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Self-sampling as the principal modality for population based cervical screening: Five-year follow-up of the PaVDaG study

Grazyna A. Stanczuk[1,2] | Heather Currie[3] | William Forson[3] | Gwendoline Baxter[4] | James Lawrence[1] | Allan Wilson[5] | Timothy Palmer[6] | Marc Arbyn[7,8] | Kate Cuschieri[9]

[1]Department of Research and Development, Dumfries and Galloway Royal Infirmary, Dumfries, UK

[2]Global Health Academy, University of Edinburgh, Edinburgh, UK

[3]Department of Obstetrics and Gynaecology, Dumfries and Galloway Royal Infirmary, Dumfries, UK

[4]North Cumbria Integrated NHS Foundation Care Trust, Carlisle, UK

[5]Department of Pathology, Monklands Hospital, Airdrie, UK

[6]Department of Pathology, University of Edinburgh, Edinburgh, UK

[7]Unit of Cancer Epidemiology/Belgian Cancer Centre, Sciensano, Brussels, Belgium

[8]Department of Human Structure and Repair, Faculty of Medicine and Health Sciences, University Ghent, Ghent, Belgium

[9]Scottish HPV Reference Laboratory, Royal Infirmary of Edinburgh, Edinburgh, UK

Correspondence
Grazyna A. Stanczuk, Western Isles Hospital, MacAulay Road, Stornoway HS1 2AF, UK.
Email: grazyna.stanczuk@nhs.scot

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Abstract

Self-sampling provides a powerful means to engage women in cervical screening. In the original Papillomavirus Dumfries and Galloway study (PaVDaG), we demonstrated cross-sectional similarity of high-risk human papillomavirus (Hr-HPV) testing on self-taken vaginal vs clinician-taken samples for the detection of cervical intraepithelial neoplasia 2 or worse (CIN2+). Few data exist on the longitudinal performance of self-sampling; we present longitudinal outcomes of PaVDaG. Routinely screened women provided a self-taken and a clinician-collected sample. Ninety-one percent of 5136 women from the original cohort completed a further screening round. Sensitivity, specificity, positive predictive value and complement of the negative predictive value of the Hr-HPV test on self-samples for detection of CIN2+ and CIN3+ up-to 5 years after testing were determined. Additionally, clinical accuracy of Hr-HPV testing on vaginal and clinician-collected samples was assessed. A total of 183 CIN2+ and 102 CIN3+ lesions were diagnosed during follow-up. Risk of CIN2+ and CIN3+ following an Hr-HPV negative self-sample was 0.6% and 0.2%, respectively, for up to 5 years after testing. The relative sensitivity for CIN3+ and specificity for ≤CIN1 of Hr-HPV testing on self-taken specimens was slightly lower vs clinician-collected samples: 0.95 (95% CI: 0.90-0.99; $P^{McN} = .0625$) and 0.98 (95% CI: 0.95-1.00; $P^{McN} = <.0000$), respectively. The low risk of CIN2+ in women with Hr-HPV—self-sample(s) suggests, that the 3 to 5-year recall interval implemented in several cervical screening settings, based on clinician-taken samples, may be safe for self-samples. Future assessment will show if "universal" 5-year screening is appropriate for programs based on self-sampling.

KEYWORDS
cervical screening, human papillomavirus, self-sampling

Abbreviations: AGUS, atypical glandular cells of undetermined significance; ASCUS, atypical squamous cells of undetermined significance; BNA, borderline nuclear abnormality; CIN1, cervical intraepithelial neoplasia grade 1; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; FDA, Food and Drug Administration; GP, general practice; Hr-HPV, high-risk human papillomavirus; LBC, liquid-based cytology; LSIL, low grade squamous intraepithelial lesion; NPV, negative predictive value; PaVDaG, Papillomavirus Dumfries and Galloway study; PCR, polymerase chain reaction; PPV, positive predictive value.

What's new?

Primary screening for high-risk human papillomavirus (Hr-HPV) provides better protection against cervical cancer than cytology-based cervical screening. While Hr-HPV-based screening programmes create an opportunity for vaginal self-sampling, the longitudinal performance of self-sampling remains to be determined. Here, the authors provide one of the first datasets to describe the longitudinal performance of Hr-HPV testing with self-taken samples in women who attend population-based cervical screening. The low risk of high-grade disease in women with Hr-HPV-negative self-samples suggests that the three-to-five-year recall interval already implemented in cervical screening programmes based on clinician-taken samples may be appropriate for programmes based on self-sampling.

1 | INTRODUCTION

It is now well established that primary screening for high-risk human papillomavirus (Hr-HPV) provides better protection against cervical intraepithelial neoplasia grade 3 and above (CIN3+) and cervical cancer than cervical cytology.[1,2] Consequently, many cervical screening programs are now based on primary Hr-HPV testing including the United Kingdom, which converted to HPV based screening in 2019 to 2020.

While cytology based primary screening programs require a clinician-taken sample, Hr-HPV based screening programs create an opportunity for vaginal self-sampling.[3-6] Offering self-sampling to women who do not attend routine cervical screening can improve uptake, while offering performance equal to Hr-HPV testing of clinician-taken samples.[5,7-10] Self-sampling can benefit women who find it challenging to tolerate speculum examination and those with poor access to, or disengagement from, health services. Evidence also suggests that, in older women vaginal samples represent a more optimal bio-specimen for Hr-HPV detection vs LBC samples.[11]

The Papillomavirus Dumfries and Galloway (PaVDaG) study demonstrated that a Hr-HPV test using self-collected vaginal samples and clinician-collected cervical LBC samples detected CIN2+ and CIN3+ with similar accuracy.[11] Since the baseline tests were performed in PaVDaG, women have been invited to participate in the subsequent screening round based on cytology (as per the routine guidelines of the time).

Self-sampling is worthy of serious consideration for routine screening use. HPV screen-negative results associated with clinician taken samples justifies a recall interval of 5, possibly 7 years, although some programs still recall at 3 years. Such data for Hr-HPV negative self-samples is not yet available. This report presents longitudinal data on the rate of "interval" high-grade (HG) disease in a population with known HPV results 3 to 5 years after the HPV self-sampling result. The relative performance of self-sampling compared to clinician taken samples, and of self-sampling compared to LBC cytology, is also presented.

2 | MATERIALS AND METHODS

2.1 | Study setting

A longitudinal follow-up analysis of the PaVDaG cohort was conducted in the Dumfries and Galloway region of Scotland, five and half years after the end of enrolment. Dumfries and Galloway has a population of approximately 160 000 inhabitants served by 40 General Practice (GP) Clinics. Women testing HR-HPV negative in the PaVDaG study were invited routine LBC screening after 3 years if they were in the 25 to 49 age group and after 5 years if they were 50 years and older in accordance with program guidelines in Scotland.

2.2 | PaVDaG study cohort; recruitment and follow-up

A total of 5318 women were enrolled in the original PaVDaG study. Recruitment occurred between April 2013 and July 2014 and included women who received their first invitation to cervical screening in the year of their 20th birthday and their last invitation in the year of their 59th birthday. The mean age at enrolment was 41.3 years. Participants provided a self-collected vaginal sample prior to the routine cervical sample transferred into ThinPrep (PreservCyt Solution, Hologic, UK). Sample collection, processing and testing were as previously described.[11] Hr-HPV detection in both self-collected vaginal samples and cervical LBC samples was performed using the Cobas 4800 PCR-based DNA test (Roche Molecular Systems). Overall HPV positivity was 14.7% and 16.6% on cervical and vaginal samples respectively. Only 6.5% of women in the original (n = 5318) cohort would have been offered vaccination as part of the "catch up" program of the time. Consequently, analysis is not stratified according to vaccination status.

Scotland had a cytology-based screening program at the time of enrollment and during the entire period of follow-up, and clinical management of women with abnormal LBC results and histopathology findings were as per the National guidelines.[12] Participants with HG

cytology were referred for colposcopy, while women with low-grade cytology (borderline abnormality [BNA/ASCUS/AGUS] or low-grade dyskaryosis/LSIL) results were recalled for a repeat LBC after 6 months. Women with two low-grade dyskaryosis/AGUS or three BNA/ASCUS results were referred for colposcopy. Participants with unsatisfactory smears were offered repeat LBC after 3 months. Three consecutive unsatisfactory LBC results prompted colposcopy referral, as did an abnormal LBC following an unsatisfactory result.

As part of the study, all participants with normal LBC results but a positive cervical Hr-HPV test (LBC−/Hr-HPV+) were invited for repeat Hr-HPV testing after 4 to 6 months. Colposcopy was offered to LBC−/Hr-HPV+ women if they were positive for HPV 16 and/or 18 (HPV 16/18+) at baseline and/or after repeated testing. In cases with a significant disparity between colposcopy assessment and the LBC or histology results, a multidisciplinary team review was conducted (as per standard protocol).

The results of the subsequent "LBC only" screening round, including cytopathology, and histology were retrospectively accessed. All follow-up screening was based on cytology. Figure 1 details the cohort assessed for the present study, with reference both to the parent cohort and to reasons for subsequent attrition. A total of 4617 women completed the first and second round of screening with no pending clinical work-up at time of data collection (censored January 2020).

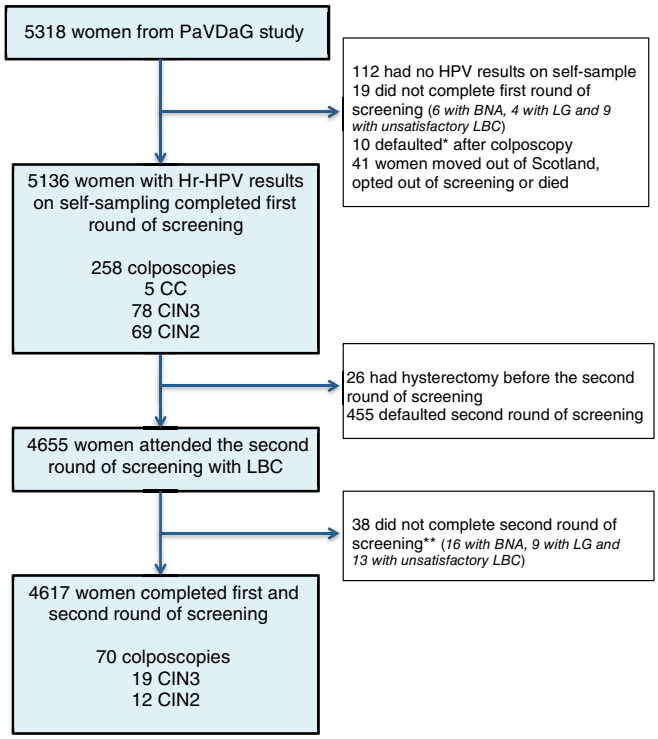

FIGURE 1 Study flow and attrition; includes distribution of outcomes after first and second round of screening. *A defaulter is the term used to describe women who have not taken up an invitation to have a cervical screening test carried out after receiving reminders. **Data collection was completed by the end of January 2020. CC, cervical cancer; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3 [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Statistical analysis

We evaluated absolute sensitivity, specificity and computed positive predictive value (PPV), and complement of negative predictive value (cNPV = 1 – NPV) of Hr-HPV testing on self-samples for detection of CIN2+ and CIN3+ at baseline and up to 5 years after the baseline Hr-HPV screen test result. Sixty-nine months was the longest time between the baseline test and diagnosis of an HG lesion. The longitudinal sensitivity includes all CIN2/3+ detected at baseline and during the whole study period including the second screening round. The computation of the longitudinal specificity was based on women who showed no evidence of previous CIN2+ (≤CIN1) who had normal LBC in at least two screening rounds. Longitudinal PPV was defined as the proportion of women who had a histologically confirmed CIN2+ lesion observed over two screening rounds, among those who participated in both screening rounds. As the Hr-HPV test used incorporates the identification of HPV 16/18, we assessed the performance of 16/18 presence for the detection of CIN2+ and CIN3+ in addition to the primary analysis based on "any" Hr-HPV.

Differences in longitudinal performance between Hr-HPV testing in vaginal self-samples vs clinician-taken were assessed by calculation of the relative accuracy, 95% confidence intervals (CIs) and by McNemars test. Finally, as a context we also determined the clinical performance of cytology in the PaVDaG cohort over the same time period with relative performance of cytology (at a threshold of borderline changes) compared to an Hr-HPV test taken on a self-sample. Stata 16.0 (College Station, Texas) was used for analysis.

3 | RESULTS

3.1 | Performance of Hr-HPV detection in self-samples for the longitudinal detection of CIN2+

During the first round of screening, 152 CIN2+ lesions were diagnosed with a further 31 CIN2+ in the second screening round. A total of 83 cases of CIN3+ were detected in the first and a further 19 in the second screening round. The performance of Hr-HPV testing on self-samples is presented in Table 1. The performance of cytology in the same cohort is included for reasons of contextualization and comparison. All performance values are given for the outcomes CIN2+ and CIN3+. The absolute sensitivity for detection of CIN2+ and CIN3+ of Hr-HPV self-sampling in the first round of screening was 91.4% (95% CI: 85.5-95.2) and 95.2% (95% CI: 87.5-98.4), respectively. The sensitivity of LBC at a threshold of borderline changes was 73.7% (95% CI: 65.8-80.3) and 77.1% (95% CI: 66.3-85.3) for CIN2+ and CIN3+, respectively. When both, CIN2+ lesions detected during the original PaVDaG protocol were combined with those detected via LBC only at the second round, the longitudinal sensitivity of Hr-HPV self-sampling to detect CIN2+ and CIN3+ remained high at 88.0% (95% CI: 82.2-92.1) and 93.1% (95% CI: 85.9-97.0), respectively. The

TABLE 1 Clinical performance of Hr-HPV testing on *self-taken* vaginal samples for the detection of CIN2+ over one to two screening rounds representing up to 69 months of follow-up on a cohort of 4617 women recruited to the PaVDaG study

	Sensitivity % (95% CI)		Specificity % (95% CI)		PPV %		cNPV %	
Test	First round	Second round	First round	Second round	First round	Second round	First round	Second round
CIN2+								
Hr-HPV (any)+	91.4 (85.5-95.2)	88.0 (82.2-92.1)	85.9 (84.8-86.8)	86.1 (85.1-87.1)	16.5	20.7	0.3	0.6
HPV 16/18+	59.9 (51.6-67.6)	55.2 (47.7-62.5)	96.2 (95.6-96.7)	96.2 (95.6-96.8)	32.5	37.5	1.3	1.9
LBC ≥ BNA	73.7 (65.8-80.3)	62.8 (55.4-69.8)	97.3 (96.8-97.8)	97.0 (96.5-97.5)	45.5	46.4	0.8	1.6
CIN3+								
Hr-HPV (any)+	95.2 (87.5-98.4)	93.1 (85.9-97.0)	84.9 (83.8-85.8)	85.1 (84.1-86.1)	9.4	11.3	0.1	0.2
HPV 16/18+	63.9 (52.5-73.9)	58.8 (48.6-68.3)	95.5 (94.9-96.1)	95.4 (94.7-96.0)	18.9	22.3	0.6	1.0
LBC ≥ BNA	77.1 (66.3-85.3)	64.7 (54.6-73.7)	96.4 (95.9-96.9)	96.0 (95.4-96.5)	26.0	26.6	0.4	0.8

Note: Data represent absolute sensitivity and specificity for CIN2+ and CIN3+ (and 95% CI), the computed PPV (positive predictive value) and cNPV (complement of the negative predictive value, 1-NPV). Hr-HPV results are stratified according to "any" Hr-HPV detected in addition to the detection of HPV 16 and/or 18 only. The performance of liquid-based cytology (LBC) at the level of borderline nuclear abnormality and above (≥BNA) is provided as context.

TABLE 2 Hr-HPV positivity in clinician-taken LBC vs *self-taken* vaginal samples stratified by underlying pathology

		Hr-HPV clinician-taken					Hr-HPV clinician-taken		
CIN2+		Pos	Neg	Total	CIN3+		Pos	Neg	Total
Hr-HPV self-taken	Pos	158	1	159	Hr-HPV self-taken	Pos	95	0	95
	Neg	12	10	22		Neg	5	2	7
Total		170	11	181[a]	Total		100	2	102
		Hr-HPV clinician-taken					Hr-HPV clinician-taken		
≤CIN1		Neg	Pos	Total	≤CIN2		Neg	Pos	Total
Hr-HPV self-taken	Neg	3715	94	3809	Hr-HPV self-taken	Neg	3723	101	3824
	Pos	178	437	615		Pos	179	500	679
Total		3893	531	4424	Total		3902	601	4503

Note: Tables depict women with CIN2+, CIN3+, ≤CIN1 and ≤CIN2 (top left from clockwise).
[a]Two CIN2 lesions had failed Hr-HPV test on cervical sample.

risk of CIN2+ and CIN3+ in women with an HPV-negative self-sample (cNPV) at the first round of screening was 0.3% for CIN2+ and 0.1% for CIN3+ and remained under 1% at the second round of screening; at 0.6% for CIN2+ and 0.2% for CIN3+.

3.2 | Women who are HPV 16/18 positive have increased short- and longer-term risks of CIN2+ and CIN3+

The PPV of women who were HPV 16 and or 18 positive on their self-sample was 37.5% over two screening rounds for CIN2+ and 22.3% for CIN3+; this compared to PPVs of 20.7% and 11.3% for CIN2+ and CIN3+ respectively, when considering positivity for "any" Hr-HPV on a self-sample. Sensitivity of HPV 16/18 detection was lower than "any" Hr-HPV detection at 55.2% (95% CI: 47.7-62.5) for CIN2+ and 58.8% (95% CI: 48.6-68.3) for CIN3 over two screening rounds vs 88.0% (95% CI: 82.2-92.1) and 93.1% (95% CI: 85.9-97.0) for CIN2+ and CIN3+ for "any" Hr-HPV detection. Notably, BNA+ cytology had higher sensitivity, higher specificity, higher PPV and lower cNPV than HPV 16/18 testing on self-samples.

3.3 | Are self-samples equivalent to clinician-taken samples?—The relative performance of self-collected vaginal vs clinician-collected cervical samples over two rounds of screening

Table 2 shows Hr-HPV positivity in self-collected vs clinician-collected samples stratified by disease outcome. Of the 181 cases of CIN2+, 159/181 were detected in self-collected samples and 170/181 by the clinician-taken samples. A total of 95/102 and 100/102 cases of CIN3+ were detected by the vaginal self-collected and clinician-taken samples respectively. Overall, 22 CIN2+ lesions

TABLE 3 Relative sensitivity and specificity of Hr-HPV testing on *self-taken* vaginal vs clinician-taken LBC samples for the detection of CIN2+ and CIN3+ over the two screening rounds

Tests	Relative sensitivity	P^{McN}	Relative specificity	P^{McN}
CIN2+				
Hr-HPV+ self-taken vs Hr-HPV+ clinician-taken	0.93 (0.90-0.98)	.0034	0.98 (0.95-1.00)	<.0000
CIN3+				
Hr-HPV+ self-taken vs Hr-HPV+ clinician-taken	0.95 (0.90-0.99)	.0625	0.98 (0.97-0.98)	<.0000

TABLE 4 Relative sensitivity and specificity of Hr-HPV testing on self-taken vaginal sample and liquid-based cytology as screening approaches for the detection of CIN2+ and CIN3+ over the two screening rounds

Tests	Relative sensitivity	P^{McN}	Relative specificity	P^{McN}
CIN2+				
Hr-HPV+ self-taken vs LBC ≥ BNA	1.40 (1.00-1.42)	.0784	0.88 (0.84-0.96)	.0027
CIN3+				
Hr-HPV+ self-taken vs LBC ≥ BNA	1.44 (1.08-1.64)	.0117	0.88 (0.84-0.97)	.0059

were missed by self-sampling and 11 CIN2+ lesions were missed by clinician-sampling. Among the 4424 women without CIN2+, 3809 and 3893 had a negative Hr-HPV result on self- and clinician-samples, respectively. Table 3 shows the relative sensitivity and specificity of Hr-HPV testing in self-collected vs clinician-taken samples. The relative sensitivity and specificity of Hr-HPV testing on a self-collected vs a clinician-collected sample for CIN2+ was 0.93 (95% CI: 0.90-0.98); P^{McN} = .0034 and .98 (95% CI: 0.95-1.00); P^{McN} = <.0001. At the level of CIN3+ relative sensitivity and specificity was 0.95 (95% CI: 0.90-0.99); P^{McN} = .0625. and .98 (95% CI: 0.97-0.98).

Comparison of Hr-HPV based screening in self-samples over the follow-up period vs liquid-based cytology at a threshold of borderline changes is shown in Table 4. Relative sensitivity was 1.40 (95% CI: 1.00-1.42) for CIN2+; P^{McN} = .0784 and 1.44 (95% CI: 1.08-1.64) for CIN3+; P^{McN} = .0117. Relative specificity of self-sampling vs cytology was 0.88 (95% CI: 0.84-0.96) for CIN2+; P^{McN} = .027.

4 | DISCUSSION

Obtaining high coverage rates is essential for cervical screening to have maximum effect. Self-sampling offers opportunities for women who are hard to reach and also those who would wish to attend for screening but who would prefer a home-use option. The saving in person and clinic time associated with self-sampling is clear. In addition, given restrictions on movements due to the SARS CoV-2 crisis; options that minimize physical time required in clinical settings, which offer the same level of technical and clinical performance are particularly relevant.[13-15] Self-sampling has also been identified as a factor that could support realization of the WHO cervical cancer elimination goals.[16]

One of the key findings of our study is that up-to 5-year risks of CIN2+ and CIN3+ are low in women who are Hr-HPV negative on a self-sample using a PCR based test. While sensitivity and specificity of HPV testing were higher in clinician-taken samples (relative sensitivity and specificity of the self-sample did not reach unity) the sensitivity for CIN3+ over the follow-up period was still high and detected 95 of a possible 102 cases. While we would welcome further reports from other programs and studies on the longitudinal performance of self-sampling, these data indicate that the 3 years screening interval for women 49 years and younger and 5 years interval for women 50 years and older are safe for women who test Hr-HPV negative on self-collected samples.

Our findings are in line with the metaanalysis, which attests to the similar performance of Hr-HPV testing in self-taken samples, particularly if a target-based amplification test is applied.[5] One caveat to this comparison is that several studies included in the metaanalysis relate to disease-enriched referral populations in European or US settings or those, which have focused on women who have defaulted from screening. The prevalence of disease and associated viral load in these two populations may not reflect that in a screening population. Furthermore, it is notable that since publication of the metaanalysis a greater number of studies have reported on the performance of self-sampling in broader populations including in low- and middle-income settings and contexts with no organized screening programs. The conclusions of the "CHIMUST" study of over 10 000 Chinese women who were screened with various modalities, including self-taken and clinician-taken samples, converged with those of the metaanalysis with respect to clinical performance.[17]

Additionally in the recent "IMPROVE" study of Polman et al,[10] the authors performed randomization of a clinician-taken or self-sample for Hr-HPV testing within the context of the routine population attending for screening in the Netherlands. The authors showed that at the level of CIN2+ "the sensitivity and specificity of HPV testing did not differ between self-sampling and clinician-based sampling." The data from Polman et al are in line with the earlier and current observations in PaVDaG and suggest that the option of self-sampling need not be confined to those who have traditionally been hard to

reach. The relative cross-sectional accuracy estimated from IMPROVE and our PaVDaG study are very similar from those in the metaanalysis, confirming the robustness of this parameter for comparison of screening testing using a screening or a follow-up setting.[5,12]

There are limitations to our study; study specific procedures outside routine practice (including colposcopy) may have led to a higher rate of disease-detection. Also, at time of recruitment, screening initiation age was 20—early by virtue of comparison with other settings. Not all Hr-HPV positive women at the initial screen were referred to colposcopy, rather, additional colposcopy for LBC negative women was confined to those who tested positive for HPV 16/18 and therefor prone to partial verification bias. However, by focusing on relative accuracy, we would anticipate that the impact of partial verification bias is minor and this was demonstrated in the aforementioned metaanalysis which showed similar relative accuracy estimated from screening studies (with typical partial verification) and colposcopy studies (with complete verification).[5] Another caveat is that the follow-up data from the second round of screening was accrued passively through evaluation of screening data, which was then based on cytology only and it is feasible that this may have led to an underdiagnosis of lesions. Finally, we accept that in this evaluation we can only attest to the performance of one sampling and one testing system when applied to a context of those who attend regular, clinician-based screening.

While demonstration of analytical and clinical performance of self-sampling is key, it will be essential to consider the practical and operational implications of self-sampling in the field and at the laboratory.[18-20] A key issue is how Hr-HPV self-sampling should be offered; should this be considered a default and mailed to all eligible women or alternatively, work to an opt-in system? The literature would suggest that the former offers higher uptake[5] but comes at additional financial and environmental costs through unused kits.[21,22] Also, preference for self-sampling over clinician-taken sampling cannot always be taken for granted as recently illustrated by De Pauw et al who, like others, have observed a group of women who prefer the "reassurance" of a health care professional.[23] Specific attitudes to devices and approaches to sampling are likely to be affected by the geography and culture of a particular context; local endeavors to quantify these are therefore helpful such as the work of Oketch et al who assessed perceptions to self-sampling in rural Kenya.[24]

With respect to laboratory processing and testing, while there are several FDA approved HPV assays to support testing of clinician-taken samples, at the time of article preparation, we are not aware of any Hr-HPV assays (and associated preanalytical systems) which have a formal claim for use of a self-sampling device. Finally, women who test Hr-HPV positive on their self-sample will require a triage test to determine follow-up. Although there has been exciting progress in molecular based triage strategies[25,26] that can be applied to the same self-sample—the bulk of "in use" systems still rely on cytology requiring a clinician visit.[27]

A key strength of our study is that it represents a population-based cohort routinely attending for primary Hr-HPV screening services associated with an entire territorial Scottish health board including registration of screening and follow-up results. Furthermore, to our knowledge, this is the first study to report longitudinal performance of self-sampling over two screening rounds in women who attend for routine screening. The data are encouraging and suggest that Hr-HPV screening based on self-sampling could work to a similar system of call and recall as clinician-taken samples. Notably, given the change to screening practice in the United Kingdom from cytology to HPV testing in 2019/2020, the next routine screening round of the cohort will be based on Hr-HPV testing. This will add a further, sensitive dimension to the longitudinal performance assessment of Hr-HPV performance on self-collected samples with up-to 10 years of follow-up data.

CONFLICT OF INTEREST

Grazyna A. Stanczuk: Employer has received donation of HPV diagnostic tests from Roche. Grazyna A. Stanczuk received travel support and honoraria for speaking from Roche and Abbott. While Roche donated Cobas 4800 PCR-based DNA test kits and consumables for the baseline study, Roche had no role in data analysis and holds no editorial rights over project data, databases or manuscripts. Kate Cuschieri: Employer has received research funding or gratis consumables to support research from the following commercial entities in the last 3 years: Cepheid, Euroimmun, GeneFirst, SelfScreen, Hiantis, Seegene, Roche, Abbott and Hologic. Marc Arbyn was supported by the Horizon 2020 Framework Programme for Research and Innovation of the European Commission, through the RISCC Network (Grant No. 847845) and the European Society for Gynaecologic Oncology; Sciensano the employer or Marc Arbyn received funding in the framework of Valgent and VALHUDES, which are two researcher induced protocols for evaluation of HPV tests on cervical and vaginal samples respectively (see Arbyn et J Clin Virol 2016 & 2018). Marc Arbyn did not receive any financial or material benefit from these projects. All other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

Data in anonymized form can be made available upon reasonable request to the senior author, and following due process of governance and the Scottish Data Protection Regulations.

ETHICS STATEMENT

This analysis represents a passive study of follow-up data. Follow-up analysis obtained institutional approval by the NHS Dumfries and Galloway Caldicott Guardian and Department of Research and Development following West of Scotland Research Ethics Service approval, Ref. 12/WS/0085 for the primary PaVDaG study.

ORCID

Grazyna A. Stanczuk https://orcid.org/0000-0002-5305-1536
Marc Arbyn https://orcid.org/0000-0001-7807-5908
Kate Cuschieri https://orcid.org/0000-0002-2604-3928

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