Should U.S. Women Be Screened for Cervical Cancer With Pap Tests, HPV Tests, or Both?

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The Papanicolaou (Pap) test, introduced in the 1940s by Dr. George Papanicolaou, is considered one of the greatest achievements in women's health. Population-wide Pap testing reduces cervical cancer deaths by 80%, and many women and physicians consider the Pap test to be the cornerstone of preventive care (1). However, it has relatively low sensitivity, especially for adenocarcinomas, and results are often poorly reproducible; thus, women must be tested frequently to reduce cancer risk. In the 1990s, Dr. Harald zur Hausen and colleagues recognized that human papillomavirus (HPV) causes nearly all cervical cancer (1). This discovery led to significant advances in cervical cancer prevention: HPV testing and prophylactic HPV vaccination.

Since HPV testing was first introduced in the late 1990s, its role in cervical cancer prevention has expanded. After the landmark ASCUS-LSIL (Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion) Triage Study in 2003 (2), HPV testing was introduced into routine practice as a method of triaging women with minimally abnormal Pap test results (atypical squamous cells of undetermined significance) to immediate colposcopy or repeated Pap testing. In 2012, cervical cancer screening guidelines from the American Cancer Society, American Society of Colposcopy and Cervical Pathology, American Congress of Obstetricians and Gynecologists, and U.S. Preventive Services Task Force recommended cotesting with HPV and Pap every 5 years or Pap testing alone every 3 years as the standard of care for women aged 30 to 65 years (**Figure**) (1). On 24 April 2014, the U.S. Food and Drug Administration approved the Cobas HPV test (Roche Diagnostics) as primary screening for cervical cancer for women aged 25 years or older; this may have ushered in a new era of cervical cancer prevention. However, professional societies have not yet produced guidelines for adopting primary HPV testing into clinical practice.

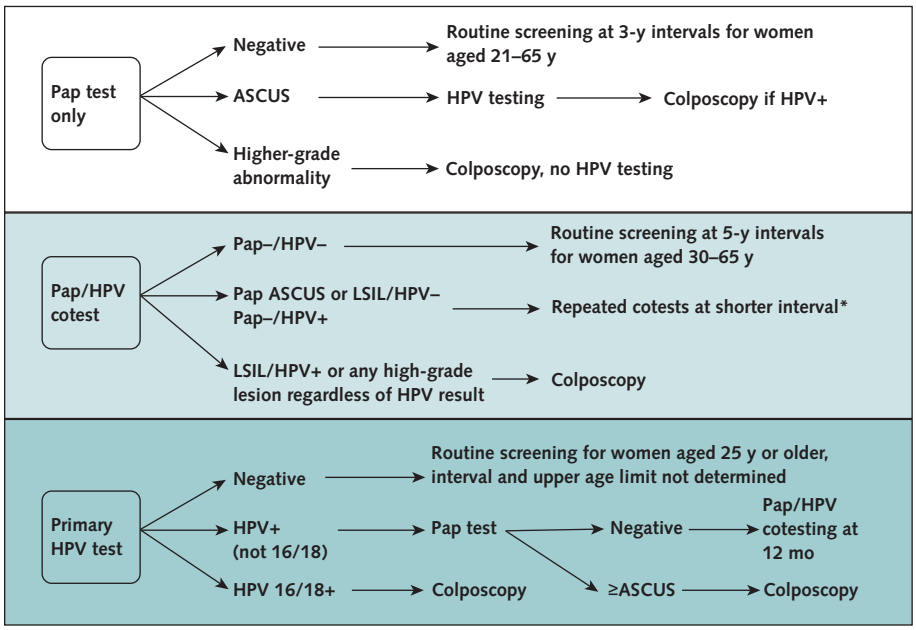
This potential switch in paradigm from Pap testing to HPV testing for cervical cancer prevention raises many questions: What is desirable in a cervical cancer screening test, how does HPV testing compare with Pap testing alone, and how does HPV testing alone compare with HPV and Pap cotesting? Cervical cancer screening tests aim to detect cervical precancer (moderate to severe cervical dysplasia) to allow timely treatment before death or impairment due to invasive cancer. When choosing a screening test, one looks for high sensitivity (the ability to detect most disease) with acceptable specificity (relatively low rates of false-positive results, which would lead to unnecessary follow-up testing). Data on more than 120 000 women in 4 countries confirm that a single HPV test is superior to a single Pap test for the detection of cervical precancer and cancer, having both higher sensitivity and specificity (3). A single screening with HPV testing (either Cobas or other commercially available HPV test) detects 95% of precancerous lesions, compared with 40% to 70% for Pap testing alone; the corresponding specificities are 94% for HPV testing and 97% for Pap testing (4, 5). To our knowledge, the only trial comparing cervical cancer incidence and mortality rates after either test compared a single Pap test, HPV test, or visual inspection in 131 000 previously unscreened women in India. Human papillomavirus testing reduced the incidence of and death due to cervical cancer by 50%, whereas a single Pap test or visual inspection had no effect (6). The ATHENA (Addressing the Need for Advanced HPV Diagnostics) trial, which specifically compared the performance of the Cobas HPV test with Pap tests processed in high-volume U.S. laboratories in a population of previously screened women, found that the risks for severe cervical dysplasia or cancer within 3 years of a negative test result were 0.78% for Pap test alone, 0.34% for HPV test alone, and 0.30% for cotesting with both HPV and Pap testing (7). The lower negative predictive value of Pap testing means that repeated screening is necessary to reduce cervical cancer rates. However, repeated Pap testing at currently recommended intervals and HPV testing may be similarly effective (8).

Pap and HPV cotesting detects more disease than either test alone, but the improvement is modest. Cotesting detects approximately twice as many cases of cervical dysplasia and cancer as Pap testing alone over a 3- to 5-year period, but only 12% to 16% more cases than HPV testing alone (7, 9). Cotesting may also detect more adenocarcinomas, squamous cell carcinomas, and endocervical cancer cases than HPV testing alone (10). In addition, a review of invasive cervical cancer in the United States found that approximately 31% of women who developed cancer had a negative HPV test result in the 3 to 5 years before diagnosis, and 30% women who developed cancer had a negative Pap test result in the 3 years before diagnosis, indicating that each test misses some cancer cases (10).

Which of the 3 potential mechanisms for preventing cervical cancer (Pap testing alone, HPV testing alone, or Pap and HPV cotesting) is best? Pap and HPV tests require speculum examinations and use specimen collection techniques identical to Pap tests alone, so the patient experi-

This article was published online first at www.annals.org on 10 June 2014.

Figure. **Comparison of screening algorithms with Pap testing, Pap and HPV cotesting, and primary HPV testing.**



High-grade lesions include HSIL, atypical glandular cells, atypical squamous cells that favor HSIL, and carcinomas. ASCUS = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; Pap = Papanicolaou.
* For Pap−/HPV+ results, testing for HPV types 16 or 18 with immediate colposcopy for positive results is an option.

ence is identical. Current data indicate that HPV testing alone is at least equal to Pap testing alone at 3-year intervals in women aged 30 years or older. Primary HPV testing in women aged 25 to 29 years would have higher false-positive rates (many young women have transient HPV infections that do not cause cervical dysplasia) but has the potential advantage of detecting early severe disease in women infected with HPV types 16 and 18. Screening intervals will affect both benefits and costs of all tests. At present, Pap and HPV cotesting is recommended at 5-year intervals, Pap testing alone is recommended at 3-year intervals (1), and no interval has yet been recommended for primary HPV testing (7). The costs of primary HPV testing compared with Pap testing alone or with Pap and HPV cotesting have not been standardized, and both the dollar value of each test and the intervals at which testing is recommended will determine the cost-effectiveness of different methods.

Although the relative merits of screening tests and screening intervals warrant additional discussion, we cannot lose sight of the fact that most cervical cancer occurs in women who have not had any recent screening. Increasing population coverage with any screening test and ensuring that women are not lost to follow-up with lengthened screening intervals are more important than the choice of test to decrease rates of invasive cervical cancer. Human papillomavirus vaccination also reduces the risk for precancer by 75% among young women vaccinated before age 14 years (11); thus, improving vaccination rates in young adolescents will also be crucial in the prevention of future disease.

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Acknowledgment: The authors thank Dr. L. Stewart Massad for his review of the manuscript and insight into the benefits and limitations of cervical cancer screening options.

Grant Support: By American Cancer Society Mentored Research Scholar Grant (MRSG-09-151-01).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1043.

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Ann Intern Med. 2014;161:295-297. doi:10.7326/M14-1043

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Final approval of the article: R.B. Perkins, E.A. Stier.
Collection and assembly of data: R.B. Perkins, E.A. Stier.