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RESEARCH ARTICLE

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The Sansure® Human Papillomavirus DNA Diagnostic Kit offers excellent reproducibility performance for the detection of high-risk HPV

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Abstract

Cervical cancer screening is a cornerstone of cervical cancer elimination. Detection of high-risk human papillomavirus (hrHPV) is recommended as the first step in screening provided that the assay used has been adequately validated. The Sansure® Human Papillomavirus DNA Diagnostic Kit is a new assay designed to detect HPV16, HPV18 and 13 other HPV in aggregate. The study aimed to evaluate the intra- and interlaboratory reproducibility of the assay according to international guidelines. Five hundred and fifty cervical residual cell samples from women attending cervical cancer screening were selected from the biobank of the HPV National Reference Centre in Belgium and used in this study. After DNA extraction, HPV was tested using the Sansure® Human Papillomavirus DNA Diagnostic Kit. The lower 95% confidence limit around the general reproducibility of this assay should be greater than or equal to 87%, with $\kappa \geq 0.50$. Five hundred and thirty-three samples had valid results. The Sansure® Human Papillomavirus DNA Diagnostic Kit demonstrated an excellent intra-laboratory reproducibility of 93.8% (95% confidence interval [CI]: 91.4–95.7, $\kappa = 0.85$). The interlaboratory reproducibility was 93.4 (95% CI: 91.0–95.4, $\kappa = 0.84$). Intra and interlaboratory reproducibility were also excellent at the genotype level. Excluding HPV53 single infection samples from the analyses also resulted in excellent agreement. These data show that the Sansure® Human Papillomavirus DNA Diagnostic Kit is highly reproducible.

KEYWORDS

cervical cancer, HPV testing, reproducibility, Sansure, screening, validation

1 | INTRODUCTION

Cancer of the cervix represents a major issue worldwide with more than 600 000 new cases and >300 000 deaths estimated in 2020 with most of them occurring in low and middle-income countries.[1–3] Persistent infection with a high-risk human papillomavirus (hrHPV) has been recognized as the causal factor for cervical cancer.[4] Among 400 types identified, 12 HPV (HPV16/18/31/33/35/39/45/51/52/56/58/59) are recognized as carcinogenic, one (HPV68) is probably carcinogenic and 12 others (HPV26/30/34/53/66/67/69/70/73/82/85/

97) are possibly carcinogenic.[5,6] Effective primary (HPV vaccination) and secondary (screening) prevention strategies have been developed and implemented in many countries to fight against cervical cancer.[7] Full implementation of these prevention strategies, using the most effective tools, is central to the World Health Organization initiative to accelerate cervical cancer elimination.[8]

Cervical cancer screening, initially based on cytological examination of cervical smears, has recently been switched to hrHPV testing due to its superiority, particularly in terms of performance for detecting high-grade cervical lesions or cancer.[9,10] To identify those suitable for cervical cancer screening from the hundreds of HPV tests available worldwide,[11] international guidelines and frameworks have been established to validate HPV tests.[12] These guidelines are based on a comparative assessment of clinical accuracy against comparator tests (Hybrid Capture 2 [Qiagen] or GP5 +/6 + PCR). The benchmarks for non-inferior sensitivity and specificity of a new index versus a comparator test are fixed at 0.90 and 0.98, respectively. This means that the left bound of the 90% confidence interval bound around the relative sensitivity and specificity should not be lower than this benchmark. Evaluations should include at least 60 smears from women with high-grade cervical neoplasia or worse (CIN2+) and at least 800 smears without CIN2+. Finally, the validation requires intra- and interlaboratory reproducibility testing of at least 500 smears, one-third of which being positive for an hrHPV.[12] A list of validated tests that meet these international performance criteria and are suitable for cervical cancer screening is periodically up-dated.[13,14]

The Sansure® Human Papillomavirus DNA Diagnostic Kit (PCR-Fluorescence Probing) (Sansure Biotech Inc.) is a new test dedicated to cervical cancer screening. This is a real-time PCR-based assay dedicated to the detection of HPV16 and HPV18 separately and 13 other HPV in aggregate. The aim of this reproducibility study is to assess one of the three parameters required to validate HPV assays suitable for primary cervical cancer screening.

2 | METHODS

2.1 | Sansure® Human Papillomavirus DNA Diagnostic Kit (Sansure® HPV Kit)

The Sansure® HPV Kit (Sansure Biotech Inc.) is a single tube multiplex real-time PCR that detects the viral HPV DNA with an uracil-*N*-glycosylase (UNG) enzyme + dUTP contamination-proof system. Twelve carcinogenic hrHPV types (HPV16/18/31/33/35/39/45/51/52/56/58/59) plus the probably carcinogenic type HPV68 and the possibly carcinogenic types HPV53 and HPV66 are identified in 3 fluorescent channels (Cyanine5 [Cy5] for HPV16, Carboxyfluorescein [FAM] for HPV18 and carboxy-X-rhodamine [ROX] for the other 13 HPV in aggregate). In addition, a region of the β-globin gene is amplified which is used as an endogenous control with a fluorescence detected in a 4th channel (Hexachlorofluorescein, HEX). Ct (Crossing threshold) for positivity is ≤40.5 for beta-globin, HPV16, HPV18, and the other 13 HPV in aggregate.

2.2 | Study panel

Five hundred and fifty cervical cell specimens were randomly selected from the cervical cytology biobank of the Algemeen Medisch Laboratorium (AML), which is part of the Belgian reference laboratory for HPV. The specimens, collected in PreservCyt (Hologic), were taken from women who participated in cervical cancer (CC) screening during the fourth quarter of 2022 and were identified with an administrative code for primary CC screening. Sample quality was thoroughly assessed. Only specimens with a sufficient number of cells and an adequate human beta-globin result were included in the study. As recommended by international guidelines, this panel presented approximately one-third of hrHPV positivity with the RIATOL qPCR, an external hrHPV DNA assay.[12,15–18] Seven samples had insufficient volume for analyses and were excluded from the study. Finally, 176 RIATOL qPCR positive cases and 367 RIATOL qPCR negative cases (hrHPV positivity rate of 32.4%) were selected. All samples were confirmed with the Abbott M2000 hr-HPV assay before final inclusion in the study.

2.3 | Study design

After homogenization, three 1 mL aliquots of each cervical sample stored in PreservCyt/ThinPrep (Hologic) were prepared and kept at room temperature until processing. The first two aliquots were processed at center 1 (AML), between January 12 and February 19 2024, for intralaboratory reproducibility and the third aliquot was sent to center 2 (French HPV National Reference Laboratory) for interlaboratory reproducibility which was processed between March 3-11 2024. The results obtained from the first (testing 1) and the second (testing 2) aliquots at center 1 were used to assess the intralaboratory reproducibility. The results obtained from the first aliquot (testing 1) at center 1 and from the third aliquot (testing 3) at center 2 were used to assess interlaboratory reproducibility.

2.4 | DNA extraction

After homogenization, 300 µL of each aliquot was transferred to the sample plate of a Nucleic Acid Extraction-Purification Kit (Sansure Biotech Inc.) containing the lysis buffer. A volume of 20 µL Proteinase K was added to each well and the 48-well plate was transferred to the Natch 48 Nucleic Acid Extraction System (Sansure Biotech Inc.) for DNA extraction using magnetic beads. After washing, the DNA was eluted in 80 µL elution buffer.

2.5 | HPV DNA detection

Detection of HPV DNA was performed using the Sansure® HPV Kit (Sansure Biotech Inc.). Briefly, 10 µL of purified DNA was mixed with 36 µL of the HPV-PCR Mix and 4 µL of the HPV-Enzyme Mix provided in the kit. PCR amplification was then performed using the SLAN-96P

Real-Time PCR System (Sansure Biotech Inc.). The cycle parameters were set at 50°C for 2 min for UNG activity, and 94°C for 5 min followed by 45 cycles of denaturation at 94°C for 15 s and annealing, extension and fluorescence collection at 57°C for 30 s. A positive and a negative control provided in the kit were added to each PCR plate. The software SLAN Real-Time PCR System 8.2.2. software was used to process the raw amplification data.

2.6 | Excluding HPV53 single infection

HPV53 belongs to the possibly carcinogenic group (group 2B) of HPV as defined by the International Agency for Cancer Research (IARC) [18]. Therefore, its detection in cervical screening is unlikely to be relevant for cervical cancer screening. Since primers and probe targeting HPV53 are included in the group of 13 other HPV types for detection, Riatol qPCR results were used to identify samples with a single HPV53 infection.

2.7 | Statistical analysis

Samples where the human beta-globin gene was not amplified in at least one of the three aliquots were removed from statistical analysis. The intra- and interlaboratory reproducibility for the presence of hrHPV DNA (defined as positive for at least one of the 15 hrHPV) were assessed by the general reproducibility and Cohen's κ values with 95% confidence intervals (CIs). The Sansure® HPV Kit should demonstrate a general reproducibility with lower 95% CI bound exceeding 87% and a kappa (κ) of at least 0.50 to fulfill the third criterion for HPV test validation—besides the demonstration of noninferior clinical sensitivity and specificity compared to a standard comparator test.[12] The statistical analysis was performed for hrHPV, HPV16, HPV18, and the other 13 hrHPV (or 12 hrHPV after exclusion of HPV53 positive samples) types as aggregate. HPV reproducibility was categorized as excellent ($1.00 \geq \kappa > 0.80$), good ($0.80 \geq \kappa > 0.60$), moderate ($0.60 \geq \kappa > 0.40$), fair ($0.40 \geq \kappa > 0.20$), and poor ($0.20 \geq \kappa > 0.00$), according to Landis and Koch[19] and VALGENT guidelines.[20]

Statistical analyses were carried out with STATA version 16 (College Station).

2.8 | Statement on ethical approval

Ethical approval for this study was obtained from the Ethics Committee of the Ghent University Hospital (Belgium) on June 29, 2022 (reference number ONZ-2022-0171).

3 | RESULTS

3.1 | Cervical sample adequacy

Of the 543 cervical samples selected for the study, 10 showed no amplification of the beta-globin gene in at least one testing. They were therefore excluded from further analysis, which included a total of 533 samples.

3.2 | Intra- and interlaboratory reproducibility for overall HPV detection

The intralaboratory comparison showed 500 concordant and 33 discordant results leading to an overall intralaboratory reproducibility of 93.8% (95% CI: 91.4%–95.7%) with Cohen's κ of 0.85 (Table 1). The interlaboratory comparison showed 498 concordant and 35 discordant results leading to an overall interlaboratory reproducibility of 93.4% (95% CI: 91.0%–95.4%) with Cohen's κ of 0.84 (Table 1). An interlaboratory comparison was also made by comparing testing 2 in center 1 with testing 3 in center 2. The overall agreement was also excellent (93.2%) with a κ of 0.84 (Supplementary Table 1).

3.3 | Intra- and interlaboratory reproducibility for genotype-specific detection

The genotype-specific intra- and interlaboratory reproducibility is presented in Table 2. The intralaboratory genotype-specific level agreement for HPV16, HPV18, HPV16&18, and other HPV was 98.9%, 99.1%, 98.1%, and 94.2%, respectively, with Cohen's κ of 0.87, 0.73, 0.84, and 0.85, respectively. The interlaboratory genotype-specific level agreement was 98.3%, 100.0%, 98.7%, and 93.4% for HPV16, HPV18, HPV16 & 18, and other HPV, respectively, with high Cohen's κ of 0.82, 1.00, 0.88, and 0.82 respectively.

3.4 | Intra- and interlaboratory reproducibility without HPV53 single infection

Fourteen samples were found to have a single HPV53 infection and were removed from the analysis to provide a clearer picture of the

TABLE 1 Intra- and interlaboratory reproducibility of the Sansure® Human Papillomavirus DNA Diagnostic Kit.

Intralaboratory reproducibility					
		Testing 1—Center 1			
		Positive	Negative	Total	Reproducibility: 93.8% (95% CI: 91.4%–95.7%)
Testing 2 Center 1	Positive	138	17	155	
	Negative	16	362	378	κ: 0.85
	Total	154	379	533	(95% CI: 0.80–0.90)
Testing 3 Center 2	Positive	135	16	151	Reproducibility: 93.4% (95% CI: 91.0%–95.4%)
	Negative	19	363	382	κ: 0.84
	Total	154	379	533	(95% CI: 0.79–0.89)

TABLE 2 Genotype-specific level agreement of the Sansure® Human Papillomavirus DNA Diagnostic Kit for intra- and interlaboratory analysis.

HPV type	-/-[a]	+/+[a]	-/+[a]	+/-[a]	General agreement (95% CI)	κ (95% CI)
Intralaboratory analysis (Testing 1 vs. Testing 2)						
HPV16	505	22	3	3	98.9% (97.6%–99.6%)	0.87 (0.78–0.97)
HPV18	521	7	5	0	99.1% (97.8%–99.7%)	0.73 (0.51–0.96)
HPV16 & 18	495	28	7	3	98.1% (96.6%–99.1%)	0.84 (0.74–0.94)
Other HPV[b]	384	118	14	17	94.2% (91.8%–96.0%)	0.85 (0.79–0.90)
Interlaboratory analysis (Testing 1 vs. Testing 3)						
HPV16	502	22	6	3	98.3% (96.8%–99.2%)	0.82 (0.71–0.94)
HPV18	526	7	0	0	100.0% (99.3%–100.0%)[c]	1.00 (1.00–1.00)
HPV16 & 18	498	28	4	3	98.7% (97.3%–99.5%)	0.88 (0.80–0.97)
Other HPV[b]	384	114	14	21	93.4% (91.0%–95.4%)	0.82 (0.77–0.88)

[a]-/-: both runs are concordantly negative; +/+: both runs are concordantly positive; -/+: Testing 1 negative at Center 1, Testing 2 positive at Center 1| Testing 3 positive at Center 2; +/-: Testing 1 positive at Center 1, Testing 2 negative at Center 1 | Testing 3 negative at Center 2.

[b]Other HPV includes the aggregate of HPV types 31/33/35/39/45/51/52/53/56/58/59/66/68.

[c]One-sided statistics, 97.5% confidence interval.

TABLE 3 Genotype-specific level agreement of the Sansure® Human Papillomavirus DNA Diagnostic Kit for intra- and interlaboratory analysis after removal of single HPV53 infections from analysis.

HPV type	-/-[a]	+/+[a]	-/+[a]	+/-[a]	General agreement (95% CI)	κ (95% CI)
Intralaboratory analysis (Testing 1 vs. Testing 2)						
All HPV[b]	355	131	17	16	93.6% (91.2%–95.6%)	0.84 (0.79–0.90)
HPV16	491	22	3	3	98.8% (97.5%–99.6%)	0.87 (0.77–0.97)
HPV18	507	7	5	0	99.0% (97.8%–99.7%)	0.73 (0.51–0.96)
HPV16&18	481	28	7	3	98.1% (96.5%–99.1%)	0.84 (0.74–0.94)
Other HPV[c]	377	111	14	17	94.0% (91.6%–95.9%)	0.84 (0.78–0.89)
Interlaboratory analysis (Testing 1 vs. Testing 3)						
All HPV[b]	356	130	16	17	93.6% (91.2%–95.6%)	0.84 (0.79–0.90)
HPV16	488	22	6	3	98.3% (96.7%–99.2%)	0.82 (0.71–0.94)
HPV18	512	7	0	0	100.0% (99.3%–100.0%)[d]	1.00 (1.00–1.00)
HPV16&18	484	28	4	3	98.7% (97.2%–99.5%)	0.88 (0.80–0.97)
Other HPV[c]	377	109	14	19	93.6% (91.2%–95.6%)	0.83 (0.77–0.88)

[a]-/-: both runs are concordantly negative; +/+: both runs are concordantly positive; -/+: Testing 1 negative at Center 1, Testing 2 positive at Center 1| Testing 3 positive at Center 2; +/-: Testing 1 positive at Center 1, Testing 2 negative at Center 1 | Testing 3 negative at Center 2.

[b]All HPV includes HPV types 16/18/31/33/35/39/45/51/52/53/56/58/59/66/68 but excluding HPV53 single infection.

[c]Other HPV includes the aggregate of HPV types 31/33/35/39/45/51/52/53/56/58/59/66/68 but excluding HPV53 single infection.

[d]One-sided statistics, 97.5% confidence interval.

reproducibility of the other 12 hrHPV types (i.e., HPV31/33/35/39/45/51/52/56/58/59/66/68) in the Sansure® Human Papillomavirus DNA Diagnostic Kit. The overall and genotype-specific intra- and interlaboratory reproducibility remained excellent when comparing testing 1 with testing 2 or testing 3 (Table 3). Similarly, the comparison between testing 2 and testing 3 showed excellent reproducibility and Cohen's κ (Supplementary Table 2).

4 | DISCUSSION

This study evaluated the intra- and interlaboratory reproducibility of the Sansure® HPV Kit for the detection of hrHPV DNA from cervical specimens. From a practical point of view, this new HPV assay requires only a 2-h video training session to get started. The automated extraction process is highly time-efficient, requiring only

20 min to obtain a DNA extract suitable for downstream PCR applications. The preparation of the qPCR plate is also streamlined, involving the simple mixing of two reagents followed by the addition of sample DNA and the controls provided in the kit. The thermocycler software is user-friendly and facilitates easy and rapid interpretation of positivity for the cellular control, HPV16, HPV18, and other HPV types.

Both intra- and interlaboratory reproducibility for hrHPV positivity was excellent, as demonstrated by high levels of agreement and Cohen's $\kappa > 0.8$. Excellent intra- and interlaboratory reproducibility was also observed when HPV16, HPV16/18 and the 13 other HPV types were considered. Reproducibility was good ($\kappa = 0.73$) when only HPV18-positive samples were considered in the intralaboratory reproducibility testing, which may be due to the small number of HPV18 samples. These data demonstrate that the reproducibility of the Sansure® HPV Kit meets the international criteria for overall hrHPV, HPV16, HVP18 and the 13 other HPV types separately.[12] In the framework of a systematic review conducted to prepare WHO Target Product Profiles for HPV test, the intra- and interlaboratory reproducibility of a hrHPV positive result ranged for all the clinically validated HPV tests between 89% and 100% (Arbyn, HPV World 2024). The intra- and interlaboratory reproducibility of hrHPV positivity observed for the SanSure assay evaluated in the current study was 94% and 93%, respectively, which is nicely within the range observed for HPV tests that are already fully validated.

According to the IARC, HPV53 is a possibly carcinogenic (2B)[5,6] virus that is not relevant for cervical screening. To specifically assess the intra- and interreproducibility of the Sansure® HPV Kit without considering HPV53, analyses were performed secondarily after the removal of HPV53 single infections. Actually, removing this genotype did not impact the performance of the test and the overall and genotype-specific intra- and interlaboratory reproducibility remained excellent. It may be recommended to remove this genotype from the pool of HPV detected in the aggregate. Indeed HPV53 is quite common in the population but very rarely involved in carcinogenesis. Its inclusion in assays may therefore compromise its clinical specificity.[21,22] Other HPVs with lower oncogenic potential (e.g., HPV66 or HPV68) are included in many HPV tests that have been validated for cervical cancer screening.[21] This is why HPV66 and HPV68 were kept in our reproducibility analyses. A recent population-based study showed that the impact of cervical cancer screening depends on the HPV genotypes included in the screening tests.[23] Particularly, testing for HPV with the lowest oncogenic potential would have little impact on the screening efficiency, especially in young women. Thus, full or extended genotyping-based screening may probably help distinguishing women most at risk for cervical cancer. In addition, there is a growing consensus in the HPV community that new tests should preferentially target only the 12 cancer-causing types and that, as recently discussed, the lower oncogenic HPV genotypes (including HPV66 and HPV68) should probably not be included in screening.[24] Another reason for recommending the removal of HPV53 is that clinical validations of HPV tests, such as the VALGENT studies,[20] compare clinical sensitivity and specificity with a standard comparator test that explicitly does not detect this genotype.[13]

The next step in the full validation of the Sansure® HPV Kit for cervical screening is to evaluate its relative sensitivity and specificity compared to a standard comparator assay for the detection of CIN2+ lesions. This could be assessed in the upcoming VALGENT study, which is currently in preparation. Experience within the VALGENT framework has learnt us that it is more easy and less costly to start with the evaluation of the reproducibility. If reproducibility is not satisfactory, it is not appropriate setup the more challenging and costly evaluation of the relative clinical sensitivity and relative clinical specificity compared to a standard comparator tests. In the future, manufacturers will be recommended to start first with a reproducibility assessment and if successful followed by the clinical validation. Manufacturers may also opt to go for a full validation study immediately.

The author believes that this assay is an excellent candidate for HPV detection in low- and middle-income countries due to its user-friendly protocol and instrumentation. Given the significant burden of HPV-related disease in these regions, the ability of this assay to provide effective screening is critical. The procedure requires minimal manual skills beyond basic pipetting, making it accessible to laboratories with limited trained personnel. The compact size of the instrument also means that it requires minimal bench space, which is advantageous for space-constrained laboratories. In addition, the assay supports high-throughput testing, allowing large numbers of samples to be processed efficiently in a relatively short period of time. This high-throughput capability is particularly beneficial in resource-limited settings where there is a need to screen large populations for HPV.

5 | CONCLUSION

The new real-time PCR-based Sansure® HPV Kit showed excellent performances in terms of intra- and interlaboratory reproducibility. This was observed for the detection of all HPV as well as for the detection of HPV16, HPV18, and the other 13 HPV in aggregate. Once the relative sensitivity and specificity of the Sansure® HPV Kit against a comparator test have been validated, this kit can be safely used for cervical cancer screening.

AUTHOR CONTRIBUTIONS

Marc Arbyn developed the generic design of the reproducibility study which was adapted for the reproducibility of the The Sansure® Human Papillomavirus DNA Diagnostic Kit by Pui Yan Jenny Chung, Sharonjit K. Dhillon, Jean-Luc Prétet, and Davy Vanden Broeck. Yuliya Tkachenka and Davy Vanden Broeck selected samples from the biobank; have prepared and shipped aliquots to center 2; and performed the intralaboratory testing. Alice Baraquin and Killian Jacquot have performed the interlaboratory testing of aliquoted specimens. Jean-Luc Prétet and Quentin Lepiller analyzed row data for center 2. Pui Yan Jenny Chung compiled and analyzed the data received from

the centers. Jean-Luc Prétet wrote the manuscript. All (co-)authors have reviewed and/or edited the manuscript. All (co-)authors have approved the submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no personal conflict of interests. This study is an extension of the VALGENT (VALidation of HPV GENotyping tests) project in the framework of validating new HPV assay.[20] VALGENT is an independent researcher-induced research project where manufacturers can have their HPV assays evaluated, under the condition that they provide equipment, kits and cover costs for laboratory work and statistical analysis. Manufacturers cannot influence the publication of manuscripts. JLP's institution received funding, free-of-charge reagents and consumables from Fujirebio, Primadiag, Genfirst, Atila BioSystems and Sansure.

Davy Vanden Broeck and Yuliya Tkachenka are employed by AML (Antwerp, Belgium), one of the HPV National Reference Centres, a private lab performing routine cervical cytology and HPV testing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

No data were deposited in a repository. Data sets generated by validation studies are stored locally and securely at Sciensano. Anonymized data can be made available by request to the corresponding author on a case-by-case basis pending approval from the information security coordinator at Sciensano.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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