Management of Abnormal Cervical Cancer Screening Test Results and Cervical Cancer Precursors

Knowledge of the natural history, epidemiology, and basic science of human papillomavirus (HPV) and precancerous lesions of the cervix is rapidly evolving. Guidelines have been revised several times over the past decade to incorporate new evidence and technologies (1, 2). The American Society for Colposcopy and Cervical Pathology (ASCCP) clinical management guidelines were revised again in 2012 (3), and this Practice Bulletin is adapted with permission from the ASCCP publication 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Important changes to these guidelines include the following:

- Defining when to return to routine screening after treatment or resolution of abnormalities given the longer screening intervals recommended by the updated American Cancer Society screening guidelines (4)
- Improving incorporation of HPV testing
- Applying guidelines previously developed for adolescents to individuals aged 21–24 years
- Integrating new data on risk of high-grade precursor lesions and cancer

The ASCCP–College of American Pathologists Lower Anogenital Squamous Terminology Standardization (LAST) Project recommended standardizing histopathologic terminology for HPV-associated squamous intraepithelial lesions and superficially invasive squamous carcinoma across all lower anogenital tract sites (5). The purpose of this document is to present the most recent revisions to guidelines for managing abnormal cervical cancer screening test results and cervical cancer precursors, describe the LAST Project terminology, and provide guidance on applying the new management guidelines with this terminology.

Background

**Natural History of Cervical Intraepithelial Neoplasia**

Infection with high-risk human papillomavirus (HPV) is a necessary but not sufficient factor for the development of squamous cervical neoplasia and nearly all types of cervical cancer. Only a small fraction of women infected with HPV will develop high-grade cervical abnormalities and cancer. The current model of cervical carcinogenesis suggests that HPV infection results in either transient or persistent infection (6, 7). Most HPV infection is transient and poses little risk of progression. Few
infections persist, but persistence at 1 year and 2 years strongly predicts subsequent risk of high-grade cervical intraepithelial neoplasia 3 (CIN 3+) regardless of age (4, 8, 9). These persistent infections, manifested by CIN 2+ histology, are true cancer precursors.

Factors determining which HPV infections will persist are incompletely understood. The HPV genotype appears to be the most important determinant of persistence and progression. Human papillomavirus 16 has the highest carcinogenic potential and accounts for approximately 55–60% of all cases of cervical cancer worldwide. Human papillomavirus 18 is the next most carcinogenic type of HPV and it is responsible for 10–15% of cases of cervical cancer. Approximately 10 other genotypes of HPV are associated with the remainder of cases of cervical cancer (10–12). Risk factors known to increase the likelihood of persistence include cigarette smoking, a compromised immune system, and human immunodeficiency (HIV) infection (13, 14).

Human papillomavirus infection is most common in teenagers and women in their early 20s. In one study, HPV infection occurred at least once over a 3-year period in 60% of young women (15). Although prevalence decreases as women age, the lifetime cumulative risk is at least 80% (16–20). Most young women, especially those younger than 21 years, have an effective immune response that clears the infection in an average of 8 months or reduces the viral load in 85–90% of women to undetectable levels in an average of 8–24 months (21–27). Concomitant with infection resolution, most cervical neoplasia will also spontaneously resolve in this population (23, 25, 28–31).

Cervical intraepithelial neoplasia 1 is a manifestation of acute HPV infection and has a high rate of regression to normal cells. These lesions usually can be managed expectantly. Cervical intraepithelial neoplasia 2 seems to represent a mix of low-grade and high-grade lesions not easily differentiated by routine histology rather than a specific intermediate-grade lesion (32, 33). Cervical intraepithelial neoplasia 3 and adenocarcinoma in situ (AIS) are clearly cancer precursors. Progression from persistent infection to cancer is slow, and the time course from CIN 3 to invasive cancer averages between 8.1 years and 12.6 years (34–36). Because of the risk of cancer in untreated patients, the threshold for treatment is CIN 2+ except in a few special populations, particularly young women and pregnant women.

The key to effectively managing cervical abnormalities is to distinguish true cervical cancer precursors from benign cervical abnormalities with little premalignant potential. Cervical intraepithelial neoplasia 1 lesions, which have little premalignant potential, can be safely observed because most will regress on their own. Cervical intraepithelial neoplasia 2+ lesions are cancer precursors that need to be treated. A low-grade squamous intraepithelial lesion (LSIL) cytology test result is generally associated with transient HPV infection. A high-grade squamous intraepithelial lesion (HSIL) cytology test result is associated with persistent and transforming infection and cancer risk. However, as many as 28% of women with LSIL cytology results have CIN 2 or CIN 3, about two thirds of which is identified by colposcopy (34). Although the vast majority of abnormal cytology test results do not represent underlying CIN 2+, two thirds of CIN found on histology testing presents with cytologic “lesser abnormalities,” particularly atypical squamous cells of undetermined significance (ASC-US), and LSIL (37). This necessitates the evaluation of all abnormal cytology test results.

**Human Papillomavirus Testing**

All references to HPV testing in this document refer to high-risk (oncogenic) HPV testing only. There is no indication for low-risk HPV testing. Human papillomavirus testing is more reproducible and more sensitive but less specific than cytology testing (38–42). Several U.S. Food and Drug Administration (FDA)-approved tests are commercially available. Current screening and management guidelines were developed based on HPV tests that have specific clinical performance characteristics similar to those of the HPV tests used in the supporting evidence (3, 4, 43). These clinical performance characteristics are best documented by FDA approval or publication in peer-reviewed scientific literature (44, 45). The use of non-FDA approved tests with excessive analytic sensitivity may result in harm from unnecessary testing and treatment (46). Tests with poorer sensitivity may result in harm from undetected disease. Test kits should be used on their approved collection media. Use of unapproved collection media requires rigorous validation as a laboratory-developed test. Questions regarding whether this validation has been done should be directed to the processing laboratory.

**Colposcopy**

Colposcopy with directed biopsy remains the standard for disease detection and is the technique of choice for treatment decisions. Evaluation of colposcopy sensitivity has, until recently, focused on populations with identified lesions sufficient to produce abnormal cytology test results. Older studies that compared directed biopsy with conization demonstrated considerable underdiagnosis of CIN 2 and CIN 3 (47, 48). Some recent studies have used colposcopy with endocervical curettage (ECC) and blind four-quadrant ectocervical biopsies or the loop electrosurgical excision procedure (LEEP) as the diag-
Diagnostic criteria (49, 50). This approach permits a more realistic evaluation of the sensitivity of colposcopy with directed biopsy. The presence of CIN 2+ was missed on directed biopsy but detected on the random four-quadrant biopsies in 18.6–31.6% of CIN 2+ cases (50, 51). These figures may underestimate the prevalence of CIN 2+ missed on colposcopy directed biopsy because excisions were not performed on women with normal screening test results. In the ASC-US LSIL Triage Study (ALTS), women with previous LSIL or ASC-US and HPV-positive test results and a CIN 1 biopsy were offered LEEP after 2 years of follow-up (49). Of the 189 women with CIN 2+ diagnosed during the 2-year study in the “immediate colposcopy” arm of the trial, only 106 (56%) women received the diagnosis on the initial colposcopy. The other cases were identified after HSIL cytology, an exit colposcopy, or LEEP.

Additional biopsies clearly improve detection. During another screening study, the diagnosis of CIN 2+ was made on a colposcopically directed biopsy in 57.1% of women, random biopsy in 37.4%, and ECC in 5.5% (52). Each additional biopsy significantly increased the identification of CIN 2+ (53). In another analysis of ALTS, the sensitivity of colposcopy did not vary with the expertise of the colposcopist but was significantly greater when two or more biopsies were taken. The level of colposcopic training contributed less to the sensitivity of colposcopy than taking two biopsies rather than one (54).

Results of these studies indicate that biopsies of all visible lesions are warranted regardless of colposcopy impression. Also, follow-up should include multiple colposcopy examinations over time for those women with abnormal cytology or histology test results who have persistent low-grade abnormalities or persistently positive HPV test results.

Endocervical Sampling

Endocervical sampling may be conducted either by traditional ECC with a sharp curette, with vigorous endocervical brushing, or both. Compared with curettage, the brush technique is more sensitive with similar specificity and fewer reports of insufficient specimens, although grading may be more difficult (55–58). It is also better tolerated. Both are acceptable for endocervical sampling and many clinicians combine both, using a sharp curette to disrupt the endocervix and a brush to collect the specimen.

The ASCCP 2012 guidelines include some recommendations regarding use of endocervical sampling, which are outlined in the “Clinical Considerations and Recommendations” section in this document. Endocervical curettage should not be performed in pregnancy. In general, endocervical sampling should be considered in the following circumstances:

- In women with ASC-US or LSIL cervical cytology test results, endocervical sampling is preferred when no lesion is identified on colposcopy, when the colposcopic examination is unsatisfactory, and in women with previous excision or ablation of the transformation zone or if ablative treatment such as cryotherapy or laser ablation is contemplated (2, 3). When the colposcopy is satisfactory and a lesion is identified in the transformation zone, endocervical sampling is acceptable (2, 3) although very few cases of cancer are identified (59, 60).

- In women with atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H), HSIL, atypical glandular cells (AGC), or AIS cytology test results, endocervical sampling should be considered as part of the initial colposcopic evaluation (61) unless excision is planned. If an excision is planned, endocervical sampling may be omitted (62), although it may be performed at the time of the procedure after the excision to assess the completeness of the procedure.

Revised Management Guidelines

The guidelines in this document, as in the 2008 Practice Bulletin follow the consensus management guidelines developed by the ASCCP. The ASCCP held a consensus conference in 2012 to revise the 2006 consensus guidelines for the management of abnormal cervical cancer screening test results and cervical cancer precursors. These management guidelines were revised for a number of important reasons:

- In 2012, the American Cancer Society (ACS), the U.S. Preventive Services Task Force, and the American College of Obstetricians and Gynecologists released updated recommendations for cervical cancer screening (4, 43, 63). These revised screening guidelines extended the screening interval to 3 years using cytology testing alone in women younger than 30 years. For women aged 30–65 years, the interval was extended to every 3 years after negative cytology test results alone or 5 years following negative results from cytology and HPV co-testing. In the 2006 management guidelines, several pathways concluded by returning women to “routine screening” but did not define this term. At the time, routine screening intervals were shorter, and with the new extended screening intervals, referring women to “routine screening” at 3-year intervals with cytology testing or 5-year intervals with...
co-testing needed reassessment. Although extended screening intervals are appropriate for women with negative screening histories, women with a history of CIN 2+ have an increased risk of recurrence for up to 20 years after completion of treatment (64, 65).

- The 2006 guidelines relied heavily on the analysis of data from ALTS (34). This study only provided evidence on the initial management of women with minor cytologic abnormalities; therefore, management of women after colposcopy and guidelines for women with more severe cytologic abnormalities were based on extrapolation. In 2012, a database became available that provided the 8-year experience of almost 1.4 million women in the Kaiser Permanente Northern California (KPNC) Medical Care Plan (66–73).

- HPV testing was not fully integrated into the 2006 guidelines. The KPNC database provided additional data to guide recommendations for HPV testing.

- Prior management guidelines included guidelines for managing abnormalities in adolescents, which should no longer be relevant with the clear recommendations in the new screening guidelines (63) to not begin screening until age 21 years. Women aged 21–24 years are at a low risk of cervical cancer similar to adolescents, raising the question of whether the guidelines for adolescents should be extended to this age group.

Based on an extensive literature review and analysis of the data from the KPNC database, the ASCCP consensus conference was able to reaffirm most prior guidelines, revise others, and fill in some of the gaps that existed in the prior consensus guidelines. The ASCCP guidelines include specific definitions of terms such as “recommended” and “preferred” used for recommendations, which are also used in this document (Table 1).

There are several important principles in interpreting these guidelines. The revised guidelines were based on the best data available at the time of the 2012 consensus conference. Management strategies were developed based on risk where diagnoses with similar risk should have the same management (67, 74). Clinical judgment is necessary in the application of these guidelines to individual patients. Currently available strategies cannot eliminate the risk of developing cancer, and attempts to completely eliminate risk often result in unanticipated harm from excessive evaluation and overtreatment.

The guidelines apply to women identified with abnormalities during screening, and as with the 2006 guidelines, immunosuppressed women with abnormal results should be managed the same as immunocompetent women (1–3). Women with symptoms of a potential cervical disease require appropriate evaluation, which typically requires more than screening tests alone (3). In some instances, recommendations vary by age, particularly for 21–24 year olds. At other times, recommendations are specified for “young women,” a definition (Table 1) intended to reflect an individual woman’s desire to minimize the effect of treatment on future pregnancy, and does not specify any particular age. Women younger than 21 years should not undergo screening (4). If a woman younger than 21 years is inadvertently screened and has an abnormal test result, the result should not be ignored and should be managed based on the guidelines for 21–24-year-old women.

The recommendations have always been complicated, and the revised guidelines are no exception (75). Health care providers have traditionally used the written documents and supplementary flow chart diagrams as

### Table 1. Definitions

<table>
<thead>
<tr>
<th>Definitions</th>
<th>CIN 2+</th>
<th>CIN 2, CIN 3, AIS, or cancer</th>
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<tbody>
<tr>
<td>CIN 3+</td>
<td>CIN 3, AIS, or cancer</td>
<td></td>
</tr>
<tr>
<td>CIN 2,3</td>
<td>High-grade lesion that either cannot be differentiated between CIN 2 and CIN 3, or where the pathologist has chosen not to</td>
<td></td>
</tr>
<tr>
<td>HSIL+</td>
<td>HSIL, AGC, or cancer</td>
<td></td>
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<tr>
<td>Young women</td>
<td>Those who after counseling by their clinicians consider risk to future pregnancies from treating cervical abnormalities to outweigh the risk of cancer during observation of those abnormalities—no specific age threshold is intended</td>
<td></td>
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<tr>
<td>Lesser abnormalities</td>
<td>HPV 16 or HPV 18 positivity, persistent untyped oncogenic HPV, ASC-US, and LSIL cytology reports</td>
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<tr>
<td>Recommended</td>
<td>Good data to support use when only one option is available</td>
<td></td>
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<tr>
<td>Preferred</td>
<td>Option is the best (or one of the best) when there are multiple options</td>
<td></td>
</tr>
<tr>
<td>Acceptable</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Not recommended</td>
<td>Weak evidence against use and marginal risk for adverse consequences</td>
<td></td>
</tr>
<tr>
<td>Unacceptable</td>
<td>Good evidence against use</td>
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tools to implement the guidelines. “Apps” for handheld devices such as the ones developed by ASCCP (http://www.asccp.org/Guidelines) are now available, and greatly simplify applying the guidelines in practice. In applying the algorithms, health care providers need to pay particular attention to ensuring they are at the correct point in the decision tree. Management frequently varies by patient age, and care also needs to be used to ensure that the age-appropriate management recommendation is applied.

**The LAST Project**

The 2001 Bethesda system update is the standard terminology for reporting cervical cytology test results in the United States, and it is used throughout this document (49, 63). Until recently, histopathologic terminology was much less standardized. Histology terms used included dysplasia (mild, moderate, and severe) and cervical intraepithelial neoplasia 1, 2, and 3. Cervical intraepithelial neoplasia 1 generally reflects transient HPV infection. Severe dysplasia or CIN 3 also has been equated with carcinoma in situ. These different terminologies for biologically equivalent lesions created a potential for miscommunication among pathologists and clinicians and increased the risk of overtreating patients. The intermediate category (moderate dysplasia, CIN 2) is poorly reproducible among pathologists and thought to represent an equivocal category not unlike the ASC-US category of cervical cytology. It is thought to represent a mixture of low-grade viral infections and true precancerous conditions that cannot reliably be distinguished on routine histologic exam alone. For these reasons, many pathologists began using a two-tiered system (low-grade CIN and high-grade CIN). Because of these concerns, the College of American Pathologists (CAP) and the ASCCP held a consensus conference in 2012 on Lower Anogenital Tract Squamous Terminology (LAST Project) that recommended using unified two-tiered histopathological nomenclature for HPV-associated squamous cervical disease (5). The LAST histopathology terminology is similar to that used in the Bethesda system: low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). Histologic LSIL results reflect productive HPV infection, the majority of which are transient and unlikely to progress to cancer; HSIL lesions are considered truly precancerous. The LAST Project recommendations include specific guidelines for using biomarkers (p16) to distinguish precancer from benign conditions that mimic cancer and to separate equivocal specimens previously categorized as CIN 2 into LSIL or HSIL.

Practitioners need to be aware of this revised terminology because its use will likely become more frequent. The ASCCP management guidelines continue to use the CIN nomenclature, but provides guidance for applying the revised guidelines with LAST Project terminology (3). The guidelines recommended that histology test results reported as LSIL be managed as CIN 1 and those results reported as HSIL be managed as CIN 2,3. Because the clinical management guidelines for young women differ for CIN 2, CIN 2,3, and CIN 3, the LAST Project terminology allows HSIL lesions to be further subclassified into CIN 2, CIN 2,3, and CIN 3. The CIN terminology will continue to be used in this document for consistency with the revised ASCCP management guidelines. As use of LAST Project terminology becomes more widespread, health care providers will need to pay attention to whether they are working with cytologic reports or histologic reports that use the LAST Project terminology.

**Clinical Considerations and Recommendations**

**How should women with unsatisfactory cytology test results be managed?**

For women with unsatisfactory cytology test results and no, unknown, or a negative HPV test result, repeat cytology testing in 2–4 months is recommended. Triage using reflex HPV testing is not recommended. Treatment to resolve atrophy or obscuring inflammation when a specific infection is present is acceptable. In women aged 30 years and older with a positive HPV co-test result, repeat cytology testing in 2–4 months or colposcopy is acceptable. Colposcopy is recommended for women with two consecutive unsatisfactory cytology test results.

An unsatisfactory cervical cytology test result is, by definition, unreliable for detecting epithelial abnormalities. In the past, studies have shown a higher risk of disease in women with unsatisfactory cytology test results caused by obscuring blood, inflammation, or other processes (76, 77). Now that most cytology testing performed in the United States involves the use of liquid-based media that minimize obscuring blood and inflammation in processing, unsatisfactory specimens are usually the result of insufficient squamous cells (78). A single study suggests the risk for high-grade disease in women with unsatisfactory cervical cytology test results associated with a negative HPV result is low (79). Some currently available HPV tests lack a control for epithelial cellularity, so an HPV result may be falsely negative because of an insufficient sample.
How should women who have negative cervical cytology test results with an absent or insufficient endocervical–transformation zone component be managed?

For women aged 21–29 years with negative cytology test results with an absent or insufficient endocervical–transformation zone component, routine screening is recommended; HPV testing is unacceptable. For women aged 30 years and older with cytology test results reported as negative with an absent or insufficient endocervical–transformation zone component and no or unknown HPV test result, HPV testing is preferred. Repeat cytology testing in 3 years is acceptable if HPV testing is not performed. If the HPV test is performed and the result is negative, return to routine screening is recommended. If the HPV test result is positive, repeating both tests in 1 year is acceptable. Genotyping is also acceptable; if HPV 16 or HPV 18 is present, colposcopy is recommended. If HPV 16 and HPV 18 are absent, repeat co-testing in 12 months is recommended (3).

A cytology test result reported as negative with an absent or insufficient endocervical–transformation zone component has adequate cellularity for interpretation but lacks endocervical or metaplastic cells, suggesting that the squamocolumnar junction may not have been adequately sampled. These reports are present in 10–20% of all cervical cytology specimens and are more common in older women (80, 81). Although an absent or insufficient endocervical–transformation zone component suggests increased risk for missed disease, women with this finding have fewer concurrent cytologic abnormalities and do not have a higher risk of CIN 2+ over time than women with a satisfactory endocervical–transformation zone component (82). A recent systematic review found that negative cytology test results had good specificity and negative predictive value despite an absent or insufficient endocervical–transformation zone component (83). Human papillomavirus testing appears to be independent of transformation zone sampling, and co-testing offers an added margin of safety for women aged 30 years and older (84). An absent endocervical–transformation zone component is not associated with an increased incidence of cervical disease after treatment of high-grade abnormalities (80).

What is the appropriate follow-up for women aged 30 years and older with normal cervical cytology screening test results and positive HPV co-test results?

For women 30 years of age and older with HPV-positive but cytology-negative co-testing results, repeat co-testing at 1 year is acceptable. At the 1-year repeat co-test, if the HPV test result is positive or cytology is ASC-US or worse, colposcopy is recommended. If the 1-year repeat co-test result is HPV-negative and cytology negative, repeat co-testing in 3 years is recommended.

Human papillomavirus genotyping is also acceptable. If the HPV 16 and HPV 18 test results are positive, colposcopy is recommended. If HPV 16 and HPV 18 test results are negative, repeat co-testing in 1 year is recommended (3).

Women with normal cervical cytology test results and a single positive HPV test result have a 2.2–6.1% risk of CIN 2+ (85, 86). Most of these HPV infections will clear spontaneously within 1 year (22); HPV infections that persist for at least 1 year are associated with a higher risk of CIN 2+ (8, 71). Because the risk of CIN 2+ is small in a woman with a single positive HPV test result and a negative cytology test result, repeat co-testing in 1 year is reasonable, allowing transient infections to resolve and limiting further evaluation to the much smaller group with persistent HPV. Women whose subsequent screening results remain persistently HPV-positive are at higher risk of CIN 3+ and meet the threshold for referral to colposcopy (87).

Since the 2006 guidelines, HPV genotyping has become available. Women who have positive test results for HPV 16 have a risk of CIN 3+ over the next several years approaching 10% (86, 88), which is sufficiently high to justify colposcopy. Because cervical cytology testing is particularly insensitive for detecting cervical glandular neoplasia, HPV 18 positive women also deserve special attention (3). Consequently, immediate reflex genotyping for HPV 16 and HPV 18 is also an acceptable option for women whose cytology test results are negative but HPV test results are positive.

Repeat co-testing in 3 years is a change from the 2011 screening guidelines (4, 63), which recommended return to routine screening following negative co-test results. In the KPNC cohort, women remained at a slightly elevated risk of CIN 3+ despite their HPV test results returning to negative (71); therefore, an immediate return to routine screening is not appropriate. For the corresponding ASCCP treatment algorithm see Figure 1.

What is the initial management approach for women aged 25 years and older with cervical cytology screening test results reported as ASC-US?

For women with ASC-US cytology test results, reflex HPV testing is preferred. For women with HPV-negative ASC-US, whether from reflex HPV testing or co-testing, repeat co-testing at 3 years is recommended. For women with HPV-positive ASC-US, whether from reflex
HPV testing or co-testing, colposcopy is recommended. When colposcopy does not identify CIN in women with HPV-positive ASC-US, co-testing at 12 months is recommended. If at that time, the HPV is still positive or the cytology test result is ASC-US or worse, repeat colposcopy is recommended. If the co-test result is HPV-negative and cytology is negative, return for age-appropriate testing in 3 years is recommended. If all test results are negative at the time of the 3-year co-test, routine screening is recommended. It is recommended that HPV testing in follow-up after colposcopy not be performed at intervals of less than 12 months.

For women with ASC-US cytology test results and no HPV test result, repeat cytology testing at 1 year is acceptable. If the result is ASC-US or worse, colposcopy is recommended; if the result is negative, return to cytology testing at 3-year intervals is recommended.

Endocervical sampling is preferred for women in whom no lesions are identified and for those with an inadequate colposcopy finding. It is acceptable for women with an adequate colposcopy finding and a lesion identified in the transformation zone. Because of the potential for overtreatment, the routine use of diagnostic excisional procedures such as LEEP for women with an initial ASC-US result in the absence of CIN 2+ is unacceptable.

Postmenopausal women with ASC-US results should be managed in the same manner as women in the general population, except when considering discontinuation of screening for women aged 65 years and older. For those women, HPV-negative ASC-US results should be considered abnormal. Additional surveillance is recommended with repeat screening in 1 year; co-testing is preferred but cytology testing is acceptable (3).

The 2006 ASCCP management guidelines were based on data from ALTS (1, 89). Three management options were studied: 1) repeat cytology at 6 months and 12 months with colposcopy for abnormal results, 2) reflex HPV testing with colposcopy for women with positive results, or 3) immediate colposcopy. Reflex HPV testing was the preferred option because it identifies more CIN 3+ lesions, with fewer referrals to colposcopy (89). One significant finding from the KPNC cohort was the relatively low (3%) 5-year risk of CIN 3+ in women aged 30 years and older with ASC-US cytology test results. One potential reason for this lower risk compared with the 2-year risk seen in ALTS is that ALTS was done before the Bethesda 2001 update that distinguished between ASC-US and ASC-H. The 3% risk in the expanded KPNC cohort was at the threshold for annual rather than semiannual follow-up cytology testing. Another significant finding from the KPNC cohort was that women with HPV-negative ASC-US had a slightly higher risk than women with negative co-test results (72). The 2011 ACS screening guidelines, developed before the expanded KPNC data were available, equated CIN 3+ risk in women with HPV-negative ASC-US with negative co-test results and recommended rescreening these women in 5 years (4). In the KPNC cohort, CIN 3+ risk was actually comparable to that among women with negative cytology test results alone;
therefore, using the principle of managing women with similar risk in the same way, these women should have follow-up co-testing in 3 years rather than 5 years (3). If their 3-year co-test results are negative, they can then return to age-appropriate routine screening. Another important finding in the KPNC cohort is that women older than 60 years with HPV-negative ASC-US had a higher risk of cancer than women with negative co-test results (72). This finding prompted an additional change from the 2011 ACS screening guidelines (4). The new management guidelines recommend that for women aged 65 years and older, HPV-negative ASC-US should be considered abnormal when considering discontinuation of screening. These women should be restested in 1 year with co-testing (preferred) or cytology testing alone (acceptable) (3).

The cumulative 5-year risk of CIN 3+ after an HPV-positive ASC-US result from the KPNC study was 6.8%, slightly higher than for LSIL (5.2%) and high enough to justify colposcopy irrespective of genotype (72). Women with ASC-US who are HPV 16 or HPV 18 positive have twice the risk of CIN 3+ compared with women with HPV-positive ASC-US with other high-risk HPV types (90–92). The revised recommendations do not recommend genotyping; therefore, all women aged 25 years and older with HPV-positive ASC-US should undergo colposcopy (3). For the corresponding ASCCP treatment algorithm see Figure 2.

### How should women aged 25 years and older with cervical cytology screening test results reported as LSIL be managed?

For women with LSIL cytology results and no HPV test or a positive HPV test result, colposcopy is recommended. If co-testing shows HPV-negative LSIL, repeat co-testing at 1 year is preferred, but colposcopy is acceptable. If repeat co-testing at 1 year is elected, and if the cytology result is ASC-US or worse or the HPV test result is positive (ie, if the co-testing result is other than HPV-negative, cytology negative), colposcopy is recommended. If the co-testing result at 1 year is HPV-negative and cytology negative, repeat co-testing after an additional 3 years is recommended. If all test results are negative at that time, routine screening is recommended.

Acceptable options for the management of postmenopausal women with LSIL and no HPV test include obtaining HPV testing, repeat cytologic testing at 6 months and 12 months, and colposcopy. If the HPV test result is negative or if CIN is not identified at colposcopy, repeat cytology testing in 12 months is recommended. If either the HPV test result is positive or the repeat cytology test result is ASC-US or greater, colposcopy is recommended. If two consecutive repeat cytology test results are negative, return to routine screening is recommended (3).

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The recommendations incorporate use of HPV testing in women aged 30 years and older, where HPV testing may have been performed as part of co-testing. Co-testing should not be performed in women younger than 30 years; therefore, HPV test results should generally not be available. Women aged 25–29 years with LSIL should undergo colposcopy, even if HPV test results are available.

In ALTS, 27.6% of women with LSIL had CIN 2+ either on colposcopically directed biopsies or on close follow-up over the next 2 years. Seventy-seven percent of women with LSIL are HPV-positive, making HPV triage inappropriate in this population (93). However, some women 30 years of age and older undergoing co-testing will be found to have HPV-negative LSIL. Data from the KPNC cohort shows that their risk of CIN 3+ is similar to that of women with ASC-US cytology test results (without the benefit of HPV reflex testing) (71). For the corresponding ASCCP treatment algorithm see Figure 3.

How should women aged 21–24 years with cervical cytology screening test results of ASC-US or LSIL be managed? 

For women aged 21–24 years with ASC-US cytology test results, cytology testing alone at 12-month intervals is preferred, but reflex HPV testing is acceptable. If reflex HPV testing is performed in women with ASC-US results and the HPV result is positive, repeat cytology in 12 months is recommended. Immediate colposcopy or repeat HPV testing is not recommended. If reflex HPV testing is performed and the result is negative, return for routine screening with cytology testing alone in 3 years is recommended.

For women aged 21–24 years with LSIL cytology test results, follow-up with cytology testing at 12-month intervals is recommended. Colposcopy is not recommended. For women with ASC-H, AGC, or HSIL+ results at the 12-month follow-up cytology testing, colposcopy is recommended. If the 12-month cytology result is negative, ASC-US, or LSIL, cytology should be repeated again 12 months later. For women with ASC-US results or worse at the 24-month follow-up cytology testing, colposcopy is recommended. For women with two consecutive negative results, return to routine screening is recommended (3).

The 2011 screening guidelines recommended against screening before the age of 21 years, making the 2006 management guidelines for adolescents unnecessary (1, 4, 43). The 2012 consensus conference extended the conservative management approach previously used for adolescents to women aged 21–24 years. Although their risk of cervical cancer (1.4/100,000) is 10-fold greater than for adolescents (94), the risk is still low enough to justify following lower grade cytologic abnormalities without colposcopic evaluation (3). An analysis of the data from the KPNC cohort showed that women aged 21–24 years with LSIL cytology results have a lower risk of CIN 3+ than older women (68, 95). Adolescents who are inadvertently screened and found to have abnormal cytology test results may be followed using these guidelines. For the corresponding ASCCP treatment algorithm see Figure 4.

What is the initial management approach for women aged 25 years and older with cervical cytology screening test results reported as ASC-H?

For women with ASC-H cytology test results, colposcopy is recommended regardless of HPV result. Reflex HPV testing is not recommended (3).

Data from the KPNC cohort confirmed that the risk of CIN 3+ over time in women with ASC-H cytology results is higher than for those with ASC-US or LSIL results, but lower than for women with HSIL cytology results (66, 96). Most women with ASC-H results are HPV-positive (97). Women with HPV-negative ASC-H results have a 2% 5-year invasive cancer risk (66). Because neither a positive nor a negative HPV test result will change the recommendation for immediate colposcopy in women with ASC-H results, HPV triage is not recommended (3).

What is the initial management approach for women aged 25 years and older with cervical cytology test results reported as HSIL?

For women with HSIL cytology test results, immediate LEEP or colposcopy is acceptable, except in special populations. Triage involving the use of either repeat cytology testing alone or reflex HPV testing is unacceptable. For women not managed with immediate excision, colposcopy is recommended regardless of HPV result obtained at co-testing. Accordingly, reflex HPV testing is not recommended.

A diagnostic excisional procedure is recommended for women with HSIL cytology test results when the colposcopic examination is inadequate, except during pregnancy. Women with CIN 2, CIN 3, and CIN 2,3 should be managed according to the appropriate 2012 ASCCP consensus guideline (see “How should women with biopsy confirmed CIN 2, CIN 3, and CIN 2,3 be managed?”).

Ablation is unacceptable in the following circumstances: when colposcopy has not been performed, when CIN 2,3 is not identified with histologic testing, and when the endocervical assessment identifies CIN 2, CIN 3, CIN 2,3 or ungraded CIN (3).

Approximately 60% of women with HSIL cytology test results have CIN 2+ on colposcopically directed biopsy (97–99) and 2% have cervical cancer (68). The 5-year cancer risk is 8% among women aged 30 years and older with HSIL results (73). This rate is high enough to justify the option of immediate excision of the transformation zone (“see and treat”) in women with HSIL cytology test results who have completed childbearing (3).

Most women with HSIL results are HPV-positive. Furthermore, the 5-year risk for CIN 3+ is 29% and the invasive cancer risk is 7% in women with HPV-negative HSIL results (73). This means that neither a positive nor
a negative HPV test result will change the recommendation for immediate colposcopy or immediate treatment in women with HSIL cytology results; therefore, triage with HPV testing is not recommended (3). For the corresponding ASCCP treatment algorithm see Figure 5.

**How should women aged 21–24 years with cervical cytology test results reported as ASC-H or HSIL be managed?**

For women aged 21–24 years with ASC-H or HSIL cytology test results, colposcopy is recommended. Immediate treatment (ie, see-and-treat) is unacceptable. When CIN 2+ is not identified with histologic testing, observation for up to 24 months using both colposcopy and cytology testing at 6-month intervals is recommended, provided the colposcopic examination is adequate and endocervical assessment is negative or CIN 1. If CIN 2, CIN 3, or CIN 2,3 is identified with histologic testing, management according to the 2012 consensus guideline for the management of young women with CIN 2, CIN 3, or CIN 2,3 is recommended (see “How should CIN 2 and CIN 3 detected on biopsy be managed in ‘young women’?”). If during follow-up a high-grade colposcopic lesion is identified or HSIL persists for 1 year, biopsy is recommended. If HSIL persists for 24 months without identification of CIN 2+, a diagnostic excisional procedure is recommended. A diagnostic excisional procedure is recommended for women aged 21–24 years with HSIL when colposcopy findings are inadequate or CIN 2, CIN 3, CIN 2,3, or ungraded CIN is identified on endocervical sampling. After two consecutive negative cytology test results and no evidence of high-grade colposcopic abnormality, return to routine screening is recommended (3).

Because the 2011 screening guidelines recommended that screening should not begin before the age of 21 years, the 2006 management guidelines for adolescents are no longer necessary (1, 4, 43). The 2012 consensus conference extended the conservative management guidelines previously used for adolescents to women aged 21–24 years. Even though the likelihood of cancer in women aged 21–24 years is 10-fold higher than for adolescents, it remains quite small. Although the overall risk of CIN 3+ for women aged 21–24 years is lower than for older women, data from the KPNC cohort confirmed that the risk of CIN 3+ over time in women with ASC-H cytology test results is higher than for those with ASC-US or LSIL but lower than women with HSIL cytology test results (68). As in older women, the management of ASC-H cytology test results follows the recommendations for HSIL rather than LSIL. For the corresponding ASCCP treatment algorithm see Figure 6.

**How should cervical cytology test results reported as AGC be managed?**

**Initial workup.** For women with all subcategories of AGC and AIS except atypical endometrial cells, colposcopy with endocervical sampling is recommended regardless of HPV test result. Accordingly, triage by

Subsequent management. For women with AGC—not otherwise specified (AGC-NOS) cytology test results in whom CIN 2+ is not identified, co-testing at 12 months and 24 months is recommended. If both co-test results are negative, return for repeat co-testing in 3 years is recommended. If any test result is abnormal, colposcopy is recommended. If CIN but no glandular neoplasia is identified with histologic testing during the initial work-up of a woman with atypical endocervical, endometrial, or glandular cells not otherwise specified, management should be provided according to the 2012 Consensus Guidelines for the lesion found.

For women with AGC “favor neoplasia” or endocervical AIS cytology test results, if invasive disease is not identified during the initial colposcopic workup, a diagnostic excisional procedure is recommended. It is recommended that the type of diagnostic excisional procedure used in this setting provide an intact specimen with interpretable margins. Endocervical sampling after excision is preferred (3).
commonly associated with squamous rather than glandular lesions, and CIN is found in approximately one half of women with AIS (102, 106, 107). Adenocarcinoma in situ is difficult to identify on colposcopy and is often found coincidentally at the time of excision of a squamous lesion. Although cervical adenocarcinoma is associated with HPV, predominantly HPV 18, and can be detected with HPV testing, endometrial, ovarian and fallopian tube cancer are not HPV-associated. Although a positive HPV test result may be suggestive of cervical disease, a negative HPV test result does not obviate the need for further evaluation, particularly in older women or those with a history of vaginal bleeding.

Because the risk of neoplasia (including invasive cancer) is high in women with AGC “favor neoplasia” and AIS, a diagnostic excisional procedure is recommended for these women when invasive cancer is not found as part of the initial evaluation (3). It is important that the excision procedure chosen provides an intact specimen with interpretable margins; therefore, cold knife conization may be preferable for these patients (1). For the corresponding ASCCP treatment algorithm see Figure 7.

How should a patient aged 25 years or older be managed when colposcopy performed for the evaluation of “lesser abnormalities” shows no lesion or biopsy-confirmed CIN 1?

“Lesser abnormalities” include HPV 16 or HPV 18 positivity, persistent untyped oncogenic HPV, ASC-US, and LSIL. Following these abnormalities when the evaluation shows no lesion or biopsy confirmed CIN 1, co-testing at 1 year is recommended. If both the HPV test and cytology test results are negative, then age-appropriate retesting 3 years later is recommended (cytology testing if age is younger than 30 years, co-testing if 30 years of age or older). If all test results are negative, then...
return to routine screening is recommended. If any test result is abnormal, then colposcopy is recommended.

If CIN persists for at least 2 years, either continued follow-up or treatment is acceptable. If treatment is selected and the colposcopic examination is adequate, either excision or ablation is acceptable. A diagnostic excisional procedure is recommended if the colposcopic examination is inadequate; the endocervical sampling contains CIN 2, CIN 3, CIN 2.3 or ungraded CIN; or the patient has been previously treated. Treatment modality should be determined by the judgment of the clinician and should be guided by experience, resources, and clinical value for the specific patient. In patients with CIN 1 and an inadequate colposcopic examination, ablative procedures are unacceptable. Podophyllin or podophyllin-related products are unacceptable for use in the vagina or on the cervix. Hysterectomy as the primary and principal treatment for CIN 1 diagnosed with histology testing is unacceptable (3).

Cervical intraepithelial neoplasia 1 is the histologic manifestation of HPV infection. Most CIN 1 regresses spontaneously and progression to CIN 2+ is uncommon (34). The importance of CIN 1 is that it may be a sentinel for occult CIN 2+ not detected by colposcopy or it may progress to CIN 2+. The risk of occult CIN 2+ among women with CIN 1 on a colposcopic biopsy is directly related to the risk conveyed by the referring cytology result. Because a single colposcopic examination can miss important lesions, women referred for colposcopy and not found to have CIN 2+ require some form of additional follow-up. In ALTS, the initial colposcopic examination in women with ASC-US or LSIL cytology testing identified only 58% of CIN 2+ lesions. For women not found to have CIN 2+ on their initial colposcopic examination, the approximate 10–13% rate of CIN 2+ during follow-up was unaffected by whether there were negative findings, negative biopsy of suspected lesions, or CIN 1 on biopsy (34). The overall risk of occult CIN 3+ in women with CIN 1 preceded by ASC-US, LSIL, or negative cytology test results associated with a positive HPV 16 or HPV 18 test result or a persistently positive untyped high-risk HPV test result over a 1-year period was similar to that of women with LSIL or HPV-positive ASC-US, which suggests that the management should be similar (34). In ALTS, 13% of women presenting with HPV-positive ASC-US or LSIL who had CIN 1 on the initial colposcopic biopsy were found to have CIN 2+ and 8.9% were found to have CIN 3 during the 24-month follow-up period. In the KPNC cohort, women with CIN 1 after LSIL or HPV-positive ASC-US had a 5-year risk of CIN 3+ of 3.8% (69). Because the rate of regression of CIN 1 is so high, and the risk of progression to CIN 2+ is so low, initial treatment of CIN 1 is not recommended (3, 34, 109). For the corresponding ASCCP treatment algorithm see Figure 8.

How should women aged 25 years and older with no lesion or a biopsy diagnosis of CIN 1 or less during the initial evaluation of an ASC-H or HSIL cytology test result be managed?

When CIN 2+ is not identified with histologic testing, either a diagnostic excisional procedure or observation with co-testing at 12 months and 24 months is recommended, provided in the latter case that the colposcopic examination is adequate and the endocervical sampling result is negative. In this circumstance, it is acceptable to review the cytologic, histologic, and colposcopic findings; if the review yields a revised interpretation, management should follow guidelines for the revised interpretation. If observation with co-testing is elected and both co-test results are negative, return for retesting in 3 years is recommended. If any test result is abnormal, repeat colposcopy is recommended. A diagnostic excisional procedure is recommended for women with repeat HSIL cytology test results at either the 1-year or 2-year visit (3).

Several possibilities may explain the failure to identify CIN 2+ in women with ASC-H or HSIL cytology test results. The cytologic abnormality may be caused by a vaginal lesion, presence of occult CIN 2+ not identified because of the insensitivity of colposcopy, or over-reading of a non–high-grade cytology specimen by the responsible cytologist. Vaginal lesions may be identified by a careful examination of the vagina using both 3–5% acetic acid and Lugol solution. In such a case, the cytology result is correct despite the lack of a cervical lesion. Application of Lugol solution to the cervix also may help to identify high-grade cervical lesions not previously appreciated.

The risk of occult CIN 2+ among women with CIN 1 or no lesion on a colposcopic examination is directly related to the risk conveyed by the referring cytology. Data from the KPNC cohort showed that in women with CIN 1 detected on biopsy, the 5-year risk of CIN 3+ was 3.8% after LSIL or HPV-positive ASC-US and 15% after HSIL, although occult carcinoma is unlikely (69). The risk in women with ASC-H cytology was closer to that of women with HSIL than women with LSIL, which provides the justification for managing women with ASC-H similarly to women with HSIL (3). This represents a change from the 2006 guidelines where these women were managed similarly to those with LSIL. Close follow-up is required for women not undergoing a diagnostic excisional procedure. There are few studies on the natural history of HSIL managed without treatment; therefore, these management recommendations are based on expert opinion (69).

Another possible explanation for HSIL with noncorrelating colposcopy findings is that the report represents assignment by the cytologist of a more severe diagnosis than is actually present (“cytological over-call”). Cytologic interpretation is subjective. In ALTS, expert review downgraded HSIL to LSIL in 27% of cases, HSIL to ASC-US in 23% of cases, and HSIL to a negative result in 3% of cases (110). Both the possibility of missed disease and the potential for overtreatment must be considered, and management must be individualized based on the patient’s needs and future risks of high-grade disease and cancer. For the corresponding ASCCP treatment algorithm see Figure 9.

How should CIN 1 detected on biopsy be managed in women aged 21–24 years?

For women aged 21–24 years with CIN 1 or no lesions after an ASC-US or LSIL cytology test result, repeat cytology testing at 12-month intervals is recommended. Follow-up with HPV testing is unacceptable. For women with ASC-H or HSIL+ at the 12-month follow-up, colposcopy is recommended. For women with ASC-US or worse at the 24-month follow-up, colposcopy is recommended. After two consecutive negative cytology test results, routine screening is recommended.

For women aged 21–24 years with CIN 1 or no lesions after an ASC-H or HSIL cytology test result, observation for up to 24 months using both colposcopy and cytology testing at 6-month intervals is recommended, provided the colposcopic examination is adequate and endocervical assessment is negative. If CIN 2, CIN 3, or CIN 2,3 is identified with histologic testing, management should follow the guideline for the management of young women with CIN 2, CIN 3, or CIN 2,3. If during follow-up a high-grade colposcopic lesion is identified or HSIL persists for 1 year, biopsy is recommended. If HSIL persists for 24 months without identification of CIN 2+, a diagnostic excisional procedure is recommended. When colposcopy is inadequate or CIN 2, CIN 3, CIN 2,3 or ungraded CIN is identified on endocervical sampling, a diagnostic excisional procedure is recommended. Regardless of antecedent cytology test results, treatment of CIN 1 in women aged 21–24 years is not recommended (3).

Colposcopy is not recommended in women aged 21–24 years after ASC-US or LSIL unless ASC-US or LSIL is present in the second of two annual follow-up cytology tests, or unless either of the annual follow-up cytology test results is ASC-H, HSIL, or AGC. In this situation, if a colposcopically directed biopsy reveals either CIN 1 or no lesion is found, repeat cytology testing at 12-month intervals is again recommended. If CIN 3 is specified on biopsy, treatment is preferred.
How should women with biopsy confirmed CIN 2, CIN 3, and CIN 2,3 be managed?

For women with a histological diagnosis of CIN 2, CIN 3, or CIN 2,3 and adequate colposcopic examination, both excision and ablation are acceptable treatment modalities, except in special circumstances. A diagnostic excisional procedure is recommended for women with recurrent CIN 2, CIN 3, or CIN 2,3. Ablation is unacceptable and a diagnostic excisional procedure is recommended for women with a histological diagnosis of CIN 2, CIN 3, or CIN 2,3 and inadequate colposcopy or endocervical sampling showing CIN 2, CIN 3, CIN 2,3 or CIN not graded. Observation of CIN 2, CIN 3, or CIN 2,3 with sequential cytology testing and colposcopy is unacceptable, except in special circumstances. Hysterectomy is unacceptable as primary therapy for CIN 2, CIN 3, or CIN 2,3.

The goals for cervical cancer screening are identification and treatment of true cervical cancer precursors;
CIN 3 is a definite cervical cancer precursor. The prevalence of CIN 3 peaks between the ages of 25 years and 30 years and progression to cancer usually takes at least a decade longer (14). Cervical intraepithelial neoplasia 3 is more likely to progress and less likely to regress than CIN 2. In one review of the natural history of untreated CIN 3, 32% of lesions regressed, 56% persisted, and 14% of lesions progressed to cancer. With untreated CIN 2, 43% regressed, 35% persisted, and 22% progressed to CIN 3 (114). Because of the moderate cancer risk associated with CIN 2, it is the consensus threshold for treatment in the United States except in special populations (3). For the corresponding ASCCP treatment algorithm see Figure 5.

**How should CIN 2 and CIN 3 detected on biopsy be managed in “young women”?**

For young women with a histological diagnosis of CIN 2,3 not otherwise specified, either treatment or observation for up to 12 months using both colposcopy and cytology testing at 6-month intervals is acceptable, provided the colposcopy finding is adequate. When a histological diagnosis of CIN 2 is specified for a young woman, observation is preferred but treatment is acceptable. When a histological diagnosis of CIN 3 is specified or when the colposcopy finding is inadequate, treatment is recommended. If the colposcopic appearance of the lesion worsens or if HSIL or a high-grade colposcopic lesion persists for 1 year, repeat biopsy is recommended. If CIN 2, CIN 3, or CIN 2,3 persists for 2 years, treatment is recommended. After two consecutive negative cytology test results, an additional co-test 1 year later (ie, at 24 months) is recommended. If the additional co-test result is negative, then repeat co-testing in 3 years is recommended (ie, at 5 years from initial diagnosis). Colposcopy is recommended if either the 2-year or 5-year test result is abnormal. For women aged 21-24 years who are treated, follow-up according to ASCCP guidelines for treated CIN 2, CIN 3, or CIN 2,3 is recommended. Treatment is recommended if CIN 3 is subsequently identified or if CIN 2, CIN 3, or CIN 2,3 persists for 24 months (3).

In this context, young women is defined as women who, after counseling by their clinicians consider risk to future pregnancies from treating cervical abnormalities to outweigh the risk of cancer during observation of the those abnormalities. In this context no specific age threshold is intended (3).

Excisional treatments for CIN are associated with an increased risk of preterm delivery (115, 116). Cervical intraepithelial neoplasia appears to also be a risk factor for preterm delivery, which may explain part of the increased risk compared with that of women without cervical disease, but excision by itself appears to increase risk because risk increases with depth and volume of the excised tissue and with repeat excision (117–119).
Cervical intraepithelial neoplasia 3 is a definite cervical cancer precursor; therefore, it should be treated regardless of age or fertility concerns. Cervical intraepithelial neoplasia 2 is poorly reproducible among pathologists and has a regression rate as high as 43% in adults and 65% in adolescents (30, 114). Furthermore, once colposcopy findings exclude cancer, progression to cancer is very uncommon in the short term (120). Given the potential risk of treatment and the significant chance of spontaneous regression, close follow-up is reasonable for young women with CIN 2 or CIN 2,3 not otherwise specified.

Management of young women with high-grade lesions is an area in which applying the new LAST terminology may cause some confusion. Recommendations for management are different for CIN 2 and CIN 3, but histopathology reported with LAST terminology may not differentiate the two. If the CIN grade is included in the report, the patient should be managed with the recommendations for the reported level of CIN. If no additional subclassification is reported, the patient should be managed based on the guidelines for CIN 2,3. For the corresponding ASCCP treatment algorithm see Figure 11.

What is the best treatment for CIN?

Ablative treatments (eg, cryotherapy or laser vaporization) should be used only after rigorously excluding invasive cancer. When endocervical assessment shows CIN, the colposcopy result is inadequate, cytology test results or colposcopy examinations suggest cancer, or after prior therapy, occult cancer may be present and ablative therapy is not appropriate (121, 122). Excisional therapy (eg, LEEP, laser conization, and cold-knife conization) may be used whenever treatment is appropriate. Randomized trials that compared these different modalities show similar efficacy, ranging from 90% to 95% (123–126). In all cases, treatment must encompass the entire transformation zone. Most failures occur within the first 2 years after treatment, but patients remain at risk of developing cancer for up to 20 years after treatment (127, 128). Margin status, available only after an excisional procedure, has been used to predict recurrence after treatment, although it does not appear to be an independent risk factor after controlling for age and lesion grade (129, 130).

Selection of the appropriate treatment modality depends on the operator’s experience, available equipment, and lesion size. Alternatively, if the lesion extends onto the vagina, laser ablation may be more appropriate than other modalities because it can be tailored to encompass the entire lesion with excellent depth control. A combination of laser ablation and excision is also possible. Microinvasive cancer and AIS require accurate assessment of the conization margins to exclude cancer. When microinvasive cancer or AIS is suspected, accurate assessment of the specimen margins is essential. Although the ASCCP guidelines no longer specify cold-knife conization, many health care providers still prefer this procedure given the potential advantages in avoiding cautery artifact. If LEEP or laser conization is

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**Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2,3 (CIN2,3) in Special Circumstances**

**Young Women with CIN2,3**

Observation — Colposcopy & Cytology

- 2x Cytology Negative and Normal Colposcopy
- Cotest in 1 year
- Both tests negative
- Cotest in 3 years

Treatment using Excision or Ablation of T-zone

- Colposcopy worsens or High-grade Cytology or Colposcopy persists for 1 year
- CIN3 or CIN2,3 persists for 24 months
- Treatment Recommended

performed, careful attention is required to ensure interpretable margins.

► **How should a patient's condition be monitored after treatment for CIN 2, CIN 3, or CIN 2,3?**

For women treated for CIN 2, CIN 3, or CIN 2,3, co-testing at 12 months and 24 months is recommended. If both co-test results are negative, retesting in 3 years is recommended. If any test result is abnormal, colposcopy with endocervical sampling is recommended. If all test results are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age. Repeat treatment or hysterectomy based on a positive HPV test result is unacceptable (3).

Women treated for CIN require long-term surveillance. Although most recurrent or persistent CIN is found within the first 2 years, pooled follow-up data showed that treated women are at increased risk of subsequent invasion for at least 10 years, and cases of cancer have been found as late as 20 years after initial therapy (65, 126, 131). Although protocols for follow-up after treatment of CIN have not been evaluated in randomized trials, evidence suggests that HPV testing is more sensitive but less specific than cytology testing in posttreatment follow-up and may result in earlier diagnosis of persistent or recurrent disease (132). A meta-analysis of 16 studies showed that HPV testing predicted residual disease more quickly and with higher sensitivity and similar specificity than histological assessment of margins or follow-up cytology testing. The sensitivity of HPV testing to predict treatment failure averaged 94.4% (93). Few women with CIN 2,3 present with invasive cancer soon after treatment. In women with negative margins, the risk is so small that repeat evaluation using co-testing in 1 year is appropriate. The outcomes after treatment of recurrent or persistent disease are unaffected by a short delay in diagnosis as long as persistent disease is identified and eradicated before invasion occurs. For the corresponding ASCCP treatment algorithm see Figure 12.

► **Does management of CIN 2 or CIN 3 differ for women who are HIV positive?**

Initial management of CIN 2+ in HIV-positive women should follow recommendations for the general population (3). Follow-up will differ slightly because HIV-positive patients should return to annual cytology after two negative co-test results.

Effective treatment of CIN requires immunologic clearance or suppression of HPV to avoid recurrence (133). Women who are HIV positive or taking immunosuppressive medications have difficulty clearing HPV and are at increased risk of recurrent disease in direct relation to their level of immunosuppression (134–136). Treatment of CIN 2+ should be pursued despite high recurrence rates (greater than 50% recurrence rate after standard treatment) because it can effectively interrupt...
progression to invasive cancer (137–139). Women who are HIV positive also appear more likely to have positive surgical margins, which may contribute to increased recurrence rates (140). Because studies reported a lower prevalence of high-grade disease and HPV positivity among immunosuppressed women, the 2006 consensus guidelines recommended that the management of these conditions be similar to that in the general population (141–143). The 2012 guidelines reaffirmed this recommendation (3); the Centers for Disease Control and Prevention’s guidelines recommended management consistent with the 2006 guidelines and have not yet been updated (144). The role of highly active antiretroviral therapy in the management of precancerous cervical lesions remains unclear (145). Cervical intraepithelial neoplasia 2+ should be treated similarly in women who are HIV positive regardless of their use of antiretroviral therapy. HIV infected women should undergo routine annual screening with cytology testing alone; therefore, patients should return to screening with annual cytology after two consecutive negative co-test results (144).

**How should AIS detected on biopsy be managed? How should patients with AIS be monitored after treatment?**

Hysterectomy is preferred for women who have completed childbearing and have a histologic diagnosis of AIS on a specimen from a diagnostic excisional procedure. Conservative management is acceptable if future fertility is desired. If conservative management is planned and the margins of the specimen are involved or endocervical sampling obtained at the time of excision contains CIN or AIS, reexcision to increase the likelihood of complete excision is preferred. Reevaluation at 6 months, using a combination of co-testing and colposcopy with endocervical sampling, is acceptable in this circumstance. Long-term follow-up is recommended for women who do not undergo hysterectomy (3).

Although the overall incidence of AIS is increasing, it remains relatively rare compared with CIN 2,3 (145, 146). Between 1991 and 1995, the overall incidence of squamous carcinoma in situ of the cervix among white women in the United States was 41.4 per 100,000, whereas the incidence of AIS was only 1.25 per 100,000 (147). Management of AIS differs from squamous disease because cytology screening and colposcopy detection of AIS are so challenging and the clinical behavior of AIS is different from CIN 2,3. The colposcopy changes associated with AIS can be minimal or unfamiliar to most colposcopists. Adenocarcinoma in situ is frequently multifocal, may have “skip lesions,” and frequently extends for a considerable distance into the endocervical canal, making complete excision difficult. An intact, deep diagnostic excisional procedure in which margins are interpretable is important to assess for invasive cancer. However, negative margins on the diagnostic excisional specimen do not necessarily mean that the lesion has been completely excised.

Hysterectomy continues to be the treatment of choice for AIS in women who have completed childbearing (3). A deep excisional procedure is curative in many patients. For women who wish to maintain fertility, close observation after a deep conization is an option, but it carries a risk of persistent AIS of up to 10% and a small risk of cancer even when the cone excisional margins are negative (3, 146, 148, 149). Margin status and endocervical sampling at the time of an excisional procedure are predictive of residual disease (150). If conservative therapy is elected, care must be taken to make certain that the specimen remains intact and that the margins are interpretable. Most clinicians elect to use cold-knife conization to ensure these criteria. The need for long-term follow-up after conservative management is emphasized in the ASCCP guidelines, although the guidelines do not detail long-term follow-up because there are insufficient long-term follow-up data to make specific recommendations.

**How should a patient suspected of having early invasive cancer be managed if the colposcopic evaluation result is inconclusive?**

A colposcopic evaluation result that is inconclusive for cancer should be followed by excision to determine whether cancer is present and to permit treatment planning. The management of early invasive cervical cancer depends on the depth of invasion and the presence or absence of lymph and vascular space invasion. Biopsy alone does not adequately provide this information. Cold-knife conization is preferred for this purpose because it maintains tissue orientation in a single specimen, which is essential to permit pathologic evaluation of depth of invasion and other variables that define stage and treatment (151). Laser excision and LEEP are acceptable in experienced hands. However, hysterectomy is not recommended as first-line management.

**How should management proceed if LEEP or cone biopsy reveals a positive margin?**

If CIN 2, CIN 3, or CIN 2,3 is identified at the margins of a diagnostic excisional procedure or in an endocervical sample obtained immediately after the procedure, reassessment using cytology testing with endocervical
sampling at 4–6 months after treatment is preferred. Performing a repeat diagnostic excisional procedure is acceptable. Hysterectomy is acceptable if a repeat diagnostic procedure is not feasible. A repeat diagnostic excisional procedure or hysterectomy is acceptable for women with a histological diagnosis of recurrent or persistent CIN 2, CIN 3, or CIN 2,3 (3).

A positive margin or positive postprocedure endocervical sampling is a marker for increased risk of recurrence; however, only age, lesion size, and CIN grade are independent risk factors (152, 153). Even with a positive endocervical margin, 70–80% will be cured. In women with positive margins, the higher risk of persistent or recurrent disease justifies more intense initial surveillance.

► When is hysterectomy appropriate in women with CIN 2+?

Hysterectomy is unacceptable as primary therapy for CIN 2+ but may be acceptable in women with recurrent disease on their repeat diagnostic procedure or if a repeat diagnostic procedure is not feasible (3). One example is when there is insufficient residual cervix to allow safe repeat conization without risk of bladder or vaginal injury. In such cases, the risk of hysterectomy may be less than the risk of a diagnostic excisional procedure. In women who have completed their childbearing and have recurrent disease, hysterectomy is acceptable after adequate counseling as to the relative risk of the alternative procedures. Before proceeding to hysterectomy, adequate assessment should be performed to exclude the possibility of invasive cancer. If hysterectomy is performed, it should be performed by the route that appropriately balances safety and patient recovery; as usual, a vaginal approach is preferred when feasible.

► How should pregnant women with abnormal screening test results or CIN be managed? ⇆

Management options for pregnant women with ASC-US are identical to those described for nonpregnant women, with the exception that deferring colposcopy until 6 weeks postpartum is acceptable. Endocervical curettage in pregnant women is unacceptable. For pregnant women who have no cytologic, histologic, or colposcopically suspected CIN 2+ at the initial colposcopy, postpartum follow-up is recommended. For pregnant women who have a histologic diagnosis of CIN 1, follow-up without treatment is recommended. Treatment of pregnant women for CIN 1 is unacceptable.

In the absence of invasive disease or advanced pregnancy, additional colposcopy examinations and cytologic tests are acceptable in pregnant women with a histologic diagnosis of CIN 2, CIN 3, or CIN 2,3 at intervals no more frequent than every 12 weeks. Repeat biopsy is recommended only if the appearance of the lesion worsens or if the cytology test result suggests invasive cancer. Deferring reevaluation until at least 6 weeks postpartum is acceptable. A diagnostic excisional procedure is recommended only if invasion is suspected. Unless invasive cancer is identified, treatment is unacceptable. Reevaluation with cytology testing and colposcopy is recommended no sooner than 6 weeks postpartum (3).

In pregnancy, the only diagnosis that may alter management is invasive cancer. The presence of cancer may change treatment goals or change the route and timing of delivery. Colposcopy during pregnancy should have the exclusion of invasive cancer as its primary goal. The management of cytologic abnormalities during pregnancy depends on the grade of the abnormality. Recommendations for the management of ASC-US or LSIL during pregnancy are unchanged from previous guidelines. Management of LSIL and HPV-positive ASC-US during pregnancy should be the same as for women who are not pregnant.

All pregnant women with HSIL should undergo colposcopy. The goal of cytology testing and colposcopy during pregnancy is to identify invasive cancer that requires treatment before or around the time of delivery. Unless cancer is identified or suspected, treatment of CIN is contraindicated during pregnancy; CIN has no effect on the woman or fetus, whereas cervical treatments designed to eradicate CIN can result in fetal loss, preterm delivery, and maternal hemorrhage.

Colposcopy during pregnancy is challenging because of cervical hyperemia, the development of prominent normal epithelial changes that mimic the appearance of preinvasive disease, obscuring mucus, contact bleeding,
The following recommendations are based on limited and inconsistent scientific evidence (Level B):

- For women 30 years of age and older with HPV-positive but cytology-negative co-test results, repeat co-testing at 1 year is acceptable. For women with HPV-negative ASC-US, whether from reflex HPV testing or co-testing, repeat co-testing at 3 years is recommended.

- When colposcopy does not identify CIN in women with HPV-positive ASC-US, co-testing at 12 months is recommended. If the co-test result is HPV-negative and cytology negative, return for age-appropriate testing in 3 years is recommended.

- For women aged 21–24 years with ASC-US cytology test results, cytology testing alone at 12-month intervals is preferred, but reflex HPV testing is acceptable.

- For women aged 21–24 years with LSIL cytology test results, follow-up with cytology testing at 12-month intervals is recommended. Colposcopy is not recommended.

- For pregnant women with LSIL, colposcopy is preferred.

- For women with ASC-H cytology test results, colposcopy is recommended regardless of HPV result. Reflex HPV testing is not recommended.

- For women with HSIL cytology test results, immediate LEEP or colposcopy is acceptable, except in special populations.

- A diagnostic excisional procedure is recommended for women with HSIL cytology test results when the colposcopic examination is inadequate, except during pregnancy.

- For women aged 21–24 years with ASC-H or HSIL test results, colposcopy is recommended. Immediate treatment (ie, see-and-treat) is unacceptable.

- For women with all subcategories of AGC and AIS except atypical endometrial cells, colposcopy with endocervical sampling is recommended regardless of HPV test result. Endometrial sampling is recommended in conjunction with colposcopy and endocervical sampling in women 35 years of age and older with all subcategories of AGC and AIS. Endometrial sampling is also recommended for women younger than 35 years with clinical indicat-
tions that suggest they may be at risk of endometrial neoplasia.

- No further evaluation is recommended for asymptomatic premenopausal women with benign endometrial cells, endometrial stromal cells, or histiocytes. For postmenopausal women with benign endometrial cells, endometrial assessment is recommended regardless of symptoms.

- For women aged 25 years and older with CIN 1 or no lesion preceded by "lesser abnormalities," co-testing at 1 year is recommended. If both the HPV test and cytology test results are negative, then age-appropriate retesting 3 years later is recommended. If all test results are negative, then return to routine screening is recommended. If any test result is abnormal, then colposcopy is recommended. If CIN persists for at least 2 years, either continued follow-up or treatment is acceptable.

- When CIN 1 is detected on endocervical sampling after lesser abnormalities but no CIN 2+ is detected colposcopically directed biopsies, management should follow ASCCP management guidelines for CIN 1, with the addition of repeat endocervical sampling in 12 months.

- For women aged 21–24 years with CIN 1 after an ASC-US or LSIL cytology test result, repeat cytology testing at 12-month intervals is recommended. Follow-up with HPV testing is unacceptable.

- Regardless of antecedent cytology test results, treatment of CIN 1 in women aged 21–24 years is not recommended.

- Treatment of pregnant women for CIN 1 is unacceptable.

- Hysterectomy is unacceptable as primary therapy for CIN 2, CIN 3, or CIN 2,3.

- For women treated for CIN 2, CIN 3, or CIN 2,3, co-testing at 12 months and 24 months is recommended. If both co-test results are negative, retesting in 3 years is recommended. If any test result is abnormal, colposcopy with endocervical sampling is recommended. If all test results are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- For women with an unsatisfactory cytology test result and no, unknown, or a negative HPV test result, repeat cytology testing in 2–4 months is recommended.

- For women aged 21–29 years with negative cytology test results and absent or an insufficient endocervical–transformation zone component, routine screening is recommended. For women aged 30 years and older with cytology test results reported as negative and with an absent or insufficient endocervical–transformation zone component and no or unknown HPV test result, HPV testing is preferred.

- Acceptable options for the management of postmenopausal women with LSIL and no HPV test include obtaining HPV testing, repeat cytology testing at 6 months and 12 months, and colposcopy.

- For women aged 21–24 years with HSIL cytology test results, when CIN 2+ is not identified on histology testing, observation for up to 24 months using both colposcopy and cytology testing at 6-month intervals is recommended, provided the colposcopic examination is adequate and endocervical assessment is negative or CIN 1.

- When CIN 2+ is not identified on histologic testing, either a diagnostic excisional procedure or observation with co-testing at 12 months and 24 months is recommended, provided in the latter case that the colposcopic examination is adequate and the endocervical sampling is negative. In this circumstance, it is acceptable to review the cytologic, histologic, and colposcopic findings.

- For women aged 21–24 years with CIN 1 or no lesions preceded by "lesser abnormalities," co-testing at 1 year is recommended. If both the HPV test and cytology test results are negative, then age-appropriate retesting 3 years later is recommended. If all test results are negative, then return to routine screening is recommended. If any test result is abnormal, then colposcopy is recommended. If CIN persists for at least 2 years, either continued follow-up or treatment is acceptable.

- When CIN 1 is detected on endocervical sampling after lesser abnormalities but no CIN 2+ is detected colposcopically directed biopsies, management should follow ASCCP management guidelines for CIN 1, with the addition of repeat endocervical sampling in 12 months.

- For women aged 21–24 years with CIN 1 after an ASC-US or LSIL cytology test result, repeat cytology testing at 12-month intervals is recommended. Follow-up with HPV testing is unacceptable.

- Regardless of antecedent cytology test results, treatment of CIN 1 in women aged 21–24 years is not recommended.

- Treatment of pregnant women for CIN 1 is unacceptable.

- Hysterectomy is unacceptable as primary therapy for CIN 2, CIN 3, or CIN 2,3.

- For women treated for CIN 2, CIN 3, or CIN 2,3, co-testing at 12 months and 24 months is recommended. If both co-test results are negative, retesting in 3 years is recommended. If any test result is abnormal, colposcopy with endocervical sampling is recommended. If all test results are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age.

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- Acceptable options for the management of postmenopausal women with LSIL and no HPV test include obtaining HPV testing, repeat cytology testing at 6 months and 12 months, and colposcopy.

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- When CIN 2+ is not identified on histologic testing, either a diagnostic excisional procedure or observation with co-testing at 12 months and 24 months is recommended, provided in the latter case that the colposcopic examination is adequate and the endocervical sampling is negative. In this circumstance, it is acceptable to review the cytologic, histologic, and colposcopic findings.

- For women aged 21–24 years with CIN 1 or no lesions preceded by "lesser abnormalities," co-testing at 1 year is recommended. If both the HPV test and cytology test results are negative, then age-appropriate retesting 3 years later is recommended. If all test results are negative, then return to routine screening is recommended. If any test result is abnormal, then colposcopy is recommended. If CIN persists for at least 2 years, either continued follow-up or treatment is acceptable.

- When CIN 1 is detected on endocervical sampling after lesser abnormalities but no CIN 2+ is detected colposcopically directed biopsies, management should follow ASCCP management guidelines for CIN 1, with the addition of repeat endocervical sampling in 12 months.

- For women aged 21–24 years with CIN 1 after an ASC-US or LSIL cytology test result, repeat cytology testing at 12-month intervals is recommended. Follow-up with HPV testing is unacceptable.

- Regardless of antecedent cytology test results, treatment of CIN 1 in women aged 21–24 years is not recommended.

- Treatment of pregnant women for CIN 1 is unacceptable.

- Hysterectomy is unacceptable as primary therapy for CIN 2, CIN 3, or CIN 2,3.

- For women treated for CIN 2, CIN 3, or CIN 2,3, co-testing at 12 months and 24 months is recommended. If both co-test results are negative, retesting in 3 years is recommended. If any test result is abnormal, colposcopy with endocervical sampling is recommended. If all test results are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age.
bearing and have a histologic diagnosis of AIS on a specimen from a diagnostic excisional procedure.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists’ own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–April 2013. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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