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Validation of a new HPV self-sampling device for cervical cancer screening: The Cervical and Self-Sample In Screening (CASSIS) study

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HIGHLIGHTS

- Self-samples using HerSwab™ are sensitive for detecting high-grade cervical lesions.
- High agreement was found between self- and physician-sampling in detecting HPV.
- Women expressed positive feelings towards using HerSwab™.
- Women preferred self- over physician-sampling.

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ABSTRACT

Objective. We compared the self-sampling performance of the newly designed HerSwab™ device with a physician-collected cervical sample and another self-sample using the cobas® PCR Female swab for the detection of cervical intraepithelial neoplasia (CIN) and cancer.

Methods. Women referred for colposcopy at McGill University affiliated hospital clinics collected two consecutive self-samples, one with HerSwab™ and one with cobas® swab, after receiving instructions. The order of sampling was randomized. The colposcopist then collected a cervical sample and conducted a colposcopic examination. Samples were tested for human papillomavirus (HPV) DNA. Sensitivity and specificity to detect CIN2+ and respective 95% confidence intervals (CI) were calculated to compare sampling approaches. The HPV testing agreement between samples was measured using the Kappa statistic.

Results. Of 1217 women enrolled, 1076 had complete results for HPV and cytology; 148 (13.8%) had CIN1, 147 (13.7%) had CIN2/3, and 5 (0.5%) had cancer. There was very good agreement between methods for HPV detection (HerSwab™ versus physician: kappa = 0.84; cobas® swabs versus physician: kappa = 0.81; HerSwab™ versus cobas® swabs: kappa = 0.87). The sensitivity of HPV detection for CIN2+ was 87.6% (95%CI: 79.8–93.2) with self-sampling using HerSwab™, 88.6% (95%CI: 80.9–94.0) with self-sampling using the cobas® swab, and 92.4% (95%CI: 85.5–96.7) with physician sampling. Corresponding estimates of specificity were 58.1% (95%CI: 54.1–62.1), 55.0% (95%CI: 50.9–59.0) and 58.7% (95%CI: 54.6–62.6). Cytology (ASC-US or more severe) done on the physician-collected specimen was 80.2% (95%CI: 70.8–87.6) sensitive and 61.4% (95%CI: 57.2–65.5) specific for CIN2+.

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Conclusions. The HerSwab™ had good agreement with physician sampling in detecting HPV, and adequate performance in detecting high-grade lesions among women referred to colposcopy for abnormal cytology.

1. Introduction

With the advent of testing for human papillomavirus (HPV) nucleic acid in cervical cancer screening there has been growing interest in the introduction of cervicovaginal self-sampling to simplify and increase the coverage of screening programs [1,2], as well as to enable a patient-centered approach to empower women as key actors in the control of gynecologic cancers. Self-sampling is an attractive approach to improve cervical cancer screening coverage in low resource countries and/or to extend coverage to remote areas in middle and high resource countries, where women typically have higher rates of cervical cancer incidence and mortality [3].

The benefits of HPV self-sampling are twofold. HPV testing on self-collected samples is reported to have equivalent or better sensitivity than cytology to detect cervical precancerous lesions [4–6], and offering women a simple and convenient means of self-testing increases cervical screening participation [7,8]. Conceivably, although there is some loss of sensitivity and specificity in screening for cervical cancer in a specimen that is not directly collected from the ecto- and endo-cervix, the overall accuracy of the self-collected HPV test results remains superior to that of physician-collected Pap smears in identifying the presence of cervical precancerous lesions [9–11].

Canada is gradually transitioning from cytology to HPV testing in its provincial cervical cancer screening programs [12]. Given the size of its territory, low population density, and size of its aboriginal populations, Canada is ideally suited for large-scale implementation of self-sampling to augment its forthcoming provincial, HPV-based cervical cancer screening programs. In this context, we sought to validate a new collection device, the HerSwab™ (referred to hereafter as HerSwab) self-collection system, designed by a Canadian company (Eve Medical, Toronto, ON). The HerSwab device was designed to be anatomically comfortable in allowing women to collect a self-sample of exfoliated cervicovaginal cells.

2. Methods

2.1. Study design and population

The Cervical And Self-Sample In Screening (CASSIS) study was designed to compare the diagnostic performance of HPV testing in self-collected samples with standard physician-collected samples for the detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and cervical cancer among women referred for colposcopy. The performance of HerSwab was also compared with that of a second self-sample via the cobas® PCR Female swab (referred to as cobas swab). Women collected both self-samples, but the order of sampling was determined by randomization. We hypothesized that the HerSwab sample would yield sensitivity and specificity that are no worse than those with the physician-collected sample, while providing results that are better than or equivalent to those with the self-sample based on the cobas swab. As a performance benchmark, we used cytology results from physician-collected conventional Pap smears in the same patients. As a secondary objective, we measured and compared patient satisfaction with the three sampling approaches.

CASSIS is a 3-arm study carried out from June 22, 2015 through April 15, 2016 in colposcopy clinics at three McGill University affiliated hospitals in Montreal, Canada. Women aged 21–74 were eligible to participate if they had been referred to the participating colposcopy clinic because of an abnormal cervical cancer screening result or for initial treatment of a cervical lesion. We excluded women referred for follow-up post-treatment of a cervical lesion. The study was approved by the McGill University and respective study hospitals' Institutional Review Boards. It was registered in clinicaltrials.gov (NCT02397252).

2.2. Study procedures and data collection

Depending on the study site, a trained study nurse or research assistant approached women attending the colposcopy clinic to explain the study and distribute information leaflets. After receiving written informed consent, each participant was verbally instructed on how to perform the cervicovaginal self-sampling techniques using bilingual, illustrated instructions (Supplemental Fig. 1). These were also posted in designated areas (restroom, changing area or examination room) in which the unsupervised self-sampling was performed. The study representative indicated to the participant the sequence of the two self-sampling methods, depending on results from a priori computer-generated randomization. Women were given a two-section tray, numbered to indicate which self-sample to perform first. Once both self-samples were collected, the woman was then seen by the attending colposcopist for a physician-collected cervical sample and colposcopy following the standard of care at each clinic. The physician-collected sample was always obtained after the two self-samples to ensure that the use of a speculum would not interfere with exfoliation of the vaginal canal.

Cytology was based on the actual colposcopy visit sample if performed at that time; otherwise, it was based on the referral cytology report. Cytology results, based on the actual CASSIS visit or referral cytology, were interpreted according to the Bethesda classification as NILM: Negative for Intraepithelial Lesion or Malignancy; ASC-US: Atypical Squamous Cells- of Undetermined Significance; ASC-H Atypical Squamous Cells- cannot exclude HSIL; LSIL: Low Squamous Intraepithelial Lesion; HSIL: High Squamous Intraepithelial Lesion; AGC: Atypical Glandular Cells; and cancer [13]. Colposcopy protocol followed clinical practice guidelines by the Society of Canadian Colposcopists. Biopsies were taken from all areas on the cervix that appeared abnormal and were histologically assessed and classified as normal, CIN1, CIN2, CIN3, or invasive cancer, based on the most severe histology grading. Respecting local clinical practice norms, we did not require that blind biopsies be taken if the cervix had no visible lesional tissue on colposcopic examination. Endocervical curettage was performed when the transformation zone could not be visualized. Negative colposcopy results with no biopsies but with visualization of the transformation zone were considered in one set of analyses to indicate no disease. Since colposcopy was performed a few minutes after the collection of samples, colposcopists were obviously blinded to the results of self- and physician-collected screening tests. Pathologists assessing study outcomes were blinded to HPV test results. Colposcopical and histopathological biopsy examinations were conducted by senior McGill gynecologists and pathologists, respectively.

After specimen collection, participants completed a short survey about their experience with HerSwab relative to the other two sampling methods. It consisted of 10 questions on the ease of use, comfort, embarrassment, and clarity of instructions when using HerSwab and the cobas swab as compared to the physician-collected sample. The questionnaire has been previously used in evaluating HerSwab for other medical conditions [14].

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2.3. HPV detection

Prior to HPV testing, cellular material was immediately suspended in 20 ml of PreservCyt solution (for physician-collected samples and self-collected samples using HerSwab) and in cobas® PCR media (for self-collected samples using the cobas swab), with all samples stored at 4 °C until use. Each sample was tested for the presence of DNA of carcinogenic HPV types with the clinically-validated and FDA-approved cobas® 4800 HPV Test at the Microbiology Laboratory of the McGill University Health Centre. The test separately identifies HPV16 and HPV18 and concurrently detects in a single pool 12 other high-risk types (HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Results were made available to colposcopists within eight weeks post-consultation.

2.4. Statistical analysis

We conducted analyses based on according-to-protocol (ATP) and intention-to-treat (ITT) principles. For the ATP analysis, we only included women who had a complete set of results, i.e., all three HPV results (2 self-samples and physician's sample) and a cytology report. This permitted the comparison among tests based on exactly the same subset of participants. For the ITT analysis, we included all participants who had at least one evaluable test result. In this report, we only present the results for overall HPV positivity without specifying partial genotyping results.

We calculated kappa statistics with respective 95% confidence intervals (CI) to assess the concordance among sampling methods in detecting HPV positivity, overall and according to histological endpoints using the ITT analysis set. Kappa coefficients vary between 0 and 1. We used the following semi-quantitative scale to judge the extent of agreement: >0.8 (very good), 0.61–0.80 (good), 0.41–0.60 (moderate), 0.21–0.40 (fair), <0.21 (slight) [15].

We calculated sensitivity, specificity, and their respective exact binomial 95% CI to evaluate the diagnostic performance of the three HPV sampling approaches relative to that of cervical cytology. For the latter we used two abnormality grade thresholds to correlate with lesion status: ASC-US or worse, and LSIL or worse. Histology-confirmed CIN2+ (CIN2, CIN3 and cancer) formed the study outcome. Analyses were also performed for a more stringent case definition (i.e., CIN3/cancer). The McNemar's test was used to compare performance measures between collection methods. Since awareness of the referral cytology results might have influenced the physician's decision to perform a biopsy, estimates of sensitivity and specificity were also derived for a subset of women who underwent cervical biopsy and cytology at the actual CASSIS visit. Since the order of self-sample collections had been randomized, we also explored the influence on test performance by which one was done first. Data were analyzed using SAS v9.4 (SAS Inc., Cary, NC, USA).

3. Results

Fig. 1 shows the study flowchart for both sets of analyses. Of the 1243 eligible women, 1076 (86.6%) contributed a full set of test results and were included in the ATP analysis, whereas 1217 (97.9%) were included in the ITT analysis. In the ATP analysis, cytology was performed for most women (892/1076) at the participating colposcopy clinics at the actual CASSIS visit (referral cytology results were used for the remaining 184 women) and lesions were clinically suspected and biopsied in 72.5% of participants.

Table 1 presents a breakdown of HPV positivity in self- and physician- collected samples by cytological and histological endpoints. Overall, HPV positivity in the ATP analysis set via HerSwab self-sampling was detected in 47.4% (510/1076) of women, which was comparable to the positivity in physician-collected samples (47.5%, 511/1076) or in cobas swabs (50.3%, 541/1076). Corresponding ITT values were 46.0% (560/1217), 45.5% (554/1217), and 48.7% (593/1217). HPV positivity in the three collected samples did not differ by cytology results and histological categories. A detailed breakdown of HPV positivity, cytology, and histology results by clinic for both analysis sets is provided in Supplemental Table 1.

Agreement statistics between sampling methods in the ITT analysis set is presented in Table 2. There was very good agreement in HPV detection between HerSwab and physician samples (kappa = 0.84), between cobas swab and physician samples (kappa = 0.81) and between HerSwab and cobas swab (kappa = 0.87). The level of agreement was similar in women with normal histology and lower in those with CIN2+.

Table 3 shows the clinical performance of HPV testing in self- and physician-collected samples (and cytology in physician-collected samples) for two thresholds of lesion grade to define disease, i.e., CIN2+ and CIN3+, in both analysis sets. Regardless of analysis set, the sensitivity of HPV detection via self-sampling devices was numerically lower than that of physician-collected swabs, for both disease thresholds. However, confidence intervals largely overlapped (refer also to Supplemental Tables 2 and 3 for McNemar's p-values). Disease detection by

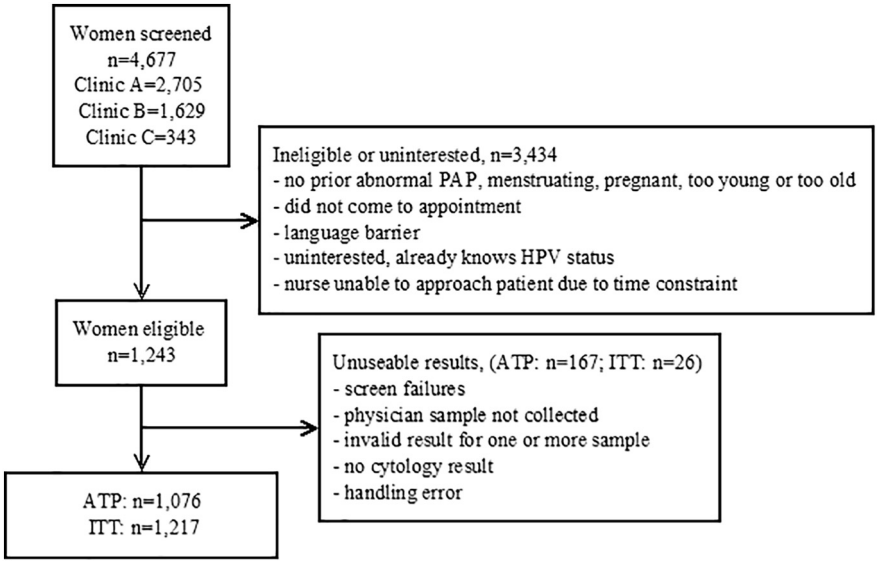

Fig. 1. Overview of CASSIS study flowchart the According-to-protocol (ATP) analysis included a full set of test results (three samples per woman plus cytology) whereas the intention-to-treat (ITT) analysis included results for at least one sample or availability of cytology report per participant.

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Table 1
HPV positivity [n (%)] in self- and physician- collected samples for both sets of analyses, overall and by cytological interpretation and histological endpoints.

	According-to-protocol				Intention-to-treat[a]			
	n	HerSwab	Cobas	Physician	n	HerSwab	Cobas	Physician
Overall	1076	510 (47.4)	541 (50.3)	511 (47.5)	1217	560 (46.0)	593 (48.7)	554 (45.5)
Cytology								
NILM	520	171 (32.9)	186 (35.8)	162 (31.1)	550	177 (32.2)	190 (34.6)	165 (30.0)
ASC-US	182	86 (47.2)	91 (50.0)	82 (45.0)	190	86 (45.3)	92 (48.4)	83 (43.7)
ASC-H	66	37 (56.1)	34 (51.5)	39 (59.1)	70	39 (55.7)	37 (52.9)	41 (58.6)
LSIL	200	130 (65.0)	136 (68.0)	131 (65.5)	214	137 (64.0)	143 (66.8)	135 (63.1)
HSIL	93	78 (83.8)	85 (91.4)	88 (94.6)	96	79 (82.3)	86 (89.6)	88 (91.7)
AGC	6	1 (16.7)	2 (33.3)	1 (16.7)	8	1 (12.5)	3 (37.5)	1 (12.5)
Cancer	9	7 (77.8)	7 (77.8)	8 (88.9)	9	7 (77.8)	7 (77.8)	8 (88.9)
Missing	0	–	–	–	80	34 (42.5)	35 (43.8)	33 (41.2)
Histology								
Normal with biopsy	480	168 (35.0)	181 (37.7)	160 (33.3)	545	187 (34.3)	202 (37.1)	176 (32.3)
Normal based on colposcopy	296	139 (47.0)	149 (50.3)	135 (45.6)	345	152 (44.1)	162 (47.0)	143 (41.4)
CIN1	148	79 (53.4)	86 (58.1)	82 (55.4)	161	86 (53.4)	93 (57.8)	89 (55.3)
CIN2	68	53 (77.9)	55 (80.9)	59 (86.8)	73	55 (75.3)	58 (79.5)	62 (84.9)
CIN3	72	62 (86.1)	62 (86.1)	64 (88.9)	81	71 (87.7)	70 (86.4)	73 (90.1)
HSIL[b]	7	5 (71.4)	5 (71.4)	6 (85.7)	7	5 (71.4)	5 (71.4)	6 (85.7)
Cancer	5	4 (80.0)	3 (60.0)	5 (100.0)	5	4 (80.0)	3 (60.0)	5 (100.0)

Abbreviations: AGC: Atypical Glandular Cells; ASC-US: Atypical Squamous Cells- of Undetermined Significance; ASC-H Atypical Squamous Cells- cannot exclude HSIL; CIN: Cervical Intraepithelial Neoplasia; HSIL: High Squamous Intraepithelial Lesion; LSIL: Low Squamous Intraepithelial Lesion; NILM: Negative for Intraepithelial Lesion or Malignancy.

[a] HPV results were missing for 35 HerSwab- (13 with normal biopsy, 18 with normal based on colposcopy, 1 with CIN1, and 3 with CIN2), 32 cobas- (12 with normal biopsy, 16 with normal based on colposcopy, 2 with CIN1, and 2 with CIN2), and 47 physician- (14 with normal biopsy, 27 with normal based on colposcopy, 4 with CIN1, and 2 with CIN2) collected samples.

[b] No distinction was made between CIN2 and CIN3.

cytology based at an ASC-US threshold was largely comparable to that of HPV via the physician sample and higher, albeit non-significantly, than that of self-samples in all combinations. Expectedly, at an LSIL abnormality threshold, cytology had lower sensitivity but higher specificity than HPV testing in all three samples.

Since the preference to take a biopsy could be related to the physician's knowledge of the referral Pap test, we repeated the above comparisons, but restricted to women who underwent cytology at the actual CASSIS visit and, additionally, had a biopsy taken (Table 4). Sensitivity and specificity estimates of HPV testing for CIN2+ and CIN3+ were largely comparable in all three samples. As expected, HPV testing had better sensitivity and lower specificity than the cytology taken at the same time (i.e., not the referral cytology) for both disease endpoints in all three samples.

As shown in Supplemental Table 4, we found no material difference in clinical performance of the two self-collection methods depending on the randomization order (i.e. whether HerSwab or the cobas swab was used first to collect the vaginal sample).

Table 5 shows the responses of 1202 participants who completed the questionnaire regarding their preferences concerning self-sampling. More women (56.6%) had a distinct preference for self-sampling, whereas 37.8% favored physician-sampling and 5% expressed no preference. Of the 740 women who favored self-sampling or had no preference, 56.9% found it to be more private, 51.5% less painful, 39.9% less invasive, and 30.5% cited it as less embarrassing. Of the 514 women who favored physician sampling or had no preference, 91.8% said correct sample collection was important. When self-sampling, 54.7% of women preferred HerSwab and 36.6% preferred cobas swab. Of the 481 women who preferred cobas swab or had no preference, 58.8% found it easier to use, 53.6% found it more comfortable, 35.3% found it less painful, and 16.4% trusted that cobas swab performed better than HerSwab. Of the 699 women who preferred HerSwab or had no preference, 57.7% found it easier to use, 49.9% believed it to collect a better sample, 41.2% found it more comfortable, and 19.7% said it caused less pain. Overall, 79.1% found HerSwab very easy to use, 82% thought the instructions were clear, 41.2% said it was very comfortable, and 46.3% found it more comfortable than the physician. A total of 623 women (51.8%) affirmed that they would prefer to use HerSwab at home, and 55.7% were confident that HerSwab would collect a better sample than the cobas swab.

4. Discussion

We found that self-collection of vaginal samples in a university-based colposcopy setting provides adequate specimens for molecular HPV detection relative to a physician-collected cervical sample for the same purpose; they provide comparable yields of disease detection, while being comparable or superior to a physician-collected Pap test at the time of colposcopy. Notably, more women preferred self- to physician-sampling, with privacy being the most cited reason. Of those who preferred physician sampling, being confident that a proper sample would be collected was overwhelmingly the most important reason.

Table 2
Agreement on HPV positivity between collected samples in an intention-to-treat analysis, overall and by histological endpoints.

	HerSwab and physician		Cobas and physician		HerSwab and cobas	
	n	Kappa (95% CI)	n	Kappa (95% CI)	n	Kappa (95% CI)
Overall	1160	0.84 (0.81–0.87)	1163	0.81 (0.78–0.85)	1175	0.87 (0.84–0.90)
Histology						
Normal with biopsy	526	0.83 (0.78–0.88)	527	0.80 (0.74–0.85)	528	0.85 (0.80–0.90)
Normal based on colposcopy	314	0.86 (0.80–0.92)	316	0.81 (0.74–0.87)	325	0.90 (0.85–0.95)
CIN1	157	0.82 (0.73–0.91)	156	0.84 (0.76–0.93)	159	0.87 (0.80–0.95)
CIN2	70	0.50 (0.24–0.76)	71	0.47 (0.19–0.74)	70	0.64 (0.42–0.87)
CIN3/cancer	86	0.59 (0.31–0.86)	86	0.62 (0.37–0.87)	86	0.81 (0.62–0.99)

Abbreviations: CIN: Cervical Intraepithelial Neoplasia.

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Table 3
Diagnostic accuracy of HPV positivity (three collected samples) and cytology (physician-collected samples) for both sets of analyses by histological endpoints.

Analytical principle	Histological endpoint	Test and threshold	Type of sample	Sensitivity (95% CI)	Specificity (95% CI)
ATP, n = 1076	CIN2+[a], n = 152	HPV positivity	Self-collected, HerSwab	81.6 (74.5–87.4)	58.2 (55.0–61.4)
		HPV positivity	Self-collected, Cobas swab	82.2 (75.2–88.0)	55.0 (51.7–58.2)
		HPV positivity	Physician-collected	88.2 (81.9–92.8)	59.2 (56.0–62.4)
		Cytology, ASC-US+	Physician-collected	86.8 (80.4–91.8)	54.1 (50.8–57.4)
		Cytology, LSIL+	Physician-collected	71.7 (63.8–78.7)	71.3 (68.3–74.2)
	CIN3+[b], n = 77	HPV positivity	Self-collected, HerSwab	85.7 (75.9–92.7)	55.8 (52.6–58.9)
		HPV positivity	Self-collected, Cobas swab	84.4 (74.4–91.7)	52.5 (49.4–55.7)
		HPV positivity	Physician-collected	89.6 (80.6–95.4)	56.1 (52.9–59.2)
		Cytology, ASC-US+	Physician-collected	92.2 (83.8–97.1)	51.6 (48.5–54.8)
		Cytology, LSIL+	Physician-collected	80.5 (69.9–88.7)	69.1 (66.1–71.9)
ITT, n = 1217	CIN2+[a], n = 166	HPV positivity	Self-collected, HerSwab	82.8 (76.1–88.3)	58.3 (55.2–61.3)
		HPV positivity	Self-collected, Cobas swab	82.9 (76.3–88.4)	55.2 (52.1–58.3)
		HPV positivity	Physician-collected	89.0 (83.2–93.4)	59.4 (56.3–62.5)
		Cytology, ASC-US+	Physician-collected	87.1 (80.8–91.9)[c]	54.0 (50.8–57.1)[c]
		Cytology, LSIL+	Physician-collected	72.3 (64.5–79.1)[c]	71.0 (68.0–73.8)[c]
	CIN3+[b], n = 86	HPV positivity	Self-collected, HerSwab	87.2 (78.3–93.4)	55.9 (52.9–58.9)
		HPV positivity	Self-collected, Cobas swab	84.9 (75.5–91.7)	52.8 (49.8–55.8)
		HPV positivity	Physician-collected	90.7 (82.5–95.9)	56.4 (53.3–59.4)
		Cytology, ASC-US+	Physician-collected	92.2 (83.8–97.1)[d]	51.5 (48.4–54.5)[d]
		Cytology, LSIL+	Physician-collected	80.5 (69.9–88.7)[d]	68.7 (65.8–71.5)[d]

Abbreviations: ASC-US: Atypical Squamous Cells- of Undetermined Significance; ATP: According-to-protocol; CIN: Cervical Intraepithelial Neoplasia; ITT: Intention-to-Treat; LSIL: Low Squamous Intraepithelial Lesion.
[a] Disease free group includes CIN1.
[b] Disease free group includes CIN1 and CIN2. Seven HSIL biopsies were excluded because no distinction was made between CIN2 and CIN3.
[c] Based on n = 155, 11 cytology results were missing.
[d] Based on n = 77, 9 cytology results were missing.

We confirmed our original hypothesis that HerSwab is no less reliable than physician-collected samples for HPV and disease detection and performs comparably to a more standard Dacron swab-like device. Our estimates are consistent with other reports on the accuracy of HPV testing by self-collected samples and on the high level of concordance between self- and physician-collected samples [6,9,16–20]. In our ATP set, there were only 89 discordant pairs of HPV positive results: 45 samples were negative in HerSwab but positive in physician-obtained samples, and 44 positive samples by HerSwab yielded negative results in physician-obtained samples. The equivalent values in the ITT set were 94 discordant with exactly 47 being missed by either sample while being positive in the other.

At first, our findings that HPV testing was less sensitive than cytology to detect high grade lesions were not coherent with the overwhelming evidence of substantial, superior sensitivity of HPV testing over cytology to identify high-grade dysplasia [21–23]. We hypothesized that these unexpected observations could be explained by the context in which CASSIS study participants were recruited. A colposcopist's likelihood of performing a biopsy was arguably conditional on the grade of abnormality of the referral cytology, which would lead to an upward bias in the sensitivity for the latter test by creating a statistical dependency between disease discovery and the cytological grade. To control for this bias, we restricted comparisons exclusively to participants with a cytology result at the colposcopy visit (same as the CASSIS study visit) and

Table 4
Diagnostic accuracy of HPV positivity (three collected samples) and cytology (physician-collected samples) for both sets of analyses by histological endpoints. Comparisons were restricted to women who underwent cervical biopsy and cytology at the actual CASSIS visit.

Analytical principle	Histological endpoint	Test and threshold	Type of sample	Sensitivity (95% CI)	Specificity (95% CI)
ATP, n = 623	CIN2+[a], n = 96	HPV positivity	Self-collected, HerSwab	86.5 (78.0–92.6)	59.6 (55.3–63.8)
		HPV positivity	Self-collected, Cobas swab	88.5 (80.4–94.1)	56.6 (52.2–60.8)
		HPV positivity	Physician-collected	91.7 (84.2–96.3)	60.5 (56.2–64.7)
		Cytology, ASC-US+	Physician-collected	80.2 (70.8–87.6)	61.3 (57.0–65.5)
		Cytology, LSIL+	Physician-collected	64.6 (54.2–74.1)	75.5 (71.6–79.1)
	CIN3+[b], n = 44	HPV positivity	Self-collected, HerSwab	95.5 (84.5–99.4)	56.3 (52.1–60.4)
		HPV positivity	Self-collected, Cobas swab	95.5 (84.5–99.4)	53.1 (49.0–57.3)
		HPV positivity	Physician-collected	93.2 (81.3–98.6)	56.3 (52.1–60.4)
		Cytology, ASC-US+	Physician-collected	86.4 (72.7–94.8)	58.2 (54.0–62.3)
		Cytology, LSIL+	Physician-collected	70.5 (54.8–83.2)	72.7 (68.8–76.3)
ITT, n = 700	CIN2+[a], n = 105	HPV positivity	Self-collected, HerSwab	87.6 (79.8–93.2)	58.2 (54.1–62.2)
		HPV positivity	Self-collected, Cobas swab	88.6 (80.9–94.0)	55.0 (50.9–59.0)
		HPV positivity	Physician-collected	92.4 (85.5–96.7)	58.7 (54.6–62.6)
		Cytology, ASC-US+	Physician-collected	80.2 (70.8–87.6)	61.4 (57.2–65.5)
		Cytology, LSIL+	Physician-collected	64.6 (54.2–74.1)	75.4 (71.6–78.9)
	CIN3+[b], n = 51	HPV positivity	Self-collected, HerSwab	96.1 (86.5–99.5)	55.1 (51.2–59.0)
		HPV positivity	Self-collected, Cobas swab	94.1 (83.8–98.8)	51.9 (47.9–55.8)
		HPV positivity	Physician-collected	94.1 (83.8–98.8)	54.8 (50.9–58.7)
		Cytology, ASC-US+	Physician-collected	86.4 (72.7–94.8)	58.4 (54.4–62.4)
		Cytology, LSIL+	Physician-collected	70.5 (54.8–83.2)	72.6 (68.9–76.2)

Abbreviations: ASC-US: Atypical Squamous Cells- of Undetermined Significance; ATP: According-to-protocol; CIN: Cervical Intraepithelial Neoplasia; ITT: Intention-to-Treat; LSIL: Low Squamous Intraepithelial Lesion.
[a] Disease free group includes CIN1.
[b] Disease free group includes CIN1 and CIN2. Five HSIL biopsies were excluded because no distinction was made between CIN2 and CIN3.

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Table 5
Participants' preferences and opinions regarding the sampling methods (n = 1202).

Question	Participant answer	n (%)
Did you prefer the doctor collecting the sample or collecting the sample yourself?	Myself	680 (56.6)
	Doctor	454 (37.8)
	Same	60 (5.0)
	Missing	8 (0.7)
If you chose "Myself" what was the reason?[a]	More private	421 (57.8)
	Less embarrassing	226 (31.0)
	Less painful	381 (52.3)
	Less invasive	295 (40.5)
	Other	39 (5.4)
	Missing	33 (4.5)
If you chose "Doctor" what was the reason?[b]	Less complicated	73 (14.5)
	Less painful	25 (5.0)
	I trust the doctor to do it correctly	472 (94.0)
	Other	16 (3.2)
	Missing	23 (4.6)
When collecting your own sample, which device did you prefer?	HerSwab™	658 (54.7)
	cobas®PCR	440 (36.6)
	Both	41 (3.4)
	Missing	63 (5.2)
If you chose HerSwab™, why?[c]	Easier to use	403 (57.7)
	More comfortable	288 (41.2)
	Less painful	191 (27.3)
	Collect better sample	296 (42.3)
	Other	13 (1.9)
	Missing	64 (9.2)
If you chose cobas®PCR Swab, why?[d]	Easier to use	283 (58.8)
	More comfortable	258 (53.6)
	Less painful	170 (35.3)
	Collect better sample	79 (16.4)
	Other	8 (1.7)
	Missing	69 (14.3)
Which self-sampling device would you prefer to use at home?	HerSwab™	623 (51.8)
	cobas®PCR Swab	339 (28.2)
	No preference	54 (4.5)
	Neither	40 (3.3)
	Missing	146 (12.2)
Which self-sampling device do you think would collect a better sample?	HerSwab™	669 (55.7)
	cobas®PCR Swab	249 (20.7)
	No preference	21 (1.8)
	Neither	93 (7.7)
	Missing	170 (14.1)
How comfortable or uncomfortable was using HerSwab™?	Very comfortable	495 (41.2)
	Somewhat comfortable	252 (21.0)
	Neutral	206 (17.1)
	Somewhat uncomfortable	185 (15.4)
	Very uncomfortable	45 (3.7)
	Missing	19 (1.6)
How would you rate the comfort of using HerSwab™ compared to a tampon?[e]	Much more comfortable than tampon	286 (23.8)
	Somewhat more comfortable than tampon	226 (18.8)
	Same as tampon	322 (26.8)
	Somewhat less comfortable than tampon	178 (14.8)
	Much less comfortable than tampon	33 (2.8)
	I do not use tampons	187 (15.6)
	Missing	9 (0.8)
How would you rate the comfort of HerSwab™ compared to a doctor collecting the sample with a speculum?[e]	Much more comfortable than physician	557 (46.3)
	Somewhat more comfortable than physician	327 (27.2)
	Same as physician	197 (16.4)
	Somewhat less comfortable than physician	83 (6.9)
	Much less comfortable than physician	23 (1.9)
	Missing	16 (1.3)
How clear were the HerSwab™ instructions?[e]	Very clear	986 (82.0)
	Somewhat clear	123 (10.2)
	Neutral	68 (5.7)
	Somewhat confusing	15 (1.2)
	Very confusing	2 (0.2)
	Missing	10 (0.8)
Overall, how easy was it to use HerSwab™?[e]	Very easy	951 (79.1)
	Somewhat easy	148 (12.3)
	Neutral	60 (5.0)
	Somewhat difficult	33 (2.8)
	Very difficult	3 (0.3)
	Missing	8 (0.7)

[a] Percentages based on n out of 728 participants who chose "Myself" as a preference for sample collection.
[b] Percentages based on n out of 502 participants who chose "Doctor" as a preference for sample collection.
[c] Percentages based on n out of 699 participants who chose "HerSwab™" as a preference for self-sampling.
[d] Percentages based on n out of 481 participants who chose "cobas®PCR Swab" as a preference for self-sampling.
[e] Percentages based on n out of 1202 participants, with some participants choosing multiple options.

who underwent a biopsy. This permitted comparing the performance of the 3 HPV tests against a concurrently taken cytology among women with histological ascertainment of disease, thus in conditions in which the physician would be completely blinded to all test results.

With regards to women's acceptability, experience, comfort, and preference, our findings echo those from other studies within diverse populations. On the one hand, women perceived self-sampling to be more convenient, less embarrassing, less uncomfortable and less painful than physician-sampling [24–26]. Women also expressed preference for self- over physician-sampling, provided that they can be instructed on how to properly collect the sample [17,27]. On the other hand, lack of trust in the accuracy of HPV self-sampling results, concerns about one's ability to properly self-sample, and more confidence in a familiar and established procedure (i.e., collection of Pap smears) were equally identified [26]. Most recently, a meta-analysis of 37 studies reported a high level of acceptability of self-sampling among women from 24 countries [28]. Ease of use, no embarrassment, privacy and comfort were the most common reasons women preferred self over physician sampling.

A critical feature in enhancing women's acceptance of and adherence to the self-sampling approach for cervical cancer screening and HPV surveillance studies is the convenience of the device used for collection. Ideally, sampling devices should be anatomically correct to facilitate insertion, and the sampling surface that will retain the exfoliated cells should be protected from contact with the labia and lower vaginal mucosa while the device is inserted, with the objective of sampling cells that are mostly from the cervix and upper vaginal area. The HerSwab device, found by most study subjects to be comfortable and easy to use, was designed with these issues in mind. One theoretical advantage of HerSwab is the ability to rotate and retract the brush back into the device prior to being removed from the vagina, thus preventing the bristles to pick up additional cellular exfoliation from the vulva. However, we could not use the device as originally intended. We instructed women to not retract the brush back into the sleeve before pulling it out of the vagina because of the risk that the brush could break and detach from the device while being rotated. It is conceivable that this limitation may have caused the two self-samples to behave similarly as both were likely contaminated with vulvar cells, which may have diluted the specimen relative to its cervical cellularity, thus adversely affecting sensitivity and specificity.

One of the strengths of CASSIS was the ability to compare the performance of collection methods in a referral population with a high prevalence of high-grade lesions, which enabled measuring sensitivity efficiently. CASSIS included 152 histologically-confirmed precancerous lesions and cancer, i.e., 12.5% of the entire study sample. A screening study conducted in average risk women of the same age would have required a sample size around 30,000 participants to attain the same precision to measure the sensitivity of the various test modalities we had.

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On the other side of this argument is the limitation in generalizability of CASSIS, i.e., the uncertainty that our findings are applicable to asymptomatic women undergoing routine screening. However, we intentionally designed CASSIS to enable efficient comparison of self-sampling devices against benchmarks of physician collected Pap and HPV tests, which made a case-enriched context, i.e., a study conducted in colposcopy clinics the most efficient design.

The performance and acceptability of HerSwab and similar devices in the general population are yet to be determined along with other factors such as logistics, ability to recruit unscreened women, identification of personal and system-related barriers, and compliance with specimen's collection and shipment.

In conclusion, our results indicate that HerSwab is a reliable and well-accepted device in a colposcopy setting. Its use to reach women who are reluctant to participate in the regular screening program needs to be evaluated.

Conflict of interest and disclosure statements

E.L Franco: His institution received funding from Eve-Medical Inc. and Roche Diagnostics to partially cover the costs of performing the reported study. He has served as an occasional advisor for companies involved with HPV vaccines (Merck, GSK) and HPV diagnostics (Roche Diagnostics) and as a Steering Committee Member for a publicly funded study in Finland that received support from GSK.

There were no disclosures by the other authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.04.004.

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