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Cervical Screening by Pap Test and Visual Inspection Enabling Same-Day Biopsy in Low-Resource, High-Risk Communities

The recently published study Tao et al[1] in the December 2018 issue has serious statistical issues, and the proposed implementation is not feasible. The authors did not biopsy test-negative patients; this would be reasonable if there were few cases of cervical intraepithelial neoplasia (CIN) 2 or worse within this group. Unfortunately, the combination of negative screening tests in this study (cervical cytology and visual inspection) does not exclude CIN 2 or worse. The authors' failure to detect CIN 2 or worse within test-negative patients results in inaccurate and misleading test sensitivity calculations for CIN 2 or worse.

Pathology has a history of being undervalued in China. After the cultural revolution, it was viewed as a technical specialty, and even today the great workloads are discouraging for young students as they choose their future specialties. Today, pathology residencies are quite young and many are still working to adapt to standard curricula. It is estimated that 470 million women need cervical cancer screening in China. Currently there are fewer than 20,000 pathologists (less than half from structured programs), with 5–8% who do varying amounts of cytology. To suggest that any screening program that includes primary cytology screening is applicable to low-resource settings is misguided.[2]

We now have high-risk human papillomavirus assays with the throughput of thousands per day at a cost of $5.00–6.00 or less (U.S. dollars). These assays are highly sensitive, with both direct and self-collection using a variety of collection and transport methods. Some of these technologies are currently reaching women by the thousands per week in China, with entire villages being routinely screened in a day. In addition, these assays provide results that can effectively triage for management protocols.

We applaud the authors for doing a study aimed at defining how to screen the medically underserved. Having worked in multiple provinces in rural China for more than 20 years, we appreciate the commitment required. Applying study results to achieve population solutions requires a careful assessment of both human and financial resources.

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Cervical Screening by Pap Test and Visual Inspection Enabling Same-Day Biopsy in Low-Resource, High-Risk Communities

I read with great interest Tao and colleagues'[1] article in the December 2018 issue. The development of rapid, low-cost cervical cancer screening is clearly important, as only 20.7% of Chinese women have ever been screened.[2] I am concerned, however, that, in an attempt to show the cost-effectiveness of their proposed screening strategy, the cost of human papillomavirus (HPV) virus testing was incorrectly inflated. Specifically, the authors state that the cost of HPV virus testing is $60.00 (U.S. dollars). This statement is misleading because of the availability in China of the *care*HPV system, which is a simple, fast, low-cost, portable, and robust method of HPV testing that was created based on the gold-standard Hybrid Capture 2 System.[3] The *care*HPV system was developed with a grant from the PATH foundation and is designed to work in low-resource settings such as those described in the authors' article. The *care*HPV system tests 90 specimens in 2.5 hours, and the cost per specimen is only $6.00. As such, both the cost and rapidity of HPV virus testing is equivalent to the screening strategy proposed in their study.

In general, the World Health Organization has recommended that cervical cancer screening programs in low-resource countries move away from cytology-based testing and move toward HPV-based screening.[4] Specifically, the time delay of obtaining and then reading Pap tests prevents same-day screen-and-treat strategies. In addition, there is a deficiency of well-trained cytopathologists in resource-poor countries, including China.[5] Although the authors are to be applauded for the rapid interpretation of Pap tests in their study, the main limitation of their strategy is that it requires the presence of a certified senior cytopathologist to interpret the Pap tests in real time. Unfortunately, there are not enough cytopathologists worldwide to implement this strategy for accurate screening of approximately 2 billion women in low-resource countries. In contrast, HPV-based screening has no such limitations. Furthermore, women can self-swab to obtain specimens, thereby greatly increasing the number of women screened.[6]

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In Reply:

Based on extensive reviews of published literature in 2018, the U.S. Preventive Services Task Force on Screening for Cervical Cancer recommends that women aged 21–29 years be screened every 3 years with cytology alone, and women aged 30–65 years should be screened every 3 years with cytology alone or every 5 years with cytology and human papillomavirus (HPV) testing (cotesting).[1] Clearly, cytology is at center stage in screening for cervical cancer and precancers.

The single-visit cervical screening strategy[2] adheres to these recommendations by the U.S. Preventive Services Task Force[1] and highlights two critical points: first, cytology (Pap test) is incorporated in the strategy, and, second, this strategy enables same-day biopsy (screen-and-diagnosis)[2] for histologic diagnosis, which is a gold-standard for adequate management of cervical cancer and precancers. In China, and certainly in the United States and Europe, medical procedures not following appropriate guidelines will result in medical–legal issues, which has been a big challenge for Chinese medical professionals in the past decades.

The letters by Belinson et al and Goldstein raise the cost issue of HPV testing in developing countries. We have learned the following facts:

1) The Chinese local government–negotiated bulk purchase price of $6.00 per test (U.S. dollars) for *care*HPV is for organized screenings and not applicable to individual health care facilities.
2) The *care*HPV test requires an initial investment of at least RMB¥200,000 (U.S. $29,200) for the *care*HPV test equipment.[3]
3) *care*HPV kits have to be sent to a central laboratory, and each run takes 2.5 hours for 48 or 96 specimens, suggesting a turnaround time of several days.
4) A self–HPV test kit costs about U.S. $58.00 in China and requires a central laboratory for processing.

Apparently, $6.00 per *care*HPV test in item 1 above is dependent on item 2, which is simply not affordable at most, if not all, primary health care facilities in developing countries. On the other hand, in health care facilities without cytologists or pathologists, we have proposed to use courier services to transport either or both Pap slides and biopsies to a pathology laboratory for histologic diagnoses, whose importance is to reduce loss to follow-up if Pap test and biopsy can be performed on the same day.[2] In summary, available HPV tests have no advantage over the "screen-and-diagnosis" single-visit screening strategy[2] in terms of the cost, effectiveness, and the U.S. Preventive Services Task Force recommendations[1] in low-resource settings.

Belinson et al also raise the statistical concern regarding biopsying women with negative results. We stated in the article that, owing to local customs and ethical issues, we were unable to biopsy women with negative screening results; however, we corrected sensitivity and specificity to reflect objective results (Table 2 in the article),[2] which was also encountered by others in an HPV testing study.[4] Furthermore, our single-visit screen-and-diagnosis strategy indeed had superior detection rates of cervical cancer and precancers compared with eight other screening programs carried out in low-resource settings in China, all having a historically high prevalence of cervical cancer (Appendix 4 in the article, http://links.lww.com/AOG/B193).[2]

Training of cytologists and pathologists is a challenge for all low- and middle-income countries. However, the shortage of these professionals should not be an excuse to give up on reasonable guidelines in cervical screening. In recent years, owing to employment pressures in all medical specialties, we are happy to see more medical graduates entering pathology residency training. Furthermore, many pathology departments, including ours, are establishing telepathology services, which will help reduce the pressure in demand for pathology services in primary and some secondary health care facilities in China. Nevertheless, overcoming the shortage of pathology professionals is a national policy for all low- and middle-income countries.

More than 2,000 years ago, Confucius, the distinguished Chinese philosopher and educator, told us that if you don't want to do something yourself, don't ask someone else to do it. In terms of following appropriate medical guidelines, medical ethics should have an equal standard among developed and developing countries whenever possible. We would like to emphasize again that no single screening strategy is globally suitable for all low-resource settings.[2] Therefore, choosing an affordable yet effective strategy to control cervical cancer is largely dependent on individual settings.

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