Journal of Clinical Virology 99–100 (2018) 22–30

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

# 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

Maarit K. Leinonen[a,*], Kristina Schee[a], Christine M. Jonassen[b,c], A. Kathrine Lie[b], Camilla F. Nystrand[b], Anbjørg Rangberg[b], Ingegerd E. Furre[d], Marzena J. Johansson[b], Ameli Tropé[e,f], Katrine D. Sjøborg[g], Philip E. Castle[h], Mari Nygård[a]

[a] Department of Research, Cancer Registry of Norway, 0379 Oslo, Norway
[b] Center for Laboratory Medicine, Østfold Hospital Trust, 1714 Grålum, Norway
[c] Faculty of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, 1432 Ås, Norway
[d] Department of Pathology, Oslo University Hospital, 0379 Oslo, Norway
[e] Department of Cervical Cancer Screening, Cancer Registry of Norway, 0379 Oslo, Norway
[f] Department of Gynecologic Cancer, Division of Cancer Medicine, Oslo University Hospital, 0379 Oslo, Norway
[g] Department of Obstetrics and Gynaecology, Østfold Hospital Trust, 1714 Grålum, Norway
[h] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA

## ARTICLE INFO

*Keywords:*
HPV test
Vaginal smear
Self-sampling
Device
Performance
Acceptability

## ABSTRACT

*Background:* Comparative data on different self-collection methods is limited.
*Objectives:* To assess the impact of hrHPV testing of two self-collection devices for detection of cervical carcinoma and high-grade lesions.
*Study design:* Three hundred ten patients collected two cervicovaginal specimens using a brush (Evalyn®Brush) and a swab (FLOQSwabs™), and filled a questionnaire at home. Then, a physician at the clinic took a cervical specimen into PreservCyt® buffer for hrHPV testing and cytology. All specimens were tested using Anyplex™ II HPV28, Cobas® 4800 HPV Test and Xpert®HPV.
*Results:* Performance comparison included 45 cervical carcinomas and 187 patients with premalignant lesions. Compared to the physician-specimen, hrHPV testing of Evalyn®Brush showed non-inferior sensitivity for CIN3+ (relative sensitivity of Anyplex™ 0.99; Cobas® 0.96; Xpert®HPV 0.97) while hrHPV testing of FLOQSwabs™ showed inferior sensitivity (relative sensitivity of Anyplex™ 0.91; Cobas® 0.92; Xpert®HPV 0.93). Similar results were observed for invasive carcinomas albeit that FLOQSwabs™ was statistically non-inferior to the physician-specimen. Self-collection by either Evalyn®Brush or FLOQSwabs™ was more sensitive for CIN3+ than LSIL or worse cytology. Significant decrease in sensitivity for CIN3+ were observed for FLOQSwabs™ when specimens were preprocessed for hrHPV testing after 28 days. Both devices were well accepted, but patients considered Evalyn®Brush easier and more comfortable than FLOQSwabs™.
*Conclusions:* Self-collection is comparable to current screening practice for detecting cervical carcinoma and CIN3+ but device and specimen processing effects exist. Only validated procedure including collection device, hrHPV assay and specimen preparation should be used.

*Abbreviations:* ACIS, adenocarcinoma in situ; ASC-H, atypical squamous cells, cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; AGUS, atypical glandular cells of undetermined significance; CI, confidence interval; CIN1, cervical intraepithelial neoplasia grade 1; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; CIN3+, cervical intraepithelial neoplasia grade 3 or more severe diagnosis; CRN, Cancer Registry of Norway; hrHPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; LSIL+, low-grade squamous intraepithelial lesion or worse; OUH, Oslo University Hospital; PPA, Proportion of positive agreement; PNA, Proportion of negative agreement; ØHT, Østfold Hospital Trust

* Corresponding author at: Ullernchausseen 64, 0379 Oslo, Norway.
*E-mail address:* maarit.leinonen@kreftregisteret.no (M.K. Leinonen).

https://doi.org/10.1016/j.jcv.2017.12.008
Received 26 October 2017; Received in revised form 8 December 2017; Accepted 15 December 2017

## 1. Background

A high participation rate is essential for an effective screening programme. A variety of personal and provider level factors influence screening participation [1,2]. One promising approach to reach screening non-responders is to offer them self-collection devices for high-risk human papillomavirus (hrHPV) testing [3–6].

HrHPV testing on self- and physician-collected specimens has similar sensitivity when a clinically validated PCR-based HPV assay is used. While the meta-analysis revealed obvious test effects, no strong conclusions about device effects were possible to draw [7]. To date, we have limited evidence on the comparative performance and acceptance of different devices [6,8–14].

Currently, European guidelines recommend HPV test as a primary screening test for women above age of 30 years, when specimen is collected by medical professional but not, yet, self-collection as a primary option [15]. However, some PCR-based hrHPV tests on self-specimens could be considered for routine screening after careful evaluation of feasibility, acceptability, logistics and costs in the local setting [7]. Still, there has been a concern whether HPV assays can detect underlying cancer from the self-collected specimen. Very few studies so far have included more than 10 cancers and results have been inconsistent [16–19].

## 2. Objectives

We performed a methodologic study assessing the impact of hrHPV testing of two self-collection devices on sensitivity for cervical cancer and high-grade lesions. We evaluated: 1) analytical and clinical sensitivity of self-collection to physician-collected specimen tested by three hrHPV assays and cytology among patients with cervical carcinoma and premalignant cervical lesions and 2) women's experiences and attitudes towards screening and self-collection.

## 3. Study design

### 3.1. Study participants

Cancer Registry of Norway (CRN) conducted this study in cooperation with two secondary and one tertiary care centers in the capital and South East region of Norway. Patients referred for treatment of premalignant lesions were recruited from the Østfold Hospital Trust (ØHT) and Oslo University Hospital (OUH), Ullevål. Prior to the scheduled conisation, CRN mailed to patients a package that included an information letter, self-collection devices with written instructions, and a consent form. Patients also received a questionnaire addressing the acceptance of the self-sampling devices, screening history, sexual habits and lifestyle. Patients with confirmed cervical carcinoma or carcinoma suspicion were recruited at the Norwegian Radium Hospital. Patients were informed about the study during their first consultation, and they received a similar package which they could explore at home. Recruitment period lasted from December 2014 to September 2016.

Altogether, 953 women received the study package, of which 310 (33%) returned the informed consent and the questionnaire. The recruited study population consisted of 249 patients with cervical premalignant lesion and 61 women with carcinoma diagnosis or carcinoma suspicion (Fig. 1). Mean age at specimen collection was 38 years (range from 21 to 80 years).

### 3.2. Interventions

Participants performed self-collection at home using two sampling devices the day before their appointment at the hospital. Each woman used a dry brush (Evalyn®Brush, Rovers Medical Devices, Lekstraat, The Netherlands) and a dry swab (FLOQSwabs™, COPAN, Brescia, Italy). The order of the device use was randomized, and clearly indicated on the study instructions. Women brought self-collected specimens, questionnaires and signed informed consents to their appointment from where they were transported to the CRN.

Before the gynecologic procedure, a physician took a cervical specimen using a brush. The specimen was rinsed directly into PreservCyt® buffer (Hologic, Inc., Marlborough, MA) for HPV testing, and for cytopathological evaluation using ThinPrep® 2000 System. For all specimen types, the date of specimen-collection was the appointment date at the hospital or, if not available, one day before the CRN received the specimens.

At the CRN, self-collection devices were re-labelled and sent dry to the laboratory of ØHT at room temperature. The time interval between specimen-collection and shipment to the laboratory ranged from four to 194 days, median time being 23 days. At the laboratory, Evalyn®Brush and FLOQSwabs™ heads were suspended with 4.6 ml ThinPrep medium each, and further processed accordingly to a published protocol [20]. A resuspension volume of 4.6 ml was chosen to allow for aliquoting 4 × 1 ml, and to leave some material available for re-analysis. The choice was made based on personal communication with Dutch and Scottish experienced scientists. Tubes with self-specimens were then aliquoted in 4 × 1 ml, and aliquots were refrigerated or kept at −20C before further analysis. Self-specimens were preprocessed on average within six days [range 0, 28] after they were sent to the laboratory.

Anyplex™ II HPV28 Detection (Seegene Inc., Seoul, Korea) is a multiplex real-time PCR-based assay that targets the viral L1 region and provides simultaneous detection and genotyping of 28 HPV types. A panel A includes 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and a panel B 14 possibly carcinogenic or non-cancer causing types (HPV 6, 11, 26, 40, 42, 43, 44, 53, 54, 61, 69, 70, 73, 82). The panel A corresponds to a kit that complies with international consensus validation metrics [21]. DNA was extracted from 1 ml of each specimen type using the semi-automated extraction platform NucliSENS® easyMag® (Biomerieux, Marcy L'Etoile, France), and eluted in 50 µl. The Anyplex™ was then performed at ØHT according to the manufacturer's instructions. Briefly, the detection consists of two PCR reactions (panel A and B). Both were performed in a total volume of 20 µl containing 5 µl DNA, 5 µl Mastermix and 5 µl A or B Oligomix. PCR was performed on CFX96™ Real-time PCR system (Bio-Rad Laboratories GmbH, Munich, Germany).

Cobas® 4800 HPV Test (Roche Molecular Diagnostics, Pleasanton, CA) is a fully automated real-time PCR targeting the viral L1 region and simultaneously detecting 14 hrHPV types. The test specifically identifies HPV types 16 and 18 while concurrently detecting twelve other hrHPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Assay is validated as formulated in international guidelines [22]. For all specimen types, a 1 ml aliquot was loaded on the Cobas® instrument, and all procedures performed according to the manufacturers' instructions at the OUH.

Xpert®HPV (Cepheid, Sunnyvale, CA, USA) is an automated PCR-based assay which targets the viral E6 and E7 oncogenes. It detects 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and provides concurrent partial genotyping (HPV 16 and HPV 18/45). Xpert® HPV has been recently validated for primary cervical screening [23]. For all specimen types, we added a 1 ml aliquot to the Xpert cartridge, and followed the manufacturer's instructions on either GeneXpertIV or GeneXpert Infinity throughout the analysis at the ØHT.

Of all study participants, 59 patients were not hrHPV tested. We excluded 18 patients because postal services failed to deliver their specimens from the CRN to the laboratory, 32 because of a missing physician-specimen, 8 patients who used one device only, and one cancer patient who was advised to withdraw by her gynecologist (Fig. 1). For all assays, we repeated the analysis on diluted samples whenever specimen gave an invalid result. However, we could not dilute 20 specimens (2 Evalyn®Brush and 18 FLOQSwabs™) from 19 patients because there was not enough material for re-analysis. To avoid detection bias in performance analyses, these patients were excluded

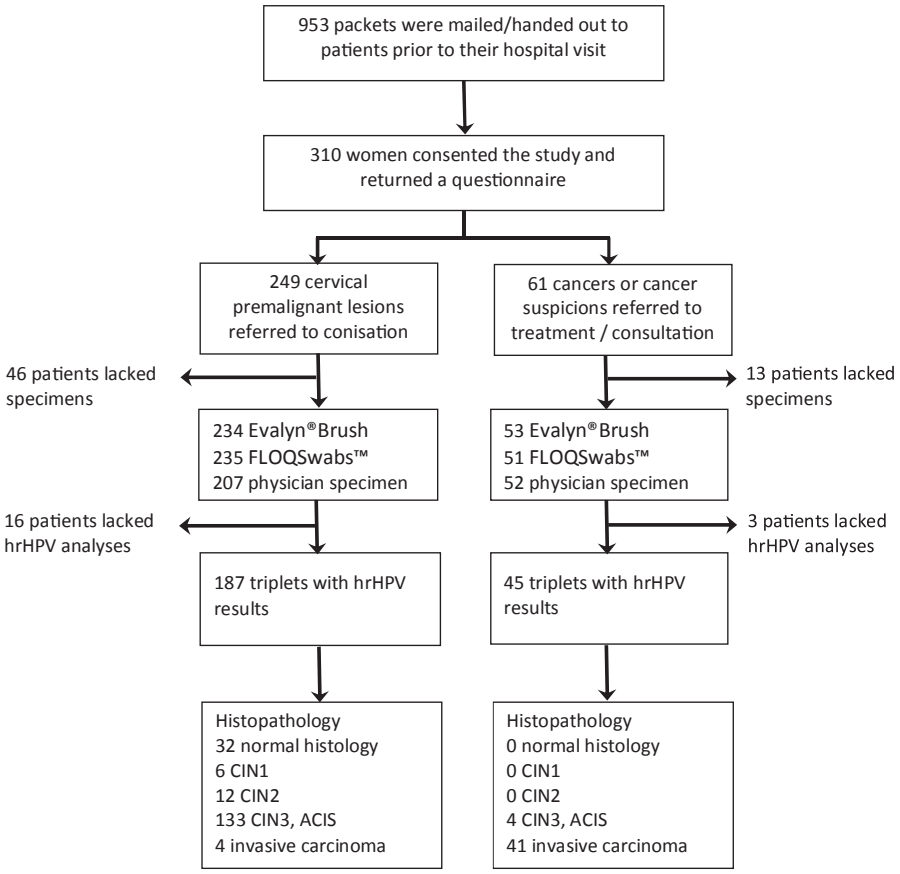


**Fig. 1.** Included cases in the study with their final histological outcomes.

leaving 232 patients with complete triplet of HPV test results for comparison.

One experienced cytotechnologist and one cytopathologist performed cytopathological evaluation according to the Bethesda classification 2015 [24] without knowledge of the hrHPV status or histology. Pathologists at local laboratories examined cervical biopsies, cone specimens and hysterectomies and reported histology to the CRN which we used as a study outcome. For premalignant lesions, we used histology from a cone specimen, whereas for carcinoma or carcinoma suspicion, we used the most severe diagnosis either from a biopsy or from treatment.

### 3.3. Statistical analyses

Cohen's kappa (κ) was used to measure agreement of self- and physician-collected specimen regarding hrHPV positivity by different assays. Bias corrected 95% confidence intervals (CI) were estimated using the bootstrap method provided in an ado file, kapci, written by Michael E. Reichenheim using Stata (version 15.0 StataCorp, College Station, TX, USA). We also calculated proportion of positive and negative agreement. Landis and Koch's categorization was used to define agreement from "poor" to "almost perfect" [25]. The sample size was powered to detect substantial agreement (κ = 0.80) between self- and physician-collected specimen with a 5% a significance level.

We calculated absolute sensitivity for cervical carcinoma and CIN3+ including ACIS. We estimated relative sensitivity with 90% CIs using exact McNemar $\chi^2$. $P_{McN}$ of > 0.05 indicated no difference in sensitivity between screening methods. Clinical performance of hrHPV test on self-collected specimen was also compared to cytology at cut-off of low-grade squamous intraepithelial lesion or worse (LSIL+). We assessed non-inferiority at 5% significance level by calculating the 90% CI for the difference in performance between the screening methods, and examining the lower bound of the CI [26,27]. If the lower bound exceeded the predefined margin −0.10 for relative sensitivity [28], hrHPV test on self-specimen was deemed non-inferior.

Questionnaire included 12 questions on women's experiences and attitudes towards self-collection. Response alternatives were on a 4-level scale ("Fully agree"; "Somewhat agree"; "Disagree" and "No opinion"). Here we grouped first two as "Agree" and "No opinion" and not answered as one group. Furthermore, we present some of the questions complementary to the original so that "Agree" would represent the most positive experience for each question. Wilcoxon matched-pairs signed-rank test was used to study possible device effects on experiences. We also tested whether women's age, self-reported marital status or education were associated with the perceptions on self-sampling using a two-sided Fisher's exact test. All 310 women who returned the questionnaire were included in these analyses.

## 4. Results

Two-hundred eight women (90%) tested positive for hrHPV in the physician-specimen on any of the three assays. The hrHPV positivity of the physician-collected specimen was 89% using Anyplex™, 86% using Cobas®, and 86% using Xpert®HPV. Overall agreement between Evalyn®Brush and physician-specimens was 94% (κ = 0.68) using Anyplex™, 91% (κ = 0.64) using Cobas®, and 91% (κ = 0.66) using Xpert®HPV. Evalyn®Brush showed slightly higher concordance and higher proportion of positive agreement with physician-specimens than FLOQSwabs™ for all hrHPV assays (Table 1). FLOQSwabs™ resulted more often in invalid result on hrHPV testing with all studied HPV assays. Proportion of invalid results on undiluted FLOQSwabs™ was 18% for Cobas®, 16% for the Xpert®HPV and 2% for Anyplex™.

The cytology diagnoses were carcinoma (n = 18), ACIS (n = 4), HSIL (n = 84), AGUS (n = 13), ASC-H (n = 36), LSIL (n = 11), ASC-US (n = 21), normal (n = 10) and unsatisfactory (n = 35). Of 45 histologically verified cervical carcinomas, 28 were squamous cell carcinomas,

**Table 1**
Agreement of self- and physician-collected specimen regarding hrHPV positivity by sampling method and HPV assay (n = 232).

| Screening method | hrHPV test result | | | | | | | | | | | Agreement hrHPV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Physician<br>Self-specimen | Pos<br>Pos | Pos<br>Neg | Pos<br>Fail | Neg<br>Pos | Neg<br>Neg | Neg<br>Fail | Fail<br>Pos | Fail<br>Neg | Fail<br>Fail | Pos[a] | Pos[b] | Overall | PPA | PNA | Kappa (95% CI) |
| Anyplex™ II HPV28 | | | | | | | | | | | | | | | |
| Evalyn®Brush | 201 | 6 | 0 | 8 | 17 | 0 | 0 | 0 | 0 | 207 | 209 | 94.0% | 93.5% | 54.8% | 0.68 (0.52–0.83) |
| FLOQSwabs™ | 186 | 20 | 1 | 7 | 18 | 0 | 0 | 0 | 0 | 207 | 193 | 87.9% | 86.9% | 40.0% | 0.50 (0.33–0.64) |
| Cobas® 4800 | | | | | | | | | | | | | | | |
| Evalyn®Brush | 188 | 11 | 1 | 7 | 23 | 1 | 1 | 0 | 0 | 200 | 196 | 91.0% | 90.4% | 54.8% | 0.64 (0.49–0.77) |
| FLOQSwabs™ | 179 | 13 | 8 | 5 | 26 | 0 | 1 | 0 | 0 | 200 | 185 | 88.4% | 86.9% | 59.1% | 0.60 (0.44–0.73) |
| Xpert®HPV | | | | | | | | | | | | | | | |
| Evalyn®Brush | 188 | 11 | 0 | 9 | 24 | 0 | 0 | 0 | 0 | 199 | 197 | 91.4% | 90.4% | 54.5% | 0.66 (0.52–0.80) |
| FLOQSwabs™ | 181 | 16 | 2 | 7 | 25 | 1 | 0 | 0 | 0 | 199 | 188 | 88.8% | 87.9% | 51.0% | 0.60 (0.45–0.73) |

hrHPV = High-risk human papillomavirus; Pos = Positive; Neg = Negative; Fail = Invalid result; PPA = Proportion of positive agreement; PNA = Proportion of negative agreement.
[a] Overall hrHPV positivity in physician-collected specimen with given HPV assay.
[b] Overall hrHPV positivity in self-collected specimen with given HPV assay.

15 adenocarcinomas and two of other carcinoma type. Of 187 patients with premalignant lesions, histological diagnoses from cone specimens were ACIS (n = 9), CIN3 (n = 128), CIN2 (n = 12), CIN1 (n = 6) and normal (n = 32).

Clinical performance of different screening methods for invasive carcinoma and CIN3+ is presented in Table 2. In comparison with LSIL + cytology, hrHPV test on physician-specimen had higher sensitivity. Anyplex™ detected 93% of carcinomas and 96% of CIN3+ when used on physician-specimens. Absolute sensitivities for invasive carcinoma and CIN3+ using Cobas® and Xpert®HPV on physician-specimen were close to sensitivities of Anyplex™. Relative sensitivity of any hrHPV test on Evalyn®Brush was non-inferior to that of physician-specimen for all study outcomes, whereas lower sensitivities were demonstrated with FLOQSwabs™ for CIN3+. Results were very similar when we used CIN2 or more severe diagnosis as an endpoint (data not shown).

Finally, we studied if delay in specimen preparation had an effect on performance of self-collection. By adding together median delay in shipment and specimen preparation at the laboratory (see above), we defined 29 days to be reasonable throughput time in our material. We rounded this to four full calendar weeks and stratified our analysis into specimens prepared within 28 days (n = 111) and those prepared after 28 days (n = 121). Results from repeated analysis show that both devices were non-inferior to physician-specimen in detecting all cervical lesions up to 28 days of storage. While Evalyn®Brush remained rather stable with respect to hrHPV test performance, analytical and clinical sensitivity of FLOQSwabs™ declined notably after 28 days of storage (Table 3).

Overall, both devices were well accepted (Fig. 2a and b). Self-collection was generally considered easy, but it was easier using Evalyn®Brush than FLOQSwabs™ (95% vs. 90%, P = 0.014). Evalyn®Brush was also evaluated to be slightly more comfortable (76% vs. 69%, P = 0.032) than FLOQSwabs™. Women with ≥13 years of education tended to have more positive experiences on self-collection compared to women with shorter education (Table 4). Experiences on self-collection did not differ consistently by age (< 40 vs. ≥40 years of age) or marital status of woman (married vs. unmarried).

88% of participants considered self-collection to be a good alternative for physician-collection, although 84% of women had more confidence in physicians. Overall, 87% of women reported self-collection to be more convenient than visiting a physician. Women with longer education had more positive experiences on convenience compared to women having < 13 years of education (90% vs. 78%, P = 0.014) as shown in Supplementary Table 1. Younger women regarded self-collection as a good alternative more often than women aged ≥40 years (92% vs. 80%, P = 0.002). Women with less than 13 years of education reported self-collection to be less painful than conventional sampling more often than women with longer education (77% vs. 64%, P = 0.036). Otherwise, we did not observe differences on attitudes towards self-collection by age, marital status, or level of education (Supplementary Table 1).

**Table 2**
Sensitivity of self- and physician-collected specimen regarding presence of invasive carcinoma and cervical high-grade lesion by sampling method and HPV assay.

| Screening method | Sensitivity for CIN3+ (n = 182) | | | Sensitivity for invasive carcinoma (n = 45) | | |
|---|---|---|---|---|---|---|
| | Absolute% | Relative (90% CI) | $P_{McN}$ | Absolute% | Relative (90% CI) | $P_{McN}$ |
| Anyplex™ II HPV28 | | | | | | |
| Physician HPV | 95.6% | Ref. | | 93.3% | Ref. | |
| Evalyn®Brush | 94.5% | 0.99 (0.96–1.02) | 0.727 | 91.1% | 0.98 (0.91–1.05) | 1.000 |
| FLOQSwabs™ | 87.4% | 0.91 (0.88–0.95) | < 0.001 | 86.7% | 0.93 (0.85–1.02) | 0.375 |
| LSIL+ cytology | 79.7% | 0.83 (0.78–0.89) | < 0.001 | 88.8% | 0.95 (0.86–1.05) | 0.688 |
| Cobas® 4800 | | | | | | |
| Physician HPV | 94.0% | Ref. | | 91.1% | Ref. | |
| Evalyn®Brush | 90.7% | 0.96 (0.93–1.00) | 0.146 | 86.7% | 0.95 (0.90–1.01) | 0.500 |
| FLOQSwabs™ | 86.3% | 0.92 (0.88–0.96) | 0.001 | 82.2% | 0.90 (0.83–0.98) | 0.125 |
| LSIL+ cytology | 79.7% | 0.85 (0.80 − 0.90) | < 0.001 | 88.8% | 0.98 (0.88–1.09) | 1.000 |
| Xpert®HPV | | | | | | |
| Physician HPV | 94.5% | Ref. | | 93.3% | Ref. | |
| Evalyn®Brush | 91.2% | 0.97 (0.93–1.00) | 0.146 | 86.7% | 0.93 (0.87–1.00) | 0.250 |
| FLOQSwabs™ | 87.9% | 0.93 (0.90–0.97) | 0.002 | 82.2% | 0.88 (0.80–0.97) | 0.063 |
| LSIL + cytology | 79.7% | 0.84 (0.79–0.90) | < 0.001 | 88.8% | 0.95 (0.86–1.05) | 0.688 |

CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe diagnosis; $P_{McN}$ = P-value exact McNemar $\chi^2$; Ref. = Reference.

**Table 3**
Effect of delay in specimen preparation on ability to detect the presence of hrHPV DNA and underlying disease from self-collected versus clinician collected specimen by sampling method and HPV assay.

| Screening method | ≤ 28 days (n = 111) | | | | > 28 days (n = 121) | | | |
|---|---|---|---|---|---|---|---|---|
| | hrHPV positive | | Relative sensitivity for CIN3+ | | hrHPV positive | | Relative sensitivity for CIN3+ | |
| | % | Kappa (95% CI) | (90% CI) | $P_{McN}$ | % | Kappa (95% CI) | (90% CI) | $P_{McN}$ |
| Anyplex™ II HPV28 | | | | | | | | |
| Evalyn®Brush | 93.7 | 0.74 (0.55–0.92) | 0.99 (0.95–1.02) | 1.000 | 94.2 | 0.56 (0.27–0.85) | 0.99 (0.95–1.03) | 1.000 |
| FLOQSwabs™ | 90.1 | 0.63 (0.43–0.83) | 0.94 (0.89–0.99) | 0.125 | 86.0 | 0.35 (0.11–0.57) | 0.89 (0.84–0.95) | 0.006 |
| Cobas® 4800 | | | | | | | | |
| Evalyn®Brush | 92.8 | 0.76 (0.60–0.89) | 0.97 (0.93–1.02) | 0.625 | 89.3 | 0.46 (0.21–0.71) | 0.96 (0.91–1.01) | 0.289 |
| FLOQSwabs™ | 91.0 | 0.72 (0.55–0.86) | 0.95 (0.90–1.00) | 0.219 | 86.0 | 0.45 (0.22–0.66) | 0.89 (0.83–0.95) | 0.006 |
| Xpert®HPV | | | | | | | | |
| Evalyn®Brush | 92.8 | 0.77 (0.62–0.92) | 0.96 (0.92–1.01) | 0.375 | 90.1 | 0.45 (0.18–0.71) | 0.97 (0.92–1.01) | 0.453 |
| FLOQSwabs™ | 92.8 | 0.77 (0.59–0.91) | 0.97 (0.95–1.00) | 0.500 | 85.1 | 0.40 (0.17–0.61) | 0.89 (0.84–0.95) | 0.006 |

hrHPV = high-risk human papillomavirus; CIN3+ = cervical intraepithelial neoplasia grade 3 or more severe diagnosis; $P_{McN}$ = P-value exact McNemar $\chi^2$

Women were asked which screening method they would choose in the future, and only 19% of respondents preferred physician. Of 245 respondents in favor of self-collection, one third responded that device does not matter, both were equally good. Of rest, slightly higher proportion would rather use Evalyn®Brush than FLOQSwabs™ (37% vs. 29%, P = 0.013). We did not observe differences on future's preferences for self-collection by sociodemographic status (data not shown).

## 5. Discussion

Our study revealed device effects in analytical and clinical

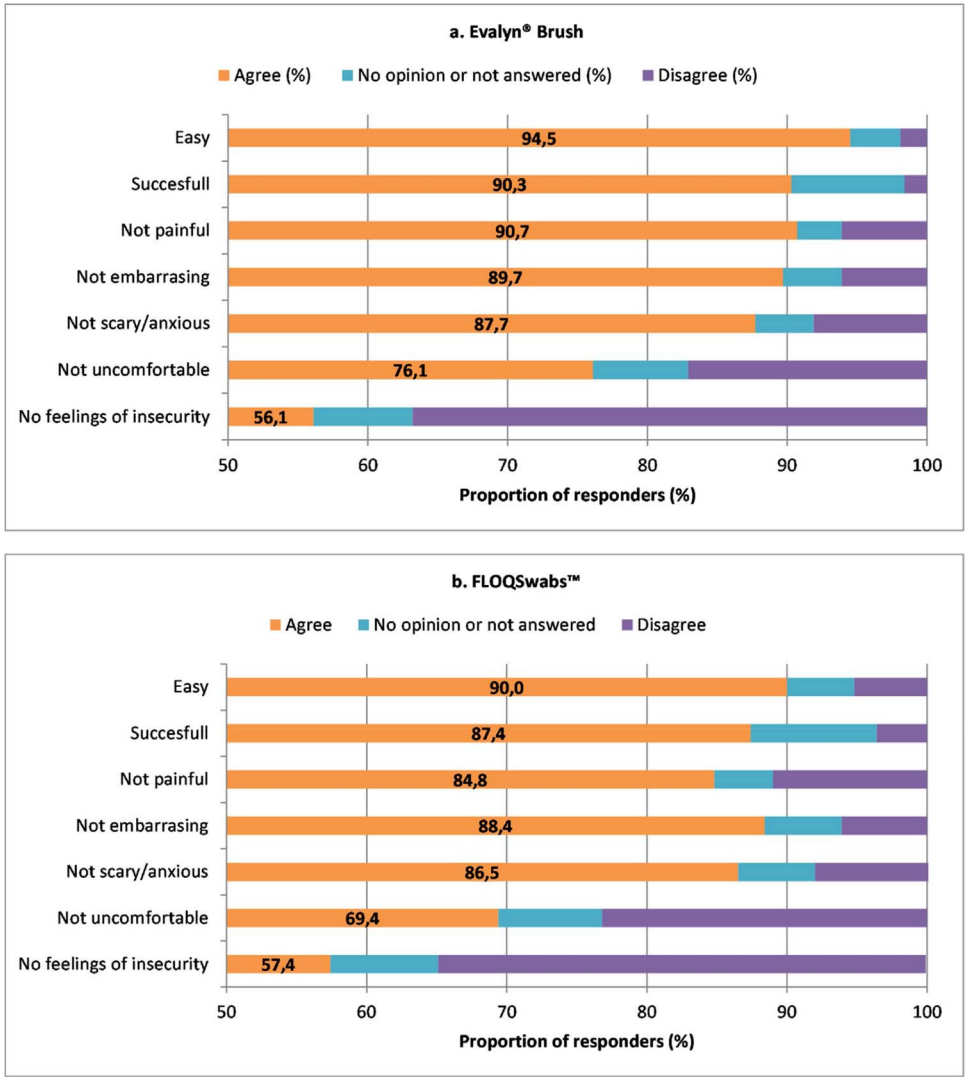


**Fig. 2.** Women's experiences on self-collection using Evalyn®Brush (a) and FLOQSwabs™ (b).

**Table 4**
Women's experiences on self-collection both devices combined by sociodemographic status.

| | Age | | | Marital status | | | Education | | |
|---|---|---|---|---|---|---|---|---|---|
| | < 40 years n (%) | Age ≥ 40 years n (%) | $P_F$ | Married n (%) | Unmarried n (%) | $P_F$ | < 13 years n (%) | ≥ 13 years n (%) | $P_F$ |
| Easy | | | 0.533 | | | 0.615 | | | 0.060 |
| Agree | 192 (98%) | 110 (96%) | | 96 (99%) | 206 (97%) | | 60 (94%) | 242 (98%) | |
| Disagree | 0 (−) | 1 (1%) | | 0 (−) | 1 (1%) | | 1 (2%) | 0 (−) | |
| No opinion or not answered | 4 (2%) | 3 (3%) | | 1 (1%) | 6 (3%) | | 3 (5%) | 4 (2%) | |
| successful | | | 0.027 | | | 0.666 | | | 0.033 |
| Agree | 188 (96%) | 103 (90%) | | 93 (96%) | 198 (93%) | | 56 (88%) | 235 (96%) | |
| Disagree | 0 (−) | 3 (3%) | | 0 (−) | 3 (1%) | | 1 (2%) | 2 (1%) | |
| No opinion or not answered | 8 (4%) | 8 (7%) | | 4 (4%) | 12 (6%) | | 7 (11%) | 9 (4%) | |
| No feelings of insecurity | | | 0.091 | | | 0.600 | | | 0.017 |
| Agree | 102 (52%) | 49 (43%) | | 45 (46%) | 106 (50%) | | 23 (36%) | 128 (52%) | |
| Disagree | 87 (44%) | 55 (48%) | | 45 (46%) | 97 (46%) | | 34 (53%) | 108 (44%) | |
| No opinion or not answered | 7 (4%) | 10 (9%) | | 7 (7%) | 10 (5%) | | 7 (11%) | 10 (4%) | |
| Not uncomfortable | | | 0.318 | | | 0.161 | | | 0.010 |
| Agree | 121 (62%) | 79 (69%) | | 70 (72%) | 130 (61%) | | 36 (56%) | 164 (67%) | |
| Disagree | 64 (33%) | 28 (25%) | | 22 (23%) | 70 (33%) | | 19 (30%) | 73 (30%) | |
| No opinion or not answered | 11 (6%) | 7 (6%) | | 5 (5%) | 13 (6%) | | 9 (14%) | 9 (4%) | |
| Not painful | | | 0.414 | | | 0.053 | | | 0.089 |
| Agree | 160 (82%) | 97 (85%) | | 87 (90%) | 170 (80%) | | 49 (77%) | 208 (85%) | |
| Disagree | 33 (17%) | 14 (12%) | | 8 (8%) | 39 (18%) | | 12 (19%) | 35 (14%) | |
| No opinion or not answered | 3 (2%) | 3 (3%) | | 2 (2%) | 4 (2%) | | 3 (5%) | 3 (1%) | |
| Not embarrasing | | | 0.002 | | | 0.899 | | | 0.229 |
| Agree | 171 (87%) | 108 (95%) | | 89 (92%) | 190 (89%) | | 55 (86%) | 224 (91%) | |
| Disagree | 20 (10%) | 1 (1%) | | 5 (5%) | 16 (8%) | | 5 (8%) | 16 (7%) | |
| No opinion or not answered | 5 (3%) | 5 (4%) | | 3 (3%) | 7 (3%) | | 4 (6%) | 6 (2%) | |
| Not scary/anxious | | | 0.360 | | | 0.255 | | | 0.044 |
| Agree | 166 (85%) | 102 (89%) | | 88 (91%) | 180 (85%) | | 55 (86%) | 213 (87%) | |
| Disagree | 24 (12%) | 8 (7%) | | 6 (6%) | 26 (12%) | | 4 (6%) | 28 (11%) | |
| No opinion or not answered | 6 (3%) | 4 (4%) | | 3 (3%) | 7 (3%) | | 5 (8%) | 5 (2%) | |

$P_F$ = P-value Fisher's exact test

sensitivity of hrHPV testing of self-collected specimens. Lower sensitivity of hrHPV test on FLOQSwabs™ compared to Evalyn®Brush was consistent for all studied assays. Clinical performance of both self-sampling devices was non-inferior to the physician-collected specimen when self-specimens were preprocessed within four weeks since the specimen-collection.

Overall agreement regarding hrHPV positivity was in line with findings of the meta-analysis [29] and with more recent studies [11,20,30–34]. Dutch studies comparing brush and lavage devices did not observe clear device effects on hrHPV positivity rates [11,12], or difference in agreement between a dry and a wet brush [30]. In contrast, a study from Switzerland found differences in hrHPV detection in favor of the FLOQSwabs™ over a brush applied to an FTA cartridge [13]. In our study, FLOQSwabs™ showed somewhat lower analytical sensitivity and resulted more often in re-analysis because of invalid result on hrHPV testing. This may be due to high concentration of cellular material collected with FLOQSwabs™ when suspended in 4.6 ml of ThinPrep, as they often yielded a conclusive result when hrHPV test was repeated on diluted specimens. Whether specimen suspension in larger volumes or use of a swab with smaller sampling head could lead to better results warrants further exploration. It is also possible that specifically designed collection devices better reach the upper vagina whereas a brush or a swab is not inserted as high in the vagina. Lower viral load of vaginal hrHPV that is detectable using more sensitive assays may also contribute to lower sensitivity of FLOQSwabs™ in our study [35].

Among women referred for colposcopy, the absolute pooled sensitivity of self-collected specimen to detect high-grade cervical lesion is around 85% [7]. In our study, sensitivity for CIN3+ of hrHPV testing of Evalyn®Brush was 91–95% and of FLOQSwabs™ was 86–88% depending on the hrHPV assay. Importantly, our study adds to the existing evidence that hrHPV test of self-collected specimens can identify women with invasive carcinoma from self-specimen.

Sensitivity of cytology in our study was in accordance with the literature [7,36], but it was clearly inferior to both hrHPV testing on physician-and self-specimens. We had high proportion of CIN3+ lesions, thus, obscuring blood most likely have impaired the correct cytology diagnosis. Moreover, we used ThinPrep which seem to be less sensitive and results more frequently in unsatisfactory smears than SurePath [37,38].

Specimens collected at home might be delayed before reaching the laboratory due to a variety of reasons. No previous studies have reported that delays have different effect on performance of different devices. We found that sensitivity of both devices regarding presence of CIN3+ was non-inferior to physician when self-specimens were preprocessed within 28 days. Furthermore, concordance between self- and physician-specimens for hrHPV positivity was substantial using both devices when preprocessed on timely manner. Analytical and clinical sensitivity of Evalyn®Brush was more stable over time whereas delays had notable effect on performance of FLOQSwabs™. Long storage at dry state may have lead into microbial growth which could potentially impair the DNA extraction processes and destroy DNA in the specimens. We hypothesize that FLOQSwabs™ are more sensitive to delays in specimen processing perhaps because they absorb more moisture than brushes. In terms of screening programmes, dry self-collection devices are appealing as they could be sent by regular mail [20]. Our study support the use of dry self-collection devices as long as smooth specimen logistics and timely testing is ensured. However, Evalyn®Brush remained analytically stable in room temperature and humidity for months and, therefore, seems a promising device also for remote areas with extreme temperatures [31,39].

Our results were consistent with the literature showing high

acceptability and positive attitudes towards self-collection [4,8,12,20,39–46]. Similar to others, we did not observe differences in preference for self-collection based on age group, level of education or marital status [4,8,43,45,46]. In line with previous studies, the majority of women had more confidence in physician-specimens but they still preferred self-collection at home over standard clinical-sampling. One study, however, demonstrated that women would prefer self-collection at a clinic, or that a provider would collect the vaginal sample [47]. Use of collection devices with indicators of adequate insertion and adequate specimen may reduce concerns of performing the self-collection properly [39]. Alternative approach could be to offer self-collection option at clinic where women have a possibility to ask questions and get assistance if needed [46,47].

In our study, both devices were well accepted but women considered Evalyn®Brush easier and more comfortable than FLOQSwabs™. Some previous studies report no difference in user comfort [10,12], while others report slightly more positive experiences with a lavage device than with a brush [8,14]. Women in Switzerland preferred FLOQSwabs™ over a brush with an FTA cartridge [13]. A previous study from Oslo region asking exactly the same questions on women's experiences reported a trend towards higher acceptability in favor of a brush over a lavage device [6]. Acceptability is of great importance if self-sampling is offered for women who do not comply with regular screening and may depend on the setting. Thus, it is important that performance and acceptability of self-collection device is piloted before national implementation.

Main strengths of our study are its large size and its setting in the population with high prevalence of cervical carcinoma. Moreover, we used validated hrHPV assays and participants served as their own controls, limiting potential biases. Our study was conducted among patients referred to the secondary care due to cervical abnormalities and results might not be generalizable to under- and unscreened women due to selection bias.

Among women referred to conisation, we had relatively high proportion of normal histology in the cone specimens. Plausible explanations could be spontaneous regression between biopsy and treatment, or that the lesion has been removed by the preoperative biopsy. Furthermore, we did not perform a histopathological review but used diagnoses given by local pathologists. The interobserver variability of the preinvasive lesions may be substantial between the community and panel pathologists [48].

Another limitation is that we did not exclude cases with invalid hrHPV results. We wanted to assess the realistic performance of self-sampling in which a quality of sample is one determinant. Due to logistical challenges, specimen preparation was not occasionally started before several weeks or even months had passed. This allowed us to study effect of delays but it can also affect our results on sensitivity favoring Evalyn®Brush which seem very robust to environmental conditions at least up to 8 weeks [49]. Currently, there are no recommendations on the length of storage at dry state for self-collected specimens. Some disagreement between HPV assays and screening methods may also be attributed to inadequate cellularity. Here we only took into account the overall hrHPV positivity, and did not examine discordant pairs in detail. Discordance may be affected e.g. by age, morphology and different fidelity for the targeted hrHPV types in studied assays. All these aspects will be subject to further investigation.

## 6. Conclusion

hrHPV DNA detection in self-collected specimens provides an objective screening method that is comparable to routine screening for detecting cervical carcinoma and high-grade lesions. Performance of self-collection is determined by its constituting parts including collection device, hrHPV assay, specimen preparation and delays in specimen logistics and preparation. If self-collection will be included in screening programmes, only validated procedure should be used, and delays in specimen testing should be minimized.

## Conflict of interest

MN has received self-collection devices at a reduced or no cost from Rovers Medical Devices and COPAN; CMJ has received HPV tests and assays at a reduced cost from Seegene and Cepheid; PEC has received HPV tests and assays at a reduced or no cost for research from Roche, Becton Dickinson, Cepheid and Arbor Vita Corporation; no other relationships or activities that could appear to have influenced the submitted work.

## Funding

Norwegian Cancer Society (grant 5777899) and Cancer Registry of Norway. Sponsors had no role in study design, data collection, analysis, and interpretation of data; in the writing of the report or the decision to submit the article for publication.

## Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2014-655). Trial registration: ClinicalTrials.gov NCT02945891 and www.kliniskestudier.helsenorge.no.

## Acknowledgements

CMJ, MN and PEC designed the study; AKL, AR, AT, CFN, IEF, KDS, KS, MJJ and MKL collected the data; MKL analyzed the data and drafted the paper. All the authors contributed to the final version of the manuscript. The authors wish to thank Torunn Søland, Thomas Thaulow, Gunnar Kristensen, Marianne Olsen, Per Arne Stensager, Aud Jaaval, Karin Skogsfjord and other doctors and nurses at all recruitment hospitals for their collaboration and contribution; Madleen Orumaa, Line Ragna Aakre Karlsson, Espen Enerly and Linda Vos at the Cancer Registry of Norway; and Teresa Xavier from University of Oslo for their contribution for this study. We also thank Rovers Medical Devices for providing Evalyn®Brush at reduced price; Seegene and Cepheid for providing HPV tests at reduced price; and COPAN for providing FLOQSwabs™ for free.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jcv.2017.12.008.

## References

[1] J. Waller, M. Jackowska, L. Marlow, J. Wardle, Exploring age differences in reasons for nonattendence for cervical screening: a qualitative study, BJOG 119 (2012) 26–32.
[2] M.K. Leinonen, S. Campbell, O. Klungsøyr, S. Lönnberg, B.T. Hansen, M. Nygård, Personal and provider level factors influence participation to cervical cancer screening: a retrospective register-based study of 1.3 million women in Norway, Prev. Med. 94 (2017) 31–39, http://dx.doi.org/10.1016/j.ypmed.2016.11.018.
[3] C.S. Racey, D.R. Withrow, D. Gesink, Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis, Can. J. Public Health 104 (2013) e159–e166.
[4] A. Virtanen, P. Nieminen, M. Niironen, T. Luostarinen, A. Anttila, Self-sampling experiences among non-attendees to cervical screening, Gynecol. Oncol. 135 (3) (2014) 487–494.
[5] F. Verdoodt, M. Jentschke, P. Hillemanns, C.S. Racey, P.J.F. Snijders, M. Arbyn, Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of

randomised trials, Eur. J. Cancer 51 (16) (2015) 2375–2385, http://dx.doi.org/10.1016/j.ejca.2015.07.006.
[6] E. Enerly, J. Bonde, K. Schee, H. Pedersen, S. Lönnberg, M. Nygård, Self-sampling for human papillomavirus testing among non-attenders increases attendance to the Norwegian Cervical Cancer Screening Programme, PLoS One 11 (4) (2016) e0151978, http://dx.doi.org/10.1371/journal.pone.0151978.
[7] M. Arbyn, F. Verdoodt, P.J.F. Snijders, V.M. Verhoef, E. Suonio, L. Dillner, S. Minozzi, C. Bellisario, R. Banzi, F.H. Zhao, P. Hillemanns, A. Anttila, Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis, Lancet Oncol. 15 (2014) 172–183, http://dx.doi.org/10.1016/S1470-2045(13)70570-9.
[8] S. Igidbashian, S. Boveri, N. Spolti, D. Radice, M.T. Sandri, M. Sideri, Self-collected human papillomavirus testing acceptability: comparison of two self-sampling modalities, J. Womens Health 20 (3) (2011) 397–402, http://dx.doi.org/10.1089/jwh.2010.2189.
[9] J.L. Belinson, H. Du, B. Yang, R. Wu, S.E. Belinson, X. Qu, R.G. Pretorius, X. Yi, P.E. Castle, Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing, Int. J. Cancer 130 (2012) 1855–1860, http://dx.doi.org/10.1002/ijc.26202.
[10] I. Eperon, P. Vassilakos, I. Navarria, P.A. Menoud, A. Gauthier, J.C. Pache, M. Boulvain, S. Untiet, P. Petignat, Randomized comparison of vaginal self-sampling by standard vs. dry swabs for Human papillomavirus testing, BMC Cancer 13 (2013) 353, http://dx.doi.org/10.1186/1471-2407-13-353.
[11] A.T. Hesselink, J. Berkhof, M.L. van der Salm, A.P. van Splunter, T.H. Geelen, F.J. van Kemenade, M.G. Bleeker, D.A. Heideman, Clinical validation of the HPV-risk assay, a novel real-time PCR assay for detection of high-risk human papillomavirus DNA by targeting the E7 region, J. Clin. Microbiol. 52 (3) (2014) 890–896, http://dx.doi.org/10.1128/JCM.03195-13.
[12] R.P. Bosgraaf, V.M.J. Verhoef, L.F.A.G. Massuger, A.G. Siebers, J. Bulten, G.M. de Kuyper-de Ridder, C.J. Meijer, P.J. Snijders, D.A. Heideman, J. IntHout, F.J. van Kemenade, W.J. Melchers, R.L. Bekkers, Comparative performance of novel self-sampling methods in detecting high-risk human papillomavirus in 30,130 women not attending cervical screening, Int. J. Cancer 136 (2015) 646–655, http://dx.doi.org/10.1002/ijc.29026.
[13] R. Catarino, P. Vassilakos, A. Bilancioni, M. Vanden Eynde, U. Meyer-Hamme, P.A. Menoud, F. Guerry, P. Petignat, Randomized comparison of two vaginal self-Sampling methods for human papillomavirus detection: dry swab versus FTA cartridge, PLoS One 10 (12) (2015) e0143644, http://dx.doi.org/10.1371/journal.pone.0143644.
[14] L. Karjalainen, A. Anttila, P. Nieminen, T. Luostarinen, A. Virtanen, Self-sampling in cervical cancer screening: a brush- based and a lavage-based cervicovaginal self-sampling device, BMC Cancer 16 (2016) 221, http://dx.doi.org/10.1186/s12885-016-2246-9.
[15] A. Anttila, G. Ronco, F. Nicula, P. Nieminen, M. Primic Zakelj, Organization of cytology-based and HPV-based cervical cancer screening. S2, in: A. Anttila, A. Arbyn, H. De Vuyst, J. Dillner, L. Dillner, S. Franceschi, J. Patnick, G. Ronco, N. Segnan, E. Suonio, S. Törnberg, L. von Karsa (Eds.), European Guidelines for Quality Assurance in Cervical Cancer Screening, Second Edition, Office for Official Publications of the European Union, Luxembourg, 2015Supplements.
[16] F.R. Lorenzato, A. Singer, L. Ho, L.C. Santos, L. Batista Rde, T.M. Lubambo, G. Terry, Human papillomavirus detection for cervical cancer prevention with polymerase chain reaction in self-collected samples, Am. J. Obstet. Gynecol. 186 (5) (2002) 962–968.
[17] F. Garcia, B. Barker, C. Santos, E.M. Brown, T. Nuño, A. Giuliano, J. Davis, Cross-sectional study of patient- and physician-collected cervical cytology and human papillomavirus, Obstet. Gynecol. 102 (2003) 266–272.
[18] A. Daponte, S. Pournaras, I. Mademtzis, C. Hadjichristodoulou, E. Kostopoulou, A.N. Maniatis, I.E. Messinis, Evaluation of HPV 16 PCR detection in self- compared with clinician-collected samples in women referred for colposcopy, Gynecol. Oncol. 103 (2) (2006) 463–466.
[19] S.S. Seo, Y.S. Song, J.W. Kim, N.H. Park, S.B. Kang, H.P. Lee, Good correlation of HPV DNA test between self-collected vaginal and clinician-collected cervical samples by the oligonucleotide microarray, Gynecol. Oncol. 102 (1) (2006) 67–73.
[20] R. van Baars, R.P. Bosgraaf, B.W. ter Harmsel, W.J. Melchers, W.G. Quint, R.L. Bekkers, Dry storage and transport of a cervicovaginal self-sample by use of the Evalyn®Brush Brush, providing reliable human papillomavirus detection combined with comfort for women, J. Clin. Microbiol. 50 (2012) 3937–3943, http://dx.doi.org/10.1128/JCM.01506-12.
[21] A.T. Hesselink, R. Sahli, J. Berkhof, P.J. Snijders, M.L. van der Salm, D. Agard, M.C. Bleeker, D.A. Heideman, Clinical validation of Anyplex™TM II HPV HR Detection according to the guidelines for HPV test requirements for cervical cancer screening, J. Clin. Virol. 76 (2016) 36–39, http://dx.doi.org/10.1016/j.jcv.2016.01.009.
[22] D.A. Heideman, A.T. Hesselink, J. Berkhof, F. van Kemenade, W.J. Melchers, N.F. Daalmeijer, M. Verkuijten, C.J. Meijer, P.J. Snijders, Clinical validation of the Cobas® 4800 HPV test for cervical screening purposes, J. Clin. Microbiol. 49 (11) (2011) 3983–3985, http://dx.doi.org/10.1128/JCM.05552-11.
[23] K. Cuschieri, D. Geraets, J. Cuzick, L. Cadman, C. Moore, D. Vanden Broeck, E. Padalko, W. Quint, M. Arbyn, Performance of a cartridge-based assay for detection of clinically significant human papillomavirus (HPV) infection: lessons from VALGENT (Validation of HPV genotyping tests), J. Clin. Microbiol. 54 (2016) 2337–2342, http://dx.doi.org/10.1128/JCM.00897-16.
[24] R. Nayar, D.C. Wilbur, The Bethesda System for Reporting Cervical Cytology, third edition, Springer, Switzerland, 2015.
[25] J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, Biometrics 33 (1) (1977) 159–174.
[26] N.S. Tang, M.L. Tang, I.S. Chan, On tests of equivalence via non-unity relative risk for matched-pair design, Stat. Med. 22 (8) (2003) 1217–1233.
[27] E. Walker, A.S. Nowacki, Understanding equivalence and non-inferiority testing, J. Gen. Intern. Med. 26 (2) (2010) 192–196.
[28] C.J. Meijer, J. Berkhof, P.E. Castle, A.T. Hesselink, E.L. Franco, G. Ronco, M. Arbyn, F.X. Bosch, J. Cuzick, J. Dillner, D.A. Heideman, P.J. Snijders, Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older, Int. J. Cancer 124 (3) (2009) 516–520, http://dx.doi.org/10.1002/ijc.24010.
[29] P. Petignat, D.L. Faltin, I. Bruchim, M.R. Tramèr, E.L. Franco, F. Coutlée, Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis, Gynecol. Oncol. 105 (2007) 530–535.
[30] C.H. Lenselink, R.P. de Bie, D. van Hamont, J.M. Bakkers, W.G. Quint, L.F. Massuger, R.L. Bekkers, W.J. Melchers, Detection and genotyping of human papillomavirus in self-obtained cervicovaginal samples by using the FTA cartridge: new possibilities for cervical cancer screening, J. Clin. Microbiol. 47 (2009) 2564–2570, http://dx.doi.org/10.1128/JCM.00285-09.
[31] I. Gustavsson, K. Sanner, M. Lindell, A. Strand, M. Olovsson, I. Wikström, E. Wilander, U. Gyllensten, Type-specific detection of high-risk human papillomavirus (HPV) in self-sampled cervicovaginal cells applied to FTA elute cartridge, J. Clin. Virol. 51 (2011) 255–258, http://dx.doi.org/10.1016/j.jcv.2011.05.006.
[32] M.G. Dijkstra, D.A. Heideman, F.J. van Kemenade, K.J. Hogewoning, A.T. Hesselink, M.C. Verkuijten, W.M. van Baal, G.M. Boer, P.J. Snijders, C.J. Meijer, Brush-based self-sampling in combination with GP5+/6+-PCR-based hrHPV testing: high concordance with physician-taken cervical scrapes for HPV genotyping and detection of high-grade CIN, J. Clin. Virol. 54 (2012) 147–151, http://dx.doi.org/10.1016/j.jcv.2012.02.022.
[33] L. Darlin, C. Borgfeldt, O. Forslund, E. Hénic, J. Dillner, P. Kannisto, Vaginal self-sampling without preservative for human papillomavirus testing shows good sensitivity, J. Clin. Virol. 56 (2013) 52–56.
[34] D.T. Geraets, R. van Baars, I. Alonso, J. Ordi, A. Torné, W.J. Melchers, C.J. Meijer, W.G. Quint, Clinical evaluation of high-risk HPV detection on self-samples using the indicating FTA-elute solid-carrier cartridge, J. Clin. Virol. 57 (2013) 125–129, http://dx.doi.org/10.1016/j.jcv.2013.02.016.
[35] J.L. Belinson, S. Hu, M. Niyazi, R.G. Pretorius, H. Wang, C. Wen, J.S. Smith, J. Li, F.J. Taddeo, R.J. Burchette, Y.L. Qiao, Prevalence of type-specific human papillomavirus in endocervical, upper and lower vaginal, perineal and vaginal self-collected specimens: implications for vaginal self-collection, Int. J. Cancer 127 (2010) 1151–1157, http://dx.doi.org/10.1002/ijc.25144.
[36] Q.J. Pan, S. Hu, X. Zhang, P.W. Ci, W.H. Zhang, H.Q. Guo, J. Cao, F.H. Zhao, A. Lytwyn, Y.L. Qiao, Pooled analysis of performance of liquid based cytology in population-based cervical cancer screening studies in China, Cancer Cytopathol. 121 (9) (2013) 473–482, http://dx.doi.org/10.1002/cncy.21297.
[37] D. Fontaine, N. Narine, C. Naugler, Unsatisfactory rates vary between cervical cytology samples prepared using ThinPrep and SurePath platforms: a review and meta-analysis, BMJ Open 2 (2012) e000847, http://dx.doi.org/10.1136/bmjopen-2012-000847.
[38] K. Rozemeijer, S.K. Naber, C. Penning, L.I. Overbeek, C.W. Looman, I.M. de Kok, S.M. Matthijsse, M. Rebolj, F.J. van Kemenade, M. van Ballegooijen, Cervical cancer incidence after normal cytological sample in routine screening using SurePath, ThinPrep, and conventional cytology: population based study, BMJ 356 (2017) j504, http://dx.doi.org/10.1136/bmj.j504.
[39] P.E. Gravitt, J.L. Belinson, J. Salmeron, K.V. Shah, Looking ahead: a case for HPV testing of self-sampled vaginal specimens as a cervical cancer screening strategy, Int. J. Cancer 129 (3) (2011) 517–527, http://dx.doi.org/10.1002/ijc.25974.
[40] J. Huynh, M. Howard, A. Lytwyn, Self-collection for vaginal human papillomavirus testing: systematic review of studies asking women their perceptions, J. Low. Genit. Tract Dis. 14 (4) (2010) 356–362, http://dx.doi.org/10.1097/LGT.0b013e3181dc115b.
[41] I. Wikström, M. Lindell, K. Sanner, E. Wilander, Self-sampling and HPV testing or ordinary Pap-smear in women not regularly attending screening: a randomised study, Br. J. Cancer 105 (2011) 337–339.
[42] S. Castell, G. Krause, M. Schmitt, M. Pawlita, Y. Deleré, N. Obi, D. Flesch-Janys, Y. Kemmling, A.M. Kaufmann, Feasibility and acceptance of cervicovaginal self-sampling within the German National Cohort (Pretest 2), Bundesgesundheitsbl 57 (2014) 1270–1276, http://dx.doi.org/10.1007/s00103-014-2054-9.
[43] C.S. Racey, D.S. Gesink, A.N. Burchell, S. Trivers, T. Wong, A. Rebbapragada, Randomized intervention of self-collected sampling for human papillomavirus testing in under-screened rural women: uptake of screening and acceptability, J. Womens Health (Larchmt) 25 (5) (2016) 489–497, http://dx.doi.org/10.1089/jwh.2015.5348.
[44] F. Sultana, R. Mullins, D.R. English, J.A. Simpson, K.T. Drennan, S. Heley, C.D. Wrede, J.M. Brotherton, M. Saville, D.M. Gertig, Women's experience with home-based self-sampling for human papillomavirus testing, BMC Cancer 15 (2015) 849, http://dx.doi.org/10.1186/s12885-015-1804-x.
[45] M. Ma'som, N. Bhoo-Pathy, N.H. Nasir, J. Bellinson, S. Subramaniam, Y. Ma, S.H. Yap, P.P. Goh, P. Gravitt, Y.L. Woo, Attitudes and factors affecting acceptability of selfadministered cervicovaginal sampling for human papillomavirus (HPV) genotyping as an alternative to Pap testing among multiethnic Malaysian women, BMJ Open 6 (2016) e011022, http://dx.doi.org/10.1136/bmjopen-2015-011022.

[46] R.L. Winer, A.A. Gonzales, C.J. Noonan, S.L. Cherne, D.S. Buchwald, Collaborative to improve native cancer outcomes (CINCO) assessing acceptability of self-sampling kits, prevalence, and risk factors for human papillomavirus infection in american indian women, J. Commun. Health 41 (2016) 1049–1061, http://dx.doi.org/10.1007/s10900-016-0189-3.

[47] P. Bansil, S. Wittet, J.L. Lim, J.L. Winkler, P. Paul, J. Jeronimo, Acceptability of self-collection sampling for HPV-DNA testing in low-resource settings: a mixed methods approach, BMC Public Health 14 (2014) 596, http://dx.doi.org/10.1186/1471-2458-14-596.

[48] M.H. Stoler, B.M. Ronnett, N.E. Joste, W.C. Hunt, J. Cuzick, C.M. Wheeler, New Mexico HPV pap registry steering committee the interpretive variability of cervical biopsies and its relationship to HPV status, Am. J. Surg. Pathol. 39 (6) (2015) 729–736.

[49] D.M. Ejegod, H. Pedersen, J. Bonde, Time and temperature stability of self-taken samples for HPV self-sampling; (Abstract FC 08-02)), Presented at the EUROGIN 2017, October 9, 2017, Amsterdam, 2017 (Available at: http://eurogin.com/2017/images/doc/eurogin-2017-abstracts-part-2.pdf ).