STANDARD M10 Hr-HPV

STANDARD™ M10 Hr-HPV

REF M10-HPV-02

INSTRUCTIONS FOR USE

For use with STANDARD™ M10 system

www.sdbiosensor.com

SD BIOSENSOR

Contents

1. Intended Purpose

STANDARD M10 Hr-HPV is a multiplex real-time PCR test intended for use with STANDARD M10 system for the qualitative detection of Human papillomavirus (HPV) DNA in cervical specimens collected by healthcare providers. The STANDARD M10 Hr-HPV is used for the detection of a high-risk HPV infection, which is associated with increased risk of cervical precancerous lesions and cervical cancer.

The STANDARD M10 Hr-HPV separately detects genotypes 16, 18 and reports 12 high-risk HPV types (i.e., 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in a pooled result. The STANDARD M10 Hr-HPV is indicated for use as a cervical cancer screening test to assess the presence or absence of high risk HPV genotypes.

Results are for the identification of 14 high-risk HPV DNA genotypes. Positive results are indicative of the presence of HPV DNA; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status.

Positive results do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease.

Negative results do not preclude HPV infection (or cervical cancer) and should not be used as the sole basis for treatment or other patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

This test is intended to be performed by health-care professionals in a laboratory setting or a health-care institution.

2. Summary and Explanation

HPV infection is caused by human papillomavirus, a DNA virus from the Papillomaviridae family. HPV are transmitted by skin-to-skin contact and sexual contact. HPV infection results in either warts or precancerous lesions. These lesions increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth.

Human papillomavirus is small double-stranded circular DNA virus. The circular genome is approximately 7.9 kb. Currently, there are more than 100 different known HPV genotypes that have been grouped into low-risk and high-risk categories. Nearly all cervical cancer is due to HPV; two strains, HPV 16, and HPV 18, account for 70% of cases.

The STANDARD M10 Hr-HPV test is a molecular in vitro diagnostic test that aids in the detection and diagnosis of HPV and is based on widely used nucleic acid amplification technology. The STANDARD M10 Hr-HPV test contains primers and probes and internal control (IC) used in Real-time PCR for the in vitro qualitative detection of HPV DNA in cervical swab specimens.

[Cartridge Description]

The STANDARD M10 Hr-HPV cartridge is a disposable plastic device that allows performance of fully automated molecular assays by containing all reagents required for the test.

Within the cartridge, multiple steps are automatically performed in sequence using pneumatic pressure to transfer samples and fluids via the chamber to their intended destinations.

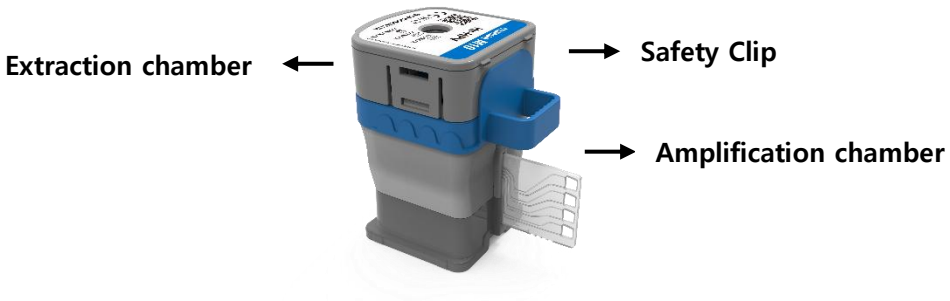

Figure 1. Layout of the STANDARD M10 Hr-HPV cartridge

3. Principle of the Procedure

The STANDARD M10 Hr-HPV test is an automated in vitro diagnostic test for qualitative detection of nucleic acid from HPV. The STANDARD M10 Hr-HPV test is performed on STANDARD M10 system.

The STANDARD M10 system automates and integrates sample preparation, nucleic acid extraction, real-time polymerase chain reaction (RT-PCR), and detection of the target sequences in various specimens using molecular diagnostic assays. The system consists of the STANDARD M10 Module and the STANDARD M10 Console with preloaded software for running tests and viewing the results. The system requires the use of single-use disposable cartridges that hold the RT-PCR reagents and host the RT-PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, see the STANDARD M10 system User Manual.

The STANDARD M10 Hr-HPV test includes reagents for the detection of DNA from HPV in cervical cells. The cartridge is present to control for adequate processing of the sample and RT-PCR reaction.

The table below indicates which target is designed to be detected by which channel.

The STANDARD M10 Hr-HPV separately detects results as follows : "HPV 16"; for HPV 16, "HPV 18"; for HPV 18, "G1" for the result of HPV type 51, "G2" for the pooled result of any of HPV types 33, 52, 58, "G3" For the pooled result of either of HPV types 31 or 35, "G4" for the pooled result of either of HPV types 45 or 59, "G5" for the pooled result of either of HPV types 39 or 68, "G6" for the pooled result of either of HPV types 56 or 66.

Table 1. Fluorescent channel of each target gene

Target	Channel	Notation
HPV 16	*FAM*	*HPV 16*
HPV 18	*FAM*	*HPV 18*
HPV 51	*FAM*	*G1*
HPV 33, 52, 58	*CY5*	*G2*
HPV 31, 35	*FAM*	*G3*
HPV 45, 59	*CY5*	*G4*
HPV 39, 68	*CY5*	*G5*
HPV 56, 66	*CY5*	*G6*
Internal control (IC)	*HEX*	*IC*

4. Active Ingredient

- Sodium dodecyl sulfate 5 mg
- Taq DNA Polymerase 220U
- Target primers and probes 3 – 20 pmol

5. Materials Provided

The STANDARD M10 Hr-HPV contains sufficient reagents to process 10 specimens or quality control samples.

Table 2. Contents of the STANDARD M10 Hr-HPV kit

	Contents	Quantity	Usage in each reaction
1	*Cartridge*	*10*	*1ea*
2	*Quick Reference Instructions*	*1*	*-*

6. Storage and Handling

Store STANDARD M10 M10 Hr-HPV kit at 2-28 °C (36-82 °F). If the cartridge has been refrigerated, perform the test after stabilizing it for 4 hours at 15±2°C (59 ± 3.6°F).

Do not store the cartridge upside-down. If stored upside-down, it remains stable for up to 20 days. Do not remove the Safety Clip of the cartridge and do not press the cartridge until actual use. Do not use a cartridge that has leaked or is wet. Under these conditions, cartridges can be stored until the expiration date printed on the packaging.

7. Materials Required but Not Provided

- *STANDARD M10 system with user manual*
  At least one STANDARD M10 Console (Cat. No. 11M1011) and one STANDARD M10 Module (Cat. No. 11M1012)
- *Vortex mixer*
- *Sample transfer pipettes*
  - STANDARD™ Disposable dropper (1㎖) (Cat No. 90DR40)
  - Micropipette with filter tips
- *Sample collection tools*
  - *ThinPrep® PreservCyt® Solution (Hologic, Inc.)*
  - *BD SurePath™ Collection Vial (Becton, Dickinson and Company)*
- *PPE (Personal Protective Equipment)*

8. Warnings and Precautions

1) *This kit is only for in vitro diagnosis.*
2) *Please read the Instructions for Use carefully before testing.*
3) *Since this kit is optimized for LBC specimens, it is recommended to use only LBC specimens. If samples other than LBC specimens are used, operation errors or incorrect results may be obtained.*
4) *Improper specimen collection, transfer, storage, and processing may cause erroneous test results.*
5) *Do not remove the safety clip of the cartridge before use.*
6) *Do not press the cartridge until actual use.*
7) *Do not use a cartridge that has leaked or is wet.*
8) *Keep the cartridge away from UV/sunlight and keep dry.*
9) *Do not use the kit after its expiration date.*
10) *Do not shake, tilt, or invert the cartridge especially after pressing the cartridge to punch the seal. It may yield invalid or false test results.*
11) *Do not use a cartridge with a damaged barcode label.*
12) *Do not reuse processed cartridges.*
13) *All specimens should be handled as if these samples are infectious.*
14) *All materials should be considered potentially infectious and should be handled with precautions.*
15) *As this test involves extraction of viral DNA and PCR amplification, care should be taken to avoid contamination. Regular monitoring of laboratory contamination is recommended.*
16) *Clinical laboratories should be equipped with equipment and operators in strict accordance with the "Code of Practice for Clinical Gene Amplification Laboratories".*
17) *When using this kit, it should be operated strictly in accordance with the instructions and follow the technical requirements of the clinical gene amplification laboratory.*
18) *Follow your institution's environmental waste procedures for proper disposal of used cartridges.*
19) *Do not use the cartridge if more than 1 month have passed since the silver foil pouch was opened.*
20) *Any serious incident that has occurred in relation to this kit shall be reported to the manufacturer or its authorized representative, and to the competent authority of the Member State in which the user and/or the patient is established, in accordance with the requirements of Regulation (EU) 2017/746.*
21) *The Summary of Safety and Performance is available on EUDAMED database.*

9. Chemical Hazards

This kit contains components classified as follows in accordance with the regulation (EC) No. 1272/2008:

*** Hazard pictogram:**

-Not applicable

*** Hazard statements:**

-Not applicable

*** Precautionary statements:**

1) Prevention

-Not applicable

2) Response

-Not applicable

3) Storage

-Not applicable

4) Disposal

-Not applicable

10. Specimen Collection and Storage

Proper sample collection, transportation, and storage are critical to the performance of the test. Improper sample collection, inappropriate sample handling and/or transportation can lead to false results.

9.1 Specimen Collection

Collect cervical swab following your institution's standard protocol for sample collection and testing.

9.2 Specimen Storage and Transport

Store and transport the specimen at 25°(77°F) for 18 weeks and refrigerated temperature(2 - 8°C, 36~46°F) for 9 months.

11. Procedure

11.1 Starting the STANDARD M10 system

Note	*For the detailed instructions, refer to the STANDARD M10 system user manual.* *If you have scanned the cartridge barcode in the STANDARD M10 and the software version is not compatible, a 'Not Supported Device' error message appears. Update the software before proceeding the test.*

1) *Turn on the STANDARD M10 system.*
2) *Check the STANDARD M10 Console and the STANDARD M10 Module are connected and functional.*

Figure 2. Power connection

3) *Enter the User ID and Password on the Log In screen of the STANDARD M10 Console and click the Log In button.*
4) *Touch the STANDARD M10 Module to run on the Home screen.*
(The door of the selected STANDARD M10 Module will automatically open for cartridge loading.)

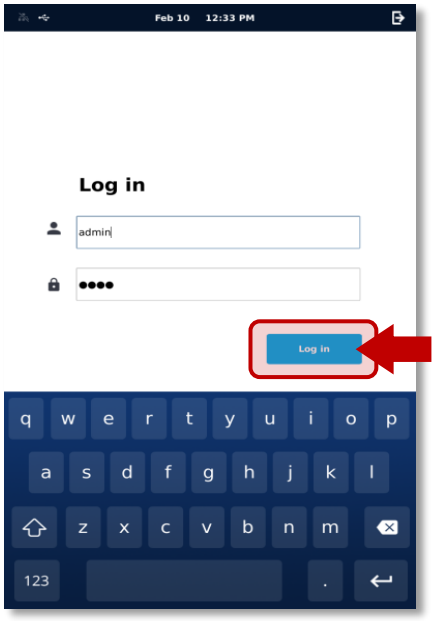

Figure 3. Log In screen

Figure 4. Home screen, Status of M10 Module

5) *Enter a Patient ID by scanning the barcode or using virtual keyboard on the M10 Console screen. (Patient ID is optional. You can turn off the Patient ID option from the 'Settings'.)*

6) *Enter a Sample ID by scanning the barcode of the specimen or using virtual keyboard on the M10 Console screen. Make sure that the specimen tube cap is firmly closed when scan the ID barcode printed on the specimen tube. (For quality control test, tick the QC check box.)*

Figure 5. Entering Sample ID

Figure 6. Scanning a cartridge

7) *Scan the STANDARD M10 Hr-HPV cartridge to be used. The STANDARD M10 Console automatically recognizes the assay to be run based on the cartridge barcode.*

Note	*If you have scanned the cartridge barcode in the STANDARD M10 and the expiration date has expired, An 'Expired Device' error message appears. Check validity period and test with unexpired cartridges.*

11.2 Loading a sample into the STANDARD M10 Hr-HPV cartridge

Caution	*If the cartridge has been refrigerated, perform the test after stabilizing it for 4 hours at 15±2°C (59 ± 3.6°F)* *Once the sample has been loaded into the cartridge, start the test within 30 minutes.*
Note	*False negative results may occur if insufficient sample is added into the cartridge.*

1) *Remove the safety clip located underneath the lid of the cartridge.*
2) *Pierce the sealed cartridge by pressing down the lid until fully engaged into the cartridge groove.*

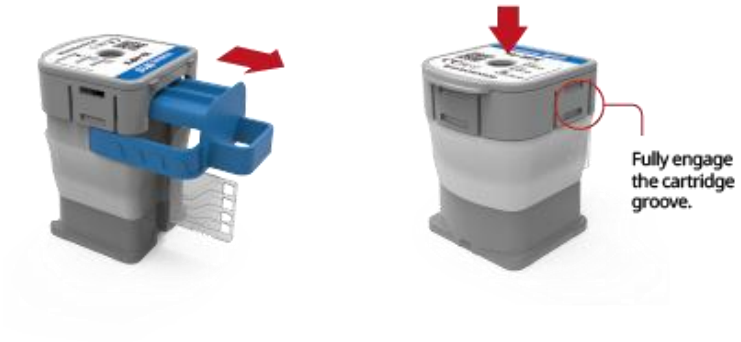

Figure 7. Pierce the sealed cartridge

3) *Open the lid and check that the seal is completely punctured before loading a sample.*
4) *Mix sample by rapidly inverting the specimen 5~10 times. Carefully open the cap of the specimen tube.*
5) *Dispense 1㎖ of the sample into the hole in the lower right corner of the cartridge using a 1㎖ disposable dropper or a pipette with a filter tip.*

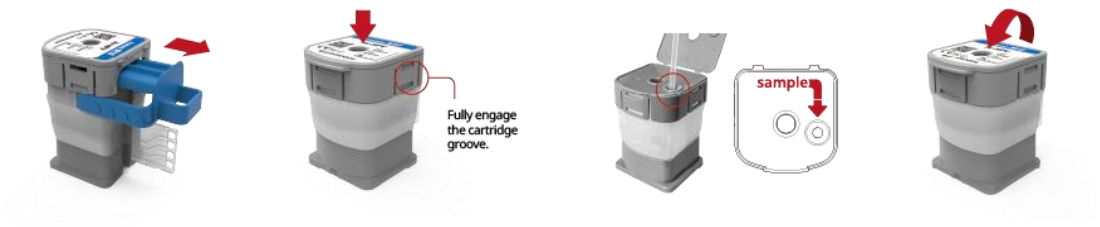

Figure 8. Loading a sample

6) *After a few seconds, Sample Guide screen will automatically change to the Insert Cartridge screen. Touch the Sample Guide screen if you want to skip the guide.*
7) *Close the lid.*

Figure 9. Sample Guide screen

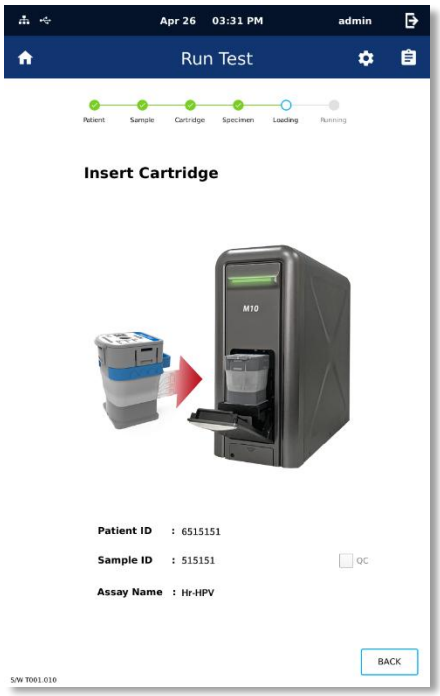

Figure 10. Insert Cartridge screen

11.3 Running a test

1) *Load the cartridge on the selected STANDARD M10 Module with the Amplification chamber facing the inside of the module. (The status indicator of the selected module will blink green.)*
2) *Close the door completely.*
3) *After confirming the sample and cartridge information, touch the OK button on the screen. (Touch the Reset button to re-input the information.)*
4) *Assay starts automatically, and remaining time will appear on the screen.*

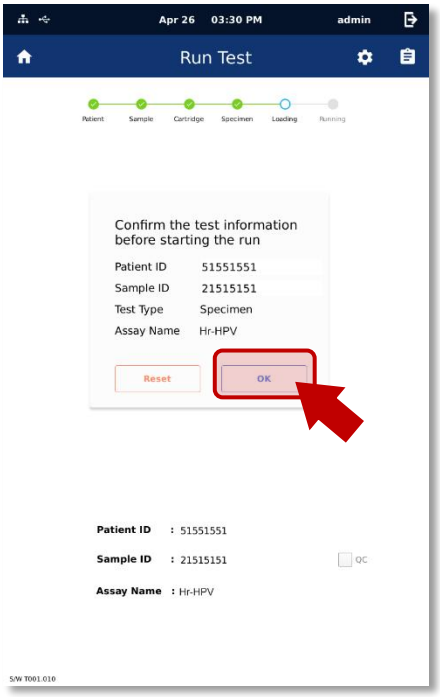

Figure 11. Confirm the test screen

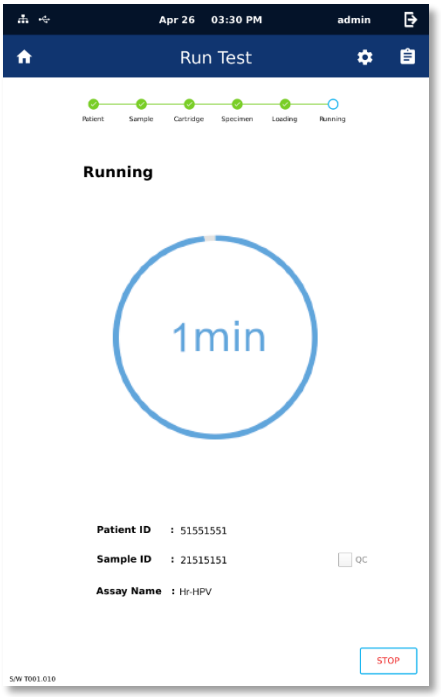

Figure 12. Running screen

5) *When the run is finished, it switches to the Review screen and the result is displayed.*
6) *Dispose of used cartridges in the appropriate biohazard waste container according to your institution's standard practices.*
7) *To run another test, touch the Home icon and repeat the process.*
(If another STANDARD M10 Module connected to the STANDARD M10 Console is available, you can start a new test while another test is running.)

12. Interpretation of Results

The results are interpreted automatically by the STANDARD M10 Console and are clearly shown in the Review screen. The STANDARD M10 Hr-HPV test provides test results based on the detection of targets according to the algorithms shown in Table 3, 4.

Table 3. Interpretation of results

Outcome (Home screen)	Result (Review screen)	Description
Positive		*At least one pathogen is positive.*
Negative		*No pathogen was detected.*
Invalid		*IC signal does not have a Ct value within the valid range.*
Error		*The test failed because either an error occurred or the test was canceled by the user.*

Table 4. Description of IC results

Outcome (Summary screen)	Result (Summary screen)	Description
IC Valid		*IC has a Ct within the valid range.* *: The test was completed. Report positive/negative results of target according to the interpretation shown in table 5.*
IC Invalid		*All pathogen are not detected and IC signal does not have Ct value within the valid range.*
Error		*The test failed because either an error occurred or the test was canceled by the user. Repeat the test.*

Table 5. Interpretation of results

Result	HPV 16	HPV 18	HPV others	IC
HPV 16 Positive	+	-	-	+/-
HPV 18 Positive	-	+	-	+/-
Other high-risk HPV Positive	-	-	+	+/-
High-risk HPV Negative	-	-	-	+
Invalid	-	-	-	-
Error	*No result*			

** There may be co-infection with each target (HPV 16, HPV 18, other high-risk HPV)*

Result	Interpretation
HPV 16 Positive	*HPV16 viral DNA is detected.* *• The HPV 16 signal has a Ct within the valid range.* *• IC: N/A (not applicable); IC is ignored because each target amplification occurred.*
HPV 18 Positive	*HPV18 viral DNA is detected.* *• The HPV 18 signal has a Ct within the valid range.* *• IC: N/A (not applicable); IC is ignored because each target amplification occurred.*
Other high-risk HPV Positive	*Other high-risk HPV viral DNA is detected.* *• The other high-risk HPV signal has a Ct within the valid range.* *• IC: N/A (not applicable); IC is ignored because each target amplification occurred.*
High-risk HPV Negative	*HPV16, HPV18, and/or Other high-risk HPV viral DNA are not detected.* *• IC: Valid; IC has a Ct value.*
Invalid	*IC does not meet acceptance criteria and all targets are not detected. Repeat the test.* *• IC: Invalid; IC and viral DNA signals do not have a Ct within valid range.*
Error	*The test failed because either an error occurred or the test was canceled by the user.* *Presence or absence of target nucleic acids cannot be determined. Repeat the test.*

Table 6. HPV Genotypes

Notation		HPV genotype
HPV 16		*HPV 16*
HPV 18		*HPV 18*
HPV Others	*G1*	*HPV 51*
	G2	*HPV 33, 52, 58*
	G3	*HPV 31, 35*
	G4	*HPV 45, 59*
	G5	*HPV 39, 68*
	G6	*HPV 56, 66*

13. Quality Control

STANDARD Quality Control procedures are intended to monitor cartridge and assay performance. If the controls are not valid, the patient results cannot be interpreted.

Internal control (IC): Ensures a proper sample has been applied, reagents in the cartridge are well functioning, there were no other interfering factors in the sample, and the procedure was performed correctly. In clinical samples showing positive signal for Human papillomavirus, the IC is reluctant and is ignored. If the IC fails where no Human papillomavirus are detected the result is invalid.

External controls should be performed in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's standard quality control procedures.

For external controls, it is recommended to use the list below. Please comply with the information stated on the user manual.

External control (Positive control, Negative control)

- *ONBOARDx™ High-Risk HPV Kit (RUO) (Microbix, VP-K-HPV-02)*
- *PROCEEDx™ hr-HPV Negative Sample (Microbix, RED-62-67)*
- *ACCURUN® 873 HPV DNA Negative Control (SeraCare, Cat No.2035-0005)*

Products other than the mentioned substance can be used after being evaluated and validated for efficacy by each country or hospital independently.

[Test procedure]

1) *Prepare 1 vial each of the following from ONBOARDx™ High-Risk HPV Kit as positive control: HPV 16/18/45(VP-62-M1), HPV 31/33/66(VP-62-M2) and HPV 39/51/52(VP-62-M3).*
2) *Prepare PROCEEDx™ hr-HPV Negative Sample or ACCURUN® 873 HPV DNA Negative Control as negative control.*
3) *Dilute three positive controls and one negative control each 1/10 using with ThinPrep® PreservCyt® (HOLOGIC), BD SurePath™ Collection Vial (Becton, Dickinson and Company) or distilled water. A total 1000µl, 900µl PreservCyt®, BD SurePath™ solution or distilled water and 100µl of control, is tested.*

Material	Product	Control vol.(µl)	Diluent vol.(µl)
Negative Control	*PROCEEDx™ hr-HPV Negative Sample / ACCURUN® 873 HPV DNA Negative Control*	*100*	*900*
Positive Control 1	*HPV 16/18/45(VP-62-M1)*	*100*	*900*
Positive Control 2	*HPV 31/33/66(VP-62-M2)*	*100*	*900*
Positive Control 3	*HPV 39/51/52(VP-62-M3)*	*100*	*900*

4) *Dispense 1,000µl of the sample into the hole in the lower right corner of STANDARD M10 Hr-HPV using 1000µl of disposal dropper or a pipette with a filter tip.*
5) *Tick the QC check box and running a test.*

14. Performance

14.1. Limit of Detection Test

The product was evaluated for the detection of 14 high-risk HPV types using HPV-positive cell lines, the WHO 1st International Standard for HPV, and recombinant virus-based positive reference materials. These materials were serially diluted in negative cervical swab specimens suspended in liquid-based cytology (LBC) solution. Testing was conducted using two different lots across eight concentration levels, with 24 replicates per concentration. Based on the experimental results, the Limit of Detection (LoD) for each target was determined through Probit analysis, and the LoD values are as follows.

Table 7. Limit of Detection levels : HPV Positive Cell Lines

Type	Genotype	LoD
		ThinPrep® PreservCyt Solution
HPV Positive Cell Lines	SiHa(HPV 16)	21.46 cell/mL
	HeLa S3(HPV 18)	9.88 cell/mL
	MS751(HPV 45)	24.59 cell/mL
	ME-180(HPV 68)	29.81 cell/mL

Table 8. Limit of Detection levels : WHO-NIBSC

Type	Genotype	LoD
		ThinPrep® PreservCyt Solution
WHO 1st International Standard for HPV	HPV 16	360.44 IU/mL
	HPV 18	137.85 IU/mL
	HPV 31	238.87 IU/mL
	HPV 33	741.55 IU/mL
	HPV 45	363.11 IU/mL
	HPV 52	203.82 IU/mL
	HPV 58	318.84 IU/mL

Table 9. Limit of Detection levels : Recombinant virus

Type	Genotype	LoD
		ThinPrep® PreservCyt Solution
Recombinant virus	HPV 16	42.12 copies/mL
	HPV 18	16.49 copies/mL
	HPV 31	13.12 copies/mL
	HPV 33	88.55 copies/mL
	HPV 35	35.70 copies/mL
	HPV 39	17.26 copies/mL
	HPV 45	22.19 copies/mL

	HPV 51	43.91 copies/mL
	HPV 52	15.82 copies/mL
	HPV 56	13.13 copies/mL
	HPV 58	35.69 copies/mL
	HPV 59	16.92 copies/mL
	HPV 66	14.67 copies/mL
	HPV 68	19.15 copies/mL

14.2. Precision (Repeatability & Reproducibility)

[Repeatability]

The repeatability study, which included within-run, between-run, between-day, and within-laboratory precision, was conducted by analyzing the results of a single lot tested twice daily over 20 days, with two replicates for each concentration level (Negative, 0.1X, 1X, and 3X LoD). Based on the results, the repeatability of the product was confirmed with SD < 2.0 and CV < 5%.

[Reproducibility]

The reproducibility (Between-sites, Between-instruments, Between-operators, Between-lots) was conducted by analyzing the results of measuring for 5 days and 5 replicates for each concentration level (Negative, 0.1X, 1X, and 3X LoD) with the same sample. Based on the results, the reproducibility of the product was confirmed with CV < 5%.

14.3. Cross-reactivity

A total of 54 cross-reactive substances, including those with genetic relevance to the product's targets or those associated with similar symptoms, were selected for testing. These substances were diluted in negative cervical swab samples to the test concentration and evaluated in three replicates at both the negative sample level and at 3X LoD concentrations for the HPV 16 target. The results confirmed that there was no cross-reactivity at the tested concentrations for any of the 54 substances listed below.

Table 10. Substances tested in Cross-reactivity

#	Virus/Bacteria/Parasite	Test concentration	#	Virus/Bacteria/Parasite	Test concentration
1	*Bacteriodes fragilis*	$1X10^6$ CFU/mL	28	*Human Adenovirus 40*	$1X10^5$ PFU/mL
2	*Bifidobacterium adolescentis*	$1X10^6$ CFU/mL	29	*Cytomegalovirus (CMV)*	$1X10^5$ PFU/mL
3	*Bifidobacterium breve*	$1X10^6$ CFU/mL	30	*Epstein Barr virus (EBV)*	$1X10^5$ copy/mL
4	*Candida albicans*	$1X10^6$ CFU/mL	31	*Hepatitis B virus (HBV)*	$1X10^5$ IU/mL
5	*Chlamydia trachomatis Serovar D*	$1X10^6$ IFU/mL	32	*Hepatitis C virus (HCV)*	$1X10^5$ IU/mL
6	*Clostridium perfringens*	$1X10^6$ CFU/mL	33	*Human immunodeficiency virus 1 (HIV-1)*	$1X10^5$ IU/mL
7	*Corynebacterium xerosis*	$1X10^6$ CFU/mL	34	*Herpes simplex virus 1 (HSV-1)*	$1X10^5$ PFU/mL
8	*Enterobacter cloacae*	$1X10^6$ CFU/mL	35	*Herpes simplex virus 2 (HSV-2)*	$1X10^5$ PFU/mL
9	*Enterococcus faecalis*	$1X10^6$ CFU/mL	36	*HPV 6*	$1X10^5$ IU/mL
10	*Escherichia coli*	$1X10^6$ CFU/mL	37	*HPV 11*	$1X10^5$ IU/mL
11	*Fusobacterium nucleatum*	$1X10^6$ CFU/mL	38	*HPV 67*[1)]	$1X10^5$ copies/mL
12	*Klebsiella pneumoniae*	$1X10^6$ CFU/mL	39	*HPV 70*[1)]	$1X10^5$ copies/mL
13	*Lactobacillus acidophilus*	$1X10^6$ CFU/mL	40	*HPV 85*[1)]	$1X10^5$ copies/mL

14	*Lactobacillus crispatus*	1X10^6 CFU/mL	41	HPV 16[2)]	1X10^5 copies/mL
15	*Lactobacillus jensenii*	1X10^6 CFU/mL	42	HPV 18[2)]	1X10^5 copies/mL
16	*Neisseria gonorrhoeae*	1X10^6 CFU/mL	43	HPV 31[2)]	1X10^5 copies/mL
17	*Peptostreptococcus anaerobius*	1X10^6 CFU/mL	44	HPV 33[2)]	1X10^5 copies/mL
18	*Proteus mirabilis*	1X10^6 CFU/mL	45	HPV 35[2)]	1X10^5 copies/mL
19	*Proteus vulgaris*	1X10^6 CFU/mL	46	HPV39[2)]	1X10^5 copies/mL
20	*Pseudomonas aeruginosa*	1X10^6 CFU/mL	47	HPV 45[2)]	1X10^5 copies/mL
21	*Staphylococcus aureus*	1X10^6 CFU/mL	48	HPV 51[2)]	1X10^5 copies/mL
22	*Staphylococcus epidermidis*	1X10^6 CFU/mL	49	HPV 52[2)]	1X10^5 copies/mL
23	*Streptococcus agalactiae*	1X10^6 Cell/mL	50	HPV 56[2)]	1X10^5 copies/mL
24	*Streptococcus pyogenes*	1X10^6 CFU/mL	51	HPV 58[2)]	1X10^5 copies/mL
25	*Trichomonas vaginalis*	1X10^6 CCU/mL	52	HPV 59[2)]	1X10^5 copies/mL
26	*Mycoplasma hominis*	1X10^6 CCU/mL	53	HPV 66[2)]	1X10^5 copies/mL
27	*Ureaplasma urealyticum*	1X10^6 CCU/mL	54	HPV 68[2)]	1X10^5 copies/mL

[1)] Synthesized plasmid DNA
[2)] The target genotypes for STANDARD M10 Hr-HPV

14.4. Potentially Interfering Substances

A total of 16 endogenous and exogenous interfering substances, which may potentially be present in the specimen, were tested. These substances were diluted to the test concentration using negative cervical swab samples and evaluated under conditions with and without the addition of interfering substances in both negative and 2X LoD concentration samples, with three replicates per condition. The results confirmed that there was no interference up to the specified test concentrations for the 16 substances listed below.

Table 11. Interfering substances tested in Interfering Substance test

Type	#	Factor	Substance	Final concentration
Exo-genous	1	Douche	Yeast Gard Douche	10% w/v
	2	Anti-yeast medication	Clotrimazole Vaginal Cream	0.25% w/v
	3		Vagisil Moisturizer	0.25% w/v
	4	Antiviral cream	Zovirax Cold Sore Cream	0.25% w/v
	5	Antifungal cream	Monistant1	0.25% w/v
	6	feminine hygiene products	Norforms Feminine Deodorant Suppositories	10% w/v
	7	Vaginal lubricant	KY Jelly Personal Lubricant	10% w/v
	8		X3 Love gel	0.5% w/v
	9	Feminine hygiene deodorant spray	summer's eve feminine spray	10% v/v
	10	Acetic acid	Glacial Acetic acid	5% v/v
	11	Spermicide	Nonoxynol-9	5% w/v
	12	intravaginal hormones	Progesterone	20 ng/ml
	13	intravaginal hormones	β-Estradiol	1.36 ng/ml
Endo-genous	14	Others	Whole Blood	2% v/v
	15		Leukocytes (PBMC)	1x10^6 cells/mL
	16		cervical mucus	5% v/v

14.5. Carry-over Contamination

High-concentration HPV 16 and HPV 18 positive samples were tested in cross-validation using one lot of the product, with the test repeated five times.

The results showed that all high-concentration positive samples yielded positive results, and all negative samples yielded negative results, confirming that there was no cross-contamination between the dedicated equipment used to run the product (STANDARD M10 System) and the test samples.

14.6. Clinical Performance Study

A clinical performance study was conducted using the STANDARD™ M10 Hr-HPV assay with 890 anonymized remnant cervical specimens collected during cervical cancer screening in Belgium in ThinPrep® PreservCyt® Solution. The sample panel was confirmed stable and compliant with the Meijer protocol, including a balanced distribution of HPV genotypes. Among the panel, 90 specimens were confirmed as CIN2+ or higher: 58 were CIN3+, 30 were CIN2+, and 2 were confirmed squamous cell carcinoma (SCC). Additionally, 800 specimens were classified as ≤CIN1. Testing was performed in random order by seven blinded and independent operators using two different lots of the assay. The assay demonstrated a diagnostic sensitivity for CIN2+ and CIN3+ of 96.6% [95% CI: 90.6%-98.8%] and a diagnostic specificity for ≤CIN1 of 90.6% [95% CI: 88.4%- 92.4%]

	Clinical Status		Total
STANDARDTM M10 Hr-HPV	CIN2+/CIN3+	≤ CIN1	161
POSITIVE	86	75	727
NEGATIVE	3	724	
INVALID	1	1	2
Total	90	800	890

Diagnostic Sensitivity for CIN2+ and CIN3+ = 96.6% (86/89) with Wilson 95% CI: 90.6%- 98.8%

Diagnostic Specificity for ≤ CIN1 = 90.6% (724/799) with Wilson 95% CI: 88.4%- 92.4%

In addition, relative performance was assessed against a reference RT-PCR-based high-risk HPV assay. The STANDARD™ M10 Hr-HPV assay demonstrated:

Relative Sensitivity = 97.7% [95% CI: 93.4%–102.2%]

Relative Specificity = 99.1% [95% CI: 96.2%–102.3%]

Relative diagnostic metrics to evaluate the agreement with the comparator assay were used to assess equivalency between IVD assays. McNemar's test ($p = 0.49$) and Cohen's Kappa (≥ 0.8) supported high concordance between the two assays.

15. Limitations

1) *Performance characteristics of this test have been established with the specimen types listed in the Intended Purpose Section only. The performance of this assay with other specimen types or samples has not been evaluated.*
2) *A false negative result may occur if :*
   - *Sample concentrations is near or below the limit of detection of the test.*
   - *A specimen is improperly collected, transported or handled.*
   - *Inadequate numbers of organisms are present in the specimen.*
   - *Cartridges are exposed to improper environmental factors (temperature / humidity).*

3) *False positive results may happen from cross-contamination between specimens, specimen mix-up and/or DNA contamination during product handling.*
4) *Qualitative detection of positive results in this kit does not indicate the presence of live virus. It is recommended to use other methods for confirmation at the same time.*
5) *This kit only classifies and identifies Human papillomavirus (HPV 16, 18 and 12 high-risk HPV types (i.e., 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68)). The test results are for clinical reference only. The clinical diagnosis and treatment of patients should be combined with their symptoms / signs, medical history, other laboratory tests and treatment responses considering.*
6) *Potential mutations within the target regions covered by the primer and/or probes of the test may result in failure to detect the presence of the pathogen.*
7) *M10 Hr-HPV performance has not been evaluated in patients less than 30 years of age.*
8) *M10 Hr-HPV performance has not been evaluated in patients who have undergone cervical cancer treatment, such as surgery (e.g., hysterectomy), chemotherapy, or radiotherapy.*

16. References

1) *Schiffman, Mark, Gary Clifford, and Franco M. Buonaguro. "Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline." Infectious agents and cancer 4.1 (2009): 1-8.*
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3) *Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. Journal of Pathology. 1999; 189(1):12-19.*
4) *Clinical and Laboratory Standards Institute. 2008. Verification and Validation of Multiplex Nucleic Acid Assays: Approved Guideline. MM17-A. Clinical and Laboratory Standards Institute, Wayne PA.*
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6) *Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, Rush BB, Glass, AG, Schiffman M. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. Journal of the National Cancer Institute. 2005; 97(14):1072-79*
7) *REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on the classification labeling and packaging of substances and mixtures amending and repealing, List of Precautionary Statements, Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.*

16. Symbols

	*Reference number*		*Batch code*
	*Consult Instructions for Use*		*Manufacturer*
	*Contains Sufficient for <n> Tests*		*Date of manufacture*
	*Caution*		*Use-by date*
	*Do not re-use.*		*Keep away from sunlight*
	*Temperature limit*		*Do not use if packaging is damaged*
	*In vitro diagnostics medical device*		Not for Near-Patient Testing
	Authorized representative in the European Community		CE marking – European Conformity
	*keep dry*		

For further information on

STANDARD M10
Hr-HPV

Please contact your
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CE 0123 IVD

IVD **For *In Vitro* Diagnostic Use Only**

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L28MHREN3R0 / Issue date: 2025.10