Anal Cancer and Screening Guidelines for Human Papillomavirus in Men

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The association between human papillomavirus (HPV) and anal cancer and the similarities between the “transitional zones” within the cervix and anus have raised questions regarding the medical biology of anal cancer. In recent years, increased rates of HPV infection and anal cancer among men have encouraged the medical community to search for causes and ways to identify the less insidious precursor, anal intraepithelial neoplasia. The “alphabet soup” terminology describing anal cytologic findings obtained by Papanicolaou (Pap) tests and the anal histologic findings obtained from biopsy specimens need to be better understood as distinct entities. Risk factors for the development of anal cancer have been identified and should be discussed with patients—especially those infected with human immunodeficiency virus—who have a much higher than normal risk of anal cancer. The anal Pap test has been used by the Northwest Pennsylvania Rural AIDS Alliance to detect potential precursors to cancer and degrees of anal dysplasia in patients with HIV infection. The Alliance has been instrumental in creating guidelines for anal Pap testing and encouraging other medical professionals and clinics to do the same, and these guidelines are provided herein.

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changes that may indicate a trend toward anal cancer, and perhaps other men at risk of anal cancer should also be screened.

Many clinicians are unfamiliar with the procedure and the purpose of anal Pap testing. Appropriate triage and referral for care of anal cytologic abnormalities should ideally be clearly defined before implementation of anal Pap test screening. As more laboratories are becoming familiar with this test, procedural policies are being written. Industry standards have been in the developmental stages during the timeframe of this article, and early concerns noted by the author (R.A.O.) have inhibited the processing of anal Pap specimens. For example, clerical laboratory errors have occurred because of laboratory workers’ unfamiliarity with the test. Cervical cancer screening with cervical cytology is routine, but there is no equivalent widely accepted procedure guidelines for men with possible exposure to HPV that can lead to dysplasia, and there are no universal guidelines on screening. Available research, however, identifies HPV as a cofactor in the development of anogenital cancer. The information presented here will show that screening and testing methods for anal dysplasia are available and need to be communicated.

Case Presentation
R.S., a 40-year-old man, presented to his family physician with the chief complaint of rectal bleeding found on toilet tissue during the past week. He had penile and perianal condylomas 15 years ago, but there has been no recurrence that he is aware of. His answers concerning his present illness reveal no history of anal trauma or penetration, rectal pain or discharge, perianal itch, or change in bowel movement habits or appearance. The patient has felt no mass or sores on his genitalia or perianal area and reports no dysuria, frequent urination, or penile discharge. He reports using condoms during every vaginal and anal penetration during his past 2 relationships with women, which occurred within the past 2 years. He also has a 23-pack-per-year history of smoking tobacco. His family, medical, and surgical histories are unremarkable for this complaint of rectal bleeding.

During the physical examination, the patient’s genitalia are found to be without mass, discharge, lesions, or evidence of a hernia, and his perianal area is pink, warm, dry, and intact. With his permission, the physician performs a digital rectal examination and palpates a nondescript thickened area at the 12-o’clock position posteriorly and 2 cm into the anus. No blood is grossly visible on the glove, and the guaiac test result is negative. Other areas of examination are found to be noncontributory.

What are the presumptive diagnoses in this man? What are the next steps in his diagnostic workup? In the following sections, we describe the anatomy of the anogenital area; highlight characteristics and vaccines for HPV; and provide a thorough look at the epidemiology, risk factors, diagnosis, and screening of anal cancer. Case follow-up is provided at the end of the present article.

Anatomy Review
Understanding the basic anatomy and histologic characteristics of the anus and perianal area is essential in comprehending the pathologic possibilities of the region. Figure 1 has been adapted from a common sketch found in the literature to illustrate the areas of concern. Just as in cervical Pap test screening, in the anal Pap test, the presence of both rectal glandular columnar mucosal cells and anal squamous mucosal cells (reported simply as columnar cells and squamous cells) verifies the accuracy of the area needed by confirming the sampling at the most proximal area, which is the transition zone, for full interpretation in screening for squamous cell carcinoma (SCC). (Other sources have stated, however, that cyto logic specimens without the presence of columnar cells should not be rejected solely on this basis.)

Human Papillomavirus
Virologic Characteristics
Human papillomavirus has been found in most types of anal cancers. It is a double-stranded DNA virus that repli-

![Figure 1](http://jaoa.org/)

**Figure 1.** The anal canal is approximately 4 cm long from the anal verge (margin) to the transitional zone. The dentate line (also called the pectinate line) is located at the proximal end of the anus. The flat squamous cells of the anal canal end here. The transitional (transition, transformation) zone has been considered synonymous with the dentate line owing to their proximity, but the transitional zone is actually just proximal to the dentate line, is considered part of the anus, and contains cube-shaped cells called transitional cells. It is the junction between rectal columnar epithelium and anal squamous epithelium, similar to the cervical transitional zone. Above the transitional zone is the rectum with its columnar epithelium. Adapted from Netter.
cates in the nucleus of squamous epithelial cells, thus its association with cervical, anogenital, and oral areas. Hundreds of papillomavirus types are capable of infecting humans. Most cases of anal cancer are linked to infection by HPV-16, which is closely associated with cervical cancer. The infection is initiated by a breach in the skin, permitting the virus entry and access to binding sites. Once the virus binds, it is endocytosed into the host cell. Replication of the virus is closely associated with the differentiation state of the host squamous epithelial cell.

Vaccines
An HPV quadrivalent (HPV4) vaccine was approved by the Food and Drug Administration for vaccination of females between the ages of 9 and 26 years. The antigens included in the vaccine generate protective antibodies to HPV types 6, 11, 16, and 18; HPV-6 and HPV-11 are related to genital condylomas in males and females, and HPV-16 and HPV-18 cause most cervical cancers. The Centers for Disease Control and Prevention (CDC) recommend that all females be vaccinated against HPV, starting at age 11 or 12 years. The CDC also report studies showing that the vaccine, working against HPV-16 and HPV-18, can protect against cancers of the vagina and vulva. The HPV4 vaccine is also licensed to be safe and effective for preventing genital condylomas in males aged 9 to 26 years, but it has not been placed on the recommendation schedule as a standard vaccine for males because of clinical trial findings suggesting that the best way to prevent HPV diseases in both males and females is to vaccinate females.

A bivalent HPV vaccine is also approved for use in the United States and contains viruslike particle antigens for HPV-16 and HPV-18. Both HPV vaccines are designed to lower the risk of cervical cancer in women. Surveillance Epidemiology and End Results estimated that 12,200 women would be diagnosed with cervical cancer in 2010 and that 4210 women would die of the disease. Vaccination is expected to decrease those numbers substantially.

Although no definitive studies have revealed protection against other HPV-related health concerns, it is conceivable that both the quadrivalent and bivalent vaccines will be shown to prevent cancers of the head and neck, penis, and anus due to HPV-16 or HPV-18. The vaccination of boys to prevent anogenital and oral cancers and their transfer to females as cervical cancer has been discussed as a possibility, but as of 2010, many investigators have concluded that there is no economic benefit to doing so.

Anal Cancer Statistics
The death of actress Farrah Fawcett in 2009 gave anal cancer a higher public profile, but it still has a very low incidence. About 0.16% of men and women born today will have cancer of the anus, anal canal, or anorectum sometime during their life. Approximately 5260 men and women would have these cancers diagnosed in 2010.

How do those numbers stack up against those for other forms of cancer? For the same time frame, the estimates for other common cancers were as follows: 207,090 diagnosed cases of breast cancer in women, 1,217,730 diagnosed cases of prostate cancer in men, and 222,520 diagnosed cases of lung and bronchus cancer in men and women. The majority of anal cancer cases occur in women, with 2010 diagnosis estimates of 2000 in men and 3260 in women.

Risk Factors and At-Risk Populations
Before addressing risk factors, one needs to understand what the term anal cancer comprises. Tumors that arise from the transitional or squamous mucosa of the anus are termed squamous cell carcinoma (SCC). These terms, anal cancer and SCC, are used interchangeably in most studies and will be used interchangeably in the present review as well. Other cancers are also categorized as anal cancers because of their location; these include cloacogenic carcinomas (subset of SCC), developing in the transitional zone; adenocarcinomas, arising mostly from the rectum; basal cell carcinomas, derived from the skin in the perianal area; and malignant melanoma, developing from the skin or anal lining.

Not all HPV types have been associated with dysplasia. According to the CDC, oncogenic HPV types are believed to be the causative agent in up to 90% of anal cancers. Persistent HPV infection with any of these 13 high-risk types (ie, oncogenic HPV strains 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) is the cofactor leading to the dysplastic changes of AIN seen before anal invasive carcinoma is diagnosed. As with cervical cancer, HPV is the principal cause of anal cancer. A minority of anal cancer cases have not been shown to have a connection with any HPV infection, and no discernible differences have been noted between these cancers and HPV-associated cancers in terms of patient age, adjacent dysplasia, ductal differentiation, or prognosis.

Anal HPV infection was present in 24.8% of immunocompetent heterosexual men in a recent study. These infections have been transient, with a low incidence of persistent infection. Immunosuppressed patients, such as transplant recipients and patients with HIV infection, have opposite results, with higher rates of persistent HPV infection, and these persistent infections lead to a higher incidence of HPV-associated malignancies.

The prevalence of HPV infection is highest in MSM, HIV-infected men, and transplant recipients, all of whom are in the at-risk population. Even HIV-infected men without a history of anal intercourse have a higher risk of AIN than do the general population.

Most of the research data on HPV and anal cancer in men have been collected in HIV-positive men, especially MSM assumed to be anal receptive. In HIV-negative MSM, the identifiable risk factors for anal cancer include HPV infection, a greater number of HPV types present, the number of receptive anal sex partners, and injection drug use. No association has been seen between age and AIN prevalence in HIV-negative MSM.

In the general population, other risk factors for anal cancer include a history of anal intercourse, a history of perianal...
condylomas, chronic immunosuppression (seen in patients taking immunosuppressive medications, those who are HIV positive, or those who have received organ transplants), age older than 50 years, multiple sexual partners (increasing the risk of HPV infection), and smoking (increasing the risk of non-clearing HPV infection). In one study, cigarette smoking and lifetime number of sexual partners were associated with an increased prevalence of anal cancer.

Receptive anal intercourse is the most prominent risk factor for anal HPV infection, but infection can also be acquired from contact with other infected genital areas, particularly the vulva in women and the penis in men. Contact of fingers and sex toys with infected fluids may also be associated with anal HPV infection.

When interviewing a patient, the physician should always ask about the patient’s sexual history, especially when the examination involves the anogenital area. When the examination involves the anal area, the physician should ask questions to discern whether objects, fingers, or other body parts have been inserted into the anus. This type of questioning is appropriate because it provides information relevant to the patient’s health. The history should also identify MSM who may practice anal receptive intercourse; such patients must be educated about potential risk factors for acquiring HPV infection amongst other infections.

In heterosexual patients, the causes of anal HPV infection may not be as obvious. In all men, the incidence of HPV infection has increased nearly 3-fold in the past 30 years. The prevalence of anal HPV infection in heterosexual men without a history of anal or oral sex with a man has been shown to be 24.8%–33.3% of these infections are with oncogenic HPV types. Therefore, anal HPV infection in heterosexual men, even those without any visible or palpable signs of anal condylomas or masses—which are usually caused by nononcogenic, high-risk, HPV types—could be considered common. Risk factors for heterosexual men include a large lifetime number of female sex partners and a high frequency of sexual intercourse just before diagnosis. A possible association with lack of circumcision has also been seen.

Other possible risk factors related to sexual behavior include self-initiated or partner-initiated anal massage with an object, anal massage or insertion with a finger, nonpenetrating sex (finger-vulvar, penile-vulvar, and oral-penile contact associated with female genital HPV infection), and oral-anal sex. Non-sexual behavioral risk factors include hand carriage, as in hygiene care, from the genitals to the anus and transference from objects of any kind used to manage genital HPV infection.

Clinical Manifestation
With advanced anal cancer, patients may experience multiple symptoms. With developing anal cancer, the number, type, and intensity of symptoms may vary. Patients with rectal bleeding commonly assume the problem is due to hemorrhoids. Those with rectal cancer may present with rectal bleeding as the most common initial symptom; it occurs in 45% of cases. Thirty percent of patients with anal cancer present with a mass sensation or with pain in the anal area, and 20% have no symptoms at all. The pain or sensation of fullness may be constant, and it may manifest with bowel movement or with mechanical manipulation involving a partner or device during sexual activity. The sensation of fullness may provoke the frequent urge to empty the bowels. Other symptoms may include perianal itching, anal discharge, changes in bowel habits, or changes in the shape of stool.

When listening to the patient’s medical history, the physician must note past or present anorectal condylomas. The presence of HPV-causing condylomas may suggest co-infection with oncogenic HPV types and require testing for cytologic changes. Patients with SCC in one study had a history of anogenital condylomas, with rates of 50% in homosexual men and less than 30% in women and heterosexual men, significantly higher than rates found in the general population (ie, 1%–2%). Any of the above symptoms or risk factors should encourage physicians to rule out the diagnosis of anal cancer. The physician would then perform a physical (including perianal) examination. Before performing a digital rectal examination requiring lubrication, the physician should decide whether an anal Pap test is required, because the lubricant may make it difficult to interpret the Pap test results, as in cervical Pap screening. If digital rectal examination reveals a macroscopic lesion or the anal Pap test reveals any abnormalities, high-resolution anoscopy (HRA) is recommended. High-resolution anoscopy is similar to colposcopy for cervical abnormalities; it involves using a microscope to examine the anus for abnormalities, such as ulcerated areas, thickened areas, and lesions containing abnormal vessels. These areas are then assessed, and biopsy specimens are obtained during the examination. This procedure is discussed later in the present article.

Precursors of Anal Cancer
In the general population, the good news is that only a fraction of people with anal HPV infection will experience a lasting case of AIN, and even fewer will go on to have anal cancer. Figure 2 illustrates the progression of persistent HPV infection in the cells of the cervix, which are comparable to that in anal cells. Figure 3 displays the cytologic and histologic “alphabet soup” that makes up the terminology within Pap (cytologic) and biopsy (histologic) reports.

High-grade squamous intraepithelial lesions (HSILs) are the precursor of invasive cancer in the cervix, and although the connection has not been proven, mounting evidence indicates that anal HSILs are the comparable precursor for anal cancer, and they are generally recognized as such. The progression of HSILs to invasive anal SCC is caused by many interrelated factors: HIV seropositivity, low CD4+ T-cell count, HPV subtype (oncogenic HPV-13), and higher levels of oncogenic subtypes in the anal canal.

Anal cancer is an increasing health concern in the entire male population, but especially in MSM, both HIV positive and HIV negative. Men who have sex with men have a high risk of HSILs and
invasive anal cancer,\textsuperscript{1} independent of HIV status.\textsuperscript{26,29} Most MSM who have a history of receptive anal sex carry anal HPV, with rates of more than 60\% in HIV-negative MSM and nearly 100\% in HIV-positive MSM, leading to dysplastic changes.\textsuperscript{1}

Compared with HIV-negative MSM, HIV-positive MSM have a greater risk of anal squamous intraepithelial lesions. Lower CD4+ T-cell counts increase the risk of such lesions more than counts that are higher than 500 cells/mm\textsuperscript{3} (within the possible low normal range in laboratory reporting), but all HIV-positive MSM have a higher risk than HIV-negative MSM.\textsuperscript{30} One study found a 60-fold increased risk of AIN in HIV-positive MSM.\textsuperscript{16} In another study with 357 HIV-positive MSM in San Francisco, 81\% of subjects had AIN (grades 1-3), 52\% had high-grade AIN (grade 2 or 3), and 98\% were HPV positive.\textsuperscript{16}

Also, HIV-positive men are at greater risk of developing HSIL than are HIV-negative men, and the men’s cases have been shown to advance from low-grade squamous intraepithelial lesions (LSILs) to HSILs.\textsuperscript{20} Continuous immunosuppression by HIV is associated with a progression from LSILs to HSILs or invasive SCC.\textsuperscript{31,32} This finding is also seen in recipients of solid organ transplants who have been subjected to long-term immunosuppression.\textsuperscript{33} Human papillomavirus infections and HPV-associated malignancies are seen at higher rates in HIV-infected patients, regardless of sexual practices.\textsuperscript{30} There is increasing evidence of the progression from HSILs to anal cancer, but the time frame has not been verified. Anal Pap tests or cytologic examinations are the primary screening tests for identifying anal tissue dysplasia in persons at risk. Once abnormal cytologic findings have been identified, the use of HRA is recommended to identify dysplastic lesions as a tissue histologic diagnosis.\textsuperscript{16}

### Screening for Precursors

The pathophysiologic characteristics of anal cancer are similar to those of other intraepithelial neoplasms found on the cervix, penis, oral tissue, and vulva.\textsuperscript{16} The standard of care for cervical cancer screening is the Pap test. Anal cytology (ie, the anal Pap test) has been recommended by several research groups for screening at-risk populations for anal cancer; this test is adapted from the principles of cervical screening.\textsuperscript{16} In specific populations, anal cytology has been projected as a cost-effective way to prevent the occurrence of anal cancer and manage its precursors. Specificity and sensitivity findings comparing anal cytologic Pap test results and histologic biopsy results were similar to those comparing cervical cytologic and biopsy results. In one study, the positive predictive value of anal cytologic Pap test abnormalities for anal dysplasia was 95.7\%.\textsuperscript{16} Anal cytologic abnormalities seen with Pap tests appear to be highly predictive of anal dysplasia seen at histologic biopsy.\textsuperscript{16} Populations in whom anal Pap screening is recommended include HIV-infected patients with a history of anal condylomata or dysplasia or with CD4+ T-cell counts of less than 200 cells/mm\textsuperscript{3}; this screening has also been projected to be cost-effective.\textsuperscript{34}

Even though the cervical Pap test is within the standard of care, its findings may be nonspecific; in particular, atypical squamous cells of undetermined significance (ASCUS), with a US incidence ranging from 1\% to 10.4\%, have a low specificity, so colposcopy often reveals normal nondysplastic findings.\textsuperscript{1} These cells have a higher incidence in the anal canal—14\% to 78\% in HIV-positive and 12\% in HIV-negative MSM.\textsuperscript{1} The specificity of anal ASCUS relative to pathologic abnormalities has been found to be lower than that for cervical ASCUS. Therefore, some men with ASCUS will proceed to HRA with possible biopsy without having HSILs or AIN. The sensitivity of ASCUS can be increased by considering the patient's oncogenic HPV status.\textsuperscript{1} Two other studies showed that more than 33\% of patients with anal Pap results reporting ASCUS or LSILs have high-grade findings at biopsy reports, which support the need to perform HRA with biopsy even in patients with LSILs, regardless of HIV status, when they are
Given all of the available data and given that the anal Pap test is an uncomplicated and quick procedure, the rates of abnormal anal cytologic findings and should be screened. Anal Pap test screening has been proposed to be cost-effective in preventing anal cancer in HIV-positive and HIV-negative MSM when performed every 1 to 2 years.25

Regarding HPV screening with the anal Pap test, Figure 4 summarizes the Cleveland Clinic recommendations for the timing of HPV testing and how results should be followed up (personal communication, Alan J. Taege, MD, February 2011).

### Guidelines for Anal Pap Test Screening

In 2008, the Northwest Pennsylvania Rural AIDS Alliance27 attempted to create a program to screen men for HPV and anal cytologic changes. The challenges included the following: laboratory concerns related to specimen acquisition, equipment, codes, and internal laboratory policy; state licensure problems involving who was licensed to read anal Pap tests; and the lack of established policies from other clinics to use for guidance. Laboratories and pathologists are now more knowledgeable about the technique and the rationale for anal Pap tests, clerical staff have been educated about the test so that specimens are not discarded for having the “wrong” source (ie, anus) on the laboratory requisition, and laboratory policies have been written.

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### Table: Anal Cytology (Anal Pap Test) vs Anal Histology (Anal Biopsy)

<table>
<thead>
<tr>
<th>Anal Cytology (Anal Pap Test)</th>
<th>Anal Histology (Anal Biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>■ ASCUS</strong> Atypical Squamous Cells Undetermined Significance</td>
<td><strong>■ AIN</strong> Anal Intraepithelial Neoplasia</td>
</tr>
<tr>
<td><strong>■ ASCH</strong> Atypical Squamous Cells suspicious for HSIL</td>
<td>** ■ AIN 1** mild dysplasia</td>
</tr>
<tr>
<td>** ■ ASIL** Atypical Squamous Intraepithelial Lesion</td>
<td>** ■ AIN 2** moderate dysplasia</td>
</tr>
<tr>
<td><strong>■ LSIL</strong> Low-grade Squamous Intraepithelial Lesion</td>
<td>** ■ AIN 3** severe dysplasia/carcinoma in situ</td>
</tr>
<tr>
<td>** ■ HSIL** High-grade Squamous Intraepithelial Lesion</td>
<td><strong>■ SCC</strong> Squamous Cell Carcinoma</td>
</tr>
<tr>
<td><strong>■ AIN</strong> Anal Intraepithelial Neoplasia</td>
<td><strong>■ Invasive Anal Carcinoma</strong></td>
</tr>
</tbody>
</table>

*ASCUS and ASCH do not have all the characteristics of HSIL but are not classified as benign.*

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**Figure 3. Distinguishing the cytologic terminology (ASCUS, ASCH, ASIL, LSIL, HSIL), as used in the cytology reports from anal Papanicolaou tests, from the histologic terminology (AIN), as used in biopsy reports, makes understanding the “alphabet soup” much easier. Many studies and literature items combine the 2 types of nomenclature in reporting.25,27 Neoplasia is the pathologic process that results in the formation and growth of a tumor as identified histologically; dysplasia is abnormal tissue development. LSIL corresponds to AIN 1 and condylomata on biopsy; HSIL corresponds to AIN 2 or AIN 3 or carcinoma in situ counterpart on biopsy.**

(continued...)

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and updated to reflect the growing need for anal Pap screening.

The Northwest Pennsylvania Rural AIDS Alliance of Clarion University of Pennsylvania has enacted a policy regarding anal Pap test screening. Appropriate screening for anal cancer should always include the baseline visual inspection of external genitalia, palpation, and digital rectal examination to identify such abnormalities as warts, lesions that bleed, lesions of uncertain origin, lesions with hypo- or hyperpigmented plaques, and palpable internal lesions. Because bleeding is the most common presenting symptom of anal cancer, it is important to determine its cause. The digital rectal examination with lubrication must be performed after the anal Pap test with the HPV test because the lubrication interferes with the Pap test’s ability to identify cells.

**Obtaining specimen for anal cytology**—The anal Pap test involves collection and examination of cells with techniques similar to those used for cervical Pap tests. Obtaining an adequate anal cytology specimen involves the following steps:

1. Moisten a Dacron swab with water. It is important to use a Dacron swab, not a cotton swab, because cotton clings to the specimen cells, making examination difficult.¹⁰
2. Insert the swab 1.5 to 2 inches into the anal canal and proceed through the dentate line and transitional zone between the squamous and columnar epithelia. This transitional zone is subject to infection with HPV or neoplastic transformation by HPV. Precancerous lesions of the anal squamous epithelium can develop and are classified as low or high grade, according to the Bethesda criteria nomenclature.²⁰
3. Moisten a Dacron swab with water or use a brush from an HPV kit.
4. Insert the swab 1.5 to 2 inches into the anal canal.
5. Rotate the swab firmly with lateral pressure while slowly inserting and withdrawing in a tight spiral motion for 15 to 20 seconds.
6. Place the swab in liquid-based medium (eg, Digene specimen transport medium [Digene Corp, Gaithersburg, Maryland] transport medium), leave it in the container, cap the container, and shake it vigorously for 10 seconds.

7. Dispose of the swab; cap and label the specimen jar.

**Obtaining specimens for HPV testing**—To obtain an adequate anal specimen for HPV testing, perform the following steps:

1. Moisten a Dacron swab with water or use a brush from an HPV kit.
2. Insert the swab 1.5 to 2 inches into the anal canal.
3. Rotate the swab firmly with lateral pressure while slowly inserting and withdrawing in a tight spiral motion for 15 to 20 seconds.
4. Place the swab in liquid-based medium (eg, ThinPrep CytoLyt solution [Hologic Inc, Marlborough, Massachusetts]) and swish the swab vigorously for 15 to 20 seconds.

**Testing frequency and follow-up**—Although there are no formal guidelines for the use of anal Pap test screening in HIV-positive individuals, experts on anal Pap testing recommend the following:

1. When an HIV diagnosis is made, an anal Pap test should be offered as part of the initial evaluation for men and women.
2. If the initial anal Pap test results are reported as normal for HIV-positive MSM, the test should be repeated annually. Although the recommenda-

<table>
<thead>
<tr>
<th>Anal Cytology (Anal Papanicolaou Test)</th>
<th>HPV Test*</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>New</td>
<td>New</td>
<td>Await results</td>
</tr>
<tr>
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<td>Negative</td>
<td>Annual screen</td>
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<td>Positive</td>
<td>6 months rescreen</td>
</tr>
<tr>
<td>ASCUS</td>
<td>Negative</td>
<td>6 months rescreen</td>
</tr>
<tr>
<td>ASCUS</td>
<td>Positive</td>
<td>Refer for HR anoscopy</td>
</tr>
<tr>
<td>LSIL or HSIL</td>
<td>Negative or Positive</td>
<td>Refer for HR anoscopy</td>
</tr>
</tbody>
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**Figure 4. Cleveland Clinic recommendations for human papillomavirus (HPV) screening and follow-up.** *Positive identifies at least 1 of 13 oncologic, high-risk types. Abbreviations: ASCUS, abnormal atypical squamous cells of undetermined significance; HR, high-resolution; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. Adapted from Cleveland Clinic recommendations (personal communication, Alan J. Taeger, MD, February 2011).

**Completing laboratory requisitions**—The following are recommendations for the local laboratories that support the Northwest Pennsylvania Rural AIDS Alliance. They may be adapted to individual laboratory situations:

1. Provide complete identifying patient information.
2. Select ICD-9 diagnosis codes of 042 (AIDS) or V08 (HIV infection) and V692 (high-risk sexual behavior).
3. Under “Tissue Pathology and Non-

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Figure 5. Flow chart of a practical algorithm to follow in response to abnormal results of an anal Pap test. Abbreviations: AIN, anal intraepithelial neoplasia; ASCUS, abnormal atypical squamous cells of undetermined significance; HIV, human immunodeficiency virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

GYN Cytology Test Offerings,” select the appropriate code for anal-rectal cytology.
4. In the test box identified as “Additional Tests,” write “high-risk HPV and low-risk HPV.”
5. Submit specimen to laboratory with requisition form.

Grading and results of anal pap tests—The Bethesda 2001 system categorizes cervical disease in increasing order of severity. Because anal cytologic findings demonstrate similar histologic changes, they are graded the same way:
1. Negative: negative for intraepithelial lesion or malignancy
2. AIN: anal intraepithelial neoplasia, as seen in histology
3. ASCUS: atypical squamous cells of undetermined significance
4. ASC-H: atypical squamous cells suspicious for HSIL
5. LSIL: low-grade squamous intraepithelial lesion
6. HSIL: high-grade squamous intraepithelial lesion
7. SCC: squamous cell carcinoma

Figure 5 illustrates a practical algorithm for guiding follow-up when abnormal results are received from an anal Pap test.

Guidelines for HRA
When anal cytologic findings are abnormal, HRA should be performed to detect anal dysplasia. As with colposcopy, specialized training and equipment are necessary. After a clear plastic anoscope is placed approximately 2 inches into the anus, allowing visualization of the dentate line and transitional zone, a 3% acetic acid solution is applied to the surface of the perianal area, anal canal, transformation zone, and distal portion of the rectum. Using a standard gynecologic colposcope with a light source and binocular lenses having 20- to 30-fold magnification, the examiner looks for a white coating or plaque that reflects areas of dysplasia from HIV-infected cells. Lugol iodine solution is then applied to identify intraanal lesions of dysplasia. The normal mucosal tissue stains dark brown; the dysplastic cells, which do not absorb the solution, remain unstained and yellow. The abnormal cells may reveal punctuation and mosaicism, which are signs of HPV infection. Vascular changes, such as neovascularization, increased vascularization, vessel interruption, and vessel caliber variation, are suggestive of malignant tissue. The presence of any of these changes would necessitate biopsy for definitive histologic diagnosis.

We stated previously that all abnormal findings at anal cytologic screening deserve further investigation with HRA. The converse—that normal cytologic findings do not warrant HRA—is not necessarily true. One study demonstrated that even with normal Pap findings, the probability of neoplasia is not low enough to rule out the need for HRA. Therefore, for optimal care, HRA should also be recommended for patients at high risk for HPV or anal dysplasia, including those with visible or palpable lesions or prior HSILs.

Case Follow-Up
R.S., the patient whose case was presented at the beginning of this article, was offered an anal Pap test, to which he agreed. Because of the lubricant used for the digital rectal examination, the test was performed a few days after his initial visit for rectal bleeding. Given the patient’s history of perianal condyloma, an anal HPV test was also performed. The results, received 1 to 2 weeks later, were positive for the HPV high-risk group, and the cytologic results revealed LSIL. The patient was set up with a physician specializing in HRA. Biopsy was performed, and the histologic examination revealed AIN III. The patient was scheduled for a return visit to discuss options for managing this precursor to anal SCC.

Conclusion
Physicians should become more familiar with anal Pap tests and when, how, and why to perform them. Changing patterns of human sexual activity generally may make HPV infection more common in all men, leading to more challenging pathologic conditions associated with the same pathogens. The known precursors to anal cancer need to be recognized, and screening should be per-
formed in those at risk for this preventable disease. The knowledge provided by anal Pap screening must be used to reduce the occurrence of other virus-associated malignancies. Investigation into the logistics and advantages of immunizing more people for HPV may also help prevent these malignancies. More longitudinal studies are needed to solidify and support what we know today.

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References


