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The Next Generation of Cervical Cancer Screening: Should Guidelines Focus on Best Practices for the Future or Current Screening Capacity?

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MODERATOR STATEMENT

Rebecca B. Perkins, MD, MS

From approximately 1950–2000, cervical cancers were prevented by using cytology (Pap tests), clinician-collected samples of cervical cells that used microscopic evaluation to detect precancerous changes, allowing treatment before the development of cancer. Population-wide screening at 1- to 3-year intervals with cytology led to dramatic declines in cervical cancer rates, and cytology has been touted as one of the most effective cancer prevention measures to date. However, the discovery that human papillomavirus (HPV) is responsible for nearly all cases of cervical cancer, and the subsequent advent of HPV vaccination and HPV testing has the potential to revolutionize cervical cancer prevention.

In the United States, both cytology and HPV testing are currently available for screening women. However, these tests perform very differently. Cytology can be thought of as an analysis of the cervix in its current state. Cells are removed and deemed either positive or negative for the possible presence of precancer. Cytology has low sensitivity, missing up to 50% of present lesions, and a single negative test does not provide long-term reassurance that cancer will not develop. Human papillomavirus testing, in contrast, detects 95% of precancer with a single screen. In addition, because persistent HPV infection is a necessary precursor of cervical precancer, a negative HPV test today means that a woman's risk of precancer is greatly reduced for the next several years. However, because HPV infections are common and most are transient, HPV testing has a higher false-positive rate, meaning that for every test performed, more women will be sent for additional testing and no precancer will be found.

Current guidance exist for cytology alone, HPV tests alone, and Pap and HPV co-testing.^{1,2} These guidelines allow for flexibility related to the resources available in different settings nationwide but also generate confusion because clinicians struggle to determine which test or combination of tests to use, how often to

perform them, and how the results of different testing combinations should be interpreted. Adding to the challenge is the aging of vaccinated women into the screening population. Because HPV vaccination substantially reduces the risk of precancer,^{3–5} fewer women with “positive” screening results will actually have precancer, changing the predictive value of a given screening test for vaccinated women.

The question addressed in this forum is how the next set of guidelines should shape US screening practices. Should guidelines be aspirational, looking ahead 5 to 10 years in the future and presenting the best case scenario in terms of equal access and correct implementation of the highest quality screening tools, or should guidelines be practical, focusing on the tools and resources available today, but with the understanding that frequent revisions will be needed as we look to the future?

SIDE 1

Cervical Cancer Screening Guidelines Should Be Aspirational, Focusing on Best Practices for the Future, as Represented by HPV Testing Alone at 5-Year Intervals

Philip E. Castle, PhD, MPH

I. Introduction: Benefits and Harms

A current, impassioned debate about cervical-cancer prevention in the United States is how (cytology vs. HPV and cytology “co-testing” vs. HPV testing alone) and how frequently (once every 3–5 years) to screen adult women for prevention of cervical cancer. Screening for any disease in the general, average-risk population is a public-health intervention. Most people undergoing screening, even those who screen positive, will be healthy with respect to the target disease. The average lifetime risk of cervical cancer in an unscreened population is estimated to be approximately 2%.^{1,2} Thus, the consequences of screening to the 98% of women who will never get cervical cancer must factor into the decision about who and how to screen. Guidelines for screening must consider factors such as costs/cost-effectiveness and potential harms to healthy individuals in making recommendations for who should get screened and how often.

Because clinical trials and observational studies do not often collect data on, or have sufficient sample sizes to, directly measure harms of screening, the number of women referred to colposcopy has been used as a proxy for measuring harms.³ No women, no matter how well educated, enjoy getting a positive cancer screening result, nor do they want to be referred to colposcopy for a pelvic examination and biopsy, which can lead to finding some cases of transient intraepithelial neoplasia grade 2 (CIN 2) associated with a benign HPV infection that could be overtreated.

Another guiding principle of screening is that no test or intervention has perfect (100%) sensitivity. Thus, fundamental to developing guidelines for screening is accepting that more could always be done to prevent, treat, or provide care for a disease... with increased harms and added cost. If cervical cancer prevention

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is the only consideration for women's health and well-being, the logical but ludicrous conclusion is that all adult women should undergo hysterectomy to remove the cervix, such as prophylactic oophorectomy in breast cancer susceptibility gene-positive women for whom there is no screening alternative for preventing ovarian cancer. Alternatively, women could be co-tested every 6 months (vs. every 3 or 5 years) to further reduce cervical cancer risk if cost is not an issue. These absurd examples illustrate the problem of screening recommendations for cervical-cancer prevention that do not consider the impact on women's overall health and society. It is in this context of balancing benefits and harms for the women that the advantages of screening using HPV testing every 5 years, as suggested recently in draft recommendations from the US Preventive Service Task Force,⁴ are discussed hereinafter.

II. HPV Testing Every 5 Years vs. Cytology Every 3 Years

Human papillomavirus testing is more sensitive^{5–10} and reliable^{11–13} for detection of precancerous lesions, CIN 3, and adenocarcinoma in situ (AIS), and cervical cancer (together, \geq CIN 3) of the cervix than cervical cytology. The increased sensitivity of HPV testing over Pap testing for CIN 3 or greater translates into 2 important benefits: (a) earlier detection of CIN 3/AIS lesions that if treated results in a reduced incidence of cervical cancer within 4 to 5 years¹⁴ and related death within 8 years¹⁵ and (b) greater reassurance against cancer (lower cancer risk) after a negative result for many years,^{14–19} which permits screening at an extended interval of 5–10 years. Importantly, cytology poorly detects cervical adenocarcinoma and AIS,^{14,20} and adenocarcinoma incidence has not decreased in many countries despite an effective cytology program that has reduced the incidence of squamous cell carcinoma.^{21–24} However, despite that HPV testing-based screening has become the new standard of care for cervical screening nationally and internationally, cytology-based screening will need to be retained in the United States, at least temporarily, to accommodate health systems that have not yet adopted HPV testing.

III. HPV Testing vs. Co-Testing Every 5 Years

Although screening with co-testing increases the cross-sectional sensitivity for CIN 3, AIS, and invasive cervical cancer (together, \geq CIN 3) by approximately 5% compared HPV testing alone,^{25,26} there is no evidence that co-testing reduces the risk of incidence cervical cancer or cervical cancer-related mortality more than HPV testing alone. Similarly, a negative co-test provides only slightly greater reassurance against cancer risk that HPV testing alone^{17,27,28} but increases the likelihood of falsely testing positive. Analogously, adjunctive use of ultrasound or magnetic resonance imaging with mammography for breast cancer screening is not recommended for average-risk women.

Screening with co-testing substantially increases (~60% greater than HPV testing alone) the cost of screening compared with HPV testing alone. In contrast, primary HPV testing with reflex cytology should reduce costs without adding complexity, because triage of positive results would simply require pulling the residual specimen from HPV-positive women for a cytologic evaluation. This should be similar logistically to reflex HPV testing to triage atypical squamous cells of undetermined significance cytology, which became widely, albeit imperfectly, adopted in the United States^{29–31} after its recommendation in 2001.³² Another advantage of using HPV testing alone is that it will simplify clinical management after a positive/nonnormal result.³³

One of the most important advantages of introducing primary HPV testing is the possibility of using self-collected specimens for HPV testing, which could increase screening in underscreened or unscreened populations of women, in whom a

large proportion of cancers diagnosed in the United States occur. Self-collected specimens tested for HPV can be as accurate as using provider-collected specimens^{34,35} and are preferred by women living in low-income countries³⁶ or in impoverished regions of high-income countries.^{37,38}

IV. HPV Testing Every 5 Years vs. 3 Years

Similar small increases in sensitivity as co-testing can also be achieved *programmatically* by screening more frequently, every 3 years with HPV testing, compared with HPV testing every 5 years. However, screening every 3 years with HPV testing will similarly increase costs of screening to that of co-testing. Another consequence of screening more frequently is that more benign, transient HPV infections and associated CIN 2 will be found. That is, screening more frequently shifts the emphasis from detecting persistent HPV infections that are more strongly linked to CIN 3 or greater to transient HPV infections, some of which manifest as CIN 2 diagnoses. Because some CIN 2 diagnoses do not represent true precancers, they can result in unnecessary excision treatments, which have been linked to preterm delivery,^{39,40} a relevant outcome for women who are still considering bearing children.

One concern of using 5-year (vs. 3-year) intervals for screening, which apply to both HPV testing and co-testing, is the increased likelihood of women missing the next screen. This is a legitimate concern and applies mainly to women switching healthcare systems because electronic medical records from one health system are generally not shared with another. Cloud computing-based strategies in which the electronic medical records is kept on an individual basis (“personal health record”) and accessed by health systems is one potential future solution to overcome these barriers to providing care for individuals across healthcare systems.⁴¹

V. Using Risk to Guide Recommended Screening Interval

Given that achieving 100% cervical-cancer prevention would be nearly impossible to achieve and cost prohibitive to do so, the question of who and how to screen can only be answered by defining what is the “maximum acceptable risk” after a negative screening test, i.e., what is the risk we are willing to tolerate for a screening interval and what is the residual lifetime risk that we can accept to exit women from screening at older ages? If we can answer these questions, choice about how and who to screen becomes straightforward: the strategy that achieves the maximum acceptable risk at the lowest cost and fewest screens (least harms).

VI. Conclusions

Aspirational guidelines, specifically adopting HPV testing every 5 years, will conform to international standards and will create a global standard of care for cervical screening to prevent cervical cancer. Human papillomavirus testing every 5 years provides the best balance of all these considerations. It is feasible, what is best for women and for our population, and the most effective use of resources in context of escalating healthcare costs.⁴²

SIDE 2

Cervical Cancer Screening Guidelines Should Be Practical and Able To Be Easily and Effectively Implemented in Many Settings

Sarah Feldman MD MPH

I. Introduction: Benefits and Harms of a Simple System

The most successful cancer screening test ever developed was the annual Pap test to screen for cervical cancer. The advice

to initiate Pap testing at the age of 18 years or with the onset of sexual activity and to evaluate and treat all abnormalities was easy to remember for patients and doctors, easy to implement at annual visits, and easy to combine with other health care needs. It was practical, and this led in part to its success. Because cervical cancer screening guidelines have lengthened cytology intervals from 1 to 3 years and added HPV co-testing for women older than 30 years with a screening interval of 5 years, clinician and patient behavior has been difficult to change. According to Watson et al.,⁴³ in a study using National Health Interview data of 10,596 women published in 2017, appropriate Pap testing has decreased, with only 21% to 35% of women older than 30 years getting co-testing, and only 81% of women aged 21 to 65 years receiving a Pap within 3 years. Thus, the development of guidelines that are practical and easy to implement is paramount to ensure that future cervical cancer screening is better, not worse, for women.

Successful screening guidelines must account for access to care, availability of recommended tests, knowledge and preferences of both patients and providers, and systems for tracking patients and ensuring appropriate management of abnormalities.

II. Primary HPV Screening Is the Eventual Goal

Ultimately, primary HPV screening should be the standard of care for cervical cancer screening both in the United States and worldwide. A recent large study by Castle et al. shows the high negative predictive value of successive rounds of negative HPV tests, increasing our ability to predict women who are at low risk for developing cervical cancer.⁴⁴ Many studies, however, while demonstrating an increase in the detection of precancer, especially in the first few years of testing, also show an increase in the detection of cellular changes associated with transient HPV infection, as well as an increase in the number of colposcopies and excisional procedures, e.g. LEEP, performed to detect these abnormalities,⁴⁵ which are both costly and stressful for patients.

III. Necessity of a Transition Plan

To get to a successful program of primary HPV testing, we will likely need a transition plan that incorporates a comprehensive and coordinated cervical cancer prevention approach: primary vaccination of all adolescents and young adults before exposure, screening either by cytology or HPV testing based on the feasibility and acceptability of these tests in different settings, increased use of primary HPV testing, as well as access to self-collected specimens for HPV testing, especially among women not currently being screened, as well as a simplified approach to management of abnormalities that takes into account both underlying risk, effectiveness, management options, human behavior, provider and patient preference, and cost.⁴⁶

The existence of effective technology and appropriate guidelines do not guarantee uptake or correct use with patients. For example, well studied advances in screening and prevention, such as cytology/HPV co-testing and HPV vaccination have been Food and Drug Administration (FDA) approved, recommended in consensus guidelines by most professional physician organizations, and widely available for more than 10 years, yet uptake has been slow and cervical cancer rates have not changed meaningfully.^{43,47} Confusion about how to manage abnormalities and inadequate systems to help busy providers manage screening test results has further impeded progress.⁴⁸

Although primary HPV screening is the ultimate goal, HPV testing is not yet available to most women. The only HPV test currently FDA approved for primary screening is the Cobas test, based on 3 years of initial data in the United States. However, many laboratories in the United States do not have Cobas testing

but instead have machinery for HPV testing by other platforms currently only approved in the co-testing or reflex testing setting. Transitioning to other technology or awaiting FDA approval for other tests will take time. Although off-label use is an option, laboratories and healthcare organizations may not endorse this for primary screening of entire populations. Thus, many women do not currently have access to the only FDA-approved HPV test for primary screening. It is not clear whether these other tests will perform similarly in the screening setting and how and when (if other tests are not validated quickly or at all) patients will have access to appropriate testing. Furthermore, patients managed in research studies are followed according to highly controlled algorithms that include more frequent visits than those that might be recommended in guidelines. To feel comfortable recommending primary testing for all women at 5-year intervals, we need more studies in a variety of “real-world” settings.

IV. Necessity of Continued Incremental Revision of Guidelines

As practice evolves, underlying rates of precancer will change. Human papillomavirus vaccination will drive down rates of infection and subsequent pre-cancer, and HPV testing, which detects more disease at the initial screen, results in lower rates of precancer in subsequent screening rounds. This in turn affects the accuracy of any given test (both in terms of positive and negative predictive value), and thus, appropriate recommendations or guidelines and priorities will likewise need to be updated. To complicate implementation, rates of HPV vaccination and access to screening, in particular HPV testing, vary widely in different parts of the United States and the world.

So what is the role of a guideline? Guidelines are intended to standardize care using the best available evidence supplemented by expert opinion to decrease rates of disease and improve the health of populations. To be successful, guidelines must be implementable and useful to patients and providers in a wide variety of clinical and programmatic settings that may have varied resources and priorities. Testing and treatment options also need to be culturally and emotionally acceptable to patients. Thus, to be effective, guidelines must be evidence based but also flexible, and they must reflect the roles of access, acceptability, availability, and cost of different testing and management options.⁴⁹ Furthermore, for screening guidelines to have the maximum impact at preventing cancer, they must incorporate easy and straightforward recommendations for management of abnormalities and include other best practices such as primary vaccination. Not only does “one size” not fit all in this age of personalized medicine, but also as care evolves with new scientific advances, “evidence” is also likely to evolve and guidelines developed now will need to be constantly re-evaluated to reflect new rates of precancer, vaccine uptake and HPV infection rates, as well as additional molecular testing options. Even guidelines that may now seem aspirational will need frequent reassessment to ensure they are working as hoped, that cancer is being prevented and that yet new and better approaches have not been developed.

Rebuttal by Dr. Castle

A *time-limited* transition plan and clinical decision-support tools are needed to facilitate adoption of HPV testing at 5-year intervals and to improve the quality of care provided to women. The rationale for recommending these alternatives in this transition period should be transparent and should not misrepresent the facts and/or use scare tactics to maintain the status quo for vested interests.⁵⁰ A “risk calculator” and decision-support tool will help optimize cervical screening and management,⁵¹ but must be user-friendly, and present

the necessary information in a clear and direct manner to assist the busy clinician.

A major challenge to providing optimized cervical screening to women in the United States is the lack of compliance with any guideline, primarily resulting in overscreening with HPV testing. A recent survey of primary care physicians and obstetrician-gynecologists found that approximately 30% of them would recommend asymptomatic women aged 30 years and older undergo annual screening with HPV testing.⁵² Financial incentives/disincentives may be a solution, but the jury is still out as to whether payment-for-performance strategies improves adherence.^{53,54}

Rebuttal by Dr. Feldman

Dr. Castle's editorial argues for primary HPV testing every 5 years as compared with co-testing with cytology and HPV every 3 to 5 years. He makes many assumptions about the options available for screening, women's preferences and behavior, and what constitutes acceptable risk and cost in different settings and with different priorities.

As Kinney and Huh note⁵⁵ and I have observed in a busy clinical practice, patients have a wide variety of preferences related to the tradeoff between a small increase in the risk of cancer versus the discomfort or risk of undergoing colposcopy, whether due to their previous medical experience, their anxiety about cancer, their preferences regarding future fertility, and their need for reassurance. Furthermore, clinicians may have genuine concerns or actual barriers to changing practice, which may include their belief in the efficacy of this approach, the availability of primary HPV testing in their setting, systems for tracking care and patient reminders, and medical-legal concerns about missing cancer in an individual patient. To be successful at preventing cancer, guidelines must reflect the actual options available, proven behavior, and the flexibility to adapt options to a variety of care settings and for patients at different risk and in different settings. If we want to aspire to international standards, we should use the model of Australia⁶⁷—vaccinate all of our children, screen and treat all our existing precancers, track all patients in a registry, which helps clinicians manage patients, and see how we are doing—and then, we may safely transition to less frequent primary HPV testing.

Summary

Rebecca B. Perkins, MD, MS

To what extent should cervical cancer screening guidelines look to the future versus focusing on current clinical practice? Dr. Castle and Dr. Feldman seem to agree that HPV testing should ultimately become the standard for cervical cancer screening. Human papillomavirus testing detects more disease with the first round of screening, and negative testing provides longer-term reassurance against future precancer and cancer than cytology testing alone. When compared with HPV testing alone, screening with co-testing detects very little additional disease in an average-risk population.

Yet how guidelines should evolve at the current time is controversial. Dr. Castle argues that current guidelines should be aspirational: primary HPV testing every 5 years. If we know where to go, clinicians, healthcare systems, insurers, and patients can pave their own paths to get there. Dr. Feldman argues that guidelines should be implementable within current practice and provide incrementally advancing recommendations that may eventually encourage primary HPV testing but will provide more rigorous guidance during the transition period. Arguments can be made for both approaches. Adoption of guidelines often takes several years; therefore, creating aspirational recommendations that are unlikely to change in the near future may facilitate broader adoption over time. However, the implementation of primary HPV

screening guidelines may be challenging within existing health-care systems, many of which lack primary HPV screening capability, use HPV testing platforms that are designed and FDA approved only for use with concurrent cytology, or have staff dedicated to reading cytology specimens that cannot be easily reassigned. As we strive to decrease cancer rates while simultaneously decreasing unnecessary testing and treatment, we must work diligently to evolve current practice to improve care for women.

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