

*A Quick Reference Guide  
for Clinicians®*

## Managing HPV: A New Era in Patient Care

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## Using This Guide

Cervical cancer is highly preventable with screening and early intervention. Despite this fact, about 11,150 new cases of cervical cancer occur annually in the United States.

Cervical cancer is the long-term sequela of a sexually transmitted and persistent infection with the human papillomavirus (HPV). Evidence suggests that persistent infection with a high-risk type of HPV is necessary for progression to a cancer precursor lesion and to invasive cervical cancer. Current evidence also suggests a strong association between infection with high-risk HPV and cancer of the penis, vagina, vulva, anus, and oropharynx.

For a patient with cervical cytology abnormalities and a positive HPV DNA test result, ideal management must balance (1) the need to identify and treat abnormalities that are likely to progress to invasive cancer with (2) the need to avoid unnecessary treatment of abnormalities related to transient HPV infection that is unlikely to lead to invasive cancer. Testing for HPV infection, screening for HPV-related disease, and managing HPV-associated conditions can be challenging topics for health care providers to master, especially with the shifts in recommendations about management that have occurred in response to the introduction of HPV DNA testing and liquid-based Pap tests.

This *Quick Reference Guide for Clinicians* offers concise guidance on the HPV-related issues that tend to be the most perplexing for front-line providers: the realities of HPV transmission and natural history, current recommendations for cervical cancer screening, efficacy and safety of the HPV vaccine, and key counseling messages for HPV and HPV-related diseases. For information about related topics that are covered thoroughly elsewhere, such as diagnosis and management of external genital warts and management of abnormal screening results for cervical cancer, please refer to Appendix B (page 33) or visit ARHP's online HPV resource center at [www.arhp.org/Topics/Reproductive-Cancers](http://www.arhp.org/Topics/Reproductive-Cancers).

Only a well-informed health care professional can effectively communicate with patients about HPV-related risks, dispel myths, and supply accurate information about the virus, associated conditions, and appropriate medical care. We hope this *Quick*

*Reference Guide* will highlight important areas of concern, clarify the optimal screening for and management of HPV-related disease, and provide useful tips for counseling patients about HPV, ultimately helping providers close the gap between ideal and delivered care.

Abbreviations and Acronyms used in this Guide:

ACIP	Advisory Committee on Immunization Practices
ACS	American Cancer Society
AGC	atypical glandular cells
ACOG	American College of Obstetricians and Gynecologists
AIN	anal intraepithelial neoplasia
AIS	adenocarcinoma in situ
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	atypical squamous cells cannot exclude HSIL
ASC-US	atypical squamous cells of undetermined significance
CDC	Centers for Disease Control and Prevention
CIN	cervical intraepithelial neoplasia
DES	diethylstilbestrol
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
ITT	intention to treat
LSIL	low-grade squamous intraepithelial lesion
NOS	not otherwise specified
OC	oral contraceptive
SCC	squamous cell carcinoma
STIs	sexually transmitted infections
USPSTF	United States Preventive Services Task Force

## Introduction to HPV-Related Diseases

### Impact

- Genital HPV infection is the most commonly diagnosed sexually transmitted infection in the United States, on the basis of estimates from HPV DNA testing.<sup>1</sup>
- HPV infection is now known to be necessary to development of cervical cancer.<sup>2</sup>
- Virtually all cervical cancers are associated with persistent infection with high-risk types of HPV.<sup>3</sup>
- High-risk HPV also is associated with external genital warts and cancer of the penis, vagina, vulva, anus, and oropharynx.<sup>4</sup>
- More than half of all cases of invasive cervical cancer and death from cervical cancer occur in women who infrequently or never received proper screening.<sup>5,6</sup>
- In the United States in 2007, there were an estimated 11,150 cases of cervical cancer and 3,670 deaths.<sup>3</sup>
- Cervical cancer screening in the United States is estimated to cost \$3.4 billion annually.<sup>7</sup>
- Almost 900,000 women have an abnormal Pap test result associated with HPV 16, one of the high-risk types, each year in the United States.<sup>8,9</sup>

### Incidence and Prevalence

- Approximately 6.2 million new HPV infections occur in the United States each year.<sup>10</sup>
- At any given time, about 26.8% of women 14–59 years old have an HPV infection.<sup>11</sup>
- The lifetime risk of HPV infection is about 75% for sexually active individuals.<sup>12</sup>
- HPV prevalence varies by age and is highest for young women.<sup>13</sup>
- New HPV infection is common in young women.<sup>14</sup>
- In one study of female college students, 39% of those who initially had a negative result for HPV DNA tested positive two years later.<sup>14</sup>

## Transmission

- Sexual intercourse is the primary route of transmission for HPV.
- HPV is transmitted through direct genital contact rather than body fluids, like most sexually transmitted infections (STIs).<sup>14,15</sup>
- Intercourse is not necessary for infection; transmission through non-penetrative sexual contact has been documented. The primary mode of transmission is through genital skin-to-skin contact.<sup>14,16</sup>
- Genital contact in the absence of intercourse is a plausible means for HPV transmission, but the risk associated with this contact is much lower than that for intercourse.<sup>15,17</sup>
- The virus also can be transmitted through oral-genital contact.<sup>14,16</sup>
- Receptive anal intercourse is strongly associated with HPV infection.<sup>17</sup>
- HPV is not thought to survive for long on inanimate objects, making transmission by means of such objects unlikely.<sup>15</sup> However, it is possible that transmission could occur through objects shared in the short term, such as sex toys.

## Natural History

- Progression to precancer occurs when infection with high-risk HPV types persists over time.

Table 1: HPV Types Associated with Cancer and External Genital Warts<sup>12, 20, 21</sup>

	High-Risk Types	Low-Risk Types
Selected types	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82	6, 11, 40, 42, 43, 44, 54, 61, 72, 81
Associated abnormalities	Low-grade cervical lesions High-grade cervical lesions Anogenital cancers	Low-grade cervical lesions External genital warts

- Only a small minority of women who test positive by HPV DNA assay have concurrent microscopic cervical abnormalities; however, when tested one to three years later, as many as 25% to 40% of these women will have developed such abnormalities.<sup>18</sup>
- In most cases, HPV infection—with low- or high-risk types—is cleared by the immune system.
- In a study of female college students, more than 90% of women infected with high-risk HPV had cleared the infection when tested 24 months later.<sup>19</sup>
- Studies have shown that viral clearance is not often followed by subsequent reinfection with the same genotype.<sup>18</sup>
- Less than half of women who develop HPV infection with a high-risk type will have persistence of the same high-risk HPV type 12 months later.<sup>1</sup>
- The average episode of HPV infection lasts four to 20 months.<sup>1</sup>
- Persistent infection has been defined as detection of the same high-risk HPV genotype two or more times within a given interval of time; however, the duration of time that defines “persistence” is not yet agreed upon.<sup>18</sup>
- HPV type 16 persists longer than other types and also is especially carcinogenic, with a risk of cervical intraepithelial neoplasia-3 (CIN-3) of 40% at five years.<sup>18</sup>
- There is currently no data on the natural history of high-risk HPV infection in men.<sup>15</sup>

### HPV Types

- More than 120 types of HPV have been identified.<sup>22, 23</sup>
- About 40 types can infect the genital tract.<sup>2</sup>
- Approximately 13 to 19 types are considered high risk, meaning that persistent infection with these types is associated with an increased risk of cervical, anogenital, and other cancers. (The number considered high risk types has varied in different studies).<sup>21-23</sup>

- The most important high-risk types are 16 and 18. Type 16 alone causes 50% of all cases of cervical cancer. Type 18 causes another 20% of all cases.<sup>21</sup>
- Low-risk HPV types, the most important of which are 6 and 11, are associated with external genital warts, or condylomata acuminata, and with low-grade cervical lesions.<sup>24</sup> Approximately 12 HPV types have been classified as low-risk types.<sup>2</sup>

### Risk Factors for HPV Infection

- The most consistent predictors of HPV infection are measures of sexual activity, such as:<sup>17</sup>
  - Lifetime number of partners
  - Younger age at sexual debut
  - Lack of condom use
  - Partner with a history of multiple partners
- In a study of female college students, the strongest risk factor for incident infection was having a main regular sexual partner who had six or more lifetime partners (adjusted relative risk of 10.1).<sup>19</sup>
- Because the virus is transmitted by skin-to-skin contact, condoms do not completely prevent infection. According to one study, however, women whose partners used condoms consistently were 70% less likely to acquire an HPV infection than women whose partners did not use condoms consistently.<sup>14</sup>

### Role of Persistent Infection in Progression to Invasive Cervical Cancer

- The current etiologic model for the development of invasive cervical cancer highlights infection with high-risk HPV types as a necessary, but not sufficient, cause of cervical cancer. This model also incorporates the role of co-factors, such as smoking, nutritional deficiencies, oral contraceptive (OC) use, and parity status in the development of cancer.
- Persistent infection with high-risk types of HPV is necessary for the progression of high-grade lesions to invasive cancer.<sup>1</sup>
- Certain HPV types (e.g., type 16) are more likely to induce progression toward malignancy.<sup>2</sup>

- Smoking is clearly associated with neoplastic progression.<sup>2,17</sup> Some, but not all, studies have demonstrated a longer persistence of infection among ever smokers than non-smokers.<sup>25</sup>
- Recent studies have suggested that condom use reduces the risk of high-grade cervical lesions and increases HPV clearance.<sup>26</sup>
- Women with human immunodeficiency virus (HIV) have prolonged HPV persistence, even if their CD4 counts are normal.<sup>27</sup>
- Some studies have suggested that OC use and the presence of other STIs may act as co-factors in neoplastic progression, persistence of HPV infection, or both.<sup>1</sup> However, OC use may be a proxy for the behaviors associated with increased risk of HPV infection, which were listed previously. There is insufficient evidence to recommend that women who have infection with a high-risk HPV type should discontinue OC use.
- Persistence of infection with high-risk HPV leads to abnormal clonal progression in the cervical epithelium and eventually may lead to invasive cervical carcinoma.<sup>18</sup>
- Researchers believe that carcinoma develops from infections that persist with continued viral replication within the squamous epithelium.<sup>1</sup>
- Infection with HPV type 16 tends to persist longer than infection with other HPV types.<sup>1</sup>

### Counseling Points

When counseling a patient about **HPV prevalence, transmission, and risk factors**, make sure she understands these points before she leaves your office or clinic:

- The primary risk factor for HPV infection is sexual activity. Virtually any person who has engaged in sexual activity is likely to have been exposed to HPV.
- HPV is very common. Most people who have been sexually active have had HPV.
- HPV is spread through close contact of genital skin, usually during vaginal or anal intercourse. HPV can be transmitted with nonpenetrative sexual activity.

### Counseling Points (continued)

- HPV infection usually causes no symptoms, and most people never know they are infected.
- It may not be possible to know who gave you HPV or when you got it.
- Condom use reduces but does not completely prevent the spread of HPV.
- People who have same-sex partners can be infected by HPV.
- In most cases, the body clears HPV infection on its own.

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## Screening for HPV-Related Diseases

The goal of cervical cancer screening is to identify and treat high-grade precursors to cervical cancer, thus reducing a woman's risk of developing invasive cervical cancer:

- Cytology showing low-grade squamous intraepithelial lesion (LSIL) identifies many women who have very little risk for cervical cancer.
- In contrast, cytology showing high-grade squamous intraepithelial lesion (HSIL) may reflect the presence of a high-grade cancer precursor and will identify women who need additional testing or treatment.
- Positive HPV test results allow for risk stratification and identification of women in need of additional follow-up.

### Cervical Cancer Screening: Pap Test

- Both conventional Papanicolaou tests and liquid-based cytology are acceptable screening methods.
- Recent well-controlled clinical trials have found little difference in performance of the two methods for identifying high-grade disease.<sup>1-3</sup>
- One benefit of liquid-based cytology is that its use facilitates "reflex" HPV DNA testing in which the original sample is used to determine HPV status, thus avoiding a second visit.

### Age to Start Cervical Cancer Screening: Considerations

- HPV infections are very common in young women and frequently result in abnormal Pap test results.
- The prevalence of HPV infection drops considerably with increasing age.
- Concurrently, the incidence of CIN-3 and cancer increases with age.
- The positive predictive value of HPV testing increases as women age.
- The evaluation of minor cytological abnormalities in young women is expensive, causes considerable anxiety, and can result in unnecessary exams and tests for follow-up.

## Recommendations on Age to Start Screening

- Based on the considerations listed above, women should begin combined HPV testing and cytology at age 30.<sup>4</sup>
- ACS, ACOG, and USPSTF all recommend that cervical cancer screening should start three years after sexual intercourse starts or no later than 21 years old.<sup>5-7</sup>

## Recommendations on Age to Stop Cervical Cancer Screening<sup>5-7</sup>

- ACS
  - Can stop cervical cancer screening if woman is age 70 or older and has three documented, consecutive normal Pap tests results within preceding 10 years
  - Does not apply to women with a history of exposure to diethylstilbestrol (DES), cervical cancer, or immunosuppression
  - If HPV positive, continue screening
- ACOG
  - No age to stop screening specified
- USPSTF
  - No age to stop screening specified but recommends against routine screening in women >65 years old, if there has been adequate recent screening and the woman is not otherwise at high risk

## Recommendations for Screening Frequency<sup>5-7</sup>

- ACS
  - Annual screening with conventional Pap test
  - Every two years for screening with liquid-based test
  - At age 30 if a woman has had three normal consecutive Pap tests results, can change to every two to three years (but not if she has history of DES exposure or immunosuppression)
- ACOG
  - Annually if <30 years old
  - At age 30 if a woman has had three normal consecutive Pap test results, can change to every two to three years (but not if

she has history of DES exposure or immunosuppression)

- For women age 30 or older, either Pap or Pap plus HPV can be used for screening
- At age 30 if HPV and Pap are both negative, change to no more frequently than every three years
- USPSTF
  - At least every three years

#### Screening Post-Hysterectomy

- ACS, ACOG, and USPSTF all recommend against routine screening of women who have had a hysterectomy for benign disease.

#### Cervical Cancer Screening: HPV DNA Testing

- Hybrid Capture 2 is an assay that uses a pooled mixture of probes to detect 13 of the high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), but is not HPV-type specific.<sup>11</sup>
- Some laboratories routinely test for both high- and low-risk types; health care providers should request that the test for low-risk types not be performed.<sup>11</sup>

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#### Clinical Uses of HPV DNA Testing

- In the clinical setting, HPV testing is performed to identify high-risk types only.
- There are no clinical applications for low-risk HPV testing.

#### Pap Test Classification System<sup>8</sup>

##### Squamous cell abnormalities

- Atypical squamous cells of undetermined significance (ASC-US)
- Atypical squamous cells cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade intraepithelial lesion (HSIL)
- Squamous cell carcinoma (SCC)

##### Glandular cell abnormalities

- Atypical glandular cells (AGC)
  - endocervical-endometrial
  - not otherwise specified
- Atypical glandular cells, favor neoplastic
  - endometrial
  - not otherwise specified
- Adenocarcinoma in situ (AIS)
- Adenocarcinoma

**Table 2: Clinical Significance of Cervical Cytological Abnormalities<sup>8-10</sup>**

Abnormality	Epidemiology and Impact	Clinical Significance
ASC-US	<p>The most common cytological abnormality in the United States (mean rate 4.7% in 2003).</p> <p>The prevalence of CIN-2/3 among women with ASC-US is 7%–12% in the United States.</p> <p>Almost half of all cases of CIN-2/3 are diagnosed in women with ASC-US.</p>	<p>Women with a cytological result of ASC-US require additional follow-up.*</p> <p>Most high-grade disease is found in women who have minor cytologic abnormalities.</p>
ASC-H	<p>It's an uncommon finding (mean rate of 0.43% in 2003 in the United States).</p> <p>The risk of CIN-2/3 is higher for ASC-H than ASC-US (40% vs 15%).</p> <p>The prevalence of CIN-2/3 among women with ASC-H ranges from 26% to 68%.</p>	<p>ASC-H is a designation given to specimens that show atypical squamous cells for which HSIL cannot be excluded; clinicians should consider specimens given this designation to represent equivocal HSIL.</p> <p>All women with this Pap result will require colposcopy and management according to published guidelines.*</p>
LSIL	<p>Prevalence is moderate (mean rate of 2.6% in 2003 in the United States).</p> <p>A pooled estimate showed that 77% of women with LSIL are positive for high-risk HPV.</p> <p>Prevalence of CIN-2/3 among women with LSIL ranges from 12% to 16%.</p>	<p>LSIL is a common cytology abnormality that usually represents self-limited HPV infection.</p> <p>Except in special populations, colposcopy is recommended.*</p>

Table 2 (continued)

Abnormality	Epidemiology and Impact	Clinical Significance
HSIL	<p>Is relatively uncommon (mean rate of 0.7% in 2003 in the United States).</p> <p>Prevalence varies with age:</p> <ul style="list-style-type: none"> <li>– 0.6% in women 20–29 years old</li> <li>– 0.2% in women 40–49 years old</li> </ul> <p>Prevalence of CIN 2/3 in women evaluated using a loop excision 84% to 97%.</p> <p>Approximately 2% of women with HSIL have invasive cancer.</p>	<p>More often associated with persistent infection and progression than LSIL.</p> <p>Detecting CIN 2/3 has emerged as the central purpose of screening.</p> <p>Either colposcopy with endocervical assessment or loop electrosurgical excision is recommended, except in special populations.*</p>
AGC-NOS	<p>AGC is relatively uncommon (mean rate of 0.7% in 2003 in the United States).</p> <p>AGC is more common in women <math>\geq</math>40 years old.</p> <p>Recent series have reported that 3%–17% of women with AGC have invasive cancer.</p>	<p>AGC represents a possible abnormality of glandular epithelium.</p> <p>These lesions are difficult to assess by Pap testing because they develop higher in the cervical canal than other lesions. For the same reasons, glandular lesions are more difficult to identify at colposcopy than other lesions. All categories of AGC require endometrial sampling in women who are &gt;35 years old or at risk for endometrial neoplasia.*</p>
AGC-Favor Neoplasia	See AGC-NOS.	Represents a high degree of suspicion for significant disease or denocarcinoma in situ. Requires a diagnostic excisional procedure.*
<p><i>*See ASCCP guidelines for complete information on management, available at <a href="http://www.asccp.org/consensus.shtml">www.asccp.org/consensus.shtml</a>.</i></p>		

- Well-established clinical uses of HPV DNA testing include:<sup>11</sup>
  - As an adjunct to cytology (either liquid-based or conventional) for screening women age 30 and older
  - Management of women with ASC-US cervical cytology results starting at age 21
  - Post-colposcopy follow-up of women with abnormal cytology results
  - Post-treatment follow-up of women who have been treated for CIN-2/3 [Note: This applies to follow-up after any treatment and should not be conducted until six months after the treatment.]
  - To triage menopausal women with LSIL
- Use of HPV testing allows for less frequent screening because a normal Pap result and a negative HPV test result give a high assurance that cervical cancer is not present and will not likely occur in the next few years.<sup>12</sup>
- The addition of the HPV test increases the accuracy of screening.
- The risk of unidentified CIN-2 and CIN-3 or cervical cancer is approximately 1 in 1,000 in women with concurrent negative HPV and cervical cytology (ACOG Level A recommendation).<sup>13</sup>
- HPV DNA testing also identifies women who need increased surveillance because a positive HPV test result and a normal Pap result reflect increased risk for either missed disease or for the subsequent development of CIN-2/3 and cancer.<sup>12</sup>

#### Situations in Which HPV DNA Testing Is NOT Appropriate

- HPV DNA testing should NOT be used:<sup>14</sup>
  - To triage women with Pap results other than ASC-US (with the exception of post-menopausal women with LSIL)
  - As an adjunct to Pap testing in primary screening of women <30 years old (Concurrent Pap and HPV DNA testing in women <30 years old is not recommended because HPV is highly prevalent and the prevalence of cervical cancer is low.)
  - As an adjunct to Pap testing in primary screening of women after a total hysterectomy for benign disease
  - To triage women <21 with ASC-US

## Recommendations on Use of HPV DNA Testing for Screening of Women Age 30 and Older

- ASCCP has published guidelines for the use of HPV DNA testing as an adjunct to cytology for primary screening of women age 30 and older.
- A clinical scenario that has received a great deal of attention is the HPV DNA positive/cytology negative result.
- ASCCP recommends that women who are HPV DNA positive but have a negative cytology result should have repeat Pap and HPV testing in 12 months.<sup>10,15</sup> Recommendations for subsequent follow-up based on testing at 12 months are shown in Table 4.

**Table 3: Screening Frequency for Combined Pap and HPV Testing: Primary Screening<sup>10,15</sup>**

HPV Result	Cytology	Recommended Management
Negative	Negative	No screening for three years
Negative	ASC-US	Repeat Pap test in 12 months
Positive	ASC-US	Colposcopy
Any	LSIL or greater	Colposcopy
Positive	Negative	Repeat HPV and Pap tests in 12 months

**Table 4: Management of Repeat Testing After HPV Positive/Cytology Negative Result<sup>10,15</sup>**

HPV Result	Cytology	Recommended Management
Negative	Negative	Routine screening at three years
Negative	ASC-US	Repeat Pap test in 12 months
Positive	ASC-US	Colposcopy
Any	LSIL or greater	Colposcopy

## Counseling Points

When counseling a patient about **screening for cervical cancer**, make sure she understands these points before she leaves your office or clinic:

- HPV infections are very common in young women and frequently result in abnormal Pap test results. At the same time, cervical cancer is relatively rare in this age group compared with older women.
- For these reasons, experts recommend that women begin cervical cancer screening three years after initiation of sexual intercourse or no later than 21 years old.
- HPV DNA testing detects whether or not a woman has a current infection with one of the high-risk types of HPV. It does not detect all high-risk types, nor does it detect the types that cause genital warts.
- In women age 30 or older, HPV DNA testing can be used in combination with Pap testing to improve the effectiveness of screening for cervical cancer or precancer. If both are negative, screening needs to be done only every 2-3 years.
- If HPV testing and Pap testing were used together to screen women younger than 30, the tests would be positive in many women who actually have HPV infections that will go away on their own. It would also be expensive, cause considerable anxiety, and result in unnecessary exams and tests for follow-up.
- Studies on the effectiveness of male testing have not yet been completed.

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### Screening for HPV Associated Anal Lesions

- HPV-associated anal lesions include high-grade precursor lesions (anal intraepithelial neoplasia [AIN]) and anal cancer.
- These lesions are associated with infection with high-risk HPV types. As with cervical cancer, HPV type 16 is most common, followed by type 18.<sup>16</sup>
- Risk factors include 15 or more lifetime sexual partners, receptive anal intercourse, current smoking, HIV infection, and in women, a history of CIN.<sup>17,18</sup>
- In one study, 95% of 357 gay males had anal HPV and 50% had high-grade AIN.<sup>19</sup>
- The role of routine screening for AIN and anal cancer in high-risk individuals is controversial:
  - Advocates believe that cytology is as effective for detecting anal disease as for cervical disease and note that cost-effective studies suggest that anal screening is an attractive option.
  - Opponents point out that at present there are no data confirming that treatment of AIN prevents cancer.
- Currently the Centers for Disease Control and Prevention (CDC), USPSTF, ACS, and the Infectious Diseases Society of America do not recommend routine anal cytology screening.
- New York State Department of Health recommends anal cytology for individuals who are infected with HIV and meet at least one of the following criteria:<sup>20</sup>
  - Men who have sex with men
  - History of genital warts
  - History of CIN

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## HPV Screening and Management in Adolescents

### HPV Infection in Adolescents

- Guidelines for cervical cancer screening and management of abnormal results differ based on age.
- Adolescents have a much lower incidence of cervical cancer and higher incidence of HPV infection than older females.<sup>1,2</sup>
- One study of adolescents 14–17 years old found that 80% of participants had high-risk HPV at some point during the two-year study period.<sup>3</sup> Of the eleven adolescents (out of 60) who did not test positive for HPV during the study, three denied any sexual exposure.

### Cervical Cancer Screening

- Cervical cancer screening should begin three years after initial sexual intercourse or by age 21, whichever occurs first.<sup>4-6</sup>
- The upper age limit of 21 encourages screening for young women who may be unwilling to disclose sexual activity or abuse.
- Although the prevalence of ASC-US and LSIL are quite high in adolescents because of the high prevalence of HPV, cervical cancer is rare.<sup>2,7</sup> Use of the HPV DNA test to triage these results in adolescents would refer many to colposcopy despite the low risk of cervical cancer.
- Most high-risk HPV infections and associated abnormal cellular changes will resolve in a short time.
- Delaying the onset of screening until three years after initiation of sexual intercourse allows time for the clearance of these cellular changes, reducing unnecessary diagnostic procedures and treatment.
- 2006 Consensus Guidelines recommend one-year follow-up for adolescents (ages 20 and under) who have ASC-US.<sup>8</sup> If a woman with ASC-US inadvertently receives an HPV test for triage and the test result is positive, it should not alter the recommendations for management of the abnormal Pap test result.<sup>9</sup>

## Combined HPV and Cytology Testing

- Combined HPV and cytology testing for primary screening is NOT recommended in adolescents.
- The ideal age to start screening with combined HPV testing and cytology is at 30 years of age.<sup>10</sup>
- The rationale for this recommendation is based on several factors:
  - HPV infections are very common in young women and frequently result in abnormal Pap results.
  - There is a high prevalence of HPV infection in younger women, which drops considerably as women age. At the same time, the incidence of cervical cancer increases with age and is relatively rare in younger age groups.
  - As the prevalence of HPV declines with age, the incidence of CIN-3 and cancer increases.
  - The evaluation of minor cytological abnormalities in young women is expensive, causes considerable anxiety, and can result in unnecessary exams and tests for follow-up.

## Management of Abnormal Cytology Results in Adolescents

- All adolescents who have ASC-US, LSIL, or CIN-1 should have repeat cytology in 12 months regardless of HPV status.<sup>8</sup>
- All adolescents who have HSIL should undergo colposcopy.<sup>8</sup>

For a list of resources that provide detailed management guidelines, see Appendix B.

### Counseling Points

When counseling an **adolescent patient about cervical cancer screening**, make sure she understands these points before she leaves your office or clinic:

- HPV infection is very common among sexually active adolescents.
- HPV tests detect the virus that causes cell changes and cancer of the cervix.

### Counseling Points (continued)

- Testing for HPV infection in adolescents would frequently show positive results, but most of these infections go away on their own.
- Pap tests are used to detect cell changes and precancer that are caused by HPV.
- Pap tests are used starting three years after the first episode of intercourse or by age 21.
- A sexually active adolescent needs cervical cancer screening with the Pap test, even if she has received the HPV vaccine.

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## HPV Vaccines

### Background Information on HPV Vaccines

- The quadrivalent vaccine for HPV 6, 11, 16, and 18 (Gardasil™), manufactured by Merck, was approved for marketing in the United States by the Food and Drug Administration (FDA) in June of 2006.
- In November 2006, the HPV quadrivalent vaccine was included in the Vaccines for Children Program, a federally funded vaccine program that provides vaccines for free to both children and adolescents through their 19<sup>th</sup> birthday who are uninsured or underinsured.
- The Advisory Committee on Immunization Practices (ACIP), an advisory committee of the Centers for Disease Control and Prevention, released recommendations for vaccination using the HPV vaccine in 2007.

Table 5: Comparison of HPV Vaccines<sup>1-5</sup>

	Quadrivalent (Gardasil)	Bivalent (Cervarix)
Targeted HPV types	6, 11, 16, 18	16, 18
HPV-related diseases potentially prevented	Cervical cancer and precancer, vulvar and vaginal cancer and precancer, low-grade lesions. External genital warts.	Cervical cancer and precancer, vulvar and vaginal cancer and precancer, low-grade lesions.
Indication	Females ages 9–26 years for prevention of cervical cancer, cervical cancer precursors, vaginal and vulvar cancer precursors, and anogenital warts related to the four HPV types targeted by the vaccine.	Information is not yet available.
Dosing and administration	Intramuscular injection of three separate 0.5-ml doses at 0, 2, and 6 months.	Intramuscular injection of three separate 0.5-ml doses at 0, 1, and 6 months.

Table 5 (continued)		
	Quadrivalent (Gardasil)	Bivalent (Cervarix)
Efficacy	<p>Among young women (ages 16–26 years) who previously had not been exposed to any of the four HPV types in the vaccine:</p> <ul style="list-style-type: none"> <li>– 100% efficacy in preventing CIN-2/3 caused by the targeted HPV types (efficacy 30% for CIN-2 and 12% for CIN-3 by ITT analysis)</li> <li>– Nearly 100% efficacy in preventing vulvar and vaginal precancers caused by the targeted HPV types (63% by ITT analysis)</li> <li>– Nearly 100% efficacy in preventing genital warts caused by the targeted HPV types (73% by ITT analysis)</li> </ul>	<p>Among young women (15–25 years of age) who previously had not been exposed to either of the two HPV types in the vaccine:</p> <ul style="list-style-type: none"> <li>– 100% efficacy in preventing CIN-2/3 caused by the targeted HPV types</li> </ul>
Local adverse events	Injection site pain, swelling, erythema, pruritus.	Injection site pain, swelling, erythema.
Systemic adverse events	<p>Rate of events similar between placebo and treated groups.</p> <p>Vaccine-related serious adverse events occurred in &lt;0.1% of participants in clinical trials.</p> <p>Postmarketing reports have identified syncope, or fainting, as an adverse event; prescribing information recommends that patients remain seated for 15 minutes after vaccination.</p>	<p>Low rates of events.</p> <p>No subject withdrawals due to serious adverse events.</p>
<p><i>*ITT = intention-to-treat. ITT analysis includes all subjects who begin treatment, whether or not they complete the study.</i></p>		

- GlaxoSmithKline has developed a bivalent vaccine for HPV 16 and 18 (Cervarix™), which is currently undergoing FDA review for approval.

## Frequently Asked Questions

The answers to these questions are based on information from ACIP and CDC.<sup>2,6</sup>

**What is the target age for the vaccine?** According to ACIP recommendations, the target age is 11 to 12 years old for routine vaccination of females, although the series can be started as young as age 9 years.

**What about missed vaccines?** If the schedule for the quadrivalent HPV vaccine is interrupted, the vaccine series does not need to be restarted. If the interruption occurs after the first dose, the second dose should be administered as soon as possible, with the second and third doses separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.

**Does it make sense for a female older than 12 to be vaccinated?** “Catch-up” vaccines can be given to females ages 13 to 26 who were not previously vaccinated or who did not complete the full series. Vaccinating a woman who has already been sexually active also could offer some benefit. Even if she is already sexually active, she may not have been exposed to all four of the HPV types against which the vaccine offers protection. Although the vaccine may not provide full protection, it might provide some benefit.

**Who should not receive the vaccine?** According to ACIP recommendations, the HPV vaccine should not be administered to:

- Pregnant women. The quadrivalent vaccine is designated as Pregnancy Category B; its use has not been associated with adverse outcomes of pregnancy or adverse events to the developing fetus. However, because data on vaccination in pregnancy are limited, it is recommended that vaccination be postponed until after delivery. If a woman has started the series and has been found to be pregnant, she should discontinue the series and recommence after delivery.

- Individuals with a history of immediate hypersensitivity to any vaccine component or to yeast.

Administration should be delayed in individuals with moderate or severe acute illnesses (although it can be administered to individuals with minor acute illnesses, such as diarrhea or mild upper respiratory infection). The vaccine CAN be administered to immunocompromised individuals; however, efficacy might be less than that in immunocompetent individuals.

**How does previous HPV exposure affect the efficacy of the vaccine?** The HPV vaccine is a preventive rather than a therapeutic vaccine. The vaccine is effective in preventing HPV-related disease associated with HPV types to which an individual has not yet been exposed. It is not effective in preventing infection with HPV types to which an individual has already been exposed.

**Why shouldn't I test for HPV status before vaccination?** Pap testing and screening for HPV DNA are not needed before vaccination. Many women have not been exposed to all four HPV types present in the quadrivalent vaccine, making pretesting an unnecessary and additional burden and expense. Additionally, at this time, FDA-approved type-specific HPV DNA tests are not available.

**My patients don't understand why they need to continue cervical cancer screening after vaccination. What should I tell them?** It is important for females who receive the HPV vaccine to continue with regular cervical cancer screening for three reasons:

- The vaccine does not protect against all of the HPV types that cause cervical cancer. Rather, the vaccine protects against HPV types that are responsible for 70% of cervical cancers.
- An individual may be at risk for HPV-related disease if she was infected with a high-risk type of HPV before vaccination.
- An individual who does not complete the vaccine series may not receive the full benefits of the vaccine and thus may be at risk for HPV-related disease.

**Do the vaccines provide cross-protection to other HPV types?** At this time, there is insufficient evidence to answer this question with certainty.

**Does the quadrivalent vaccine provide protection against external genital warts?** Yes. In a combined analysis of three clinical trials, the efficacy of the quadrivalent vaccine was 98.9% against external genital warts that were associated with HPV types included in the quadrivalent vaccine.<sup>4</sup>

**What about the use of the vaccine in males?** Efficacy studies are being conducted in males, but results are not yet available. At this time, in the United States the vaccine is indicated only for use in females. In other parts of the world, the vaccine has been approved for males.

**Does the HPV vaccine help treat existing disease?** No. Because the HPV vaccine is a preventive rather than a therapeutic vaccine, it is not effective against existing disease, including existing HPV infection, cervical cytological abnormalities, and external genital warts. It is important to note that there is no evidence that the vaccine exacerbates existing disease.

### Counseling Points

When counseling a patient about **HPV vaccination**, make sure she understands these points before she leaves your office or clinic:

- The HPV vaccine currently available prevents infection from two of the most common types of HPV that cause 7 of 10 cases of cervical cancer. The HPV vaccine also prevents infection from two of the most common types of HPV which together cause 9 of 10 cases of genital warts. It does not protect against the other, less common, types of HPV.
- The vaccine provides the possibility of full protection when given before a person becomes sexually active. For this reason, it is recommended that young girls (as young as age 9) receive the vaccine.
- Testing for HPV DNA is not recommended before vaccination.
- The HPV vaccine will not treat cervical precancer or cancer that is already present, and it will not treat external genital warts that are already present.

### Counseling Points (continued)

- There is no evidence that vaccination will make existing disease worse.
- Girls and young women who receive the vaccine will still need cervical cancer screening with the Pap test.

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## Counseling Tips

### Lack of Information About HPV

- Data from a national survey show that only 40% of women had ever heard of human papillomavirus or HPV.<sup>1</sup>
- Of these, less than half were aware that HPV causes cervical cancer.

### General Educational Messages About HPV

- HPV is sexually transmitted.
- HPV is very common.
- Most women with HPV will not get cervical cancer.
- HPV infection usually clears by itself.
- HPV tests are used to detect the virus that causes cell changes and cancer of the cervix.
- Pap tests are used to detect cell changes and precancer that are caused by HPV.
- Most women who test positive for HPV do not have precancer or cervical cancer on further evaluation.
- However, some women with HPV infection that doesn't clear quickly will develop cervical cell changes.
- A positive Pap test result likely indicates a woman has cell changes caused by HPV.
- A positive Pap test result usually means that a woman will need additional testing to make sure she doesn't have serious cell changes or cancer.
- If a woman is found on additional testing to have serious cell changes or cancer, effective treatment is available.
- HPV types that are not covered by the vaccine cause 30% of cervical cancers.<sup>2</sup>
- Because 30% of cervical cancers are associated with HPV types that are not covered by the vaccine, women will continue to need cervical cancer screening even if they are vaccinated.

## Educational Messages for Women Who Test Positive for HPV

- HPV is very common. Almost 8 out of 10 women will get HPV at some point in their lives.
- There is no way of knowing how long HPV has been present or who transmitted the virus.
- Having HPV is not a sign of infidelity or promiscuity.
- Most women who have HPV do not develop abnormal cells or cancer.
- Women who have HPV in their cells a long time are at greater risk for developing abnormal cells or cancer.
- If you have a positive HPV test result, your health care provider will want to examine your cervix more closely or more frequently than usual.

## Educational Messages for Women Age 30 or Older Who Test Positive for HPV But Have a Negative Pap Test Result

- The positive HPV test is an indicator that closer follow-up is warranted.
- It's a good sign that the Pap test result is negative, but diligent follow-up is important.
- Follow-up means that you should come back in 12 months for a Pap and HPV test.
- If HPV is still present at follow-up, colposcopy will be recommended even if the Pap result is still negative.<sup>3</sup>

## General HPV Counseling Tips

- Proactively dispel the myths that abound about HPV. Ask your patient what she knows about the virus and provide accurate information as needed.
- Provide information about HPV relevant to the clinical situation, then ask your patient if she has any questions. Tell her how to contact you if she has questions after she leaves your office.
- To minimize patient anxiety, be sure to clarify that a positive HPV DNA test result is not a cancer diagnosis. Explain that

because of the high prevalence of HPV infection and the relatively small risk of cancer, many patients will have positive test results but never develop cervical cancer.

- Clearly communicate about any necessary follow-up, including the timing, any procedures or testing that will be done, and the approximate length of the follow-up appointment.

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## Appendix A: Resources for Patients

### General Information About HPV

American College of Obstetricians and Gynecologists  
[www.acog.org/publications/patient\\_education/bp073.cfm](http://www.acog.org/publications/patient_education/bp073.cfm)

American Social Health Association  
[www.ashastd.org/hpv/hpv\\_learn.cfm](http://www.ashastd.org/hpv/hpv_learn.cfm)

Association of Reproductive Health Professionals  
[www.arhp.org/patient-resources](http://www.arhp.org/patient-resources)

Centers for Disease Control and Prevention  
[www.cdc.gov/STD/HPV](http://www.cdc.gov/STD/HPV)

National Cancer Institute  
[www.cancer.gov/cancertopics/factsheet/risk/HPV](http://www.cancer.gov/cancertopics/factsheet/risk/HPV)

National Women's Health Resource Center  
[www.healthywomen.org/healthtopics/humanpapillomavirus](http://www.healthywomen.org/healthtopics/humanpapillomavirus)

Planned Parenthood® Federation of America  
[www.plannedparenthood.org/health-topics/stds-hiv-safer-sex/hpv-4272.htm](http://www.plannedparenthood.org/health-topics/stds-hiv-safer-sex/hpv-4272.htm)

### Information About the HPV Vaccine

Immunization Action Coalition  
[www.immunize.org/vis/hpv.pdf](http://www.immunize.org/vis/hpv.pdf)

National Cervical Cancer Coalition  
[www.nccc-online.org/patient\\_info/vaccine.html](http://www.nccc-online.org/patient_info/vaccine.html)

National Cancer Institute  
[www.cancer.gov/cancertopics/factsheet/risk/HPV-vaccine](http://www.cancer.gov/cancertopics/factsheet/risk/HPV-vaccine)

National Network for Immunization Information  
[www.immunizationinfo.org/hpv.cfm](http://www.immunizationinfo.org/hpv.cfm)

### Information About HPV DNA Testing

American Cancer Society  
[www.cancer.org/docroot/CRI/content/CRI\\_2\\_6x\\_Thinking\\_About\\_Testing\\_for\\_HP.V.asp](http://www.cancer.org/docroot/CRI/content/CRI_2_6x_Thinking_About_Testing_for_HP.V.asp)

American Society for Colposcopy and Cervical Pathology  
[www.asccp.org/pdfs/patient\\_edu/hpv\\_testing.pdf](http://www.asccp.org/pdfs/patient_edu/hpv_testing.pdf)

## Appendix B: Resources for Additional Information

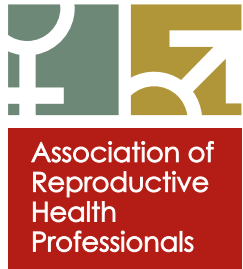
### Diagnosis and management of external genital warts

Ferris D, Cox JT, O'Connor D, Wright VC, Foerster J. *Modern Colposcopy: Textbook and Atlas. Revised 2nd ed.* American Society for Colposcopy and Cervical Pathology. February 2008. (See the chapters on Management of Lower Genital Tract Neoplasia and Treatment of External Genital Warts.) Textbook is available for purchase at [www.asccp.org/bookstore.shtml](http://www.asccp.org/bookstore.shtml).

### Management of abnormal cervical cancer screening results

Consensus Guidelines created by the American Society for Colposcopy and Cervical Pathology can be downloaded from [www.asccp.org/consensus.shtml](http://www.asccp.org/consensus.shtml).

Pocket-sized algorithms are available for purchase at [www.asccp.org/bookstore.shtml](http://www.asccp.org/bookstore.shtml).



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