Will COVID-19 Be the Tipping Point for Primary HPV Self-sampling?

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ABSTRACT

Self-sampling is poised to be a disruptor for cervical screening. So far, cancer screening has been a causality of COVID-19; however, the opposite may transpire for self-sampling. Self-sampling enables socially distanced cervical screening with an outreach that extends to underserved populations. As evidence mounts that self-sampling is noninferior to clinician-taken samples, the focus for self-sampling is now as a primary screening option for all women. Now, we have evidence from a modeling study (using Australia as an exemplar) to suggest that program effectiveness with primary self-sampling would be better than the current program, even if sensitivity is lower. Regulatory issues, suitable triage strategies, and clear communication about self-sampling are hurdles yet to be overcome. Nevertheless, existing evidence coupled with COVID-19 could be the tipping point for wider introduction of self-sampling.

See related article by Smith et al., p. 268

Self-sampling is poised to be a disruptor for cervical screening (1). Its appeal is obvious—women can collect a simple vaginal sample at home, forgoing the intimate (and often dreaded) speculum examination. This makes self-sampling less invasive and substantially more convenient than conventional screening. The implementation of wider scale use of self-sampling could not come at a better time. The self-sampling approach chimes with two of the biggest global, social challenges we face today: COVID-19 (the need to social distance) and the empowerment of women.

Those familiar with cervical screening will be aware that it is no stranger to change. Technological advances including the advent of vaccination and testing for human papillomavirus (HPV) have drastically improved our ability to detect and treat cervical disease (2). Paradoxically, these advances have occurred on a backdrop of falling screening attendance. This downward trend has been impervious to interventions other than self-sampling (∼10% increase in participation; ref. 3).

The initial focus for self-sampling was on underscreened women due to purported inferior test accuracy (4). Two key pieces of evidence emerged in 2018 to change this. First, an updated meta-analysis (5) found that HPV testing on self-samples in the nonattendee population is similarly accurate to clinician-taken samples when using polymerase chain reaction–based assays (pooled relative sensitivity for $CIN2^{+}$ 0.99; 95% confidence interval: 0.97–1.02). A second step forward came from a noninferiority trial (6) carried out in a routine screening population that also reported similar accuracy of self-collected versus clinician-taken samples for detecting high-grade disease. Consequently, the focus for self-sampling is now as a primary screening option for all women.

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Although further studies will be needed to confirm noninferior clinical accuracy of self-sampling in a routine screening population (in particular, data on the long-term negative predictive value), the Dutch screening program is already planning a move toward primary self-sampling (7). As more countries begin to contemplate the same, an important question will be whether a potential loss of sensitivity is an acceptable and worthwhile trade-off for improved coverage. Smith and colleagues (1) have provided the first evidence to help answer this question. Their study modeled the impact of offering self-sampling to all women on cervical cancer incidence and mortality within the Australian screening program. They found that even using pessimistic assumptions about self-sampling sensitivity and uptake, and with 100% switching to self-sampling, program effectiveness under primary self-sampling was better than the current program. These findings will help provide the confidence and assurances policy makers need to move toward what is set to be the next frontier for cervical screening.

Several outstanding issues with self-sampling still need to be resolved. Regulatory issues have been, and remain, a major hurdle for self-sampling implementation. The pace of innovation and emerging evidence is at odds with the pace of the required regulatory approvals. None of the available HPV assays have a claim for a self-sampling device and assay combination, and none are on-label for self-sampling. This leaves laboratories in the uncomfortable position of having to navigate regulatory requirements, take on the manufacturer's liability, and potentially undertake extensive validation studies (8). Regulatory issues have substantially held up England's first foray into integrating self-sampling into the national cervical screening program. YouScreen (9) is a large implementation feasibility clinical trial of offering self-sampling to nonattenders that has taken over 2 years to set up. These delays are a reflection of the limited ability of regulatory authorities and governing bodies to flex and support innovation at pace amid the regulatory constraints. In addition, the fact that women who screen positive on a self-sample require triage with a clinician sample remains an important drawback. As such, the true potential of self-sampling will only be realized with a fully molecular solution, and loss to follow-up in these women should be closely monitored with scale-up. The lack of automation of laboratory processes is a further constraint, but fortunately this is surmountable and a resolution is already in process (10).

The introduction of primary self-sampling will require a paradigm shift in cervical screening. The idea that cervical screening needs to be

performed by a trained professional is deeply ingrained in both women and health care providers. Clear communication about self-sampling will be fundamental to success. This is evidenced in both research and real-world settings. Women's concern about test accuracy and taking the sample correctly is a consistent finding in studies for both nonattendee and attendee populations (5, 11). Yet, women report higher confidence in the accuracy of urine self-samples that, in reality, have inferior test performance compared with vaginal self-samples (12). This highlights the need to shift perceptions for cervical screening in the context of self-sampling. It is imperative that both women and health care providers receive communication that provides reassurance and confidence in test accuracy that is commensurate with the evidence. Although self-sampling has been offered to underscreened women in The Netherlands since 2017, currently only 8% (13) of women screened are by self-sample. However, a survey of Dutch women found that only 37% knew that self-sampling was an available option (S. van Dijk-de Bruin; personal communication). This indicates that clear communication about the availability of a self-sampling offer will also be essential.

Providing a choice of screening tests will also be important. Despite self-sampling's high acceptability and wide appeal (14), it is clear that some women prefer clinician sampling (11, 12). Fortunately, HPV testing lends itself to innovation that could accommodate this, such as clinician-collected vaginal samples without a speculum (nonspeculum sampling; ref. 15). Such flexibility is an advantage and signals that cervical screening will continue to evolve over the coming years. Further improvements to self-sampling are already in the pipeline that will broaden appeal and outreach. Among these are urine self-sampling (16), which could benefit populations in whom vaginal sampling is unacceptable (e.g., victims of sexual abuse, victims of female genital mutilation, or transgender men; ref. 17), and the possibility of a fully digital results reporting system (18).

Going forward, there will be much to learn with the wider implementation of self-sampling (e.g., what the optimal pathway will be and its resource implications). There may be unintended consequences related to de-skilling of clinicians in primary care as pelvic examination becomes rare. Potentially, some women may consistently take poor samples. Therefore, it may be important to either alternate the option of self-sampling or consider having at least one mandatory clinician-taken sample. Further lessons will arise with the efficacy of self-sampling in vaccinated cohorts who may require only one to two screens in their lifetime (19). Indeed, Smith and colleagues' modeling study found that program effectiveness was slightly lower for population-wide self-sampling in vaccinated cohorts when uptake in non-attenders was low. Self-sampling is also likely to play an important role in the World Health Organization's global strategy toward cervical cancer elimination (20). The reduced infrastructure required to operationalize self-sampling—the fact that self-samples can be posted and withstand a range of temperatures—makes self-sampling a favorable solution for developing countries.

COVID-19 has caused major disruptions to cancer screening services (21). The downstream impact on cervical cancer incidence and mortality is as yet unknown but a cause for concern. Self-sampling offers a socially distanced approach to cervical screening that is safer for both women and health care workers and will substantially free up clinic appointments. As we continue to navigate "lockdowns" and reduced capacity in health care services, self-sampling will increasingly be looked to as a solution to help ensure women are screened. A further advantage of self-sampling in the COVID-19 era is its ability to reach underserved populations (22), a welcome counterbalance to the widening inequities in access to healthcare. One of the lessons that has emerged from the current pandemic is the need for adaptability. With this in mind, perhaps COVID-19 will be the black swan that finally brings the tipping point for wider introduction of self-sampling.

Author's Disclosures

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