2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests

Thomas C. Wright Jr, MD; L. Stewart Massad, MD; Charles J. Dunton, MD; Mark Spitzer, MD; Edward J. Wilkinson, MD; Diane Solomon, MD, for the 2006 American Society for Colposcopy and Cervical Pathology–sponsored Consensus Conference

A group of 146 experts representing 29 organizations and professional societies met September 18-19, 2006, in Bethesda, MD, to develop revised evidence-based, consensus guidelines for managing women with abnormal cervical cancer screening tests. Recommendations for managing atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesion (LSIL) are essentially unchanged. Changes were made for managing these conditions in adolescents for whom cytological follow-up for 2 years was approved. Recommendations for managing high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells (AGC) also underwent only minor modifications. More emphasis is placed on immediate screen-and-treat approaches for HSIL. Human papillomavirus (HPV) testing is incorporated into the management of AGC after their initial evaluation with colposcopy and endometrial sampling. The 2004 Interim Guidance for HPV testing as an adjunct to cervical cytology for screening in women 30 years of age and older was formally adopted with only very minor modifications.

Key words: atypical squamous cells of undetermined significance, cervical cancer screening, cervical cytology, high-grade squamous intraepithelial lesion, human papillomavirus testing, low-grade squamous intraepithelial lesion

Since the publication of the 2001 consensus guidelines, new information has become available, which includes the key follow-up results from the National Cancer Institute (NCI)–sponsored ASCUS (atypical squamous cells of undetermined significance)/LSIL (low-grade squamous intraepithelial lesions) Triage Study (ALTS).[1,2] Moreover, molecular testing for high-risk types of human papillomavirus (HPV) is being used together with cervical cytology for screening in women 30 years of age and older. Although "interim guidance" for the use of HPV DNA testing in the screening setting was proposed in 2004, recommendations for how to manage the combination of test results have not formally been evaluated by a large, multidisciplinary group.[3] Once the 2001 guidelines were implemented in a variety of clinical settings, it became apparent that there were a number of areas in which changes were needed. This pertains particularly to special populations such as adolescents and postmenopausal women. Therefore, in 2005, the American Society for Colposcopy and Cervical Pathology (ASCCP), together with its partner professional societies and federal and international organizations (listed in Appendix A), began the process of revising the guidelines. This culminated in the 2006 consensus conference that was held at the National Institutes of Health in September 2006. This report provides the recommendations developed with respect to managing women with cytological abnormalities. Recommendations for managing women with cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ (AIS) appear in the accompanying article. A more comprehensive discussion of the recommendations and their supporting evidence will be made available on the ASCCP website (www.asccp.org).

From the Department of Pathology, College of Physicians and Surgeons of Columbia University, New York, NY (Dr Wright); Department of Obstetrics and Gynecology, Washington University School of Medicine, St Louis, MO (Dr Massad); Department of Obstetrics and Gynecology, Lankenau Hospital, Wynnewood, PA (Dr Dunton); Department of Obstetrics and Gynecology, Brookdale University Hospital and Medical Center, Brooklyn, NY (Dr Spitzer); Department of Pathology, University of Florida College of Medicine, Gainesville, FL (Dr Wilkinson); and National Institutes of Health and National Cancer Institute, Bethesda, MD (Dr Solomon).

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Reprints: Thomas C. Wright Jr, MD, Department of Pathology, College of Physicians and Surgeons of Columbia University, Room 16-404, P&S Building, 630 West 168th St, New York, NY 10032; tcw1@columbia.edu

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See related editorial, page 337, and related article, page 340.

Guideline Development Process

The process used to develop the 2006 Consensus Guidelines was similar to that for the previous guidelines and is discussed in depth in other publications.[4,5] Guidelines were developed through a multistep process. Working groups reviewed literature published after 2000 before developing guidelines that were subsequently revised based on input from the professional community at large, obtained using an Internet-based bulletin board. At the consensus conference, guidelines with supporting evidence were presented and underwent discussion, revision, and approval. The terminology utilized in the new guidelines is identical to that used previously, as is the 2-part rating system (Table).[4,5] The terms "recommended," "preferred," "acceptable," and "unacceptable" are used in the guidelines to describe various interventions. The letters A through E are used to indicate strength of recommendation for or against the use of a particular option. Roman numerals I-III are

TABLE
Rating the recommendations

Strength of Recommendation*

- **A** Good evidence for efficacy and substantial clinical benefit support recommendation for use.
- **B** Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use.
- **C** Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds.
- **D** Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
- **E** Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Quality of Evidence*

- **I** Evidence from at least 1 randomized, controlled trial.
- **II** Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center) or from multiple time-series studies or dramatic results from uncontrolled experiments.
- **III** Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Terminology used for recommendations†

Recommended	Good data to support use when only 1 option is available.
Preferred	Option is the best (or 1 of the best) when there are multiple other options
Acceptable	One of multiple options when there are either data indicating that another approach is superior or when there are no data to favor any single option.
Unacceptable	Good data against use.

* Modified from references.[80,81]

† The assignment of these terms represents an opinion ratified by vote by the Consensus Conference.

used to indicate the "quality of evidence" for a given recommendation. The "strength of recommendation" and "quality of evidence" are provided in parentheses after each recommendation.

2006 Consensus Guidelines

General comments

Although the guidelines are based on evidence whenever possible, for certain clinical situations, there is limited high-quality evidence, and in these situations the guidelines have, by necessity, been based on consensus expert opinion. It is also important to recognize that these guidelines should never substitute for clinical judgment. Clinical judgment should always be used when applying a guideline to an individual patient because it is impossible to develop guidelines that apply to all situations.

The 2001 Bethesda System terminology is used for cytologic classification.[6] This terminology utilizes the terms low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) to refer to low-grade lesions and high-grade cervical cancer precursors, respectively. The histologic classification used is a 2-tiered system that applies the terms CIN 1 to low-grade lesions and CIN 2,3 to high-grade precursors. It is important to note that cytologic LSIL is not equivalent to histologic CIN 1 and cytologic HSIL is not equivalent to histologic CIN 2,3. Algorithms detailing the different management recommendations are available at the ASCCP website (www.asccp.org). A glossary of terms used in the guidelines is in Appendix B.

The current guidelines expand clinical indications for HPV testing based on studies using validated HPV assays. One cannot assume that management decisions that are based on results of HPV tests that have not been similarly validated will result in the outcomes that are intended by these guidelines. Furthermore, the application of these guidelines using such tests may increase the potential for patient harm. The appropriate use of these guidelines requires that laboratories utilize only HPV tests that have been analytically and clinically validated with proven acceptable reproducibility, clinical sensitivity, specificity, and positive and negative predictive values for cervical cancer and verified precancer (CIN 2,3), as documented by Food and Drug Administration (FDA) approval and/or publication in peer-reviewed scientific literature. It is also important to stress that testing should be restricted to high-risk (oncogenic) HPV types.[7,8] Testing for low-risk (nononcogenic) HPV types has no role in the evaluation of women with abnormal cervical cytological results. Therefore, whenever "HPV testing" is referred to in the guidelines, it applies only to testing for high-risk (oncogenic) HPV types.

Special populations

The exact same cytologic result has a different risk of CIN 2,3 or cancer (CIN 2+) in various groups of women. One such special population is adolescent women (aged 20 years and younger) who have a high prevalence of HPV infections, more minor-grade cytologic abnormalities (atypical squamous cells [ASC] and LSIL) but very low risk for invasive cervical cancer, compared with older women.[9,10] This is because the vast majority of HPV infections spontaneously clear within 2 years after infection and are of little long-term clinical significance.[11,12] Therefore, performing colposcopy for minor cytologic abnormali-

ties in adolescents should be discouraged because it can potentially result in harm through unnecessary treatment.

Pregnant women are also considered a special population. The only indication for therapy of cervical neoplasia in pregnant women is invasive cancer. Therefore, it is reasonable to defer colposcopy in pregnant women at low risk for having cancer. Finally, it should be cautioned that endocervical curettage is contraindicated in pregnant patients.

Atypical squamous cells

ASC is subcategorized into atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells, cannot exclude HSIL (ASC-H). There are several factors that need to be taken into consideration when managing women with ASC. One is that a cytological result of ASC is the least reproducible of all cytologic categories.[13-15] Another is that the prevalence of invasive cancer is low in women with ASC (approximately 0.1-0.2%).[16] Finally, it is important to note that the prevalence of CIN 2,3 is higher among women with ASC-H than women with ASC-US. Because of this, ASC-H should be considered to represent equivocal HSIL.

Clinical data from ALTS and other studies[1,17-19] have demonstrated that 2 repeat cytologic examinations performed at 6-month intervals, testing for HPV, and a single colposcopic examination are all safe and effective approaches to managing women with ASC-US. Therefore, the 2001 Consensus Guidelines recognized that all 3 approaches were acceptable for managing women with ASC-US. The scientific basis for the 2001 recommendation has been strengthened over the last 5 years by additional clinical studies, additional analyses of the ALTS data, and metaanalyses of published studies.[18,20-25] "Reflex" testing refers to testing either the original liquid-based cytology residual specimen or a separate sample cocollected at the time of the initial screening visit for HPV testing. This approach eliminates the need for women to return to the office or clinic for repeat testing, rapidly assures many women that they do not have a significant lesion, spares 40-60% of women from undergoing colposcopy, and has been shown to have a favorable cost-effectiveness ratio.[26,27]

Because a single colposcopic examination can miss significant lesions, women who are referred for colposcopy and found not to have CIN 2,3 require additional follow-up. ALTS evaluated different postcolposcopy follow-up strategies and found that HPV testing performed 12 months after the initial colposcopy and 2 repeat cytology examinations performed at 6 month intervals performed similarly.[28] Combining cytology with HPV testing did not increase sensitivity and reduced specificity.[28]

Special populations

The prevalence of HPV DNA positivity changes with age among women with ASC-US. Rates of HPV DNA positivity are much higher in younger, compared with older, women with ASC-US.[29,30] Thus, using HPV testing to manage adolescents with ASC-US would refer large numbers of women at low risk for having cancer to colposcopy. ASC-US is less common in postmenopausal than premenopausal women, and the risk of significant pathology in postmenopausal women with a history of cervical cancer screening is relatively low.[10,31,32] HPV testing is actually more efficient in older, compared with younger, women with ASC-US because it refers a lower proportion to colposcopy.[31,33,34]

ASC-US is quite common in HIV-infected women.[35,36] Previously, based on studies that had reported a high prevalence of both HPV DNA positivity and significant cervical pathology in this population,[4] it was recommended that all immunosuppressed women with ASC-US undergo colposcopy. More recent studies have found a lower prevalence of CIN 2,3 and HPV DNA positivity; therefore, immunosuppressed women should be managed in the same manner as women in the general population.[37,38] The risk of cancer is relatively low among pregnant women with ASC-US, and some studies have found that antepartum colposcopic evaluation does not add to management.[39]

Recommended Management of Women with ASC-US

General management approaches

A program of DNA testing for high-risk (oncogenic) types of HPV, repeat cervical cytologic testing, or colposcopy are all acceptable methods for managing women over the age of 20 years with ASC-US. (AI) When liquid-based cytology is used or when cocollection for HPV DNA testing can be done, "reflex" HPV DNA testing is the preferred approach. (AI)

Women with ASC-US who are HPV DNA negative can be followed up with repeat cytologic testing at 12 months. (BII) Women who are HPV DNA positive should be managed in the same fashion as women with LSIL and be referred for colposcopic evaluation. (AII) Endocervical sampling is preferred for women in whom no lesions are identified (BII) and those with an unsatisfactory colposcopy (AII) but is acceptable for women with a satisfactory colposcopy and a lesion identified in the transformation zone. (CII) Acceptable postcolposcopy management options of women with ASC-US who are HPV positive, but in whom CIN is not identified, are HPV DNA testing at 12 months or repeat cytological testing at 6 and 12 months. (BII) It is recommended that HPV DNA testing not be performed at intervals less than 12 months. (EIII)

When a program of repeat cytologic testing is used for managing women with ASC-US, it is recommended that cytologic testing be performed at 6-month intervals until 2 consecutive "negative for intraepithelial lesion or malignancy" results are obtained. (AII) Colposcopy is recommended for women with ASC-US or greater cytologic abnormality on a repeat test. (AII) After 2 repeat "negative for intraepithelial lesion or malignancy" results are obtained, women can return to routine cytologic screening. (AII)

When colposcopy is used to manage women with ASC-US, repeat cytologic testing at 12 months is recommended for women in whom CIN is not identified.

(BIII) Women found to have CIN should be managed according to the 2006 Consensus Guidelines for the Management of Cervical Intraepithelial Neoplasia.

Because of the potential for overtreatment, the routine use of diagnostic excisional procedures such as the loop electrosurgical excision procedure is unacceptable for women with an initial ASC-US in the absence of histologically diagnosed CIN 2,3. (EII)

ASC-US in Special Populations

Adolescent women

In adolescents with ASC-US, follow-up with annual cytologic testing is recommended. (BII) At the 12-month follow-up, only adolescents with HSIL or greater on the repeat cytology should be referred to colposcopy. At the 24-month follow-up, those with an ASC-US or greater result should be referred to colposcopy. (AII) HPV DNA testing and colposcopy are unacceptable for adolescents with ASC-US. (EII) If HPV testing is inadvertently performed, the results should not influence management.

Immunosuppressed and postmenopausal women

HIV-infected, other immunosuppressed women, and postmenopausal women with ASC-US should be managed in the same manner as women in the general population. (BII)

Pregnant women

Management options for pregnant women over the age of 20 years with ASC-US are identical to those described for nonpregnant women, with the exception that it is acceptable to defer colposcopy until at least 6 weeks postpartum. (CIII) Endocervical curettage is unacceptable in pregnant women. (EIII)

Recommended Management of Women with ASC-H

The recommended management of women with ASC-H is referral for colposcopic evaluation. (AII) In women in whom CIN 2,3 is not identified, follow-up with HPV DNA testing at 12 months or cytological testing at 6 and 12 months is acceptable. (CIII) Referral to colposcopy is recommended for women who subsequently test positive for HPV DNA or who are found to have ASC-US or greater on their repeat cytologic tests. (BII) If the HPV DNA test is negative or if 2 consecutive repeat cytologic tests are negative for intraepithelial lesion or malignancy, return to routine cytologic screening is recommended. (AI)

LSIL

Over the last decade, the rate of LSIL has increased in the United States and in 2003 the mean LSIL reporting rate was 2.9% for liquid-based specimens.[40] A result of LSIL is a good indicator of HPV infection. A recent metaanalysis reported that the pooled estimate of high-risk (oncogenic) HPV DNA positivity among women with LSIL was 76.6%.[41] The prevalence of CIN 2 or greater identified at initial colposcopy among women with LSIL is 12-16%.[2,42,43]

Data from ALTS indicate that the risk of CIN 2,3 is the same in women with LSIL and those with ASC-US who are high risk (oncogenic) HPV DNA positive.[23] This supports managing both groups of women in an identical manner except in special populations such as postmenopausal women.

Special Populations

Prospective follow-up studies of adolescents with LSIL have shown very high rates of regression to normal, although it is not unusual for regression to take years to occur.[44] As with ASC-US, the high prevalence of HPV DNA positivity in adolescents with LSIL makes HPV testing of little value in this population. Some, but not all, studies have found that the prevalence of both HPV DNA positivity and CIN 2,3 decline with age in women with LSIL.[33,45] This suggests that postmenopausal women with LSIL can be managed less aggressively than premenopausal women and that triage using HPV testing may be attractive.

Recommended Management of Women with LSIL

Colposcopy is recommended for managing women with LSIL, except in special populations (see following text). (AII) Endocervical sampling is preferred for nonpregnant women in whom no lesions are identified (BII) and those with an unsatisfactory colposcopy (AII), but is acceptable for those with a satisfactory colposcopy and a lesion identified in the transformation zone. (CII) Acceptable postcolposcopy management options for women with LSIL cytology in whom CIN 2,3 is not identified are testing for high-risk (oncogenic) types of HPV at 12 months or repeat cervical cytologic testing at 6 and 12 months. (BII) If the HPV DNA test is negative or if 2 consecutive repeat cytologic tests are negative for intraepithelial lesion or malignancy, return to routine cytologic screening is recommended. (AI) If either the HPV DNA test is positive or if repeat cytology is reported as ASC-US or greater, colposcopy is recommended. (AI) Women found to have CIN should be managed according to the appropriate 2006 Consensus Guidelines on the Management of Cervical Intraepithelial Neoplasia. In the absence of CIN identified histologically, diagnostic excisional or ablative procedures are unacceptable for the initial management of patients with LSIL. (EII)

LSIL in Special Populations

Adolescents

In adolescents with LSIL, follow-up with annual cytologic testing is recommended. (AII) At the 12-month follow-up, only adolescents with HSIL or greater on the repeat cytology should be referred to colposcopy. At the 24-month follow-up, those with an ASC-US or greater result should be referred to colposcopy. (AII) HPV DNA testing is unacceptable for adolescents with LSIL. (EII) If HPV DNA testing is inadvertently performed, the results should not influence management.

Postmenopausal women

Acceptable options for the management of postmenopausal women with LSIL include "reflex" HPV DNA testing, repeat

cytological testing at 6 and 12 months, and colposcopy. (CIII) If the HPV DNA test is negative or CIN is not identified at colposcopy, repeat cytology in 12 months is recommended. If either the HPV DNA test is positive or the repeat cytology is ASC-US or greater, colposcopy is recommended. (AII) If 2 consecutive repeat cytologic tests are negative for intraepithelial lesion or malignancy, return to routine cytologic screening is recommended.

Pregnant women

Colposcopy is preferred for pregnant, nonadolescent women with LSIL cytology. (BII) Endocervical curettage is unacceptable in pregnant women. (EIII) Deferring the initial colposcopy until at least 6 weeks postpartum is acceptable. (BIII) In pregnant women who have no cytologic, histologic, or colposcopically suspected CIN 2,3 or cancer at the initial colposcopy, postpartum follow-up is recommended. (BIII) Additional colposcopic and cytologic examinations during pregnancy are unacceptable for these women. (DIII)

HSIL

The mean reporting rate of HSIL in US laboratories is 0.7%.[40] The rate of HSIL varies with age. In 1 US center, the rate of HSIL in women 20-29 years of age is 0.6%, compared with 0.2% and 0.1% in women 40-49 years and 50-59 years of age, respectively.[10] The finding of a HSIL result on cytology carries a high risk for significant cervical disease. A single colposcopic examination identifies CIN 2 or greater in 53-66% of women with HSIL and CIN 2 or greater is diagnosed in 84-97% of women evaluated using a loop electrosurgical excision procedure.[42,46,47] Approximately 2% of women with HSIL have invasive cancer.[48]

There is a considerable risk of a CIN 2 or greater and a high prevalence of HPV DNA positivity in women with HSIL, and intermediate triage using HPV testing or cytology is inappropriate.[42,45,46,48,49] Because colposcopy can miss a significant number of CIN 2,3 lesions, failure to detect CIN 2,3 at colposcopy in a woman with HSIL does not necessarily mean a CIN 2,3 lesion is not present. As a result, most women with HSIL eventually undergo a diagnostic excisional procedure. Because of this, many have advocated see-and-treat approaches for managing women with HSIL in which a loop electrosurgical excision is used for initial evaluation.[47,50,51] It should be recognized, however, that many CIN 2,3 lesions, especially in adolescents and young adults, spontaneously regress.[52,53]

Recommended Management of Women with HSIL

An immediate loop electrosurgical excision or colposcopy with endocervical assessment is an acceptable method for managing women with HSIL, except in special populations (see following text). (BII) When CIN 2,3 is not identified histologically, either a diagnostic excisional procedure or observation with colposcopy and cytology at 6 month intervals for 1 year is acceptable, provided in the latter case that the colposcopic examination is satisfactory and endocervical sampling is negative. (BIII) In this circumstance it is also acceptable to review the cytological, histological, and colposcopic findings; if the review yields a revised interpretation, management should follow guidelines for the revised interpretation. (BII) If observation with cytology and colposcopy is elected, a diagnostic excisional procedure is recommended for women with repeat HSIL cytological results at either the 6 or 12 month visit. (CIII) After 1 year of observation, women with 2 consecutive "negative for intraepithelial lesion or malignancy" results can return to routine cytological screening.

A diagnostic excisional procedure is recommended for women with HSIL in whom the colposcopic examination is unsatisfactory, except in special populations (eg, pregnant women). (BII) Women with CIN 2,3 should be managed according to the appropriate 2006 Consensus Guideline for the Management of Women with Cervical Intraepithelial Neoplasia. Ablation is unacceptable in the following circumstances: when colposcopy has not been performed, CIN 2,3 is not identified histologically, or the endocervical assessment identifies CIN of any grade. (EII) Triage utilizing either a program of only repeat cytology or HPV DNA testing is unacceptable. (EII)

HSIL in Special Populations

Adolescent women

In adolescents with HSIL, colposcopy is recommended. Immediate loop electrosurgical excision (ie, "see-and-treat") is unacceptable in adolescent women. (AII) When CIN 2,3 is not identified histologically, observation for up to 24 months using both colposcopy and cytology at 6-month intervals is preferred, provided the colposcopic examination is satisfactory and endocervical sampling is negative. (BIII) In exceptional circumstances, a diagnostic excisional procedure is acceptable. (BIII) If during follow-up a high-grade colposcopic lesion is identified or HSIL cytology persists for 1 year, biopsy is recommended. (BIII) If CIN 2,3 is identified histologically, management should follow the 2006 Consensus Guideline for the Management of Women with Cervical Intraepithelial Neoplasia. (BIII) If HSIL persists for 24 months without identification of CIN 2,3, a diagnostic excisional procedure is recommended. (BIII) After 2 consecutive "negative for intraepithelial lesion or malignancy" results, adolescents and young women without a high-grade colposcopic abnormality can return to routine cytological screening. (BIII) A diagnostic excisional procedure is recommended for adolescents and young women with HSIL when colposcopy is unsatisfactory or CIN of any grade is identified on endocervical assessment (BII).

Pregnant women

Colposcopy is recommended for pregnant women with HSIL. (AII) It is preferred that the colposcopic evaluation of pregnant women with HSIL be conducted by clinicians who are experienced in the evaluation of colposcopic changes induced by pregnancy. (BIII) Biopsy of lesions suspicious for CIN 2,3 or cancer

is preferred; biopsy of other lesions is acceptable (BIII). Endocervical curettage is unacceptable in pregnant women. (EIII) Diagnostic excision is unacceptable unless invasive cancer is suspected based on the referral cytology, colposcopic appearance, or cervical biopsy. (EII) Reevaluation with cytology and colposcopy is recommended no sooner than 6 weeks postpartum for pregnant women with HSIL in whom CIN 2,3 is not diagnosed. (CIII)

Atypical glandular cells (AGC)

AGC results are relatively uncommon, with a mean reporting rate of only 0.4% in the United States in 2003.[40] Although AGC is frequently caused by benign conditions, such as reactive changes and polyps, clinicians should be aware that it is not uncommon for AGC to be associated with a significant underlying neoplastic condition including adenocarcinomas of the cervix, endometrium, ovary, and fallopian tube. Recent series have reported that 9-38% of women with AGC have significant neoplasia (CIN 2,3, AIS, or cancer), and 3-17% have invasive cancer.[54,55,56,57]

The rate and type of significant findings in women with AGC varies with age.[55] Although a variety of glandular lesions, including malignancies, are associated with AGC, CIN is the most common significant finding identified in women with AGC.[58] Gynecologic malignancy is less common in women under the age of 35 years than in older women.[54] Pregnancy does not appear to change the underlying associations between AGC and gynecologic neoplasia.

Neither HPV testing nor repeat cervical cytology has the requisite sensitivity to be utilized alone as an initial triage test for women with AGC.[57,59,60] Because of the spectrum of neoplasia linked to AGC, initial evaluation must include multiple testing modalities.[57,59] These include colposcopy, endocervical evaluation and sampling, HPV testing, and endometrial evaluation. Because of the high incidence of neoplasia and the poor sensitivity of all test modalities, diagnostic excisional procedures may be necessary, despite initial negative testing, for women with AGC-favor neoplasia," AIS, or repeat AGC cytology.[4]

Other Glandular Abnormalities

Benign-appearing endometrial cells in a woman 40 years of age and older and endometrial stromal cells or histiocytes are occasionally encountered cytologically. Approximately 0.5-1.8% of cervical cytology specimens from women 40 years of age and older will have endometrial cells.[61] Benign-appearing exfoliated endometrial cells in premenopausal women are rarely associated with significant pathology.[61] Similarly, the presence of endometrial stromal cells/histiocytes rarely has clinical significance. In contrast, benign-appearing endometrial cells in postmeonopausal women are not infrequently associated with significant endometrial pathology.[62] Although hormone replacement therapy can increase the rate of shedding of benign-appearing endometrial cells, the prevalence of significant pathology remains elevated in this setting.[61,62] Benign-appearing glandular cells derived from small accessory ducts, foci of benign adenosis, or prolapse of the fallopian tube into the vagina are sometimes seen in cytology specimens after total hysterectomy and have no clinical significance.

Recommended Management of Women with AGC

Initial workup

Colposcopy with endocervical sampling is recommended for women with all subcategories of AGC and AIS. (AII) Endometrial sampling is recommended in conjunction with colposcopy and endocervical sampling in women 35 years and older with all subcategories of AGCs and AIS. (BII) Endometrial sampling is also recommended for women under the age of 35 years with clinical indications suggesting they may be at risk for neoplastic endometrial lesions. These include unexplained vaginal bleeding or conditions suggesting chronic anovulation. It is recommended that women with atypical endometrial cells be initially evaluated with endometrial and endocervical sampling. Colposcopy can be either performed at the initial evaluation or deferred until the results are known. If no endometrial pathology is identified, colposcopy is recommended. (AII) If not already obtained, HPV DNA testing at the time of colposcopy is preferred in women with atypical endocervical, endometrial, or glandular cells not otherwise specified (NOS). (CIII) The use of HPV DNA testing alone or a program of repeat cervical cytology is unacceptable for the initial triage of all subcategories of AGC and AIS. (EII)

Subsequent evaluation or follow-up

The recommended postcolposcopy management of women of known HPV status with atypical endocervical, endometrial, or glandular cells NOS who do not have CIN or glandular neoplasia identified histologically is to repeat cytologic testing combined with HPV DNA testing at 6 months if they are HPV DNA positive and at 12 months if they are HPV DNA negative. (CII) Referral to colposcopy is recommended for women who subsequently test positive for high-risk (oncogenic) HPV DNA or who are found to have ASC-US or greater on their repeat cytologic tests. If both tests are negative, women can return to routine cytologic testing. (BII) The recommended postcolposcopy management of women of unknown HPV status with atypical endocervical, endometrial, or glandular cells NOS who do not have CIN or glandular neoplasia identified histologically is to repeat cytologic testing at 6-month intervals. After 4 consecutive "negative for intraepithelial lesion or malignancy" results are obtained, women can return to routine cytologic testing. (CIII)

If CIN, but no glandular neoplasia, is identified histologically during the initial workup of a woman with atypical endocervical, endometrial, or glandular cells NOS, management should be according to the 2006 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia. If invasive disease is not identified during the initial colposcopic workup, it is recommended that women with atypical endocervical

or glandular cells "favor neoplasia" or endocervical AIS undergo a diagnostic excisional procedure. (AII) It is recommended that the type of diagnostic excisional procedure used in this setting provide an intact specimen with interpretable margins. (BII) Concomitant endocervical sampling is preferred. (BII)

AGC in Special Populations

Pregnant women

In pregnant women, the initial evaluation of AGC should be identical to that of nonpregnant women, except that endocervical curettage and endometrial biopsy are unacceptable. (BII)

Other Forms of Glandular Abnormalities

Benign-appearing endometrial cells

For asymptomatic premenopausal women with benign endometrial cells, endometrial stromal cells, or histiocytes, no further evaluation is recommended. (BII) For postmenopausal women with benign endometrial cells, endometrial assessment is recommended regardless of symptoms. (BII)

Benign-appearing glandular cells after hysterectomy

For posthysterectomy patients with a cytologic report of benign glandular cells, no further evaluation is recommended. (BII)

HPV DNA Testing When Used for Screening

Despite the successes of cytology as a cervical cancer screening method, cytology has a number of significant limitations.[63] These limitations have led to considerable interest in using a combination of HPV testing and cytology for screening.[64] Most newly acquired HPV infections clear spontaneously and the prevalence of HPV DNA positivity drops with age from a peak in adolescents and women in their 20s.[11,65] Therefore, HPV testing should be used only for routine screening in women 30 years of age and older.[3,66] A number of large studies have evaluated screening using a combination of HPV testing and cervical cytology (either liquid-based or conventional cytology).[67,68] In screening studies from North America and Europe, the pooled sensitivity and specificity of HPV testing for the detection of CIN 2 or greater in women 35 years and older is 95% and 93%, respectively.[69] For comparison, pooled sensitivity and specificity of cytology at a threshold of ASC-US are 60% and 97%, respectively. Sensitivity using a combination of HPV testing and cytology is significantly higher than that of either test alone with negative predictive values of 99-100%.[69,70]

Molecular testing for high-risk (oncogenic) types of HPV is now approved by the FDA for use as an adjunct to cervical cytology for screening in women 30 years of age and older.[71] Interim guidance on how to manage women with different combinations of screening results was developed by a NCI, ASCCP, and American Cancer Society joint workshop in 2003.[3] The 2006 Consensus Conference formally reviewed and modified the previous interim guidance. The two controversial areas are when women negative by both cytology and HPV testing should be rescreened and how to manage cytology-negative, HPV-positive women. Women who are negative by both cytology and HPV testing have a less than 1 in 1000 risk of having CIN 2 or greater, and prospective follow-up studies have shown that the risk of developing CIN 3 over a 10-year period is quite low.[3,72,73] Less than 2% of cytology- and HPV-negative Danish women 40-50 years of age developed CIN 3 or greater during 10 years of follow-up.[72] Identical results have been reported for women 30 years of age and older in Portland, OR.[73] Health policy modeling studies demonstrate that 3 year screening using a combination of cytology and HPV testing in women 30 years and older provides equivalent or greater benefits than those provided by annual conventional cytology.[74] Therefore, women who are negative by both cytology and HPV testing should not be rescreened before 3 years.

Many women in screened populations who test positive for HPV will have a negative cervical cytology. In a series of more than 213,000 women 30 years and older enrolled in Kaiser Northern California, the overall prevalence of HPV positivity was 6.5%, and 58% of the HPV-positive women had a concurrent negative cytology.[60] HPV-positive women require counseling with respect to their risk for CIN 2 or greater, source of their infection, and their infectivity. The risk of having an undetected CIN 2 or greater is quite low in cytology-negative, HPV-positive women in screened populations, ranging from 2.4-5.1%.[75-78] For comparison, CIN 2 or greater was detected at enrollment colposcopy in 10.2% of women of unknown HPV status with ASC-US in ALTS.[1] It is also important to note that even in women 30 years and older, the majority of HPV-positive women become HPV negative during follow-up. After a median follow-up of 6 months, 60% of HPV-positive women in a prospective study from France became HPV-negative.[78] Based on these considerations, conservative follow-up with repeat cytology and HPV testing at 12 months appears to be the best management approach for cytology-negative, HPV-positive women. Women who on repeat testing are persistently HPV positive should undergo colposcopy, whereas women who are negative on both tests can be rescreened in 3 years.

HPV Genotyping

Emerging data suggest that the specific type of high-risk (oncogenic) HPV that a woman has may be an important indicator of her risk for CIN 2 or greater. Among cytology-negative women 30 years of age and older in the Portland study, CIN 3 was identified during 10 years of follow-up in 21% and 18% of those with HPV 16 or 18, respectively, at enrollment.[73] In contrast, the risk of CIN 3 among women with other high-risk HPV types was only 1.5%. Schlecht et al[79] also found a higher incidence of cytological HSIL during follow-up in Brazilian women who were positive for HPV 16 or 18, compared with women with other high-risk HPV types, although the difference in incidence was not as marked as observed in Portland.

Genotyping assays to determine specific high-risk HPV type(s) have not

yet been approved by the FDA. However, should the FDA approve HPV genotyping assays, it would be reasonable to utilize genotyping in cytology-negative, HPV-positive women in the same manner as high-risk HPV testing is utilized in women with ASC-US. Samples from cytology-negative, HPV-positive women would be genotyped for specific high-risk types of HPV, and women with specific high-risk types, such as HPV 16 or 18, would be referred for colposcopy.[73] Women with other high-risk types would be told to return in 12 months for retesting for both cytology and HPV. This would allow women at increased risk for having a false-negative cytology result to be referred to colposcopy.

Recommended Management Different Combinations of Results

General recommendations

It is recommended that HPV DNA testing target only high-risk (oncogenic) HPV types. There is no clinical utility in testing for other (nononcogenic) types. (AI) Testing for other (nononcogenic) HPV types when screening for cervical neoplasia, or during the management and follow-up of women with abnormal cervical cytology or cervical neoplasia, is unacceptable. (EI)

Recommendations for women with different combinations of results

For women 30 years of age and older who have a cytology result of "negative for an intraepithelial lesion or malignancy" but test positive for HPV, repeat cytology and HPV testing at 12 months is preferred. (BII) If on repeat testing HPV is detected, colposcopy is recommended. (AII) Women found to have an abnormal result on repeat cytology should be managed according to the appropriate 2006 Consensus Guidelines outlined earlier.

Recommendations for HPV genotyping

Until an FDA-approved assay becomes available, a recommendation for use of type-specific HPV genotyping cannot be made. Once such assays are FDA approved, emerging data support the triage of women 30 years of age and older with a cytology result of "negative for an intraepithelial lesion or malignancy" but who are HPV positive with HPV genotyping assays to identify those with HPV 16 and 18. (AII) ■

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APPENDIX A
Participants and participating organizations

Organizer: American Society for Colposcopy and Cervical Pathology (ASCCP)

Participants: A complete listing of all of the participants and formal observers of the 2006 Consensus Conference and their institutions is available at www.asccp.org.

Participating organizations: American Academy of Family Physicians; American Cancer Society; American College Health Association; American College of Obstetricians and Gynecologists; American Social Health Association; American Society for Clinical Pathology; American Society for Colposcopy and Cervical Pathology; American Society of Cytopathology; Association of Reproductive Health Professionals; Centers for Disease Control and Prevention, Division of Viral and Rickettsial Disease; Centers for Disease Control and Prevention, Division of Cancer Prevention and Control; Centers for Disease Control and Prevention, Division of Laboratory Systems; Centers for Medicaid and Medicare Services; College of American Pathologists; Food and Drug Administration; International Academy of Cytology; International Federation for Cervical Pathology and Colposcopy; International Federation of Gynecology and Obstetrics; International Gynecologic Cancer Society; International Society of Gynecological Pathologists; National Cancer Institute; National Association of Nurse Practitioners in Women's Health; Papanicolaou Society of Cytopathology; Pan American Health Organization; Planned Parenthood Federation of America; Society of Canadian Colposcopists; Society of Gynecologic Oncologists; Society of Gynecologic Oncologists of Canada; Society of Obstetricians and Gynaecologists of Canada.

APPENDIX B
Definitions of terms (copyright 2001, 2006 ASCCP)

Colposcopy is the examination of the cervix, the vagina, and, in some instances the vulva with the colposcope after the application of a 3-5% acetic acid solution coupled with obtaining colposcopically directed biopsies of all lesions suspected of representing neoplasia.

Endocervical sampling includes obtaining a specimen for either histological evaluation using an endocervical curette or cytobrush or for cytological evaluation using a cytobrush.

Endocervical assessment is the process of evaluating the endocervical canal for the presence of neoplasia using either a colposcope or endocervical sampling.

Endometrial sampling including obtaining a specimen for histologic evaluation using an endometrial biopsy or a "dilatation and curettage" or hysteroscopy.

Diagnostic excisional procedure is the process of obtaining a specimen from the transformation zone and endocervical canal for histological evaluation and includes laser conization, cold-knife conization, loop electrosurgical excision procedure (LEEP), and loop electrosurgical conization.

Satisfactory colposcopy indicates that the entire squamocolumnar junction and the margin of any visible lesion can be visualized with the colposcope.

Adolescent women are females 20 years of age and younger (ie, from 13th to 21st birthdays).