

Cervical cancer screening is necessarily complex, and guidelines must change fairly frequently as our understanding of the natural history of HPV infection and cervical cancer continues to evolve. Up-to-date guidelines enhance our ability to detect cervical intraepithelial neoplasia and cancer early and manage them appropriately.



CERVICAL DISEASE

Guidelines have changed again, of necessity. Here is a roundup of the major alterations and new guidance.



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In April 2013, the American Society for Colposcopy and Cervical Pathology (ASCCP) updated guidelines for the management of abnormal cervical cytology and cervical cancer precursors for the first time since 2006.¹ This update follows new cervical cancer screening guidelines published in 2012 by the ACS/ASCCP/ASCP,² the USPSTF,³ and the American College of Obstetricians and Gynecologists⁴ (and reported in OBG MANAGEMENT in June 2012⁵).

For many clinicians, all these modifications amount to a dizzying “sea change” in

the way they have been screening and managing patients to prevent cervical cancer. Clinicians often express frustration with the guidelines, both for their complexity and for what seems like all-too-frequent changes. Do they really need to change . . . again? Do they really need to get even more complex? And what about them is really new?

This article addresses these questions by reviewing the guidelines and their updates in more depth. For a specific answer to the question of “What’s new?” see the box on page 44.

Did the guidelines really need to change . . . again?

Cervical cancer screening tests—be they the Pap test or a human papillomavirus (HPV) test—are not as clear-cut as other tests used to screen for sexually transmitted infections or their effects. We treat a patient whenever her gonorrhea or Chlamydia test is positive, for example. However, other

than cytology classified as high-grade (ie, HSIL), which may prompt immediate treatment in women 25 years and older by “see-and-treat” loop electrosurgical excision procedure (LEEP), neither cervical cytology nor HPV testing is sufficiently specific for present disease (cervical intraepithelial

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What's new?

The following features of the 2013 ASCCP update to cervical cancer screening guidelines are new:

- The return to “routine” screening is now better defined
- The management of women who have “unsatisfactory” cytology or a specimen lacking endocervical or transformation-zone components now includes the results of HPV testing
- Management guidelines previously used for adolescents (<21 years) now apply to young adult women (<25 years)
- There is now advice on the management of women aged 30 and older who have discordant cotest results, including HPV-positive/cytology-negative findings and HPV-negative/cytology-positive findings of ASC-US or more severe.

neoplasia [CIN] 3 or cancer) to warrant treatment without a diagnostic work-up. That's because the cause of cervical cancer (infection with HPV) usually does not produce CIN 3 or cancer, and the cell changes that it does produce most often (atypia and koilocytosis) are very common. And other cervical-vaginal changes associated with hormonal fluctuations, tampons, intercourse, and so on, may

result in cervical cytologic changes unrelated to HPV and, therefore, do not represent a risk for cervical cancer.

How can we best sort out who needs to be evaluated without under- or overdoing it? When we find CIN, some of which is destined to progress and some not, how do we reduce the risk of overtreatment without increasing the likelihood that some will progress to cancer? If we have treated CIN or adenocarcinoma in situ (AIS), how do we make sure there is no recurrence without risking overmanagement and potential overtreatment?

The first thing we do is ensure that we use our best clinical judgment and also respect the informed wishes of the patient. Because the guidelines are based on the best available data, and on expert opinion when data are lacking, guidelines developed through a consensus process provide a framework for care that is optimal for most women at each phase of their lives. This knowledge can help the clinician—and often the patient—make the best-informed decisions.



The updated guidelines now address discordant cotest results in women aged 30 and older

Do guidelines really need to get even more complex?

Consider the myriad management decisions that confront us in the field of cervical cancer screening, and the potential result of each choice. Even when cervical screening involves cytology alone, there are five major categories for abnormal results, each associated with a different level of risk requiring a unique level of management:

- **atypical squamous cells – undetermined significance** (ASC-US)
- **atypical squamous cells – cannot rule out a high-grade lesion** (ASC-H)
- **atypical glandular cells** (AGC)
- **low-grade squamous intraepithelial lesion** (LSIL)
- **high-grade squamous intraepithelial lesion** (HSIL).

Add in HPV testing with cervical cytology for women 30 years and older, and there is one more abnormal category—**normal Pap/HPV-positive**. And these categories just cover *initial* management. Also needed are guidelines for appropriate follow-up of women who undergo colposcopy for each abnormal cytologic result when no CIN 2, CIN 3, or AIS is found that requires treatment, as well as guidelines for managing women following treatment when high-grade histology is found.

As our understanding of the natural history of HPV and cervical oncogenesis has increased, it has become clearer that we must further adjust management decisions on the basis of age, essentially creating many

parallel sets of guidelines for women aged 21 to 24, 25 to 29, and 30 years and older.

Yes, cervical screening and management are complex. We are fortunate that the Internet and new “apps” for smartphones give us easy access to guidelines for most of the potential combinations of clinical findings and results. The guideline algorithms are available at www.asccp.org, and full explanatory articles are available at www.jlgt.com and www.greenjournal.org (comprehensive apps are available for download for almost every smartphone device).

Remember, it is impossible to create guidelines for every possible clinical

Potential harms from cervical cancer screening

- Anxiety from an abnormal test that the patient might fear to be a sign of cancer
 - Stigma from diagnosis of a ubiquitous sexually transmitted infection (HPV)
 - Time and patient expense related to screening and management
 - Pain and injury from the procedures and treatment
 - Increased risk of premature delivery and pregnancy loss.
-

situation, so clinical judgment must always be paramount when applying guidelines to individual patients.¹

What are the major changes of the latest set of guidelines and its update?

Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol. 2013;121(4):829–846. [Also published in J Low Genit Tract Dis. 2013;17(5 Suppl 1):S1–S27.]

Let's start by focusing on how the experts crafted the 2012 guidelines. New evidence to guide decisions about the management of abnormal screening tests, CIN, and AIS emerged in 2012 from a review of the world literature and from analyses of a large 7-year clinical database (1.4 million women) at the Kaiser Permanente Northern California Medical Care Plan, conducted in collaboration with scientists from the National Cancer Institute.¹

Most of the 2006 guidelines remain valid, but new evidence has modified some of the guidelines and created others where gaps existed. Guideline developers recognized that cervical cancer prevention is a process that entails both benefits and potential harms, and that the potential risks cannot be reduced to zero with the strategies currently

available. Attempts to achieve zero risk could result in unbalanced harms, including over-treatment.

Defining acceptable risk levels

Applying the concept of “similar management for similar risks,” guideline developers benchmarked risks to the risks associated with accepted screening and management strategies. Because the 5-year risk for CIN 3+ for a woman with an LSIL Pap finding is about 5.2%, and the recommendation for LSIL is colposcopy, 5.2% was set as the lower limit of the level of risk that provides enough benefit (detection of CIN 3+) to balance the potential harms of colposcopy.¹ (See the box on harms above.)

When women return to prolonged screening as follow-up to abnormal cytology or a positive HPV test, acceptable risk was considered to be that approximating the risk for CIN3+ three years after negative cytology or 5 years after negative cotesting—as these risks were considered acceptable to guide recent primary cervical screening guidelines.^{2–4}



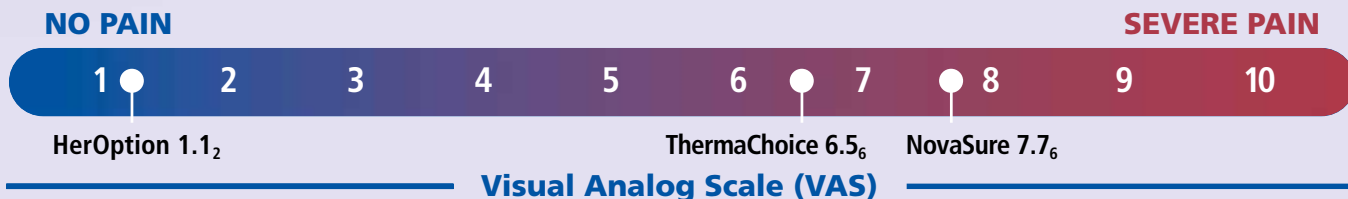
Clinical judgment must be paramount when applying guidelines to individual patients

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UPDATE

cervical disease

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FAST TRACK

Women aged 21 to 24 years are at high risk for HPV infection but very low risk for cancer

To be as precise as possible, experts stratified the guidelines by risk, according to the woman's age, cytologic diagnosis, and HPV status, including HPV genotyping for types 16 and 18, when tested. Of course, guidelines for management apply only to women who are found to have abnormalities during routine screening.¹ **Women who experience postcoital or unexplained abnormal vaginal bleeding, pelvic pain, abnormal discharge, or a visible lesion need individualized evaluations.¹**

Only changes or additions to the guidelines are listed here, so be sure to read the published guidelines and supplemental articles and/or visit the Web sites listed earlier for a review of all the guidelines.

What's new in managing women with unsatisfactory Pap results?

In general, cytology should be repeated in 2 to 4 months.

If the unsatisfactory Pap test is part of a cotest, then the following strategies are appropriate:

- If the HPV test is positive, either repeating the Pap test or moving directly to colposcopy is acceptable
- If HPV genotyping was reported and is positive for type 16 or 18, colposcopy is indicated.

Colposcopy also is recommended when two consecutive Pap tests are unsatisfactory.

What's new in managing women with normal cytology but no, or insufficient, endocervical cells/transformation-zone component?

The answer varies by age:

- For women 21 to 29 years – routine screening with cytology in 3 years is recommended
- For women 30 years and older:
 - When cotesting is done, the HPV result guides management:
 - HPV-negative: routine screening with cotesting in 5 years is preferred
 - HPV-positive: either cotesting in 1 year or immediate genotyping is recommended
 - If HPV testing was not done, then HPV testing is recommended, with management guided by results.

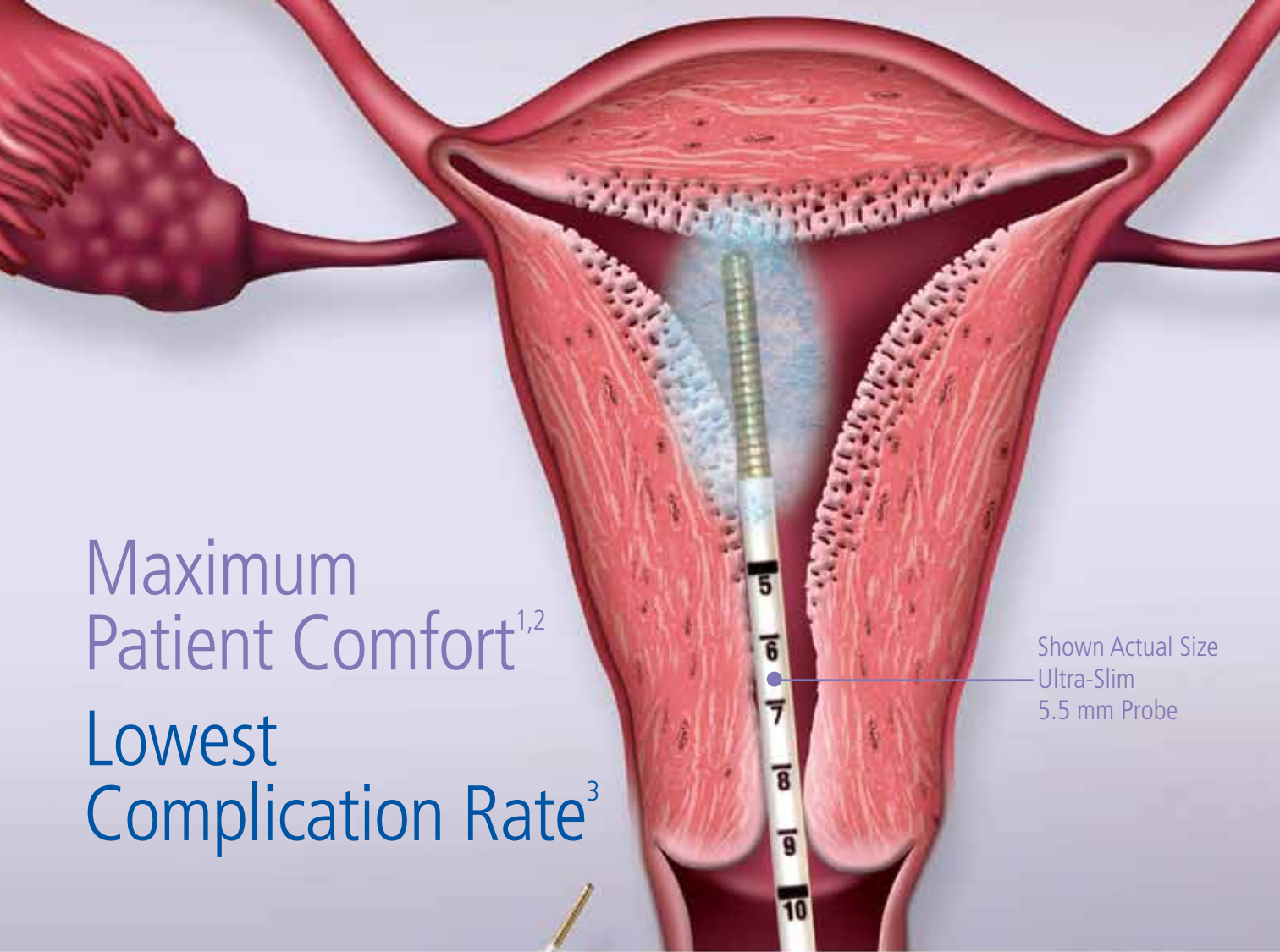
What's new in managing women aged 21 to 24 with abnormal cervical cytology or CIN?

Young women of this age are at high risk for HPV infection but very low risk for cancer. Aggressive management usually involves more harm than benefit, promoting observation. Adolescents are no longer screened; management previously reserved for adolescents is now appropriate for women aged 21 to 24 years.

If the Pap result is:

- **ASC-US or LSIL:**
 - No colposcopy is needed. The Pap test

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1, 2, 3, 4, 5 For reference details see <http://www.coopersurgical.com/Documents/HerOptionBrochure.pdf>
6 Clark et al; Bipolar Radiofrequency Compared with Thermal Balloon Endometrial Ablation in the Office; Obstetrics & Gynecology; Jan 2011

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Which HPV tests are recommended?¹⁻⁴

Because only high-risk HPV types cause cervical cancer, testing should be restricted to high-risk (oncogenic) HPV types. Do not test for low-risk HPV types.

The guidelines are intended for use only with HPV tests that have been analytically and clinically validated, as documented by US Food and Drug Administration licensing and approval or by publication in peer-reviewed scientific literature. This distinction is important because management based on results of HPV tests that have not been similarly validated may not result in outcomes intended by these guidelines and may increase the potential for patient harm.

should be repeated annually for 2 years, with colposcopy after 1 year only when the finding is HSIL and after 2 years if ASC-US or LSIL findings persist

- HPV triage for ASC-US is not recommended, but if it is done:
 - HPV-negative women should continue routine screening with a Pap test in 3 years
 - HPV-positive women should have annual cytology for 2 years, with colposcopy after 1 year only if the result is HSIL and after 2 years if ASC-US or LSIL findings persist.
- **ASC-H or HSIL:**
 - **Colposcopy is recommended, but immediate treatment (see-and-treat LEEP) is unacceptable**
 - Women with no CIN 2 or CIN 3 at colposcopy should be followed with colposcopy and cytology every 6 months for as long as 2 years, until two consecutive Pap tests are negative and no high-grade colposcopic abnormality is observed
 - Repeat biopsies are indicated if cytology at 1 year is again ASC-H or HSIL
 - Diagnostic excision is recommended if HSIL cytology persists for 2 years.

Changes in the management of histologic findings

If CIN 1 is detected, management depends on the antecedent cytology report:

- If the prior Pap finding was ASC-US or LSIL, observation with annual cytology is recommended
- If the prior Pap finding was ASC-H or HSIL,

observation for as long as 24 months is recommended, using both colposcopy and cytology at 6-month intervals, provided the colposcopic examination is adequate and endocervical assessment is negative.

If CIN 2 is detected, observation is preferred but treatment is acceptable (see the guidelines for detailed recommendations).

If CIN 2/CIN 3 (not otherwise differentiated) is detected, either observation or treatment is acceptable (see the guidelines for detailed recommendations).

If CIN 3 is detected in a woman of any age, treatment is indicated.

What's new in managing women 30 years and older who have discordant cotest results?

Use cotesting management recommendations only for women 30 years and older.

If the finding is:

- **HPV-positive/Pap-negative (HPV+/ Pap-)**, the two options are:
 - Repeat cotesting in 1 year, with colposcopy if the finding is again HPV+ or the Pap is ASC-US or more severe (including HPV-/ASC-US), and repeat cotesting in 3 years if results for both the HPV test and the Pap are negative (HPV-/Pap-)
 - Genotyping, with colposcopy if HPV 16 or 18 is identified and repeat cotesting in 1 year if both HPV 16 and 18 are negative
- **HPV-/ASC-US:**
 - Repeat the cotest in 3 years
- **HPV-/LSIL**, the options are:
 - Cotesting in 1 year (preferred)
 - Colposcopy (acceptable)



Do not test for low-risk (nononcogenic) HPV types


- **HPV+/LSIL or LSIL/no HPV result:**
 - Colposcopy
- **HPV-/HSIL or HPV-/ASC-H:**
 - Colposcopy
- **HPV-/AGC**
 - Colposcopy, often with endometrial sampling.

New terminology unifies all lower genital tract HPV intraepithelial neoplasia

Darragh TM, Colgan TJ, Cox JT, et al; LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. J Low Genit Tract Dis. 2012;16(3):205-242.

In 2012, the Lower Anogenital Squamous Terminology (LAST) standardization project created new histology terminology for HPV-related lesions of the lower genital tract. The LSIL finding was designated as the all-encompassing term for CIN 1, vaginal intraepithelial neoplasia 1 (VaIN 1), vulvar intraepithelial neoplasia 1 (VIN 1), penile intraepithelial neoplasia 1 (PeIN 1), perianal intraepithelial neoplasia 1 (PAIN 1) and anal intraepithelial neoplasia 1 (AIN 1). Intraepithelial neoplasia (IN) graded 2, 2/3, and 3 from each of these areas is designated HSIL.⁵

When CIN 2 and CIN 3 can be differentiated, these designations can be reported

along with the HSIL diagnosis. However, after thoughtful deliberation, the delegates to the ASCCP consensus conference decided that there is not yet enough outcome data available to determine different management strategies when using the new LAST histopathology terminology. They recommended that, until evidence is available, results reported as histologic (not cytologic) LSIL should be managed as CIN 1, and histologic (not cytologic) HSIL should be managed as CIN 2/CIN 3. 

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Guidelines for the management of abnormal cervical cytology, CIN, and AIS are necessarily complicated, but they provide the best basis for evidence-based management of these medical challenges. The Web provides easy access to all of the ASCCP guidelines via www.asccp.org, www.ligtd.com, and www.greenjournal.org.



Histologic results reported as LSIL should be managed as CIN 1, and histologic HSIL should be managed as CIN 2/CIN 3

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