testing for high-risk HPV by any method in the case of disease recurrence is not reimbursable if testing was previously performed on the primary tumor.

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Introduction

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