EDITORIAL

Are we ready for primary HPV testing for the prevention of cervical cancer?

We may be at a tipping point where the iconic Pap smear is largely replaced by HPV testing for cervical cancer screening

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Cervical cancer screening represents one of the great public health successes of the 20th Century. Two physician-scientists, George Papanicolaou, MD, PhD (1883–1962), and Harald zur Hausen, MD (1936–), made extraordinary contributions to the evolution of effective cervical cancer screening programs. Dr. Papanicolaou led development of the iconic Pap smear, creating techniques for collecting specimens and using cytologic techniques to identify cervical cancer and its precursors, and Dr. zur Hausen discovered the association of human papillomavirus (HPV) infection with cervical cancer.[1,2]

Although it is but a distant memory, *in the 1930s cervical and uterine cancer caused more deaths among women than breast, lung, or ovarian cancer.* The successful deployment of Pap smear screening resulted in a decrease in cervical cancer rates in developed countries. Cervical cancer deaths remain common in many parts of the world, however. Cervical cancer screening programs can reduce cervical cancer incidence by greater than 80%.[3] In the United States between 1973 and 2006, the invasive cervical cancer age-adjusted incidence rates dropped from 10.28 to 3.97 per 100,000 women.[4]

HPV causes cervical cancer

Dr. zur Hausen dedicated his career to identifying viral causes of human cancer. In his Nobel Laureate autobiography, he reported that during his 2-year rotating residency, he loved his obstetrics and gynecology experience, but found it "physically highly demanding" and decided to focus his career in microbiology and immunology.[5] After proving that herpes simplex virus did not cause cervical cancer he began to explore the role of HPV in the disease process. He first identified HPV types 6 and 11 and showed that these agents caused genital warts. He then used low-stringency hybridization techniques to identify HPV types 16 and 18 in specimens of cervical cancer. Later, he and his colleagues proved that two HPV proteins, E6 and E7, interfere with the function of cell cycle control proteins p53 and retinoblastoma protein, resulting in dysregulated cell growth and cancer.[2] These findings permitted the development of both HPV vaccines and nucleic acid–based tests to identify high-risk oncogenic HPV (hrHPV) in cells and tissue specimens.

HPV vaccination

Dr. zur Hausen was an energetic and vocal advocate for the development and widescale deployment of HPV vaccines, including vaccination of males and females.[6] Initially his ideas were rejected by the pharmaceutical industry, but eventually, with advances in virology and vaccine development, multiple companies pursued the development of HPV vaccines, the first cancer prevention vaccines. The best approach to cervical cancer prevention is intensive population-wide HPV vaccination of both boys and girls before exposure to the HPV virus. Beyond its beneficial effect on the incidence of cervical cancer, HPV vaccination also reduces the population incidence of anal, vulvar, and oropharyngeal cancer.[7]

Instant Poll

When do you think we in the United States will transition to primary HPV screening for cervical cancer?

Tell us at rbarbieri@mdedge.com Please include your name and city and state.

Prevention of oropharyngeal cancer is especially important for men, supporting the recommendation for vaccination of all boys.[8]

Population-wide HPV vaccination will result in a lower prevalence of cervical cancer precursors and reduce the sensitivity of cytology, thereby making primary HPV screening more attractive.[9] Based on one modelling study, universal HPV vaccination can reduce cervical cancer rates by greater than 50% over current levels, and introduction of primary HPV screening will reduce cervical cancer rates by an additional 20%.[10] In an era of widespread vaccination for HPV, screening for cervical cancer should be intensified for nonvaccinated women.[10]

Primary cervical cancer screening with cytology

Primary screening with cervical cytology alone remains an option supported by many authorities and professional society guidelines.[11] Most studies report that HPV testing has greater sensitivity than cervical cytology alone, especially for the detection of adenocarcinoma of the cervix.[12] In one Canadian study, 10,154 women were randomly assigned to HPV or cervical cytology testing. The sensitivity of HPV testing and cervical cytology for detecting cervical intraepithelial neoplasia grade 2 or 3 was 95% and 55%, respectively, with a specificity of 94% and 97%, respectively.[13] When used together the sensitivity and specificity of cotesting was 100% and 93%, respectively, but resulted in an increased number of colposcopies, which may be costly and add stress for the patient. Many countries are beginning to move away from cervical cancer screening with cytology or cotesting to programs built upon a foundation of primary HPV testing.

Primary cervical cancer screening with HPV testing

The knowledge that hrHPV is a more sensitive test for cervical cancer and its precursors, as well as the relatively lower sensitivity of cytology, is the foundation for transitioning from primary screening with cervical cytology to primary screening with HPV testing. In the Netherlands[14] and Australia[15,16] HPV testing with reflex cytology is the nationwide approach to cervical cancer screening. The basic components of the Dutch primary HPV screening program, as explained by Dr. Lai van Zulyan Mandres, are[14]:

1. Samples are collected by a general practitioner and sent to one of 5 central testing facilities for DNA testing for hrHPV.
2. If all previous samples tested negative, the screening occurs at ages 30, 35, 40, 50, and 60 years, a minimum of 5 screens per woman.
3. If there is a history of a previously positive hrHPV, the screening is intensified, with additional specimens collected at ages 45, 55, and 60 years.
4. If the sample is hrHPV negative, the patient continues screening at the standard intervals. No cytology testing is performed.
5. If the sample is hrHPV positive, reflex cytology is performed using the original collected sample. If the cytology shows no intraepithelial lesion or malignancy (NILM), another specimen is obtained for cytology within 6 months. If the second cytology specimen shows atypical squamous cells of undetermined significance (ASCUS) or a more worrisome cytology finding, the patient is sent for colposcopy. If two NILM cytology specimens have been obtained, the patient resumes primary hrHPV screening every 5 years.
6. If the specimen is hrHPV positive and cytology is ASCUS or more worrisome the patient is referred for colposcopy (**FIGURE,** page 14).[14] The Dutch estimate that primary hrHPV screening will reduce the number of cervical cytology specimens by 90% annually.

Australia also has implemented nationwide primary HPV testing for cervical cancer screening. This change was implemented following a 10-year program of universal school-based vaccination of girls and boys, and biennial cytology screening for all women. The Australian screening program initiates hrHPV testing at age 25 years and thereafter every 5 years until age 74. If the hrHPV test is positive, reflex testing for HPV types 16 and 18 are performed on the original specimen along with cervical cytology. Women who test positive for HPV 16 or 18 are immediately referred for colposcopy. If the hrHPV test is positive and reflex testing for HPV 16 and 18 is negative, cervical cytology demonstrating ASCUS, low- or high-grade squamous intraepithelial lesions, or more worrisome results trigger a referral for colposcopy. The Australian program supports testing of self-collected vaginal samples for women who are underscreened or have never been screened.[15,16]

Pros and cons of switching approaches

Deployment of new technology often yields benefits and challenges. A putative benefit of primary HPV screening is a reduction in health care costs without an increase in cervical cancer deaths. Another benefit of primary HPV screening is that it may enable self-collection of specimens for analysis, thereby increasing access to cervical cancer screening for underserved and marginalized populations of women who are not

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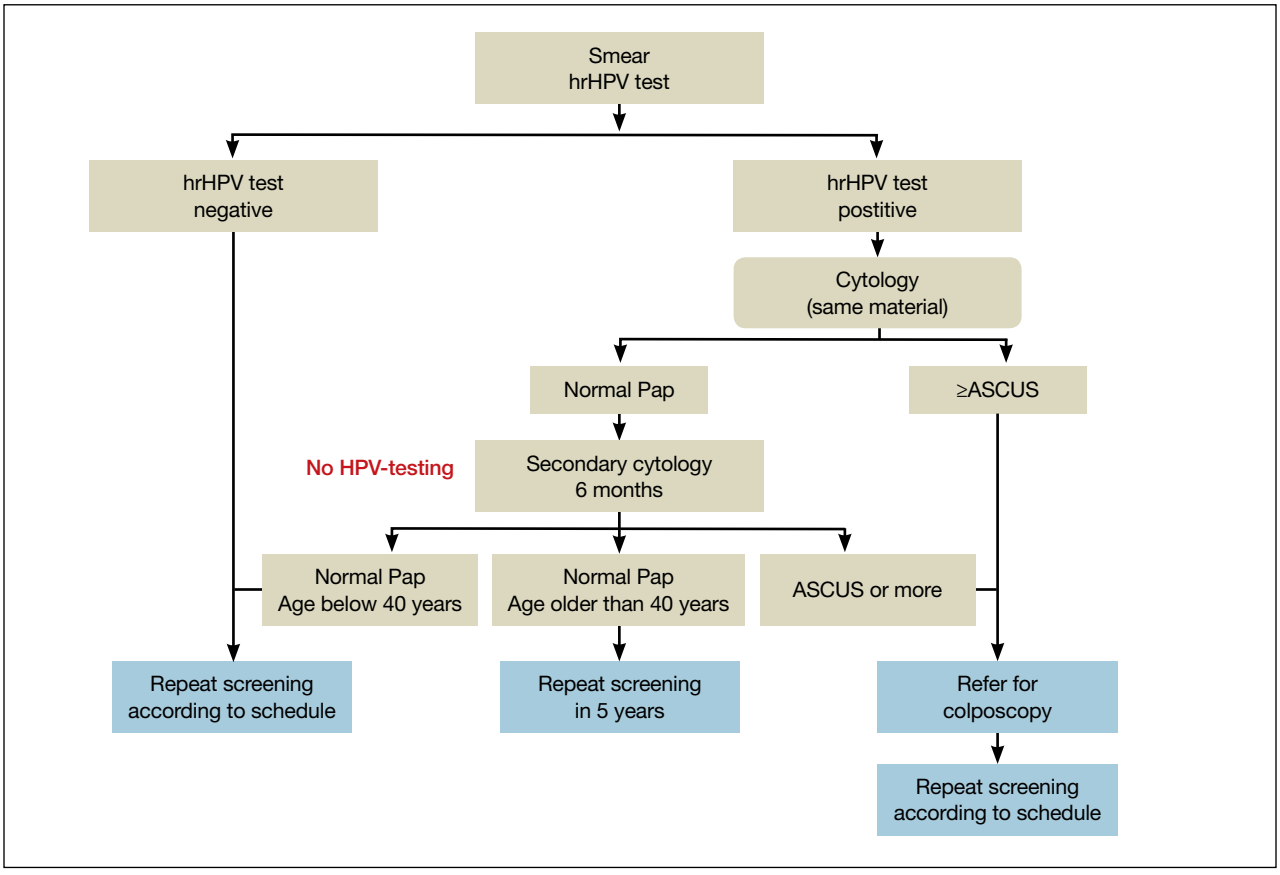
FIGURE Netherlands algorithm for cervical cancer screening[14]



Abbreviations: ASCUS, atypical squamous cells of undetermined significance; hrHPV, high-risk human papillomavirus.

currently participating in cervical cancer screening programs.[17] One challenge is that many women are unaware that hrHPV is the cause of most invasive cervical cancers. The detection of hrHPV in a woman in a long-term relationship who was previously negative for hrHPV may cause the emotions of surprise, fear, anxiety, and anger, thereby stressing the relationship.[18]

Another concern is that many women are worried about no longer receiving the familiar "Pap smear" cancer screening test in which they have tremendous faith. When Australia transitioned to primary HPV screening, more than 70,000 women signed a petition to "save women's lives" by permitting continued access to the cervical cytology testing.[19] Primary HPV testing may result in a transient increase in the number of women referred for colposcopy, potentially overwhelming the capacity of the health care system to deliver this vital service.[20,21] The HPV types that most often cause cervical cancer may vary among countries. For example, in Thailand, HPV 52 and 58 are frequently detected in women with high-grade squamous lesions, and including these subtypes in reflex genotyping may be of regional benefit.[22]

Primary cervical cancer screening with HPV testing: When will it be used widely in the United States?

In contrast to the United States, the Netherlands is a small, densely populated country that has a highly integrated health system with centralized laboratory centers, a nationwide electronic health record, and clinicians organized to perform as an integrated team. These features ensure that all lifetime tests results are available in one record, that HPV testing is highly standardized, and that clinicians will follow a prescribed care pathway. The Netherlands' health system is organized to support the successful transition, in a single step, to primary HPV testing. The United States is the third most populous country in the world, following China and India, with a diverse approach to health care, a highly mobile population, no single interoperable electronic health record, and minimal central

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control of clinical practice. The United States is not organized to make a "big bang" transition to primary HPV cervical cancer screening. It is likely that the introduction of primary HPV screening will occur first in highly integrated health systems that control the clinical, laboratory, and electronic records of a large population.

The results of the ATHENA study provide a clear clinical algorithm for implementing a primary HPV screening program for cervical cancer in the United States.[23–25] Samples are collected for hrHPV testing at a specified interval, 3 or 5 years, beginning at age 25 years. Women younger than age 25 years should be screened with cytology alone. Detection of hrHPV results in reflex viral typing for HPV 16 and 18. Women with samples positive for HPV 16 and 18 are immediately referred for colposcopy. Samples positive for hrHPV and negative for HPV 16 and 18 have reflex cytology testing performed on the original HPV specimen. If cytology testing reports NILM, repeat cotesting is performed in one year. If cytology testing reports ASCUS or a more concerning result, the woman is referred for colposcopy.

Malcolm Gladwell, in his book *The Tipping Point,* identified 3 processes that help push an innovative new approach from obscurity into widespread use.[26] First, authoritative voices that can catalyze change need to consistently communicate their shared vision for the future. Second, there must be a clear message that galvanizes the many to change their approach. Third, the historical context must be supportive of the change. Over the next decade we are likely to hit a tipping point and transition from cervical cancer screening that relies on cervical cytology to an approach that prioritizes hrHPV testing. When that change will occur in the United States is unclear. But our colleagues in other countries already have transitioned to primary hrHPV testing for cervical cancer screening. ●

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