

REVIEW

Widening the offer of human papillomavirus self-sampling to all women eligible for cervical screening: Make haste slowly

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Abstract

Self-collection of samples for human papillomavirus (HPV) testing has the potential to increase the uptake of cervical screening among underscreened women and will likely form a crucial part of the WHO's strategy to eliminate cervical cancer by 2030. In high-income countries with long-standing, organised cervical screening programmes, self-collection is increasingly becoming available as a routine offer for women regardless of their screening histories, including under- and well-screened women. For these contexts, a validated microsimulation model determined that adding self-collection to clinician collection is likely to be cost-effective on the condition that it meets specific thresholds relating to (1) uptake and (2) sensitivity for the detection of high-grade cervical intraepithelial neoplasia (CIN2+). We used these thresholds to review the 'early-adopter' programme-level evidence with a mind to determine how well and how consistently they were being met. The available evidence suggested some risk to overall programme performance in the situation where low uptake among underscreened women was accompanied by a high rate of substituting clinician sampling with self-collection among well-screened women. Risk was further compounded in a situation where the slightly reduced sensitivity of self-sampling vs clinician sampling for the detection of CIN2+ was accompanied with lack of adherence to a follow-up triage test that required a clinician sample. To support real-world programmes on their pathways toward implementation and to avoid HPV self-collection being introduced as a screening measure in good faith but with counterproductive consequences, we conclude by identifying a range of mitigations and areas worthy of research prioritisation.

KEYWORDS

cervical cancer, cervical intraepithelial neoplasia, human papillomavirus, mass screening, self-collection

1 | THE FUTURE OF CERVICAL SCREENING RELIES ON SELF-SAMPLING

The increased popularity of self-sampling for cervical screening¹ relies on decades of research that attest to the credibility of high-risk

human papillomavirus (HPV) testing for the detection of high-grade cervical intraepithelial neoplasia (CIN) and cervical cancer.² Traditionally, a trained clinician would take a cervical sample through intimate, speculum examination, which some women find physically and/or psychologically challenging.³ For reasons such as privacy and

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

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TABLE 1 Outcomes of HPV self-sampling which, if observed concurrently, could lead to an overall loss of effectiveness in a quality-assured cervical screening programme achieving high coverage rates with clinician sampling

<i>Changes associated with self-collection for HPV testing</i>	<i>Screening programme will be less effective if this is</i>
Screening participation among high-risk, underscreened women	Low
Proportion of previously well-screened women who would switch to self-collection	High
Detection of CIN2+ compared with clinician sampling	Low

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

avoidance of embarrassment many women prefer self-collection.⁴ While screening uptake has been declining in several countries,^{5,6} the finding that some women who do not engage in ‘regular’ screening may be willing to provide a self-collected sample⁷ is significant. Consequently, self-sampling has earned support from health care providers, patient organisations and policy makers,⁸⁻¹¹ and is a critical component of the WHO’s global strategy to eliminate cervical cancer.¹²

2 | ROLE FOR HPV SELF-SAMPLING IN ORGANISED SCREENING PROGRAMMES IN HIGH-INCOME COUNTRIES

Here, we reflect on the evidence to support the implementation of self-sampling in high-income settings with free-of-charge, quality-assured, population-based screening programmes based on clinician sampling, which are saving thousands of lives annually.¹³ We discuss this evidence through the lens of a study by Rozemeijer et al who explored the implications of implementing HPV self-sampling within the Dutch-organised screening programme.¹⁴ The study employed the well-validated MISCAN microsimulation model¹⁵ and established, under a wide range of scenarios, that cervical screening combining both collection methods could save more lives at a societally acceptable cost than screening using clinician collection alone.¹⁴

This said, the study also identified conditions under which self-sampling introduced into a high-quality screening programme may inadvertently become counterproductive.¹⁴ These conditions were defined as co-existence of the following outcomes (Table 1):

1. a low uptake of self-sampling among underscreened women, especially those with a higher-than-average background risk of cervical cancer, and
2. a substantial proportion of women who usually undergo clinician-based screening switch to self-collection, and
3. a lower detection of CIN2+ compared to clinician sampling.

Rozemeijer et al identified several combinations of critical thresholds for these three outcomes (Table 2).¹⁴ If all three thresholds were

met concurrently, a screening programme offering self-collection would save fewer quality-adjusted life years, that is, be less effective in decreasing the population burden of cervical cancer than a programme relying solely on clinician collection. The exact values of these critical thresholds would likely be different had their study been undertaken more recently or in a different country. Nevertheless, they describe a consistent pattern in which even relatively modest levels of switching from clinician collection to self-collection could become counter-productive in good faith if, concurrently, self-sampling were unable to motivate a significant proportion of underscreened, high-risk women to participate and struggled to achieve a comparable detection of CIN2+. An independent microsimulation study from Norway by Burger and colleagues largely corroborated these conclusions.¹⁶

This framework lends itself to identification of the core challenges relevant to the implementation of self-sampling and potential mitigations (Table 3). Now that several high-income countries are accelerating their plans to introduce self-sampling as a routine offer not only to nonparticipating women, but to all women of screening age irrespective of their previous engagement with clinician-based programmes,¹⁷⁻²² these considerations are time-critical.

3 | UPTAKE IN UNDERSCREENED WOMEN

Many research studies from high-income countries have shown that self-collection can engage previously underscreened women in providing an HPV sample. The observed proportions have ranged between ~10% and ~30%.²³⁻³¹ With coverage rates for clinician sampling often reaching ~70%,^{5,6} this means that self-sampling may be able to engage an additional ~3% to 9% of the target population.

Data from early-adopter programmes show a more varied picture. The programme in the Danish Capital Region, which has contacted women overdue for screening since 2017, reported that 17% of the women returned a self-collected sample.³² This would increase screening coverage from ~73% to ~77%.^{32,33} Some of the women who were offered these self-collection kits underwent clinician sampling instead, although for them the role of the self-sampling invitation remains unclear. Elsewhere, the results have been far less encouraging. In Australia, self-sampling for underscreened women has been available since 2018. From the catchment area of a laboratory in Victoria, where the uptake with clinician sampling was ~60%, only 1067 underscreened women provided self-collected samples in the first 17 months of the service compared to 290 000 clinician samples analysed during the same period³⁴; if this rate was sustained, the overall screening coverage would increase by <0.5%. In the Netherlands, all women invited for cervical screening have been able to order a self-sampling kit since 2017. Before the disruption caused by the SARS CoV-2 pandemic, around 8% of participants chose self-collection.^{5,35} Around 29% of the women who chose self-collection were previous nonparticipants, compared to 12% among those who chose clinician collection.³⁶ Although self-collection may have motivated more previously unscreened women to provide a sample, the

TABLE 2 Selected quantified thresholds for the uptake of HPV self-sampling among well-screened women provided by Rozemeijer et al¹⁴ with specific combinations of the relative sensitivity for the detection of CIN2+ and the uptake among underscreened women, beyond which a screening programme offering self-collection would not remain effective, that is, would generate fewer quality-adjusted life years than a programme without self-collection

Relative sensitivity for the detection of CIN2+ ^a	0.95-0.96		0.89-0.90			
Increased uptake among nonparticipants ^b	6% (including high-risk women) ^{c,d}	3% (including high-risk women), ^{c,d} or 6% (only average-risk women)	6% (no high-risk women)	6% (including high-risk women) ^{c,d}	3% (including high-risk women), ^{c,d} or 6% (only average-risk women)	6% (no high-risk women)
Switching among women who would otherwise undergo clinician collection ^e	[Always effective] ^f	>50%	>30%	>70%	>30%-40%	>20%

Abbreviations: CIN, cervical intraepithelial neoplasia.

^aFor self-collection vs clinician collection. The authors did not report the outcomes of scenarios in which the relative detection of CIN2+ achieved with self-sampling was lower than 0.89 compared with clinician collection. In all scenarios, the authors assumed that 92% of women with positive self-collected HPV tests undergo clinician-collection for triage cytology at baseline, and that 68% attend at early recall compared to 92% of the women who were screened with clinician collection at baseline.

^bAs a proportion of the programme's target population.

^cThe authors did not report the outcomes of scenarios in which the extra uptake among nonattending women was higher than 6% (this choice was in line with an earlier Dutch clinical study), or those where the extra uptake was lower than 3%.

^dWhen their scenarios included high-risk women, the authors assumed that 29% of nonattenders who provide a self-collected sample never attend regular screening and have a higher background risk of cervical cancer (by a factor of 1.7 compared to women who attend screening with clinician collection).

^eAll else equal, the estimates for the proportion of women switching from clinician to self-collection tended to be lower than the levels reported in this table if screening were to also satisfy the criteria for cost-effectiveness.

^fWith the given increase in screening attendance among underscreened, high-risk women and the given relative sensitivity, a screening programme would remain effective even when 100% of well-screened women switched to self-sampling.

overall screening coverage did not increase.⁵ We discuss the experience from these and other countries in more detail below.

3.1 | Improving the uptake among underscreened women

The programmes now require in-depth understanding into why underscreened women do not use self-collection even when it is offered for free and signposted in an invitation letter. This work may require innovative qualitative studies. Elfström et al, for example, analysed interactions between trial coordinators and the women they approached for a study, and reported that some had been discouraged once they realised that self-collection did not obviate a clinic visit should they test positive.²⁷ Trying to elucidate why some women do not participate in bowel screening, which also relies on self-collection at home, Kotzur et al interviewed women with different bowel screening histories and categorised them according to their participation in breast and cervical screening.³⁷ They compared women who fully followed recommendations for organised screening in Scotland and participated in screening for all three cancers, those who partially followed the recommendations and participated in breast and cervical screening but not bowel screening, and those who did not follow any of the recommendations and remained unscreened for all three cancers. Using our study design, the authors confirmed that women in all three groups expressed disgust at the sample collection process and thus, unlike previous studies, demonstrated that disgust did not discriminate well between participants and nonparticipants. Disgust is,

therefore, an imprecise basis from which to develop effective interventions to increase screening participation. The authors then identified a cluster of actionable factors such as perceiving the process as burdensome or forgetting to accommodate sample collection into daily life, which were all more prevalent among nonparticipants. They argued that these could be addressed with pragmatic interventions such as by providing a planning support tool to increase women's ability to complete the test, or stating a deadline in the invitation letter for the sample to be returned to a laboratory.³⁷ It is likely that similar research could provide a list of pragmatic interventions to increase the uptake of HPV self-sampling.

Another area worthy of further investigation is the wording and the format of the invitations. Research studies have tended to include underscreened women, emphasising in their invitation letters that the women were being offered self-collection because of the higher risk of cancer after having missed previous screening opportunities. When self-sampling is offered to all women regardless of their screening histories, standard invitation letters may be unable to directly address specific subgroups of women. Furthermore, women have been used to receiving the same format of invitations for clinician sampling for years and may not realise that new-style invitations offer a wider range of options to collect a screening sample. In the Netherlands, for example, only half of the women who received the standard invitation letter realised that they could now order a self-sampling kit.³⁸ Several programmes still rely on written letters, which is arguably out of step with the digital age. Letters are also static, whereas an online environment may provide real-time opportunities for the user to seek further clarification and supportive information. Adaptation and customisation of

TABLE 3 Anticipated risks for the implementation of HPV self-sampling as a cervical screening offer for all women, and suggestions for mitigation, with the required information to be collected either through research or through on-going monitoring within real-world implementation efforts

Anticipated risk	Contributing factors	Suggestions for mitigation
Uptake among underscreened women	Low participation	<p>Identify reasons for not collecting a sample that can be turned into targets for intervention through, for example, innovative qualitative research</p> <p>Consider tailored wording and the design of the invitation letters, develop consistent messaging appropriate for the specific target (sub-)group(s)</p> <p>Optimise women's experience with the handling of the sample from collection to posting, and develop accessible platforms to order self-sampling kits if using an opt-in strategy</p> <p>Identify locally preferred self-sampling device(s) and determine the feasibility of allowing women to choose a preferred device</p> <p>Consider the feasibility of nonmailout self-sampling kit delivery models, for example, for specific subgroups of the target population</p> <p>Signpost where information and other resources are available, and consider outreach initiatives for hard-to-reach groups</p> <p>Engage with and provide core training to primary care and other health care practitioners involved in cervical screening</p>
	Detection of high-grade CIN	<p>Identify and optimise sample and workflow parameters causing lower detection of lesions in primary screening</p> <p>Identify ways to enhance sample workflow and processing steps to optimise biospecimen quality for robust HPV testing</p> <p>Undertake in-depth comparisons between self-sampling devices and assay combinations</p> <p>Provide improved real-life data on the detection of high-grade CIN:</p> <ul style="list-style-type: none"> • Stratification by the women's risk (eg, by age, deprivation, screening history) • Longitudinal data to better understand the risk of lesions after negative self-taken tests • Observational data from early adopters <p>Standardise workflows between laboratories and, if possible, between screening settings</p> <p>De-prioritise approval and funding of studies undertaken in nonrepresentative populations without histological endpoints, to increase confidence in the technology and accelerate regulatory approval</p> <p>Be reactive to new commercial offers of platforms and tests that are deliberately tuned to detect HPV in self-collected samples</p> <p>Provide data on test accuracy and adequacy for urine with similar degrees of robustness as has been made available for vaginal self-sampling</p> <p>Consider implementing a safety net for women with negative HPV tests on self-collected samples, for example, in the form of shorter routine recall intervals than for women screened with clinician-collected samples</p> <p>Enhance access to quality-assured biobanked material representative of primary screening populations, with reliable linkage to disease outcomes</p>
	Lower adherence to clinician-collected triage testing	<p>Identify effective interventions to reduce nonadherence with clinician sampling for cytology</p> <p>Prioritise development and validation of triage methods that can be performed on a self-sample, with fresh or biobanked sample material</p> <p>Determine any other parts of the follow-up process, for example, early recall (for triage-negative women) or colposcopy referral (for triage-positive women), that also result in a lower adherence</p>

invitations to ensure that they are appropriate for a particular demographic or for subgroups with specific screening histories should be informed through collaboration with experts on the communication of health-care messages.

Furthermore, programmes may consider a range of options in terms of the design and the distribution of the self-collection kit. Given the evidence to suggest that women may differ in their preferences for a particular kit,^{39,40} allowing choice of more than one validated option may increase uptake. Another much-discussed topic has

been whether to offer self-sampling in a mailout delivery model as an 'opt-out' service (whereby a self-sampling kit is part of an invitation pack sent to all women) or an 'opt-in' service (whereby invited women are asked to order a kit from the screening service; this avoids some plastic waste). Although opt-out usually results in higher uptake,^{27,41,42} opt-in can be an effective alternative particularly when supported with suitable communication platforms that simplify the kit ordering process.^{28,42,43} Self-collection for HPV testing, in fact, allows greater flexibility in approaching underscreened women, and delivery

models other than those relying on mailout have also been frequently discussed. In countries with well-screened populations these have included, for example, an opportunistic offer of a self-sampling kit in primary care to women attending for unrelated reasons,^{44,45} organising distribution of self-sampling kits through a network of local pharmacies,⁴⁶ recruitment through home visits by health care workers,⁴⁷ or via community campaigns and other outreach activities.^{48,49} Although such approaches may successfully engage some or even very large proportions of underscreened women to provide a screening sample, they require additional resources. Their suitability for routine use in mass screening programmes would benefit from further study.

The poor uptake of self-sampling among underscreened women in Australia has been studied thoroughly and attributed to a variety of early-implementation operational issues, several of which originated from lack of clarity on regulatory approval and on the eligibility criteria.^{34,50-54} Due to insufficient HPV assay manufacturer claims for self-sampling as 'intended use', local validation of a specific self-sampling utensil was required by the Australian national regulator. This was initially only completed by a single laboratory, likely as a consequence of limited incentives due to a perception of a small target population.⁵¹ The eligibility criteria used to be relatively restrictive, providing cost reimbursement only in case women were at least 2 years overdue for their screening test.^{34,51,53} Initially, the policy also required that women perform self-collection in health care facilities rather than at home,⁵⁵ which limited access for women who do not engage with health care.⁵³ Further reducing the effectiveness of this implementation was the need to confirm eligibility in real-time by looking up an individual woman's screening history, hindered by a delayed arrival of certain functionalities of the national screening register.^{34,50-52} This was compounded by underinvestment into promoting the availability of HPV self-sampling as a new feature of the renewed national screening guidelines^{51,52} and insufficient education and training for health care practitioners, among whom a significant proportion expressed lack of confidence and comfort in recommending self-sampling to eligible women.^{52,54} Although the Australian programme is now addressing these issues,⁵⁶ the learnings are highly instructive for other programmes. Australian experience shows that uncertainty regarding technical specifications of new screening technologies and insufficient investment into its promotion can easily translate into unclear public messaging and, ultimately, into not reaching the target population.^{50,51} In general, navigation of the process for validation and approval of self-sampling devices in cervical screening is a global issue that we further discuss below.

Finally, women from more deprived backgrounds and those unscreened for a very long time (two prominent risk factors for cervical cancer) may be particularly difficult to engage even with self-collection.^{25,28,32,57} Reasons include, for example, not having a fixed address, a generalised suspicion of health care interventions, comprehension challenges and coping with issues that mean screening cannot compete for time, resources or attention. To improve screening participation in these groups of women, programmes may need to consider bespoke outreach interventions.^{58,59}

4 | SWITCHING OF WELL-SCREENED WOMEN TO SELF-SAMPLING

Observational data from real-world implementation describing the frequency of substituting clinician with self-collection have been scarce. Notably, before the SARS CoV-2 pandemic, self-sampling was used by only 8% of participants in the Netherlands but in 2020, this proportion increased to 16%.⁵ This proportion is likely to increase further, as the National Health Council recommended in 2021 that a self-sampling kit should be included in the invitation letter, rather than being available on demand.²⁰

Research studies have typically reported that half or more of routinely screened women expressed a preference for self-sampling over clinician sampling, and that those who tried out self-sampling are more likely to seek it out again in the future.⁶⁰⁻⁶⁸ With changes that may tempt women toward self-sampling such as an increasing variety of self-sampling options to choose from (including urine sampling discussed below), an increasing propensity for programmes to offer national distribution of self-sampling kits to entire target populations,^{20,69} and increased familiarity with at-home microbial testing owing to the SARS CoV-2 pandemic, self-collection may eventually become the chosen cervical screening method for millions of women.

Within this context, it may be useful to add that switching from clinician-collection to self-collection among a certain proportion of well-screened women would be a likely outcome even when self-collection is only offered to underscreened women.⁷⁰ As underscreened women would typically be invited for self-sampling after a specific period of nonresponse to a screening invitation, well-screened women wishing to be part of that offer would need to actively delay their participation to qualify. Hence, unauthorised extension of screening intervals among a proportion of previously well-screened women may be one of the unintended consequences of limiting the self-sampling offer to women overdue for screening.

When HPV self-sampling leads to a similar detection of CIN2+ as HPV testing relying on clinician-collection, screening can remain highly (cost-)effective even when all well-screened women switch from clinician-collection to self-collection.^{51,71} Consequently, addressing any issues associated with a lower detection of CIN2+ through self-sampling will be key in avoiding an unintended deterioration in the effectiveness of screening programmes (Tables 1 and 2).

5 | SENSITIVITY OF SELF-SAMPLING FOR THE DETECTION OF CIN2+

One of the most influential pieces of work on this topic has been the meta-analysis in which the relative sensitivity for the detection of CIN2+ with self-sampling vs clinician sampling was estimated at 0.99 (95% CI: 0.97-1.02), particularly if sensitive target amplification HPV DNA tests were used.⁴¹ As others have pointed out, however, these findings are challenging to generalise to populations served by quality-assured screening programmes because the meta-analysis

included predominantly small studies in populations without access to organised screening.^{72,73} It was also dominated by studies of women referred to colposcopy because of abnormal cytology. CIN2+ associated with abnormal cytology appear to be more easily detectable with any HPV method than CIN2+ associated with negative cytology,⁷⁴ potentially because abnormal cytology tends to be associated with higher HPV viral loads.⁷⁵ The high relative detection of CIN2+ for self-collection vs clinician samples observed in the meta-analysis is therefore at risk of spectrum bias⁷⁶ that is, may overestimate the relative detection that would have been observed in primary organised screening where women are managed according to their HPV result rather than cytology. The meta-analysis did, in fact, include four primary screening studies using target amplification HPV assays. However, three of those were undertaken in previously unscreened populations where the characteristics of the prevalent HPV infections tend to be different than in well-screened populations, and used assays that have not been used for large-scale screening implementation in high-income countries.⁷⁷

Recent reports from settings with long-standing screening programmes show a more nuanced picture. Randomised studies from Sweden and the Netherlands reported similar detection of high-grade CIN for self-sampling vs clinician sampling arms.^{72,78,79} These studies employed HPV assays that have either not been commercialised or clinically validated according to the international metrics.⁷⁷ The uptake was higher in self-sampling arms, albeit to varying degrees and further stratification of CIN detection by women's screening histories would be informative.

Another Dutch study used data from the early phase of the routine implementation of self-sampling in the population-based screening programme.⁷³ Our study, whose nonrandomised and unpaired design may be seen as a limitation, reported a relative detection of CIN2+ of 0.91 (95% CI: 0.88-0.96) for HPV self-sampling using the cobas 4800 assay on samples collected with the Evalyn brush. The estimate was 0.79 (95% CI: 0.67-0.92) when only women who participated in the previous screening round were included. A reanalysis of these data, adjusting for screening history, age, screening region and various sociodemographic characteristics including income, household composition and migration background, reported the relative detection of CIN2+ as 0.76 (95% CI: 0.70-0.82) overall and 0.73 (95% CI: 0.65-0.83) among previously screened women.³⁶ The authors considered the resuspension volume (20 mL) of self-collected samples in the PreservCyt liquid as a potential contributor to these findings,⁷³ which further underscores the need for end-to-end optimisation of sample processing protocols (see below). Finally, a paired study in which consecutive women invited by the Scottish organised programme contributed both clinician and self-collected samples, reported a relative detection of CIN2+ of 0.93 (95% CI: 0.90-0.98) for samples which were self-collected with the cobas PCR female swabs and tested on the cobas 4800 assay.⁸⁰

These two real-world studies suggest that the sensitivity of self-sampling for the detection of CIN2+ may be almost 10% lower than that achieved with clinician sampling on average, and potentially even lower among regularly screened women ('switchers'). The reasons for

this difference have not yet been fully elucidated. Potentially, weaker signals in regularly screened women who tend to attend their routine recall with more recent HPV infections may account for some of the observed difference; this would, however, require further study.

Recognising the current shortcomings of the testing technologies and supporting their further development is a key task for stakeholders involved in the implementation of HPV self-sampling. This is underscored by the risk that a lower detection of CIN2+ could manifest itself after several years as a higher incidence of interval cancers,² resulting in loss of life and adding pressure to the already complex task of steering a screening programme.

5.1 | Improving the sensitivity of self-sampling for the detection of CIN2+

Most HPV assays and their operational protocols were calibrated with clinician-collected samples in mind. Self-collected samples appear to have a lower concentration of viral material (cellularity) than clinician-collected samples; furthermore, cellularity may differ between self-sampling devices, and these differences may influence clinical performance.^{73,81-84} Thus, it seems reasonable to suggest that optimisation on self-collected samples could enhance HPV testing performance. While re-calibration of assay cut-offs to suit self-collection is not a trivial undertaking, particularly if regulatory approval is sought, it may nevertheless be justified if self-collection is to be deployed increasingly for routine use.

Another relevant issue is what constitutes a valid vs invalid self-sample for HPV testing and whether this is differentially affected according to population, device, assay or preanalytical stages including pretest storage time or temperature (eg, while in transport from a woman's home to a laboratory). Optimisation of these technical aspects will benefit from more granular reporting on preanalytical steps and the definitions used for unsuitability and invalidity.^{85,86}

Currently, preanalytic processing of self-collected samples remains relatively manual compared to the systems set up for clinician-taken samples, to an extent that they may be unsuitable for high-throughput routine settings.⁸² Due to this and other factors including the lack of longitudinal performance data, HPV self-sampling technology still lags behind with respect to formal validation and inclusion in manufacturer claims, with only few manufacturers having a CE-marked claim for self-collected samples⁸⁷ and, to our knowledge, at time of preparation of this review, no manufacturer has an FDA-approved claim. Given the increased appetite for HPV self-sampling, it is very likely that an increasing number of formally approved options will emerge from the commercial sector. Screening programmes and funders may also prioritise primary screening projects that have the potential to facilitate best-practice around operationalising of HPV testing on self-collected samples including all preanalytical stages. Shared international learning from project and programme experience will be helpful in the creation of quality assurance frameworks and guidance consistent with good clinical and laboratory practices while remaining mindful of the changing technology.

While waiting until longitudinal evidence becomes available, self-sampling policy can be guided by the outcomes of well-designed cross-sectional validation studies so as not to unduly delay its implementation. In light of the low specificity of HPV infections for the detection of CIN2+, however, studies should ideally continue to validate the performance of self-sampling tests against histologically confirmed endpoints,^{88,89} even if virological endpoints appear to lead to quicker answers.⁹⁰

This work could be expedited by having access to biobanked collections of samples from primary screening populations that have been linked to subsequent CIN2+ outcomes. Stored samples represent credible biospecimens for HPV testing and have been used successfully to expedite the clinical and technical performance validation of several HPV assays, including through the Meijer noninferiority validation criteria or the VALGENT exercise.⁹¹⁻⁹³ Furthermore, given the low prevalence of CIN2+ in well-screened populations, biobanks provide the opportunity to enrich for primary screening samples associated with CIN2+ to support retrospective assessments. Clearly, biobanks require both human and physical resource as well as strong support to ensure appropriate governance is in place and data linkages are robust.⁹⁴ However, having well-annotated archives that include self-taken samples provides opportunities to assess the ever-expanding list of emerging HPV assays, including in terms of comparative performance. In NHS England, as part of a programme-endorsed technical evaluation of self-collection devices and tests within clinical and primary care settings, a biobanking component has been included for these reasons.²¹

5.2 | Implications of low compliance with triage testing on the detection of CIN2+

Women with HPV-positive self-collected samples are required to make an appointment for a new, clinician-collected, sample for cytological evaluation, which is at present the most thoroughly validated method for triage to colposcopy.² If women do not take this step in the screening process, they are most likely unable to proceed to colposcopy and receive a diagnosis and treatment of any prevalent CIN2+ lesions. Because screening is most effective if progressive lesions are treated early, this would mean the benefit they gained from self-collection was negligible. In the Dutch real-world implementation, 78% to 79% of HPV-positive women attended for clinician-collected triage sampling within a year of the screening sample.⁵ Somewhat higher adherence, ~90%, was observed among underscreened women in routine implementation in Denmark and in a trial using a mailout model of self-sampling kit distribution in Australia,^{32,95} although in the latter case <60% of women with HPV-positive, cytology-negative screening tests adhered with early-recall testing.⁹⁵ Similarly low adherence with early recall testing has been reported in the Australian national statistics for HPV-positive women whose samples were taken by a clinician.⁹⁶ In other countries, however, the success of self-sampling strategies in retaining HPV-positive women on their pathways to diagnosis will be scrutinised against considerably more effective follow-up adherence models. In England, for example, the proportion of women who were HPV-positive on a clinician-collected sample and completed early recall

testing in 12 and 24 months after initially negative cytology was ~85%, whereas the proportions undergoing colposcopy remained at >90% regardless of whether the woman was referred at baseline or after one of the two early recalls.⁹⁷

Working on the assumption that women who do not attend for clinician-collected triage testing have the same risk of CIN2+ as women who do, nonadherence further reduces the relative detection of CIN2+ with self-sampling from just over 90% as described above to just over 70%. This is the most favourable estimate from the Dutch programme ($91\%^{73} \times 79\%$),⁵ although it could be as low as around 60% ($73\%^{36} \times 78\%^5$). Even with 90% attendance for triage and 90% relative sensitivity, the detection of CIN2+ would still lag well behind that of clinician collection, at ~80%.

5.3 | Improving the triage pathway

Interventions improving adherence with clinician sampling when the triage approach obligates it—at baseline and at early recall—will be key in achieving high detection of CIN2+ in women screened with self-collection. Previous studies have shown that patient-provider communication using for example, reminders or counselling and educational sessions can improve adherence after abnormal screening tests.⁹⁸ How these interventions could be optimally applied within the context of self-collection would require further study.

Importantly, molecular biomarkers which can be applied directly on the self-collected HPV-positive screening test would bypass the issue of attendance for a clinician-collected sample. While limited genotyping for HPV16/18 would be practically straightforward and may be routinely available according to the read-out of the screening test, it requires a second triage test (this is usually cytology) to identify the group of women with CIN2+ lesions caused by other high-risk genotypes. Increasing the genotyping capacity beyond HPV16/18 may well have promise, and it is interesting that a greater number of new HPV platforms provide assay read-outs as risk ‘clusters’ where the 14 genotypes traditionally considered high-risk are aggregated into tiers according to their ultimate risk of high-grade CIN. Much work has also been devoted to the assessment of methylation biomarkers as a triage option for self-taken samples and data show a good sensitivity particularly at the level of CIN3+. Various methylation targets (viral, host, both) and protocols have been described.⁹⁹⁻¹⁰¹ However, scalability and automation remain an issue and efforts to improve this are welcome.¹⁰² Finally, it is worth noting that the expansion in molecular diagnostics in the last 2 years has followed an unprecedented acceleration due to SARS CoV-2. Collateral value may well be conferred to HPV-relevant biomarker developments because of increased access to skilled workforce and sophisticated platforms.¹⁰³

5.4 | Emerging collection methods

Urine is fast becoming another viable option for woman-friendly collection of cervical screening samples. Studies using a new collection

device (Colli-Pee) have shown increased detection and improved sensitivity for CIN2+ compared to collection of urine in a sterile pot.^{104,105} This device collects first-void urine, which contains washed away cervical exfoliated cellular debris containing significantly more HPV DNA compared to subsequent urine fractions.¹⁰⁶ However, studies remain few and the true clinical accuracy needs to be proven in larger primary screening populations studies using a range of HPV PCR assays.

Optimisation of testing protocols is necessary to provide assurance for a role of this sample type in population-based screening. The crucial considerations include those regarding the choice of the preservative, concentration volumes, the timing for adding the urine to the preservative to prevent DNA degradation resulting in invalid or false-negative HPV samples, and stability at different temperatures during transport to the laboratory.¹⁰⁷ Additionally, all considerations regarding triage discussed for vaginal self-collection also apply to urine self-collection, although proof-of-concept work has demonstrated that urine can be used with limited genotyping and methylation analysis.¹⁰⁸ This is currently being developed in feasibility studies, which are beginning to provide additional reassurance for the use of methylation analysis to discern between low-grade and high-grade histological lesions in HPV-positive women.¹⁰⁹

6 | CLOSING REMARKS

Delaying an implementation of new-generation life-saving screening tests costs lives,¹¹⁰ especially considering the potential of HPV self-sampling to accelerate the elimination of cervical cancer globally. HPV self-sampling has other nontrivial benefits in cervical screening, such as a reduction of the psychological burden which some women experience in association with providing a screening sample.^{4,65,68}

Nevertheless, although various modelling studies have by now helpfully demonstrated that HPV self-sampling could be a (cost-)effective addition to cervical screening programmes,^{14,16,51,71} an implementation leading to a substantially lower detection of CIN2+ without increasing participation among high-risk underscreened women could reduce the number of lives that could be saved through screening.^{14,16} In light of this, the observations from early adopters reviewed here have been helpful in identifying various levers which could be used to steer the implementation process and, acknowledging the drawbacks of the currently available technologies, offer HPV self-sampling to women using models consistent with the principles of informed choice. Precaution and mitigations are particularly relevant for countries with established call recall programmes that have achieved high screening uptake and have traditionally operated a very high-quality screening service, which places a high burden of proof on new technologies.

Without advocating for the pursuit of the perfect at the expense of the good, translation into real-world implementation now needs to focus on mitigations that would prevent unfavourable scenarios (Table 3). Planning that considers local contexts will be crucial in supporting a streamlined self-sampling service. Pilot studies may be

helpful in this regard and would also allow screening programmes to fine-tune any governance and communication issues, test logistics, triangulate communication between the different levels of care, and test external but linked systems such as postal services.

The amount of the work ahead of us remains substantial, but we hope that this review provides a good starting point and are certain that satisfactory solutions could be within sight if we enhance international collaboration between experts from various disciplines.

AUTHOR CONTRIBUTIONS

Matejka Rebolj: Conceptualisation; Literature review; Writing (original draft); Writing (review and editing); Decision to submit. **Alexandra Sargent:** Literature review; Writing (review and editing); Decision to submit. **Sisse Helle Njor:** Literature review; Writing (review and editing); Decision to submit. **Kate Cuschieri:** Literature review; Writing (review and editing); Decision to submit. The work reported in the article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST

Matejka Rebolj: Public Health England provided financing for the epidemiological evaluation of the English HPV screening pilot and the HPVvalidate study in HPV self-sampling; member of various expert groups providing advice to the English Cervical Screening Programme including on HPV self-sampling; attended meetings with various HPV assay manufacturers; fee for lecture from Hologic paid to employer. **Alexandra Sargent:** Member of various expert groups providing advice to the English Cervical Screening Programme including on HPV self-sampling; holds an honorary contract with The University of Manchester to support research into HPV testing in urine samples and Professional Clinical Advisor to the English Cervical Screening Programme. **Sisse Helle Njor:** Declares no conflict of interest related to this review. **Kate Cuschieri:** Research funding or consumables to support research in the last 3 years from Cepheid, Euroimmun, GeneFirst, SelfScreen, Hiantis Seegene, Roche, Abbott and Hologic, paid to employer. Professional Clinical Advisor to the English Cervical Screening Programme; member of various expert groups providing advice to the English Cervical Screening Programme including on HPV self-sampling; member of the working group that has provided advice to the Scottish Cervical Screening Programme on the potential use of HPV self-sampling within the programme.

DATA AVAILABILITY STATEMENT

The authors cannot provide access to the data discussed in the article, as the review was based entirely on previously published data collected by multiple research groups.

ETHICS STATEMENT

No ethics approval has been sought as this review was based on previously published data.

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REFERENCES

- Serrano B, Ibanez R, Robles C, Peremiquel-Trillas P, de Sanjose S, Bruni L. Worldwide use of HPV self-sampling for cervical cancer screening. *Prev Med.* 2022;154:106900.
- Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet.* 2014;383:524-532.
- Korfage IJ, van Ballegooijen M, Wauben B, Looman CW, Habbema JD, Essink-Bot ML. Having a Pap smear, quality of life before and after cervical screening: a questionnaire study. *BJOG.* 2012;119:936-944.
- Nelson EJ, Maynard BR, Loux T, Fatla J, Gordon R, Arnold LD. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. *Sex Transm Infect.* 2017;93:56-61.
- Rijksinstituut voor Volksgezondheid en Milieu. Monitor bevolkingsonderzoek baarmoederhalskanker 2009-2021. <https://www.rivm.nl/bevolkingsonderzoek-baarmoederhalskanker/professionals/monitoring-en-evaluatie>. Accessed June 30, 2022.
- NHS Digital. Cervical Screening Programme, England - 2020-21. Official statistics, national statistics. <https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-annual/england--2020-2021>. Accessed June 30, 2022.
- Yeh PT, Kennedy CE, de Vuyst H, Narasimhan M. Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis. *BMJ Glob Health.* 2019;4:e001351.
- Wood B, Lofters A, Vahabi M. Strategies to reach marginalized women for cervical cancer screening: a qualitative study of stakeholder perspectives. *Curr Oncol.* 2018;25:e8-e16.
- Richards M. Report of the independent review of adult screening programmes in England (Publication reference 01089). <https://www.england.nhs.uk/wp-content/uploads/2019/02/report-of-the-independent-review-of-adult-screening-programme-in-england.pdf>. Accessed June 30, 2022.
- European Cancer Organisation. Self-sampling and HPV screening in Europe. Position Paper. https://www.europecancer.org/index.php?option=com_attachments&task=download&id=659:ECO_Position-Paper_Self-Sampling-and-HPV-Screening-in-Europe_2021. Accessed June 30, 2022.
- Meierhans J. Covid smear-test delays prompt calls for home HPV tests. <https://www.bbc.com/news/health-55663186>. Accessed June 30, 2022.
- Arbyn M, Gultekin M, Morice P, et al. The European response to the WHO call to eliminate cervical cancer as a public health problem. *Int J Cancer.* 2021;148:277-284.
- Landy R, Pesola F, Castanon A, Sasieni P. Impact of cervical screening on cervical cancer mortality: estimation using stage-specific results from a nested case-control study. *Br J Cancer.* 2016;115:1140-1146.
- Rozemeijer K, de Kok IM, Naber SK, et al. Offering self-sampling to non-attendees of organized primary HPV screening: when do harms outweigh the benefits? *Cancer Epidemiol Biomarkers Prev.* 2015;24:773-782.
- de Kok IM v RJ, Dillner J, Arbyn M, Sasieni P, Iftner T, van Ballegooijen M. Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model. *BMJ.* 2012;344:e670.
- Burger EA, Sy S, Nygard M, Kim JJ. The cost-effectiveness of cervical self-sampling to improve routine cervical cancer screening: the importance of respondent screening history and compliance. *Cancer Epidemiol Biomarkers Prev.* 2017;26:95-103.
- Socialstyrelsen. Tillfällig möjlighet till screening med HPV-självprovtagning med anledning av covid-19-pandemin. <https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-screeningprogram/slutliga-rekommendationer/livmoderhalscancer/tillfallig-mojlighet-till-screening-med-hpv-sjalvprovtagning-med-anledning-av-covid-19-pandemin/>. Accessed June 30, 2022.
- Canfell K, Smith MA, Bateson DJ. Self-collection for HPV screening: a game changer in the elimination of cervical cancer. *Med J Aust.* 2021;215:347-348.
- New Zealand Ministry of Health. *National Cervical Screening Programme: HPV Primary Screening Clinical Pathway to Introduce Self-Testing: Public Consultation*. Wellington: Ministry of Health; 2021.
- Health Council of the Netherlands. Options for improving population screening for cervical cancer. No 2021/40, The Hague, October 19, 2021. Executive summary for the Advisory Report. <https://www.healthcouncil.nl/documents/advisory-reports/2021/10/19/options-for-improving-population-screening-for-cervical-cancer>. Accessed June 30, 2022.
- Stubbs R. ‘Significant breakthrough’ toward cervical screening self-sampling. <https://phscreening.blog.gov.uk/2020/12/21/significant-breakthrough-towards-cervical-screening-self-sampling/>. Accessed June 30, 2022.
- Sundhedsstyrelsen. Screening for livmoderhalskræft; Anbefalinger 2018. <https://www.sst.dk/-/media/Udgivelser/2018/Screening-for-livmoderhalskr%C3%A6ft---anbefalinger-maj-2018.ashx>. Accessed June 30, 2022.
- Bais AG, van Kemenade FJ, Berkhof J, et al. Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect nonresponders in cervical screening programs. *Int J Cancer.* 2007;120:1505-1510.
- Wikstrom I, Lindell M, Sanner K, Wilander E. Self-sampling and HPV testing or ordinary pap-smear in women not regularly attending screening: a randomised study. *Br J Cancer.* 2011;105:337-339.
- Gok M, Heideman DA, van Kemenade FJ, et al. Offering self-sampling for human papillomavirus testing to non-attendees of the cervical screening programme: characteristics of the responders. *Eur J Cancer.* 2012;48:1799-1808.
- Kitchener HC, Gittins M, Rivero-Arias O, et al. A cluster randomised trial of strategies to increase cervical screening uptake at first invitation (STRATEGIC). *Health Technol Assess.* 2016;20:1-138.
- Elfstrom KM, Sundstrom K, Andersson S, et al. Increasing participation in cervical screening by targeting long-term nonattenders: randomized health services study. *Int J Cancer.* 2019;145:3033-3039.
- Lam JU, Rebolj M, Moller Ejegod D, et al. Human papillomavirus self-sampling for screening nonattenders: opt-in pilot implementation with electronic communication platforms. *Int J Cancer.* 2017;140:2212-2219.
- Sultana F, English DR, Simpson JA, et al. Home-based HPV self-sampling improves participation by never-screened and under-screened women: results from a large randomized trial (iPap) in Australia. *Int J Cancer.* 2016;139:281-290.
- Cadman L, Wilkes S, Mansour D, et al. A randomized controlled trial in non-responders from Newcastle upon Tyne invited to return a self-sample for human papillomavirus testing versus repeat invitation for cervical screening. *J Med Screen.* 2015;22:28-37.
- Szarewski A, Cadman L, Mesher D, et al. HPV self-sampling as an alternative strategy in non-attenders for cervical screening - a randomised controlled trial. *Br J Cancer.* 2011;104:915-920.
- Ejegod DM, Pedersen H, Pedersen BT, Serizawa R, Bonde J. Operational experiences from the general implementation of HPV self-sampling to Danish screening non-attenders. *Prev Med.* 2022;160:107096.
- Styregruppen for DKLS. Årsrapport DKLS 2019: Dansk Kvalitetsdatabase for Livmoderhalskræftscreening, Årsrapport 2019. <https://>

- www.sundhed.dk/content/cms/82/4682_dkls_aarsrapport_2019_off_version.pdf. Accessed June 30, 2022.
34. Creagh NS, Zammit C, Brotherton JM, et al. Self-collection cervical screening in the renewed National Cervical Screening Program: a qualitative study. *Med J Aust*. 2021;215:354-358.
 35. Aitken CA, van Agt HME, Siebers AG, et al. Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. *BMC Med*. 2019;17:228.
 36. Aitken CA, Inturrisi F, Kaljouw S, et al. Sociodemographic characteristics and screening outcomes of women preferring self-sampling in the Dutch cervical cancer screening programme: a population-based study. *Cancer Epidemiol Biomarkers Prev*. Online ahead of print.
 37. Kotzur M, McCowan C, Macdonald S, et al. Why colorectal screening fails to achieve the uptake rates of breast and cervical cancer screening: a comparative qualitative study. *BMJ Qual Saf*. 2020;29:482-490.
 38. Rijksinstituut voor Volksgezondheid en Milieu. *The Dutch Cervical Cancer Screening Programme and the Use of Self-Sampling*. Factsheet 2021. Bilthoven: RIVM; 2021.
 39. Leinonen MK, Schee K, Jonassen CM, et al. Safety and acceptability of human papillomavirus testing of self-collected specimens: a methodologic study of the impact of collection devices and HPV assays on sensitivity for cervical cancer and high-grade lesions. *J Clin Virol*. 2018;99-100:22-30.
 40. Bosgraaf RP, Verhoef VM, Massuger LF, et al. Comparative performance of novel self-sampling methods in detecting high-risk human papillomavirus in 30,130 women not attending cervical screening. *Int J Cancer*. 2015;136:646-655.
 41. Arbyn M, Smith SB, Temin S, Sultana F, Castle P. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ*. 2018;363:k4823.
 42. Tranberg M, Bech BH, Blaakaer J, Jensen JS, Svanholm H, Andersen B. Preventing cervical cancer using HPV self-sampling: direct mailing of test-kits increases screening participation more than timely opt-in procedures - a randomized controlled trial. *BMC Cancer*. 2018;18:273.
 43. Ivanus U, Jerman T, Fokter AR, et al. Randomised trial of HPV self-sampling among non-attenders in the Slovenian cervical screening programme ZORA: comparing three different screening approaches. *Radiol Oncol*. 2018;52:399-412.
 44. Lim AW, Hollingworth A, Kalwij S, Curran G, Sasieni P. Offering self-sampling to cervical screening non-attenders in primary care. *J Med Screen*. 2017;24:43-49.
 45. Peeters E, Cornet K, Cammu H, Verhoeven V, Devroey D, Arbyn M. Efficacy of strategies to increase participation in cervical cancer screening: GPs offering self-sampling kits for HPV testing versus recommendations to have a pap smear taken - a randomised controlled trial. *Papillomavirus Res*. 2020;9:100194.
 46. Giorgi Rossi P, Fortunato C, Barbarino P, et al. Self-sampling to increase participation in cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies, and recall letter. *Br J Cancer*. 2015;112:667-675.
 47. Dutton T, Marjoram J, Burgess S, et al. Uptake and acceptability of human papillomavirus self-sampling in rural and remote aboriginal communities: evaluation of a nurse-led community engagement model. *BMC Health Serv Res*. 2020;20:398.
 48. Zehbe I, Jackson R, Wood B, et al. Community-randomised controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus papanicolaou cytology. *BMJ Open*. 2016;6:e011754.
 49. McLachlan E, Anderson S, Hawkes D, Saville M, Arabena K. Completing the cervical screening pathway: factors that facilitate the increase of self-collection uptake among under-screened and never-screened women, an Australian pilot study. *Curr Oncol*. 2018;25:e17-e26.
 50. Smith M, Hammond I, Saville M. Lessons from the renewal of the National Cervical Screening Program in Australia. *Public Health Res Pract*. 2019;29:2921914.
 51. Smith MA, Hall MT, Saville M, et al. Could HPV testing on self-collected samples be routinely used in an organized cervical screening program? A modeled analysis. *Cancer Epidemiol Biomarkers Prev*. 2021;30:268-277.
 52. Sultana F, Roeske L, Malloy MJ, McDermott TL, Saville M, Brotherton JML. Implementation of Australia's renewed cervical screening program: preparedness of general practitioners and nurses. *PLoS One*. 2020;15:e0228042.
 53. Foo YM, Goswami P, Grogan J, et al. Incorporation of human papillomavirus self-sampling into the revised National Cervical Screening Program: a qualitative study of GP experiences and attitudes in rural New South Wales. *Aust J Prim Health*. 2021;27:284-290.
 54. Sweeney SO, Cheng Y, Botfield JR. Renewal of the National Cervical Screening Program: health professionals' knowledge about screening of specific populations in NSW, Australia. *Public Health Res Pract*. 2022;32:31122104.
 55. Australian Government Department of Health. Medicare benefits schedule book; category 6; operating from December 1, 2017. [http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/%20Content/81D3D41DCEAE03F0CA2581C60013304B/\\$File/201712-Cat6.pdf](http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/%20Content/81D3D41DCEAE03F0CA2581C60013304B/$File/201712-Cat6.pdf). Accessed June 30, 2022.
 56. Cancer Council. Screening by self-collection a 'game-changer' for eliminating cervical cancer in Australia. <https://www.cancer.org.au/media-releases/2021/screening-by-self-collection-a-game-changer-for-eliminating-cervical-cancer-in-australia>. Accessed June 30, 2022.
 57. Karjalainen L, Anttila A, Nieminen P, Luostarinen T, Virtanen A. Self-sampling in cervical cancer screening: comparison of a brush-based and a lavage-based cervicovaginal self-sampling device. *BMC Cancer*. 2016;16:221.
 58. Lofters AK, Baker NA, Corrado AM, et al. Care in the Community: opportunities to improve cancer screening uptake for people living with low income. *Prev Med Rep*. 2021;24:101622.
 59. Tatari CR, Andersen B, Brogaard T, Badre-Esfahani S, Jaafar N, Kirkegaard P. The SWIM study: ethnic minority women's ideas and preferences for a tailored intervention to promote national cancer screening programmes-a qualitative interview study. *Health Expect*. 2021;24:1692-1700.
 60. Kraut RY, Manca D, Lofters A, et al. Attitudes toward human papillomavirus self-sampling in regularly screened women in Edmonton, Canada: a cross-sectional study. *J Low Genit Tract Dis*. 2021;25:199-204.
 61. Waller J, McCaffery K, Forrest S, et al. Acceptability of unsupervised HPV self-sampling using written instructions. *J Med Screen*. 2006;13:208-213.
 62. Smith LW, Khurshed F, van Niekerk DJ, et al. Women's intentions to self-collect samples for human papillomavirus testing in an organized cervical cancer screening program. *BMC Public Health*. 2014;14:1060.
 63. Datta GD, Mayrand MH, Qureshi S, Ferre N, Gauvin L. HPV sampling options for cervical cancer screening: preferences of urban-dwelling Canadians in a changing paradigm. *Curr Oncol*. 2020;27:e171-e181.
 64. Hanley SJ, Fujita H, Yokoyama S, et al. HPV self-sampling in Japanese women: a feasibility study in a population with limited experience of tampon use. *J Med Screen*. 2016;23:164-170.
 65. Polman NJ, de Haan Y, Veldhuijzen NJ, et al. Experience with HPV self-sampling and clinician-based sampling in women attending routine cervical screening in The Netherlands. *Prev Med*. 2019;125:5-11.

66. Ketelaars PJW, Bosgraaf RP, Siebers AG, et al. High-risk human papillomavirus detection in self-sampling compared to physician-taken smear in a responder population of the Dutch cervical screening: results of the VERA study. *Prev Med.* 2017;101:96-101.
67. Mullins R, Scalzo K, Sultana F. Self-sampling for cervical screening: could it overcome some of the barriers to the pap test? *J Med Screen.* 2014;21:201-206.
68. Drysdale H, Marlow LA, Lim A, Sasieni P, Waller J. Self-sampling for cervical screening offered at the point of invitation: a cross-sectional study of preferences in England. *J Med Screen.* 2022;29:194-202.
69. Regionala Cancercentrum i Samverkan. Vårdprogram får nytt kapitel om självprovtagning för HPV-analys. <https://cancercentrum.se/samverkan/om-oss/nyheter/2021/maj/varprogram-far-nytt-kapitel-om-sjalfprovtagning-for-hpv-analys/>. Accessed June 30, 2022.
70. Enerly E, Bonde J, Schee K, Pedersen H, Lonnberg S, Nygard M. Self-sampling for human papillomavirus testing among non-attenders increases attendance to the Norwegian Cervical Cancer Screening Programme. *PLoS One.* 2016;11:e0151978.
71. Pedersen K, Portnoy A, Sy S, et al. Switching clinic-based cervical cancer screening programs to human papillomavirus self-sampling: a cost-effectiveness analysis of vaccinated and unvaccinated Norwegian women. *Int J Cancer.* 2021;150:491-501.
72. Polman NJ, Ebisch RMF, Heideman DAM, et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol.* 2019;20:229-238.
73. Inturrisi F, Aitken CA, Melchers WJG, et al. Clinical performance of high-risk HPV testing on self-samples versus clinician samples in routine primary HPV screening in The Netherlands: an observational study. *Lancet Reg Health Eur.* 2021;11:100235.
74. Rebolj M, Njor S, Lynge E, et al. Referral population studies underestimate differences between human papillomavirus assays in primary cervical screening. *Cytopathology.* 2017;28:419-428.
75. Snijders PJ, van den Brule AJ, Meijer CJ. The clinical relevance of human papillomavirus testing: relationship between analytical and clinical sensitivity. *J Pathol.* 2003;201:1-6.
76. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med.* 1978;299:926-930.
77. Arbyn M, Simon M, Peeters E, et al. 2020 list of human papillomavirus assays suitable for primary cervical cancer screening. *Clin Microbiol Infect.* 2021;27:1083-1095.
78. Aarnio R, Isacson I, Sanner K, Gustavsson I, Gyllensten U, Olovsson M. Comparison of vaginal self-sampling and cervical sampling by medical professionals for the detection of HPV and CIN2+: a randomized study. *Int J Cancer.* 2021;148:3051-3059.
79. Gustavsson I, Aarnio R, Berggrund M, et al. Randomised study of HPV prevalence and detection of CIN2+ in vaginal self-sampling compared to cervical specimens collected by medical personnel. *Int J Cancer.* 2019;144:89-97.
80. Stanczuk GA, Currie H, Forson W, et al. Self-sampling as the principal modality for population based cervical screening: five-year follow-up of the PaVDaG study. *Int J Cancer.* 2021;150:1350-1356.
81. Cadman L, Reuter C, Jitlal M, et al. A randomized comparison of different vaginal self-sampling devices and urine for human papillomavirus testing-predictors 5.1. *Cancer Epidemiol Biomarkers Prev.* 2021;30:661-668.
82. Jentschke M, Chen K, Arbyn M, et al. Direct comparison of two vaginal self-sampling devices for the detection of human papillomavirus infections. *J Clin Virol.* 2016;82:46-50.
83. Ertik FC, Kampers J, Hulse F, et al. CoCoss-trial: concurrent comparison of self-sampling devices for HPV-detection. *Int J Environ Res Public Health.* 2021;18:10388.
84. Klischke L, von Ehr J, Kohls F, et al. Performance of a six-methylation-marker assay on self-collected cervical samples - a feasibility study. *J Virol Methods.* 2021;295:114219.
85. Arbyn M, Latsuzbaia A, Castle PE, Sahasrabudhe VV, Broeck DV. HPV testing of self-samples: influence of collection and sample handling procedures on clinical accuracy to detect cervical precancer. *Lancet Reg Health Eur.* 2022;14:100332.
86. Hawkes D, Keung MHT, Huang Y, et al. Self-collection for cervical screening programs: from research to reality. *Cancers (Basel).* 2020;12:1053.
87. BD. BD announces industry-first CE marked assay for HPV screening from at-home self-collected vaginal samples. <https://news.bd.com/2021-05-13-BD-Announces-Industry-First-CE-Marked-Assay-for-HPV-Screening-from-At-Home-Self-Collected-Vaginal-Samples>. Accessed June 30, 2022.
88. Meijer CJ, Berkhof J, Castle PE, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer.* 2009;124:516-520.
89. Brentnall AR, Rebolj M. Comments on: 'meta-analysis of agreement/concordance statistics in studies comparing self- vs clinician-collected samples for HPV testing in cervical cancer screening'. *Int J Cancer.* 2022;151:481-483.
90. Arbyn M, Castle PE, Schiffman M, Wentzensen N, Heckman-Stoddard B, Sahasrabudhe VV. Meta-analysis of agreement/concordance statistics in studies comparing self- versus clinician-collected samples for HPV testing in cervical cancer screening. *Int J Cancer.* 2022;151:308-312.
91. Heideman DA, Hesselink AT, van Kemenade FJ, et al. The Aptima HPV assay fulfills the cross-sectional clinical and reproducibility criteria of international guidelines for human papillomavirus test requirements for cervical screening. *J Clin Microbiol.* 2013;51:3653-3657.
92. Heideman DA, Hesselink AT, Berkhof J, et al. Clinical validation of the cobas 4800 HPV test for cervical screening purposes. *J Clin Microbiol.* 2011;49:3983-3985.
93. Arbyn M, Depuydt C, Benoy I, et al. VALGENT: a protocol for clinical validation of human papillomavirus assays. *J Clin Virol.* 2016;76-(Suppl 1):S14-S21.
94. Alcañiz Boada E, Dillner J, Cuschieri K. The importance of biobanking to support HPV-based research. https://www.hpvworld.com/media/29/media_section/1/2/1112/Alcaniz.pdf. Accessed June 30, 2022.
95. Sultana F, Gertig DM, English DR, et al. HPV self-sampling and follow-up over two rounds of cervical screening in Australia - the iPap trial. *J Med Screen.* 2022;29:185-193.
96. Australian Government - Australian Institute of Health and Welfare. National Cervical Screening Program monitoring report 2021. <https://www.aihw.gov.au/getmedia/2a26ae22-2f84-4d75-a656-23c329e476bb/aihw-can-141.pdf.aspx?inline=true>. Accessed June 30, 2022.
97. Green LI, Mathews CS, Waller J, Kitchener H, Rebolj M. Attendance at early recall and colposcopy in routine cervical screening with human papillomavirus testing. *Int J Cancer.* 2020;148:1850-1857.
98. Eggleston KS, Coker AL, Das IP, Cordray ST, Luchok KJ. Understanding barriers for adherence to follow-up care for abnormal pap tests. *J Womens Health (Larchmt).* 2007;16:311-330.
99. Verlaet W, Snoek BC, Heideman DAM, et al. Identification and validation of a 3-gene methylation classifier for HPV-based cervical screening on self-samples. *Clin Cancer Res.* 2018;24:3456-3464.
100. Del Mistro A, Frayle H, Rizzi M, et al. Methylation analysis and HPV genotyping of self-collected cervical samples from women not responding to screening invitation and review of the literature. *PLoS One.* 2017;12:e0172226.
101. Luttmer R, De Strooper LM, Dijkstra MG, et al. FAM19A4 methylation analysis in self-samples compared with cervical scrapes for

- detecting cervical (pre)cancer in HPV-positive women. *Br J Cancer*. 2016;115:579-587.
102. Verhoef L, Floore AN, Doorn S, et al. Direct bisulphite conversion of cervical samples for DNA methylation analysis. *Epigenetics*. 2021;17:1173-1179.
 103. Poljak M, Cuschieri K, Waheed DE, Baay M, Vorsters A. Impact of the COVID-19 pandemic on human papillomavirus-based testing services to support cervical cancer screening. *Acta Dermatovenol Alp Pannonica Adriat*. 2021;30:21-26.
 104. Pattyn J, Van Keer S, Biesmans S, et al. Human papillomavirus detection in urine: effect of a first-void urine collection device and timing of collection. *J Virol Methods*. 2019;264:23-30.
 105. Leeman A, Del Pino M, Molijn A, et al. HPV testing in first-void urine provides sensitivity for CIN2+ detection comparable with a smear taken by a clinician or a brush-based self-sample: cross-sectional data from a triage population. *BJOG*. 2017;124:1356-1363.
 106. Vorsters A, Van den Bergh J, Micalessi I, et al. Optimization of HPV DNA detection in urine by improving collection, storage, and extraction. *Eur J Clin Microbiol Infect Dis*. 2014;33:2005-2014.
 107. Sargent A, Fletcher S, Bray K, Kitchener HC, Crosbie EJ. Cross-sectional study of HPV testing in self-sampled urine and comparison with matched vaginal and cervical samples in women attending colposcopy for the management of abnormal cervical screening. *BMJ Open*. 2019;9:e025388.
 108. Van Keer S, Pattyn J, Tjalma WAA, et al. First-void urine: a potential biomarker source for triage of high-risk human papillomavirus infected women. *Eur J Obstet Gynecol Reprod Biol*. 2017;216:1-11.
 109. Van Keer S, van Splunter AP, Pattyn J, et al. Triage of human papillomavirus infected women by methylation analysis in first-void urine. *Sci Rep*. 2021;11:7862.
 110. Castanon A, Rebolj M, Sasieni P. Is a delay in the introduction of human papillomavirus-based cervical screening affordable? *J Med Screen*. 2019;26:44-49.

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