

Human Papillomavirus: HPV Information for Clinicians

- Transmission
- Prevention
- Detection
- Clinical Management

Centers for Disease Control
and Prevention

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HPV
Common Infection.
Common Reality.™

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Section I: Genital HPV Infection

Why is it Important to Know About HPV?

Genital infection with human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States (U.S.) today.¹ Over half of sexually active women and men are infected with HPV at some point in their lives.²

In most cases, infections with HPV are not serious. Most HPV infections are asymptomatic, transient, and resolve without treatment. However, in some individuals, HPV infections result in genital warts, Pap test abnormalities, or, rarely, cervical cancer.³

The Pap test is useful in early detection of cervical cancer, one of the possible outcomes of an HPV infection. Early detection and treatment of pre-cancerous lesions can prevent development of cervical cancer.⁴

What is HPV?

Papillomaviruses are DNA tumor viruses that are widely distributed throughout animal species; these viruses are species-specific. The papillomavirus

that infects humans is called human papillomavirus, or HPV. HPV commonly causes epithelial proliferations at cutaneous and mucosal surfaces.

Types of HPV

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

Over 40 types infect mucosal surfaces, including the anogenital epithelium (e.g., cervix, vagina, vulva, rectum, urethra, penis, and anus). For most of these HPV types, there are sufficient data to divide them into “high-risk” (e.g., oncogenic or cancer-associated) types and “low-risk” (e.g., non-oncogenic) types (see *Table 1* on page 2).

How Common is HPV?

Approximately 20 million Americans 15 to 49 years of age (approximately 15% of the population) are currently infected with HPV.⁵ Others may have been infected in the past and may no longer have the virus. About half of those who are infected with HPV are sexually active adolescents and young adults 15 to 24 years of age.⁵ Between 5% and 30% of individuals infected with HPV are infected with multiple types of HPV.⁶

- Each year, about 6.2 million people in the U.S. become newly infected.¹
- Estimates for the incidence and prevalence of genital warts

caused by low-risk types of HPV are imprecise. About 1% of sexually active adults have visible genital warts at any point in time.⁷

Table 1: Types of HPV

| High-risk (oncogenic or cancer-associated) types | Low-risk (non-oncogenic) types |
|--|--|
| <p>Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82</p> | <p>Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 73, 81</p> |
| <p>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).</p> <ul style="list-style-type: none"> • <i>HPV 16</i> is the most common high-risk type, found in almost half of all cervical cancers. It is also one of the most common types found in women without cancer.⁸ • <i>HPV 18</i> is another common high-risk virus, found not only in squamous lesions but also in glandular lesions of the cervix. HPV 18 accounts for 10% to 12% of cervical cancers.⁸ <p>All of the other high-risk types can be associated with cervical cancer, but much less frequently than HPV 16 and 18. HPV types 31, 33, 45, 52, and 58 each account for between 2% to 4% of cancers. Each of the other high-risk types account for 1% or less of cancers.⁹</p> | <p>These can cause benign or low-grade cervical cell changes and genital warts but are rarely, if ever, found in association with invasive cancers.</p> <ul style="list-style-type: none"> • <i>HPV 6</i> and <i>HPV 11</i> are the low-risk viruses that are most commonly found in genital warts.⁸ |

Table 2: Factors Strongly Associated with Acquisition of HPV Infection in Women^{2, 10, 11, 12}

A number of prospective studies conducted primarily in young women have defined the risk factors for HPV acquisition.

- Young age (less than 25 years)
- Increasing number of sex partners
- Early age at first sexual intercourse (16 years or younger)
- Male partner has (or has had) multiple sex partners

How is Genital HPV Transmitted?

HPV is usually transmitted through direct skin-to-skin contact, most often during penetrative genital contact (vaginal or anal sex). Other types of genital contact in the absence of penetration (oral-genital, manual-genital, and genital-genital contact) can lead to HPV infection, but those routes of transmission are much less common than sexual intercourse.¹³

Genital HPV infections are uncommon in women reporting no previous sexual intercourse, appearing in less than 2% of this population.^{13, 14, 15}

Sexual behavior is the most constant predictor of acquiring infection. Most importantly, the number of sex partners is

proportionately linked to the risk of HPV infection.^{10, 11, 13}

Having sex with a new partner may be a stronger risk factor for initial HPV acquisition than having sex with a steady partner.^{13, 16}

For women, the sexual activity of their partner(s) is also important for determining risk of HPV acquisition. For adolescent females and college students, the risk of acquiring HPV is increased if a woman's partner has had or currently has other partners.¹⁶

HPV infections are also common in men who have sex with men (MSM) and women who have sex with women.¹⁷ HPV DNA can be detected in swabs from the anal canal in over 50% of MSM.¹⁸

HPV infection can be detected on inanimate objects, such as clothing or environmental surfaces. However, transmission is not known to occur by this route.^{19, 20}

Natural History of Genital HPV Infections

Most genital HPV infections are transient and asymptomatic.

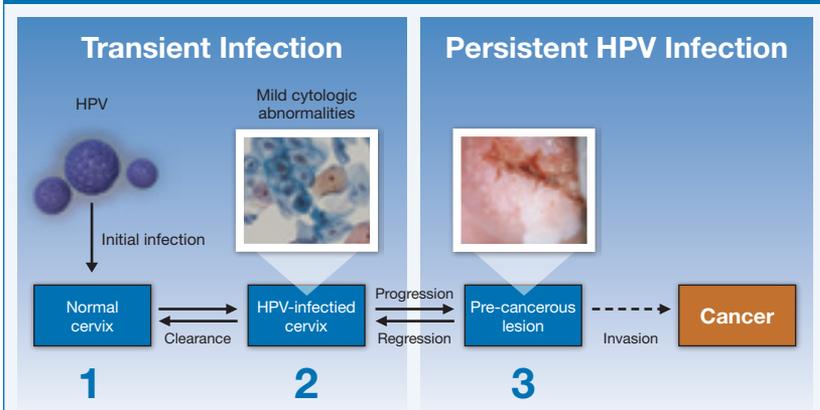
Approximately 70% of women with HPV infections become HPV DNA negative within one year, and as many as 91% of them become HPV DNA negative within two years.^{10, 16, 21, 22} The median

duration of new infections is typically eight months.¹⁰

HPV 16 infections tend to persist longer than infection with other HPV types, but most HPV 16 infections become undetectable within two years.¹⁰

The gradual development of an effective immune response is thought to be the likely mechanism for HPV DNA clearance.⁴ However, it is also possible that the virus remains in a non-detectable dormant state and then reactivates many years later. This may explain why HPV may be newly detected in some

The Three Steps of Cervical Carcinogenesis



The steps can be conceptualized as infection with specific high-risk types of human papillomavirus (HPV), progression to a precancerous lesion, and invasion. HPV infections are usually transient and are often associated with mild cytologic abnormalities. Persistent infection with high-risk types of HPV is uncommon and is required for progression.

Reprinted from "Adding a test for human papillomavirus DNA to cervical-cancer screening." Wright TC and Schiffman M. *New England Journal of Medicine* 2003 Feb 6; 348(6): 489-490. Copyright 2003 Massachusetts Medical Society. All rights reserved.

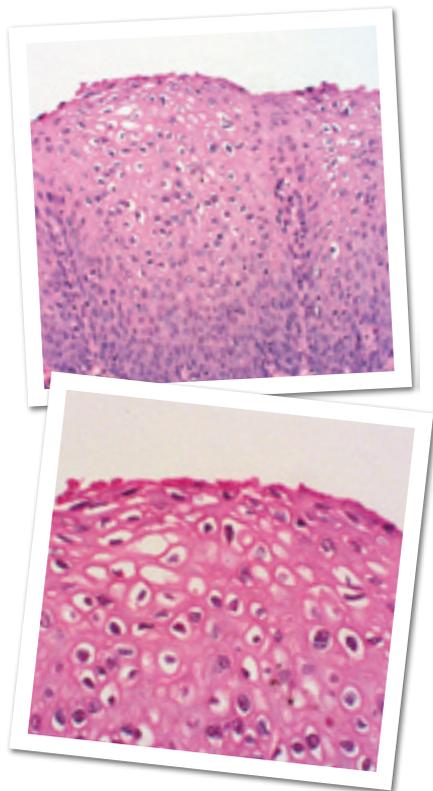
older women who have been in a long-term mutually monogamous relationship.¹

Many women with transient HPV infections may develop atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL), as detected on a Pap test. These are mild cytologic abnormalities that represent the cytopathic effect caused by HPV infection, and they may spontaneously regress.

Only about 10% of women infected with HPV develop persistent HPV infections.²³

Women with persistent high-risk HPV infection are at greatest risk for developing high-grade cervical cancer precursors and cancer. The risk of developing moderate to severe dysplasia, or grades 2 or 3 cervical intraepithelial neoplasia (CIN 2, 3) lesions, for women with persistent high-risk HPV infection is not well defined. However, the risk is greater than that of women whose infections clear spontaneously.^{24, 25}

Currently, there are no data available on the natural history of HPV infection in men.



Top: The epithelium of the CIN 1 lesion is thickened and the upper layers contain cells characterized by perinuclear halos, multinucleation, and significant nuclear atypia. Such cells are referred to as “koilocytes.”

Bottom: This high-powered magnification of a CIN 1 lesion shows the nuclear irregularities typically seen in “koilocytes.”

Factors Influencing HPV Persistence and Progression to Cervical Cancer

Several risk factors have been identified that appear to be associated with HPV persistence as well as progression to cervical cancer. **The single most important factor associated with invasive cervical cancer is the factor of never or rarely being screened for cervical cancer.** The National Institutes of Health (NIH) estimates that half of the women who receive cervical cancer diagnoses have never been screened for cervical cancer and that an additional 10% have not been screened in the previous five years.⁴

Immunosuppression from any cause, including HIV infection, is recognized to increase HPV persistence and to be associated with increased risk of invasive cervical cancer.^{22, 26}

Cigarette smoking has been associated with HPV persistence and risk of cervical cancer. Multiple case-control studies show a moderate and statistically significant association between smoking and cervical cancer, even after adjusting for the effects of HPV.²⁷

Other epidemiologic factors associated with risk of cervical cancer include long-term use of oral contraceptives,²⁷ co-infections such as Chlamydia,²⁸ parity, and nutritional factors.^{29, 30, 31, 32}

However, in populations that are screened regularly, as is typical in the U.S., cervical cancer develops rarely in women, even with persistent HPV infection. This is because women with high-grade precursor lesions are usually identified through cytologic screening, and the development of cancer can be prevented through early detection and treatment.

What are Potential Outcomes Associated with Genital HPV Infection?



An exophytic invasive cervical cancer of the cervix.

Most HPV infections are asymptomatic, and they resolve without treatment. However, some infections result in changes to the epithelium—or cancer.

Women

Genital infection with low-risk types of HPV is associated with genital warts in women.

Persistent infection with high-risk types of HPV is associated with almost all cervical cancers and many cancers of the vulva, vagina, and anal regions. However, the risk for anal, vulvar, and vaginal cancers is considerably less than the risk for cervical cancer.

In 2002 (most recent year for which data are available), the age-adjusted incidence rate* for invasive cervical cancer in the U.S. was 8.7 per 100,000 women (12,085 new cases). In

comparison, the age-adjusted incidence rates for anal, vulvar, and vaginal cancers were 1.5, 2.3, and 0.7 per 100,000 women, respectively.³³

While infection with high-risk HPV is necessary for the development of cervical cancer, most infections do not result in cancer.

Women with HPV infection who spontaneously clear their infection and continue to be HPV DNA negative appear to be at very low risk for subsequently developing cervical cancer.

Men

Genital infection with low-risk types of HPV is associated with genital warts in men.

Infection with high-risk types of HPV is associated with a proportion of preinvasive squamous lesions of the penis

* The number of new cases of a disease that occur in a population in a given year, accounting for the age differences between populations.

(penile intraepithelial neoplasia or PIN) and with penile cancer, as well as with preinvasive squamous lesions of the anus (anal intraepithelial neoplasia or AIN) and with anal cancer.

Invasive penile cancer is quite uncommon, especially in circumcised men. In 2002, the age-adjusted incidence rate for penile cancer in the U.S. was 0.8 per 100,000 men (985 new cases).

The age-adjusted incidence rate for anal cancer was 1.2 per 100,000 men (1,453 new cases). However, the risk of anal cancer for MSM is significantly higher.^{34, 35} Because of the increased incidence of anal cancer in MSM, especially HIV-infected MSM, some specialists recommend screening for AIN by cytology in this population. However, there are limited data on the natural

history of AIN, the reliability of screening methods, the safety and response to treatments, and the programmatic considerations that would support this screening approach. Until more data are generated on screening for AIN, this screening approach is not recommended.³⁶

Children

Very rarely, genital HPV infections can be transmitted from mother to baby during delivery.³⁷ Perinatally transmitted infections with low-risk HPV types can result in respiratory tract warts in children, a condition known as recurrent respiratory papillomatosis (RRP). RRP is very rare. Estimates of the incidence rate for RRP are imprecise but range from 0.4 to 1.1 cases per 100,000 live births to women with a history of genital warts.³⁸

It is unclear whether cesarean delivery prevents RRP in infants and children; thus, cesarean delivery should not be performed solely to prevent HPV infection in the newborn. Cesarean delivery may be indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.



Multiple condylomata acuminata on penis. Included with permission from the Cincinnati STD/HIV Prevention Training Center.

Prevention of Genital HPV Infection

Prevention of genital HPV infection is important in reducing the prevalence of genital warts, abnormal Pap tests, and cancer.

HPV Vaccines

Quadrivalent HPV Vaccine

- A new quadrivalent vaccine, Gardasil[®], protects against four HPV types (6, 11, 16, 18), which are responsible for 70% of cervical cancers and 90% of genital warts.
- This prophylactic vaccine is made from non-infectious HPV-like particles (or virus-like particles, VLP); it does not contain thimerosal or mercury.
- The vaccine is administered through a series of three intramuscular injections over a six-month period (at 0, 2, and 6 months).
- On June 8, 2006, this vaccine was licensed by the Food and Drug Administration (FDA), becoming the first licensed vaccine developed to prevent cervical cancer and other diseases in females caused by genital HPV infection.

- On June 29, 2006, the Advisory Committee on Immunization Practices (ACIP) voted to recommend use of the quadrivalent vaccine in females, ages 9 to 26 years of age.

ACIP Recommendations for HPV Vaccine

The vaccine should be administered to 11- to 12-year-old girls and can be administered to girls as young as 9 years of age. The vaccine also is recommended for 13- to 26-year-old females who have not yet received or completed the vaccine series.

- Ideally, the vaccine should be administered before onset of sexual activity. However, females who are sexually active also may benefit from vaccination. Females who already have been infected with one or more HPV type would only get protection from the vaccine type(s) they have not acquired.
- For more information about the ACIP recommendations, including indications and contraindications for use, see *MMWR* 56(RR02);1-24, or www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm.

Vaccine Safety, Efficacy, and Duration of Protection

- In studies of over 11,000 females (9 to 26 years of age), the vaccine has been found to be safe and to cause no serious side effects. Adverse events were mainly mild injection site pain.
- Clinical trials have demonstrated 100% efficacy in preventing cervical precancers caused by the targeted HPV types and nearly 100% efficacy in preventing vulvar and vaginal precancers and genital warts caused by the targeted HPV types among women ages 16 to 26 years, who were naive to the specific HPV vaccine types.³⁹
- Data do not indicate that the vaccine has any therapeutic effect on HPV infection or HPV-associated disease, including existing Pap test abnormalities or genital warts.
- While it is possible that vaccination of males with the quadrivalent vaccine may offer direct health benefits to males and indirect health benefits to females, there are currently no efficacy data available to support use of HPV vaccine in males. Efficacy studies in males are ongoing.
- The duration of vaccine protection is unclear.⁴⁰ Current studies (with five-year followup) indicate that the vaccine is effective for at least five years.

There is no evidence of waning immunity during that time period.

HPV Vaccine Cost and Coverage

- The private-sector list price of the vaccine is \$119.75 per dose (about \$360 for the full series).
- The federal Vaccines for Children (VFC) Program will provide free vaccines to children and adolescents under 19 years of age who are uninsured, Medicaid-eligible, American Indian, or Alaska Native. The VFC Program also allows children and adolescents to receive VFC vaccines through Federally Qualified Health Centers or Rural Health Centers, if their private health insurance does not cover the vaccine.
- Some states also provide free or low-cost vaccines at public health department clinics to people without health insurance coverage for vaccines.
- While some insurance companies may cover the vaccine and cost of administration, others may not. Most large group insurance plans usually cover the cost of recommended vaccines. However, there is often a short lag-time after a vaccine is recommended and before it is available and covered by health plans.

Although this vaccine offers a promising new approach to the prevention of HPV and associated conditions, this vaccine will not replace other prevention strategies, such as cervical cancer screening or protective sexual behaviors, because the vaccine will not protect against all types of genital HPV infection.⁴¹ Cervical cancer screening recommendations have not changed for females who receive the HPV vaccine.

Vaccine providers should notify vaccinated females that:

- They will need regular cervical cancer screening as the vaccine will not provide protection against all types of HPV that cause cervical cancer.
 - They should practice protective sexual behaviors (e.g., abstinence, monogamy, limiting their number of sex partners, and using condoms), as the vaccine will *not* prevent all cases of genital warts—nor will it prevent other STIs.
 - They may not receive the full benefits of the vaccine if they receive the vaccine after they have become sexually active (and may have acquired a vaccine HPV type) or if they do not complete the full vaccine series.
-

Counseling messages for prospective vaccine recipients are provided in an insert at the end of this booklet.

Other Vaccines in Development

- A bivalent HPV vaccine was submitted to FDA in March 2007 and may be licensed in the next year. This vaccine would protect against the two types of HPV (16, 18) that cause 70% of cervical cancers.
- Therapeutic HPV vaccines—vaccines that prevent development of pre-cancerous cells in women already infected with HPV—are not as far along in clinical trials.

For updates on HPV vaccines, please visit:

Centers for Disease Control and Prevention (CDC) Division of STD Prevention's HPV website, www.cdc.gov/std/hpv

CDC's National Immunization Program website, www.cdc.gov/nip

ACIP's website, www.cdc.gov/nip/ACIP

VFC website, www.cdc.gov/nip/vfc

Other Strategies to Prevent HPV Infection

Other strategies to prevent HPV transmission may include (a) reducing the duration of infectiousness, (b) decreasing the efficiency (likelihood) of transmission, and (c) reducing the number of sex partners.

(a) Reduce the Duration of Infectiousness

The most common approach to reducing infectiousness of an STI is treatment. However, there is no effective systemic treatment for genital HPV, and treatment is not recommended for subclinical genital HPV infection (diagnosed by colposcopy, biopsy, or acetic acid application or detected by laboratory tests) in the absence of squamous intraepithelial lesions (SIL).³⁶ There is minimal evidence that treatment of HPV-associated lesions can prevent HPV transmission.

- Treatment for genital HPV may be applied to lesions, such as genital warts (see *Genital Warts* section, page 23), or cervical cancer precursors (using treatments, such as cryotherapy, electrocautery, or surgical excision).⁴²
- Some evidence suggests that treatment of genital warts reduces the amount of HPV DNA that can be found in the tissue. However, it is unknown whether treatment reduces infectivity of partners.^{41, 43}

- It is unclear what proportion of HPV-infected persons who spontaneously become HPV DNA negative truly clear HPV, and in what proportion of such individuals HPV simply becomes dormant or undetectable.

(b) Decrease the Efficiency of Transmission

The most common approach to decreasing the efficiency of transmission of an STI is to use physical barriers, such as condoms.

As reported in CDC's *Sexually Transmitted Diseases (STD) Treatment Guidelines, 2006*:³⁶

- Condom use might reduce the risk for HPV-associated diseases (e.g., genital warts and cervical cancer⁴⁴) and mitigate the adverse consequences of infection with HPV. The use of condoms has been associated with higher rates of regression of CIN and clearance of HPV infection in women⁴⁵ and with regression of HPV-associated penile lesions in men.⁴⁶
- A limited number of prospective studies have demonstrated a protective effect of condoms on the acquisition of genital HPV. One recent prospective study among newly sexually active college women demonstrated that consistent condom use

was associated with a 70% reduction in risk for HPV transmission.⁴⁷

- However, HPV infection can occur in areas that are not covered or protected by a condom (e.g., scrotum, vulva, or perianus).

(c) Reduce the Number of Sex Partners

- The surest way to prevent HPV infection is to abstain from any genital contact, including non-penetrative intimate contact of the genital area.¹³
- 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.⁴⁸ However, it is usually impossible to determine whether a partner who was sexually active in the past is currently infected with HPV, as most infected people are asymptomatic and have never had evidence of HPV-related conditions, such as genital warts or Pap test abnormalities.²
- For those choosing to be sexually active, but who are not in long-term mutually monogamous relationships, reducing the number of sex partners is another effective strategy to avoid acquisition of genital HPV infection. Choosing a partner who is

less likely to be HPV-infected (e.g., a partner with no or few previous sex partners) may help reduce the risk of acquiring genital HPV.¹³

Detection of Genital HPV Infection

HPV DNA Test

Molecular tests can be used to detect HPV DNA. The only such test that is currently approved by the FDA is Digene's Hybrid Capture II® HPV Test, a solution hybridization method to test for high-risk HPV DNA. Samples that can be tested with this technology include exfoliated cervical cells collected with a specially designed brush and placed into a liquid medium or in residual fluid left over from liquid-based cytology specimens. This HPV DNA test is designed to detect high-risk types of HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The HPV DNA test detects whether one or more types of HPV are present; it does not identify individual HPV types.

The FDA has approved this high-risk HPV DNA assay for use in some women in the context of cervical cancer

screening (see FDA-Approved Indications for High-Risk HPV DNA section, page 19). The principal utility of the test is in identifying women with high-risk HPV who are at risk for having or developing pre-cancerous or cancerous changes (CIN 2, 3 lesion) in the 36 months following initial testing.

Another test is available to detect low-risk types of HPV, but this test is not FDA-approved and there are no clinical indications for this test.^{1, 28, 29, 49}

Direct-to-consumer advertising may prompt demand for the HPV test. However, while patients may request an HPV test, use of this test should be limited to the uses recommended by professional organizations (see FDA-Approved Indications for High-Risk HPV DNA Testing, page 19).

There is currently no FDA-approved HPV DNA test for males, nor is HPV testing of males recommended. There is no clinical utility in testing men for HPV; infection does not indicate increased risk of disease for the man or his partner. While HPV is common in men, HPV-associated cancers are rare.

HPV DNA testing should not be used:

- for men;
- to check the HPV status of patients with genital warts or other STIs;
- to check the HPV status of partners of patients with genital warts or other STIs;
- to check the HPV status of partners of women with cervical cancer abnormalities; or
- to check the HPV status of pregnant women.

Other HPV Tests

There are no routine methods for culturing HPV. Serology tests are available for HPV, but these tests are used only in research settings. Many persons with detectable HPV DNA do not have antibodies, so these tests are not a good method to indicate infection with HPV.⁵⁰

Although primary prevention and detection are generally clinical objectives for STI care, HPV infection offers unique challenges. Infection is both very common in sexually active individuals, and it is generally asymptomatic. The ubiquitous nature of the virus, coupled with a relative rarity of clinical signs and symptoms, suggests focusing on the detection, prevention, and treatment of the potential consequences of HPV infection.

Section II: Prevention of Cervical Cancer

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 pre-cancerous cervical abnormalities have resulted in a marked reduction in the incidence of and mortality due to cervical cancer in the U.S.³ The American Cancer Society (ACS) estimates that in 2006, approximately 9,710 cases of invasive cervical cancer will be diagnosed, and 3,700 women will die from this disease in the U.S.

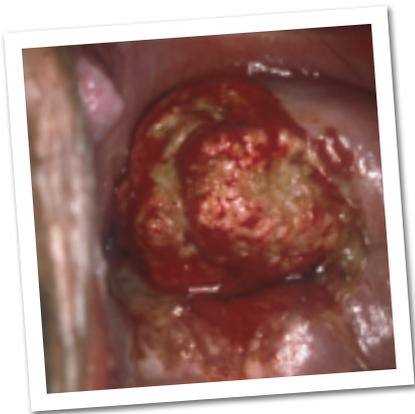
The advent of an HPV vaccine (see HPV Vaccines, page 9) now offers an additional, promising method of preventing up to

70% of cervical cancer cases through primary prevention. However, regular cervical cancer screening will still be necessary for vaccinated women because:

1. The vaccine will NOT provide protection against all types of HPV that cause cervical cancer.
2. Women may not receive the full benefits of the vaccine if they do not complete the vaccine series.
3. Women may not receive the full benefits of the vaccine if they receive the vaccine after they have already acquired a vaccine HPV type.

Key Public Health Message

Approximately half of all cervical cancers occur in women who have never been screened.³¹ Therefore, screening is particularly important in women who have never or rarely been screened.



An exophytic invasive cervical cancer of the cervix is present. When cancers are not necrotic they can sometimes be mistaken for a large cervical condyloma.

The following section focuses on secondary prevention of cervical cancer through cytology and HPV DNA testing. For an overview of primary prevention through vaccines, please see the *HPV Prevention* section on page 9.

Table 3: Cervical Cancer Screening Guidelines

| | |
|---|---|
| | <p>American Cancer Society¹ www.cancer.org (ACS, Nov 2002)</p> |
| When to start | Approximately 3 years after onset of vaginal intercourse, but no later than age 21 |
| <p>Intervals</p> <ul style="list-style-type: none"> • Conventional Pap test • If liquid-based cytology used** • If HPV testing used** | <ul style="list-style-type: none"> • Annually; every 2-3 years for women ≥ 30 with 3 negative cytology tests* • Every 2 years; every 2-3 years for women ≥ 30 with 3 negative cytology tests* • Every 3 years if HPV negative, cytology negative |
| When to stop | Women >70 years with >3 recent, consecutive negative tests & no abnormal tests in prior 10 years* |
| Post total hysterectomy | Discontinue if for benign reasons & no prior history of high-grade CIN* |

* Some exceptions apply (e.g., women who are immunocompromised, have a history of prenatal exposure to DES). See guidelines for details.

** See Table 2 at www.cdc.gov/std/hpv/screening (entitled, "Recommendations for Liquid-Based Cytology and HPV Testing") for recommended use.

| | |
|---|--|
| <p>U.S. Preventive Services Task Force² www.ahrq.gov/clinic/uspstfix.htm (USPSTF, Jan 2003)</p> | <p>American College of Obstetricians and Gynecologists³ www.acog.org (ACOG, Aug 2003)</p> |
| <p>Within 3 years of onset of sexual activity or age 21, whichever comes first</p> | <p>Approximately 3 years after onset of sexual intercourse, but no later than age 21</p> |
| <ul style="list-style-type: none"> • At least every 3 years • Insufficient evidence • Insufficient evidence | <ul style="list-style-type: none"> • Annually; every 2-3 years for women ≥ 30 with 3 negative cytology tests* • Annually; every 2-3 years for women ≥ 30 with 3 negative cytology tests* • Every 3 years if HPV negative, cytology negative |
| <p>Women >65 years with negative tests, who are not otherwise at high risk for cervical cancer</p> | <p>Inconclusive evidence to establish upper age limit</p> |
| <p>Discontinue if for benign reasons</p> | <p>Discontinue if for benign reasons & no prior history of high-grade CIN*</p> |

1. Saslow D, et al. American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer. *CA Cancer J Clin* 2002; 52: 342-362. Available at <http://caonline.amcancersoc.org/cgi/content/full/52/6/342>
2. USPSTF. Screening for Cervical Cancer. Jan 2003. Available at: <http://www.ahrq.gov/clinic/uspstf/uspstfscerv.htm>
3. ACOG. Cervical Cytology Screening. ACOG Practice Bulletin No. 45. ACOG 2003;102: 417-427. See also: http://www.acog.org/from_home/publications/press_releases/nr07-31-03-1.cfm

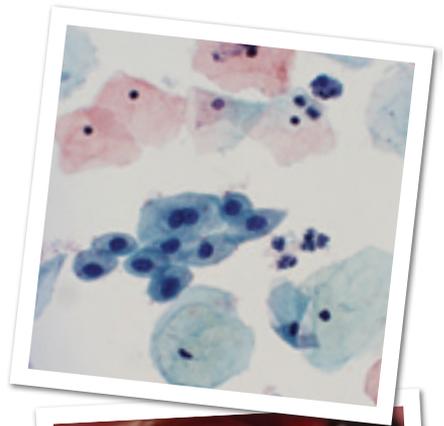
Screening with Cervical Cytology

The purpose of cervical cancer screening is to identify cervical cancer precursors that can be treated before they progress to cervical cancer.

There are three major professional organizations that issue cervical cancer screening guidelines: the U.S. Preventive Services Task Force[†] (USPSTF); the American College of Obstetricians and Gynecologists (ACOG); and the ACS. Their screening recommendations are summarized in *Table 3* on page 16.

Both conventional Pap tests (smear and slide) and a new liquid-based cytology (a method in which cervical cells are collected into a liquid medium) can be used to screen for cervical cancer.

- The sensitivity of the conventional Pap test ranges from 30% to 87%, and the specificity ranges from 86% to 100%⁵³
- The sensitivity of liquid-based cytology ranges from 61% to 95%, and the specificity ranges from 78% to 82%^{52, 53}



Top: There is a cluster of cells with enlarged, hyperchromatic nuclei present. Several binucleated cells are present in this cluster. However, very few atypical cells were present on slide and although the cells are suggestive of SIL, they are not diagnostic of SIL.

Bottom: This cervix has a well-circumscribed area of acetowhitening that appears low-grade. However, cervical biopsy was diagnosed as CIN 2,3.

[†] The U.S. Preventive Services Task Force is an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services.

HPV DNA Testing for High-Risk Types

A high-risk HPV DNA test is commercially available and approved for use in women in the setting of cervical cancer screening and management.

FDA-Approved Indications for High-Risk HPV DNA Testing

Testing is approved for:

- **Use in the management of women with ASC-US cervical cytology results.** This test can be used to help determine which women (of any age) with ASC-US cervical cytology results should be referred for colposcopy and which can be followed up with cytological screening in 12 months.⁵⁴
- **Routine adjunctive screening with cervical cytology screening for women ages 30 and older (e.g., use in conjunction with a Pap test for primary screening).** This test is not approved for use with cervical cytology screening in women younger than age 30 because HPV infection is highly prevalent and usually transient in women at younger ages, while the prevalence of cervical cancer is relatively low, compared to older women.

Use of HPV DNA Testing in Managing Women with ASC-US⁵⁵

Borderline cytologic abnormalities referred to as ASC-US are quite common in the U.S. Approximately 4% to 5% of all cervical cytology results are reported as ASC-US.

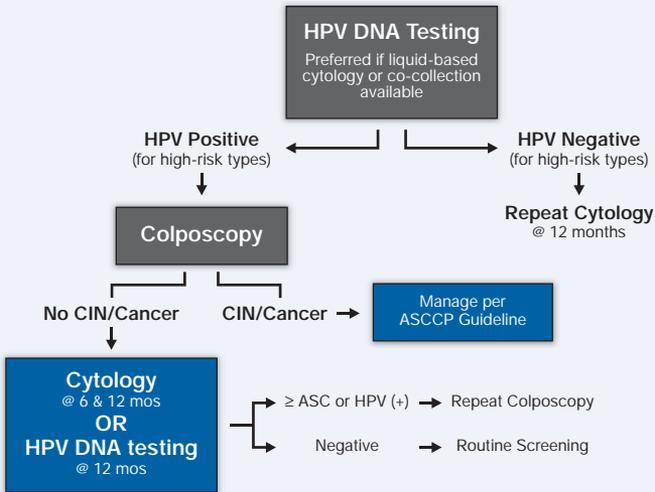
Use of the HPV DNA test in the management of women with ASC-US Pap test results is recommended as an option by the American Society for Colposcopy and Cervical Pathology (ASCCP, www.asccp.org/index.html), ACS, and ACOG. The USPSTF found the evidence insufficient in its last review (2003) to recommend for or against the use of HPV DNA testing in this setting.⁵⁶

Management of Women with ASC-US Using HPV DNA Testing

According to ACOG, ACS, and ASCCP guidelines:

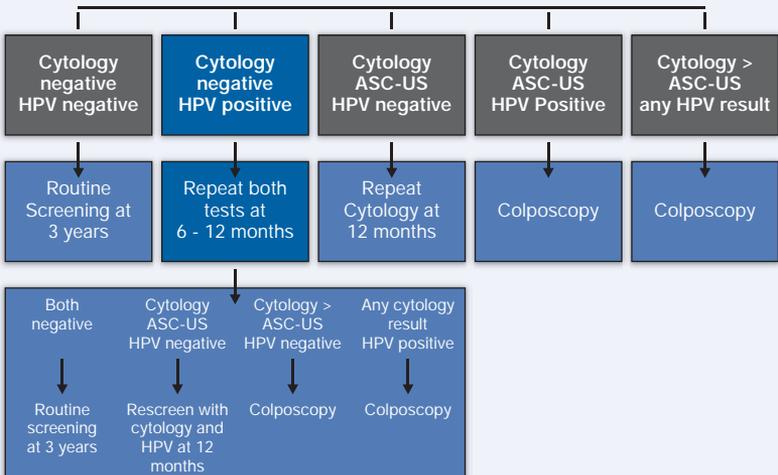
- If the woman is found to be HPV DNA positive, refer to colposcopy.
- If the woman is found to be HPV DNA negative, repeat cytology in 12 months.

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)



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Management of Women Ages 30 and Older, Based on Cytology and HPV DNA Testing Results



Reprinted from "Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening." Wright TC, Schiffman M, Solomon D, et al. *Obstetrics and Gynecology* 2004; 103(2): 304-309 fig. 1.

High-risk HPV DNA testing may be a practical approach to managing women with ASC-US whenever liquid-based cytology is used for screening or when co-collection of a sample for HPV DNA testing can be performed. This is because HPV DNA testing may be more convenient for patients than their returning for a repeat cytology; approximately half of women with ASC-US will be high-risk HPV DNA negative and will not require colposcopy.⁵⁷ HPV DNA testing in this setting has been shown to be more cost-effective than the other management strategies.^{54, 58}

Use of HPV DNA Testing for Routine Adjunctive Screening with a Pap Test for Women Age 30 and Older⁵²

The combination of molecular testing for high-risk types of HPV together with a Pap test is considered by the ACS and ACOG to be an acceptable approach to cervical cancer screening of women age 30 and older.^{54, 59, 60} However, the USPSTF found the evidence insufficient to recommend for or against the routine use of HPV DNA testing as a primary screening test for cervical cancer.⁵⁸

Patient Followup Based on Cytology and HPV DNA Testing

According to ACS and ACOG guidelines:

- Women with negative results on both tests should not be re-screened for at least three years.
- Women who are HPV DNA positive, but cytology negative, should not be referred for colposcopy. Instead, they should be re-tested with both tests in 6 to 12 months.

Re-screening for women found to be both cytology negative and high-risk HPV DNA negative can be done at three years.⁵⁴ This is because women with negative results by both cytology and HPV DNA testing have a very low risk of having a CIN 3 lesion or of developing a CIN 3 over the next three years.^{54, 61, 62, 63} The extended testing interval of three years in women who are both cytology negative and HPV DNA negative is a benefit of HPV DNA testing.

Please see the *2001 Consensus Guidelines for Managing Women with Cytological Abnormalities and Interim Guidance for Use of HPV DNA Testing as an Adjunct to Cervical Cytology for Screening* for more information.^{54, 55}

HPV DNA testing should not be used:

- in women <30 years of age with any Pap test result other than ASC-US;
- as an adjunct to Pap for primary screening of women <30 years of age;
- as an adjunct to Pap for women who are immuno-compromised for any reason, including infection with HIV; and
- as an adjunct to Pap for women who have had total hysterectomy for benign gynecologic disease.

Other Uses of HPV DNA Testing for High-Risk Types

One professional organization also recommends use of the HPV DNA test for followup of cervical abnormalities (www.asccp.org); however there is no FDA-approved indication for this use.

Performance of HPV DNA Testing Combined with Cytology for Women Over 30 Years of Age

In international cross-sectional studies that examined both cytology and the HPV DNA test result.⁵⁴

- The sensitivity of a single Pap test for identifying CIN 2, 3 or cancer ranged from 33% to 94% (adding the HPV DNA

test to conventional cytology increased the sensitivity to 87% to 100%).

- The specificity of a single Pap test ranged from 87% to 98%. Adding the HPV DNA test to conventional cytology decreased the specificity to 69% to 95%.

Published studies have found that colposcopy is more sensitive than HPV DNA testing or repeat cytology for detection of cervical cancer precursor lesions; HPV DNA testing is more sensitive than repeat cytology.^{57, 64}

Remember:

- Women who are HPV DNA negative and cytology negative are at very low risk for having CIN 2, 3 or for developing it within the next three years and can be re-screened at 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 routinely in this circumstance. HPV DNA testing along with cervical cytology should be repeated at 6 to 12 months. If the woman is persistently high-risk HPV DNA positive, then she should receive a colposcopic examination.
-

The use of the HPV DNA test may introduce new psychological and interpersonal components to cervical cancer screening and management. Women may experience anxiety, distress, fear, anger, and guilt in response to an HPV diagnosis.⁶⁵ Providers should provide patients information and counseling when administering the test and when delivering HPV DNA test results.

Counseling messages for women receiving the HPV DNA test with Pap for cervical cancer screening are provided in an insert at the end of this booklet.

Counseling Women Infected with Genital HPV

According to a national survey conducted in 2005, less than half of American women had heard of HPV, and only 23% of women were able to identify HPV as the primary cause of cervical cancer.⁶⁶ While HPV awareness levels seem to be increasing

among women (58%), it is unclear whether knowledge of its association with cervical cancer is increasing.⁶⁷

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

The provision of patient information and counseling must be considered both when administering the HPV DNA test and when delivering test results. The manner in which this information is communicated to patients can influence the psychological effect of this diagnosis, as well as a woman's likelihood of following up with necessary testing or treatment.^{68, 69, 70}

Counseling messages for patients with a high-risk HPV DNA test result are included in an insert at the end of this booklet.

Section III: Genital Warts

Diagnosis

- Diagnosis of genital warts is made by visual inspection.
- A genital warts diagnosis may be confirmed by biopsy, although biopsy is needed only in certain circumstances.
- The use of HPV tests is not indicated for the routine diagnosis or management of visible genital warts.

Treatment

- If left untreated, genital warts may resolve on their own, remain unchanged, or increase in size or number.
- The effect of treatment on future transmission of HPV infection is unclear.
- The primary goal of treating visible genital warts is removal for cosmetic reasons.
- In most patients, treatment can remove warts. However, recurrences are frequent.
- Some patients may forego treatment as genital warts may resolve on their own.

Treatment Regimens

- A number of treatment options are available for visible genital warts. There is no definitive evidence to suggest that any one treatment is superior to others. Factors that may influence the selection of treatment include patient preference; available resources; provider experience; the size, number, anatomic site, and morphology of wart(s); and the cost, convenience, and adverse effects of treatment.
- Providers should be knowledgeable about and have available at least one patient-applied and one provider-administered treatment.

Table 4: Recommended Treatment Regimens³⁶

Patient-Applied Treatments

- Podofilox* 0.5% solution or gel
- Imiquimod* 5% cream

Provider-Applied Treatments

- Cryotherapy
- Podophyllin resin*
- Trichloroacetic Acid (TCA) or Bichloroacetic Acid (BCA) 80%–90%
- Surgical Removal—by tangential scissor excision, tangential shave excision, curettage, or electrosurgery.

Note: If possible, the health care provider should apply initial treatment to demonstrate the proper application technique and identify which warts should be treated. Follow-up visits may be useful several weeks into therapy to determine appropriateness of medication use and patient response to treatment.

* These treatments should not be used during pregnancy, as their safety during pregnancy has not been established.

Patients may prefer the privacy and convenience of patient-applied modalities.

- Many patients require a course of therapy rather than a single treatment.
- There is no evidence that the use of more than one therapy at a time will improve efficacy.
- The response to treatment and treatment side effects should be evaluated throughout the course of therapy. Treatment modality should be changed if a patient has not improved substantially.
- The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes and is encouraged.

Please refer to CDC's *Sexually Transmitted Diseases Treatment Guidelines, 2006*³⁶ (www.cdc.gov/STD/treatment) for more information about these treatments, including safety indications, directions for use, benefits, adverse effects, and possible complications.

Counseling Patients with Genital Warts

Information and counseling are important aspects of managing patients with genital warts. Counseling is most effective if provided in a non-judgmental manner appropriate to the patient's culture, language, sex, sexual orientation, age, and developmental level.

Counseling messages for patients with genital warts are included in an insert at the end of this booklet.

Special Considerations for Women

- Neither the presence of genital warts nor their treatment is associated with the development of cervical cancer in women. Therefore, the presence of genital warts is not an indication for cervical colposcopy or a change in the frequency of Pap tests for women.
- The presence of genital warts alone is not an indication for cesarean delivery in expectant women. Cesarean delivery may be indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.
- Pregnant women with genital warts should be counseled about the low risk of warts on the larynx (recurrent respiratory papillomatosis) in their infants or children. There are no controlled studies suggesting that cesarean delivery prevents this condition.

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