# Human Papillomavirus Testing in Men

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**Despite the morbidity associated with anogenital condylomas and the mortality associated with anal, penile, and cervical carcinoma as a direct consequence of human papillomavirus (HPV), the US Centers for Disease Control and Prevention currently does not recommend routine screening for HPV in immunocompetent men. However, findings of emerging research focusing on the high-risk populations of men who have sex with men and men who test positive for human immunodeficiency virus, in whom HPV infection is pervasive and persistent, suggest that these populations may benefit from screening. Therefore, HPV screening, including anal cytology, should be considered for these men in settings where appropriate follow-up, including high-resolution anoscopy, is available.**

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Human papillomavirus (HPV) is the most common sexually transmitted disease worldwide, with more than 100 types of HPV identified.[1] Approximately 30 HPV types affect the anogenital area.[1] More than 99% of cervical cancers and approximately 88% of anal cancers are associated with HPV; the most common oncogenic subtypes are 16 and 18.[2-4] Anogenital HPV is categorized as latent (asymptomatic), clinical, or subclinical. Most cases of HPV infection are latent, transient, and detectable only with tests for viral DNA, enabling HPV to be transmitted unknowingly among millions of sexually active adults. Clinical lesions, most commonly caused by HPV types 6 and 11, are visibly apparent and result in anogenital condylomas, or *condylomata acuminata*, rather than malignancies.[1] Subclinical lesions, including the oncogenic types of HPV, are identified on examination after the application of acetic acid solution (3%-5%), a procedure known as acetowhitening. Using this technique, researchers have documented that 50% to 77% of steady male partners of women with HPV infection, cervical neoplasia, or both have subclinical HPV infection.[5]

Despite the morbidity associated with anogenital condylomas and the mortality associated with anal and cervical carcinomas as direct consequences of HPV infection, the US Centers for Disease Control and Prevention currently does not recommend screening men for HPV.[6] The infectious disease literature supports this stance on several grounds: the high prevalence of infection, the lack of a test approved by the US Food and Drug Administration for the detection of HPV in men, and the absence of adequate therapy for established infection.[7] Effective treatment algorithms for cervical Papanicolaou tests, HPV DNA testing, and colposcopy have been endorsed for women because of the contribution of HPV infection to cervical dysplasia and carcinoma, but similar rec-

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ommendations are lacking for men. Although routine HPV testing is not necessary for men in the general population, findings from emerging research in high-risk populations of men who have sex with men (MSM) and men who test positive for human immunodeficiency virus (HIV) suggest that HPV infection is pervasive and persistent in these groups, warranting the adoption of additional screening measures.

## Association of HPV Infection With Penile and Anal Carcinoma

Studies have demonstrated that HPV is an etiologic factor in the development of penile cancer, penile intraepithelial neoplasia (PIN), anal cancer, and anal intraepithelial neoplasia (AIN).[8] The American Cancer Society estimated that approximately 1250 new cases of penile cancer would be diagnosed and 310 men would die of penile cancer in the United States in 2010.[9] Although the prevalence of HPV DNA in penile carcinoma is 40% to 45%,[10] HPV DNA has been isolated in 75% of patients with grade 1 PIN, 93% of patients with grade 2 PIN, and 100% of patients with grade 3 PIN.[11]

Regarding anal cancer, the American Cancer Society estimated that approximately 5260 new cases (3260 in women and 2000 in men) would be diagnosed and 720 people (440 women and 280 men) would die of the disease in the United States in 2010.[12] Eighty-eight percent to 94% of anal carcinomas are associated with HPV,[13] and HPV DNA has been identified in up to 98% of patients with grade 2 or 3 AIN.[14]

## HPV DNA Testing

Among immunocompetent heterosexual men, numerous studies have documented HPV infection rates of approximately 65%.[15,16] Research involving the distribution of HPV infection by anogenital anatomic site in heterosexual men has been conducted and reveals the penile shaft to be the most common site of infection.[17] Optimal HPV sample collection methods have also been researched; the method with the most diagnostic sensitivity involves running an emery board across the skin at multiple sites followed by a wet Dacron swab to collect cells.[17] Although 3 HPV DNA testing kits are commercially available for use in women (Hybrid Capture II [Digene Corporation, Gaithersburg, Maryland], Cervista HPV HR and Cervista HPV 16/18 [Hologic Inc, Bedford, Massachusetts]), none are approved by the Food and Drug Administration for use in men.[18]

As epidemiologic research continues to identify MSM and HIV-positive men as high-risk subgroups for HPV infection and anal cancer, questions persist regarding the need for HPV testing in this cohort. Although HPV infection is generally transient in immunocompetent heterosexual men, persistent HPV infection is common in HIV-positive MSM.[15] The prevalence of HPV infection of the anal canal in HIV-positive MSM is greater than 90%.[14,19] A study enrolling 323 HIV-positive MSM in San Francisco County, California, found that the presence of HPV infection increased the risk of AIN 15-fold.[14] The incidence of anal cancer and AIN among MSM is 25 to 50 times higher than in the general population.[20] Subsequent research involving HIV-positive MSM undergoing both HPV genotyping and anal cytology did not find HPV genotyping to be a valuable adjunct to cytologic screening; the efficacy of anal cytology in detecting cellular atypia was adequate without the contribution of HPV typing.[21]

## HPV Screening Through Anal Cytology

Researchers have proposed that an anal cancer screening program similar to cervical cancer screening, using anal cytology followed by referral of patients with abnormal results to high-resolution anoscopy and subsequent treatment of biopsy-proved AIN, may prevent the development of anal cancer.[20] The reported sensitivity and specificity of anal cytology relative to findings at biopsy (sensitivity, 69%-93%; specificity, 32%-59%, respectively) are similar to findings in studies comparing cervical cytology and cervical biopsy for the prevention of cervical cancer.[15] Although the Centers for Disease Control and Prevention does not recommend anal cytology screening, other organizations such as the New York State Department of Health do recommend annual anal cytology for MSM and any HIV-positive patients with a history of anogenital condylomas.[22] Among patients with HIV- or HPV-related lesions, histologic signs of dysplasia are apparent in more than one-fifth of those who undergo testing.[23] Among HIV-positive MSM, the positive predictive value of abnormal anal cytology to predict anal dysplasia is approximately 95%.[15]

The goal of anal cytology is to identify patients with cellular changes in the epithelial cells that line the anal canal; any patients with atypia are then referred to undergo high-resolution anoscopy. No specific preparation is necessary before anal cytology, though patients should be instructed to refrain from receptive anal sex and enemas for 24 hours before testing. If a digital rectal examination is performed in conjunction with anal cytology, the cytologic sample must be obtained before lubrication is introduced into the anal canal. The standard technique used in obtaining anal cytologic specimens involves inserting a water-moistened Dacron swab into the anal canal to above the squamocolumnar transition zone, approximately 2 cm (1 inch) from the anal verge. While mild external pressure is applied to the anal wall, the swab is gently manipulated in a craniocaudal and circular motion within the canal. After several rotations, the swab should be withdrawn and immediately immersed in methanol-based preservative-transport solution.[22]

Studies have also been conducted to evaluate the sensitivity of patient-collected samples. In a cohort study, HIV-positive patients with AIN at the University of California, San Francisco, were provided with written instructions and a cytology self-collection kit; self-collected samples were obtained within 1 month of clinician-collected samples. Approximately 91% of self-collected and 99% of clinician-collected samples were adequate for interpretation.[24] Although self-collection of anal cytologic samples may broaden screening to a larger popula-

tion, the availability of adequate follow-up and high-resolution anoscopy varies. Anal cytology should be offered only in areas where appropriate further diagnostic and therapeutic treatment alternatives are available, including high-resolution anoscopy.

## Penile HPV Screening

Penile screening for HPV is not recommended because of the high prevalence of penile HPV and the generally self-limited duration of infection in immunocompetent men.[7] In contrast to AIN and anal cancer, very little data are available regarding the natural history of HPV infection and the development of PIN or penile cancer in MSM or HIV-positive men.[15] Unlike AIN, PIN cannot be diagnosed by cytology; any suspicious penile lesion requires biopsy for pathology.

## Conclusion

There is currently no widely recognized role for HPV testing in men, but the contribution of HPV infection to the development of AIN and anal carcinoma in MSM and HIV-positive men is clinically significant. Screening measures, including anal cytology, should be considered for this population in settings where appropriate follow-up is available, including high-resolution anoscopy and treatment of biopsy-proved AIN. Before definitive guidelines on the role of anal cytology can be offered, more studies are needed to elucidate the role of early detection of AIN and the effects of AIN treatment on disease progression to invasive carcinoma.

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