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Perspective

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Making Sense of the New Cervical-Cancer Screening Guidelines

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Over the past 60 years, U.S. mortality from cervical cancer has dropped by 70%, thanks to a successful screening program. In 1995, the American College of Obstetricians and Gynecologists (ACOG) recommended screening with the Papanicolaou (Pap) smear and pelvic examination at the initiation of sexual activity or by 18 years of age and annually thereafter. Although not evidence-based, this guideline was easy to remember, timed to coincide with the onset of legal adulthood, and well received by patients and clinicians. Linking the Pap smear to an annual visit, and often to the provision of other health care services such as contraception, breast care, and blood-pressure checks, made the patient likely to comply and the physician likely to remember to offer the test as part of routine care. Furthermore, although the Pap smear's sensitivity is poor — roughly 50 to 60% — the frequency of repetition made it likely that in screened patients, an abnormality missed one year would be found the next. Hence, the system worked.

In 2002 and 2003, the ACOG, the American Cancer Society (ACS), and the U.S. Preventive Services Task Force (USPSTF) all issued guidelines addressing many issues related to screening. In 2006, the American Society for Colposcopy and Cervical Pathology (ASCCP) issued management guidelines. Despite being "evidence-based," these guidelines were different from one another, complicated, and hard to remember. Furthermore, the combination of a Pap smear with a test for human papillomavirus (HPV cotesting), which was addressed in these guidelines, was just being approved by the Food and Drug Administration (FDA) — on the basis of minimal clinical evidence that it added value. Despite recommendations indicating that Pap–HPV cotesting should be performed no more frequently than every 3 years because of its high added cost and limited additional clinical value, many patients, clinicians, and laboratories began cotesting annually.

Between 2009 and 2011, the same organizations, as well as American Society for Clinical Pathology (ASCP),[1-4] reconvened expert panels to reevaluate the evidence and issue new guidelines. Again, there are some differences of opinion and interpretation. There are, however, many points of agreement (see table) and much opportunity to use the existing evidence to maintain a high-quality cervical-cancer prevention pro-

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Summary of Recommendations for Cervical-Cancer Screening.*

Variable	ACS–ASCCP–ASCP Draft 2011	ACOG 2009	USPSTF Draft 2011
Age to start	21 yr	21 yr	21 yr
Testing frequency			
Age 21 to 29 yr (Pap alone)	Every 3 yr	Every 2 yr	Every 3 yr
Age 30 yr and older			
Pap alone	Every 3 yr	Every 3 yr	Every 3 yr
Pap and HPV cotesting	Recommended but no more frequently than every 3 yr	Allowed but no more frequently than every 3 yr	Insufficient data to recommend
Age to stop	65 yr after three negative Pap tests or two negative HPV tests in past 3 years	65–70 yr after three negative tests in preceding 10 years	65 yr after adequate screening
After hysterectomy	Discontinue if no dysplasia or cancer	Discontinue if no dysplasia or cancer	Discontinue if no dysplasia or cancer
Screening after HPV vaccination	Same as when unvaccinated	Same as when unvaccinated	Not addressed

* ACOG denotes American College of Obstetricians and Gynecologists, ACS American Cancer Society, ASCCP American Society for Colposcopy and Cervical Pathology, ASCP American Society for Clinical Pathology, HPV human papillomavirus, Pap Papanicolaou, and USPSTF U.S. Preventive Services Task Force.

gram that also safely addresses cost concerns.

Cervical cancer is rare before 20 years of age, and the incidence doesn't start to rise significantly until women reach the age of 25 or 30. Most cancers detected in screened women tend to be early-stage, so those found through screening are largely curable. For many women with early-stage disease, less-radical, fertility-sparing procedures can be curative, so even if early-stage cancers are detected, morbidity and mortality may be minimal.

Therefore, in 2009, the ACOG recommended that screening for "average-risk" women begin at the age of 21. Although the expert groups all agree that cervical cancer is rare before that age, they define high-risk younger groups somewhat differently; the ACOG defines average-risk women as immunocompetent women. Eliminating earlier screening averts overdiagnosis in young women based on transient cervical changes that their healthy immune systems would generally clear — and thereby also averts painful, costly, and possibly harmful procedures. Because there are no large prospective cohorts of immunocompromised patients, the USPSTF, which tends to be most rigorous in its evidence review, states that there is insufficient information for it to clearly recommend that screening should start before the age of 21 in immunosuppressed patients, but it offers the option of screening within 3 years after the onset of sexual activity, or by the age of 21.

Studies consistently show that for previously well-screened healthy women 30 years of age or older, the interval between Pap screenings can be lengthened to 3 years without significantly increasing their risk of cancer. It's also known that when screening takes place only every 5 years, or when women with abnormal Pap tests are not correctly triaged and treated to prevent cervical dysplasia from progressing to cancer, cancer rates increase. For women between 20 and 30 years of age, the optimal frequency is less well studied, but given the poor sensitivity of any single Pap test, the goal is to obtain at least two consecutive normal Pap results during this period to ensure that there are no missed opportunities for detecting and treating a precancerous lesion before lengthening the interval.

All the evidence and guidelines agree that HPV testing has no role in adolescents and should be performed in women 21 to 30 years of age only if a Pap test reveals atypical squamous cells of undetermined significance, an approach referred to as reflex testing. They also agree on reflex HPV testing for women 30 years of age or older under the same conditions. It is recommended that laboratories and clinicians not perform HPV screening in adolescents and that they use it only as a reflex test in women in their 20s.

The USPSTF, ACOG, and ASCCP–ACS–ASCP vary dramatically on whether evidence supports HPV cotesting for women 30 years of age or older. The USPSTF argues that Pap testing every 3 years for women over 30 is both safe and more cost-effective than cotesting and that no data support cotesting at the current screening intervals. It seems

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reasonable to use Pap testing alone every 3 years in this age group, unless the clinician seeks reassurance about lengthening the interval for a particular woman — for instance, if she has an uncertain Pap history or impaired immune status or may have difficulty complying with returning in 3 years. In such cases, HPV testing could be added or the Pap-testing interval shortened.

There is general agreement that in well-screened, low-risk women with no history of cancer or high-grade precancerous lesions, there comes a point when additional screening confers little added benefit. The USPSTF, ASCCP, and ACS agree on 65 as the age to stop screening such women. If the clinician cannot document a history of three normal Pap tests within the previous 10 years, then a Pap test should be obtained. If a patient has vaginal bleeding, vulvar discomfort, or other gynecologic or urologic symptoms, a complete pelvic examination and appropriate diagnostic testing should be performed. Furthermore, vaginal cancer is rare among women who have undergone hysterectomy, and all the guidelines agree that if such women are otherwise healthy and have no history of cancer or dysplasia, vaginal Pap testing may be discontinued.

In patients who have been treated for high-grade dysplasia, the risk of cervical cancer is increased by a factor of two to three for at least 20 years, but the risk of dying from cervical cancer is low, since most cancers are diagnosed at an early stage. Because it has long been the standard of care to screen these patients annually, we don't have good prospective data on whether this more frequent testing has contributed to early cancer diagnoses. Given that mortality rates have remained low with current practices, however, all groups recommend screening this population for at least 20 years after treatment.

Increasing screening in previously unscreened populations will further reduce the incidence of cervical cancer and related mortality. Reaching out to patients who face cultural, language, or educational barriers to care is important. Creating systems to remind clinicians that patients who come for episodic care must have appropriate cancer-screening tests is essential. Finally, making the guidelines for managing abnormalities easier for patients and clinicians to follow is important for both optimizing outcomes and containing costs for unnecessary referrals and treatment.

Health care is a limited resource, and providing the best care at the best price will become increasingly important. We need to use and understand actual data about risk and the long-term effects and costs of various strategies. Experts are often in the best position to review the data and make recommendations, but different expert panels may interpret data differently and emphasize different results in making their decisions. And even with the best consensus guidelines, some clinical judgment and personalized attention to each patient remains necessary.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. ACOG practice bulletin no. 109: cervical cytology screening. Obstet Gynecol 2009; 114:1409-20.
2. Preventive Services Task Force. Opportunities for public comment (http://www.uspreventiveservicestaskforce.org/tfcomment.htm).
3. American Society for Colposcopy and Cervical Pathology. Cervical cancer screening and prevention: the role of molecular testing (http://www.asccp.org/practice-management/molecular-screening-symposium).
4. Vesco KK, Whitlock EP, Eder M, Burda BU, Senger CA, Lutz K. Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the U.S. Preventive Services Task Force. Ann Intern Med 2011 October 17 (Epub ahead of print).

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Drug Shortages — A Critical Challenge for the Generic-Drug Market

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While the oncology community has been focusing much of its attention on the remarkable activity and enviable science related to the discovery of targeted drugs, the importance of standard cytotoxic therapeutics has suddenly become apparent, owing to shortages of the common workhorses of cancer treatment — methotrexate, leucovorin, 5-fluorouracil, cytosine arabinoside, vincristine, etoposide, the anthracyclines, paclitaxel, cisplatin, and others. The list of generic

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