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## Should Self-Sampling Be an Option for Women in the United States?

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### MODERATOR STATEMENT

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United States (US) guidelines for cervical cancer screening have recently been revised, and for the first time, the US Preventive Services Task Force recommended primary human papillomavirus (HPV) screening to be the standard of care, along with cytology alone or co-testing with both cytology and HPV.<sup>1</sup> In the US, HPV screening is currently recommended via clinician-collected sampling, similar to cytology. However, self-collected samples may also be an option for HPV primary screening, especially for underscreened women.<sup>2</sup> The benefits of screening using self-collected HPV testing include increased convenience and reductions of barriers for women. Many women find pelvic examinations undesirable for a variety of reasons, so the ability to perform screening without undergoing a pelvic examination has widespread appeal. In addition, nearly 20% of family medicine physicians and half of internists do not perform pelvic examinations,<sup>3</sup> requiring women to see a separate provider for this service—self-collected samples would obviate this inconvenience.

Human papillomavirus testing is far more sensitive than cytology for detecting precancerous lesions of the cervix; therefore, HPV self-sampling would likely increase detection over clinician-collected cytology.

The sensitivity of self-sampling closely approaches that of clinician-collection HPV screening if a target amplification HPV test such as a polymerase chain reaction (PCR)-based assay is used.<sup>4</sup> However, standalone primary screening with HPV is slightly less sensitive than clinician-collected cytology/HPV co-testing.<sup>5</sup> Although the very small differences could become noticeable when applied to millions of women, the overall effectiveness of screening might be improved if self-sampling is incorporated optimally. The details of optimal introduction are critical and not resolved. For example, if a sizable fraction of the 80% of women who do present regularly to their clinicians to receive cervical cancer screening via pelvic examination performed self-sampling instead, detection of cervical precancer could conceivably decrease slightly. However, the small decrement could be offset by increased screening participation by women who currently do not screen at all. When considering underserved women, the highest priority target for self-sampling, logistical questions about regulatory approval,

distribution of screening kits, insurance coverage for screening, and follow-up of abnormal results must be developed. In this forum, we address the question of whether self-sampling should be supported as a screening option in the US, examining both the advantages and disadvantages of this approach.

### SIDE 1

#### Human Papillomavirus Self-Sampling Is Needed in the US

**Discussant:** Jose Jeronimo

The incidence and mortality of cervical cancer are relatively low in the US, but the burden of this disease remains higher in some populations such as some racial/ethnic minorities, immigrants, and women with low educational attainment. The coverage of screening may be as low as 67% in immigrants residing in the US for less than 10 years.<sup>6</sup> In the US, and in countries with well-implemented cytology programs, most women diagnosed with invasive cervical cancer have a history of underscreening or no screening at all.<sup>7,8</sup> Barriers for accessing screening include reluctance to have a pelvic evaluation or discomfort using a male health provider.

Cervical cytology (Pap test) was used for many decades for early detection of cervical cancer precursors and cancer, but the Pap test has suboptimal sensitivity, detecting only 50% to 70% of precancerous lesions even in very competent laboratories with proper quality control. Successful implementation for reducing the incidence and mortality of cervical cancer using Pap tests relies on repeated screening at short intervals. The Pap test is also limited by the need for pelvic examination to collect a sample from the uterine cervix, which is difficult for some women. Tests for detecting the presence of oncogenic genotypes of HPV have higher sensitivity than a Pap test, even when the test is processed using vaginal samples self-collected by women.<sup>4</sup>

Primary screening with HPV testing is already recommended for primary cervical cancer screening in the US,<sup>1</sup> and there are multiple publications showing the high acceptability by women for self-collecting vaginal samples. Crosby evaluated the acceptability of self-sampling by African American women from the Mississippi Delta<sup>9</sup>; 78.4% of them preferred self-collection of vaginal samples over Pap smear. Self-sampling in this population becomes even more important considering that there is sometimes a lack of trust in doctors, and infection with oncogenic HPV may be highly prevalent (e.g., 28.7%).<sup>9</sup> Similar high acceptability for self-sampling was found in Latino and Haitian communities<sup>10</sup>; women with no Pap test in the last 3 years were offered HPV self-sampling or Pap test; most of them (67%) selected self-collecting a vaginal sample the same day; 98% of samples were adequate for HPV testing, and only 2% of women required another appointment to complete screening. Interestingly, 22% of women who selected screening with a Pap test never returned for pelvic examination and sample collection.

Women without proper screening, or no screening at all, could be facing other barriers to screening including the following: busy work schedules, geographical limitations to access a health center, lack of resources, or lack of health insurance. Whereas self-sampling in a clinic might increase screening in women seeking

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nongynecologic care for themselves or children, self-sampling could also reach women in their homes. Self-collection of vaginal samples for HPV testing could be performed at the women's homes using the postal service for sending the kit sample collection and retrieving the sample back to the laboratory. Anderson et al<sup>11</sup> mailed collection kits to a group of women with no history of Pap screening in the previous 4 years in North Carolina; 227 women (64%) mailed samples back to the laboratory. Most of them (98%) reported their willingness to repeat the self-collection in the future; the reasons cited by participants included increased convenience (53%), ease of use (32%), and preference for the privacy of their homes (23%). A minority of women (16%) reported being afraid of doing the self-collection incorrectly, something that was also reported in other countries, but which could be managed with proper education and guidance. A more recent report from the same group of researchers mailed sample collection kits to the homes of 429 women without Pap screening in the previous 4 years.<sup>12</sup> Sixty-four percent of women returned a self-collected sample to the laboratory, and 15% of them had a positive HPV result requiring a visit to the health center for a Pap smear, which was completed in most of them (82%).

Self-collection of vaginal samples for HPV testing is a valuable option that should be considered if we want to decrease the burden of cervical cancer in the communities or minority groups where the incidence and mortality are well above the national average—in some cases comparable with rates observed in developing countries.<sup>13,14</sup> This strategy could be also considered eventually for the general population, similar to what already occurs with colon cancer screening where it is a common practice to mail collection kits to patients' home.<sup>15</sup> It is important to acknowledge that the response to home-based stool collection for colon cancer screening varies between populations, and a lower response is observed in some minority groups, highlighting the importance of proper education in those populations.

There are some challenges for the implementation of self-sampling for HPV testing in the US; one of them is to accurately identify and reach women at higher risk because of inadequate screening histories and increase access to testing and follow-up care in populations without insurance or with language or cultural barriers. In addition, because a positive HPV test result could be associated with significant anxiety and shame, culturally acceptable strategies should be developed for addressing positive screening results.

## SIDE 2

### Human Papillomavirus Self-Sampling in the US Will Not Have Its Desired Impact

**Discussants:** Jennifer Young Pierce, MD, MPH, and Jennifer M. Scalici, MD

#### INTRODUCTION

As we have moved forward with HPV testing, studies have increasingly evaluated not only clinician-collected samples but also self-collected samples.<sup>16,17</sup> The data for in-office primary HPV screening are very strong and date back at least 15 years. Human papillomavirus primary screening performed by a clinician is highly sensitive for detection of cervical precancer or cancer.<sup>18</sup> Self-sampling has been suggested as an alternative to clinician-collected sampling because office-based screening creates barriers including forgetting to make an appointment and difficulty getting away from work and childcare responsibilities.<sup>2</sup> Although self-sampling in clinical offices could also increase coverage, self-sampling at home has been touted mainly as an alternative to in-office Pap test for primary screening. Self-sampling unfortunately cannot live up to these high expectations.

### Self-Sampling Will Not Overcome Ideological Barriers to Screening

Unfortunately, despite high rates of screening, the incidence of cervical cancer and more importantly the mortality from cervical cancer have not changed significantly in the last 10 years. Disparities remain, with higher cancer incidence among Hispanic and black women and higher mortality in black women in the US. Whereas lower screening rates in Hispanic women may explain some of these disparities, screening rates among black women are similar to those of white women.<sup>19,20</sup> Healthcare access, defined as available facilities and insurance coverage, is necessary for screening compliance, and the reasons for failing to screen or follow up are more complex.<sup>21</sup> A number of underscreened women have healthcare access but may fail to screen or follow up on abnormal results because of resource barriers, attitudinal issues including fatalism, anticipatory fear, and/or concerns about procedures and bad news. These issues may be compounded in minority or impoverished patients who may feel disrespected by the healthcare system.<sup>22-24</sup> Addressing ideological barriers will be crucial to increase screening and follow-up among at-risk women—and these barriers are unlikely to be addressed by self-sampling.

### Self-Sampling Is Less Sensitive Than Clinician-Collected Sampling

First, not all HPV tests are created equal and the test used is crucial to the success of self-sampling. When self-sampling is used, only DNA amplification tests yield comparable sensitivity to clinician-collected samples for self-sampling. Substantial reductions in sensitivity are found with signal amplification tests.<sup>2,4</sup> RNA-based HPV tests are not currently being considered for HPV self-sampling. Clinicians have been counseled that all FDA-approved HPV tests are to be considered equivalent for HPV/cytology co-testing, but this would not be the case for self-sampling. Thus, if clinicians or programs inappropriately repurpose all approved HPV tests for self-sampling, substantial decrements in precancer detection could occur.

Clinician-collected screening is the standard of care, and self-sampling has not been shown to reach the same sensitivity as clinician-collected sampling.<sup>4</sup> When used appropriately, the negative predictive value of office-based co-testing exceeds 99%, as do PCR-based (target amplification) self-sampling tests. However, even minute decreases in sensitivity that fail to reach statistical significance in clinical trials may become important when applied to millions of women. Although any screening is clearly superior to no screening, for the 80% of US women who currently participate in clinician-based screening, switching to self-sampling would likely represent a small decrease in precancer detection. This could result in a net decrease in the overall sensitivity of population-wide cervical cancer screening programs, especially if women do not return on time for repeat testing and prevalent lesions remain undetected for 5 years or more. A risk-benefit analysis indicated that self-sampling will have net benefit only if unscreened women are recruited and the total screening attendance increases by 6% or more. If these conditions are not met, switching a substantial portion of current screening attendees from clinician-based to self-sampling may have an overall negative health impact.<sup>25</sup>

### Switching From Office-Based Screening to Self-Sampling at Home May Have Unintended Consequences

Currently in the US and in most of the world literature, self-sampling has only been widely studied for women who do not present for routine screening. Currently, more than 80% of women already present for office-based cervical cancer screening. However, many women have expressed that if self-screening is offered

this would be preferable with a busy lifestyle. The greatest concern remains that women currently going to see a provider would switch to self-sampling. Providers performing a pelvic examination may detect cervical cancers that test negative for HPV, pelvic masses, vulvar or anal problems, abnormal bleeding, abnormal discharge, or other indications for further work-up that might diagnose cancer. Furthermore, a visit to the doctor's office is much more than a pelvic examination. Women usually undergo a clinical breast examination and, if indicated, are referred for mammograms. Women undergo assessment of weight and smoking status and counseling on weight management and smoking cessation, both of which play a significant role in cancer development. In addition, women may receive other preventive services including vaccination, blood pressure monitoring, birth control counseling, and screening for hypercholesterolemia, diabetes, depression, and domestic violence, all of which contribute to women's overall well-being and health.

### CONCLUSIONS

Self-sampling has been offered as a means to improve participation in cervical cancer screening and ultimately to offer the hope of a reduction in incidence and mortality related to the disease, especially if targeted toward underscreened women. However, given that self-sampling does not address ideological barriers to screening, may be slightly less sensitive than clinician-based testing, and could result in the erosion of primary care, the promise may be overstated. Negative effects could outweigh benefits if the net result is switching from clinician-based to self-sampling without substantially increasing the number of unscreened and underscreened women participating in screening.

#### Rebuttal by Dr. Jeronimo

I agree with Dr. Pierce that the performance of HPV testing in self-collected samples depends on the HPV test used. However, PCR-based tests have comparable results when a physician- or self-collected samples are used.<sup>4</sup> Dr. Pierce also highlights that cervical cancer rates have not changed in the last several decades. This is an undeniable fact, and it will continue unchanged if we continue implementing the same strategies that have to date failed to reach high-risk women. However, we have the possibility of reaching the highest-risk women if we make self-sampling a priority for screening populations that are not accessing clinician-based screening for cervical cancer. A recent publication by Endeshaw et al<sup>26</sup> found that foreign-born women have limited access to screening—between 10 and 28% of those women had never received a Pap smear. Dr. Pierce very accurately mentioned the challenges associated with reaching unscreened women and motivating them to collect and return a self-collected sample. Those challenges are real and need to be addressed with operational studies to evaluate new strategies for improving their response.

#### Rebuttal by Drs. Pierce and Scalici

Self-sampling for cervical cancer screening seems very attractive on the surface. However, the limitations to its success may outnumber the potential benefits, unless programs are very carefully designed. First, although the sensitivity of PCR-based amplification tests seem similar for self-sampling and clinician-collected samples in a research trial setting, small decrements in sensitivity may become apparent when applied in the clinical setting to millions of women. Furthermore, logistical barriers remain around payment and distribution of self-screening. If paid by insurance companies, how will this help reach most unscreened women who are uninsured or underinsured? These questions would all need to be answered before engaging in self-sampling on a population scale. As mentioned previously, the greatest concern remains

the drift of women currently presenting for screening to a self-sampling approach. We lose the opportunity to care for these women in multiple ways related to their wellness such as weight management, smoking cessation, and screening for other diseases. The cost to society and questions surrounding self-sampling suggest that this is not yet ready for widespread use.

### Summary

Rebecca B. Perkins, MD, MSc

Should HPV self-sampling be an option for women in the US? Dr. Jeronimo states that HPV self-sampling should be an option. Self-collected HPV specimens are substantially more accurate than cytology and may be a means to improve prevention in underscreened women, who remain those at the highest risk for cervical cancer. He describes unique barriers faced by underserved and foreign-born women, which may make self-sampling especially useful for these populations. One study comparing HPV self-sampling to free, clinic-based cytology screening among underscreened women in the Mississippi Delta region found that women were both more likely to choose and to complete HPV self-sampling, resulting in a four-fold increase in screening completion (78.4% in the HPV group vs 21.5% in the cytology group).<sup>27</sup> Self-sampling overall has high acceptability among women, because of convenience and privacy.<sup>27</sup> Indeed, 85% of medically underserved women attending emergency department visits in Texas indicated that they would be willing to self-sample if the test were available—58% were even willing to perform the test in the emergency department bathroom.<sup>28</sup> Thus, self-sampling may increase access to cervical cancer screening for marginalized women who are at the highest risk for cervical cancer.

However, Drs. Pierce and Scalici argue that many logistical issues remain to implementing self-sampling in high-risk women, including outreach and insurance coverage, both for the screening itself and follow-up of abnormal results. They further posit that shifting to self-sampling for the entire population could erode the current standard of protection provided by clinician-collected samples. A meta-analysis of clinician-collected HPV tests compared with patient-collected HPV tests found that PCR-based amplification tests were not inferior to clinician-collected samples, but concerns remain that small decreases in sensitivity may be noted when self-sampling is widely applied outside of the research setting.<sup>4</sup> They also note that clinician visits provide many essential preventive services in addition to cervical cancer screening. They raise concerns that self-sampling at home could decrease the number of women presenting for primary care, which could have net negative health consequences.

So what role should self-sampling have in cervical cancer prevention programs of the future? For women who currently participate in clinician-based screening programs, self-sampling is unlikely to provide a cancer prevention advantage. However, self-sampling should have a role in comprehensive, population-based cancer prevention programs given widespread agreement that (a) most cancers occur in underscreened women; (b) HPV self-sampling is superior to cytology, which is an accepted screening method; and (c) any screening is better than no screening. Because most cancers continue to occur in underscreened women, any increase in the number of women screened achievable by self-sampling should have an immediate positive impact. The 3 categories of women most likely to benefit from a self-sampling screening option include women in medically underserved areas who have not been reached by traditional screening programs, women who have access to clinician-based screening but poorly tolerate pelvic examinations, and women whose primary care providers do not perform pelvic examinations.

Women who are medically underserved face a host of challenges to obtaining preventive care, which are not limited to difficulties accessing cervical cancer screening. The logistics of identifying underscreened women, providing self-sampling, and ensuring adequate insurance coverage for both screening and follow-up of HPV-positive results are challenges for putting such programs in place, but these are addressable through programs such as the National Breast and Cervical Cancer Early Detection Program. In addition, attention must be paid to overcoming ideological barriers that prevent women from participating in screening regardless of access. Patient navigators and other culturally relevant programs hold promise in this area.<sup>21,29</sup>

Among women with adequate medical care, but poor compliance with screening, there may be a role for self-collected samples within primary care visits. Although most women tolerate pelvic examinations,<sup>30,31</sup> self-collection in the office setting may be preferable for women with a history of sexual trauma or pelvic pain,<sup>32</sup> for whom pelvic examinations are physically and emotionally difficult. Conversely, a nearly a quarter of family medicine and nearly half of internal medicine physicians do not perform pelvic examinations, which limits screening access among their patients.<sup>3</sup> The ability to perform self-sampling in an office setting could obviate the need for these women to seek specialty care for cervical cancer screening. Despite a preponderance of evidence on its effectiveness, self-sampling is only currently available in the context of research studies. Upcoming screening guidelines should consider addressing the use of self-collected HPV samples for at-risk women.

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