

Cervical Cancer Screening Postpandemic: Self-Sampling Opportunities to Accelerate the Elimination of Cervical Cancer

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Abstract: The persisting burden of cervical cancer in underserved populations and low-resource regions worldwide, worsened by the onset of the COVID-19 pandemic, requires proactive strategies and expanded screening options to maintain and improve screening coverage and its effects on incidence and mortality from cervical cancer. Self-sampling as a screening strategy has unique advantages from both a public health and individual patient perspective. Some of the barriers to screening can be mitigated by self-sampling, and resources can be better allocated to patients at the highest risk of developing cervical cancer. This review summarizes the implementation options for self-sampling and associated challenges, evidence in support of self-sampling, the available devices, and opportunities for expansion beyond human papillomavirus testing.

Keywords: self-sampling, self-collection, HPV testing, cervical cancer screening, COVID-19

Introduction

Cervical cancer is the fourth–most common cancer in women worldwide, primarily affecting middle-aged women, particularly in low- and middle-income countries (LMICs).¹ Despite the success of screening programs aimed at detection of precancerous and early cancerous lesions,^{2,3} limited access to and insufficient uptake of screening remain persistent barriers to cervical cancer elimination.⁴ Women who are not screened regularly or have never been screened have higher cervical cancer incidence and are diagnosed with more advanced disease with poor prognosis.^{5–7} When precancerous cervical lesions are detected early, there is nearly 100% 5-year survival, but if caught at an advanced stage, 5-year survival drops to 17%.^{4,8} Early detection and treatment of cervical neoplasia is critical, and various options for screening and prevention exist.

Since human papillomavirus (HPV) infection is known to be the primary cause of cervical cancer, high-risk HPV (hrHPV) testing is frequently recommended in guidelines for early detection of cervical precancer and cancer.^{9–11} Commercially available HPV-testing platforms have been developed to detect and report only the hrHPV infections that are clinically relevant (eg, using cervical intraepithelial neoplasia 2 [CIN2] as the outcome of interest).¹² Therefore, existing screening algorithms that incorporate HPV testing are based on these cutoffs for clinical sensitivity and are updated with approval of new testing platforms used for

screening. While analytical accuracy for the detection of individual HPV genotypes is part of the validation of the assays, clinical accuracy is used as the outcome for most of the population-based studies presented herein.

Testing for hrHPV offers several advantages over cervical cytology alone, including higher sensitivity for detecting cervical precancer and the option of detection from self-collected samples with similar clinical accuracy as clinician-collected samples.^{9,10,13} Also, self-sampling does not require women to undergo a pelvic exam and can be performed without the presence of a trained clinician, which addresses common barriers to attendance in screening, including convenience and concerns of privacy and modesty. Furthermore, self-sampling is a method to reach never- or underscreened women.^{14,15} Self-sampling offers a unique opportunity for expansion to hard-to-reach populations,^{16,17} and is one of the most feasible strategies for mid- and postpandemic catch-up screening. With these advantages, self-sampling will in the future play an important part in improving the global coverage of cervical cancer screening with highly accurate HPV-testing, which — followed by treatment of detected high-grade cervical lesions — is a prerequisite to the global goal of cervical cancer elimination, together with HPV vaccination.¹⁸

In this review, we provide a summary of the implementation options for self-sampling, evidence in support of self-sampling, and the available devices. We also review existing evidence on cytological examination of self-collected samples and emerging molecular testing, and outline opportunities for product development.

Profound Impact of the COVID-19 Pandemic on Cervical Cancer Screening

The COVID-19 pandemic has had an enormous impact on cervical cancer screening. More than half of the 155 ministries of health surveyed by the World Health Organization (WHO) postponed public screening programs in the spring of 2020 and reported disrupted cancer-treatment services.¹⁹ Among the most common reasons for reduced screening services, countries reported cancellation of planned visits, decreased public transportation availability, lack of staff, and shortages of medicines, diagnostics, and technologies.¹⁹ In a recent report, 63% of the 57 surveyed HPV reference and screening laboratories in both high- and low- to middle-income countries

reported temporary suspensions of routine cervical cancer screening due to COVID-19.¹⁷

The magnitude of these disruptions in cervical cancer screenings during lockdowns in the spring of 2020 are emerging from countries with opportunistic and organized screening.^{20–22} In June 2020, cervical cancer screenings in the US were 35% lower than their pre-COVID-19 levels. Between March 15 and June 16, a deficit of 67% in cervical cancer screenings was noted relative to the number of screenings that would be expected based on the historical average.²⁰ The suspension of inessential clinical services, including suspension of population-level screening programs, has impacted reports of cancer diagnoses worldwide,^{21,23–29} resulting in a decrease in overall cancer diagnoses compared to prepandemic data. In Slovenia, a European country with low cervical cancer burden as a result of a highly successful cervical cancer-screening program, a 2-month screening lockdown resulted in a 92% decrease in screenings and a 32% decrease in the diagnosis of high-grade lesions (CIN2⁺).²¹ This decrease in high-grade diagnoses persisted through the 5-month screening scaling-up phase, and was most notable in women aged 30–39 years (19%), outlining a new vulnerable group within the program.²¹ The number of cancer screenings has since begun to rise, but has not yet reached previously expected levels. Failure to detect and treat precancerous lesions in settings in which cervical cancer had been successfully controlled by screening may have at least a temporary impact on progress toward decreasing the cervical cancer burden worldwide.

Barriers to screening disproportionately impact socioeconomically disadvantaged and minority women worldwide.^{4,30,31} As a result, racial, sexual, and ethnic minorities and socioeconomically disadvantaged groups have higher incidence and rates of cancer-related deaths and lower rates of participation in guideline-based screening and treatment.^{32,33} Age, psychosocial issues, marital status, major life events, and competing interests (such as education, work, and childbirth) are important determinants of attendance at cervical cancer screening, and the COVID-19 pandemic may have exacerbated the effect of these determinants on screening coverage.^{34,35} After incorporation of updated screening recommendations, including hrHPV testing in 2012, an expected decrease in screening frequency among American women aged 30–65 years was observed, but an even more concerning drop in screening among women 21–29 years old.³⁶ Australia reported that participants aged >60 years had had fewer HPV tests

during COVID-19, and there was no bounce-back effect observed in this population even after the easing of pandemic-related restrictions.²²

There are also unexpected opportunities for expansion of cervical cancer screening as a result of the COVID-19 pandemic. The pandemic has expanded diagnostic molecular testing technologies and infrastructure, supply chains, and overall molecular diagnostics activity at an unprecedented pace. As part of a survey conducted by Poljak et al, five companies currently offering clinically validated HPV and SARS-CoV2 tests (Roche Diagnostics, Indianapolis, IN, USA; Abbott Laboratories, Chicago, IL, USA; Cepheid, Sunnyvale, CA, USA; Becton Dickinson, Franklin Lakes, NJ, USA; and Hologic, Marlborough, MA, USA) released a statement about their operations during the pandemic and their current and postpandemic strategies for HPV tests.¹⁷ All companies noted increases in manufacturing capacity and investment in new supply chains, molecular and core laboratory solutions, and the associated expansion for molecular diagnostics, including the use of platforms acquired for COVID-19 testing to support HPV testing in the future. The availability of both the infrastructure and highly trained personnel currently working on COVID-testing could be allocated toward increased HPV molecular testing capacity. In addition, low-cost portable testing technologies^{37–39} that have been refurbished to address large-scale testing requirements of the pandemic could be repurposed to provide affordable screening assays for HPV testing, especially in low-resource settings.

Self-Sampling Implementation and Dissemination Strategies

Improving Coverage in Organized and Opportunistic Screening

Well organized, population-based cervical cancer-screening programs have substantially decreased the incidence of and mortality from cervical cancer.^{2,3,14,15} The success of these programs is dependent on sufficient attendance for high-quality screening, as well as robust diagnostic, follow-up, and treatment services. In organized population-based programs with high screening coverage, half or more of new cases are detected in nonattenders, and these cancers are more often diagnosed in advanced stages.^{40–42}

Worldwide, self-sampling for HPV testing has been proposed as a strategy to reach nonattenders of organized screening programs.^{10,43} A meta-analysis of reported effect sizes from 29 randomized clinical trials found that women were twice as likely to use cervical cancer-screening services through self-sampling than standard-of-care screening practices (response ratio [RR] 2.13).⁴⁴ In their response to the WHO's 2020 call for cervical cancer elimination as a public health problem, a European task force considered incorporating self-sampling into organized screening programs to support the achievement of the WHO goal in Europe.¹⁸

In countries with opportunistic screening, such as Canada and the US, there are suboptimal participation rates in clinic-based screening^{31,49,50} and thus increasing interest in improving participation through self-sampling options. A recent study found that 72.7% of US women reported high willingness to use an HPV self-sample kit at home⁵¹ which is consistent with other studies from the US.^{52–58} In the first randomized controlled trial evaluating the feasibility of mailing HPV self-sampling kits to underscreened US women, more than half the women chose to return a self-collected sample, rather than schedule an in-office screening.⁵⁹ Canadian women living in rural Ontario who were overdue for cervical cancer screening were 3.7 times as likely to undergo screening with a self-sampling kit as those who received the standard-of-care opportunistic screening.⁶⁰ While HPV self-collection is not currently an FDA-approved cervical cancer screening strategy in the US or Canada, increasing evidence in support of self-collection and the effect of the pandemic on screening coverage might prompt future consideration.

In countries with organized screening programs in high-resource settings, research has focused on two approaches to offering self-collection depending on whether the self-collection device is readily available: “opt in” and “opt out.” In both approaches, women collect a self-sample outside the clinic using a variety of sampling-kit types.

In the opt-out or mail-to-all approach, self-collection devices are mailed to women's homes without them taking the initiative. Recent systematic reviews and meta-analyses have shown that this approach can significantly increase attendance and detection of high-grade cervical lesions compared to invitation or reminder letters.^{9,10,45} The most recent meta-analysis of randomized control trials showed a doubling of the likelihood of attending screening compared with controls (RR 2.27).⁴⁴

An alternative invitation scenario is the opt-in approach, in which women request a self-collection kit via email, text message, phone, website, or mail. The kit is mailed to their desired address or they pick it up at a pharmacy or clinic. This approach is more economical, especially considering the costs of implementation on a national level.^{9,10,46} However, studies evaluating this approach have shown variable response rates.^{9,46} Response rates in early randomized opt-in studies were comparable to control groups (RR 0.97, 1.22, and 1.28) in published meta-analyses,^{9,10,44} and much lower in opt-out groups (RR 1.22 vs 2.33).⁹ Recent randomized studies have shown the opt-in approach can generate a high response when compared to mailing a reminder letter (RR 1.8),⁴⁶ although lower than response rates to the opt-out approach (RR 2).^{46–48}

Door-to-door or community outreach is an approach to self-sampling that has primarily been investigated in low-resource settings or for reaching underscreened populations in high-resource settings. In this approach, an educated health worker, such as a nurse or a community health worker visits participants' homes to educate participants on cervical cancer and screening, offer a self-sampling HPV test kit to the participant, and collect the kit for lab testing. Meta-analysis of five randomized clinical trials using this approach showed that women were almost three times as likely to participate in cervical cancer screening (RR 2.37).⁴⁴ A prospective cohort study on community outreach in the rural Mississippi Delta in the US found that 80% of underscreened women responded to an offer of the HPV self-sampling kit and cervical cancer education compared to 40.5% who responded to a voucher for a free Pap test at the local clinic.⁶¹ Increasing social inequality related to the pandemic, such as loss of financial stability and health insurance, lack of transportation, and lack of childcare, is likely to primarily affect already underserved populations, and approaches such as this could be considered to reach these populations.

The key challenge in implementing self-sampling in any setting is ensuring follow-up and treatment for women with positive tests⁶² and assuring adequate training for and supervision of these services.⁶³ In low-resource settings, attendance at follow-up care is 14%–95%,⁶⁴ and in high-resource settings 41%–100%^{47,65–67} after an HPV-positive self-sampling result.

The most recent meta-analysis of 20 reports of attendance at follow-up care among women with hrHPV-

positive self-samples found that 80.5% had a follow-up examination. This was influenced by triage policy: studies with direct referral had higher attendance at follow-up care than studies with a triage policy.⁹ In low-resource settings, follow-up rates are improved by engaging community health workers,^{68,69} ensuring rapid (same day) availability of test results,⁷⁰ and offering community mobile treatment.⁷¹ In high-resource settings, follow-up in self-sampling is relatively high, but can still be improved through prescheduled appointments, personal contacts via telephone with women who did not attend, prescheduled reminders,⁴⁶ reminder letters to HPV-positive women, and direct contact with a physician to explain the test results and their consequences.⁷²

Improving Access to Cervical Cancer Screening in Resource-Limited Regions

Resource-limited regions have the highest burden of cervical cancer incidence and mortality worldwide: 90% of deaths caused by cervical cancer are recorded in LMICs.⁷³ This disparity can be attributed to a lack of organized screening programs and limited access to resources, health-care facilities, and providers.^{74,75} For example, in Uganda and Zimbabwe, only 5%–10% of women in rural areas have been screened for cervical cancer.^{69,76,77}

In resource-limited regions, the infrastructure to conduct organized screening with a Pap test is often not available, so visual inspection with acetic acid (VIAC; with/without cervicography) is used as an alternative cost-effective screening strategy.⁷⁸ VIAC involves trained nurses that examine the cervix via a speculum examination after application of acetic acid (vinegar) to identify potentially precancerous lesions. A screen-and-treat approach incorporating non-cytology-based screening with HPV testing or VIAC followed by immediate treatment using cryotherapy or thermal ablation has also been implemented in many settings successfully. This approach avoids the need for the complex health-care infrastructure required for a robust cytology-based and callback system.

Program evaluations have found that overtreatment rates with VIAC can be high and result in many women undergoing unnecessary treatments. Overtreatment can lead to future pregnancy complications in women of reproductive age.⁷⁹ Furthermore, access to VIAC in rural areas is limited, since there are few screening facilities that offer cancer screening and overburdened health-care workers may not be available for screening.^{62,80,81}

An alternative method for improving access to cervical cancer screening is through self-collected HPV testing. Self-sampling offers a unique opportunity to bring robust and high-sensitivity cervical cancer screening to resource-limited rural communities with limited transportation options, where women usually must travel to distant health facilities. Furthermore, self-sampling can encourage screening participation by respecting women's privacy, removing the need for a pelvic exam and avoiding feelings of shame and fear related to exposure of private parts, especially in the presence of a male health-care worker, thus removing the need for spousal permission and fear of social marginalization.^{82,83} In addition, the screening interval following a negative result can be extended and screening initiated at an older age, reducing the lifetime screening visits required.⁸⁴ There is increasing evidence that self-collected HPV testing is more cost-efficient than other screening strategies in developing countries.^{84,85}

Randomized trials in Africa and Latin America have used community campaigns or engaged community health workers to deliver self-sampling kits directly to women's homes or workplaces (door to door), and have shown improved response rates when compared to reminder or invitation letters (RR 2.58 for community campaigns and 2.01 for door to door).⁹ Community-based self-sampling in Ghana and Kenya has shown higher participation rates than hospital-based self-sampling.^{86,87} Community-based screening using HPV testing on self-samples in rural Zimbabwe led by community health workers showed profound increases in participation in cervical cancer screening, with an overall response rate of 82% compared to a baseline screening rate of 5%.^{69,88,89} This approach offers the possibility of reaching women living in remote locations with long travel times to health-care centers.

Self-sampling has generally been well accepted among African women,^{64,83} and has shown comparable sensitivity and specificity to detect clinically relevant infections when compared to clinician-collected samples.⁶⁴ Pooled analysis of 38 studies in LMICs showed most participants found self-sampling easy to perform (75%–97%, 18 studies), painless (60%–90%, nine studies), and preferred to provider-collected sampling (57%–100%, 14 studies).⁶⁴ However, some studies in LMICs found women feared hurting themselves⁹⁰ and expressed the need for assistance with self-sampling.^{90,91}

Although introducing self-sampling in low-resource regions is important to increase the early detection and treatment of precancerous cervical lesions and meet

screening targets, there are potential challenges that need to be addressed for optimal outcomes. The first is education and support to increase women's confidence in performing self-sampling correctly. The success of self-sampling is most impactful when women accept and prefer the method. Secondly, organized screening in high-income settings is made possible by efficient postal services and immediate communication through mobile phones, which may not be feasible in low-resource settings, due to inconsistent power supply and potential lack of privacy if their partners are the primary users of a shared mobile phone. Community-based approaches using and expanding on existing infrastructure and emphasizing education and linkage to follow-up care are critical when considering integration of self-sampling as a component of a cervical cancer-screening strategy in low-resource settings.

Diagnostic Accuracy: Latest Evidence

Self-sampling shows good agreement for detection of hrHPV, with analytical sensitivity for detection of hrHPV of 91.4%–96.8% in studies comparing self-samples with clinical collected samples.¹³ However, as outlined by Meijer et al, hrHPV-test requirements for primary cervical cancer screening should be based on clinical accuracy criteria (detection of clinically relevant infections), rather than analytical accuracy criteria (detection of hrHPV infection). The key issue for hrHPV testing in primary cervical cancer screening is to detect clinically relevant infections that are associated with or develop into CIN2 or higher and differentiate them from transient HPV infections to avoid redundant or excessive follow-up.^{12,92}

Before widespread adoption of PCR-based technology, signal-based amplification assays for the detection of hrHPV were the primary testing platform used for screening. Signal-based amplification detection of hrHPV shows lower clinical sensitivity using self-samples than clinician-collected cervical samples for detection of CIN2⁺.¹³ However, with modern hrHPV assays based on PCR technology, self-samples have clinical sensitivity comparable to clinician-collected samples (96%) for detection of CIN2⁺.⁹

The improved diagnostic accuracy of self-sampling using PCR-based HPV-testing assays has led to some countries, such as Australia, the Netherlands, and Denmark,^{93,94} to institute a self-collection option as part of their organized national screening programs to reach under- or never-

screened women and those who decline a clinician-collected sample. Other European countries with organized screening programs have been investigating the feasibility and cost-effectiveness of implementing a self-collection option following the recommendations outlined in the European guidelines for quality assurance in cervical cancer screening.^{46,48,95–97}

Emerging data support exploring the potential of self-sampling for primary cervical cancer screening,⁹⁸ and suggest that benefits of increased participation outweigh the worst case possible of 2% relative loss of sensitivity when testing on self-collected samples.⁹⁹

Types of Devices for HPV Self-Sampling

Studies of self-sampling in both rural and urban settings have employed a wide variety of devices: cervicovaginal brushes,^{46,72,100–102} vaginal swabs,^{46,61,103,104} tampon-like devices,¹⁰⁵ and lavage devices.^{46,102,106–108} All types of devices are based on collecting exfoliated cells of the cervicovaginal canal for subsequent HPV DNA detection. A comprehensive description of widely investigated self-sampling devices is presented in [Figure 1](#).

The first studies of self-sampling for cervical cancer screening were performed using standard cytobrushes that are used for clinician-based cervical sampling, or synthetic and cotton swabs used for other diagnostic purposes. In 2005, a meta-analysis by Ogilvie et al reported pooled overall sensitivity of 74% and specificity of 88% for HPV DNA detection across studies that used cytobrushes or Dacron/cotton swabs when compared to clinician-collected samples.¹⁰⁹ Most of these studies used signal amplification-based HPV assays (such as Hybrid Capture), which we now know are associated with lower sensitivity than current PCR-based assays. Self-sampling with a -cytobrush,^{110,111} as well as a synthetic (Dacron) swab,¹¹² was well accepted and considered easy to perform among participants in clinic-based studies.

Once devices specifically designed for cervicovaginal self-sampling were introduced on the market, several studies provided insights into women's preferences. Women prefer devices (brush or swab-based) that are smaller and colorful in appearance.^{55,56,113} In a recent study in the US, women were more willing to use devices that closely resemble a basic swab than three other swab- and brush-based devices.⁵¹ Interestingly, this study also found women's willingness to use a specific brush device varied

by sexual orientation: sexual minority women were more willing to use the HerSwab device than heterosexual women.

In a meta-analysis by Arbyn et al, all types of swab-, brush-, and lavage-based devices were associated with high sensitivity when used with a PCR-based HPV assay. Brush- and swab-based devices were slightly more sensitive (98%, 95% CI 0.93–1.03) than lavage-based devices (95%, 95% CI 0.87–1.04; [Figure 1](#)).⁹ In a Norwegian study, samples collected using a brush-based device had similar sensitivity for CIN3⁺ to clinician-collected samples, whereas samples collected using a swab-based device did not.¹¹⁴ There are reports suggesting a preference for brush-based devices compared to swab- or lavage-based devices,^{114,115} but these are not consistent.¹⁰²

The type of HPV self-sampling device may play an important role in women's acceptability of a screening strategy. Studies in the Netherlands and Finland found offering a brush-based device is comparable to offering a lavage-based one in terms of participation and acceptance by women; however, brush-based devices had slightly higher participation in both studies (23.8% vs 21.7% in the Finnish study and 34.6% vs 31.9% in the Dutch study).^{96,102} There were no observed differences in hrHPV-positivity rate or sample-inadequacy rate.¹⁰²

First-Void Urine Collection as an Alternative Self-Sampling Strategy

As an alternative for women reluctant to undergo clinician-based cervical cancer screening and vaginal self-sampling, home-based first-void urine collection for hrHPV testing may be valuable. Urine samples are a cheap, non-invasive, and easy-to-collect approach to self-sampling for HPV testing¹¹⁶ and have been highly accepted when offered in clinics and more recently at home.^{117–120} However, when compared to vaginal self-sampling, the diagnostic accuracy is somewhat lower. In 2014, a meta-analysis by Pathak et al found pooled sensitivity of 77% and specificity of 88% for hrHPV detection in urine samples compared with clinician-collected cervical samples.¹²¹ Similar positivity rates and sensitivity for CIN2⁺ and CIN3⁺ for urine and vaginal self-samples using dry and wet swabs were reported in another British clinic-based study.¹¹⁹ Ørnsvik et al found absolute sensitivity for CIN2⁺ of urine and vaginal self-samples was comparable to cervical clinician-collected samples (93% for urine samples and 96% for self-collected samples).¹²²




TYPE OF DEVICE	LAVAGE	BRUSH	SWAB
APPEARANCE			
DESCRIPTION	The lavage-based device is pre-filled with sterile saline which is released into the vagina after insertion. The saline then flows back into the device, thus exfoliating cells from the cervix and vagina.	The brush is attached to a plastic applicator stick or stored inside a plastic applicator. The brush is inserted into the vagina, pushed out of the plastic applicator if needed and rotated to collect the cells, then removed and stored back into the plastic applicator or removed from the applicator stick to be stored in a separate container.	A swab device consists of a plastic applicator stick with a dry or flocked swab tip that a woman inserts into the vagina without touching the external genitalia and rotates before removal.
SENSITIVITY TO DETECT CIN2+/PCR assay ¹²	0.95 (95%CI 0.87 to 1.04)	0.98 (95%CI 0.95 to 1.02)	0.98 (95%CI 0.93 to 1.03)
COMMERCIALY AVAILABLE DEVICES	Delphi Screener (Rovers Medical Devices B.V., Oss, The Netherlands)	Viba Brush, Evalyn Brush (Rovers Medical Devices B.V., Oss, The Netherlands)	HerSwab (Eve Medical, Toronto, Ontario, Canada), FLOQSwab (Copan Diagnostics, Italy), Coari (Kolplast, Sao Paulo, Brazil), Qvintip (Approvix, Uppsala, Sweden)

Figure 1 Review of the key types of self-sampling devices.
Abbreviation: CI, confidence interval.

Furthermore, a majority of studies of HPV testing on urine samples have noted lower hrHPV positivity than corresponding vaginal samples.^{118,120,123–125}

Home-based urine collection is well accepted among Danish women, and a majority of them would choose urine testing for future screening.¹²⁰ Rates of concerns about proper urine self-sample collection are 3%–20% of surveyed women.^{118,120} Large-scale participation studies of urine self-sampling are currently lacking. A first-void urine self-collection device has already been made commercially available.¹²⁶

Lessons in Women's Preferences

Women participating in self-sampling studies have consistently reported positive attitudes toward the use of self-collected samples for HPV testing^{127–130} and a preference for self-sampling to clinician-based sampling for future screening.^{96,102,130–134} Studies in nonattenders showed that women find self-sampling to be more convenient, less embarrassing, less uncomfortable, and less painful than clinician-based sampling. In Argentina, self-sampling is preferred, because it allows women to overcome barriers related to the health system (ie, long waiting times) without sacrificing time devoted to work/domestic responsibilities.¹³⁵ For women, the most appealing

features of self-sampling are cost (free), convenience (home-based), and less anticipated discomfort than a Pap test.¹³²

Across many countries and age-groups, women are able to perform self-sampling with simple written instructions.^{132,136} A study on Australian women's attitudes toward self-sampling noted small kits that fit in mailboxes are preferred over having to collect a parcel at a post office.¹³² In Finland, a combination of interventions (reminder letter and then self-sampling kit) increased total participation from 63% (regular invitation) to 78%,¹⁰⁸ suggesting that an affordable self-sampling kit or device could be included with a reminder letter to screening nonattenders.⁴³ A recent Brazilian study suggested that women were more likely to respond to screening if self-sampling were offered as an option.¹³⁷ A randomized controlled trial in Belgium noted self-sampling was particularly well accepted among postmenopausal women compared to women aged <50 years (OR 6.4 vs 2.1).¹³⁸

The most commonly raised concerns in participants to self-sampling are test accuracy and whether they are performing the procedure correctly.^{51,52,57,58,133,136,139–142} In the Dutch IMPROVE study, women reported significantly lower levels of shame, nervousness, discomfort, and pain

during self-sampling than with clinician-based sampling; however, trust in correct sampling was higher during clinician-based sampling.¹³⁰ A qualitative British study found the Muslim population was especially concerned about not performing the test correctly and would prefer to continue to be screened by a health professional.⁶⁶ A preference for clinician-based screening (73%) was also reported in a study of sexually active adolescents at an American urban teen health center undergoing both self-sampling and clinician-based sampling. This was mainly due to a lack of faith in performing the sampling correctly.¹⁴³ Lastly, some qualitative studies in middle-income countries have reported that women fear hurting themselves when taking the self-sample.^{82,135} On the other hand, nearly 20% of women indicate that they do not have any concerns about using a self-sample.⁵¹ To address women's concerns, positive feedback from large-scale studies should be presented through public-awareness campaigns, including data showing that most women are able to successfully obtain an adequate sample.^{51,96,102,115}

Implementation of self-sampling should be coupled with educational interventions that would raise awareness of the importance and impact of cervical cancer prevention in general, including HPV vaccination of children and cervical cancer screening of adult women. Educational interventions aimed at increasing awareness about HPV infection and cervical cancer risk are associated with higher acceptability of self-sampling.¹⁴⁴ Taiwanese women who perceived their cervical cancer risk as high and had high-level of HPV-related knowledge were more likely to perform HPV self-sampling.¹⁴⁵ Conversely, levels of HPV-related knowledge and perceived risk are low in underscreened women from low-income areas; however, they do perceive mailed self-sampling kits as trustworthy.¹⁴⁶ In addition, the causal relationship between cervical cancer and sexually transmitted HPV infection can result in perceived sexual promiscuity by the community and feelings of shame and blame in women who test positive for HPV.^{147,148} Stigma associated with cervical cancer and HPV can influence women's willingness to undergo an HPV test and their interpretation of screening results.^{149,150} In some settings, there are pervasive misperceptions that the "type of women" who get cervical cancer are uneducated, sexually promiscuous, and cursed.^{77,89,151} Furthermore, HPV testing can raise potentially difficult issues related to trust and fidelity within marriages in cases of a positive test result.¹¹³ Due to the financial implications of testing and treatment, women in certain

cultures often need to obtain spousal consent/approval to receive screening and care.^{77,151,152}

Self-Sampling Beyond HPV Testing Cytology

While hrHPV self-sampling has shown comparable diagnostic agreement to clinician-collected samples, self-collected Pap smears are considered insufficiently sensitive using currently available collection devices.¹⁵³ Few studies have compared the accuracy of cytology between self-samples and clinician-collected samples using different types of self-sample devices, demonstrating fair–moderate agreement and lower sensitivity on self-collected samples.^{153–158}

In one of the earliest studies of self-collected Pap tests,¹⁵⁴ sensitivity for self-collected cytology using a traditional cytobrush was significantly lower than clinician-sampled cytology (55% vs 85%); however, specificity for self-collected samples was higher (85% vs 73%). Since that time, a variety of self-collection methods and commercial and noncommercial devices have been investigated, with varying results. When reported, relative sensitivities for CIN2⁺ were low and ranged between 33% and 75%.^{159,160} Several studies have shown comparable or improved specificity of self-collected cytology compared to clinician-collected samples.^{155,157,159}

In a recent prospective cohort study, Loopik et al showed reflex cytology is feasible on hrHPV-positive self-samples and could be considered as an additional triage test for immediate referral to decrease loss to follow-up in screening.¹⁶¹ The authors also noted a lack of endocervical, endometrial, and inflammatory cells, which made interpretation of the slides easier, but not necessarily as reliable.

Despite the challenges with self-Pap, the possible increased positive predictive value when combined with self-collected HPV testing may still provide promise. Combining hrHPV self-sampling with a self-Pap could improve access to screening while increasing the positive predictive value of an hrHPV-test result. Improved devices may improve the validity of the results, but the challenge of self-guided collection of the squamocolumnar junction continues to present a significant hurdle to incorporating self-Pap collection in cancer screening. The rapid pace of discovery of potential biomarkers predictive of high-grade cervical lesions from cytology fluid may offer additional predictive value in future, and these are briefly reviewed in the next section.

Emerging Biomarkers and Molecular Approaches: The Future of the “Liquid Biopsy”

Since <10% of acute HPV infections progress to high-grade lesions or invasive cancer, there is a need for appropriate tools to triage HPV infections.¹⁶² In high-income countries, women with either an abnormal Pap smear or histology-confirmed CIN2⁺ are generally referred for follow-up or treatment, but these approaches are impractical in many low-resource settings, due to the labor and equipment required.^{62,163}

Both self-collected cervicovaginal samples and first-void urine samples will likely not fulfil the high-quality cellularity standards required for morphological review. Molecular biomarker assays may represent an alternative for detecting cervical lesions of clinical concern. In future, many of these assays may be suitable to perform on self-collected samples, and could offer additional specificity for detection of precancerous cervical lesions when combined with HPV screening. For example, high-throughput massively parallel-sequencing technologies, known as next-generation sequencing (NGS), could be applied in a “molecular Pap test” on exfoliated cells from a self-collected sample.¹⁶³ NGS-based components of this molecular Pap test might include:

- HPV genotyping. Detection of HPV types and variants, for which NGS is more sensitive than PCR,¹⁶⁴ which could be useful in triage because variants of HPV types often exhibit differences in infectivity, duration of persistence, and/or oncogenicity.¹⁶³ Infection with multiple HPV types, which occurs commonly, can be detected suitably with NGS and may be associated with reduced risk of cervical cancer.¹⁶⁴
- Identification of HPV integration sites in the host genome using high-throughput viral integration detection (HIVID); tagging, enrichment, and NGS of HPV16 (TEN16); or other NGS-based assays utilizing customized HPV-specific probes.^{164,165} HPV-integration rates are positively correlated with CIN grade and can be a predictor of likely progression to cancer.¹⁶⁴
- Host/viral gene methylation. Quantification of levels of DNA methylation, an epigenetic modification, at numerous CpG sites have been proposed as

biomarkers for cervical precancer.¹⁶⁶ Methylation levels of the HPV16 *L1* and *L2* genes can be used to identify HPV16-induced high-grade CIN with high diagnostic accuracy,¹⁶⁶ and a recent meta-analysis of methylation at the human *CADMI*, *MAL*, *MIR124-2*, *FAM19A4*, *POU4F3*, *EPB41L3*, *PAX1*, and *SOX1* genes, as well as HPV16 *L1* and *L2*, concluded that DNA methylation was significantly higher in CIN2⁺ relative to ≤CIN1.¹⁶⁷ Additionally, methylation frequency at the promoters of multiple human genes is significantly higher in cervical cancer samples than controls.¹⁶⁸ When considering performance on self-collected samples, one study found that the methylation levels at *PAX1*, *SOX1*, and *ZNF582* showed no significant differences between self-collected and clinician-collected samples in specificity or sensitivity as predictors of CIN3⁺.¹⁶⁹ However, HPV-methylation studies to date have been limited in their geographic spread and HPV types studied: most have focused on HPV16,¹⁷⁰ and few have been conducted in Africa,¹⁶⁸ despite sub-Saharan Africa having the highest incidence of cervical cancer worldwide.¹⁷¹ Further clinical studies with large cohorts are recommended to fully evaluate the performance of methylation assays as predictors of CIN2⁺.¹⁷²

The cost of NGS continues to decline dramatically, and it is predicted that NGS technologies will soon be suitable for widespread adoption in cervical cancer screening.¹⁶⁴ Nonetheless, a recent systematic review by Onyango et al concluded that dual staining for the cell cycle proteins p16 and Ki67, which is not NGS-based, currently represents the most clinically useful biomarker assay to detect CIN2⁺.¹⁷² High p16 expression is known to be associated with persistent hrHPV infection, while Ki67 is a marker of cell proliferation associated with malignant tumors. Additionally, since p16 induces cell-cycle arrest under physiological conditions, coexpression of p16 and Ki67 is observed in cells with dysregulation of the cell cycle.¹⁷³ Multiple studies have established dual p16–Ki67 staining as an appropriately sensitive and specific method for identifying HPV infections of clinical concern,^{174–177} and it has also been demonstrated that p16–Ki67 assays can be conducted accurately by minimally trained evaluators.¹⁷⁸ Limitations include variability in specificity depending on patient age and the threshold number of p16⁺–Ki67⁺ cells

used to define a positive result.¹⁷⁹ Toliman et al found dual p16–Ki67 staining had higher sensitivity in predicting high-grade disease on clinician-collected cervical specimens than self-collected vaginal specimens.¹⁸⁰ Further studies are needed before recommending dual p16–Ki67 staining as a triage test for HPV-positive women, and it may be replaced by emerging molecular markers.¹⁸¹

Other emerging biomarkers that have been proposed to predict CIN2⁺ include the HPV mRNAs E6 and E7 and various human microRNAs (miRNAs) and proteins, such as SCCAg, MCSF, and VEGF. When overexpressed, the protein products of HPV E6 and E7 inactivate human tumor suppressors, and testing for E6 and E7 appears to have diagnostic relevance in detecting CIN2⁺.¹⁸² HPV mRNA assays, many of which detect E6 and E7, have been proposed as a tool for secondary cervical cancer screening after HPV DNA testing as primary screening.¹⁸³ Pardini et al identified miR21 and miR29a as the most frequently upregulated and downregulated human miRNAs, respectively, in studies of invasive cervical cancer progression.¹⁸⁴

Cost-Effectiveness of Self-Sampling

It is generally accepted that self-sampling is a cost-effective strategy, and there is ongoing investigation into optimal screening protocols. The largest reductions in monetary costs associated with self-sampling are the decrease in excess office-based exams for women testing HPV-negative, potential reductions in unnecessary colposcopy referrals, unnecessary treatments.

The cost-effectiveness of self-sampling is largely dependent on the implementation approach. The opt-in approach offers some economic and environmental advantages. However, using mathematical modeling on data from a randomized self-sampling trial in Norway, Burger et al found that the costs saved by an opt-in approach were relatively small (2%) and overshadowed by other larger screening-related costs (eg, office-based exams, colposcopies).¹⁸⁵ Targeted 5-yearly self-sampling of women who did not respond to reminder letters or participate in organized screening have been found to reduce the lifetime risk of developing cervical cancer with an attractive cost-effectiveness profile: US\$29,630–\$29,420 per quality-adjusted life year gained compared with no screening. However, the magnitude of the health benefit and optimal self-sampling strategy was dependent on the profile and behavior of self-sampling respondents (time since last screening, never screened).¹⁸⁶ A cost-

effectiveness analysis from Sweden showed HPV self-sampling using the opt-out approach led to more women being screened and histologically diagnosed CIN2⁺ at a lower cost than midwife-collected Pap smears.¹⁸⁷

An important consideration when considering implementation of self-sampling as a screening strategy is avoiding overscreening or double-screening. Double-screening is costly, and in the era of improved sensitivity it adds no benefit. In the Norwegian pilot study, 18% of women who did not have an hrHPV infection attended an office-based exam, despite being explicitly advised that they did not need further screening.¹¹⁵ A modeling study based on these data showed that eliminating potential overscreening practices was one of the most important cost-saving practices that a self-sampling screening program could undertake.¹⁸⁶ In the Slovenian randomized pilot self-sampling trial, women in the opt-in arm could choose to order a self-sampling kit or schedule an in-office visit, while women in the opt-out arm had received self-sampling kits and had free access to screening at a clinic. In the opt-in arm, only 1.8% of women performed both screening tests, while this percentage was higher in the opt-out arm (3.6%).⁴⁶ The Australian national screening program already uses an approach where women are offered self-sampling if they decline an in-office visit.¹⁸⁸

In low-resource settings, task shifting of cancer screening to community-based models could improve screening coverage and offer substantial cost savings through early detection and decreased labor costs, as we have already outlined in previous sections. In these settings, integration of cervical cancer screening with HIV monitoring^{189,190} could allow for greater cost-effectiveness in preventing both HPV and HIV infection treatment-related costs.

Challenges and Limitations

Introduction of a new screening practice or change in an existing screening program should follow the screening principles set by Wilson and Jungner in 1968 and consolidated lately by Dobrow et al.^{191,192} These principles offer guidance to implementation success by supporting the translation of evidence into practice in such a way that there is an optimal balance between benefits and harms of the new intervention. Consolidated principles are categorized into disease/condition, test/intervention, and program/system principles.¹⁹¹ The main challenges and limitations of HPV self-sampling implementation as a test/intervention category are women's acceptance of self-sampling and HPV-test results, ensuring the use of only validated

devices/assays, and ensuring adequate follow-up for all screen-positive women, expanded on as follows.

Acceptance Despite the fact that self-sampling and HPV testing is widely accepted by women of different ages, socioeconomic, cultural, and geographic backgrounds, barriers persist. In some settings, spousal consent is needed for screening and stigmatization in cases of HPV infection or cervical cancer and limits participation. Furthermore, women express concerns regarding test accuracy and whether they are performing the procedure correctly that need to be addressed to increase the acceptance of self-testing and receiving HPV-test results. Research should be focusing on developing culturally appropriate messages and educational materials aimed at both women and their spouses to address these challenges.

Validation of self-sampling devices/assays and standard operating procedures Studies evaluating the impact that individual self-sampling devices or components of the test kit (eg, instruction materials, in-person training, supervision) have on participation and acceptability are lacking.⁴⁴ Clinical accuracy in the detection of high-grade cervical lesions using various commercially available self-sampling devices and PCR-based HPV assays needs to be systematically evaluated prior to implementation, since it is the most relevant criterion from a population-health standpoint. As more commercial HPV assays become available, validation and laboratory standard operating procedures assuring optimal sensitivity, specificity, and high intra- and interlaboratory reproducibility using international consensus criteria¹² are needed for all assays intended for primary cervical cancer screening.^{43,193}

Course of action for screen-positive women Reflex triage of HPV-positive self-samples to cytologic examination could lower the burden of overtreatment and preterm births due to the shortening of the cervix after treatment. It could also lower the burden of screening on health-care workers and screening facilities. However, due to the increased complexity and cost of screening strategies with reflex triage and the need for follow-up of screen-negative, triage-positive women, more research is needed on how different triage protocols perform in different local contexts, eg, HPV self-sampling screening with reflex triage and VIAC/treat approach for screen-positive and triage-positive women in low-resource settings. Clear and feasible guidelines should be in place on how to manage screen-positive/negative and triage-positive/negative

women to assure their compliance and not to overburden health facilities.

Furthermore, the main challenges and limitations of HPV self-sampling implementation related to program/system category that should guide further research in the field of implementation success of HPV self-sampling are as follows.

Information and participation More research is needed to understand the determinants of participation of different self-sampling implementation approaches and how to remove barriers to participation. Considering the pandemic's impact on the global economy, cost-effective, minimal-waste approaches should be investigated further. More trials are warranted to explore the effectiveness of the opt-in approach and potential avenues for improvement. Some of these improvement strategies may be campaigns to raise awareness of opting in to cervical cancer screening, offering electronic order options via text message, email, or mobile applications, and encouraging women to choose between self-sampling at home or clinician sampling.⁴⁶ In some settings, an integrated approach could be beneficial, such as integrating cervical screening with women's monthly HIV therapy or cervical cancer screening of mothers with HPV vaccination of their children; however, more research is needed on the added value and feasibility of integrated guidelines, implementation and governance.

Continuity of care To ensure that improved screening coverage leads to improved health of screened women, it is necessary to enable rapid and free access to further high-quality diagnostics, follow-up, and treatment for all women who participate in screening and are in need of those services.⁶² However, attendance at follow-up care after an HPV-positive self-sampling result has varied widely in high- and low-resource settings. To prevent loss to follow-up in women with a positive screening test, it is important to address the barriers women face in the local context, such as costs of care, lack of health insurance, distance to travel, time consumption, lack of health-care providers, and infrastructure. A community-based approach and one-step (eg, screen and treat) approaches might add value in low-resource settings; however, only high-quality and evidence-based services should be implemented to minimize the treatment of women with false-positive and reassurance of women with false-negative results.

Overdiagnosis and overtreatment One of the concerns is related to the over-detection of cervical dysplasia

related to high sensitivity of HPV testing as a screening strategy, resulting in increased overdiagnosing and overtreatment of transient infections.¹⁹⁴ In low-resource settings with shortages of clinical facilities for follow-up and treatment and a shortage of adequately trained personnel,¹⁹⁵ this is indeed worth noting. On the other hand, in most of these regions, the currently widely used low-cost visual assessment screening methods (such as VIAC) are already associated with overtreatment, due to the low specificity of these methods.^{196,197} It is also important to caution against alternative screening in young, unvaccinated women due to high HPV prevalence, which can be 20%–30% in women aged <25 years. In this population, an HPV-positive result offers a low positive predictive value.¹⁹⁸ Marketing of these tests to young women in an opportunistic setting poses a challenge requiring adequate health-care professional follow-up and education for women to prevent overdiagnosis and overtreatment.

Infrastructure Another important concern when implementing HPV testing on self-samples in low-resource settings is the challenge of acquiring the necessary facilities and trained laboratory technicians for widespread HPV testing and appropriate quality control. One of the main barriers to the integration of highly accurate and robust HPV self-sampling into cervical cancer-screening programs in low-resource settings is the availability of high-quality laboratory services. At the time that the WHO launched a global initiative to accelerate the elimination of cervical cancer in the midst of the pandemic on November 17, 2020, it was already clear that COVID-19 was not only a threat but also one of the most powerful opportunities we ever had to scale up HPV-based cervical cancer screening worldwide, due to the expansion of both the infrastructure and highly trained personnel currently working on COVID testing that could in time be allocated to increased HPV molecular testing capacity. With HPV self-sampling, more women could be reached through the expanded capacity of molecular laboratories across the world to accelerate the progress toward elimination of cervical cancer.

Economic evaluation of a comprehensive approach

Important determinants of self-sampling cost-effectiveness are related to implementation approach (economic and ecological benefits of an opt-in approach versus higher participation in opt-out and community-outreach approaches), screening policy (age of women, screening interval), and guidelines for management of screen-positive women (triage, further diagnostics, follow-up, and

treatment). Despite self-sampling in general being accepted as cost-effective, economic evaluation of self-sampling implementation should be performed in a local context, based on local screening strategy, its integration into a local health system, and local data (such as women's response to intervention, acceptability, availability of high-quality care for women with a positive screening test results, and costs).

One size does not fit all Due to cultural differences across the world that are reflected in differences in acceptance of different screening approaches and technologies, differences in access to screening and high-quality care services in cases of positive screening results and the variability of the size effect of self-sampling trials in published studies, local trials have been recommended to assess feasibility, efficacy, and cost-effectiveness before progressing to a regional or national level.⁹

Governance COVID-19 has taught us that even in well-organized screening programs, a rapid and unexpected change in the environment can disrupt decades-long, well-established dynamic equilibria of existing screening subsystems and stakeholder relations. Availability of data from dedicated screening-information systems and a clear governance structure is in such situations crucial for optimal adjustments to the program in order to minimize harms of screening disruptions and maintaining high-quality services when and where possible, as well as to plan recovery strategies. Having such structures in place is one of the prerequisites of implementation success, and should be considered and planned for in the preparatory phase.

Conclusion

Current evidence supports the use of HPV testing on self-samples for overcoming barriers to screening and reaching underscreened women. Implementation of self-sampling needs to be comprehensive, appropriate for the local context, and cover everything from screening to treatment. Offering women a choice between different screening strategies can be beneficial, both in terms of increasing participation and cost-effectiveness. In low-resource settings, offering community-based self-sampling with educated personnel to assist with the process should be considered.

The COVID-19 pandemic represents an opportunity to accelerate progress toward elimination of cervical cancer if strategies are implemented with consideration of appropriate incorporation of diagnostics, follow-up, and treatment adapted to the setting. Infrastructure, personnel, and funds

currently used for large-scale COVID-19 testing could in time be allocated to address disparities in cervical cancer burden and bring sensitive and robust cervical cancer-screening methods to resource-limited communities. Ensuring resilience of cervical cancer-screening efforts and health equity in access to screening should be one of the primary goals of designing and maintaining successful cervical cancer screening and prevention strategies in both high- and low-income settings, as well as local communities.

Author Contributions

All authors have read and approved the final manuscript. All authors made a significant contribution to the work reported, whether in its conception, design, execution, acquisition of data, analysis and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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