The incidence of anal human papillomavirus (HPV) and anal cancer among men has been shown to be a major cause, if not a necessary cofactor, in the development 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 (AIN). In the author’s (R.A.O.) clinical experience, the patterns of human sexual behavior have been changing— with changes in participant anatomy, risk behavior, external assistant devices, agents to enhance sexual performance, and numbers of partners—and sexual partners are affected by each other’s sexual history. For all of these reasons, men who do not identify themselves as homosexual or as men who have sex with men (MSM) may nonetheless be at risk and should be screened and tested for anal dysplasia and cancer. In MSM and heterosexual men who are immunocompromised, including those infected with human immunodeficiency virus (HIV), the incidence of anal dysplasia and cancer is even higher. Patients in HIV clinics are offered anal Papanicolaou (Pap) tests to screen for cellular
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 for many years, 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 cytologic 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-
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, 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; adenoscarcinomas, 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 those in 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 (fingervulvar, 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 terminiology 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, independent of HIV status. 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.

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/mm³ (within the possible low normal range in laboratory reporting), but all HIV-positive MSM have a higher risk than HIV-negative MSM. One study found a 60-fold increased risk of AIN in HIV-positive MSM. 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.

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. Continuous immunosuppression by HIV is associated with a progression from LSILs to HSILs or invasive SCC. This finding is also seen in recipients of solid organ transplants who have been subjected to long-term immunosuppression. Human papillomavirus infections and HPV-associated malignancies are seen at higher rates in HIV-infected patients, regardless of sexual practices. 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.

**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. 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. 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%. Anal cytologic abnormalities seen with Pap tests appear to be highly predictive of anal dysplasia seen at histologic biopsy. 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/mm³; this screening has also been projected to be cost-effective.

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. These cells have a higher incidence in the anal canal—14% to 78% in HIV-positive and 12% in HIV-negative MSM. 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. 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
higher risk for anal cancer.  

Given all of the available data and given that the anal Pap test is an uncomplicated and quick procedure, the rates seen for anal cancer screening in the clinical setting are low, as noted by Kreuter and Wieland and the clinical experience of the author (R.A.O.), especially among MSM. Primary care physicians should consider the potential benefits of anal cancer screening in that select population of patients and find ways to discuss these benefits with patients, as they discuss other screening advice. Primary care physicians also need an appropriate referral system for patients with abnormal cytologic findings and should consider training in HRA.

The screening process for anal pathologic abnormalities begins with a thorough physical examination and an appropriate history. In our opinion, patients who have negative examination findings but whose history places them in an at-risk population should undergo anal cancer screening with Pap testing. Those with any abnormal Pap test findings are then offered histologic confirmation with HRA. This is a common strategy incorporated by many anal cancer screening programs.

To our knowledge, there have been no universal, formal recommendations to use anal Pap tests to screen for abnormal anal cells because more research is thought to be needed to show that identifying and removing abnormal cells prevent future development of anal cancer. The CDC have not recommended routine anal Pap test screening for anyone or any sub-group. However, they do state that “anal cytology screening of HIV-infected men who have sex with men ... might become useful preventive measures. However, studies of screening and treatment programs for anal HSILs need to be implemented before recommendations for anal cytology screening can be made.” The New York State Department of Public Health AIDS Institute has published guidelines stating that “screening for cellular dysplasia is prudent and recommended, particularly in persons at high risk for infection with papilloma viruses.”

Chin-Hong and Palefsky have proposed an anal cancer screening program based on the principles of cervical cancer screening used today. The program recommends that anal cancer screening be performed in high-risk-populations: HIV-positive men and women, MSM, women with a history of vulvar or cervical cancer, and organ transplant recipients. Mentioned by Palefsky in a slide presentation, which was given by personal communication with the author (R.A.O.), those with perianal condylomata should also 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.

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 Alliance 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.

### Table 1: Anal Cytology (Anal Pap Test) and Anal Histology (Anal Biopsy)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ ASCUS*</td>
<td>Atypical Squamous Cells Undetermined Significance</td>
<td>□ AIN</td>
<td>Anal Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>□ ASCH*</td>
<td>Atypical Squamous Cells suspicious for HSIL</td>
<td>□ AIN 1</td>
<td>mild dysplasia</td>
</tr>
<tr>
<td>□ ASIL</td>
<td>Atypical Squamous Intraepithelial Lesion</td>
<td>□ AIN 2</td>
<td>moderate dysplasia</td>
</tr>
<tr>
<td>□ LSI L</td>
<td>Low-grade Squamous Intraepithelial Lesion</td>
<td>□ AIN 3</td>
<td>severe dysplasia/carcinoma in situ</td>
</tr>
<tr>
<td>□ HSIL</td>
<td>High-grade Squamous Intraepithelial Lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ SCC</td>
<td>Squamous Cell Carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ASCUS and ASCH do not have all the characteristics of HSIL but are not classified as benign.
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.
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.
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, 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.
5. 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.
5. 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.
6. Patients with a low CD4+ T-cell count (<500 cells/mm³) should be monitored more frequently than noted above. There is no recommendation for frequency, I (R.A.O.) suggest a frequency of every 6 to 9 months.

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 HPV-positive MSM, the test should be repeated annually. Although the recommendation for HPV-positive women is not as clear and is without expert agreement, they should probably undergo similar screening.
3. If the Pap test shows abnormal findings—either ASCUS, LSIL, or HSIL—the patient should be further evaluated with HRA and biopsy according to the algorithm shown in Figure 5.
4. If AIN I (LSIL) is found at biopsy, routine follow-up should be performed every 6 to 12 months.
5. For patients with AIN II or III (HSIL), therapy is recommended. Observation with repeated evaluation is an option for patients with AIN I (LSIL).

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 V69.2 (high-risk sexual behavior).
3. Under “Tissue Pathology and Non-

---

### Table: Anal Cytology (Anal Papanicolaou Test) vs HPV Test

<table>
<thead>
<tr>
<th>Anal Cytology (Anal Papanicolaou Test)</th>
<th>HPV Test*</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>New</td>
<td>Await results</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Annual screen</td>
</tr>
<tr>
<td>Negative</td>
<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>
</table>

---

*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. Taege, MD, February 2011).
Figure 5. Flow chart of a practical algorithm to follow in response to abnormal results of an anal Pap test.44 **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.

**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 preven-
table disease. The knowledge pro-
vided by anal Pap screening must be
used to reduce the occurrence of other
virus-associated malignancies. Investi-
gation into the logistics and advantages
of immunizing more people for HPV
may also help prevent these malig-
nancies. More longitudinal studies are
needed to solidify and support what we
know today.

Acknowledgment
We thank our contributor, Leah Magagnotti,
RN, Clinic Nurse Manager of the Northw est
Pennsylvania Rural AIDS Alliance of Clarion
University of Pennsylvania. One of her many
roles and responsibilities is the creation and
maintenance of policies, including the policy
on anal Pap tests discussed in the present
article.

References
1. Goldstone MD, Enyinna CS, Davis TW. Detec-
tion of oncogenic human papillomavirus and other
predictors of anal high-grade dysplasia in men
who have sex with men with abnormal cytology.
of and risk factor for human anal papillomavirus
infection in heterosexual men. J Infect Dis. 2008;197
(12):1676-1684.
3. Ryan DP, Willett CG. Classification and epi-
demiology of anal cancer. UpToDate. March 13,
2008.
4. Chin-Hong PV, Palefsky JM. Human papillo-
mavirus-related malignancies with and without
HIV: epidemiology, diagnosis and management.
In: Volberding PA, Palefsky J, eds; Walsh CC, assist
ed. Viral and Immunological Malignancies.
Hamilton, Ontario, Canada: BC Decker; 2006:224-
241.
Anatomy. 3rd ed. Teterboro, NJ: Icon Learning Sys-
tems; 2003.
6. New York State Department of Health. HIV cli-
cal resource: human papillomavirus (HPV). http://
www.hivguidelines.org/Guidelines.aspx?pageID
=257&guideLineID=1-2&type=txt. Accessed February
20, 2008.
In: Knipe DM, Howley, PM, eds. Fields Virology. 5th
ed. Philadelphia, PA: Lippincott Williams & Wilkins,
2007:2289-2340.
8. HPV vaccines: questions and answers. Centers
9. SEER stat fact sheets: cervix uteri. Surveillance, Epi-
cancer.gov/statfacts/html/cervix.html. Accessed Jan-
uary 31, 2011.
10. SEER stat fact sheets: anal cancer. Surveillance,
cancer.gov/statfacts/html/anus.html. Accessed Jan-
uary 31, 2011.
11. SEER stat fact sheets: breast. Surveillance, Epi-
31, 2011.
12. SEER stat fact sheets: prostate. Surveillance, Epi-
31, 2011.
13. SEER stat fact sheets: lung and bronchus. Surveil-
lance, Epidemiology, and End Results Web site.
14. HPV and men fact sheet. Centers for Disease Control
31, 2011.
15. Williams GR, Lu QL, Love SB, Talbot IC, Northover JM. Properties of HPV-positive and HPV-
negative anal carcinomas. J Pathol. 1996;180(4):378-
382.
16. Kreuter A, Wieland U. Human papillomavirus-
associated diseases in HPV-infected men who have
109-114.
prevalence of anal human papillomavirus infec-
tion in HIV-negative sexually active men who have
2004;190(12):2070-2076.
18. Anal cancer. University of California, San Fran-
cisco, Medical Center Web site. http://www.ucsf
health.org/conditions/oncERAL_cancer. Accessed
January 31, 2011.
tices in the etiology of anal cancer. Cancer. 2004;
20. Levine AM. Non-AIDS-defining cancers in the
era of HAART [module]. In: HIV/AIDS Annual Update
http://www.clinicalcareoptions.com/HIV
/Annual%20Updates/2008%20Annual%20Update/
Modules/Cancers.aspx
papillomavirus DNA on the fingers of patients with
22. Ferenczy A, Bergeron C, Richart RM. Human
papillomavirus DNA in fomites on objects used for
the management of patients with genital human
74(6):950-954.
23. Singh R, Nime F, Mittelmann A. Malignant
epithelial tumors of the anal canal. Cancer. 1981;
24. Schneider TC, Schulte WJ. Management of carci-
Depth of invasion, location and size of cancer of the
anus dictate operative treatment. Cancer. 1983;51
(7):1291-1295.
26. What is Anal Cancer? American Cancer Society
Web site. http://www.s cancerc.org/docroot/CR/con-
ten/CR1_2_2_3X_How_is_anal_cancer_found.47.asp?
27. Lowy D, Schiller J. Prophylactic human papillo-
mavirus vaccines. J Clin Invest. 2006;116(5):1167-
1173.
28. Palefsky JM, Holly EA, Ralston ML, Jay N. Preva-
ence and risk factors for human papillomavirus infec-
tion of the anal canal in human immuno-
deficiency virus (HIV)-positive carcinomas. J Infect
29. Peters RK, Mack TM. Patterns of anal carci-
noma by gender and marital status in Los Angeles
30. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry
JM, Darragh TM. High incidence of anal high-grade
squamous intra-epithelial lesions among HIV-posi-
tive and HIV-negative homosexual and bisexual
31. Critchlow CW, Suravicz CM, Holmes KK, et al. Prospective study of high grade anal squamous
intraepithelial neoplasia in a cohort of homosexual
men: influence of HIV infection, immunosuppres-
sion and human papillomavirus infection. AIDS.
32. Melybe M, Sprogel P. Aetiological parallel
between anal cancer and cervical cancer. Lancet.
33. Penn I. Incidence and treatment of neoplasia
after transplantation. J Heart Lung Transplant.
34. Goldie S, Kuntz KM, Weinstein MC, Freedberg
KA, Welton ML, Palefsky JM. The clinical effect-
viveness and cost-effectiveness of screening for
anal squamous intraepithelial lesions in homo-
sexual and bisexual HIV positive men. JAMA.
resolution anoscopy finding in men who have sex
with men: inaccuracy of anal cytology as a pre-
dictor of histologic high grade anal intraepithe-
elial neoplasia and the impact of HIV serostatus.
36. Kaplan JE, Masur H, Holmes KK; USPHS; Infect-
itus Disease Society of America. Guidelines for
Preventing Opportunistic Infections Among HIV
Infected Persons—2002: Recommendations of the
US Public Health Service and the Infectious Dis-
eses Society of America. MMWR Recomm Rep.
Anal Pap Smear Rectal Exam Policy. Clarion, PA:
Northwest Pennsylvania Rural AIDS Alliance; June
3, 2008.
38. Palefsky J. Screening for anal and cervical dys-
plasia in HIV-infected patients. PRN Notebook.
Group Members; Bethesda 2001 Workshop. The
2001 Bethesda System: terminology for reporting
results of cervix cytology. JAMA. 2002;287(16):
2114-2119.
40. American Academy of HIV Medicine. Funda-
mentals of HIV Medicine. Washington, DC: Amer-