Clinicians' Educational Pamphlet on Genital Human Papillomavirus (HPV)

Why Is HPV Important?

Genital infection with human papillomavirus (HPV) is the most common sexually transmitted infection in the United States today.(1) An estimated 80% of sexually active women—and probably an equal percentage of men—are infected with HPV at some point in their lives.(2)

In most cases, infections are asymptomatic, transient, and resolve without treatment, but it is now accepted that persistent infection with high-risk types of HPV cause nearly all cervical cancer.(3)

Cervical cancer can be prevented by early detection of abnormal cell changes. When cervical cancer is detected at an early stage and treated promptly, survival rates are over 90%.(4)

What Is HPV?

Papillomaviruses are DNA tumor viruses that are widely distributed throughout animal species. Human papillomavirus (HPV) commonly causes epithelial proliferations at cutaneous and mucosal surfaces.

Types of HPV

There are more than 100 different types of HPV.(5) They differ in terms of the types of epithelium that they infect. Some infect cutaneous sites whereas others infect mucosal surfaces.

Over 30 types infect anogenital epithelium, including the cervix, vagina, vulva, rectum, urethra, penis, and anus.(6) These are divided into "low-risk" and "high-risk" types:

High-risk HPV types	Low-risk HPV types	Types whose risk is not yet well established
Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82	Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 81	Common types: 26, 53, 66, 73

- **High-risk HPV types:** These are considered high-risk because they can be found in association with invasive cancers of the cervix, vulva, penis, or anus (as well as other sites).
  - *HPV 16* is the most common high-risk virus, found in almost half of all cervical cancers. It's also the one of the most common types found in women without cancer.(7)
  - *HPV 18* is another common high-risk virus, found not only in squamous lesions, but also in glandular lesions of the cervix. It accounts for 10%-12% of cervical cancers.(7)

- **Low-risk HPV types:** These can cause benign or low-grade cervical cell changes and genital warts, but are rarely if ever found in association with invasive cancers.
  - *HPV 6 and 11* are the low-risk viruses that are most commonly found in genital warts.(7)

- **Types whose risk is not yet well established:** These are occasionally associated with cervical cancer.

How Common Is HPV?
HPV is one of the most common sexually transmitted infections.

Infection with high-risk types of HPV is much more common than infection with low-risk types.(8) Five to 30% of individuals infected with HPV are infected with multiple types of HPV.(8)

- About 20 million Americans (approximately 15% of the population) are currently infected with HPV and are actively shedding sufficient amounts of HPV DNA to be detected using a molecular test.(9)

- Of these, an estimated 9.2 million are sexually active adolescents and young adults 15 - 24 years of age.(10)

- About 6.2 million people become newly infected each year.(11)

- At least half of all sexually active men and women acquire HPV at some point in their lifetime.(12) Recent prospective studies of college age women indicate that up to 80% of those who are sexually active become infected with genital HPV.(13) It's likely that comparable rates would be found in men if good HPV testing methods existed for men. (3)

- Estimates for prevalence of genital warts caused by low-risk types of HPV are relatively imprecise. However estimates indicate that as many as 100 per 100,000 people develop genital warts.(14) About 1.4 million people (about 1% of sexually active people) currently have genital warts.(15)

What Are the Risk Factors for Acquiring a Genital HPV Infection?

Risk factors for acquiring HPV infection in women:
● Young age (less than 25 years) ● Multiple sex partners ● Early age at first sexual intercourse (16 years or younger) ● Male partner has (or has had) multiple sex partners
Less commonly identified risk factors:
● Active or passive cigarette smoking ● Oral contraceptive use ● Nutritional deficiencies ● Lack of circumcision of male partner(s)

How Is HPV Transmitted?

- Unlike HIV and most other sexually transmitted diseases, HPV is not transmitted through semen or bodily fluids, but through skin-to-skin contact.

- Genital HPV is transmitted primarily by penetrative genital contact, usually through vaginal or anal sex.(16)

- Other types of genital contact in the absence of penetration (oral-genital, manual-genital, and external genital-genital contact) can lead to HPV infection, but these routes of transmission are much less common than sexual intercourse.(16) Genital HPV infection with low-risk types are rarely transmitted from mother to baby during delivery.(17)

- Genital HPV infections are very rare among women reporting no previous sexual intercourse, appearing in 0%-8%.(18)

- Sexual behavior is the most consistent predictor of acquiring infection. Most importantly, the number of sex partners is strongly linked to risk of prevalence and incidence of HPV infection.(19) In women, risk of acquiring a genital HPV infection increases with increasing number of lifetime male sex partners.(19)

- Having sex with a new partner may be a stronger risk factor for initial HPV acquisition than having sex with a steady partner.(20)

- For women, the sexual activity of their partner(s) is also important for determining risk of HPV acquisition. Among adolescent females and college students, risk of acquiring HPV is increased if a woman's partner has had previous partners.(20)

- Although very uncommon, genital HPV infection also may be transmitted by non-sexual routes. In rare instances, transmission can occur from a mother to a newborn baby.(21) It has been hypothesized that transmission can occur by inanimate objects such as clothing or environmental surfaces (although this has never been documented).(22)

Natural History of Genital HPV Infections

- Most genital HPV infections are transient and asymptomatic, causing no clinical problems.

- 70% of new HPV infections spontaneously clear within one year, and as many as 91% clear within two years.(23) The median duration of new infections is typically 8 months.(23)

- HPV 16 infections tend to persist longer than other HPV types, but most HPV 16 infections become undetectable within 2 years.(23)

- It is unclear whether women who become HPV DNA negative actually clear the virus from their bodies. It is possible that in some women the virus remains in a nondetectable dormant state for a considerable period of time and then reactivates many years later. This may

explain why some older women in a mutually monogamous relationship can begin to shed genital HPV.(11)

- The gradual development of an effective immune response is thought to be the likely mechanism for HPV DNA clearance.(4)

- Many women with transient HPV infections will develop atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL). These are mild cytologic abnormalities that represent the cytopathic effect caused by a productive HPV infection in the infected epithelium.

- Only about 10% of women infected with HPV develop persistent HPV infections.(24) Only women who develop these persistent infections are at risk for developing high-grade cancer precursors and cancers.

- One study found that the risk for developing a high-grade cervical cancer precursor over a two-year period was 14 times higher for women examined at four-month intervals who had three positive tests for HPV compared with that for women who had negative tests.(25)

What Is the Risk Associated with Genital HPV Infection?

Risks to Women

Infection with high-risk types of HPV causes almost all cervical cancers and many cancers of the penis, vulva, vagina, and anal region.

The relative risk for invasive cervical cancer associated with persistent infection with a high-risk HPV is considerable. One large case-control study reported relative risks of over 100 for cervical cancer for all of the high-risk types of HPV.(26)

Although infection with HPV is necessary for the development of cervical cancer, it is not sufficient to cause cancer on its own. The vast majority of women who are infected with HPV do not develop cancer.

Only those women who develop persistent high-risk HPV infections are at risk for developing cancer.

Studies show a number of other factors that influence whether a person with HPV will develop high-grade cancer precursors and cancer:(3)
● Immunosuppression ● Chronic inflammation associated with infection with other STDs such as chlamydia ● Long-term use of oral contraceptives ● A high number of live births ● Active or passive cigarette smoking ● Nutritional deficiencies ● Having a mother who took diethylstilbestrol (DES) ● Lack of adequate Pap test screening

Risk to Infants Born to Mothers with HPV Infections
Genital HPV infection with low-risk types are only rarely transmitted from mother to baby during delivery.(17) The risk appears to be greatest for women with genital warts during pregnancy.(27)

Perinatally transmitted HPV infection can result in respiratory tract warts in the baby, known as recurrent respiratory papillomatosis (RRP). Estimates of the incidence rate for RRP are imprecise, but range from 0.4 to 1.1 cases per 100,000 children.(17)

Although data are limited, cesarean delivery does not appear to be protective.(28)

Prevention of Genital HPV Infection
Prevention of genital HPV infection is important to reduce the incidence of genital warts and abnormal Papanicolaou (Pap) tests, precancerous cervical lesions, and invasive cervical cancer.

In the absence of a vaccine, transmission of most sexually transmitted infections can be reduced by strategies to:

1. Reduce the duration of infectiousness by treatment;
2. Decrease the efficiency of transmission by measures aimed at reducing infectivity; and
3. Reduce the number of sex partners.(29)

1. Reduce the duration of infectiousness
There is no effective systemic treatment for genital HPV. Genital HPV infections occurring in the absence of detectable lesions are not treated.

- Treatment for genital HPV is directed to lesions such as genital warts (treated with topical pharmacologic agents) or cervical cancer precursors, treated with local measures such as cryotherapy, electrocautery, or surgical excision.(30)

- Evidence indicates that currently available therapies for HPV-related cervical cell abnormalities and genital warts may reduce infectiousness, but probably do not eliminate it.(4)

- Multiple studies clearly demonstrate that approximately 70% of HPV DNA positive women with cervical cancer precursors who undergo surgical excision subsequently become HPV DNA negative.(31)

2. Decrease the efficiency of transmission
The most common approach to decreasing the efficiency of transmission of a STD is to use physical barriers such as condoms.

- However, because HPV is transmitted through skin-to-skin contact, and infections can occur on genital areas not protected by condoms (in men: the scrotum, groin area, base of the penis, anus; in women: the outside of the vulva), condoms cannot offer complete protection from HPV infection.

- While available scientific evidence suggests that the effect of condoms in preventing HPV infection is unknown, condom use has been associated with lower rates of the HPV-associated diseases of genital warts, CIN, and cervical cancer.(4)

- Current scientific evidence does not support the use of condoms as the optimal prevention strategy for preventing genital HPV infection (although they do help, they are not 100% effective), but it does indicate that using condoms may reduce the risk of cervical cancer.(4)

No microbicides are currently available that have been shown to prevent genital HPV infection, although clinical studies are underway.

3. Reduce the number of sex partners
The most effective personal prevention approach is to avoid contact with genital HPV infection by limiting the number and type of sex partners.

- The surest way to prevent future HPV infection is to abstain from any genital contact, including non-penetrative intimate contact of the genital area.(16)

- For those who choose to be sexually active, long-term mutual monogamy with a single uninfected partner is likely to be the next most effective approach to prevent infection.(32) However, it is difficult to determine whether a partner who has been sexually active in the past is currently infected with HPV because most infected people are asymptomatic and have never had evidence of HPV-related conditions of genital wars, Pap test abnormalities, or cervical cancer.(15)

- For those choosing to be sexually active who are not in long-term mutually monogamous relationships, reducing the number of sex partners and choosing a partner who is less likely

to be HPV infected (e.g., partner with no or few previous sex partners) may reduce the risk of genital HPV.(16)

Counseling People Infected with Genital HPV

Limited Knowledge

The general United States population has very limited knowledge regarding HPV and its relationship with cervical cancer. In fact, only about one-third of men and women in the U.S. general population have heard of HPV.(33)

Although nearly all university students have heard of genital warts, between 28% and 67% have never heard of HPV.(34)

Among those who have heard of HPV, few are aware that it is associated with cervical cancer, that it can be present without symptoms, or that it can be transmitted by both penetrative and non-penitrative genital contact, regardless of whether a condom has been used.(35)

Anxiety and Concern

Although there is limited information on this subject, some studies demonstrate a high level of anxiety and concern among individuals when informed that they are infected with HPV.(36)

Both men and women diagnosed with a first episode of genital warts may have considerable psychological difficulties including anxiety/insomnia, social dysfunction, and depression. These responses are similar to those seen in patients with other STDs.(37)

Some studies indicate that women told that they have an abnormal Pap test and are also infected with HPV are more anxious, distressed, and concerned than women who are told they have only an abnormal Pap test.(38)

One study found that women who were most anxious about the possibility of testing positive for HPV were most likely to refuse HPV DNA testing.(6)

Need for More Information

Qualitative surveys indicate that women want more information about HPV, specifically with respect to transmission, prevention, progression, and treatment, as well as risk of cancer.(3)

Unfortunately, because the amount of time that clinicians have available for counseling about HPV is limited and the messages are reasonably complex, women often receive cursory and confusing information.

Providing written educational material or videos before one-on-one discussions with patients facilitates counseling. Health-care providers must be prepared to answer questions factually and to discuss the questions that don't currently have answers.

The key educational messages that patients should get are:

- ✓ HPV infection is very common in sexually active women, but very few will develop cervical cancer.
- ✓ Having HPV is not a reliable indicator of a woman's sexual behavior or that of her partner.
- ✓ Most HPV infections are transient, harmless, have no signs or symptoms, and are cleared by the immune system.
- ✓ Persistent infection over many years with a high-risk HPV type is necessary but not sufficient for the development of cervical cancer.
- ✓ Cervical cancer can be prevented by early detection of abnormal cell changes.
- ✓ The most important tool to prevent cervical cancer is regular cervical cancer screening with the Pap test for all sexually active women.

HPV Vaccines

Over the last decade pharmaceutical companies have been developing HPV vaccines. Two of the most promising vaccines are now in the final stages of clinical testing. These vaccines consist of recombinant HPV capsid proteins that coassemble to form viral-like particles (VLPs) that resemble infectious virions, but are non infectious since they lack viral DNA.

These two vaccines are both prophylactic and should ideally be administered before onset of sexual activity. Both vaccines contain HPV 16 and 18 VLPs. One of the vaccines also includes HPV 6 and 11 to prevent the development of genital warts.

Although the vaccines are not yet licensed for use by the FDA, extremely promising results have been observed in Phase II clinical trials.(39)

Recently, a vaccine for HPV 16 given to adolescent girls demonstrated 91% efficacy in preventing HPV 16 infection and essentially complete protection (100% efficacy) in preventing persistent HPV 16 infection. (39)

Mathematical models indicated that the vaccines will reduce an individual's lifetime risk of developing cervical cancer by about 50%.(41)

After FDA licensure of HPV vaccines, advisory groups will need to consider recommendations for appropriate use of these vaccines.

Therapeutic vaccines—vaccines that prevent the development of precancerous cells—are also in progress but are in earlier stages of development.(42)

Prevention of Cervical Cancer

Rationale for and Impact of Screening with Cervical Cytology
The purpose of cervical cancer screening is to identify high-grade cervical cancer precursors that can be treated before they progress to cervical cancer.(43)

Cervical cancer once claimed the lives of more American women than any other type of cancer. But over the last 40 years, widespread cervical cancer screening using the Pap test and treatment of precancerous cervical abnormalities has resulted in a marked reduction in the incidence of and mortality due to cervical cancer in the U.S.(3)

According to the American Cancer Society, in 2005 there will be only 10,370 cases of cervical cancer and 3,710 deaths in the U.S.(43)

Age to initiate and end screening and screening frequency		
Parameter	**ACS Guidelines**	**USPSTF Guidelines**
Age to start screening	Three years after onset of sexual activity, but no later than 21 years	Three years after onset of sexual activity, but no later than 21 years
Age to stop screening	At 70 years—if three consecutive normal Pap smears and no history of abnormal cytology tests in the last 10 years	At 65 years—if adequate recent screening with normal Pap smears and not otherwise at high risk for cervical cancer
Screening post-hysterectomy for benign disease	Not indicated if documented that hysterectomy was for benign disease	Not indicated if documented that hysterectomy was for benign disease
Cytologic screening—interval up until age 30	Annually with conventional Pap or every two years with liquid-based cytology	Every three years
Cytologic screening—interval after age 30	After three consecutive negative Pap smears, can screen every two to three years unless history of DES exposure, or are HIV+ or immunocompromised	Every three years

ACS=American Cancer Society (45)
USPSTF=U.S. Preventive Services Task Force (44)

Key Public Health Message
Approximately half of all cervical cancers occur in women who have never been screened.(46) Therefore clinicians should ensure that all patients who have never or rarely been screened receive screening.

HPV DNA Testing
A molecular test to detect HPV DNA is used to determine if a person has HPV. These tests detect people who are actively shedding HPV but do not detect those with dormant infections who are producing a minimal amount of virus.

Available Testing Methods
There are no routine culture methods for culturing HPV. HPV serologic (blood) tests that detect antibodies to HPV are not routinely used because only 50%-70% of people with detectable HPV DNA develop antibodies. In addition, antibodies against genital HPV types are found in women who have not had sexual intercourse.(4)

The only molecular test for detecting HPV DNA that is currently FDA-approved is a solution hybridization method.

This test is configured to detect either high-risk types of genital HPV DNA (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) or low-risk types of HPV DNA (6, 11, 42, 43, 44).

There are no accepted clinical uses for testing for the low-risk types.(47)

Sensitivity of the Test
- The sensitivity of the solution hybridization test is 5,000 copies of HPV DNA. This sensitivity was selected to result in optimal detection of women with CIN 2,3 or cancer while identifying as few women as possible without CIN 2,3 or cancer as being HPV DNA positive.

- Using this test, 90%-95% of women with CIN 2,3 are classified as high-risk HPV DNA positive. (48)

- However, the sensitivity of the test means that a person who is negative on the test may in fact have an HPV infection.

- Therefore the test is not used to determine whether someone is infected with HPV but rather whether they are at risk for having or developing a CIN 2,3 lesion in the next three years.

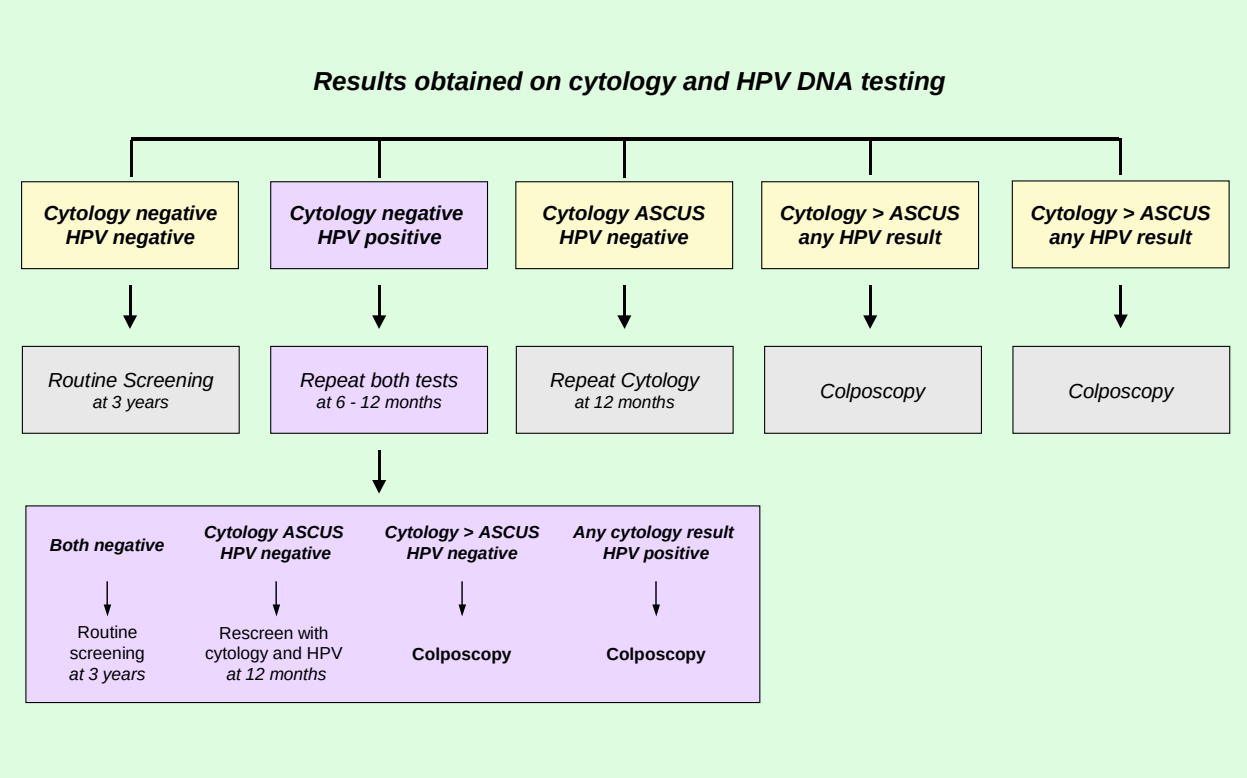
Use of the Test in Males
The performance of molecular tests for HPV DNA in males is not as well validated as in women. In large part this reflects problems with collecting an adequate sample of epithelial cells from ano-genital surfaces for analysis. In order to collect sufficient material for testing, relatively abrasive methods are required.(49)

Clinical Management Issues

Clinical Uses of HPV DNA Testing

The solution HPV DNA test is currently FDA-approved for:

- Use in management of women with cervical cytology results of atypical squamous cells of undetermined significance (ASC-US); and
- Routine adjunctive screening with a Pap test for women age 30 and older (e.g., use in conjunction with a Pap test for primary screening).



The 2001 Consensus Guidelines for Managing Women with Cytologic Abnormalities also indicate that testing for high-risk HPV DNA can be useful in the following settings:

- Post-treatment surveillance of women with CIN 2,3 who have undergone treatment;
- Follow-up post-colposcopy among women with abnormal Pap test results who require additional follow-up; and
- Follow-up among women with biopsy-confirmed CIN 1.

Use of HPV DNA Testing in Managing Women with ASC-US(47)

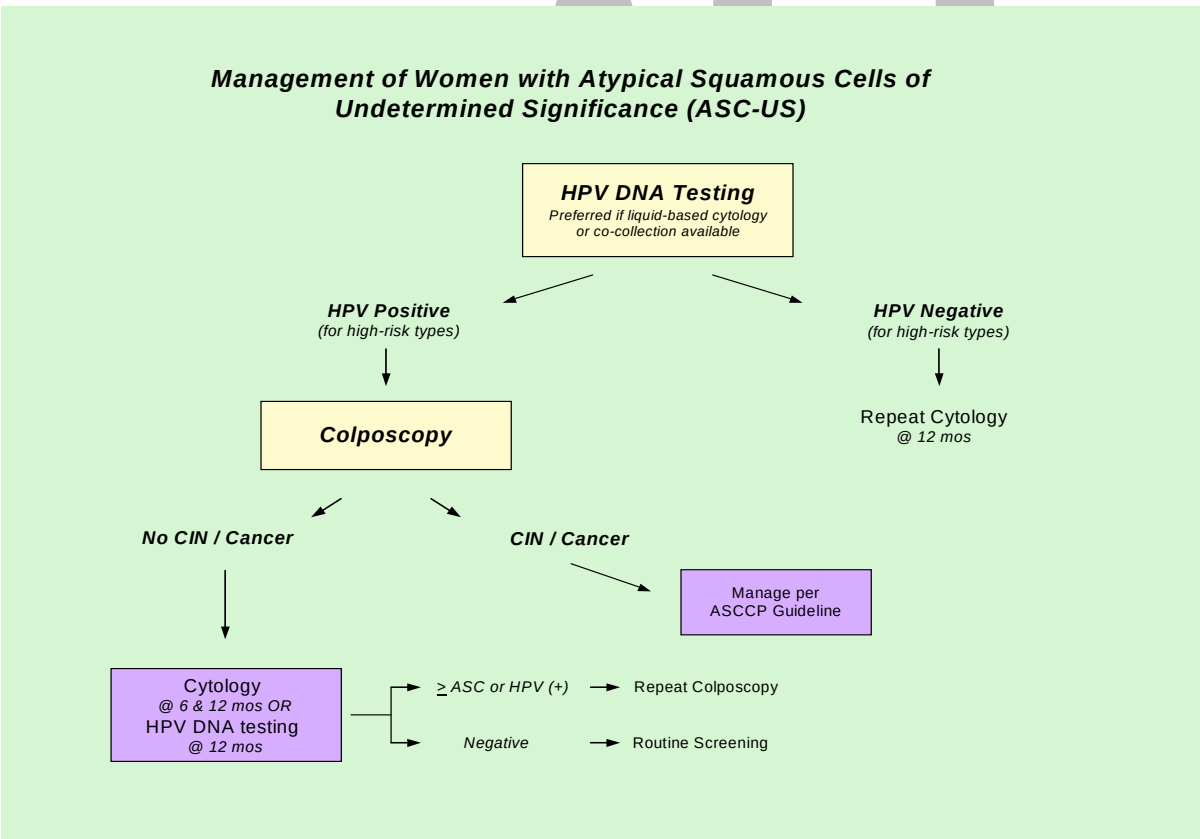
Borderline cytologic abnormalities referred to as atypical squamous cells of undetermined significance (ASC-US) are quite common in the U.S. Approximately 4%-5% of all cervical cytology results are reported as ASC-US.

There are three acceptable approaches to managing women with ASC-US:

- Repeat cytology testing at 4-6 month intervals until two consecutive negative cytology results are obtained;
- Immediate colposcopy; or
- High-risk HPV DNA testing with referral to colposcopy if the woman is found to be HPV DNA positive.

In the published studies, HPV DNA testing appears to be more sensitive than repeat cytology and appears to refer fewer patients to colposcopy compared to a program of repeat cytology.

High-risk HPV DNA testing is the preferred approach to managing women with ASC-US whenever liquid based cytology is used for screening or co-collection of a sample for HPV DNA testing can be performed.



Use of HPV DNA Testing for Routine Adjunctive Screening with a Pap Test for Women Age 30 and Older(50)

Combining molecular testing for high-risk types of HPV together with a Pap test is considered by the ACS and the American College of Obstetricians and Gynecologists (ACOG) to be an acceptable approach to cervical cancer screening in women age 30 and older.

The U.S. Preventive Services Task Force found the evidence insufficient to recommend for or against the routine use of HPV DNA testing as a primary screening test for cervical cancer.

Studies Comparing Performance of HPV DNA Testing with That of Pap Test
The sensitivity of a single cervical cytology for identifying women with CIN 2,3 or cancer was 33%-94% in the screening studies that have compared the performance of HPV DNA testing with that of cytology.

In most of the studies, the sensitivity of cytology was 57%-80%.

The sensitivity of a HPV DNA test in the same studies was 85%-100%.

Combining both HPV DNA testing and cytology resulted in negative predictive values (NPV) for CIN 2,3 and cancer of 0.988 or greater. In these studies and in most studies, the NPV was 0.999 or greater. However the specificity of HPV DNA testing was slightly lower than that of cervical cytology.

Concerns

- Because 5%-15% of women age 30 and older will be high-risk HPV DNA positive, there is considerable concern about potential negative impacts of the misuse of using HPV DNA testing for screening.

- Concerns relate to lack of counseling of women with respect to their risk of cervical disease, the source of their infection and their infectivity. There also is considerable concern that HPV DNA positive women without CIN 2,3 or cancer will undergo unnecessary intensive follow-up or treatment.

Recommendations (50)

- Women who are HPV DNA negative and cytology negative are at very low risk for having CIN 2,3 or developing it within the next three years and should not be rescreened before three years.

- The risk that women who are HPV DNA positive but cytology negative will have CIN 2,3 or cancer is very low. Therefore colposcopy should not be performed in this circumstance routinely. HPV DNA testing along with cervical cytology should be repeated at six to 12 months. If the woman is persistently high-risk HPV DNA positive, then she should receive a colposcopic examination.

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