cobas® HPV

Qualitative nucleic acid test
for use on the cobas® 5800/6800/8800 systems

For in vitro diagnostic use

cobas® HPV	P/N: 09040544190
cobas® HPV Positive Control Kit	P/N: 09040552190
cobas® Buffer Negative Control Kit	P/N: 09051953190

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Intended use

cobas® HPV for use on the **cobas**® 5800/6800/8800 systems (**cobas**® HPV) is an automated qualitative in vitro test for the detection of human papillomavirus (HPV) DNA in patient specimens. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies HPV16 and HPV18 while concurrently detecting the other high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) at clinically relevant infection levels. Specimens are limited to cervical cells collected in Roche Cell Collection Medium (Roche Molecular Systems, Inc.), PreservCyt® Solution (Hologic Corp.) and SurePath™ Preservative Fluid (BD Diagnostics-TriPath).

Indications for use of **cobas**® HPV are:

A. **cobas**® HPV is indicated for use in screening patients with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to determine the need for referral to colposcopy.

B. **cobas**® HPV is indicated for use in screening patients with ASC-US cervical cytology results to assess the presence or absence of HR HPV genotypes 16 and 18.

C. **cobas**® HPV is indicated for use adjunctively with cervical cytology to assess the presence or absence of HR HPV types.

D. **cobas**® HPV is indicated for use adjunctively with cervical cytology to assess the presence or absence of HPV genotypes 16 and 18.

E. **cobas**® HPV is indicated for use as a first-line primary screening test to identify women at increased risk for the development of cervical cancer or presence of high-grade disease.

F. **cobas**® HPV is indicated for use as a first-line primary screening test to assess the presence or absence of HPV genotypes 16 and 18.

cobas® HPV can also be used with healthcare worker–instructed self-collected vaginal specimens collected in Roche Cell Collection Medium or PreservCyt® Solution.

The results from **cobas**® HPV, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. The results of **cobas**® HPV are not intended to prevent women from proceeding to colposcopy.

Summary and explanation of the test

Background

Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).[1-3] The presence of HPV has been implicated in greater than 99% of cervical cancers, worldwide.[3] HPV is a small, non-enveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 140 different genotypes of HPV[4,5] and approximately 40 different types that can infect the human anogenital mucosa.[6,7] However, only a subset of 14 HPV genotypes has been found to be the cause of most cervical cancer cases and precancerous cervical lesions.[3,8-13] In this document "HPV" indicates "high risk HPV", except where otherwise noted.

In developed countries with cervical cancer screening programs, cytology (Pap smear) has been used since the 1960s as the primary tool to detect early precursors to cervical cancer. Although it has dramatically decreased the incidence and death from cervical cancer in those countries, cytology is costly, requires multiple testing at short intervals, and interpretation by highly trained cytopathologists has limited reproducibility and relatively low sensitivity for the detection of precancer. The discovery of persistent HPV as the single causative agent of cervical cancer generated interest in the use of HPV tests as a screening tool for cervical cancer and subsequent studies demonstrated that HPV-based testing was more sensitive than cytology for detection of precancer.[14] In 2001 professional guidelines first recommended the use of HPV testing as an adjunct to cytology in women ≥ 21 years, and by 2012 co-testing (cytology plus HPV testing) was designated as the preferred method of cervical cancer screening in women ≥ 30 years.[15] More recently, the **cobas®** 4800 HPV Test received FDA approval in 2014 as the first-line primary screen and interim guidance supporting HPV primary screening as an option for screening women ≥ 25 years was issued by 2 professional societies in 2015.[16]

Rationale for HPV testing

Most cervical cancer cases and deaths can be prevented through early detection of pre-cancerous changes in the cervix. Pap cytology testing has been central to cervical cancer screening programs for over 50 years and has contributed to the 70% decline in rates of cervical cancer in the developed world.[15] HPV is now recognized as a single, necessary cause of cancer of the cervix and is present in 99.7% of cases of cervical cancer.[3] Thirteen HPV genotypes are classified as carcinogenic or high-risk (HR) because of their association with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and an additional genotype (66) is classified as probably carcinogenic.[17] Therefore, tests that detect infection with these HR HPV genotypes are now being used increasingly in cervical cancer screening programs. The 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests[18] describes the utility of using a combination of cervical cytology, tests for HR HPV infection, and type-specific HPV Testing for women undergoing screening for cervical cancer. In these guidelines, the timing of additional investigations (e.g. colposcopy) and the interval for re-screening depends on the result of these tests. These guidelines have recently been revised and now recommend the combination of cytology and HR HPV testing (co-testing) as the preferred method of screening, with HPV 16/18 genotype-specific testing an added option.[15] HPV Testing provides a more sensitive method for cervical cancer screening than cytology[19] and its medical value has been clearly demonstrated as an adjunct to cytology, triage of ASC-US cytology, and as a first-line test.

Explanation of the test

cobas® HPV is a qualitative real-time[20,21] PCR test that detects 14 high-risk HPV genotypes. **cobas®** HPV uses primers to define a sequence of approximately 200 nucleotides within the polymorphic L1 region of the HPV genome. A pool of HPV primers present in the Master Mix is designed to amplify HPV DNA from 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68).[3,9-13,22] This test utilizes β-globin DNA as an internal control to monitor the entire sample preparation and PCR amplification process so an additional primer pair targets the human β-globin gene (330 base pair amplicon). Fluorescent oligonucleotide probes bind to polymorphic regions within the sequence defined by these primers. In addition, the test utilizes a low titer positive and a negative control.

cobas® HPV is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification[23] and detection. The **cobas®** 5800 system is designed as one integrated instrument. The **cobas®** 6800/8800 systems consist of a sample supply module, transfer module, processing module(s), and analytic module, all integrated as one instrument. Automated data management is performed by the **cobas®** 5800 or **cobas®** 6800/8800 systems software which assigns test results for all tests as positive, negative or invalid. Results can be reviewed directly on the system screen, exported, or printed as a report.

Nucleic acid (DNA) from patient samples and external controls is simultaneously extracted. In summary, nucleic acid is released by addition of proteinase and lysis reagent to the sample. The released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cellular debris and potential PCR inhibitors are removed with subsequent wash steps and purified nucleic acid is eluted from the magnetic glass particles with elution buffer at elevated temperature.

A thermostable DNA polymerase enzyme is used for PCR amplification. The HPV and β-globin sequences are amplified simultaneously utilizing a universal PCR amplification profile with predefined temperature steps and number of cycles. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythimidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon). Any contaminating amplicon from previous PCR runs are eliminated by the AmpErase enzyme, which is included in the PCR master mix, during the first thermal cycling step.[24] However, newly formed amplicon are not eliminated since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

The **cobas®** HPV master mix contains detection probes specific for twelve High Risk HPV target sequences, one detection probe specific for the HPV16 target sequence, one detection probe specific for the HPV18 target sequence and one for β-globin. The amplified signal from twelve high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) is detected using the same fluorescent dye while HPV16, HPV18 and β-globin signals are each detected with their own dedicated fluorescent dye. When not bound to the target sequence, the fluorescent signal of the intact probes is suppressed by a quencher dye. During the PCR amplification step, hybridization of the probes to the specific single-stranded DNA template results in cleavage of the probe by the 5' to 3' exonuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye increases concomitantly. Real-time detection and discrimination of PCR products is accomplished by measuring the fluorescence of the released reporter dyes for the HPV targets and β-globin, respectively.

Reagents and materials

cobas® HPV reagents and controls

Table 1 cobas® HPV

Store at 2-8°C
480 test cassette (P/N 09040544190)

Kit components	Reagent ingredients	Quantity per kit 480 tests
Proteinase Solution (PASE)	Tris buffer, < 0.05% EDTA, Calcium chloride, Calcium acetate, 8% Proteinase EUH210: Safety data sheet available on request. EUH208: Contains Subtilisin from Bacillus subtilis. May produce an allergic reaction.	38 mL
Empty Vessel (EV)	N/A	1
Elution Buffer (EB)	Tris buffer, 0.2% Methyl-4 hydroxibenzoate	38 mL
Master Mix Reagent 1 (MMX-R1)	Manganese acetate, Potassium hydroxide, < 0.1% Sodium azide	14.5 mL
HPV Master Mix Reagent 2 (HPV MMX-R2)	Tricine buffer, Potassium acetate, EDTA, Glycerol, < 18% Dimethyl sulfoxide, < 0.12% dATP, dCTP, dGTP, dUTPs, < 0.1% Tween 20, < 0.1% Sodium azide, < 0.1% Z05 DNA polymerase, < 0.10% AmpErase (uracil N-glycosylase) enzyme (microbial), < 0.1% Upstream and downstream HPV primers, < 0.01% Upstream and downstream β-globin primers, < 0.01% Fluorescent-labeled oligonucleotide probes specific for HPV and β-globin, < 0.01% Oligonucleotide aptamer	17.5 mL

Table 2 cobas® HPV Positive Control Kit

Store at 2–8°C
(P/N 09040552190)

Kit components	Reagent ingredients	Quantity per kit
HPV Positive Control (HPV (+) C)	Tris buffer, < 0.05% EDTA, < 0.1% Sodium azide, < 0.01% Non-infectious plasmid DNA (microbial) containing HPV16, HPV18 and HPV 39 sequences, < 0.01% Non-infectious plasmid DNA (microbial) containing β-globin sequences, < 0.002% Poly rA RNA (synthetic)	16 mL (16 x 1mL)

Table 3 cobas® Buffer Negative Control Kit

Store at 2-8°C
(P/N 09051953190)

Kit components	Reagent ingredients	Quantity per kit
cobas® Buffer Negative Control (BUF (-) C)	Tris buffer, < 0.1% sodium azide, EDTA, < 0.002% Poly rA RNA (synthetic)	16 mL (16 x 1mL)

cobas® omni reagents for sample preparation

Table 4 cobas® omni reagents for sample preparation*

Reagents	Reagent ingredients	Quantity per kit	Safety symbol and warning**
cobas® omni MGP Reagent (MGP) Store at 2–8°C (P/N 06997546190)	Magnetic glass particles, Tris buffer, 0.1% methyl-4 hydroxybenzoate, < 0.1% sodium azide	480 tests	Not applicable
cobas® omni Specimen Diluent (SPEC DIL) Store at 2–8°C (P/N 06997511190)	Tris buffer, 0.1% methyl-4 hydroxybenzoate, < 0.1% sodium azide	4 x 875 mL	Not applicable
cobas® omni Lysis Reagent (LYS) Store at 2–8°C (P/N 06997538190)	42.56% (w/w) guanidine thiocyanate***, 5% (w/v) polydocanol***, 2% (w/v) dithiothreitol***, dihydro sodium citrate	4 x 875 mL	 **DANGER** H302 + H332: Harmful if swallowed or if inhaled. H314: Causes severe skin burns and eye damage. H411: Toxic to aquatic life with long lasting effects. EUH032: Contact with acids liberates very toxic gas. P273: Avoid release to the environment. P280: Wear protective gloves/ protective clothing/ eye protection/face protection/ hearing protection. P303 + P361 + P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water. P304 + P340 + P310: IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/doctor. P305 + P351 + P338 + P310: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/doctor. P391: Collect spillage. 593-84-0 Guanidinium thiocyanate 9002-92-0 Polidocanol 3483-12-3 (R*,R*)-1,4-dimercaptobutane-2,3-diol
cobas® omni Wash Reagent (WASH) Store at 15–30°C (P/N 06997503190)	Sodium citrate dihydrate, 0.1% methyl-4 hydroxybenzoate	4.2 L	Not applicable

* These reagents are not included in the **cobas**® HPV kit. See listing of additional materials required (Table 8 and Table 9).

**Product safety labeling primarily follows EU GHS guidance

***Hazardous substance

Reagent storage and handling requirements

Reagents shall be stored and handled as specified in Table 5, Table 6 and Table 7.

When reagents are not loaded on the **cobas**® 5800 or **cobas**® 6800/8800 systems, store them at the corresponding temperature specified in Table 5.

Table 5 Reagent storage (when reagent is not on the system)

Reagent	Storage temperature
cobas® HPV	2–8°C
cobas® HPV Positive Control Kit	2–8°C
cobas® Buffer Negative Control Kit	2–8°C
cobas® **omni** Lysis Reagent	2–8°C
cobas® **omni** MGP Reagent	2–8°C
cobas® **omni** Specimen Diluent	2–8°C
cobas® **omni** Wash Reagent	15–30°C

Reagent handling requirements for cobas® 5800 system and cobas® 6800/8800 systems

Reagents loaded onto the **cobas**® 5800 system or **cobas**® 6800/8800 systems are stored at appropriate temperatures, their expiration is monitored and enforced by the system. The **s**ystem allows reagents to be used only if all of the reagent handling conditions shown in Table 6, Table 7 and Table 8 are met. The system automatically prevents use of expired reagents. Remaining open-kit stability and number of kit uses information for assay specific reagents is accessible through the system user interface.

Table 6 Reagent expiry conditions monitored and enforced by the **cobas**® 5800 system

Reagent	Open-kit stability	Number kit uses	On-board stability
cobas® HPV	90 days from first usage	40	36 days from loading
cobas® HPV Positive Control Kit	single use vial	16	36 days from loading
cobas® Buffer Negative Control Kit	single use vial	16	36 days from loading

Table 7 Reagent expiry conditions monitored and enforced by the **cobas**® 6800/8800 systems

Reagent	Open-kit stability	Number kit uses	On-board stability (outside on board refrigerator)
cobas® HPV	90 days from first usage	20	20 hours from loading
cobas® HPV Positive Control Kit	single use vial	16	10 hours from loading
cobas® Buffer Negative Control Kit	single use vial	16	10 hours from loading

Table 8 shows the open-kit stability of the **cobas**® **omni** reagents. Prior to each run, the system verifies the open-kit stability and ensures sufficient fill volume. Therefore, these reagents have no number of kit uses or on-board stability assigned.

Table 8 **cobas**® **omni** reagent expiry condition enforced by the **cobas**® 5800/6800/8800 systems

Reagent	Open-kit stability
cobas® **omni** Lysis Reagent	30 days from loading
cobas® **omni** MGP Reagent	30 days from first usage
cobas® **omni** Specimen Diluent	30 days from loading
cobas® **omni** Wash Reagent	30 days from loading

Additional materials required for the cobas® 5800/6800/8800 systems

Table 9 Material for use on **cobas**® 5800/6800/8800 systems

Material	P/N
cobas® **omni** Lysis Reagent	06997538190
cobas® **omni** MGP Reagent	06997546190
cobas® **omni** Specimen Diluent	06997511190
cobas® **omni** Wash Reagent	06997503190

Table 10 Consumables for use on **cobas**® 5800 system*

Material
cobas® **omni** Processing Plate
cobas® **omni** Amplification Plate
Tip CORE TIPS with Filter, 1ml
cobas® **omni** Liquid Waste Container
Solid Waste Bag or Solid Waste Bag With Insert

*For Part Numbers please refer to the **cobas**® 5800 systems User Assistance

Table 11 Consumables for use on **cobas**® 6800/8800 systems

Material
cobas® **omni** Processing Plate 24
cobas® **omni** Liquid Waste Plate 24
cobas® **omni** Amplification Plate 24
Tip CORE TIPS with Filter, 1mL
Tip CORE TIPS with Filter, 300 uL
cobas® **omni** Liquid Waste Container
Solid Waste Bag and Solid Waste Container or Solid Waste Bag With Insert and Kit Drawer
16-position tube S-carrier, complete
5-position rack R-carrier, complete
Collection Medium Container Carrier (CMC C-carrier)

*For Part Numbers please refer to the **cobas**® 6800/8800 systems User Assistance

Instrumentation and software required

The **cobas**® 5800 software, the **cobas**® 6800/8800 systems software and **cobas**® HPV analysis package (ASAPs) for **cobas**® 5800/6800/8800 systems shall be installed on the instrument.

For **cobas**® 5800 and the **cobas**® 6800/8800 systems with software version 2.0 or higher, the x800 Data Manager software and PC (or server) will be provided with the system.

For the **cobas**® 6800/8800 systems with software version 1.4, the Instrument Gateway (IG) server will be provided with the system.

Table 12 Instrumentation

Equipment	P/N
cobas® 5800 system	08707464001
cobas® 6800 system	05524245001 and 09575154001
cobas® 8800 system	05412722001 and 09575146001
Sample Supply Module for **cobas**® 6800/8800 systems	06301037001 and 09936882001

Refer to the **cobas**® 5800 system or **cobas**® 6800/8800 systems User Assistance for additional information.

Additional materials required for sample collection for cobas® HPV

Table 13 Specimen collection kits for use with **cobas**® HPV

Collection Kit	P/N
Roche Cell Collection Medium (250 Vials)	07994745190
ThinPrep Pap Test Physician's Kit (500 vials & Broom-like collection devices) ThinPrep Pap Test Physician's Kit (500 vials & Cytobrush/spatula collection devices)	Hologic 70136-001 Hologic 70136-002
SurePath™ GYN Preservative Vial Kit BD SurePath™ Collection Vial Kit (500 vials) BD SurePath™ Collection Vial Kit (25 vials)	Becton, Dickinson 490522, 490527 Becton, Dickinson 491253 Becton, Dickinson 491324
Cervical Collection Brush – 20 Bags, 25 Brushes each (500/Box) Cervical Collection Brush – sterilized & single packed (100/box)	08399832190 08779040190
Rovers® Cervex-Brush® Combi (500/Box)	VWR 89171-022
Cytobrush Plus GT - 25 Bags, 100 Brushes each (2,500/Box) Cytobrush Plus GT – 2 Bags, 500 Brushes each (1,000/Box) Cytobrush Plus GT – 10 Bags, 10 Brushes each (100/Box) Cytobrush Plus GT Sterile – 1 Brush per Pouch (40/Box) Cytobrush Plus GT Scored – 25 Bags, 100 Brushes each (2,500/Box) Pap-Perfect Plastic Spatulas (500/Box)	Medscand C0105 Medscand C0121 Medscand C0104 Medscand C0112 Medscand C0305 Medscand 11080
Copan FLOQSwabs® for vaginal self-collection, #552C.80 and Sample suspension instructions for Copan FLOQSwabs® for vaginal self-collection (552C.80)	09032932190 and 09652671001
Rovers Evalyn® Brush and Sample suspension instructions for Rovers Evalyn® Brush	09032959190 and 09907238001

Refer to the **cobas**® 5800 system or **cobas**® 6800/8800 systems User Assistance and/or User Guides for additional information for primary and secondary sample tubes accepted on the instruments.

Note: Contact your local Roche representative for a detailed order list for sample racks, racks for clotted tips and rack trays accepted on the instruments.

Additional materials for preparation of specimens

Table 14 Specimen preparation materials used with **cobas®** HPV

Material	P/N
cobas® Sample Prep Buffer (CSPB)*	06526985190
cobas® Secondary Tube Kit	07958048190
cobas® Replacement Cap Kit (for **cobas®** Secondary Tubes)	07958056190
Roche Cell Collection Medium Replacement Caps (loose, 250/bag)	08037230190 (optional)
42mm Replacement Caps for Vials (8 trays of 48/box)	07682247001 (optional)
Heat-resistant barcode labels	RACO Industries, RAC-225075-9501
Vortex Mixer (single tube)	Any vendor
Thermometer -20/150ºC	VWR 89095-600 or equivalent
Digital Heater Block 120V	VWR 75838-294 or equivalent
12-Hole Heat Block Module 16mm	VWR 13259-162 or equivalent
MPA RACK 16 MM LIGHT GREEN 7001-7050[a,b,c]	03143449001
RD5 RACK – RD Standard rack 0001-0050 LR[a,b,c]	11902997001

*An open bottle of **cobas®** Sample Prep Buffer (CSPB) may be stored at ambient temperature (15-30°C) for up to 21 days and up to 4 separate uses for the pre-analytic treatment of SurePath™ samples.

[a] RD5 or MPA racks are required in combination with the 5-position Rack Carrier on the **cobas®** 5800 system.

[b] MPA 16mm rack or 16-position tube carrier are the preferred racks for use with samples collected in **cobas®** Secondary Tubes.

[c] MPA or RD5 racks identified are example materials and part numbers. Please contact your local Roche representative for a detailed order list for sample racks and rack carriers accepted on the instruments.

Precautions and handling requirements

Warnings and precautions

As with any test procedure, good laboratory practice is essential to the proper performance of this assay. Due to the high sensitivity of this test, care should be taken to keep reagents and amplification mixtures free of contamination.

- For in vitro diagnostic use only.
- Self-collected vaginal specimens must be suspended in Roche Cell Collection Medium or PreservCyt® Solution after the sample is collected.
- False negative or invalid results may occur with self-collected samples if samples are not suspended in medium after collection.
- All patient samples should be handled as if infectious, using good laboratory procedures as outlined in Biosafety in Microbiological and Biomedical Laboratories[25] and in the CLSI Document M29-A4.[26] Only personnel proficient in handling infectious materials and the use of **cobas**® HPV and **cobas**® 5800 system or **cobas**® 6800/8800 systems should perform this procedure.
- All human-sourced materials should be considered potentially infectious and should be handled with universal precautions. If spillage occurs, immediately disinfect with a freshly prepared solution of 0.5% sodium or potassium hypochlorite in distilled or deionized water or follow appropriate site procedures.
- Do not freeze any samples stored in primary or secondary tubes.
- Use only supplied or specified required consumables to ensure established test performance.
- Safety Data Sheets (SDS) are available on request from your local Roche representative.
- Closely follow procedures and guidelines provided to ensure that the test is performed correctly. Any deviation from the procedures and guidelines may affect established test performance.
- False positive results may occur if carryover of samples is not adequately controlled during sample handling and processing.
- Inform your local competent authority and manufacturer about any serious incidents which may occur when using this assay.

Reagent handling

- Handle all reagents, controls, and samples according to good laboratory practice in order to prevent carryover of samples, reagents, or controls.
- Before use, visually inspect each reagent cassette, diluent, lysis reagent, and wash reagent to ensure that there are no signs of leakage. If there is any evidence of leakage, do not use that material for testing.
- **cobas**® **omni** Lysis Reagent contains guanidine thiocyanate, a potentially hazardous chemical. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, burns can occur.
- Do not allow **cobas**® **omni** Lysis Reagent, which contains guanidine thiocyanate, to contact sodium or potassium hypochlorite solution. This mixture can produce a highly toxic gas.
- Expended control kits contain pierced vials with residual reagent; special care should be taken during disposal to avoid spills and contact.

- **cobas**® HPV, **cobas**® HPV Positive Control Kit, **cobas**® Negative Control Kit, **cobas**® **omni** MGP Reagent, and **cobas**® **omni** Specimen Diluent contain sodium azide as a preservative. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, burns can occur. If these reagents are spilled, dilute with water before wiping dry. Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. If disposing of sodium azide containing solutions down laboratory sinks, flush the drains with a large volume of cold water to prevent azide buildup.
- Dispose of all materials that have come in contact with samples and reagents in accordance with country, state, and local regulations.

Good laboratory practice

- Do not pipette by mouth.
- Do not eat, drink, or smoke in designated work areas.
- Wear laboratory gloves, laboratory coats, and eye protection when handling samples and reagents. Avoid contaminating gloves when handling samples and controls. Gloves must be changed between handling samples and **cobas**® HPV, **cobas**® HPV Positive Control Kit, **cobas**® Buffer Negative Control Kit and **cobas**® **omni** reagents to prevent contamination.
- Wash hands thoroughly after handling samples and reagents, and after removing the gloves.
- Thoroughly clean and disinfect all laboratory work surfaces with a freshly prepared solution of 0.5% sodium or potassium hypochlorite in distilled or deionized water. Follow by wiping the surface with 70% ethanol.
- If spills occur on the **cobas**® 5800 instrument or **cobas**® 6800/8800 instruments, follow the instructions in the **cobas**® 5800 system or **cobas**® 6800/8800 systems User Assistance to properly clean and decontaminate the surface of instrument(s).

Specimen collection, transport, and storage

Note: Handle all samples and controls as if they are capable of transmitting infectious agents.

Specimen collection

Cervical specimens collected in Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid have been validated for use with **cobas**® HPV.

Vaginal specimens collected with *FLOQSwabs® for vaginal self-collection* and suspended in Roche Cell Collection Medium and PreservCyt® Solution have been validated for use with **cobas**® HPV.

Vaginal specimens collected with Evalyn® Brush and suspended in Roche Cell Collection Medium and PreservCyt® Solution have been validated for use with **cobas**® HPV.

Follow the manufacturer's instructions for collecting specimens.

Specimen transport

Specimens collected in Roche Cell Collection Medium, PreservCyt® Solution or SurePath™ Preservative Fluid can be transported at 2-30°C. Transportation of HPV specimens must comply with country, federal, state and local regulations for the transport of etiologic agents.[27]

Specimen storage

Specimens collected in Roche Cell Collection Medium and PreservCyt® Solution may be stored at 2-30°C for up to 3 months after the date of collection prior to performing **cobas**® HPV. See Roche Cell Collection Medium labeling for medium storage requirements. See PreservCyt® Solution labeling for medium storage requirements. Roche Cell Collection Medium and PreservCyt® specimens should not be frozen.

SurePath™ Preservative Fluid matrix-induced cross-links are reversed through treatment with **cobas**® Sample Prep Buffer (CSPB) prior to HPV testing. The pre-analytic treatment is a mandatory step for all cervical specimens collected in SurePath™ prior to testing with **cobas**® HPV. SurePath™ specimens should not be frozen.

Primary vials of cervical specimens collected in SurePath™ Preservative Fluid may be stored at 2-8 °C for up to 3 months or for up to 6 weeks at 15-30°C after the date of collection. If desired, SurePath™ specimens may be mixed with **cobas**® Sample Prep Buffer in a secondary tube and stored at 2-30°C for up to 6 weeks before completing the heat step as described in the "Specimens in SurePath™ Preservative Fluid" section. Alternatively, SurePath™ specimens may be stored at 2-30°C for up to 6 weeks after samples are pre-treated [as described in the "Specimens in SurePath™ Preservative Fluid" section] and prior to HPV testing.

Table 15 summarizes the acceptable specimen storage conditions prior to testing with **cobas**® HPV.

Table 15 Summary of acceptable specimen storage conditions prior to testing with **cobas**® HPV

Specimen Type		2-8°C	15-30°C
Roche Cell Collection Medium and PreservCyt®		3 months	3 months
SurePath™*	Storage of primary vial sample prior to pre-analytic treatment	3 months	6 weeks
	or		
	Storage of sample mixed with CSPB prior to heat step	6 weeks	6 weeks
	or		
	Storage of treated sample	6 weeks	6 weeks

*An open bottle of **cobas**® Sample Prep Buffer (CSPB) may be stored at ambient temperature (15-30°C) for up to 21 days and up to 4 separate uses for the pre-analytic treatment of SurePath™ samples.

Instructions for use

Suspension of self-collected specimen

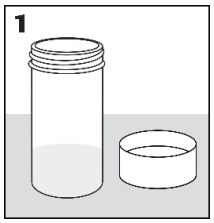
Sample suspension instructions for Copan *FLOQSwabs® for vaginal self-collection* (552C.80)

Sample handling instructions for self-collected sample using Copan FLOQSwabs® for vaginal self-collection (552C.80) for testing with the **cobas**® 4800 HPV Test or **cobas**® HPV.

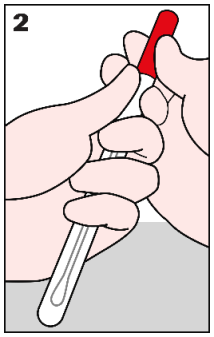
Self-collected sample must be placed into medium after sample has been collected.

- **Read all instructions before starting sample suspension.**
- For sample collection, follow the collection device manufacturer's Instructions for use.
- Once the sample has been collected, continue with the following instructions to preserve the sample:

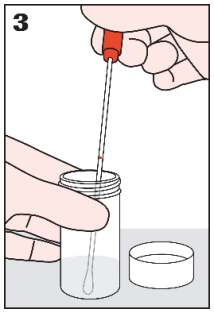
Handle the collected sample with care.



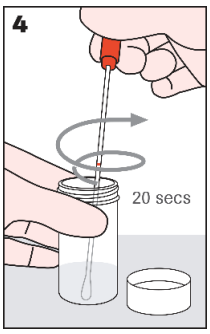
1. Carefully uncap the vial containing medium and place it on a stable, flat surface.



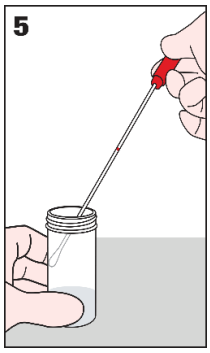
2. Slowly pull the FLOQSwab cap off to remove the swab from the tube. **Minimize touching the inner walls of the tube as you remove the FLOQSwab.**



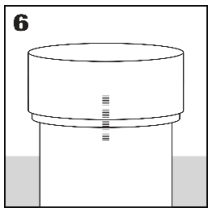
3. Hold the vial with one hand then with the other hand place the FLOQSwab tip into the vial until the FLOQSwab **tip is fully immersed in the medium** and **touching the bottom** of the vial**.**



4. Holding onto the vial**, swirl the FLOQSwab along the inner vial wall** for **20 seconds** while **ensuring the swab remains immersed** in the medium. Be careful not to splash.



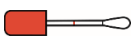
5. Carefully draw the FLOQSwab up along the inner vial wall until the tip is no longer immersed in the medium. **Hold the tip against the inner vial wall to drain fluid** off of the swab. Place the FLOQSwab into the tube and discard.



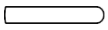
6. Re-cap the vial and tighten until **the lines on the cap and vial meet or slightly overlap** to prevent leakage. Store upright.

7. The sample can now be processed with the **cobas**® 4800 HPV Test or **cobas**® HPV**.**

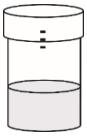
Glossary



FLOQSwab/Swab: The self–collection device used to collect sample.



Tube: A protective container that the self-collected device will come in and can be used to temporarily store the collection device after the sample has been collected.



Vial: A container which contains 20 mL of clear solution. The specimen you collect will need to be transferred into this container and this container will be sent to the lab for processing.

Medium: What the liquid that comes in the vial is called.

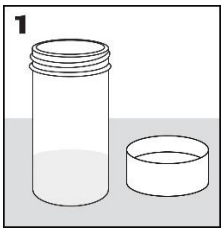
Sample suspension instructions for Rovers Evalyn® Brush

Sample handling instructions for self-collected sample using Rovers Evalyn® Brush for testing with the **cobas®** 4800 HPV Test or **cobas®** HPV.

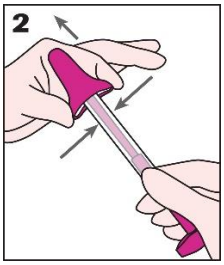
Self-collected sample must be placed into medium after sample has been collected.

- **Read all instructions before starting sample suspension.**
- For sample collection, follow the collection device manufacturer's Instructions for use.
- Once the sample has been collected, continue with the following instructions to preserve the sample:

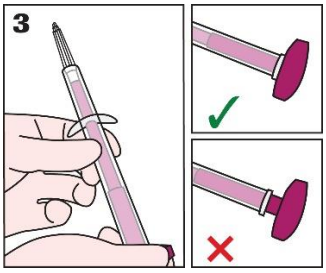
Handle the collected sample with care.



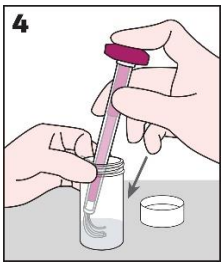
1. Carefully uncap the vial containing medium and place it on a stable, flat surface.



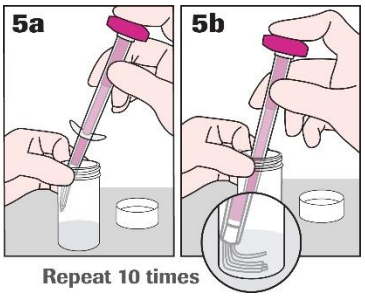
2. Remove the pink cap from the Evalyn Brush **taking care not to touch the exposed end**.



3. Press the pink plunger down until it clicks into place to expose the white brush. **Take care to keep the exposed brush from touching anything** (e.g., fingers, surfaces).

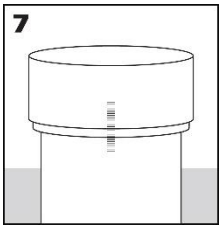


4. Hold the vial with one hand then with the other hand place the white brush into the vial so that the **bristles are fully immersed in the medium and the wings are past the opening of the vial**.



5. Holding onto the vial, vigorously plunge the brush, **smashing** the white brush **against the bottom and interior wall** of the vial **10 times to maximize sample release**. Be careful not to splash.

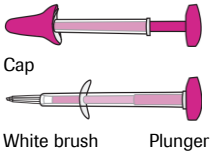
6. Remove the white brush by carefully drawing the brush up along the inner wall of the primary vial until the brush is no longer submerged in the medium. **Hold the brush against the inner vial wall to drain fluid** off the brush. Place the Evalyn brush back inside the packaging and discard.



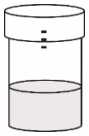
7. Re-cap the vial and tighten until **the lines on the cap and vial meet or slightly overlap** to prevent leakage. Store upright.

8. The sample can now be processed with the **cobas®** 4800 HPV Test or **cobas®** HPV.

Glossary



Evalyn Brush: The self collection device used to collect sample.



Vial: A container which contains 20 mL of clear solution. The specimen you collect will need to be transferred into this container and this container will be sent to the lab for processing.

Medium: What the liquid that comes in the vial is called.

Specimens in Roche Cell Collection Medium or PreservCyt® Solution

cobas® 5800 system

- The **cobas**® 5800 system may process specimens in Roche Cell Collection Medium and PreservCyt® Solution directly out of their primary containers with a proper barcode or out of a properly barcoded **cobas**® Secondary Tube (see **cobas**® 5800/6800/8800 system section below for optional aliquoting instructions for the **cobas**® 5800 system).
    1. With clean gloved hands, **vortex** the capped primary vial for **10 seconds** immediately prior to loading.
    2. Uncap the primary vial and place on a Cell Collection Media Carrier.
- For primary vial loading, the minimum volume required in the primary containers is 3.0 mL.

cobas® 5800/6800/8800 systems

- Specimens in Roche Cell Collection Medium or PreservCyt® Solution should be aliquoted into **cobas**® Secondary Tubes as follows, for processing on the **cobas**® 5800 system or **cobas**® 6800/8800 systems:
    1. Prepare a barcoded 13 mL **cobas**® Secondary Tube for each Roche Cell Collection Medium or PreservCyt® specimen to be tested.
    2. With clean gloved hands, **vortex** each Roche Cell Collection Medium or PreservCyt® primary specimen vial for **10 seconds** immediately prior to transfer.
    3. Uncap a primary vial and transfer at least **1.0 mL** but no more than **4.0 mL** into the prepared barcoded secondary tube from step 1. *Always use caution when transferring specimens from primary containers to secondary tube. Always use a new pipette tip for each specimen*. Transfer tube to a rack (or cap the **cobas**® Secondary Tube if testing will be performed at a future time).
    4. Re-cap the primary vial with a replacement cap before moving to the next specimen. Store the primary vial upright.
    5. Load the racks of uncapped secondary tubes onto **cobas**® 5800 system or **cobas**® 6800/8800 systems for HPV testing.

Specimens in SurePath™ Preservative Fluid

cobas® 5800/6800/8800 systems

- Specimens in SurePath™ must undergo the pre-analytic treatment described below prior to testing with **cobas**® HPV.
    1. Prepare a barcoded* 13 mL **cobas**® Secondary Tube for each SurePath™ specimen to be tested and aliquot **0.5 mL** of **cobas**® Sample Prep Buffer (CSPB) into each secondary tube.
    2. With clean gloved hands, vortex each SurePath™ primary specimen vial for **10 seconds** immediately prior to transfer.
    3. Uncap a primary vial and transfer **0.5 mL** of SurePath™ specimen into the prepared barcoded **cobas**® Secondary Tube from step 1. *Always use caution when transferring specimens from primary containers to secondary tube. Always use a new pipette tip for each specimen.*
    4. Cap the secondary tube and re-cap the primary vial with a replacement cap before moving to the next specimen. Store the primary vial upright.
    5. Vortex each secondary tube for **1 second**.
    6. Transfer tubes to the heating unit set to **95°C** and incubate for **20 minutes**.
    7. Remove tubes to a collection rack and cool at ambient temperature for **10 minutes**. *Use caution as the secondary tubes may be hot.*
    8. Vortex each secondary tube for **5 seconds**.
    9. Uncap tubes, discard caps, transfer to racks and process on the **cobas**® 5800 system or **cobas**® 6800/8800 systems for HPV testing.
    10. SurePath™ specimens treated with **cobas**® Sample Prep Buffer can be stored for future HPV testing if needed. After following the above procedure up to step 7, store the tubes with SurePath™ specimens treated with **cobas**® Sample Prep Buffer at 2-30°C for up to 6 weeks prior to HPV testing.

**Heat-resistant barcode labels are required for tubes used with the heat step to reverse matrix-induced cross-links.*

See "Additional materials for preparation of specimens" section for recommended product numbers.

Procedural notes

- Do not use **cobas**® HPV, **cobas**® HPV Positive Control Kit, **cobas**® Buffer Negative Control Kit, or **cobas**® **omni** reagents after their expiry dates.
- Do not reuse consumables. They are for one-time use only.
- Ensure that specimen barcode labels on sample tubes are visible through the openings on the side of the sample racks. Refer to the **cobas**® 5800 system or **cobas**® 6800/8800 systems User Assistance for proper barcode specifications and additional information on loading sample tubes.
- Refer to the **cobas**® 5800 system or **cobas**® 6800/8800 systems User Assistance for proper maintenance of instruments.

Running cobas® HPV on the cobas® 5800 system

cobas® HPV can be run on the **cobas**® 5800 with a minimum required sample volume of 3.0 mL for Roche Cell Collection Medium and PreservCyt® specimens from the primary vial. Aliquots of Roche Cell Collection Medium and PreservCyt® specimens in **cobas**® Secondary Tubes may be run with a minimum required volume of 1.0 mL. SurePath™ specimens that have undergone the pre-analytic procedure in a **cobas**® Secondary Tube will have a volume of 1.0mL. The pre-analytic procedure for SurePath™ specimens is described in the "Specimens in SurePath™ Preservative Fluid" section. The operation of the instrument is described in detail in the **cobas**® 5800 system User Assistance. Figure 1 summarizes the procedure.

- Roche Cell Collection Medium and PreservCyt® specimens may be run from primary vials. Vortex each specimen for 10 seconds immediately prior to loading.

  Note: Use slow and steady movements when loading and unloading the Collection Medium Container Carrier (holding the primary vials) to avoid splashing of specimens.

- Optionally, specimens may be aliquoted into barcoded 13 mL **cobas**® Secondary Tubes for processing on the **cobas**® 5800 system. Use pipettes with aerosol-barrier or positive-displacement tips to handle specimens.
- A single run can have any combination of specimens (Roche Cell Collection Medium, PreservCyt® Solution and/or SurePath™ Preservative Fluid) and specimen containers (Primary or secondary) and each specimen can be tested with either the HPV High Risk (HPV-HR) or HPV High Risk Plus Genotyping (HPV-GT) ASAPs.
- Specimens should be processed using the sample type selection in the user interface (UI) of **cobas**® HPV as described in Table 16.
- Heat-resistant barcode labels are required for tubes used for specimens collected in SurePath™ Preservative Fluid.
- Test orders may be annotated using the instrument software. Refer to the **cobas**® 5800 system User Assistance for annotation instructions.

Table 16 Sample type selection for **cobas**® HPV on **cobas**® 5800 system

Specimen	Collection medium	Supported Container		Process as Sample Type
		Primary vial	Secondary tube	
Cervical specimen	Roche Cell Collection Medium	Yes	Yes	Roche Cell Collection Medium
Cervical specimen	PreservCyt® Solution (ThinPrep)	Yes	Yes	PreservCyt®
Cervical specimen	SurePath™ Preservative Fluid	No	Yes	SurePath™
Self-collected vaginal specimen	Roche Cell Collection Medium	Yes	Yes	Self, vaginal – RCCM/PC
Self-collected vaginal specimen	PreservCyt® Solution (ThinPrep)	Yes	Yes	Self, vaginal – RCCM/PC

Figure 1 **cobas**® HPV test procedure on the **cobas**® 5800 system

1

Log onto the system

2

Refill reagents and consumables as prompted by the system

- Load test specific reagent cassette(s)
- Load control mini racks
- Load processing tips
- Load elution tips
- Load processing plates
- Load amplification plates
- Load liquid waste plates
- Load MGP Reagent
- Refill Specimen Diluent
- Refill Lysis Reagent
- Refill Wash Reagent

3

Loading specimens onto the system

- For each Roche Cell Collection Medium or PreservCyt® specimen vial:
  - Vortex primary vial for 10 seconds immediately prior to loading onto the sample rack
    or
  - Process in a **cobas**® Secondary Tube by:
    - Vortex primary vial for 10 seconds
    - Aliquot a minimum of 1 mL of Roche Cell Collection Medium or PreservCyt® specimen into a 13mL **cobas**® Secondary Tube
    - Transfer tube to sample rack
- For each primary SurePath™ specimen vial:
  - Aliquot 0.5 mL of CSPB into a 13mL **cobas**® Secondary Tube
  - Vortex primary SurePath™ specimen vial for 10 seconds
  - Aliquot 0.5 mL of SurePath™ specimen into the prepared secondary tube containing 0.5 mL of CSPB and cap tightly
  - Vortex each tube for 1 second
  - Transfer tubes to a heating unit set to 95°C and incubate for 20 minutes
  - Remove tubes to a collection rack and cool at ambient temperature for 10 minutes
  - Vortex each tube for 5 seconds
  - Un-cap tube and transfer to rack
- Load sample racks onto the system

Confirm samples have been accepted into the system

The system prepares automatically

Order Tests

- Choose “Roche Cell Collection Medium” for ordering Roche Cell Collection Medium specimens
- Choose “PreservCyt®” for ordering PreservCyt® Solution specimen
- Choose “SurePath™” for ordering SurePath™ Preservative Fluid specimens that have undergone the defined pre-analytic procedure
- Choose “Self, vaginal – RCCM/PC” for ordering self-collected vaginal specimens

Choose the Test name

4

Start the run by choosing the Start processing button on the user interface, all subsequent runs will start automatically if not manually postponed

5

Review and export results

6

Remove sample tubes. If needed, cap any sample tubes meeting the minimum volume requirements for future use.

Clean up instrument

- Unload empty control mini racks
- Unload empty test specific reagent cassette(s)
- Empty amplification plate drawer
- Empty liquid waste

Empty solid waste

Running cobas® HPV on the cobas® 6800/8800 systems

cobas® HPV can be run with a minimum required sample volume of 1.0 mL for Roche Cell Collection Medium and PreservCyt® specimens as well as for SurePath™ specimens that have undergone the pre-analytic procedure. The pre-analytic procedure is described on the following page. The operation of the instrument is described in detail in the **cobas**® 6800/8800 systems User's Guide. Figure 2 summarizes the procedure.

- It is necessary to aliquot specimens into barcoded 13 mL **cobas**® Secondary Tubes for processing on the **cobas**® 6800/8800 systems. Use pipettes with aerosol-barrier or positive-displacement tips to handle specimens.
- A single run can have any combination of specimens (Roche Cell Collection Medium, PreservCyt® Solution and/or SurePath™ Preservative Fluid) and each specimen can be tested with either the HPV High Risk (HPV-HR) or HPV High Risk Plus Genotyping (HPV-GT) ASAPs.
- Specimens should be processed using the sample type selection in the user interface (UI) of **cobas**® HPV as described in Table 17.
- Heat-resistant barcode labels are required for tubes used for specimens collected in SurePath™ Preservative Fluid.
- Test orders may be annotated using the instrument software. Refer to the **cobas**® 6800/8800 systems User's Guide for annotation instructions.

Table 17 Sample type selection in the user interface of **cobas**® HPV

Specimen	Collection medium	Process as Sample Type
Cervical specimen	Roche Cell Collection Medium	Roche Cell Collection Medium (on SW2.0) RCCM (on SW1.4)
Cervical specimen	PreservCyt® Solution (ThinPrep)	PreservCyt®
Cervical specimen	SurePath™ Preservative Fluid	SurePath™
Self-collected vaginal specimen	Roche Cell Collection Medium	Self, vaginal – RCCM/PC
Self-collected vaginal specimen	PreservCyt® Solution (ThinPrep)	Self, vaginal – RCCM/PC

Figure 2 cobas® HPV test procedure on the **cobas®** 6800/8800 systems

1	Log onto the system Press Start to Prepare the system Order Tests • Choose “RCCM” for ordering Roche Cell Collection Medium specimens • Choose “PreservCyt” for ordering PreservCyt® Solution specimen • Choose “Surepath” for ordering SurePath™ Preservative Fluid specimens that have undergone the defined pre-analytic procedure • Choose “Self, vaginal – RCCM/PC” for ordering self-collected vaginal specimens
2	Refill reagents and consumables as prompted by the system • Load test specific reagent cassette • Load control cassettes • Load pipette tips • Load processing plates • Load MGP Reagent • Load amplification plates • Refill Specimen Diluent • Refill Lysis Reagent • Refill Wash Reagent
3	Loading specimens onto the system • For each primary Roche Cell Collection Medium or PreservCyt® specimen vial: o Vortex for 10 seconds o Aliquot a minimum of 1 mL of Roche Cell Collection Medium or PreservCyt® specimen into a 13 mL **cobas®** Secondary Tube o Transfer tube to rack • For each primary SurePath™ specimen vial: o Aliquot 0.5 mL of CSPB into a 13 mL **cobas®** Secondary Tube o Vortex primary SurePath™ specimen vial for 10 seconds o Aliquot 0.5 mL of SurePath™ specimen into the prepared secondary tube containing 0.5 mL of CSPB and cap tightly o Vortex each tube for 1 second o Transfer tubes to a heating unit set to 95°C and incubate for 20 minutes o Remove tubes to a collection rack and cool at ambient temperature for 10 minutes o Vortex each tube for 5 seconds o Un-cap tube and transfer to rack • Load sample rack and clotted tip racks into the sample supply module • Confirm samples have been accepted into the transfer module
4	Start run
5	Review and export results
6	Remove sample tubes. If needed, cap any sample tubes meeting the minimum volume requirements for future use. Clean up instrument • Unload empty control cassettes • Empty amplification plate drawer • Empty liquid waste • Empty solid waste

Results

cobas® HPV automatically detects and discriminates 14 high risk HPV genotypes (HPV-HR) and/or 12 high risk genotypes with individual typing of HPV 16 and HPV 18 simultaneously (HPV-GT)

Quality control and validity of results on cobas® 5800 system and cobas® 6800/8800 systems with software version 2.0 or higher

- One **cobas**® Buffer Negative Control [(-) Ctrl] and one **cobas**® HPV Positive Control [HPV (+) C] must be processed at least every 72 hours or with every new kit lot. Positive and/or negative controls can be scheduled more frequently based on laboratory procedures and/or local regulations.
- The results of the controls are shown in the "Controls" app.
- In the software and/or report, check for flags to ensure the validity of the corresponding test results (Refer to the x800 Data Manager User Assistance for a 'List of flag codes').
- The controls are valid if no flags appear for either control.
- Controls are marked with 'Valid' in the "Control result" column if the respective targets of the control are reported valid. Controls are marked with 'Invalid' in the "Control result" column if the respective targets of the control are reported invalid.
- Controls marked with 'Invalid' show a flag in the "Flags" column. More information on why the control is reported invalid including flag information will be shown in the detail view.
- If one of the controls is invalid, repeat testing of all controls and all associated samples is required. Validation of results is performed automatically by the instrument software based on control results.

NOTE: The **cobas**® 5800 system and the **cobas**® 6800/8800 systems with software version 2.0 will be delivered with the standard setting of running a set of controls (positive and negative) with every run, but can be configured to a less frequent scheduling up to every 72 hours based on laboratory procedures and/or local regulations. Please contact your Roche service engineer or Roche customer technical support for more information.

Quality control and validity of results on cobas® 6800/8800 systems with software version 1.4

- One **cobas**® Buffer Negative Control [(–) Ctrl] and one **cobas**® HPV Positive Control [HPV (+) C] are processed with each batch of a requested result type (HPV-HR or HPV-GT).
- In the software and/or report, check for flags and their associated results to ensure batch validity.
- All flags are described in the **cobas**® 6800/8800 systems User Assistance.
- The batch is valid if no flags appear for all controls. If the batch is invalid, repeat testing of the entire batch.

Validation of results is performed automatically by the **cobas**® 6800/8800 systems software based on control results.

Interpretation of results on the cobas® 5800 system and cobas® 6800/8800 systems with software version 2.0 or higher

The results of the samples are shown in the "Results" app of the software. Display examples are shown in Figure 3 and Figure 4.

Figure 3 Example of **cobas**® HPV results display for the HPV-HR results request on **cobas**® 5800 system and **cobas**® 6800/8800 systems with software version 2.0 or higher

Sample ID	Test	Control results	Flag	Status	Result	Creation date/time
PC_HPVHRinv_01	HPV-HR	Valid	⚑	Released	HR HPV Invalid	
PC_HPVHRneg_01	HPV-HR	Valid		Released	HR HPV Negative	
RCCM_HPVHRpos_01	HPV-HR	Valid		Released	HR HPV Positive (Ct 36.52)	
SP_HPVHRneg_01	HPV-HR	Valid		Released	HR HPV Negative	
SP_HPVHRpos_01	HPV-HR	Valid		Released	HR HPV Positive (Ct 35.44)	
SC_RCCM_HPVHRpos_02	HPV-HR	Valid		Released	HR HPV Positive (Ct 34.61)	
SC_PC_HPVHRpos_02	HPV-HR	Valid		Released	HR HPV Negative	

Note: Figure applies for all sample types. The result overview shows a flag symbol in case of invalid results. Detailed flag descriptions are available in the result details.

Figure 4 Example of **cobas**® HPV results display for the HPV-GT results request on **cobas**® 5800 system and **cobas**® 6800/8800 systems with software version 2.0 or higher

Sample ID	Test	Control results	Flag	Status	Result	Creation date/time
RCCM_HPVGTneg_03	HPV-GT	Valid		Released	Other HR Negative HPV 16 Negative HPV 18 Negative	
RCCM_HPVGTpos_05	HPV-GT	Valid		Released	Other HR Positive (Ct 33.43) HPV 16 Negative HPV 18 Positive (Ct 32.54)	
SP_HPVGTpos_03	HPV-GT	Valid		Released	Other HR Negative HPV 16 Positive (Ct 35.21) HPV 18 Negative	
SP_HPVGTneg_04	HPV-GT	Valid		Released	Other HR Negative HPV 16 Negative HPV 18 Negative	
PC_HPVGTinv_01	HPV-GT	Valid	⚑	Released	Other HR Invalid HPV 16 Invalid HPV 18 Invalid	
SC_RCCM_HPVGTneg_02	HPV-GT	Valid		Released	Other HR Negative HPV 16 Negative HPV 18 Negative	
SC_PC_HPVGTpos_01	HPV-GT	Valid		Released	Other HR Negative HPV 16 Negative HPV 18 Positive (Ct 33.63)	

Note: Figure applies for all sample types. The result overview shows a flag symbol in case of invalid results. Detailed flag descriptions are available in the result details.

Check each individual sample for flags in the software and/or report. The result interpretation should be as follows:

- Samples associated with valid controls are shown as 'Valid' in the "Control result" column.
- Samples associated with a failed control are shown as 'Invalid' in the "Control result" column.
- If the associated controls of a sample result are invalid, a specific flag will be added to the sample result as follows:
- Q05D : Result validation failure because of an invalid positive control
- Q06D :Result validation failure because of an invalid negative control
- The values in "Results" column for individual sample target result should be interpreted as show in Table 18 and Table 19.

- If one or more sample targets are marked with 'Invalid' the software shows a flag in the "Flags" column. More information on why the sample target(s) is reported invalid including flag information is shown in the detail view.
- Invalid results for one or more target combinations are possible with the HPV-GT result request and are reported out specifically for each target. Refer to retesting instructions for the respective specimen type below.
- Results of this test should only be interpreted in conjunction with information available from clinical evaluation of the patient and patient history.
- For invalid target results from Roche Cell Collection Medium or PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For invalid target results from SurePath™ specimens the original specimen should be retested if there is sufficient volume. If the results are still invalid a new specimen should be obtained.

Interpretation of results on the cobas® 6800/8800 systems with software version1.4 or higher

Display examples for **cobas**® HPV for **cobas**® 6800/8800 systems with software version 1.4 or higher are shown in Figure 5 and Figure 6.

Figure 5 Example of **cobas**® HPV result display for the HPV-HR results request for **cobas**® 6800/8800 systems with software version 1.4 or higher

Test	Sample ID	Valid	Flags	Sample type	Overall result	Target 1	Target 2	Target 3
HPV-HR	C161420284084194727902	Yes		HPV (+) C	Valid	Valid		
HPV-HR	C161420284090428825772	Yes		(-) Ctrl	Valid	Valid		
HPV-HR	PC_HPVHRinv_01	NA	Y40T	PreservCyt®	NA	Invalid		
HPV-HR	PC_HPVHRneg_01	NA		PreservCyt®	NA	HR HPV Negative		
HPV-HR	RCCM_HPVHRneg_02	NA		RCCM	NA	HR HPV Negative		
HPV-HR	RCCM _HPVHRneg_03	NA		RCCM	NA	HR HPV Negative		
HPV-HR	RCCM_HPVHRpos_01	NA		RCCM	NA	HR HPV Positive		
HPV-HR	SC_RCCM_HPVHRpos_01	NA		Self, vaginal – RCCM/PC	NA	HR HPV Positive		
HPV-HR	SC_PC_HPVHRpos_01	NA		Self, vaginal – RCCM/PC	NA	HR HPV Positive		
HPV-HR	SP_HPVHRinv_01	NA	Y40T	Surepath™	NA	Invalid		
HPV-HR	SP_HPVHRneg_01	NA		Surepath™	NA	HR HPV Negative		

Note: The Target 2 and Target 3 columns are reserved for HPV16 and HPV 18 results with HPV-GT request, respectively.

Figure 6 Example of **cobas**® HPV result display for the HPV-GT results request for **cobas**® 6800/8800 systems with software version 1.4 or higher

Test	Sample ID	Valid	Flags	Sample type	Overall result	Target 1	Target 2	Target 3
HPV-GT	RCCM_HPVGTpos_02	NA		RCCM	NA	Other HR HPV Negative	HPV 16 Negative	HPV 18 Positive
HPV-GT	RCCM_HPVGTpos_01	NA		RCCM	NA	Other HR HPV Negative	HPV 16 Positive	HPV 18 Positive
HPV-GT	RCCM_HPVGTpos_04	NA		RCCM	NA	Other HR HPV Positive	HPV 16 Negative	HPV 18 Positive
HPV-GT	SC_RCCM_HPVGTpos_03	NA		Self, vaginal – RCCM/PC	NA	Other HR HPV Positive	HPV 16 Negative	HPV 18 Negative
HPV-GT	SC_PC_HPVGTpos_05	NA		Self, vaginal – RCCM/PC	NA	Other HR HPV Positive	HPV 16 Positive	HPV 18 Negative
HPV-GT	SP_HPVGTpos_06	NA		Surepath™	NA	Other HR HPV Positive	HPV 16 Positive	HPV 18 Positive
HPV-GT	SP_HPVGTpos_02	NA		Surepath™	NA	Other HR HPV Negative	HPV 16 Negative	HPV 18 Positive
HPV-GT	PC_HPVGTneg_01	NA		PreservCyt®	NA	Other HR HPV Negative	HPV 16 Negative	HPV 18 Negative
HPV-GT	PC_HPVGTpos_06	NA	C02H1	PreservCyt®	NA	Invalid	HPV 16 Positive	HPV 18 Positive
HPV-GT	PC_HPVGTpos_03	NA	C02H1	PreservCyt®	NA	Invalid	HPV 16 Positive	Invalid
HPV-GT	C161420284090390657451	Yes		HPV (+) C	Valid	Valid	Valid	Valid
HPV-GT	C161420284090419645071	Yes		(-) Ctrl	Valid	Valid	Valid	Valid

For a valid batch, check each individual sample for flags in the **cobas**® 6800/8800 systems with software version 1.4 and/or report. The result interpretation should be as follows:

- A valid batch may include both valid and invalid sample results.
- The "Valid" and "Overall Result" columns are not applicable (NA) to sample results for **cobas**® HPV and are marked with "NA". Values reported in these columns **do not** impact the validity of results reported within individual target result columns.
- Reported target results for individual samples are valid unless indicated as "Invalid" within the individual target result column.
- Invalid results for one or more target combinations are possible with the HPV-GT result request and are reported out specifically for each target. Refer to retesting instructions for the respective specimen type below.
- For invalid target results from Roche Cell Collection Medium or PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For invalid target results from SurePath™ specimens the original specimen should be retested if there is sufficient volume. If the results are still invalid a new specimen should be obtained.

Interpretation of results for cobas® 5800/6800/8800 systems

Results and their corresponding interpretation for detecting HR HPV only (Table 18) and Other HR HPV, HPV 16 and HPV 18 (Table 19) are shown below.

Table 18 cobas® HPV results and interpretation for the HPV-HR result request

Target 1	Target 2	Target 3	Interpretation
HR HPV Positive	<Blank>	<Blank>	Specimen is positive for the DNA of any one of, or combination of, the following high risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
HR HPV Negative			HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold.
HR HPV Invalid/Invalid			The result for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 is invalid.

Table 19 cobas® HPV results and interpretation for the HPV-GT result request

Target 1	Target 2	Target 3	Interpretation
Other HR HPV Positive	HPV 16 Positive, HPV 16 Negative, or HPV 16 Invalid/Invalid	HPV 18 Positive, HPV 18 Negative, or HPV 18 Invalid/Invalid	Specimen is positive for the DNA of any one of, or combination of the following high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
Other HR HPV Negative			HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were undetectable or below the pre-set threshold.
Other HR HPV Invalid/Invalid			The result for HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 is invalid.
Other HR HPV Positive, Other HR HPV Negative, or Other HR HPV Invalid/Invalid	HPV 16 Positive	HPV 18 Positive, HPV 18 Negative, or HPV 18 Invalid/Invalid	Specimen is positive for HPV type 16 DNA.
	HPV 16 Negative or		HPV type 16 DNA was undetectable or below the pre-set threshold.
	HPV 16 Invalid/Invalid		The result for HPV type 16 is invalid.
Other HR HPV Positive, Other HR HPV Negative, or Other HR HPV Invalid/Invalid	HPV 16 Positive, HPV 16 Negative, or HPV 16 Invalid/Invalid	HPV 18 Positive	Specimen is positive for HPV type 18 DNA.
		HPV 18 Negative	HPV type 18 DNA was undetectable or below the pre-set threshold.
		HPV 18 Invalid/Invalid	The result for HPV type 18 is invalid.

Procedural limitations

- **cobas**® HPV has been evaluated only for use in combination with the **cobas**® HPV Positive Control Kit, **cobas**® Buffer Negative Control Kit, **cobas**® **omni** MGP Reagent, **cobas**® **omni** Lysis Reagent, **cobas**® **omni** Specimen Diluent, and **cobas**® **omni** Wash Reagent for use on the **cobas**® 5800/6800/8800 systems.
- **cobas**® HPV has been validated for use with cervical specimens collected in Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid. Assay performance has not been validated for use with other collection media and/or specimen types. Use of other collection media and/or specimen types may lead to false positive, false negative or invalid results.
- **cobas**® HPV has been validated for testing vaginal specimens collected with *FLOQSwabs® for vaginal collection* and Evalyn Brush® which are then suspended in Roche Cell Collection Medium or PreservCyt® Solution after collection. Assay performance has not been validated for use with other collection media and/or collection devices. Use of other collection media and/or collection devices may lead to false positive, false negative or invalid results.
- **cobas**® HPV has been validated for testing cervical specimens collected in SurePath™ Preservative Fluid treated with **cobas**® Sample Prep Buffer to reverse SurePath™ Preservative Fluid matrix-induced cross-links. Processing SurePath™ specimens without following the pre-treatment protocol with **cobas**® Sample Prep Buffer or pre-treatment with alternate reagents may produce false negative or invalid results.
- **cobas**® HPV detects DNA of the high-risk types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. This test does not detect DNA of HPV low-risk types (e.g. 6, 11, 42, 43, 44) since there is no clinical utility for testing of low-risk HPV types.[18]
- **cobas**® HPV for detection of human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 is not recommended for evaluation of suspected sexual abuse and for other medico-legal indications.
- Detection of high-risk HPV is dependent on the number of copies present in the specimen and may be affected by specimen collection methods, patient factors, stage of infection and the presence of interfering substances.
- Prevalence of HPV infection in a population may affect performance. Positive predictive values decrease when testing populations with low prevalence or individuals with no risk of infection.
- Infection with HPV is not an indicator of cytologic HSIL or underlying high-grade CIN, nor does it imply that CIN2-3 or cancer will develop. Most women infected with one or more high-risk HPV types do not develop CIN2-3 or cancer.
- A negative high-risk HPV result does not exclude the possibility of future cytologic HSIL or underlying CIN2-3 or cancer.
- β-globin amplification and detection is included in **cobas**® HPV to differentiate HPV negative specimens from those that do not exhibit HPV signal due to insufficient cell mass in the specimen. All HPV negative specimens must have a valid β-globin signal within a pre-defined range to be identified as valid negatives.
- Reliable results depend on proper sample collection, storage and handling procedures.
- The addition of AmpErase enzyme into the **cobas**® HPV Master Mix enables selective amplification of target DNA; however, good laboratory practices and careful adherence to the procedures specified in this Instructions For Use are necessary to avoid contamination of reagents.

- Use of this product must be limited to personnel trained in the techniques of PCR and the use of the **cobas**® 5800 and/or **cobas**® 6800/8800 systems.
- Due to inherent differences between technologies, it is recommended that, prior to switching from one technology to the next; users perform method correlation studies in their laboratory to qualify technology differences. One hundred percent agreement between the results should not be expected due to aforementioned differences between technologies and normal variability of the tests.
- The effects of other potential variables such as vaginal discharge, use of tampons, douching, etc. and specimen collection variables have not been evaluated.
- Though rare, mutations within the highly conserved regions of the genomic DNA of Human papillomavirus covered by **cobas**® HPV's primers and/or probes may result in failure to detect the presence of the viral DNA.
- The presence of PCR inhibitors may cause false negative or invalid results.
- Products containing carbomer(s), including vaginal lubricants, creams and gels may interfere with the test and should not be used during or prior to collecting specimens. See Interference results (Table 35) for further details.
- HPV negative results are not intended to prevent women from proceeding to colposcopy.
- Positive test results indicates the presence of any one or more of the high risk types, but since patients may be co-infected with low-risk types it does not rule out the presence of low-risk types in patients with mixed infections.

  Results of this test should only be interpreted in conjunction with information available from clinical evaluation of the patient and patient history.

Clinical performance using clinical specimens

Specimens from a multi-center, prospective, population based cohort of participants in a study designed to evaluate the performance of **cobas®** HPV for identifying high-grade cervical disease (CIN2, CIN3, cervical cancer or adenocarcinoma in situ [ACIS]) were tested. Study participants represented a general screening population with histology assessment based on central pathology review panel (CPRP). Eligible women were 25-65 years of age undergoing routine cervical cancer screening that had signed informed consent and satisfied study inclusion/exclusion criteria. Two cervical samples were collected, first in SurePath™ Preservative Fluid and a second collected in PreservCyt® Solution. Three tests were performed for all subjects for each sample type: Pap cytology test, **cobas®** HPV for use on the **cobas®** 6800/8800 systems and **cobas®** 4800 HPV Test.

Women with ≥ ASC-US cytology in SurePath™ were invited to undergo colposcopy. In addition, all women with a positive test result for HR HPV DNA (positive by the **cobas®** 4800 HPV Test), as well as a randomly selected subset of women with NILM (negative for intraepithelial lesions or malignancy) cytology and negative HR HPV DNA (by the **cobas®** 4800 HPV Test), were selected to proceed to colposcopy. In order to avoid bias, both study participants and colposcopists were blinded to all HPV tests and cytology results until after the colposcopy was completed. Colposcopy was conducted according to a standardized protocol in which biopsies were obtained on all visible lesions; endocervical curettage was performed in all patients in whom the squamocolumnar junction was not visualized and a single random cervical biopsy was obtained if no lesions were visible. All biopsies were examined by a CPRP consisting of three expert pathologists, and discordant results adjudicated according to a pre-defined protocol. For each sample type, the clinical performance (sensitivity and specificity) of the **cobas®** 4800 HPV Test and **cobas®** HPV for use on the **cobas®** 6800/8800 systems was measured against CPRP histology results. The analyses were performed for those women with histology ≥ CIN2 by CPRP. A total of 995 PreservCyt® samples (Table 20) and 841 SurePath™ samples (Table 21) collected in the clinical trial with completed histology assessment were tested. There were 65 women with histologic diagnosis of ≥ CIN2.

Table 20 Performance of **cobas®** HPV and **cobas®** 4800 HPV Test for the Detection of ≥CIN2 in PreservCyt®

	cobas® HPV		**cobas®** 4800 HPV Test	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Sensitivity	93.8% (61/65)	(85.2%, 97.6%)	93.8% (61/65)	(85.2%, 97.6%)
Specificity	41.7% (387/929)	(38.5%, 44.9%)	43.3% (403/930)	(40.2%, 46.5%)

CI = Confidence interval

Table 21 Performance of **cobas®** HPV and **cobas®** 4800 HPV Test for the Detection of ≥CIN2 in SurePath™

	cobas® HPV		**cobas®** 4800 HPV Test	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Sensitivity	93.1% (54/58)	(83.6%, 97.3%)	94.8% (55/58)	(85.9%, 98.2%)
Specificity	43.4% (340/783)	(40.0%, 46.9%)	33.6% (263/783)	(30.4%, 37.0%)

CI = Confidence interval

Agreement between the cobas® HPV in SurePath™ and PreservCyt® with composite comparator

Agreement between **cobas®** HPV results and a composite comparator consisting of HPV DNA results from Qiagen Hybrid Capture 2 (hc2; high risk genotypes probe) and the **cobas®** 4800 HPV Test was assessed. A positive result from both the **cobas®** 4800 HPV Test and hc2 assays was defined as composite comparator positive, a negative result from both the **cobas®** 4800 HPV Test and hc2 was defined as composite comparator negative; samples with discordant results between the two methods were considered indeterminate and not used in calculating positive, negative and overall agreement. Positive, negative, and overall percent agreement was calculated for each media type versus the composite comparator. Final data analysis included **cobas®** HPV and composite comparator results from 2318 PreservCyt® specimens (Table 22) and 1651 SurePath™ specimens (Table 23).

Table 22 Agreement between **cobas®** HPV and composite comparator (hc2 in PreservCyt® and cobas® 4800 HPV in PreservCyt®) for samples collected in PreservCyt®

	Composite Comparator Result						
cobas® HPV Result	**Positive**	**Negative**	**Indeterminate***	**Total**	**PPA (95% CI)**	**NPA (95% CI)**	**OPA (95% CI)**
Positive	195	33	67	295	98.0% (195/199) (94.9%, 99.2%)	98.3% (1966/1999) (97.7%, 98.8%)	98.3% (2161/2198) (97.7%, 98.8%)
Negative	4	1966	53	2023			
Total	199	1999	120	2318			

CI = Confidence interval, NPA = Negative percent agreement, OPA = Overall percent agreement, PPA = Positive percent agreement

*hc2 and **cobas®** 4800 HPV Test did not agree

There were three invalid results by **cobas®** HPV

Table 23 Agreement between **cobas®** HPV and composite comparator (hc2 in PreservCyt® and cobas® 4800 HPV in SurePath™) for samples collected in SurePath™

	Composite Comparator Result						
cobas® HPV Result	**Positive**	**Negative**	**Indeterminate***	**Total**	**PPA (95% CI)**	**NPA (95% CI)**	**OPA (95% CI)**
Positive	141	13	50	204	94.0% (141/150) (89.0%, 96.8%)	99.1% (1376/1389) (98.4%, 99.5%)	98.6% (1517/1539) (97.8%, 99.1%)
Negative	9	1376	62	1447			
Total	150	1389	112	1651			

CI = Confidence interval, NPA = Negative percent agreement, OPA = Overall percent agreement, PPA = Positive percent agreement

*hc2 and **cobas®** 4800 HPV did not agree

Non-clinical performance evaluation

Performance with cervical specimens collected in Roche Cell Collection Medium has shown to be comparable to cervical specimens collected in PreservCyt® Solution. Performance testing with cervical specimens collected in SurePath™ Preservative Fluid was completed using treatment with **cobas**® Sample Prep Buffer. All concentrations listed in the following studies are reflective of the treated SurePath™ sample.

System equivalency /system comparison

System equivalency of the **cobas**® 5800, **cobas**® 6800 and **cobas**® 8800 systems was demonstrated via performance studies. The results presented in the Instructions for Use support equivalent performance for all systems

Key performance characteristics

Limit of Detection (LoD)

The LoD for HPV16 and HPV18 were assessed using SiHa and HeLa cell lines in the background of pooled HPV negative patient specimens collected in PreservCyt® Solution and SurePath™ Preservative Fluid. Cell lines were diluted to concentrations below, above and at the expected LoD levels. A minimum of 24 replicates were tested for each cell line level in both PreservCyt® Solution and SurePath™ Preservative Fluid using 3 reagent lots with an equal number of runs performed on the **cobas**® 6800 and the **cobas**® 8800 systems. The LoD was defined as the level of HPV cells in the sample that has positive test results at least 95% of the time with all concentration levels above exhibiting positive results more than 95% of the time.

The LoD for SiHa was 16 cells/mL for both PreservCyt® and SurePath™; the LoD for HeLa was 16 cells/mL in PreservCyt® and 8 cells/mL in SurePath™. Table 24 through Table 25 contain results from the reagent lot producing the most conservative (highest) LoD in the analysis for HPV16 and HPV18 in PreservCyt® Solution and in SurePath™ Preservative Fluid, respectively.

Dilution panels of HPV16 and HPV18 cell lines in the background of pooled HPV negative patient specimens collected in Roche Cell Collection Medium and PreservCyt® Solution were tested side-by-side. The limit of detection for **cobas**® HPV was comparable.

Table 24 Limit of Detection levels for HPV16 (SiHa Cell Line) in PreservCyt® Solution

SiHa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	24 / 24	100%	85.8% - 100%
16	**24 / 24**	**100%**	**85.8% - 100%**
8	22 / 24	91.7%	73.0% - 100%

Table 25 Limit of Detection levels for HPV16 (SiHa Cell Line) in SurePath™ Preservative Fluid

SiHa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	24 / 24	100%	85.8% - 100%
16	**23 / 24**	**95.8%**	**78.9% - 100%**
8	21 / 24	87.5%	67.6% - 97.3%

Table 26 Limit of Detection levels for HPV18 (HeLa Cell Line) in PreservCyt® Solution

HeLa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	24 / 24	100%	85.8% - 100%
16	**24 / 24**	**100%**	**85.8% - 100%**
8	22 / 24	91.7%	73.0% - 100%

Table 27 Limit of Detection levels for HPV18 (HeLa Cell Line in SurePath™ Preservative Fluid

HeLa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
16	24 / 24	100%	85.8% - 100%
8	**24 / 24**	**100%**	**85.8% - 100%**
4	20 / 24	83.3%	62.6% - 95.3%

Inclusivity

Plasmids for high risk genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 were tested in the background of pooled HPV negative patient specimens collected in PreservCyt® Solution and SurePath™ Preservative Fluid. All 12 of the high risk genotypes tested were detected by the assay.

Precision

Within-laboratory precision was examined using a panel with each member composed from either HPV cell lines or HPV positive clinical samples diluted into a pool of negative cervical specimen matrix collected in PreservCyt® Solution and a pool of negative cervical specimen matrix collected in SurePath™ Preservative Fluid.

The precision panel was designed to include members with very low, low and medium concentrations of HPV (High Negative, < LoD, ~ LoD and > LoD) as well as HPV negative samples for each sample type. Testing was performed with three lots of **cobas®** HPV reagents on two instruments. There was an equal number of runs performed on the **cobas®** 6800 and the **cobas®** 8800 systems over 12 days for a total of 24 runs for each panel member. A description of the precision panels and the observed hit rates are shown in Table 28 and Table 29.

All panel members tested exhibited the expected hit rates. Analysis of standard deviation and percent coefficient of variation of the Ct values from valid tests performed on positive panel members yielded overall CV (%) ranges from 4.32% to 6.34% for Other High Risk HPV (Table 30), 1.09% to 4.61% for HPV16 (Table 31) and 1.21% to 3.76% for HPV18 (Table 32)

Within-laboratory precision was also examined using panels prepared by adding SiHa and HeLa cell lines into a background of pooled HPV negative patient specimens collected in Roche Cell Collection Medium at and above the LoD. Testing of the panels prepared in Roche Cell Collection Medium demonstrated precision comparable to the precision with panels prepared in PreservCyt® Solution.

Table 28 Summary of within laboratory precision in PreservCyt® Solution

Panel Level	Expected Hit Rate	Target Source	HPV Concentration	Target Channel	N Tested	N Positive	Hit Rate	95% CI	
								LL	UL
Negative	0%	N/A	N/A	Other HR HPV	72	0	**0%**	0%	5%
Negative	0%	N/A		HPV16	72	0	**0%**	0%	5%
Negative	0%	N/A		HPV18	72	0	**0%**	0%	5%
High Negative	≤ 5%	Clinical sample	N/A	Other HR HPV	72	0	**0%**	0%	5%
High Negative	≤ 5%	Clinical sample		HPV16	72	0	**0%**	0%	5%
High Negative	≤ 5%	Clinical sample		HPV18	72	5	**7%**	2%	15%
< 1x LoD	< 95%	Clinical sample	N/A	Other HR HPV	72	30	**42%**	30%	54%
< 1x LoD	< 95%	Clinical sample	N/A	HPV16	71	33	**47%**	35%	59%
< 1x LoD	< 95%	Clinical sample	N/A	HPV18	72	49	**68%**	56%	79%
< 1x LoD	20-80%	SiHa cell line	4.8 cells/mL	HPV16	72	44	**61%**	49%	72%
< 1x LoD	20-80%	HeLa cell line	4.8 cells/mL	HPV18	72	49	**68%**	56%	79%
~ 1x LoD	≥ 95%	Clinical sample	N/A	Other HR HPV	72	72	**100%**	95%	100%
~ 1x LoD	≥ 95%	SiHa cell line	16 cells/mL	HPV16	72	72	**100%**	95%	100%
~ 1x LoD	≥ 95%	HeLa cell line	16 cells/mL	HPV18	72	72	**100%**	95%	100%
> 1x LoD	≥ 99%	Clinical sample	N/A	Other HR HPV	72	72	**100%**	95%	100%
> 1x LoD	≥ 99%	SiHa cell line	48 cells/mL	HPV16	72	72	**100%**	95%	100%
> 1x LoD	≥ 99%	HeLa cell line	48 cells/mL	HPV18	72	72	**100%**	95%	100%

CI = Confidence interval, LL = Lower limit, UL = Upper limit

Table 29 Summary of within laboratory precision in SurePath™ Preservative Fluid

Panel Level	Expected Hit Rate	Target Source	HPV Concentration	Target Channel	N Tested	N Positive	Hit Rate	95% CI	
								LL	UL
Negative	0%	N/A	N/A	Other HR HPV	72	0	**0%**	0%	5%
Negative	0%	N/A		HPV16	72	0	**0%**	0%	5%
Negative	0%	N/A		HPV18	72	0	**0%**	0%	5%
High Negative	≤ 5%	Clinical sample	N/A	Other HR HPV	72	0	**0%**	0%	5%
High Negative	≤ 5%	Clinical sample		HPV16	72	0	**0%**	0%	5%
High Negative	≤ 5%	Clinical sample		HPV18	72	0	**0%**	0%	5%
< 1x LoD	< 95%	Clinical sample	N/A	Other HR HPV	72	64	**89%**	79%	95%
< 1x LoD	< 95%	Clinical sample	N/A	HPV16	72	11	**15%**	8%	26%
< 1x LoD	< 95%	Clinical sample	N/A	HPV18	72	36	**50%**	38%	62%
< 1x LoD	20-80%	SiHa cell line	4.8 cells/mL	HPV16	72	55	**76%**	65%	86%
< 1x LoD	20-80%	HeLa cell line	2.4 cells/mL	HPV18	72	47	**65%**	53%	76%
~ 1x LoD	≥ 95%	Clinical sample	N/A	Other HR HPV	72	72	**100%**	95%	100%
~ 1x LoD	≥ 95%	SiHa cell line	16 cells/mL	HPV16	72	72	**100%**	95%	100%
~ 1x LoD	≥ 95%	HeLa cell line	8 cells/mL	HPV18	72	70	**97%**	90%	100%
> 1x LoD	≥ 99%	Clinical sample	N/A	Other HR HPV	72	72	**100%**	95%	100%
> 1x LoD	≥ 99%	SiHa cell line	48 cells/mL	HPV16	72	72	**100%**	95%	100%
> 1x LoD	≥ 99%	HeLa cell line	24 cells/mL	HPV18	72	72	**100%**	95%	100%

CI = Confidence interval, LL = Lower limit, UL = Upper limit

Table 30 Overall mean, standard deviations and coefficients of variation (%) for cycle threshold - Other High Risk HPV

			Random Effect															
			Day		Instrument		Operator		Lot		Between Run		Within Run		Residual		Total	
Level	**Hit Rate**	**Mean Ct**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Cervical samples collected in PreservCyt® Solution																		
< LoD	41.7%	33.2	0	0	0	0	0	0	0	0	0.47	1.43	0	0	1.72	5.18	1.78	5.37
~ LoD	100%	32.4	0	0	0	0	0.49	1.50	0.16	0.51	0	0	0	0	1.94	5.98	2.01	6.19
> LoD	100%	30.7	0	0	0	0	0	0	0.27	0.88	0	0	0	0	1.30	4.23	1.33	4.32
Cervical samples collected in SurePath™ Preservative Fluid																		
< LoD	88.9%	32.7	0	0	0.16	0.50	0	0	0	0	0	0	0	0	2.07	6.32	2.07	6.34
~ LoD	100%	32.1	0.45	1.41	0	0	0.32	1.01	0.75	2.32	0	0	0	0	1.65	5.13	1.89	5.89
> LoD	100%	29.9	0	0	0	0	0	0	0	0	0.31	1.04	0	0	1.82	6.09	1.85	6.18

Table 31 Overall mean, standard deviations and coefficients of variation (%) for cycle threshold - HPV16

			Random Effect															
			Day		Instrument		Operator		Lot		Between Run		Within Run		Residual		Total	
Level	**Hit Rate**	**Mean Ct**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Cervical samples collected in PreservCyt® Solution																		
< LoD	46.5%	35.7	0.84	2.34	0.29	0.80	0.85	2.39	0	0	0	0	0	0	1.10	3.07	1.65	4.61
< LoD	61.1%	36.1	0.44	0.67	0	0	0.16	0.45	0.21	0.57	0	0	0	0	0.49	1.36	0.61	1.68
~ LoD	100%	35.0	0	0	0.02	0.06	0.02	0.07	0.38	1.09	0	0	0.16	0.46	0.42	1.20	0.59	1.69
> LoD	100%	34.0	0.03	0.09	0.04	0.12	0	0	0.27	0.78	0	0	0	0	0.25	0.74	0.37	1.09
Cervical samples collected in SurePath™ Preservative Fluid																		
< LoD	15.3%	36.9	0	0	0	0	0.93	2.52	0	0	0	0	0	0	0.96	2.61	1.34	3.63
< LoD	76.4%	37.1	0.27	0.72	0.10	0.28	0	0	0.25	0.67	0	0	0.32	0.87	0.58	1.58	0.77	2.07
~ LoD	100%	36.3	0	0	0.15	0.40	0	0	0.35	0.95	0.12	0.32	0.11	0.29	0.47	1.29	0.62	1.71
> LoD	100%	35.2	0	0	0.07	0.20	0	0	0.35	0.98	0.01	0.04	0	0	0.33	0.94	0.49	1.38

Table 32 Overall mean, standard deviations and coefficients of variation (%) for cycle threshold - HPV18

			Random Effect															
			Day		Instrument		Operator		Lot		Between Run		Within Run		Residual		Total	
Level	Hit Rate	Mean Ct	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Cervical samples collected in PreservCyt® Solution																		
< LoD	68.1%	35.9	0	0	0.55	1.52	0	0	0.18	0.51	0.17	0.49	0	0	1.21	3.37	1.35	3.76
< LoD	68.1%	35.3	0.19	0.54	0	0	0.02	0.06	0	0	0	0	0	0	0.97	2.75	0.99	2.80
~ LoD	100%	33.8	0	0	0	0	0	0	0.37	1.11	0	0	0	0	0.73	2.17	0.82	2.44
> LoD	100%	32.2	0	0	0	0	0	0	0.22	0.68	0.03	0.10	0	0	0.33	1.02	0.39	1.23
Cervical samples collected in SurePath™ Preservative Fluid																		
< LoD	50.0%	37.3	0.14	0.36	0	0	0.10	0.27	0.25	0.66	0	0	0	0	0.45	1.21	0.54	1.45
< LoD	65.3%	36.3	0.23	0.65	0	0	0	0	0.27	0.74	0.15	0.42	0.20	0.55	0.54	1.49	0.70	1.92
~ LoD	97.2%	35.7	0	0	0	0	0	0	0.33	0.94	0.07	0.20	0	0	0.56	1.57	0.65	1.84
> LoD	100%	34.4	0	0	0.06	0.19	0.02	0.06	0.20	0.57	0.04	0.13	0	0	0.36	1.04	0.42	1.21

Analytical specificity/cross-reactivity

A panel of bacteria, fungi and viruses, including those commonly found in the female urogenital tract, as well as several Human papillomavirus types classified as low or undetermined risk were tested with **cobas®** HPV to assess analytical specificity. The organisms listed in Table 33 were spiked at concentrations of approximately 1 x 10^6 units*/mL for bacteria and approximately 1 x 10^5 units*/mL for viruses into pools of HPV negative cervical specimens in PreservCyt® Solution and in SurePath™ Preservative Fluid. Testing was performed with each potential interfering organism alone as well as with each organism mixed with SiHa (HPV16) and HeLa (HPV18) cell lines at approximately 3x LoD. Results indicated that none of these organisms interfered with detection of HPV16 and HPV18 DNA or produced a false positive result in the HPV negative specimen.

* All bacteria were quantified as Colony Forming Units (CFU) except *Chlamydophila psittaci* which was quantified as Elementary Bodies (EB). All viruses were quantified as units/mL as determined by $TCID_{50}$ Endpoint Dilution Assay except Epstein Barr virus which was in copies/mL. *Trichomonas vaginalis* was quantified as cells/mL.

Table 33 Microorganisms tested for analytical specificity/cross-reactivity

Adenovirus Type 40	Herpes Simplex Virus 1	*HPV82*
Bacteroides caccae	Herpes Simplex Virus 2	*HPV83*
Bacteroides ureolyticus	HPV6	*HPV84*
Bifidobacterium adolescentis	HPV11	*HPV85*
Bifidobacterium breve	HPV26	*HPV89*
Bifidobacterium longum	HPV30	*Klebsiella oxytoca*
Candida albicans	HPV34	*Lactobacillus acidophillus*
Chlamydia trachomatis	HPV40	*Neisseria gonorrhoeae*
Chlamydophila psittaci	HPV42	*Peptostreptococcus anaerobius*
Clostridium difficile (Serogroup B)	HPV53	*Peptostreptococcus asaccharolyticus*
Clostridium perfringens	HPV54	*Peptostreptococcus magnus*
Corynebacterium genitalium	HPV55	*Proteus mirabilis*
Cytomegalovirus	HPV61	*Proteus penneri*
Enterobacter aerogenes	HPV62	*Proteus vulgaris*
Enterobacter cloacae	HPV64	*Pseudomonas aeruginosa*
Enterococcus avium	HPV67	*Pseudomonas fluorescens*
Enterococcus casseliflavus	HPV69	*Pseudomonas putida*
Enterococcus faecalis	HPV70	*Staphylococcus aureus*
Enterococcus faecium	HPV71	*Staphylococcus epidermidis*
Epstein Barr Virus	HPV72	*Streptococcus agalactiae*
Escherichia coli	HPV73	*Streptococcus pyogenes*
Fusobacterium nucleatum	HPV81	*Trichomonas vaginalis*

Interference

The effects of endogenous and exogenous substances that may be present in cervical specimens were tested for potential interference. All testing for interference was performed with each potential interfering substance alone as well as with the substance mixed with SiHa (HPV16) and HeLa (HPV18) cell lines at approximately 3x LoD in pools of HPV negative cervical specimens in Roche Cell Collection Medium, PreservCyt® Solution and in SurePath™ Preservative Fluid.

Endogenous substances tested were cervical mucus, peripheral blood mononuclear cells and whole blood. Levels of endogenous substances tolerated by the assay for specimen types are shown in Table 34. Exogenous substance testing included 17 over-the-counter (OTC) feminine hygiene and prescription products that are listed in Table 35. Of OTC feminine hygiene and prescription products tested, Metronidazole Gel, Replens™, RepHresh™ Odor Eliminating Vaginal Gel and RepHresh™ Clean Balance™ Feminine Freshness Kit produced false negative results. These products contain carbomer(s). Products containing carbomer(s) have been shown to generate false negative and invalid results. Table 35 is not intended to be a comprehensive list of carbomer containing products.

Potential interference from the presence of glacial acetic acid was also tested in pools of HPV negative and HPV positive cervical specimens in Roche Cell Collection Medium and PreservCyt® Solution. Concentrations up to and including 5% (v/v) of glacial acetic acid were tolerated by the assay.

Table 34 Summary of endogenous substance concentrations that did not interfere with performance

Endogenous Substance	Roche Cell Collection Medium	PreservCyt®	SurePath™
Mucus	Presence*	Presence*	Presence*
Peripheral Blood Mononuclear Cells (PBMCs as cells/mL)	1.00E+06	1.00E+06	1.00E+05
Whole Blood (% v/v)	10%	10%	10%

*Presence refers to the amount of cervical mucus normally removed from the cervix prior to sampling

Table 35 List of substances tested for interference in cervical specimens

Product Name	
Clindamycin Phosphate Vaginal Cream	Norforms® Suppositories
CVS Tioconazole 1 (Equate™ tioconazole 1)	Premarin® Vaginal Cream
Equate™ Vagicaine Anti-Itch Cream	Replens™ Long-Lasting Vaginal Moisturizer*
Estrace® Cream	RepHresh™ Odor Eliminating Vaginal Gel*
K-Y® Ultra Gel	RepHresh™ Clean Balance™ Feminine Freshness Kit*
Metronidazole Vaginal Gel*	Summer's Eve® Feminine Deodorant Spray
Monistat® 3 Vaginal Antifungal Combination Pack	VCF® - Vaginal Contraceptive Foam
Monistat® Complete Care Itch Relief Cream	Yeast Gard Advanced®
Gyne-Lotrimin® 7	Glacial acetic acid**

* Metronidazole Vaginal Gel, Replens™, RepHresh™ Odor Eliminating Vaginal Gel and RepHresh™ Clean Balance™ Feminine Freshness Kit showed interference at levels that may potentially be present in clinical specimens.

**Concentrations of ≤ 5% (v/v) glacial acetic acid did not show interference. GAA testing was done in cervical specimens collected in PreservCyt® Solution only.

Cross contamination

Studies were performed to evaluate potential cross contamination on the **cobas**® 6800/8800 systems using **cobas**® HPV. In this performance study the sample to sample cross-contamination rate of **cobas**® HPV has been determined to be 0.139% (1/719) when alternating very high positive sample representing more than 95% of the positives in the intended use population with negative samples over multiple runs. Run to run cross-contamination has been determined to be 0% (0/470). Testing was done using samples prepared in Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid.

Whole system failure

The samples tested in the whole system failure study were pooled HPV negative clinical cervical specimens collected in Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid. Each pool of clinical specimens was spiked with SiHa (HPV16) cells and HeLa (HPV18) cells to a concentration at around 3x LoD for each sample type. The results of this study determined that the hit rate was in excess of 99% in Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid.

Method correlation

The performance of **cobas**® HPV was compared to the **cobas**® 4800 HPV Test using cervical specimens collected in PreservCyt® Solution and cervical specimens collected in SurePath™ Preservative Fluid. All SurePath™ specimens were treated with **cobas**® Sample Prep Buffer according to the pre-analytic method defined for each test.

A total of 6961 cervical specimens collected in PreservCyt® Solution and 5755 cervical specimens collected in SurePath™ Preservative Fluid were tested for this correlation analysis.

The correlation results and calculated positive, negative and overall percent agreements along with 95% confidence intervals are shown in Table 36 for PreservCyt® specimens and Table 37 for SurePath™ specimens. There were 397 discordant specimens for High Risk HPV for the two sample types, combined; of which 212 were positive by **cobas**® HPV and 185 were positive by **cobas**® 4800 HPV Test.

Table 36 Correlation between **cobas**® HPV and the **cobas**® 4800 HPV Test for cervical specimens collected in PreservCyt® Solution

		cobas® 4800 HPV Test – 14 HR Result		
		Positive	Negative	**Total**
cobas® HPV - 14 HR Result	Positive	834	146	980
	Negative	57	5924	5981
	Total	891	6070	6961

Result (%)		**95% Confidence Interval**
Positive Percent Agreement	93.6%	91.8% - 95.0%
Negative Percent Agreement	97.6%	97.2% - 98.0%
Overall Percent Agreement	97.1%	96.7% - 97.5%

Agreements for HPV16/HPV18 detection between **cobas**® HPV and the **cobas**® 4800 HPV Test are (estimate and 95% confidence interval): PPA: 99.5% (97.2%-99.9%); NPA: 98.6% (98.2%-98.8%); and OPA: 98.6% (98.3%-98.8%)

Table 37 Correlation between **cobas®** HPV and the **cobas®** 4800 HPV Test for cervical specimens collected in SurePath™ Preservative Fluid

		cobas® 4800 HPV Test – 14 HR Result		
		Positive	Negative	**Total**
cobas® HPV - 14 HR Result	Positive	701	66	767
	Negative	128	4860	4988
	Total	829	4926	5755

Result (%)		**95% Confidence Interval**
Positive Percent Agreement	84.6%	81.9% - 86.9%
Negative Percent Agreement	98.7%	98.3% - 98.9%
Overall Percent Agreement	96.6%	96.1% - 97.1%

Agreements for HPV16/HPV18 detection between **cobas®** HPV and the **cobas®** 4800 HPV Test are (estimate and 95% confidence interval): PPA: 97.7% (94.3%-99.1%); NPA: 99.0% (98.7%-99.3%); and OPA: 99.0% (98.7%-99.2%)

Comparison of test performance with Roche Cell Collection Medium and PreservCyt® Solution

A comparison of **cobas®** HPV results for cervical specimens in Roche Cell Collection Medium and cervical specimens in PreservCyt® Solution was performed. Cervical samples were co-collected from the same subjects, placed into Roche Cell Collection Medium or PreservCyt® Solution in randomized order and tested. Specimens positive for any of the 14 high risk HPV genotypes detected by the test (HPV-HR) were considered positive; specimens with negative results for all of the 14 high risk HPV genotypes detected by the test were considered negative.

Performance of **cobas®** HPV with Roche Cell Collection Medium and PreservCyt® Solution was compared using the two sample test for proportions. The 95% confidence intervals for the difference in proportions (Roche Cell Collection Medium - PreservCyt® Solution) for both HPV positives and HPV negatives were inclusive of "0" which confirmed that the results for cervical specimens collected in Roche Cell Collection Medium were not statistically dissimilar from results for cervical specimens collected in PreservCyt® Solution (Table 38).

Table 38 Two sample test for proportions for cervical specimens collected in Roche Cell Collection Medium and cervical specimens collected in PreservCyt® Solution

Count Total % Column % Row %	**14 HPV-HR Positive**	**14 HPV-HR Negative**	**Total**
Roche Cell Collection Medium (RCCM)	**490** 16.57 49.80 33.04	**993** 33.58 50.33 66.96	**1483** 50.15
PreservCyt® Solution (PCYT)	**494** 16.71 50.20 33.51	**980** 33.14 49.67 66.49	**1474** 49.85
Total	**984** 33.28	**1973** 66.72	**2957**

Two Sample Test for Proportions	**Proportion Difference**	**Lower 95% Confidence Limit**	**Upper 95% Confidence Limit**
P(14 HR HPV Positive|RCCM)-P(14 HR HPV Positive|PCYT)	-0.00473	-0.03868	0.029224
P(14 HR HPV Negative|RCCM)-P(14 HR HPV Negative|PCYT)	0.004731	-0.02922	0.038676

Correlation of results from self-collected using FLOQSwab® 552C.80 and clinician-collected specimens

A comparison of results from self-collected vaginal specimens and clinician-collected cervical specimens was performed using paired samples from 744 screening-eligible women.

Each woman first collected her sample using a FLOQSwab® #552C.80 (Copan, Italy) which was suspended into Roche Cell Collection Medium or PreservCyt® Solution after collection. A second sample was collected by a clinician during the same visit using the standard of care protocol; the clinician-collected sample was suspended in the same medium type as that of the self-collected sample.

The rate of invalid results for the self-collected and clinician-collected results were 4.7% and 0.4%, respectively. A total of 706 valid paired results were used for correlation analysis. Specimens positive for any of the 14 high risk HPV genotypes detected by the test (HPV-HR) were considered positive; specimens with negative results for all of the 14 high risk HPV genotypes detected by the test were considered negative.

The correlation results and calculated positive, negative and overall percent agreements along with 95% confidence intervals are shown in Table 39.

Table 39 Correlation of results for self-collected vaginal specimens using FLOQSwab® 552C.80 and clinician-collected cervical specimens

		Clinician-Collected Cervical Sample 14 HR Result		
		Positive	**Negative**	**Total**
Self-Collected Vaginal Sample using FLOQSwab® #552C.80 14 HR Result	**Positive**	165	43	208
	Negative	26	472	498
	Total	191	515	706

	Result (%)	95% Confidence Interval
Positive Percent Agreement	86.4%	80.8% - 90.5%
Negative Percent Agreement	91.7%	88.9% - 93.7%
Overall Percent Agreement	90.2%	87.8% - 92.2%

Correlation of results from self-collected using Evalyn® Brush and clinician-collected specimens

A comparison of results from self-collected vaginal specimens and clinician-collected cervical specimens was performed using paired samples from 784 screening-eligible women.

Each woman first collected her sample using an Evalyn® Brush (Rovers, Netherlands) which was suspended into Roche Cell Collection Medium or PreservCyt® Solution after collection. A second sample was collected by a clinician during the same visit using the standard of care protocol; the clinician-collected sample was suspended in the same medium type as that of the self-collected sample.

The rate of invalid results for the self-collected and clinician-collected results were 4.7% and 0.4%, respectively. A total of 744 valid paired results were used for correlation analysis. Specimens positive for any of the 14 high risk HPV genotypes detected by the test (HPV-HR) were considered positive; specimens with negative results for all of the 14 high risk HPV genotypes detected by the test were considered negative.

The correlation results and calculated positive, negative and overall percent agreements along with 95% confidence intervals are shown in Table 40.

Table 40 Correlation of results for self-collected vaginal specimens using Evalyn® Brush and clinician-collected cervical specimens

		Clinician-Collected Cervical Sample 14 HR Result		
		Positive	**Negative**	**Total**
Self-Collected Vaginal Sample using Evalyn® Brush 14 HR Result	**Positive**	204	50	254
	Negative	24	466	490
	Total	228	516	744

	Result (%)	**95% Confidence Interval**
Positive Percent Agreement	89.5%	84.8% - 92.9%
Negative Percent Agreement	90.3%	87.4% - 92.6%
Overall Percent Agreement	90.1%	87.7% - 92.0%

Additional information

Key assay features

Sample types	• Cervical specimen collected in Roche Cell Collection Medium • Cervical specimen collected in PreservCyt® Solution • Cervical specimen collected in SurePath™ Preservative Fluid • Self-collected vaginal specimen in Roche Cell Collection Medium • Self-collected vaginal specimen in PreservCyt® Solution
Amount of sample processed	• ≥ 1000 µL required in sample tube for Roche Cell Collection Medium samples, instrument processes 400 µL • ≥ 1000 µL required in sample tube for PreservCyt® samples, instrument processes 400 µL • 1000 µL required in sample tube for SurePath™ samples treated with **cobas®** Sample Prep Buffer, instrument processes 400 µL • On **cobas®** 5800 system, ≥ 3000 µL required for Roche Cell Collection Medium samples in primary vials, instrument processes 400 µL • On **cobas®** 5800 system, ≥ 3000 µL required for PreservCyt® samples in primary vials, instrument processes 400 µL
Test duration	• < 3.5 hours to first result

Symbols

The following symbols are used in labeling for Roche PCR diagnostic products.

Table 41 Symbols used in labeling for Roche PCR diagnostics products

Age/DOB Age or Date of Birth	Device not for near-patient testing	QS IU/PCR QS IU per PCR reaction, use the QS International Units (IU) per PCR reaction in calculation of the results.
SW Ancillary Software	Device not for self-testing	
Assigned Range [copies/mL] Assigned Range (copies/mL)	Distributor *(Note: The applicable country/region may be designated beneath the symbol)*	SN Serial number
Assigned Range [IU/mL] Assigned Range (IU/mL)	Do not re-use	Site Site
EC REP Authorized representative in the European Community	Female	Procedure Standard Standard Procedure
BARCODE Barcode Data Sheet	For IVD performance evaluation only	STERILE EO Sterilized using ethylene oxide
LOT Batch code	GTIN Global Trade Item Number	Store in dark
Biological risks	Importer	Temperature limit
REF Catalogue number	IVD In vitro diagnostic medical device	TDF Test Definition File
CE CE marking of conformity; this device is in conformity with the applicable requirements for CE marking of an in vitro diagnostic medical device	LLR Lower Limit of Assigned Range	This way up
	Male	Procedure UltraSensitive Ultrasensitive Procedure
Collect Date Collect date	Manufacturer	UDI Unique Device Identifier
Consult instructions for use	CONTROL − Negative control	ULR Upper Limit of Assigned Range
Σ Contains sufficient for <*n*> tests	NON STERILE Non-sterile	Urine Fill Line Urine Fill Line
CONTENT Content of kit	Patient Name	Rx only For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.
CONTROL Control	# Patient number	Use-by date
Date of manufacture	Peel here	
Device for near-patient testing	CONTROL + Positive control	
Device for self-testing	QS copies / PCR QS copies per PCR reaction, use the QS copies per PCR reaction in calculation of the results.	

Technical support

For technical support (assistance) please reach out to your local affiliate:
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Manufacturer and importer

Table 42 Manufacturer and importer

Roche Molecular Systems, Inc.
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EC REP Roche Diagnostics GmbH
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Document revision

Document Revision Information	
Doc Rev. 3.0 12/2024	Added system software version 2.0 information for **cobas**® 6800/8800 systems. Updated display of example results on **cobas**® 6800/8800 systems with software version 1.4. P/Ns of consumables removed, detailed information on consumables are referenced in the **cobas**® 5800 and **cobas**® 6800/8800 systems User Assistance. Removed Rx Only from front page. Updated the harmonized symbol page. Updated competent authority statement. Please contact your local Roche Representative if you have any questions.

The summary of safety and performance report can be found using the following link: https://ec.europa.eu/tools/eudamed