# Journal Pre-proof


Analytical performance of HPV assays on vaginal self-collected vs practitioner-collected cervical samples: the SCoPE study

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PII: S1386-6532(20)30117-7

DOI: https://doi.org/10.1016/j.jcv.2020.104375

Reference: JCV 104375

To appear in: *Journal of Clinical Virology*

Received Date: 11 December 2019

Revised Date: 14 April 2020

Accepted Date: 15 April 2020

Please cite this article as: Saville M, Hawkes D, Keung M, Ip E, Silvers J, Sultana F, Malloy M, Velentzis L, Canfel l K, Wrede C, Brotherton J, Analytical performance of HPV assays on vaginal self-collected vs practitioner-collected cervical samples: the SCoPE study, *Journal of Clinical Virology* (2020), doi: https://doi.org/10.1016/j.jcv.2020.104375

# Analytical performance of HPV assays on vaginal self-collected vs practitioner-collected cervical samples: the SCoPE study

Running Title: Sensitivity of self-collection across six HPV assays

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**Highlights**

- Self-collection produces similar HPV results to practitioner-collected specimens
- A variety of clinically validated HPV assays are suitable for self-collection
- A dry flocked swab is a suitable device for self-collection for HPV screening

**Abstract**

**Background: In the last decade, human papillomavirus (HPV) testing has been evaluated extensively for cervical screening, with studies finding increased sensitivity compared to cytology. Another advantage of HPV based-screening is the ability to test vaginal samples that can be collected by women themselves. Self-collection has the potential to extend cervical screening coverage by increasing participation rates, particularly among women who are under-screened or have never screened. This could have a significant impact on cervical cancer prevention, as the majority of invasive cervical cancer cases occur among under-screened women. Both the Netherlands and Australia have transitioned their national programs from cytology to HPV as the primary screening test and both countries include a pathway for self-collection.**

**Objectives: We evaluated the relative sensitivity for HPV detection of self-collection compared with practitioner-collected cervical specimens in the context of the Australian National Cervical Screening Program (NCSP).**

**Study Design: 303 women aged ≥18 years attending a single tertiary referral centre took their own sample using a flocked-swab, and then had a practitioner-collected sample taken at colposcopy. All samples were tested at a single laboratory on the six PCR-based HPV assays which can be utilised in the NCSP; Roche cobas 4800 and cobas, Abbott RealTime, BD Onclarity, Cepheid Xpert, and Seegene Anyplex.**

**Results: HPV16/18 results had high observed agreement between self- and practitioner-collected samples on all assays (range: 0.94-0.99), with good agreement for non-HPV16/18 oncogenic HPV types (range: 0.64-0.73).**

**Conclusions: Self-collection for HPV-based cervical screening shows good concordance and relative sensitivity when compared to practitionercollected samples across assays in the NCSP.**

Keywords: human papillomavirus; cervical cancer; screening; self-collection; diagnostic testing

**Background**

In the last decade, human papillomavirus (HPV) nucleic acid testing has been evaluated extensively for cervical screening, with studies finding increased sensitivity compared to cytology for the detection of high grade cervical intraepithelial neoplasia (CIN), the obligate precursor lesion of cervical cancer and the target for identification and treatment by screening (1-6). A number of long-term studies have also shown a lower risk of subsequent CIN 3+ and invasive cervical cancer in women testing negative for oncogenic HPV, compared to women with a negative cytology test (6-10). The Netherlands and Australia have transitioned their national screening programs from cytology to HPV as the primary screening test and several other countries and regions, such as New Zealand, Ireland, Sweden, Portugal, Malaysia, Panama, and England are in the process of transitioning their programs to HPV testing.

An added advantage of HPV based screening, using assays calibrated to detect oncogenic HPV at levels associated with underlying, histologically confirmed CIN2+, is the ability to test vaginal samples collected by the women themselves. This is possible because HPV nucleic acids are shed from the infected cervical cells into the vagina. Self-sampling has the potential to extend cervical screening coverage by increasing participation rates of women who under-screen or never screen (11, 12). This could have a significant impact on cervical cancer prevention as the majority of invasive cervical cancer cases occur among women who have never been screened (13). Importantly, self-collected samples have been found to have comparable sensitivity and specificity to practitioner-collected samples for detecting CIN2 or worse when tested on clinically validated PCR-based assays (12, 14-17).

Under Australia's renewed National Cervical Screening Program (NCSP), women 30 years of age or older who have never participated in screening or who are overdue for cervical screening by over two years, and refuse a practitioner collected specimen (i.e. collected during a speculum examination), are eligible for HPV testing of self-collected samples under the supervision of a healthcare professional (18).

**Objectives**

The objective of this study is to determine if virological detection of HPV from self-collected samples is comparable to practitioner-collected samples when analysed on HPV assays eligible for use in the NCSP. These requirements mandate that HPV assays used on self-collected samples are PCR-based and contain an internal cellularity control to assess the quality of the sample collected (19). Samples for this study were tested with six HPV assays: cobas 4800 and cobas (Roche Diagnostics, Basel, Switzerland), BD Onclarity HPV assay (BD Diagnostics, Sparks, MD, USA), Xpert HPV test

(Cepheid, Inc., Sunnyvale, CA, USA), Anyplex II HPV HR Detection test (Seegene, Seoul, Korea) and Abbott Realtime HPV (Abbott Laboratories, Abbott Park, IL, USA). This study was conducted by VCS Pathology (VCS).

**Study Design**

**Study participants**

Women 18 years of age or older, attending the Dysplasia Clinic at the Royal Women's Hospital in Melbourne, and scheduled to undergo a colposcopic examination were invited to participate. Following written informed consent, participants were given written instructions (20) on how to obtain a self-collected vaginal specimen using a flocked-swab (FLOQSwab 552C, Copan, Brescia, Italy) in the clinic. After self-collection, participants returned the swab to the health practitioner. A cervical specimen was then collected by a practitioner using usual practice (Cervex-Brush, Rovers Medical Devices, Lekstraat, The Netherlands) and rinsed in 20ml of PreservCyt solution (Hologic, Marlborough, MA, USA) as per usual practice, as part of a scheduled, colposcopic examination. Each pair of self-collected and practitioner-collected samples were labelled with a unique identifier and sent to VCS for testing. The women's identifying information was not made available to the laboratory. The study was approved by the Royal Women's Hospital Research and Human Ethics Committee (reference number: 17/15).

**Laboratory processes and HPV assays**

Using a method adapted from other studies(21-23), self-collected flocked-swabs were stored at ambient room temperature for a week before placing into 5ml of PreservCyt solution (Hologic Marlborough, MA, USA), swirling for 20 seconds, before removing the swab. Practitioner-collected samples were also stored at ambient temperature for one week before testing. The week-long storage time was selected to replicate the maximum expected time between specimen collection and laboratory analysis during the screening program within Victoria. This storage time and conditions may not be appropriate in other testing environments.

All samples were tested on six, real-time PCR-based assays, according to each manufacturer's instructions for testing of practitioner-collected samples in PreservCyt (Thinprep) media. The cobas 4800 HPV test, and cobas HPV test (run on the cobas 6800 system), and the Abbott HPV test detect HPV 16 and 18 individually and a pool of 12 other oncogenic HPV types (31/33/35/39/45/51/52/56/58/59/66/68). The BD Onclarity HPV assay detects 6 HPV types individually (16,

18, 31, 45, 51, and 52) and 8 types in groups (HPV 33/58, HPV 56/59/66, and HPV 35/39/68). The Xpert HPV test detects HPV16 individually and the remaining 13 HPV types in four groups (HPV18/45; HPV31/33/35/52/58; HPV51/59; and HPV39/56/66/68). Anyplex II HPV HR Detection can individually distinguish between each of the 14 oncogenic HPV types.

**Statistical analysis**

A sample size of 303 was estimated based on the HPV positivity rate in a previous study (23) in the same clinic of 40%, and an expected kappa value between the self-collected and practitioner collected samples of 0.90 with a precision of 0.05. We determined HPV positivity rates for HPV16, HPV18 (HPV18 refers to HPV18/45 for the Xpert test), other oncogenic HPV (non-HPV 16/18) or any oncogenic HPV type in the self-collected and practitioner-collected samples for each HPV assay. The difference in HPV positivity rates for each of the HPV categories, between self-collected and practitioner-collected samples, was calculated using the difference between proportions test assuming unpaired data (Table 1, Table 2) . We determined the proportion with any invalid result in self- and practitioner-collected samples for each HPV assay and any difference in the proportion of invalids using the same method, on the assumption that a sample was considered invalid when any HPV result channel was invalid. We also measured the observed agreement (the proportion of all tests in which self- and practitioner-collected samples agreed) between self- and practitioner-collected samples for all HPV categories. Gwet's $AC_1$ coefficient for inter-rater agreement was calculated to determine the percent agreement beyond that expected by chance, designated in the following way: $AC_1 \leq 0.20$ as poor, $0.21 \leq AC_1 \leq 0.40$ as fair, $0.41 \leq AC_1 \leq 0.60$ as moderate, $0.61 \leq AC_1 \leq 0.80$ as good, and $AC_1 \geq 0.81$ as very good agreement (24).

We chose Gwet's AC1 as it's been shown to be a more stable inter-rater agreement statistic than Cohen's kappa (25, 26). The sensitivity and specificity of self-collected samples for detecting HPV16, HPV18, other oncogenic HPV (non-HPV 16/18) and any oncogenic HPV were calculated using the practitioner-collected samples as the reference standard for each individual HPV assay. We also estimated the sensitivity of self- and practitioner-collected samples using an alternative reference standard where any positive result from either sampling method is indicative of infection. The binomial exact method was used to calculate 95% confidence intervals for proportions. All statistical analyses were conducted using Stata/SE version 12.1 (Stata Corp, College Station, TX, USA).

**Results**

303 participants were recruited between June 2017 and December 2017. Detection of oncogenic HPV types in the 303 samples collected, excluding any invalid results, by each sampling method is presented in Table 1. Four samples returned no result by Abbott, while Xpert and Anyplex each had one sample return no result; these were due to a lack of sample volume. A higher HPV prevalence was observed for every assay from self-collected compared with practitioner-collected samples; this difference, however, was not significant for Onclarity, Anyplex, or Abbott. There were significant differences between sample types for other oncogenic HPV types (non HPV16/18) for cobas 4800 (self 61.0% versus practitioner 49.5%; p=0.005), cobas (self 59.2% versus practitioner 50.0%; p=0.024), and Xpert (self 50.9% versus practitioner 41.4%; p=0.021).

Invalid results for each of the assays tested are presented in Table 2. Five practitioner-collected samples were returned as invalid: one on cobas, which tested negative on the other HPV assays, and 4 samples on Onclarity, of which 3 were positive on the other HPV assays. In parallel, a total of 29 self-collected samples had at least one invalid result. The highest proportion of self-collected samples with invalid results were obtained for cobas (7.6%). There was a significant difference in the proportion of invalids between self- and practitioner-collected samples on all assays except Onclarity (p=1.000). In addition to invalid results, there were samples that did not produce a result due to technical issues: 4 self-collected and 4 practitioner-collected samples on the cobas 4800, and 2 self-collected on the Xpert. None of these samples were retested due to the limited sample volumes available.

The agreement in paired samples between positive and negative results for both sample types and all HPV categories is shown in Table 3. For HPV16 and 18, the observed agreement between self- and practitioner-collected samples was high on all assays (>80%), with Gwet's $AC_1$ coefficient showing very good agreement (range: 0.94 to 0.99). Good agreement was also found between paired samples for other oncogenic HPV types (non-HPV 16/18) and any oncogenic HPV type (Gwet's $AC_1$ 0.62-0.75) across HPV assays.

The sensitivity and specificity of self-collected samples relative to practitioner-collected samples are presented in Table 4. The sensitivity of self-collected samples for detection of HPV16, HPV18, other oncogenic HPV (non-HPV16/18) and any oncogenic HPV types was high for all HPV assays (range: 80% to 100%). The specificity was also high (>95%) for

HPV16 and HPV18 (or HPV 18/45 for Xpert) but this was not maintained for the other HPV categories. The specificity of self-collected samples for other oncogenic HPV types (non-HPV 16/18) ranged from 73.1% to 82.5% and for any oncogenic HPV type across the different assays ranged between 68.7% and 80.1%. When assuming any positive result from either self-collected or practitioner-collected samples is indicative of infection, the sensitivity of the self-collected samples was higher than that of practitioner-collected samples across all platforms (Table 5) except for HPV 16 using Anyplex.

**Discussion**

The aim of this study was to examine whether a cheap, common, and multipurpose device could be used for self-collection for HPV testing. Most other HPV self-collection devices are purpose specific (e.g. Evalyn Brush or Qvintip), and are more expensive. Self-collection is generally targeted to those who are not screened, either due to a lack of an organized and accessible screening program (e.g. LMICs), or due to other reasons surrounding the specula-assisted collection procedure.

In this study, across all assays tested, self-collected samples were found to have good agreement with practitioner-collected samples in the detection of oncogenic HPV types. It is important to note that this study was not designed to assess inter assay performance but to compare HPV detection between clinician and self-samples on HPV tests already validated for use in cervical screening.

This is because variation in clinical validation requires assessment of performance using clinical outcomes of histologically confirmed disease (e.g. CIN2+), with several studies showing that whilst an assay can be both sensitive and specific for disease, it may have a relative low agreement for non-disease related infections compared with other clinically validated assays (27, 28). Recently a protocol was published (29) which seeks to examine both the analytical and clinical sensitivity of self-collected specimens against both a practitioner-collected specimens tested for HPV (across the six assays used in the current study), and histological assessment of biopsies. This methodology may become the template for a self-collection clinical validation in the same way as the Meijer Criteria.

The number of invalid results returned from HPV testing were significantly higher in self-collected samples than practitioner-collected samples for all assays except Onclarity. The proportion of invalid results returned by cobas for self-collected samples was higher than what is generally seen in population screening or cytology testing (expected

invalids with self-collected samples and cytology of approx. 3%, unpublished data, VCS Pathology). Interestingly this did not have an effect on number of positive results for in the HPV16, HPV18, Other HPV, and Any HPV groupings. The cobas assay appears to require a higher number of cells in order to return a valid result, but due to the assay design adequate cellularity is not required for a positive HPV results to be reported.

Studies using different collection devices and conducted in different settings (routine cervical screening vs referral clinic; home versus clinic setting) are not directly comparable. However, the overall good agreement obtained between sample types (self- and practitioner-collected) is in line with findings from previous studies (30, 31) that have tested samples on the cobas 4800. In a recent study (30), high level of agreement (>88.7%) was found between self-collected and general practitioner-collected samples from women with an ASC-US cytology, for the detection of oncogenic HPV types, with good concordance for the detection of HPV16/18 (0.73, 95% CI: 0.57–0.90) and other oncogenic HPV types (0.64, 95% CI: 0.51–0.78). Similar findings have also been reported by other studies using HPV detection assays other than those tested in our study (32-35).

We also found high levels of sensitivity and specificity in self-collected samples relative to practitioner-collected samples for the detection of HPV 16/18 by all assays. A previous study reported similar test accuracy for HPV 16/18 by cobas 4800 [sensitivity 82.4% (95% CI: 56.7-96.2); specificity 96.9 (95% 93.5-98.8)] (30). However, for the detection of other oncogenic HPV types (non-HPV16/18), the authors (30) reported lower sensitivity [76.9% (95% CI: 60.7–88.9%)] and higher specificity [91.4% (95% CI: 86.2–95.1%)] for self-collected samples in contrast with our findings. These results are consistent with the hypothesis, based on previous studies (36), that the first collected sample is more sensitive. In order to accommodate this possibility, we ran a secondary analysis considering positivity of either swab alone as the reference standard (Table 5).

Invalid results were higher in self-collected samples, compared to practitioner-collected samples for all assays except Onclarity (1.3% for both sample types).

A limitation of our study is that we did not collect any information from participants in terms of their age, recent cytology (and therefore reason for attending the referral clinic), nor any follow-up outcomes so as to relate their diagnosis to the detection of HPV in their samples. However, this is not a clinical validation study but a within-assay comparison of the detection of oncogenic HPV types between practitioner and self-collected samples – a virologic

performance assessment. We also did not randomise the order of collection of the specimens, with all self-collected specimens collected first, due to the reasonable likelihood of women in the clinic having a procedure at colposcopy, which would preclude collection of the self-sample after the practitioner collected one. It is probable, based on previous studies (36), that the order of specimen collection impacts upon the likelihood of HPV detection. Strengths of this study include the use of six PCR-based HPV assays, testing laboratory conditions that simulated real-life testing of clinical samples for cervical screening, and the use of paired samples from the same participant. We also used the FLOQSwab, which has previously been shown to have good observed agreement for HPV detection, and similar sensitivity for CIN3+ detection, when compared with other self-collection devices using either the cobas 4800, Xpert or Anyplex assays (37).

To the best of our knowledge, this is the first study to compare HPV detection between self-collected and practitioner-collected samples across such a large range of automated, PCR-based, clinically validated (38-43) HPV assays. Results from this study indicate that these six HPV assays can be used for cervical screening on self-collected samples.

If global elimination of cervical cancer is to be achieved, then very aggressive targets for screening participation will need to be met (44). Self-collection of a vaginal sample has been shown to be highly acceptable to women in a variety of cultural settings (12) and is much more scalable than any method of screening that requires a healthcare worker to conduct a pelvic examination involving insertion of a speculum. It is therefore very encouraging that a sample collected by a woman herself, using a low cost and widely available device, performs as well as a sample collected from the cervix by a health care worker.

**Conflict of Interest Statement**

The test kits for this study were supplied free of charge from Abbott, BD, Roche, Seegene and Cepheid. None of the manufacturers had any influence on the study design, analysis or production of this manuscript. KC is a co-PI of an investigator-initiated trial of cervical cytology and primary HPV screening in Australia (`Compass'), which is conducted and funded by the VCS foundation, a government-funded health promotion charity. DH, MS, JMLB, ELOI, MHTK, MM, FS were employed by VCS Foundation. The VCS foundation have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However neither I nor my institution on my behalf (Cancer Council NSW) receives direct funding from industry for this trial or any other project. DH has received

travel funding to attend conferences and meetings from Roche, Abbott and Seegene but has had no personal gain from any diagnostics manufacturer.

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**CRediT author Statement**

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**Acknowledgements**

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**Table 1: HPV detection in self- and practitioner-collected samples using different HPV assays.**

| HPV assay type | Oncogenic HPV type | Self-collected | | | Practitioner-collected | | | P-value |
|---|---|---|---|---|---|---|---|---|
| | | n/N | % | (95% CI) | n/N | % | (95% CI) | |
| **cobas 4800** | HPV 16 | 40/293 | 13.7 | (9.9-18.1) | 33/299 | 11.0 | (7.7-15.1) | 0.333 |
| | HPV 18 | 9/293 | 3.1 | (1.4-5.8) | 5/299 | 1.7 | (0.5-3.9) | 0.263 |
| | Other HPV (non-16/18) | 180/295 | 61.0 | (55.2-66.6) | 148/299 | 49.5 | (43.7-55.3) | 0.005 |
| | Any HPV¥ | 195/295 | 66.1 | (60.4-71.5) | 162/299 | 54.2 | (48.3-59.9) | 0.003 |
| **cobas** | HPV 16 | 41/285 | 14.4 | (10.5-19.0) | 41/302 | 13.6 | (9.9-18.0) | 0.777 |
| | HPV 18 | 15/280 | 5.4 | (3.0-8.7) | 10/302 | 3.3 | (1.6-6.0) | 0.224 |
| | Other HPV (non-16/18) | 173/292 | 59.2 | (53.4-64.9) | 151/302 | 50.0 | (44.2-55.8) | 0.024 |
| | Any HPV¥ | 194/293 | 66.2 | (60.5-71.6) | 170/302 | 56.3 | (50.5-62.0) | 0.013 |
| **Onclarity** | HPV 16 | 26/299 | 8.7 | (5.8-12.5) | 24/299 | 8.0 | (5.2-11.7) | 0.768 |
| | HPV 18 | 6/299 | 2.0 | (0.7-4.3) | 4/299 | 1.3 | (0.4-3.4) | 0.524 |
| | Other HPV (non-16/18) | 149/300 | 49.7 | (43.9-55.5) | 129/299 | 43.1 | (37.5-49.0) | 0.110 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Any HPV¥ | 162/300 | 54.0 | (48.2-59.7) | 141/299 | 47.2 | (41.4-53.0) | 0.094 |
| **Xpert$^{\beta\Phi}$** | HPV 16 | 29/291 | 10.0 | (6.8-14.0) | 30/302 | 9.9 | (6.8-13.9) | 0.990 |
| | HPV 18 | 21/291 | 7.2 | (4.5-10.8) | 18/302 | 6.0 | (3.6-9.3) | 0.537 |
| | Other HPV (non-16/18) | 148/291 | 50.9 | (45.0-56.7) | 125/302 | 41.4 | (35.8-47.2) | 0.021 |
| | Any HPV¥ | 172/291 | 59.1 | (53.2-64.8) | 149/302 | 49.3 | (43.6-55.1) | 0.017 |
| **Anyplex II$^{\beta}$** | HPV 16 | 32/292 | 11.0 | (7.6-15.1) | 33/302 | 10.9 | (7.6-15.0) | 0.990 |
| | HPV 18 | 9/292 | 3.1 | (1.4-5.8) | 7/302 | 2.3 | (0.9-4.7) | 0.565 |
| | Other HPV (non-16/18) | 171/296 | 57.8 | (51.9-63.5) | 163/302 | 54.0 | (48.2-59.7) | 0.350 |
| | Any HPV¥ | 186/296 | 62.8 | (57.1-68.4) | 177/302 | 58.6 | (52.8-64.2) | 0.290 |
| **Abbott$^{\mu}$** | HPV 16 | 26/295 | 8.8 | (5.8-12.6) | 26/299 | 8.7 | (5.8-12.5) | 0.960 |
| | HPV 18 | 6/295 | 2.0 | (0.7-4.4) | 5/299 | 1.7 | (0.5-3.9) | 0.744 |
| | Other HPV (non-16/18) | 145/296 | 49.0 | (43.2-54.8) | 137/299 | 45.8 | (40.1-51.7) | 0.439 |
| | Any HPV¥ | 162/296 | 54.7 | (48.9-60.5) | 151/299 | 50.5 | (44.7-56.3) | 0.302 |

¥ Any HPV includes samples positive for any HPV type i.e. HPV 16, HPV 18 or other HPV (co-infections counted once).
β No result was returned for one sample in Xpert and Seegene.
μ Four samples assessed using Abbott returned no result due to low volume for one of the collection methods (2 PC & 2 SC). These samples were excluded.
Φ Xpert detects HPV18/45
**NOTE: All invalid, failed and error samples are excluded from Table 1**

**Table 2: Proportion of invalid* results in self- and practitioner-collected samples using different HPV assays.**

| HPV assay type | Self-collected | | | Practitioner-collected | | | P-value** |
|---|---|---|---|---|---|---|---|
| | n/N | % | (95% CI) | n/N | % | (95% CI) | |
| cobas 4800 | 6/303 | 2.0 | (0.7-4.3) | 0/303 | 0 | (0-1.2) | 0.014 |
| cobas | 23/303 | 7.6 | (4.9-11.2) | 1/303 | 0.3 | (0.01-1.8) | <0.001 |
| Onclarity | 4/303 | 1.3 | (0.4-3.3) | 4/303 | 1.3 | (0.4-3.3) | 1.000 |
| Xpert | 9/302 | 3.0 | (1.4-5.6) | 0/302 | 0 | (0-1.2) | 0.003 |
| Anyplex II | 10/302 | 3.3 | (1.6-6.0) | 0/302 | 0 | (0-1.2) | 0.001 |
| Abbott | 4/299 | 1.3 | (0.4-3.4) | 0/299 | 0 | (0-1.2) | 0.045 |

* A sample is considered invalid when any HPV result channel is invalid.
** Comparing self-collected versus practitioner collected
**NOTE: All invalid, failed and error samples are included in Table 2**

**Table 3: Agreement in HPV DNA detection between self- and practitioner-collected samples using different HPV assays.**

| HPV assay type | Oncogenic HPV type | Paired sample | | | | Observed agreement | | | Gwet's $AC_1$ coefficient | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | SC+ & PC+ | SC+ & PC- | SC- & PC+ | SC- & PC- | n/N | % | (95% CI) | $AC_1$ | (95% CI) |
| cobas 4800 | HPV16 | 30 | 9 | 2 | 249 | 279/290 | 96.2 | (93.3-98.1) | 0.95 | (0.92-0.98) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HPV18 | 5 | 3 | 0 | 282 | 287/290 | 99.0 | (97.0-99.8) | 0.99 | (0.98-1.00) |
| | Other HPV | 139 | 39 | 8 | 106 | 245/292 | 83.9 | (79.2-87.9) | 0.68 | (0.60-0.77) |
| | Any HPV | 152 | 41 | 9 | 90 | 242/292 | 82.9 | (78.1-87.0) | 0.67 | (0.59-0.76) |
| cobas | HPV16 | 34 | 7 | 5 | 238 | 272/284 | 95.8 | (92.7-97.8) | 0.94 | (0.91-0.98) |
| | HPV18 | 9 | 6 | 0 | 264 | 273/279 | 97.8 | (95.4-99.2) | 0.98 | (0.96-1.00) |
| | Other HPV | 140 | 33 | 8 | 110 | 250/291 | 85.9 | (81.4-89.7) | 0.72 | (0.64-0.80) |
| | Any HPV | 158 | 36 | 8 | 90 | 248/292 | 84.9 | (80.3-88.8) | 0.71 | (0.63-0.79) |
| Onclarity | HPV16 | 20 | 6 | 4 | 265 | 285/295 | 96.6 | (93.9-98.4) | 0.96 | (0.93-0.99) |
| | HPV18 | 4 | 2 | 0 | 289 | 293/295 | 99.3 | (97.6-99.9) | 0.99 | (0.98-1.00) |
| | Other HPV | 111 | 35 | 18 | 132 | 243/296 | 82.1 | (77.2-86.3) | 0.64 | (0.56-0.73) |
| | Any HPV | 122 | 37 | 19 | 118 | 240/296 | 81.1 | (76.1-85.4) | 0.62 | (0.53-0.71) |
| GeneXpert | HPV16 | 23 | 6 | 5 | 257 | 280/291 | 96.2 | (93.3-98.1) | 0.95 | (0.93-0.98) |
| | HPV18/45 | 14 | 7 | 3 | 267 | 281/291 | 96.6 | (93.8-98.3) | 0.96 | (0.94-0.99) |
| | Other HPV | 112 | 36 | 8 | 135 | 247/291 | 84.9 | (80.2-88.8) | 0.70 | (0.62-0.78) |
| | Any HPV | 133 | 39 | 10 | 109 | 242/291 | 83.2 | (78.4-87.3) | 0.67 | (0.58-0.75) |
| Anyplex II | HPV16 | 28 | 4 | 5 | 255 | 283/292 | 96.9 | (94.2-98.6) | 0.96 | (0.94-0.99) |
| | HPV18 | 7 | 2 | 0 | 283 | 290/292 | 99.3 | (97.5-99.9) | 0.99 | (0.98-1.00) |
| | Other HPV | 145 | 26 | 14 | 111 | 256/296 | 86.5 | (82.1-90.2) | 0.73 | (0.66-0.81) |
| | Any HPV | 160 | 26 | 13 | 97 | 257/296 | 86.8 | (82.4-90.5) | 0.75 | (0.67-0.82) |
| Abbott | HPV16 | 23 | 3 | 3 | 266 | 289/295 | 98.0 | (95.6-99.3) | 0.98 | (0.96-1.00) |
| | HPV18 | 4 | 2 | 1 | 288 | 292/295 | 98.9 | (97.1-99.8) | 0.99 | (0.98-1.00) |
| | Other HPV | 117 | 28 | 19 | 132 | 249/296 | 84.1 | (79.5-88.1) | 0.68 | (0.60-0.77) |
| | Any HPV | 133 | 29 | 17 | 117 | 250/296 | 84.5 | (79.8-88.4) | 0.69 | (0.61-0.77) |

PC+ = Practitioner-collected sample - Positive result; PC- = Practitioner-collected sample - Negative result;
SC+ = Self-collected sample - Positive result; SC- = Self-collected sample - Negative result

**NOTE: All invalid, failed and error samples are excluded from Table 3**

**Table 4: Sensitivity and specificity (including 95% CI) for the detection of HPV for self-collected samples compared with practitioner-collected samples as the reference standard.**

| HPV assay type | Oncogenic HPV type | Sensitivity | | Specificity | |
|---|---|---|---|---|---|
| | | % | (95% CI) | % | (95% CI) |
| cobas 4800 | HPV 16 | 93.8 | (79.2-99.2) | 96.5 | (93.5-98.4) |
| | HPV 18 | 100 | (47.8-100) | 99.0 | (97.0-99.8) |
| | Other | 94.6 | (89.6-97.6) | 73.1 | (65.1-80.1) |
| | Any HPV | 94.4 | (89.7-97.4) | 68.7 | (60.0-76.5) |
| cobas | HPV 16 | 87.2 | (72.6-95.7) | 97.1 | (94.2-98.8) |
| | HPV 18 | 100 | (66.4-100) | 97.8 | (95.2-99.2) |
| | Other | 94.6 | (89.6-97.6) | 76.9 | (69.2-83.6) |
| | Any HPV | 95.2 | (90.7-97.9) | 71.4 | (62.7-79.1) |
| Onclarity | HPV 16 | 83.3 | (62.6-95.3) | 97.8 | (95.2-99.2) |
| | HPV 18 | 100 | (39.8-100) | 99.3 | (97.5-99.9) |
| | Other | 86.1 | (78.9-91.5) | 79.0 | (72.1-85.0) |
| | Any HPV | 86.5 | (79.8-91.7) | 76.1 | (68.6-82.6) |
| GeneXpert | HPV 16 | 82.1 | (63.1-93.9) | 97.7 | (95.1-99.2) |
| | HPV 18/45 | 82.4 | (56.6-96.2) | 97.5 | (94.8-99.0) |
| | Other | 93.3 | (87.3-97.1) | 79.0 | (72.1-84.8) |
| | Any HPV | 93.0 | (87.5-96.6) | 73.6 | (65.8-80.5) |
| Anyplex II | HPV 16 | 84.9 | (68.1-94.9) | 98.5 | (96.1-99.6) |
| | HPV 18 | 100 | (59.0-100) | 99.3 | (97.5-99.9) |
| | Other | 91.2 | (85.7-95.1) | 81.0 | (73.4-87.2) |
| | Any HPV | 92.5 | (87.5-95.9) | 78.9 | (70.6-85.7) |
| Abbott | HPV 16 | 88.5 | (69.9-97.6) | 98.9 | (96.8-99.8) |
| | HPV 18 | 80.0 | (28.4-99.5) | 99.3 | (97.5-99.9) |
| | Other | 86.0 | (79.1-91.4) | 82.5 | (75.7-88.1) |
| | Any HPV | 88.7 | (82.5-93.3) | 80.1 | (72.7-86.3) |

**NOTE: All invalid, failed and error samples are excluded from Table 4**

**Table 5: Sensitivity (including 95% CI) for the detection of HPV of self-collected and practitioner-collected samples using the reference standard where any positive result from either sampling method is considered indicative of infection.**

| HPV assay type | Oncogenic HPV type | Sensitivity | | | | | |
|---|---|---|---|---|---|---|---|
| | | Self-collected | | | Practitioner-collected | | |
| | | n/N | % | (95% CI) | n/N | % | (95% CI) |
| cobas 4800 | HPV 16 | 39/41 | 95.1 | (83.5-99.4) | 32/41 | 78.1 | (62.4-89.4) |
| | HPV 18 | 8/8 | 100 | (63.1-100) | 5/8 | 62.5 | (24.5-91.5) |
| | Other | 178/186 | 95.7 | (91.7-98.1) | 147/186 | 79.0 | (72.5-84.6) |
| | Any HPV | 193/202 | 95.5 | (91.7-97.9) | 161/202 | 79.7 | (73.5-85.0) |
| cobas | HPV 16 | 41/46 | 89.1 | (76.4-96.4) | 39/46 | 84.8 | (71.1-93.7) |
| | HPV 18 | 15/15 | 100 | (78.2-100) | 9/15 | 60.0 | (32.3-83.7) |
| | Other | 173/181 | 95.6 | (91.5-98.1) | 148/181 | 81.8 | (75.4-87.1) |
| | Any HPV | 194/202 | 96.0 | (92.4-98.3) | 166/202 | 82.2 | (76.2-87.2) |
| Onclarity | HPV 16 | 26/30 | 86.7 | (69.3-96.2) | 24/30 | 80.0 | (61.4-92.3) |
| | HPV 18 | 6/6 | 100 | (54.1-100) | 4/6 | 66.7 | (22.3-95.7) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Other | 146/164 | 89.0 | (83.2-93.4) | 129/164 | 78.7 | (71.6-84.7) |
| | Any HPV | 159/178 | 89.3 | (83.8-93.5) | 141/178 | 79.2 | (72.5-84.9) |
| GeneXpert | HPV 16 | 29/34 | 85.3 | (68.9-95.1) | 28/34 | 82.4 | (65.5-93.2) |
| | HPV 18/45 | 21/24 | 87.5 | (67.6-97.3) | 17/24 | 70.8 | (48.9-87.4) |
| | Other | 148/156 | 94.9 | (90.2-97.8) | 120/156 | 76.9 | (69.5-83.3) |
| | Any HPV | 172/182 | 94.5 | (90.1-97.3) | 143/182 | 78.6 | (71.9-84.3) |
| Anyplex II | HPV 16 | 32/37 | 86.5 | (71.2-95.5) | 33/37 | 89.2 | (74.6-97.0) |
| | HPV 18 | 9/9 | 100 | (66.4-100) | 7/9 | 77.8 | (40.0-97.2) |
| | Other | 171/185 | 92.4 | (87.6-95.8) | 159/185 | 86.0 | (80.1-90.6) |
| | Any HPV | 186/199 | 93.5 | (89.1-96.5) | 173/199 | 86.9 | (81.4-91.3) |
| Abbott | HPV 16 | 26/29 | 89.7 | (72.7-97.8) | 26/29 | 89.7 | (72.7-97.8) |
| | HPV 18 | 6/7 | 85.7 | (42.1-99.6) | 5/7 | 71.4 | (29.0-96.3) |
| | Other | 145/164 | 88.4 | (82.5-92.9) | 136/164 | 82.9 | (76.3-88.4) |
| | Any HPV | 162/179 | 90.5 | (85.2-94.4) | 150/179 | 83.8 | (77.6-88.9) |

**NOTE: All invalid, failed and error samples are excluded from Table 5**