

Cervical Cancer and Other Human Papillomavirus-related Diseases:

Screening and Prevention Strategies for Primary Care Clinicians

An *FPEN* Consensus Recommendation from an Expert Panel*

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FPEN



Learning Objectives:

1. Discuss the natural history of human papillomavirus infection.
2. Describe the causal relationship between HPV and genital warts and HPV and cervical cancer.
3. Discuss strategies family physicians can employ to help patients reduce their risk of acquiring HPV and developing genital warts and cervical cancer.
4. Review guidelines for managing women with abnormal cervical cytologies, and present the most commonly used options for treating precancerous cervical lesions and glandular abnormalities.
5. Recognize the role of HPV vaccines in reducing the incidence of genital warts, precancerous lesions, and cervical cancer.

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Introduction

In the United States, more than 10,000 cases of cervical cancer are diagnosed each year, and 3,700 women die of the disease despite increased access to screening and improved diagnostic tools.^{1,2} It is now known that infection with human papillomavirus (HPV) is necessary for the development of a variety of genital neoplasias, including genital warts, cervicovaginal precancerous lesions, and cervical cancer.² This information, coupled with HPV DNA testing, has resulted in new guidelines to help family physicians and other primary caregivers better manage women who have abnormal Pap tests.³ Moreover, vaccines directed against common disease-causing HPV types are in development and offer promise for preventing most HPV infections and their clinical manifestations.

The Family Practice Education Network (FPEN), coordinated by the Illinois Academy of Family Physicians (IAFP), recently convened a panel of experts to discuss the advances that have been made in the area of cervical cancer and review current screening and management protocols. Because family physicians are on the front line for women's health, they must ensure that their patients receive adequate education, screening, and follow-up to minimize their risk of developing HPV-related diseases including common genital warts and cervical cancer.

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*Contents meet criteria for Evidence-based CME.

Epidemiology

In the United States, the highest prevalence of cervical intraepithelial neoplasia (CIN), a precursor to cervical cancer, occurs in women in their 20s and 30s, the group of women who are most sexually active.⁴⁻⁶ The incidence of cervical cancer is highest among Latina women, and mortality rates for cervical cancer are highest among African American women; however, racial and ethnic disparities surrounding cervical cancer may have more to do with social and economic issues, such as inaccessibility of health care, than with genetic issues.¹

Nearly 100% of women with cervical cancer are infected with human papillomavirus, a virus that is primarily sexually transmitted.⁷ An estimated 20 million people in the United States are infected with HPV, with an annual incidence rate of over 5 million. In addition, estimates suggest that 1% of all sexually-active men and women have genital warts.⁸ While infection with one or more high-risk HPV types is common among sexually-active women, most infections do not result in cervical cancer.¹

Women who become sexually active at an early age or who have multiple sexual partners are at an increased risk for developing cervical cancer. On the other hand, even a woman who has had only one sexual partner can become infected with HPV. Cofactors such as immunosuppression, human immunodeficiency virus (HIV) infection, smoking, increased parity, and co-infection with herpes simplex virus or *Chlamydia trachomatis*, may affect the persistence of HPV infection and progression to cervical cancer (Table 1).^{9, 10}

Table 1 Risk Factors for Pre-cancerous Cervical Lesions and Cervical Cancer^{9, 10}

- Sexual activity at an early age
- Multiple sexual partners
- Immunosuppression
- HIV infection
- Smoking
- Increased parity
- Co-infection with herpes simplex virus or *Chlamydia trachomatis*

Human Papillomavirus

Most sexually-active men and women will become infected with one or more genital HPV types sometime in their lives. Although HPV is one of the most prevalent sexually transmitted diseases in the United States, public awareness remains low. Less than one-third of men and women in the population have heard of HPV, and only some are aware of its association with cervical cancer. Eighty-nine percent (89%) have never discussed HPV with a healthcare provider.¹¹

The majority of people who are infected with HPV will not have overt symptoms; however, some women will develop genital warts or pre-cancerous changes of the cervix, such as low-grade or high-grade squamous intraepithelial lesions. Research has shown that of the women who have warts or low-grade changes, only a small percentage will eventually develop cervical cancer if left untreated.⁴ Most occurrences of low-grade cervical histology regress without treatment within six years. While 50% of untreated CIN 3 lesions, high-grade cervical histology, can progress to cervical cancer, progression happens slowly, allowing time for treatment.⁴⁻⁶

There are more than 100 different types of human papillomavirus.¹² About 40 of these viruses are transmitted sexually and can infect the genital areas, including the cervical epithelium.¹³ Of the numerous HPV types, HPV 6 or 11 are detected in nearly all genital warts. Genital warts, which usually are diagnosed by visual inspection with magnification, may cause physical and emotional discomfort.⁸ Four high-risk HPV types—16, 18, 31 and 45—are responsible for causing the majority of cervical cancers, with types 16 and 18 being responsible for 66% of cases.¹² Persistent HPV infection with high-risk types is the most important risk factor for developing high-grade cervical lesions that progress to invasive cervical cancer.

The symptoms listed in Table 2 may be associated with cervical cancer and should be closely evaluated by family physicians; however, such symptoms often occur for reasons other than cancer.

Table 2 Cervical Cancer Symptoms¹

- Vaginal bleeding during or after intercourse
- Vaginal bleeding between periods
- Vaginal bleeding after douching or a pelvic exam
- A persistent abnormal discharge, with itching or burning

The Pap Test and Bethesda System

In 1928, Dr. Papanicolaou introduced the Pap smear, a microscopic examination of exfoliated cervical cells. Approximately 50 million Pap tests are administered each year in the United States; more than 3 million are classified as abnormal and require medical follow-up.^{14, 15} The Pap test is generally accepted as an effective screening tool despite its low sensitivity of between 51 and 66%.¹⁶ The success of the Pap test probably has more to do with the biologic fact that, in most cases, cervical cancer is slow to evolve, rather than with the Pap's performance as a screening test. Women who are screened properly will have many Pap tests over their lifetimes, increasing the probability of discovering an abnormality on Pap screening.

A variety of Pap test classification schemes have developed over the years. The Bethesda System is the

current standard for communicating cervical cytology results from the laboratory to clinicians. As a framework for laboratory reports, the Bethesda System includes an evaluation of specimen adequacy, a description of incidental findings, and an interpretation of any cytologic abnormalities of the specimen. The system was first created in a workshop in 1988 and was then modified in 1991 based on laboratory and clinical experience after its implementation. In 2001, more than 400 people involved in cervical cancer screening met to revise the system's terminology and to incorporate the latest scientific data. Today the 2001 Bethesda System is implemented in the majority of pathology laboratories in the United States.¹⁷

The Bethesda System 2001

Specimen Adequacy

The evaluation of specimen adequacy in the 2001 Bethesda System is crucial to maintaining quality assurance. The system requires that a Pap test specimen be accompanied by a patient history and contain enough well-fixed cells for the pathologist to analyze. Specimen types dictate minimal requirements for cell composition. To qualify as "satisfactory," an estimated 8,000 to 12,000 well-visualized squamous cells are required for conventional smears, and 5,000 squamous cells for liquid-based preparations.¹⁷ For specimens with adequate squamous cellularity, a notation is made regarding the presence or absence of an endocervical/transformation zone component. Quality indicators such as partially-obscuring inflammation or blood may also be noted.¹⁷

Interpretation/Result

In the 2001 Bethesda System, the terms "interpretation" or "result" are used rather than "diagnosis" because the workshop participants agreed that cervical cytology is primarily a screening test that sometimes is used to reach a diagnosis in conjunction with other pieces of clinical information.¹⁷

The system divides the interpretation/result section of a Pap report into two broad categories:

- **Negative for Intraepithelial Lesion or Malignancy**

When there is no cellular evidence of neoplasia, the statement "negative for intraepithelial lesion or malignancy" is used and may be accompanied by a description of the presence or absence of organisms or other non-neoplastic findings.

- **Epithelial Cell Abnormalities**

A discussion of squamous cell abnormalities can include a description of atypical squamous cells (ASC), low- and high-grade squamous intraepithelial lesions (LSIL and HSIL), and squamous cell carcinoma.

A discussion of glandular cell abnormalities can include a description of atypical endocervical, endometrial or glandular cells (AGC), and adenocarcinoma.¹⁷

Table 3 provides an abridged version of the 2001 Bethesda System.

Table 3 The 2001 Bethesda System (Abridged)¹⁷

SPECIMEN ADEQUACY

Satisfactory for evaluation (*note presence/absence of endocervical/ transformation zone component*)
 Unsatisfactory for evaluation . . . (*specify reason*)
 - Specimen rejected/not processed (*specify reason*)
 - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

GENERAL CATEGORIZATION (Optional)

Negative for intraepithelial lesion or malignancy
 Epithelial cell abnormality
 Other

INTERPRETATION/RESULT

Negative for Intraepithelial Lesion or Malignancy

Organisms
 - Trichomonas vaginalis
 - Fungal organisms morphologically consistent with *Candida* species
 - Shift in flora suggestive of bacterial vaginosis
 - Bacteria morphologically consistent with *Actinomyces* species
 - Cellular changes consistent with herpes simplex virus
 Other non-neoplastic findings (*Optional to report; list not comprehensive*)
 Reactive cellular changes associated with
 - inflammation (includes typical repair)
 - radiation
 - intrauterine contraceptive device
 Glandular cells status posthysterectomy
 Atrophy

Epithelial Cell Abnormalities

Squamous cell
 Atypical squamous cells (ASC)
 - of undetermined significance (ASC-US)
 - cannot exclude HSIL (ASC-H)
 Low-grade squamous intraepithelial lesion (LSIL)
 - encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
 High-grade squamous intraepithelial lesion (HSIL)
 - encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
 Squamous cell carcinoma
 Glandular cell
 - Atypical glandular cells (AGC) (*specify endocervical, endometrial, or not otherwise specified*)
 - Atypical glandular cells, favor neoplastic (*specify endocervical or not otherwise specified*)
 - Endocervical adenocarcinoma in situ (AIS)
 - Adenocarcinoma

Other (List not comprehensive)

Endometrial cells in a woman ≥40 years of age

AUTOMATED REVIEW AND ANCILLARY TESTING (Include as appropriate)

EDUCATIONAL NOTES AND SUGGESTIONS (Optional)

JAMA. 2002;287:2114-2119.

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Screening for Cervical Cancer

All women should be screened regularly for cervical cancer. Cervical cancer mortality is rare in women of any age who have had routine Pap tests. The risk of developing invasive cervical cancer is 3 to 10 times greater in women who have not been screened.¹⁸⁻²¹ Furthermore, early detection and treatment of localized lesions is directly related to survival. When cervical cancer is localized, 92% of women will survive more than five years.¹ In comparison, only 26% of women will survive metastatic disease.¹ Therefore, primary healthcare providers should encourage female patients to undergo screening for cervical cancer as part of a routine health maintenance plan.

Based on the natural history of HPV infection and cervical cancer, screening guidelines have been established by the American College of Obstetrics and Gynecology (ACOG) and are summarized in Table 4. The American Cancer Society (ACS) and the United States Preventive Services Task Force (USPSTF) also have issued guidelines

Practice Recommendation: The USPSTF strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix.



Strength of evidence: The USPSTF found good evidence from multiple observational studies that screening with cervical cytology (Pap smears) reduces incidence of and mortality from cervical cancer. Regarding optimal starting and stopping ages for screening and optimal screening intervals, direct evidence is limited. Indirect evidence suggests most of the benefit can be obtained by beginning screening within 3 years of onset of sexual activity or age 21 (whichever comes first) and screening at least every 3 years. The USPSTF concludes that the benefits of screening substantially outweigh potential harms (level A recommendation).

EBM Source: U.S. Preventive Services Task Force, <http://www.ahrq.gov/clinic/uspstf/uspscerv.htm>

for cervical cancer screening. All three societies recommend beginning screening within 3 years of the onset of sexual activity or by age 21, whichever comes first.

When following these guidelines, the family physician should keep in mind the potential negative impact of false-positive cytology results. These include a patient's increased anxiety and discomfort, and substantial expense from follow-up procedures.²²

Management of Abnormal Cervical Cytology

ASCCP Consensus Conference Guidelines

In 2001, a conference sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP) led to the development of consensus guidelines for the triage and management of women with abnormal cervical cytology. The guidelines are based on the 2001 Bethesda System, extensive review and evaluation of medical literature, and the recently completed Atypical Squamous Cells of Undetermined Significance (ASC-US) and Low-grade Squamous Intraepithelial Lesion (LSIL) Triage Study (ALTS), which randomized participants to a program of repeat cytology, colposcopy or HPV DNA testing.²³ In general, the guidelines define follow-up protocols based on the Bethesda 2001 abnormal cervical cytology categories (Table 5).³

Table 5 Categories of Abnormal Cervical Cytology³

- Atypical squamous cells (ASC)
- Atypical glandular cells (AGC), including adenocarcinoma *in situ* (AIS)
- Low-grade squamous intraepithelial lesions (LSIL)
- High-grade squamous intraepithelial lesions (HSIL)

Table 4 Cervical Cancer Screening Guidelines²²

• When should cervical screening begin?

Women should undergo annual cervical screening with Pap tests beginning approximately 3 years after first sexual intercourse but no later than age 21.

• How often should women be screened?

Screening intervals are based on method used:

Conventional Pap Smear: Annually for women younger than 30; in women 30 years and older who have had three negative cytology tests, screening may be extended to every 2-3 years.*

Liquid-Based Cytology: Annually for women younger than 30; in women 30 years and older who have had three negative cytology tests, screening may be extended to every 2-3 years.*

HPV DNA Testing Plus Cytology: Every 3 years if HPV negative, cytology negative.

*Women who have a history of high-grade lesions, are immunocompromised, or have a history of prenatal exposure to diethylstilbestrol, need increased surveillance, with more frequent Pap tests, colposcopy or both.

• When should screening end?

Evidence to establish an upper age limit has yet to be established.

After total hysterectomy for benign indications, women with no prior history of high-grade cervical lesions may discontinue screening.

Atypical Squamous Cells

The Bethesda System 2001 qualifies atypical squamous cells (ASC) as either “of undetermined significance” (ASC-US) or “cannot exclude high-grade intraepithelial lesion” (ASC-H).¹⁷ Of women with ASC on cervical cytology, 5 to 17% have grade 2 or 3 CIN or cervical cancer on biopsy.²³⁻²⁷ While there seems to be some lack of agreement among cytopathologists about what constitutes a Pap interpretation of ASC, the category cannot be ignored because the largest percentage of biopsy-confirmed grade 2 or 3 CIN is found in women with ASC-US.^{27, 28} Table 6 describes various grades of CIN.

ASC-US

The management of women with ASC-US can include a program of repeat Pap tests, immediate colposcopy, or DNA testing for high-risk types of HPV (Figure 1).^{2, 29} All three options are considered “safe and effective.”^{3, 27} However, if liquid-based cytology is used, then reflex HPV DNA testing, in which testing is done on the original residual sample, is preferred because it eliminates the need for an additional office visit.^{3, 30}

Post-menopausal women who receive a Pap test interpretation of ASC-US can choose to have immediate colposcopy or a trial of intravaginal estrogen therapy followed by repeat cytology. If the follow-up Pap test is read as normal, then it is repeated in 4 to 6 months. If that Pap test is normal, the patient may return to routine screening. If the abnormality persists, then immediate colposcopy is warranted.³

Immunosuppressed women and pregnant women should undergo colposcopy performed by an examiner who is comfortable managing these special circumstances.³

Table 6 A Description of Various Grades of CIN

CIN 1	Histologic abnormalities involving the lower 1/3 of cervical squamous epithelium
CIN 2	Histologic abnormalities involving the lower 2/3 of cervical squamous epithelium
CIN 3	Histologic abnormalities involving the full width of cervical squamous epithelium but not invading the basement membrane

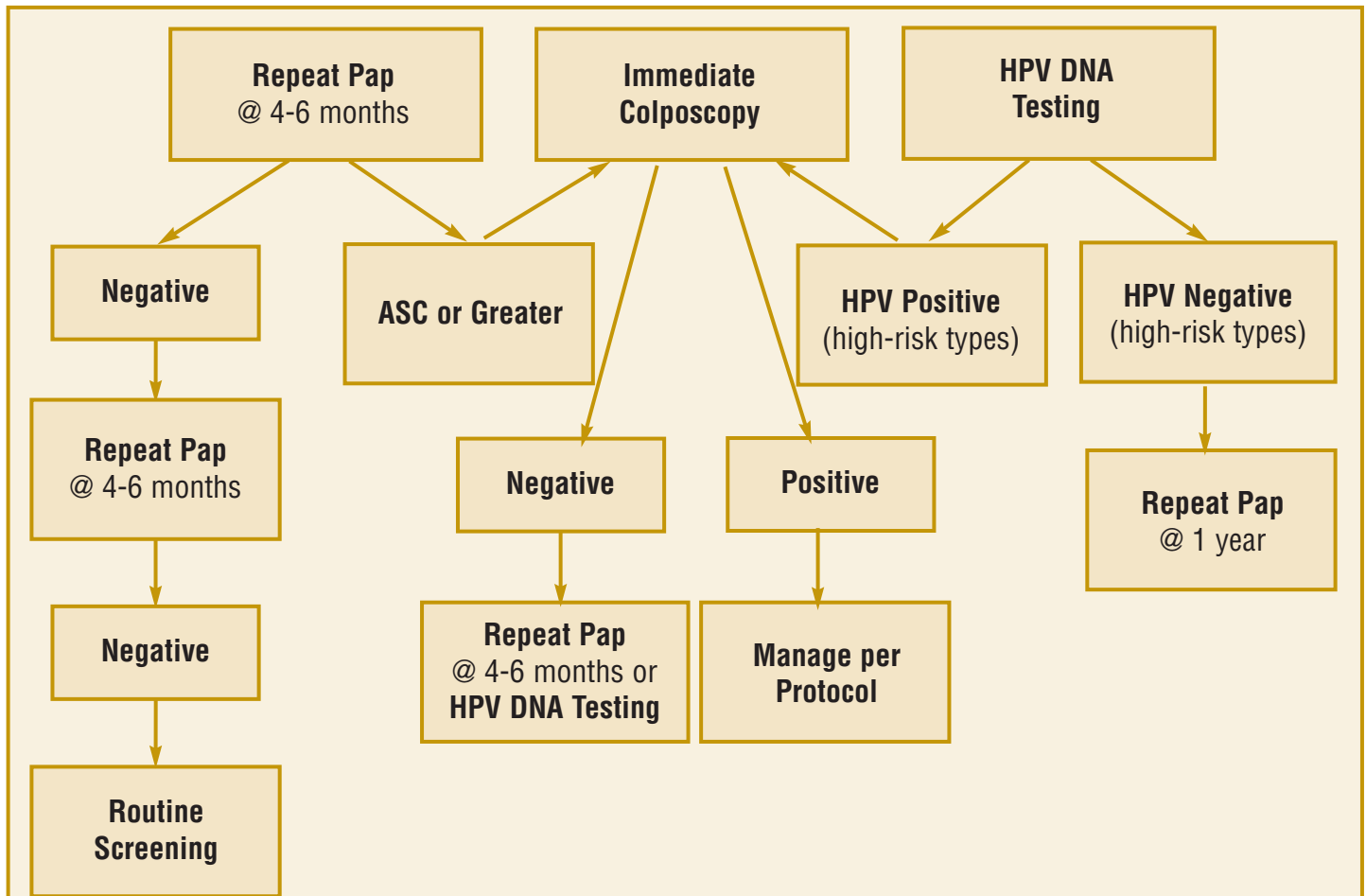


Figure 1 Management of Atypical Squamous Cells of Undetermined Significance (ASC-US)

Adapted from: ASCCP Consensus Guidelines, 2002²⁹

Practice Recommendation: Repeat cervical cytology testing, colposcopy, and DNA testing for high-risk types of HPV are all acceptable methods for managing women with ASC-US.



Strength of evidence: The recommendation was made by a panel of 121 experts in the diagnosis and management of cervical cancer precursors who participated in a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology (level A recommendation).

EBM Source: National Guideline Clearinghouse. Wright TC, Jr., Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. *JAMA*. 2002;287:2120-2129. http://www.guideline.gov/summary/summary.aspx?doc_id=3286#s24

HPV DNA Testing with ASC-US

HPV DNA testing has proven more effective in detecting CIN 3 than immediate colposcopy and repeat Pap tests. The most widely used DNA test targets a panel of HPV types and is highly sensitive in detecting CIN grades 2 and 3. HPV DNA testing also yields a diagnosis sooner than colposcopy or repeat Pap tests and reduces the number of referrals for colposcopy.^{23, 27}

According to the 2001 Consensus Guidelines, women with ASC-US who test negative for high-risk HPV types should have Pap tests repeated in one year. Women who test positive should undergo colposcopy and, depending on the results, receive treatment or be followed with serial Pap tests and HPV DNA testing at recommended intervals.^{23, 27}

At this time, HPV DNA testing appears to be cost-effective only in triaging ASC-US because the cytologic interpretations of LSIL and HSIL correlate strongly with active, high-grade HPV infection and most of the HPV tests would be positive anyway. Moreover, cytopathologists generally can reach agreement as to what constitutes an interpretation of LSIL and HSIL in any given specimen; therefore, knowing HPV status is less crucial.²³

ASC-H

“Atypical squamous cells that cannot exclude high-grade intraepithelial lesion” (ASC-H) is a less common interpretation than ASC-US; however, the cytopathologist’s use of this designation should alert the clinician to a greater possibility of an underlying high-grade lesion. Immediate colposcopy is recommended for women with ASC-H to rule out the possibility of underlying CIN 2 or 3.^{3, 27} Depending on the results of the colposcopy, treatment may be offered or the initial Pap test and histology may be reviewed to design an appropriate follow-up strategy.^{3, 27}

Practice Recommendation: Evidence suggests that compared with conventional Pap smears, the use of liquid-based cytology reduces the proportion of unsatisfactory specimens and generates fewer false negatives for ordinary populations, but not for high-risk populations. HPV testing, alone or with cytology, is more sensitive but less specific than Pap smears.



Strength of evidence: Evidence is based primarily on results from split-sample trials. Seventeen reports on 13 unique trials undertaken in 9 countries met the selection criteria for comparing liquid-based cytology and Pap smears; 23 unique trials met the criteria for comparing HPV testing and Pap smears.

EBM Source: Canadian Task Force on Preventive Health Care. Noorani HZ, Canadian Coordinating Office for Health Technology Assessment. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003. http://www.ccohta.ca/entry_e.html

Atypical Glandular Cells (AGC)

The 2001 Bethesda System divides the category of atypical glandular cells (AGC) not meeting criteria for invasive adenocarcinoma into 3 categories (Table 7).¹⁷

Table 7 Atypical Glandular Cells (AGC)^{3, 17}

- Atypical endocervical, endometrial or glandular cells not otherwise specified (AGC-NOS)
- Atypical endocervical or glandular cells, favor neoplastic (AGC favor neoplasia)
- Endocervical adenocarcinoma *in situ* (AIS)

Less than 1% of Pap tests have an interpretation of AGC.³ There is evidence, however, that glandular abnormalities are becoming more common.³¹ In any event, the AGC category carries a substantially greater risk for CIN than the ASC or LSIL categories.^{3, 32} Some studies suggest that 9 to 54% of women with AGC will have CIN, up to 8% will have AIS, and up to 9% may have an invasive adenocarcinoma.³²⁻³⁹ Additionally, squamous cells and glandular lesions can coexist.³

Because cervical cytology has a low sensitivity for detection of glandular lesions and the role of HPV DNA testing in managing AGC is unclear, women with all categories of AGC should receive colposcopy with endocervical sampling (Figure 2).^{3, 27, 29, 32, 40} In addition, endometrial sampling is recommended in women older than 35 and in younger women with AGC who have unexplained vaginal bleeding.³ It is considered unacceptable to manage women with AGC-NOS initially with a program of repeat Pap tests.^{3, 27}

If no neoplasia is found during colposcopy, however, a program of repeat Pap tests every four to six months is recommended. Once a woman has four consecutive Pap

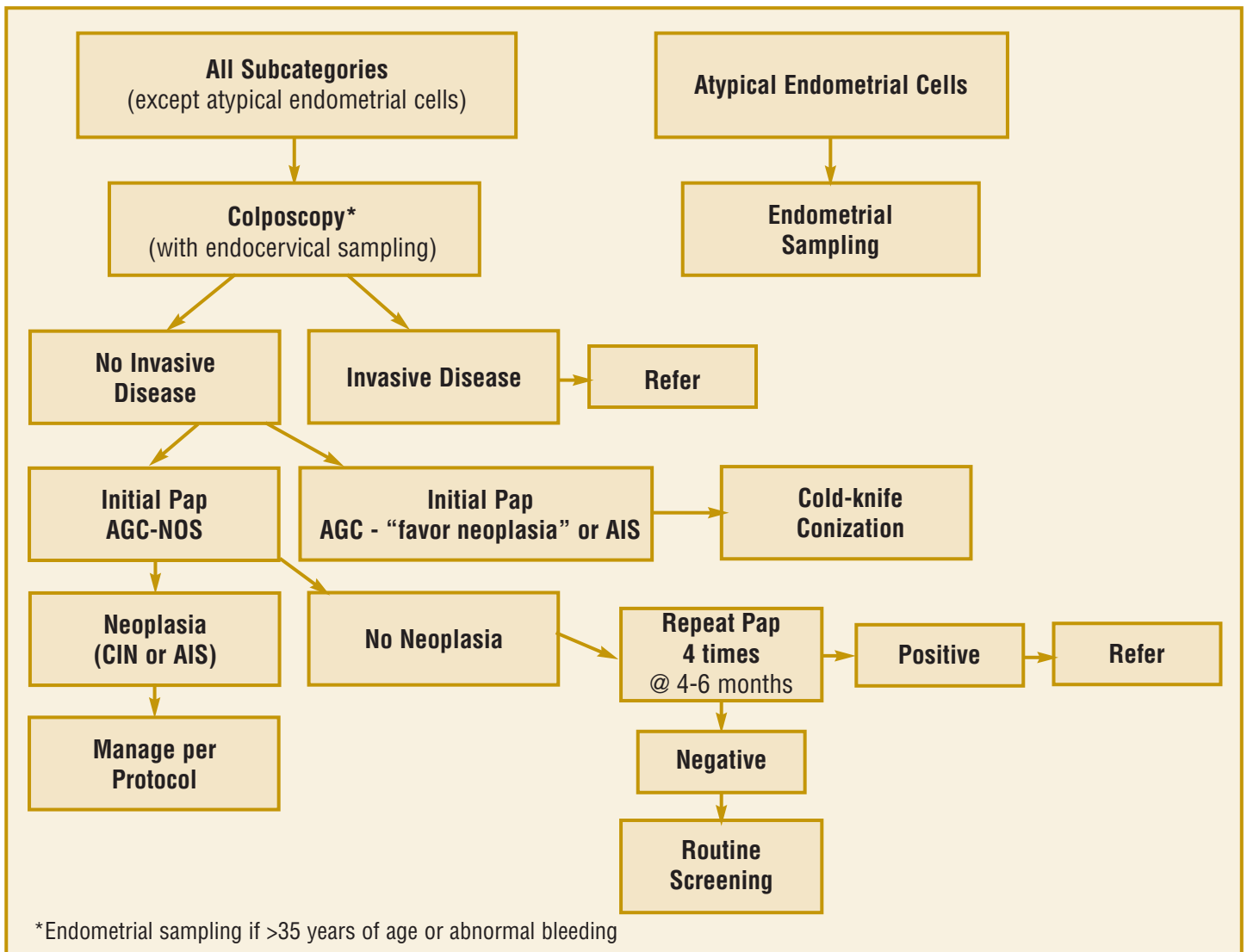


Figure 2 Management of Atypical Glandular Cells (AGC)

Adapted from: ASCCP Consensus Guidelines, 2002²⁹

tests with normal results, she may return to a regimen of normal screening.^{3, 27, 34}

Women with AGC-NOS who are proven to have biopsy-confirmed CIN should be managed according to Consensus Guidelines.^{3, 27}

Women with AGC-favor neoplasia or AIS should undergo a diagnostic excisional procedure. In an effort to evaluate the extent of disease, cold-knife conization is preferred because it offers the best surgical margins and provides a specimen from deep within the endocervical canal.^{3, 27, 41}

Management of Women with Adenocarcinoma

In cases involving adenocarcinoma, referral to a specialist who is skilled in cold-knife conization and other surgical options is recommended. Women who prove to have adenocarcinoma face difficult decisions regarding treatment. If a woman does not feel a need to maintain

fertility, a hysterectomy may be an acceptable and definitive treatment. Should a woman want to maintain fertility, cervical conization may be performed and repeated until negative surgical margins are obtained. Thereafter, when child-bearing is complete, hysterectomy should be offered.³¹

Women who prefer less aggressive treatment should be counseled and followed closely with Pap tests and endocervical curettage. Some physicians continue to treat adenocarcinoma with loop electrosurgical excision procedure (LEEP). However, this is not the preferred option because of the importance of obtaining clear-cut surgical margins.³¹

Low-grade and High-grade SIL

The management of women with a Pap interpretation of low-grade squamous intraepithelial lesions is relatively straightforward (Figure 3).^{3, 27, 29} Most women with LSIL should receive immediate colposcopy to exclude an underlying high-grade lesion.^{3, 27}

Women with high-grade squamous intraepithelial lesions should receive immediate colposcopy because 75% of nonpregnant women with this Pap interpretation are found to have biopsy-confirmed CIN grade 2 or 3. Most women who are found to have CIN 2 or CIN 3 on biopsy will undergo treatment to reduce their risk of developing cervical cancer. Three percent of women with an interpretation of HSIL will have invasive cervical cancer and are treated accordingly (Figure 4).^{3, 27, 29}

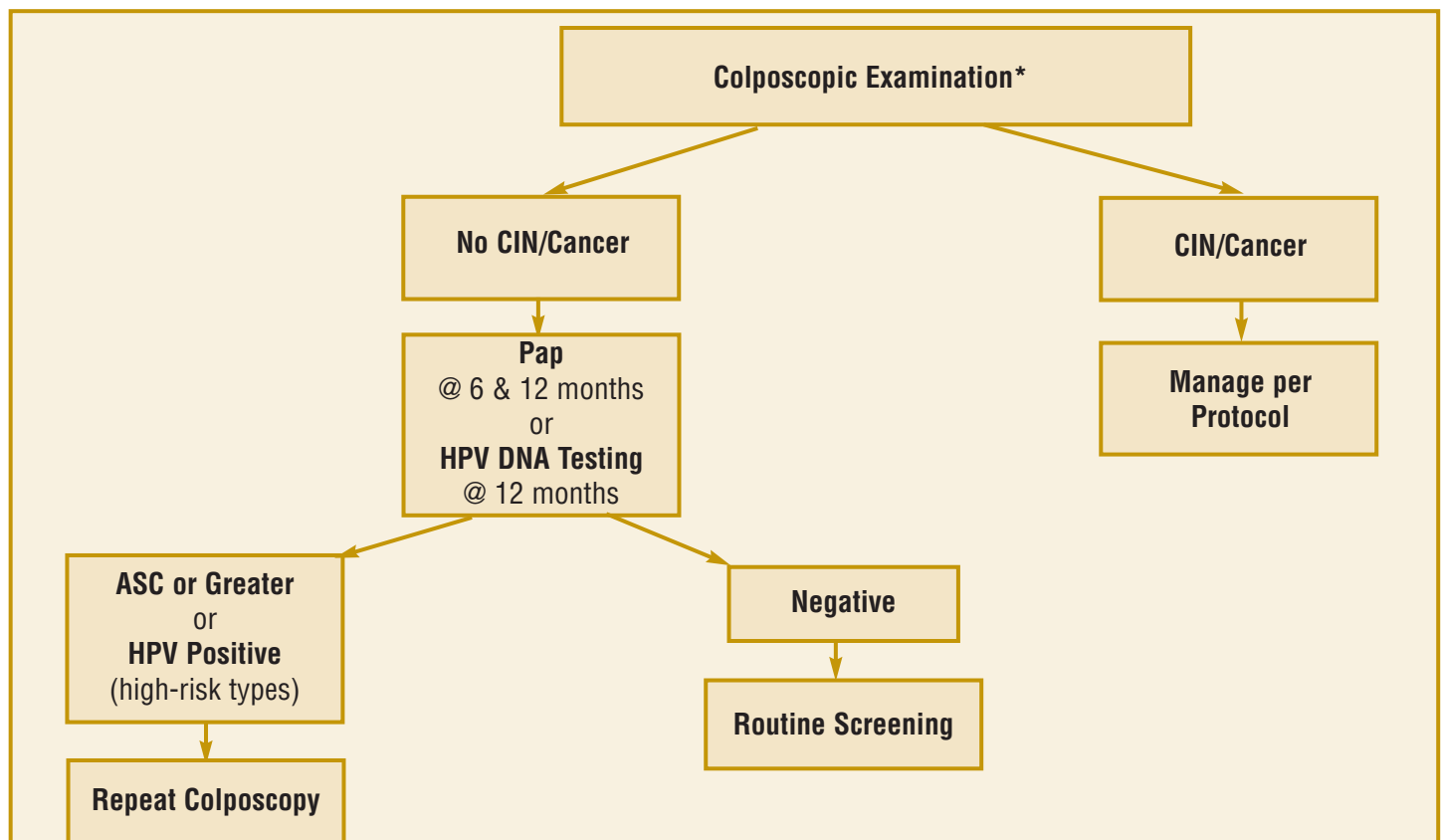
Additional guidelines have been provided for managing LSIL and HSIL in women with special circumstances, such as those who are post-menopausal or adolescent. For example, post-menopausal women with LSIL may receive intravaginal estrogen prior to a program of repeat cytology. Adolescents with LSIL may be followed with a single repeat Pap or HPV testing at one year, given that the vast majority of LSIL and HPV infection in this age group will regress spontaneously.²⁹

Additional information regarding the **2001 Consensus Guidelines for Management of Women With Cervical Cytological Abnormalities** is available on the ASCCP Web site (<http://www.asccp.org>).

Management of Cervical Lesions

There are a variety of treatments options available to women with CIN. The family physician may discuss these options with the patient, and depending on the histology, size, location and persistence of the lesion, may recommend one over the others. For example, the family physician will likely recommend that CIN 1 be watched over time to see whether it regresses without treatment. In the case of CIN 2 or CIN 3, on the other hand, the physician will likely recommend immediate treatment.³ Considering the cost-effectiveness of the treatment, possible side effects or complications, experience of the physician and patient preference also will help in determining treatment.

Table 8 lists the four options most commonly used for treating localized CIN.



*Different management options may apply for post-menopausal, adolescent or pregnant women.

Figure 3 Management of Low-grade Squamous Intraepithelial Lesions (LSIL)

Adapted from: ASCCP Consensus Guidelines, 2002²⁹

Table 8 CIN Treatment Options

Cryotherapy	A metal probe and carbon dioxide or nitrous oxide is used to kill the abnormal cells and transformation zone, which then slough off the cervix.
Laser therapy	A high-energy beam of light is used to destroy the lesion and transformation zone through vaporization.
LEEP (loop electrosurgical excision procedure)	A high-frequency electrical current passed through a fine wire loop is used to remove the transformation zone and abnormal tissue from the cervix.
Cold-knife cone	A slender scalpel is used to remove a cone-shaped portion of the cervix that encompasses the lesion.

Control of HPV

Because the causal relationship between HPV infection and cervical cancer has been acknowledged, it is possible for family physicians to discuss with patients measures they can take to help reduce the risk of developing cervical cancer. Currently, such measures focus on reducing the risk of contracting HPV (Table 9). Physicians should emphasize, however, that HPV is highly contagious and that, except for sexual abstinence, behavioral modifications have not been shown to prevent infection consistently.

Practice Recommendation: Most pre-cancerous cervical abnormalities can be successfully treated by surgical methods, but there is no clear evidence to show that any specific modality is superior to others.

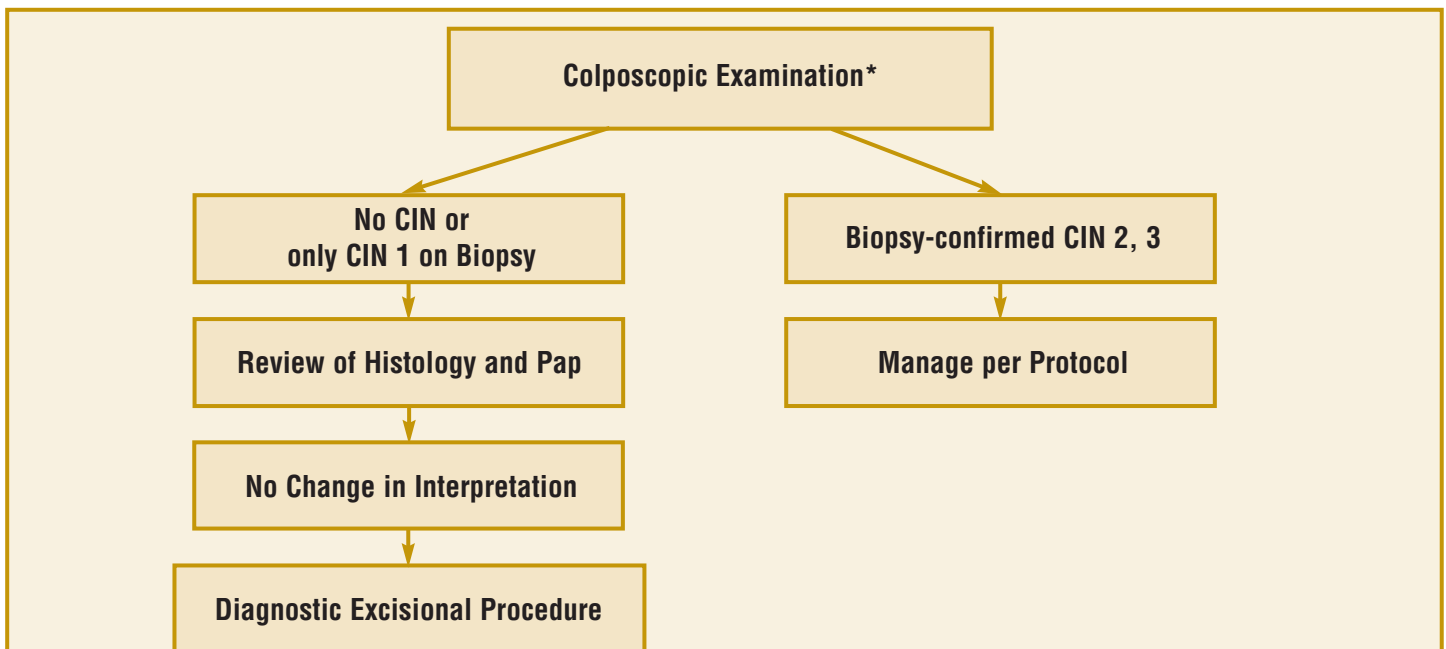


Strength of evidence: Experts identified and combined for analysis 28 randomized controlled clinical trials that supported the contention that 90% of cervical lesions are successfully treated regardless of the surgical modality employed. The combined trials were small and individually lacked sufficient power to detect minor, but nonetheless possibly important, differences in treatment modalities.

EBM Source: Cochrane Database of Systematic Reviews. Martin H. Surgery for cervical intraepithelial neoplasia. Cochrane Database of Systematic Reviews. 1, 2005. <http://www.cochrane.org/reviews/english/ab001318.html>

Table 9 Measures for Reducing the Risk of Developing Cervical Cancer

- Abstain from sexual intercourse or
- Maintain a long-term mutually monogamous relationship or
- Reduce the number of sexual partners and choose a partner who has had no or few prior partners and
- Participate in routine medical screening and management beginning with Pap tests and, possibly, DNA testing.



*Different management options may apply for post-menopausal, adolescent or pregnant women.

Figure 4 Management of High-grade Squamous Intraepithelial Lesions (HSIL)

Adapted from: ASCCP Consensus Guidelines, 2002²⁹

HPV Vaccines

Vaccines that protect against common disease-causing HPV types would be expected to reduce the incidence of HPV-associated diseases significantly.⁴³ Vaccinating against HPV 16 and 18, the most common cancer-causing HPV types, could prevent up to 70% of cervical cancers worldwide.⁴⁴ Preventative HPV vaccines under development are composed of the L1 major capsid protein that comprises the outermost layer of the virus. Because these vaccines do not contain genetic material, they are non-infectious and have no oncogenic potential.

Over the past few years, randomized clinical trials involving vaccinations directed against multiple HPV types have been conducted. In these trials, young women received doses of a monovalent HPV 16 vaccine, a bivalent HPV 16 and 18 vaccine, or a quadrivalent vaccine HPV 6, 11, 16 and 18 vaccine.⁴⁴⁻⁴⁶ Because the quadrivalent vaccine has potential to protect against four common HPV types, it could prevent the majority of genital warts, genital neoplasias, and cervical cancers.

Each of the trials has shown that vaccines are highly efficacious in preventing HPV infection and disease, and show high levels of immunogenicity. Over 99% of the women who received the vaccines seroconverted. Peak antibody titers were considerably higher in the vaccinated women than in women naturally infected with HPV. The bivalent and quadrivalent studies demonstrate that the vaccines were well-tolerated and caused no serious vaccine-related adverse events.⁴⁴⁻⁴⁶ Additional phases of the trials are ongoing.

HPV Vaccines and Genital Warts

Family physicians frequently see patients who present with genital warts. Visible genital warts usually are caused by HPV 6 or 11, in which case they carry a very low risk for causing invasive squamous cell carcinoma.⁴⁷ Less commonly, HPV 16 and 18, which carry the strongest potential for malignancy, are found in genital warts and can cause squamous intraepithelial neoplasia.¹²

Despite a generally benign course, genital warts can have a substantial psychological impact, making prevention worthwhile. The quadrivalent vaccine described above has the potential to prevent genital warts. Trials of the quadrivalent vaccine, which demonstrates high efficacy in preventing clinical disease, including genital warts, are promising.⁴⁸

Implementation of HPV Immunization Programs

Because HPV vaccines are designed to be primarily prophylactic, vaccination administered to patients before they become sexually active will provide the greatest public health benefit. Vaccines in development work by preventing infection; therefore, successful implementation will require societal acceptance. This

begins with an awareness of the prevalence and impact of HPV and some understanding of its connection to cervical cancer.

Parents of adolescents will need to be educated about the benefits of an HPV vaccination program for their children. In a recent study, parents were willing to vaccinate their children against sexually transmitted disease and were more concerned about safety and efficacy than social stigma.⁴⁹

Even when an HPV immunization program is in place, family physicians will need to continue cervical cancer screening to detect cervical abnormalities in women infected by HPV prior to vaccination or infected with HPV types not covered by the vaccine.

Conclusion

In the past several decades, the incidence and mortality rates associated with cervical cancer have been decreasing. Armed with an understanding of the connection between HPV and genital warts and cervical cancer, and with guidelines for screening, managing and treating cervical abnormalities, family physicians will continue to play a key role in helping women to reduce their risk of developing the disease. HPV vaccines may soon become available to aid in the fight to prevent the majority of genital warts and cervical cancer.

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Cervical Cancer and Other Human Papillomavirus-related Diseases: Screening and Prevention Strategies for Primary Care Clinicians

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Learning Objectives

1. Discuss the natural history of human papillomavirus infection.
2. Describe the causal relationship between HPV and genital warts and HPV and cervical cancer.
3. Discuss strategies family physicians can employ to help patients reduce their risk of acquiring HPV and developing genital warts and cervical cancer.
4. Review guidelines for managing women with abnormal cervical cytologies, and present the most commonly used options for treating precancerous cervical lesions and glandular abnormalities.
5. Recognize the role of HPV vaccines in reducing the incidence of genital warts, precancerous lesions, and cervical cancer.

For a CME certificate, please complete the test and evaluation forms on the reverse side, and send to:

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Content was useful, relevant, and timely to my profession	5	4	3	2	1
Material format was clear and informative	5	4	3	2	1
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Signature _____ Name (print) _____

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Phone _____ E-mail _____

In the space provided, indicate whether each item is True (T) or False (F).

- _____ 1. The highest prevalence of cervical intraepithelial neoplasia occurs in women in their 60s and 70s.
- _____ 2. Almost all women with cervical cancer are infected with human papillomavirus.
- _____ 3. Most occurrences of low-grade cervical histology will progress to cervical cancer.
- _____ 4. The Bethesda System requires that a Pap test specimen be accompanied by a patient history and contain enough well-fixed cells for the pathologist to analyze.
- _____ 5. Women should undergo regular cervical screening with Pap tests beginning approximately 3 years after first sexual intercourse but no later than age 21.
- _____ 6. If liquid-based cytology is used, reflex HPV DNA testing is the preferred method of managing women with ASC-US.
- _____ 7. It is considered unacceptable to manage women with AGC-NOS initially with a program of repeat Pap tests.
- _____ 8. Loop electrosurgical excision procedure (LEEP) is not the preferred option for managing women with adenocarcinoma because of the importance of obtaining clear-cut surgical margins.
- _____ 9. Maintaining a long-term mutually monogamous relationship can help reduce the risk of developing cervical cancer.
- _____ 10. Vaccination with the quadrivalent HPV vaccine has the potential to prevent cervical neoplasia as well as genital warts.

Thank you for filling out this post-test.

