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Comparison of the Clinical Accuracy of Xpert HPV Assay on Vaginal Self-Samples and Cervical Clinician-Taken Samples within the VALHUDES Framework

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The accuracy of high-risk human papillomavirus testing with the Xpert HPV assay on vaginal self-samples was compared with clinician-taken samples within the VALidation of HUman papillomavirus assays and collection DEvices for Self-samples and urine samples (VALHUDES) framework. Five-hundred and twenty-three women were recruited in five Belgian colposcopy clinics, of whom 483 (median age, 40 years; interquartile range, 31 to 49 years) were included in the main analysis (226 collected with Evalyn Brush and 257 collected with Qvintip). Cervical samples were collected with Cervex-Brush. Colposcopy and histology outcomes were considered as the reference standard. The Xpert HPV assay had similar accuracy for cervical intraepithelial neoplasia $\geq$2 on self-collected versus clinician-collected samples [relative sensitivity, 0.96 (95% CI, 0.91—1.02); and relative specificity, 0.96 (95% CI, 0.89—1.04)]. The relative accuracy slightly differed by vaginal collection device [sensitivity ratios of 0.98 (95% CI, 0.90—1.06) and 0.94 (95% CI, 0.87—1.02) for Evalyn and Qvintip, respectively; specificity ratios of 1.06 (95% CI, 0.95—1.19) and 0.88 (95% CI, 0.80—0.98) for Evalyn and Qvintip, respectively]. No difference in cycle threshold values was observed between vaginal and cervical samples. In conclusion, the sensitivity of Xpert HPV assay for cervical intraepithelial neoplasia $\geq$2 on vaginal self-samples was similar to that of cervical specimens. The clinical specificity was lower than on clinician-collected samples when self-samples were taken with Qvintip. *(J Mol Diagn 2023, 25: 702—708; https://doi.org/10.1016/j.jmoldx.2023.06.004)*

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Screening for nucleic acids of high-risk human papillomavirus (hrHPV) types, the causal agents of cervical cancer, is more effective than cytology and, therefore, recommended in most recent guidelines for secondary prevention of this neoplasia.[1–3] Moreover, human papillomavirus (HPV) assays can be applied on self-samples.[4]

HPV testing on self-samples has gained worldwide attention because of its potential in reaching out to women who do not participate in or attend regular screening.[5,6] As under-screened women remain at risk of developing cervical cancer, reaching out to this population has become a public health priority in many countries.[6] Randomized trials have demonstrated that offering a self-sample is more effective than traditional invitations to go to a clinic for collection of a cervical specimen by a health care professional.[4,5] In addition, recent studies have shown that HPV testing on adequately prepared vaginal self-samples with a validated PCR-based HPV test has similar accuracy to detect cervical precancer as HPV testing on cervical specimens.[5]

The lack of international standardized protocols on self-samples has inspired the development of a framework for VALidation of HUman papillomavirus assays and collection DEvices for Self-samples and urine samples (VALHUDES).[7] Such standardized protocols and validation have existed for cervical samples for more than a decade.[8,9] About a dozen hrHPV DNA tests have been demonstrated to fulfil the international validation criteria on clinician samples, and the list of clinically validated tests is continuously expanding.[10] Similar studies are necessary to tackle the existing challenges in HPV testing workflow on self-samples.[11] Previous VALHUDES reports demonstrated that two assays [RealTi*me* High Risk HPV assay (Abbott Molecular Diagnostics, Des Plaines, IL); and BD Onclarity HPV Assay (BD Diagnostics, Sparks, MD)] are similarly accurate to detect cervical precancer on vaginal self-samples and on first-void urine as on cervical clinician-taken samples.[12–15]

In the current VALHUDES report, we assess the analytical and clinical performance of the Xpert HPV assay (Xpert HPV; Cepheid, Sunnyvale, CA), a cartridge-based assay with point-of-care application on vaginal self-samples.[16]

Materials and Methods

Study Design

The VALHUDES protocol (NCT03064087; *https://clinicaltrials.gov*, last accessed May 20, 2023)[7] was designed to evaluate the relative clinical accuracy of HPV assays on self-collected vaginal and urine samples compared with HPV assays on clinician-taken samples, according to the Standards for Reporting of Diagnostic Accuracy Studies guidelines, as previously described.[17] Between December 2017 and January 2020, 523 women were enrolled because of an existing HPV infection or cervical abnormality. The median age of participants was 40 years (interquartile range, 31 to 49 years). Recruitment occurred at five Belgian colposcopy clinics (University Hospitals of Antwerp, Brussels, Ghent, and Liège, and the General Regional Hospital Heilig Hart Tienen). The following exclusion criteria were applied for the study: pregnancy, hysterectomy, refusal to participate, and failure to understand and sign inform consent. All enrolled study participants signed informed consent.

On arrival at the colposcopy clinics, study nurses instructed study participants to collect a vaginal self-sample with the Qvintip vaginal device (Aprovix AB, Stockholm, Sweden) or Evalyn Brush (Rovers Medical Devices, Oss, the Netherlands). Cervical samples were collected by a gynecologist using the Cervex-Brush (Rovers Medical Devices) in agreement with European guidelines.[18] Colposcopy clinics in Brussels, Liège, and Tienen initiated the study, offering participants the Qvintip device, whereas clinics in Antwerp and Ghent offered the Evalyn Brush. Self-sampling devices were switched when nearly half of the sample size was reached.

The dry heads of the vaginal brushes were stored at the colposcopy clinics at room temperature, whereas the cervical samples were resuspended in 20 mL PreservCyt medium (Hologic, Inc., Bedford, MA) after collection by the gynecologist. Both samples were shipped to Algemeen Medisch Laboratorium (Antwerp, Belgium) for storage and further processing within a maximum of 6 days after collection. On arrival at Algemeen Medisch Laboratorium, the dry vaginal samples were placed into 20-mL PreservCyt medium. All samples were stored at 4°C for a maximum of up to 3 months, followed by vortexing for 15 to 20 seconds and aliquoting into 1-mL aliquots, which were frozen at −80°C (BB190002; Biobank, Antwerp, Belgium).

HPV Testing

HPV testing was performed on 499 paired samples by transfer of a 1-mL aliquot of cervical and vaginal specimens directly into the Xpert cartridge. The cartridge contains DNA extraction reagents and primers with probes for amplification and HPV detection. Xpert HPV is based on a multiplex real-time PCR targeting *E6* and *E7* oncogenes of 14 hrHPV genotypes. Amplification was performed in five fluorescent channels to identify the following groups: HPV16, HPV18/45, HPV31/33/35/52/58, HPV51/59, and HPV39/56/66/68. Results were interpreted by GeneXpert software version 4.8 (Cepheid). The human hydroxymethylbilane synthase was detected as sample validity control for specimen adequacy and DNA amplifiability. HPV positivity was defined if cycle threshold (C_T) cutoff was $\leq$40 for HPV16 and HPV 18/45, and $\leq$38 for HPV31/35/33/52/58, HPV 51/59, and HPV39/68/56/66. Samples were considered adequate if hydroxymethylbilane synthase was $\leq$38 C_T.[19] The same cutoffs were applied for vaginal and cervical specimens.

For clinical accuracy evaluation, the authors defined HPV testing on vaginal self-samples as the index test and on cervical samples as the comparator, whereas for reference standard, colposcopy and histology outcomes were used. If no biopsy was performed and colposcopy was satisfactory and did not show suspicious findings, the outcome was classified as cervical intraepithelial neoplasia (CIN) <2.

Statistical Analysis

In total, 483 women were included in the main analyses (median age, 40 years; interquartile range, 31 to 49 years). Twenty-four women were excluded from the study because of major protocol violations, as described elsewhere.[12,14] Six cervical and five vaginal samples were retested because of system error, of which one vaginal sample remained invalid after retest. Ten cervical and five vaginal samples were excluded because of a β-globin failure on the respective specimens (Figure 1). One vaginal sample was excluded because of retest failure. Absolute and relative performance of HPV testing were evaluated for the whole study population ($N = 483$) and for women of aged ≥30 years ($N = 386$). Of participants, 47% collected a vaginal swab with Evalyn Brush (226/483) and 53% collected a vaginal swab with the Qvintip (257/483). Characteristics of the study population were reported previously.[12,15]

The authors used the McNemar test and paired 95% CIs to compare differences between cervical and vaginal samples. Cohen κ statistics were used to evaluate concordance between the specimens with the following categorization: 0.00 to 0.19, poor; 0.20 to 0.39, fair; 0.40 to 0.59, moderate; 0.60 to 0.79, good; and 0.80 to 1.00, excellent concordance. Agreement and Cohen κ were estimated for overall hrHPV positivity and genotyping groups as defined by the assay. The differences in mean C_T values between matched cervical and vaginal specimens and between CIN ≥2 and CIN <2 outcomes were evaluated with *t*-test. Statistical analyses were performed using Stata 16.1 (StataCorp LLC, College Station, TX).

Ethical Approval

The VALHUDES trial (NCT03064087) was approved by the central Ethics Committee of the University Hospital of Antwerp/University of Antwerp (B300201733869) and the local Ethics Committees of all the other involved centers. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants before enrollment.

Results

Clinical Accuracy

Clinical sensitivity of Xpert HPV to detect CIN ≥2 on vaginal self-samples collected with Evalyn Brush or Qvintip was similar to cervical samples (ratio, 0.96; 95% CI, 0.91−1.02); however, sensitivity to detect CIN3 was 9% lower (ratio, 0.91; 95% CI, 0.82−0.998). Specificity

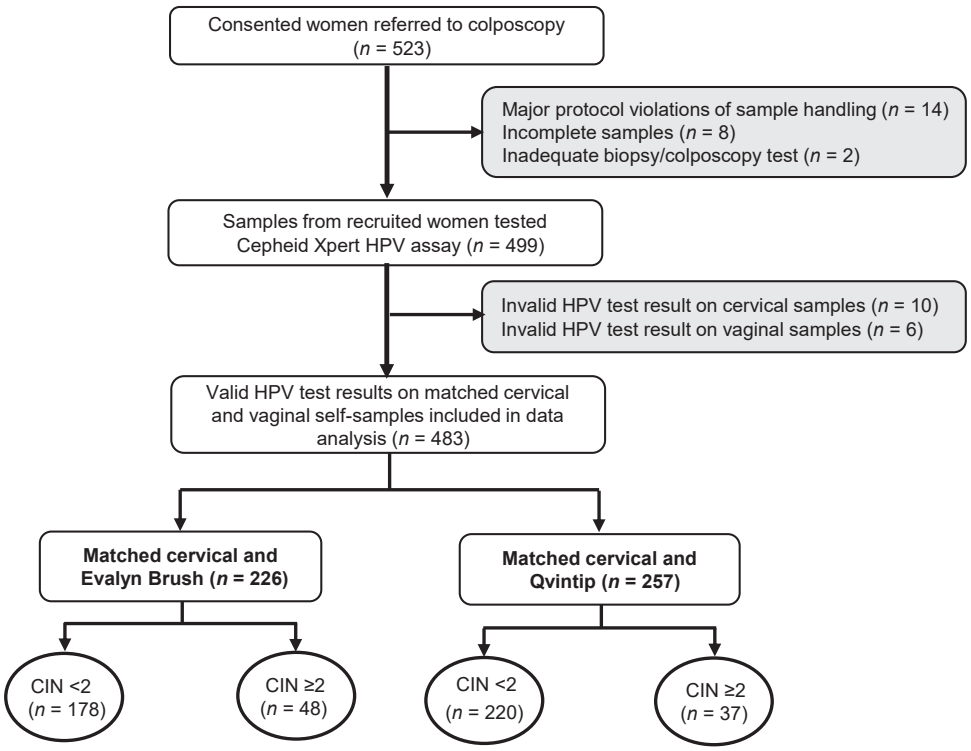

Figure 1 Flowchart of samples included in the VALHUDES trial tested with the Xpert HPV assay. **Gray boxed areas** represent excluded samples. Reasons for exclusions before human papillomavirus (HPV) testing were previously reported in detail.[12] CIN, cervical intraepithelial neoplasia.

Table 1 Relative Sensitivity and Specificity of the Cepheid Xpert HPV Assay on Clinician-Collected Samples versus Self-Samples

Study group and device	Relative sensitivity (95% CI) of CIN ≥2	Relative sensitivity (95% CI) of CIN3	Relative specificity (95% CI) of CIN <2
Total study population (n = 483)			
Vaginal (E + Q)	0.96 (0.91–1.02)	0.91 (0.82–0.998)	0.96 (0.89–1.04)
Evalyn Brush	0.98 (0.90–1.06)	0.91 (0.80–1.04)	1.06 (0.95–1.19)
Qvintip	0.94 (0.87–1.02)	0.90 (0.78–1.04)	0.88 (0.80–0.98)
Women aged ≥30 years (*n* = 386)			
Vaginal (E + Q)	0.95 (0.87–1.03)	0.88 (0.77–0.997)	0.95 (0.88–1.03)
Evalyn Brush	0.97 (0.86–1.09)	0.87 (0.71–1.06)	1.06 (0.95–1.17)
Qvintip	0.93 (0.83–1.03)	0.88 (0.74–1.05)	0.87 (0.77–0.98)

CIN, cervical intraepithelial neoplasia; E + Q, samples collected with Evalyn Brush and Qvintip combined.

for CIN <2 on vaginal self-samples was not different from cervical samples (ratio, 0.96; 95% CI, 0.89–1.04) (Table 1). Absolute accuracy is reported in Supplemental Table S1.

When stratifying the analysis by vaginal device, sensitivity for CIN ≥2 of Xpert HPV on Evalyn Brush (ratio, 0.98; 95% CI, 0.90–1.06) and Qvintip samples (ratio, 0.94; 95% CI, 0.87–1.02) was also similar to that for cervical samples. The ratio of Xpert's relative clinical sensitivity for CIN ≥2 on Evalyn Brush versus Qvintip was 1.04 (95% CI, 0.88–1.22; nonmatched comparison). Specificity of Xpert HPV on Evalyn Brush samples was not different from cervical samples (ratio, 1.06; 95% CI, 0.95–1.19), whereas on Qvintip samples, specificity was significantly lower (ratio, 0.88; 95% CI, 0.80–0.98). The specificity ratio of Evalyn Brush versus Qvintip was 1.12 (95% CI, 0.89–1.39; nonmatched comparison).

When restricting the analysis to women aged ≥30 years, accuracy was slightly lower compared with the total population (Table 1 and Supplemental Table S1).

Analytical Performance

Xpert HPV concordantly detected hrHPV in 56% (270/483) of samples, and 33% were concordantly hrHPV negative. Of specimens, 5% (24/483) were only positive on cervical samples and 6% (28/483) were only positive on vaginal self-samples. The authors observed moderate to excellent overall and type-specific test agreement between cervical and

Table 2 Overall and Type-Specific Agreement between Cervical and Vaginal (Evalyn Brush + Qvintip) Samples

Study group	HPV type	+/+	+/−	−/+	−/−	Concordance, %	κ (95% CI)
Total population (*n* = 483)	hrHPV	270	24	28	161	89.2	0.773 (0.715–0.831)
	HPV16	72	6	11	394	96.5	0.873 (0.814–0.932)
	HPV18/45	37	9	3	434	97.5	0.847 (0.762–0.932)
	HPV31/33/35/52/58	126	13	14	330	94.4	0.864 (0.814–0.914)
	HPV51/59	53	10	10	410	95.9	0.817 (0.740–0.895)
	HPV39/56/66/68	83	13	18	369	93.6	0.802 (0.736–0.869)
CIN ≥2 (*n* = 85)	hrHPV	74	4	1	6	94.1	0.674 (0.409–0.939)
	HPV16	39	2	0	44	97.7	0.953 (0.888–1.000)
	HPV18/45	7	1	1	76	97.7	0.862 (0.674–1.000)
	HPV31/33/35/52/58	33	2	1	49	96.5	0.927 (0.846–1.000)
	HPV51/59	12	1	1	71	97.7	0.909 (0.785–1.000)
	HPV39/56/66/68	17	2	5	61	91.8	0.775 (0.618–0.933)
CIN <2 (*n* = 398)	hrHPV	196	20	27	155	88.2	0.761 (0.697–0.825)
	HPV16	33	4	11	350	96.2	0.794 (0.693–0.895)
	HPV18/45	30	8	2	358	97.5	0.843 (0.749–0.938)
	HPV31/33/35/52/58	93	11	13	281	94.0	0.845 (0.785–0.905)
	HPV51/59	41	9	9	339	95.5	0.794 (0.702–0.886)
	HPV39/56/66/68	66	11	13	308	94.0	0.813 (0.755–0.870)

The κ concordance between the vaginal and cervical samples is presented as follows: 0.00 to 0.20, poor; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, good; and 0.81 to 1.00, excellent.

+/+, Positive on vaginal and cervical samples; +/−, positive only on cervical samples; −/+, positive only on vaginal samples; −/−, negative on both sample types; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hrHPV, high-risk HPV.

vaginal specimens, with κ values ranging from 0.67 to 0.93 (Table 2). Agreement by sampling device is shown in Supplemental Tables S2 and S3.

Mean C_T values for amplification of HPV and human DNA were lower for overall hrHPV and HPV16 in women with CIN $\geq$2 compared with CIN <2 in cervical samples (Supplemental Table S4). No difference in mean C_T values was found by disease status in vaginal samples (Supplemental Table S5), and no difference was observed in mean C_T values between cervical and vaginal samples (Supplemental Tables S6–S9).

Discussion

In this VALHUDES report, a similar analytical and clinical performance of Xpert HPV was demonstrated for CIN $\geq$2 on vaginal self-samples versus clinician-taken samples. As previously reported, clinical performance of hrHPV testing differed by vaginal sampling device.[14,15] Xpert on Evalyn Brush was similarly sensitive but more specific than on Qvintip. In the first VALHUDES reports, accuracies of RealTi*me* High Risk HPV assay and BD Onclarity HPV Assay were evaluated. Both assays showed similar sensitivity to detect CIN $\geq$2 in vaginal self-samples compared with clinician-taken cervical samples, although RealTi*me* High Risk HPV assay required optimization of cycle number cutoffs to reach similar sensitivity on the vaginal self-samples compared with the clinician-taken samples.[14,15]

Difference in accuracy between Evalyn and Qvintip could be explained by the device design. The Evalyn Brush has a large soft broom-like collection head, whereas Qvintip has a small hard plastic head with multiple groves on the side to collect the cervicovaginal cells. The Evalyn Brush may therefore collect more exfoliated cervical cells compared with Qvintip and, consequently, impact accuracy.

Many articles have been published on the performance of HPV testing on self-samples. In the updated meta-analysis conducted by Arbyn et al,[5] 56 accuracy studies were included. This work demonstrated similarly high accuracy of hrHPV tests to detect cervical precancer on vaginal self-samples as on clinician-collected samples if the test used was based on validated PCR-based assays, whereas signal amplification-based tests were less sensitive on self-samples. Another meta-analysis on concordance statistics that included 26 studies pooling >10,000 participants showed estimated 89% agreement with 0.72 κ value of PCR-based HPV tests on vaginal self-samples compared with cervical samples. This evidence suggests that if validated PCR-based hrHPV tests on cervical and vaginal specimens showed high agreement and κ values with new device/media, the validation could be extended to alternative devices and/or media.[20] This approach could facilitate validation of new combinations of HPV tests and self-sampling devices or media and accelerate their implementation within the screening programs.

Xpert HPV has been validated for cervical cancer screening on cervical samples stored in PreservCyt within the Validation of HPV Genotyping Tests 2 framework.[10,16] The Xpert assay was also evaluated on cervical samples of 535 women living with HIV and 586 women without HIV recruited in a context of point-of-care screening and colposcopy clinics in South Africa.[21] The authors modified HPV positivity cutoffs to improve the assay's specificity in the group of women living with HIV, because HPV prevalence and viral load are higher in these women than in the general population. The study showed that specific populations at risk might need adjusted cutoffs to find an optimal balance between sensitivity and specificity. We used a similar a posteriori cutoff optimization approach on self-samples before; however, in the current VALHUDES study, cutoff optimization was not necessary because the accuracy on self-samples versus clinician samples was similar.[12,14] Saidu et al[22] similarly evaluated Xpert assay on self-samples enrolling >1000 women from screening and colposcopy populations in South Africa, as recommended for diagnostic accuracy studies. Xpert was similarly sensitive on self-collected vaginal compared with clinician-taken cervical samples. This is in line with our findings, but lower specificity was reported by Saidu et al.[22] In a South African study, women collected self-samples using standard flock tip swab, which was placed in 4 mL of PreservCyt solution. In VALHUDES, two used vaginal devices (Evalyn and Qvintip) were resuspended in 20 mL of PreservCyt solution. Lower resuspension volume might have resulted in higher viral concentration and, therefore, lower specificity was reported by authors from South Africa.

PreservCyt and SurePath (Becton, Dickinson and Company, Franklin Lakes, NJ) media have been approved by the US Food and Drug Administration for cervical cancer screening based on cytology. PreservCyt and SurePath were designed for cell preservation, allowing cytologic interpretation, and contain methanol and ethanol, respectively, and therefore are relatively expensive to transport. In our VALHUDES data, hrHPV testing on vaginal samples using PreservCyt showed similar accuracy to hrHPV outcomes on clinician-collected cervical samples with the same medium. Because hrHPV tests are designed to detect viral DNA or RNA, alcohol-based solutions are not necessary for HPV DNA preservation. In addition, the high cost of these media would urge low-resource countries to obtain cheaper alternative solutions. Therefore, extended validation approaches are necessary to generate sufficient performance evidence of alternative transport media. Although the interest of screening stakeholders in the use of self-samples has increased, still more research is required to generate necessary knowledge on the influence of diverse pre-analytical and analytical parameters on the clinical accuracy.[11,23]

The Xpert HPV has been tested on seven dilution series (from one to seven simulated 10-fold dilutions) of artificially prepared human and viral DNA from HPV16, HPV18, and HPV31 cell lines stored in five different

transport media.[24] PreservCyt solution was compared with four non−alcohol-based solutions: phosphate-buffered saline (Thermo Fisher Scientific, Waltham, MA), Sigma Virocult (Medical Wire and Equipment, Corsham, UK), MSwab (Copan, Brescia, Italy), and Xpert Transport Media (Cepheid). Human DNA was detected in all media and all concentrations. MSwab solution was the only medium where HPV DNA was detected in the fifth 10-fold dilution in all three cell lines and, therefore, might be an alternative to PreservCyt.[24] Nevertheless, further research is required to test such media on real-life self-samples and clinician-collected samples. Combination of alternative transport media with the Xpert HPV might be a cheaper and effective approach for low-resource countries. HPV testing with the Xpert is performed using a single integrated cartridge, which contains reagents for DNA extraction and primers and probes for amplification and detection of HPV DNA.[21] Limited resources are necessary to perform the HPV testing both from laboratory and human capacity perspectives; therefore, Xpert HPV might be of particular interest in remote and low-resource countries given its applicability as a point-of-care test.

One of the VALHUDES study limitations is that women were recruited in colposcopy clinics, resulting in a high HPV positivity rate and a low absolute specificity.[12−15] These data are in line with other similar diagnostic accuracy studies performed in colposcopy settings.[5] However, it has been demonstrated that relative accuracy of HPV testing on self-samples compared with clinician-collected samples is comparable in follow-up and screening populations.[5] Thus, relative accuracy has to be considered as a robust parameter for such diagnostic accuracy evaluations. Strengths and limitations of VALHUDES were previously reported in detail.[12−15]

Conclusion

hrHPV testing with the Xpert HPV on self-collected vaginal samples was similarly accurate to detect precancer as on clinician-collected cervical samples. Accuracy can be influenced by the self-sampling device.

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Author Contributions

M.A. is the principal investigator and conceptualized the study; S.V.K., D.V.B., A.V., and M.A. developed protocol, conceptualized the study, developed methods, acquired funding, validated and curated the data, and obtained resources; A.L. and M.A. administered the project, performed formal analysis, and curated the data; A.L. wrote the manuscript; and all authors performed experiments and reviewed and edited the manuscript.

Supplemental Data

Supplemental material for this article can be found at *http://doi.org/10.1016/j.jmoldx.2023.06.004*.

References

1. Arbyn M, Ronco G, Anttila A, Meijer CJLM, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R, Peto J: Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine 2012, 30:F88−F99
2. Arbyn M, Gultekin M, Morice P, Nieminen P, Cruickshank M, Poortmans P, Kelly D, Poljak M, Bergeron C, Ritchie D, Schmidt D, Kyrgiou M, Van den Bruel A, Bruni L, Basu P, Bray F, Weiderpass E: The European response to the WHO call to eliminate cervical cancer as a public health problem. Int J Cancer 2021, 148:277−284
3. Bouvard V, Wentzensen N, Mackie A, Berkhof J, Brotherton J, Giorgi-Rossi P, Kupets R, Smith R, Arrossi S, Bendahhou K, Canfell K, Chirenje ZM, Chung MH, del Pino M, de Sanjosé S, Elfström M, Franco EL, Hamashima C, Hamers FF, Herrington CS, Murillo R, Sangrajrang S, Sankaranarayanan R, Saraiya M, Schiffman M, Zhao F, Arbyn M, Prendiville W, Indave Ruiz BI, Mosquera-Metcalfe I, Lauby-Secretan B: The IARC perspective on cervical cancer screening. N Engl J Med 2021, 385:1908−1918
4. Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, Minozzi S, Bellisario C, Banzi R, Zhao FH, Hillemanns P, Anttila A: Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol 2014, 15:172−183
5. Arbyn M, Smith SB, Temin S, Sultana F, Castle P: Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ 2018, 363:k4823
6. Serrano B, Ibáñez R, Robles C, Peremiquel-Trillas P, de Sanjosé S, Bruni L: Worldwide use of HPV self-sampling for cervical cancer screening. Prev Med 2022, 154:106900
7. Arbyn M, Peeters E, Benoy I, Vanden Broeck D, Bogers J, De Sutter P, Donders G, Tjalma W, Weyers S, Cuschieri K, Poljak M, Bonde J, Cocuzza C, Zhao FH, Van Keer S, Vorsters A: VALHUDES: a protocol for validation of human papillomavirus assays and collection devices for HPV testing on self-samples and urine samples. J Clin Virol 2018, 107:52−56
8. Meijer CJLM, Berkhof J, Castle PE, Hesselink AT, Franco EL, Ronco G, Arbyn M, Bosch FX, Cuzick J, Dillner J, Heideman DAM, Snijders PJF: Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int J Cancer 2009, 124:516−520
9. Arbyn M, Depuydt C, Benoy I, Bogers J, Cuschieri K, Schmitt M, Pawlita M, Geraets D, Heard I, Gheit T, Tommasino M, Poljak M, Bonde J, Quint W: VALGENT: a protocol for clinical validation of human papillomavirus assays. J Clin Virol 2016, 76:S14−S21
10. Arbyn M, Simon M, Peeters E, Xu L, Meijer C, Berkhof J, Cuschieri K, Bonde J, Ostrbenk Vanlencak A, Zhao FH, Rezhake R, Gultekin M, Dillner J, de Sanjosé S, Canfell K, Hillemanns P, Almonte M, Wentzensen N, Poljak M: 2020 List of human papillomavirus assays suitable for primary cervical cancer screening. Clin Microbiol Infect 2021, 27:1083−1095

11. Arbyn M, Latsuzbaia A, Castle PE, Sahasrabuddhe VV, Broeck DV: HPV testing of self-samples: influence of collection and sample handling procedures on clinical accuracy to detect cervical precancer. Lancet Reg Health Eur 2022, 14:100332
12. Van Keer S, Peeters E, Vanden Broeck D, De Sutter P, Donders G, Doyen J, Tjalma WAA, Weyers S, Vorsters A, Arbyn M: Clinical and analytical evaluation of the RealTime high risk HPV assay in Colli-Pee collected first-void urine using the VALHUDES protocol. Gynecol Oncol 2021, 162:575−583
13. Van Keer S, Latsuzbaia A, Vanden Broeck D, De Sutter P, Donders G, Doyen J, Tjalma WAA, Weyers S, Arbyn M, Vorsters A: Analytical and clinical performance of extended HPV genotyping with BD Onclarity HPV Assay in home-collected first-void urine: a diagnostic test accuracy study. J Clin Virol 2022, 155:105271
14. Latsuzbaia A, Vanden Broeck D, Van Keer S, Weyers S, Tjalma WAA, Doyen J, Donders G, De Sutter P, Vorsters A, Peeters E, Arbyn M: Clinical performance of the realtime high risk HPV assay on self-collected vaginal samples within the VALHUDES framework. Microbiol Spectr 2022, 10:e0163122
15. Latsuzbaia A, Vanden Broeck D, Van Keer S, Weyers S, Donders G, Doyen J, Tjalma W, De Sutter P, Peeters E, Vorsters A, Arbyn M: Validation of BD Onclarity HPV assay on vaginal self-samples versus cervical samples using the VALHUDES protocol. Cancer Epidemiol Biomarkers Prev 2022, 31:2177−2184
16. Cuschieri K, Geraets D, Cuzick J, Cadman L, Moore C, Vanden Broeck D, Padalko E, Quint W, Arbyn M: 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 2016, 54:2337−2342
17. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, Irwig L, Levine D, Reitsma JB, de Vet HC, Bossuyt PM: STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016, 6:e012799
18. Arbyn M, Herbert A, Schenck U, Nieminen P, Jordan J, McGoogan E, Patnick J, Bergeron C, Baldauf JJ, Klinkhamer P, Bulten J, Martin-Hirsch P: European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology. Cytopathology 2007, 18:133−139
19. Castle PE, Smith KM, Davis TE, Schmeler KM, Ferris DG, Savage AH, Gray JE, Stoler MH, Wright TC Jr, Ferenczy A, Einstein MH: Reliability of the Xpert HPV assay to detect high-risk human papillomavirus DNA in a colposcopy referral population. Am J Clin Pathol 2015, 143:126−133
20. Arbyn M, Castle PE, Schiffman M, Wentzensen N, Heckman-Stoddard B, Sahasrabuddhe VV: Meta-analysis of agreement/concordance statistics in studies comparing self- vs clinician-collected samples for HPV testing in cervical cancer screening. Int J Cancer 2022, 151:308−312
21. Kuhn L, Saidu R, Boa R, Tergas A, Moodley J, Persing D, Campbell S, Tsai W-Y, Wright TC, Denny L: Clinical evaluation of modifications to a human papillomavirus assay to optimise its utility for cervical cancer screening in low-resource settings: a diagnostic accuracy study. Lancet Glob Health 2020, 8:e296−e304
22. Saidu R, Kuhn L, Tergas A, Boa R, Moodley J, Svanholm-Barrie C, Persing D, Campbell S, Tsai WY, Wright TC, Denny L: Performance of Xpert HPV on self-collected vaginal samples for cervical cancer screening among women in South Africa. J Low Genit Tract Dis 2021, 25:15−21
23. Arbyn M, Costa S, Latsuzbaia A, Kellen E, Girogi Rossi P, Cocuzza CE, Basu P, Castle PE: HPV-based cervical cancer screening on self-samples in the Netherlands: challenges to reach women and test performance questions. Cancer Epidemiol Biomarkers Prev 2023, 32:159−163
24. Badman SG, Vallely AJ, Pardo C, Mhango LP, Cornall AM, Kaldor JK, Whiley D: A comparison of ThinPrep against four non-volatile transport media for HPV testing at or near the point of care. Pathology 2021, 53:264−266