Rx Only

cobas® HPV

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

For in vitro diagnostic use

For use on the cobas® 5800 System:

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

For use on the cobas® 6800/8800 Systems:

cobas® HPV	P/N: 07460155190 or P/N: 09040544190
cobas® HPV Positive Control Kit	P/N: 07460171190 or P/N: 09040552190
cobas® Buffer Negative Control Kit	P/N: 07002238190 or P/N: 09051953190

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Intended use

cobas® HPV for use on the **cobas**® 5800/6800/8800 Systems (**cobas**® HPV) is a qualitative *in vitro* test for the detection of high-risk Human Papillomavirus . This test detects the high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 in the specimens listed below

Clinician-collected cervical specimens should be obtained using an endocervical brush/spatula or broom and placed in the ThinPrep® Pap Test™ PreservCyt® Solution.

Self-collected vaginal specimens, obtained in a healthcare setting, can be tested as an alternative specimen type when cervical sampling is either contraindicated or cervical samples otherwise cannot be obtained.

cobas® HPV is indicated for use for routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (or adjunctive screen) with cytology, and HPV primary screening of individuals with a cervix to assess the risk for cervical precancer and cancer.

Patients should be followed-up in accordance with professional medical guidelines, results from prior screening, medical history, and other risk factors.

CONTRAINDICATIONS: None

Warnings

If a cervical specimen cannot be obtained, self-collected vaginal specimens should be obtained in a healthcare setting where samples can be processed by trained personnel and transported to a testing laboratory under controlled conditions. Recommendations for clinical management after testing of either clinician-collected cervical samples or self-collected vaginal samples should follow professional guidelines and may differ for these two specimen types.**cobas**® HPV is **NOT** intended:

- for use in determining the need for treatment (i.e., excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV16/18 positive should be monitored carefully for the development of high-grade cervical dysplasia according to current practice guidelines.
- for women who have undergone hysterectomy.
- for use with samples other than those collected by a clinician using an endocervical brush/spatula or a cervical broom and placed in the ThinPrep® Pap Test™ PreservCyt® Solution.
- For use with self-collected vaginal samples other than those collected with collection devices specifically FDA-approved or cleared for use with the cobas® HPV.

HPV-negative cancers of the cervix do occur in rare circumstances.[1,2] Also, no cancer screening test is 100% sensitive. Use of this device for primary cervical cancer screening should be undertaken after carefully considering the performance characteristics put forth in this label, as well as recommendations of professional guidelines.

The use of this test has not been evaluated for the management of women with prior ablative or excisional therapy, or who are pregnant.

Summary and explanation of the test

Background and rationale for HPV testing

Human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 140 different HPV genotypes[3,4] and approximately 40 different genotypes can infect the human anogenital mucosa.[5,6] Fourteen HPV genotypes are classified as carcinogenic or high-risk (HR): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. Please note that one of these, HPV66, was recently categorized as "possibly carcinogenic" based on its relatively low prevalence in invasive cervical carcinomas.[8,9]

Persistent infection with these high risk HPV genotypes is the central cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).[6] Sexually transmitted infections with HPV is extremely common, with estimates of up to 75% of all women experiencing exposure to HPV at some point.[10] However, most infections clear within 1-2 years.[10] Most cervical cancers and deaths from cervical cancer can be prevented through early detection of pre-cancerous lesions in the cervix, leading to timely treatment. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid based cytology methods require interpretation by highly trained cytopathologists and have a high rate of false negatives. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory or sampling variations can result in false positive cytology results. Triage of an abnormal cytology result involves repeat testing, colposcopy and biopsy to rule out the presence of high-grade precancerous lesions, (cervical intraepithelial neoplasia of grade 2 or higher; ≥CIN2). Therefore, tests that detect infection with these HR HPV genotypes are now being used increasingly in cervical cancer screening programs to improve the prevention of cervical cancers and clinical patient management.[12] Nucleic acid (DNA) testing by PCR is a non-invasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 25 years and older and reducing the need for unnecessary colposcopy and treatment in patients 21 and older with atypical squamous cells of undetermined significance (ASC-US) cytology. Therefore, tests that detect infection with these HR HPV genotypes are now being used increasingly in cervical cancer screening programs to improve the prevention of cervical cancers.[12]

The 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests recognized the utility of using a combination of cervical cytology, tests for HPV detection, and type-specific HPV testing for women undergoing screening for cervical cancer.[13] One of the earliest and most common utilization of HPV testing has been for the management (referral to colposcopy) of women with equivocal cervical cytologic abnormalities (ASC-US).[14] Further, revised and updated guidelines now recommend the combination of cytology and HPV testing (cotesting) as the preferred method of screening in women ≥30 years, with HPV 16/18 genotype-specific testing as an added option to triage women with negative cytology to colposcopy.[14] A later revision provided the option when cotesting to follow up women with low grade squamous intraepithelial lesion (LSIL)/HPV negative results in 12 months rather than refer to colposcopy.[15] Most recently, interim guidance has been issued for HR HPV DNA testing to be used as a first-line primary screening test in women ≥25 years.[16]

Nucleic acid (DNA) testing by PCR is a non-invasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 25 years and older and reducing the need for unnecessary colposcopy and treatment in patients 21 and older with ASC-US cytology.

Self-collection using PCR-based HPV tests in cervical cancer screening programs is generally accepted and desirable because it increases access and participation to screening in unscreened or underscreened women, and settings or regions with inadequate or lack of health care infrastructure and the needed logistics to perform a pelvic exam.

Explanation of the test

cobas® HPV is a qualitative real-time[17,18] 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).[7,19,20,21,22,23,24] **cobas**® HPV 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.

Principles of the procedure

cobas® HPV is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification[25] 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 is 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. External controls (positive and negative) are processed in the same way with each **cobas**® HPV run.

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.[26] However, newly formed amplicon are not eliminated since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

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

cobas® HPV

Store at 2-8°C
480 test cassette (P/N 07460155190 and 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. 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

cobas® HPV Positive Control Kit

Store at 2–8°C

(P/N 07460171190 and 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 HPV39 sequences, < 0.01% Non-infectious plasmid DNA (microbial) containing β-globin sequences, < 0.002% Poly rA RNA (synthetic)	16 mL (16 x 1 mL)

Table 3 cobas® Buffer Negative Control Kit

cobas® Buffer Negative Control Kit

Store at 2-8°C
(P/N 07002238190 and 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 1 mL)

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 Harmful if swallowed. H314 Causes severe skin burns and eye damage. H412 Harmful to aquatic life with long lasting effects. EUH032 Contact with acids liberates very toxic gas. EUH071 Corrosive to the respiratory tract. P273 Avoid release to the environment. P280 Wear protective gloves/ protective clothing/ eye protection/ face protection. P301 + P330 + P331 IF SWALLOWED: Rinse mouth. Do NOT induce vomiting. 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. 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 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 the cobas® 5800 System

Reagents loaded onto the **cobas**® 5800 System are stored at appropriate temperatures and their expiration is monitored by the system. The **s**ystem allows reagents to be used only if all of the conditions shown in Table 6 are met. The system automatically prevents use of expired reagents. Table 6 allows the user to understand the reagent handling conditions enforced by the **cobas**® 5800 System.

Table 6 Reagent expiry conditions enforced by the cobas® 5800 Systems

Reagent	Kit expiration date	Open-kit stability*	Number of runs for which this kit can be used	On-board stability
cobas® HPV	Date not passed	90 days from first usage	Max 40 runs	Max 36 days*
cobas® HPV Positive Control Kit	Date not passed	Not applicable**	Not applicable	Max 36 days*
Cobas® Buffer Negative Control Kit	Date not passed	Not applicable**	Not applicable	Max 36 days*
cobas® **omni** Lysis Reagent	Date not passed	30 days from loading*	Not applicable	Not applicable
cobas® **omni** MGP Reagent	Date not passed	30 days from loading*	Not applicable	Not applicable
cobas® **omni** Specimen Diluent	Date not passed	30 days from loading*	Not applicable	Not applicable
cobas® **omni** Wash Reagent	Date not passed	30 days from loading*	Not applicable	Not applicable

* Time is measured from the first time that reagent is loaded onto the **cobas**® 5800 System

** Single use reagent

Reagent handling requirements for the cobas® 6800/8800 Systems

Reagents loaded onto the **cobas**® 6800/8800 Systems are stored at appropriate temperatures and their expiration is monitored by the system. The **cobas**® 6800/8800 Systems allow reagents to be used only if all of the conditions shown in Table 7 are met. The system automatically prevents use of expired reagents. Table 7 describes the reagent handling conditions enforced by the **cobas**® 6800/8800 Systems.

Table 7 Reagent expiry conditions enforced by the cobas® 6800/8800 Systems

Reagent	Kit expiration date	Open-kit stability	Number of runs for which this kit can be used	On-board stability (cumulative time on board outside refrigerator)
cobas® HPV	Date not passed	90 days from first usage	Max 20 runs	Max 20 hours*
cobas® HPV Positive Control Kit	Date not passed	Not applicable**	Max 16 runs	Max 10 hours*
cobas® Buffer Negative Control Kit	Date not passed	Not applicable**	Max 16 runs	Max 10 hours*
cobas® **omni** Lysis Reagent	Date not passed	30 days from loading*	Not applicable	Not applicable
cobas® **omni** MGP Reagent	Date not passed	30 days from loading*	Not applicable	Not applicable
cobas® **omni** Specimen Diluent	Date not passed	30 days from loading*	Not applicable	Not applicable
cobas® **omni** Wash Reagent	Date not passed	30 days from loading*	Not applicable	Not applicable

* Time is measured from the first time that reagent is loaded onto the **cobas**® 6800/8800 Systems.

** Single use reagent

Additional materials required for the cobas® 5800 System

Table 8 Material and consumables for use with cobas® HPV on the cobas® 5800 System

Material	P/N
cobas® **omni** Processing Plate 24	08413975001
cobas® **omni** Liquid Waste Plate 24	08413983001
cobas® **omni** Amplification Plate 24	08499853001
Tip CORE TIPS with Filter, 1mL	04639642001
Tip CORE TIPS with Filter, 300 uL	07345607001
cobas® **omni** Liquid Waste Container	07094388001
cobas® **omni** Lysis Reagent	06997538190
cobas® **omni** MGP Reagent	06997546190
cobas® **omni** Specimen Diluent	06997511190
cobas® **omni** Wash Reagent	06997503190
Solid Waste Bag or Solid Waste Bag With insert	07435967001 or 08030073001
16-position tube S-carrier, complete	09224319001
5-position rack R-carrier, complete	09224475001
Collection Medium Container Carrier (CMC C-carrier)	09224599001

* 16-position tube carrier is the preferred rack for use with samples collected in **cobas**® Secondary Tubes.

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

Additional materials required for the cobas® 6800/8800 Systems

Table 9 Equipment, materials and consumables required for use with cobas® HPV on the cobas® 6800/8800 Systems

Material	P/N
cobas® **omni** Processing Plate	05534917001
cobas® **omni** Amplification Plate	05534941001
cobas® **omni** Pipette Tips	05534925001
cobas® **omni** Liquid Waste Container	07094388001
cobas® **omni** Lysis Reagent	06997538190
cobas® **omni** MGP Reagent	06997546190
cobas® **omni** Specimen Diluent	06997511190
cobas® **omni** Wash Reagent	06997503190
Solid Waste Bag with Insert	08030073001
Kit Drawer Solid Waste Update	08387281001
MPA RACK 16 MM LIGHT GREEN 7001-7050[a,b,c]	03143449001
RD5 RACK – RD Standard rack 0001-0050 LR[a,b,c]	11902997001

[a] MPA 16mm and RD5 racks are required to use **cobas**® HPV. Contact your local Roche representative for a detailed order list for sample racks, racks for clotted tips and rack trays accepted on the instruments.

[b] MPA 16mm rack is the preferred rack. If RD5 racks are used, ensure sample tubes are filled with the recommended minimum sample input volume. The tubes sit higher in an RD5 rack because of the rubber gasket at the bottom of each tube position. It is therefore possible that when using RD5 racks, the system could accept tubes containing less than the minimum sample input volume and cause pipetting errors later in the run.

[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.

Instrumentation and software required

The **cobas**® 5800 software and **cobas**® HPV analysis package (ASAPs) for **cobas**® 5800 shall be installed on the **cobas**® 5800 instrument. The Data Manager software and PC for **cobas**® 5800 System will be provided with the system.
The **cobas**® 6800/8800 software and **cobas**® HPV analysis packages (ASAPs) for **cobas**® 6800/8800 shall be installed on the instrument(s). The Instrument Gateway (IG) server will be provided with the system.

Table 10 Instrumentation

Equipment	P/N
cobas® 5800 System	08707464001
cobas® 6800 System (Moveable Platform)	05524245001 and 06379672001
cobas® 6800 System (Fixed Platform)	05524245001 and 06379664001
cobas® 8800 System	05412722001
Sample Supply Module for **cobas**® 6800/8800 Systems	06301037001

Additional materials required for sample collection for cobas® HPV

Table 11 Specimen collection kits for use with cobas® HPV

Collection Kit	P/N
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
Rovers® Cervex-Brush® Combi (500/Box)	VWR 89171-022
Cytobrush Plus GT - 25 Bags, 100 Brushes each (2,500/Box)	Medscand C0105
Cytobrush Plus GT – 2 Bags, 500 Brushes each (1,000/Box)	Medscand C0121
Cytobrush Plus GT – 10 Bags, 10 Brushes each (100/Box)	Medscand C0104
Cytobrush Plus GT Sterile – 1 Brush per Pouch (40/Box)	Medscand C0112
Cytobrush Plus GT Scored – 25 Bags, 100 Brushes each (2,500/Box)	Medscand C0305
Pap-Perfect Plastic Spatulas (500/Box)	Medscand 11080
Rovers® Evalyn® Brush	09032959190
Copan FLOQSwabs®#552C.RM	09032932190
Sample collection instructions for Rovers® Evalyn® Brush	
Sample collection instructions for Copan FLOQSwabs® #552C.RM	
Sample suspension instructions for Rovers® Evalyn® Brush	10270497001
Sample suspension instructions for Copan FLOQSwabs® #552C.RM	10270519001

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

Additional required materials for sample aliquoting for cobas® HPV

Table 12 Materials for aliquoting samples to test with cobas® HPV

Material	P/N
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

* Use of tubes other than those recommended above must be verified by user prior to implementation into **cobas**® HPV workflow in the laboratory.

** For further details on barcode specifications refer to the **cobas**® 6800/8800 Systems User Guide. Use of barcode labels other than those recommended above must be verified by user prior to implementation into **cobas**® HPV workflow in the laboratory.

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.
- For prescription use only.
- Self-collected vaginal specimens collected using the Copan FLOQSwabs® #552C.RM or Rovers® Evalyn® Brush must be suspended in PreservCyt® Solution after the sample is collected.
- All patient samples should be handled as if infectious, using good laboratory procedures as outlined in Biosafety in Microbiological and Biomedical Laboratories[27] and in the CLSI Document M29-A4.[28] 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 hypochlorite in distilled or deionized water (dilute household bleach 1:10) 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.

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 hypochlorite (bleach) 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 Kit, **cobas**® HPV Positive Control Kit, **cobas**® Buffer 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 Kit, **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 hypochlorite in distilled or deionized water (dilute household bleach 1:10). 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 Guide 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 PreservCyt® Solution have been validated for use with **cobas**® HPV.

Vaginal specimens collected with *FLOQSwabs*® #552C.RM and suspended in PreservCyt® Solution have been validated for use with cobas® HPV.

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

Follow the manufacturer's instructions for collecting specimens.

Specimen transport

Specimens collected in PreservCyt® Solution 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.[29]

Specimen storage

Cervical specimens collected in PreservCyt® Solution may be stored at 2-30°C for up to 3 months after the date of collection prior to performing **cobas**® HPV. Self-collected vaginal specimens suspended in PreservCyt® Solution may be stored at 2-30°C for up to 1 month after the date of collection prior to performing **cobas**® HPV. See PreservCyt® Solution labeling for medium storage requirements. PreservCyt® specimens should not be frozen.

Instructions for use

Suspension of self-collected specimen

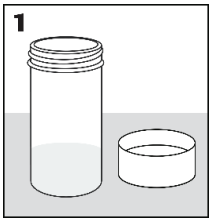
Sample suspension instructions for Copan *FLOQSwabs*® #552C.RM

Sample handling instructions for self-collected sample using Copan FLOQSwabs® #552C.RM for testing with the **cobas**® 4800 HPV Test or **cobas**® HPV.

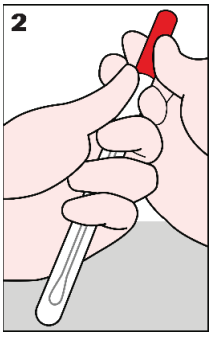
Self-collected sample must be placed into medium after sample has been collected.

- **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:

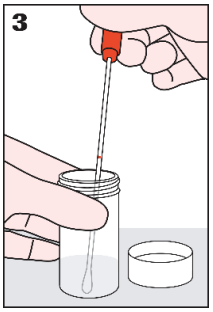
Handle the collected sample with care.



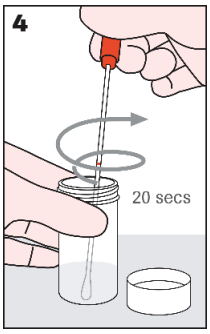
1. Carefully uncap the vial containing medium and place it on a stable, flat surface.



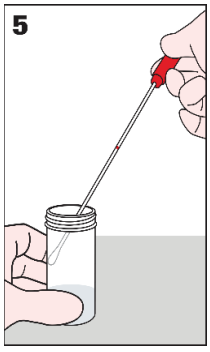
2. Slowly pull the FLOQSwab cap off to remove the swab from the tube. **Minimize touching the inner walls of the tube as you remove the FLOQSwab.**



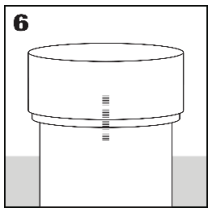
3. Hold the vial with one hand then with the other hand place the FLOQSwab tip into the vial until the FLOQSwab **tip is fully immersed in the medium** and **touching the bottom** of the vial**.**



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.

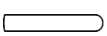


6. Re-cap the vial and tighten until **the lines on the cap and vial meet or slightly overlap** to prevent leakage. Store upright.

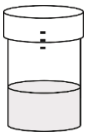
7. The sample can now be processed with the **cobas**® 4800 HPV Test or **cobas**® HPV**.**

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.

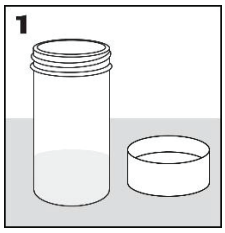
Sample suspension instructions for Rovers® Evalyn® Brush

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

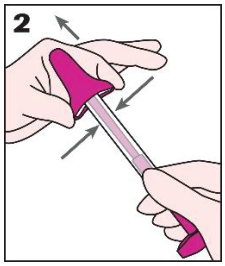
Self-collected sample must be placed into medium after sample has been collected.

- **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:

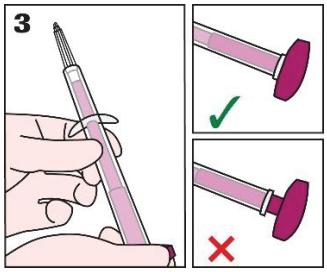
Handle the collected sample with care.



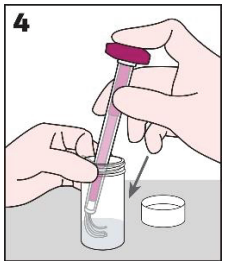
1. Carefully uncap the vial containing medium and place it on a stable, flat surface.



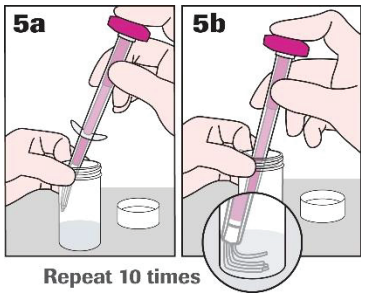
2. Remove the pink cap from the Evalyn Brush **taking care not to touch the exposed end.**



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).

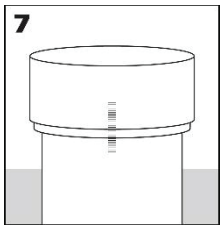


4. Hold the vial with one hand then with the other hand place the white brush into the vial so that the **bristles are fully immersed in the medium and the wings are past the opening of the vial.**



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.

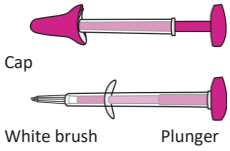
6. Remove the white brush by carefully drawing the brush up along the inner wall of the primary vial until the brush is no longer submerged in the medium. **Hold the brush against the inner vial wall to drain fluid** off the brush. Place the Evalyn brush back inside the packaging and discard.



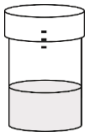
7. Re-cap the vial and tighten until **the lines on the cap and vial meet or slightly overlap** to prevent leakage. Store upright.

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.

Specimen preparation

cobas® 5800 System

- The **cobas**® 5800 System may process specimens in 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 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 PreservCyt® specimen to be tested.
  2. With clean gloved hands, vortex each 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 the **cobas**® 5800 System or **cobas**® 6800/8800 Systems for HPV testing.

Procedural notes

- Do not use **cobas**® HPV Kit, **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 and/or User Guide for proper barcode specifications and additional information on loading sample tubes.
- Refer to the **cobas**® 5800 System or **cobas**® 6800/8800 Systems User Assistance and/or User Guide 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 PreservCyt® specimens from the primary vial. Aliquots of PreservCyt® specimens in **cobas**® Secondary Tubes may be run with a minimum required volume of 1.0 mL. The operation of the instrument is described in detail in the **cobas**® 5800 System User Assistance and/or User Guide. Figure 2 summarizes the procedure.

- The **cobas**® 5800 System may process specimens in PreservCyt® Solution 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 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 13.

Table 13 Sample type selection for cobas® HPV on cobas® 5800

Specimen	Collection medium	Supported Container Primary vial	Supported Container Secondary tube	Process as Sample Type
Cervical specimen	PreservCyt® Solution (ThinPrep)	Yes	Yes	PreservCyt®
Self-collected vaginal specimen	PreservCyt® Solution (ThinPrep)	Yes	Yes	Self, vaginal

Figure 1 cobas® HPV 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 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 PreservCyt® specimen into a 13mL **cobas®** Secondary Tube
    - Transfer tube to sample rack
- Load sample racks onto the system

Confirm samples have been accepted into the system

The system prepares automatically

Order Tests

- Choose “PreservCyt®” for ordering PreservCyt® Solution specimens
- Choose “Self, vaginal” for ordering self-collected vaginal specimens in PreservCyt® Solution

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. 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 specimen tested with either the HPV High Risk (HPV-HR) or HPV High Risk Plus Genotyping (HPV-GT) ASAPs.
- Cervical specimens should be processed using the "PreservCyt®" sample type selection in the user interface (UI) of **cobas**® HPV. Self-collected vaginal specimens should be processed using the "Self, vaginal" sample type selection in the user interface (UI) of **cobas**® HPV.

Figure 2 cobas® HPV procedure on the cobas® 6800/8800 Systems

1	Log onto the system Press Start to Prepare the system Order Tests • Choose "PreservCyt" for ordering specimens collected in PreservCyt® Solution • Choose "Self, vaginal" for ordering self-collected vaginal specimens in PreservCyt® Solution
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 PreservCyt® specimen vial: o Vortex for 10 seconds o Aliquot a minimum of 1 mL of PreservCyt® specimen into a 13 mL **cobas**® Secondary Tube o Transfer tube 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 14 high risk HPV genotypes (HPV-HR) and/or 12 high risk genotypes with individual typing of HPV16 and HPV18 simultaneously (HPV-GT).

Quality control and validity of results on the cobas® 5800 System

- One **cobas**® Buffer Negative Control [(-) Ctrl] and one 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 **cobas**® 5800 software in the "Controls" app.
- In the **cobas**® 5800 System software and/or report, check for flags to ensure the validity of the corresponding test results (Refer to the x800 Data Manager User Assistance and/or User Guide 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 all Targets of the control are reported valid. Controls are marked with 'Invalid' in the "Control result" column if one or both Target 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 the positive control is invalid, repeat testing of the positive control and all associated samples. If the negative control is invalid, repeat testing of all controls and all associated samples.

Validation of results is performed automatically by the **cobas**® 5800 software based on control results.

NOTE: The **cobas**® 5800 System 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 the cobas® 6800/8800 Systems

- One **cobas**® Buffer Negative Control [(–) Ctrl] and one HPV Positive Control [HPV (+) C] are processed with each batch of a requested result type (HPV-HR or HPV-GT).
- In the **cobas**® 6800/8800 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 Guide.
- 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 software based on negative and positive control performance.

Interpretation of results

cobas® HPV for cobas® 5800 System Software v1.0 or higher

The results of the samples are shown in the **cobas**® 5800 software in the "Results" app. Display examples for **cobas**® HPV on the **cobas**® 5800 System Software are shown in Figure 3 and Figure 4.

Figure 3 Example of cobas® HPV results display for the HPV-HR results request for cobas® 5800 System

Sample ID	Test	Control results	Flag	Result
PC_HPVHRinv_01	HPV-HR	Valid	⚑	**HR HPV Invalid**
PC_HPVHRneg_01	HPV-HR	Valid		**HR HPV Negative**
PC_HPVHRpos_01	HPV-HR	Valid		**HR HPV Positive (Ct 36.52)**
PC_HPVHRneg_01	HPV-HR	Valid		**HR HPV Negative**
PC_HPVHRpos_01	HPV-HR	Valid		**HR HPV Positive (Ct 35.44)**

Note: 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 for cobas® 5800 System

Sample ID	Test	Control results	Flag	Result
PC_HPVGTneg_03	HPV-GT	Valid		**Other HR Negative HPV 16 Negative HPV 18 Negative**
PC_HPVGTpos_05	HPV-GT	Valid		**Other HR Positive (Ct 33.43) HPV 16 Negative HPV 18 Positive (Ct 32.54)**
PC_HPVGTpos_03	HPV-GT	Valid		**Other HR Negative HPV 16 Positive (Ct 35.21) HPV 18 Negative**
PC_HPVGTneg_04	HPV-GT	Valid		**Other HR Negative HPV 16 Negative HPV 18 Negative**
PC_HPVGTinv_01	HPV-GT	Valid	⚑	**Other HR Invalid HPV 16 Invalid HPV 18 Invalid**

Note: 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 **cobas**® 5800 System 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 shown in Table 14 and Table 15.
- If one or more sample targets are marked with "Invalid" the cobas® 5800 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 channel. For invalid target results, 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.
- Results of this test should only be interpreted in conjunction with information available from clinical evaluation of the patient and patient history.

cobas® HPV for cobas® 6800/8800 System Software v1.4 or higher

Display examples for **cobas**® HPV for **cobas**® 6800/8800 System Software v1. 4 or higher are shown are shown in Figure 5 and Figure 6.

Figure 5 Example of cobas® HPV result display for the HPV-HR result request for cobas® 6800/8800 System Software v1.4 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	HPVHRinv_01	NA	Y40T	PreservCyt®	**NA**	Invalid		
HPV-HR	HPVHRneg_01	NA		PreservCyt®	**NA**	HR HPV Negative		
HPV-HR	HPVHRpos_01	NA		PreservCyt®	**NA**	HR HPV Positive		

Note: The Target 2 and Target 3 columns are reserved for HPV16 and HPV18 results with HPV-GT request, respectively.

Figure 6 Example of cobas® HPV result display for the HPV-GT result request for cobas® 6800/8800 System Software v1.4 or higher

Test	Sample ID	Valid	Flags	Sample type	Overall result	Target 1	Target 2	Target 3
HPV-GT	HPVGTpos_01	NA		PreservCyt®	**NA**	Other HR HPV Negative	HPV 16 Negative	HPV 18 Positive
HPV-GT	HPVGTpos_02	NA		PreservCyt®	**NA**	Other HR HPV Negative	HPV 16 Positive	HPV 18 Positive
HPV-GT	HPVGTpos_03	NA		PreservCyt®	**NA**	Other HR HPV Positive	HPV 16 Negative	HPV 18 Positive
HPV-GT	HPVGTpos_04	NA		PreservCyt®	**NA**	Other HR HPV Positive	HPV 16 Negative	HPV 18 Negative
HPV-GT	HPVGTpos_05	NA		PreservCyt®	**NA**	Other HR HPV Positive	HPV 16 Positive	HPV 18 Negative
HPV-GT	HPVGTpos_06	NA		PreservCyt®	**NA**	Other HR HPV Positive	HPV 16 Positive	HPV 18 Positive
HPV-GT	HPVGTpos_07	NA		PreservCyt®	**NA**	Other HR HPV Negative	HPV 16 Negative	HPV 18 Positive
HPV-GT	HPVGTneg_01	NA		PreservCyt®	**NA**	Other HR HPV Negative	HPV 16 Negative	HPV 18 Negative
HPV-GT	HPVGTpos_08	NA	C02H1	PreservCyt®	**NA**	Invalid	HPV 16 Positive	HPV 18 Positive
HPV-GT	HPVGTpos_09	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 software 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 channel. Refer to retesting instructions for the respective specimen type below.
- For invalid target results from 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.

Results and their corresponding interpretation for detecting HR HPV only and Other HR HPV, HPV16 and HPV18 are shown in Table 14 and Table 15.

Table 14 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.
Invalid			The result for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 is invalid.

Table 15 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 Invalid	HPV 18 Positive, HPV 18 Negative, or 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.
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 Invalid	HPV 16 Positive	HPV 18 Positive, HPV 18 Negative, or Invalid	Specimen is positive for HPV type 16 DNA.
	HPV 16 Negative		HPV type 16 DNA was undetectable or below the pre-set threshold.
	Invalid		The result for HPV type 16 is invalid.
Other HR HPV Positive, Other HR HPV Negative, or Invalid	HPV 16 Positive, HPV 16 Negative, or 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.
		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 by a clinician using an endocervical brush/spatula or a cervical broom and placed in the ThinPrep® Pap Test™ PreservCyt® Solution. 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* (552C.RM) and Evalyn® Brush which are then suspended in PreservCyt® Solution after collection. 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 cervical specimens. See Interference results (Table 28, Table 30) for further details.
- Use of over-the-counter products Dove Advanced Care Clear Finish Antiperspirant Dry Spray, Replens™, RepHresh™ Vaginal Gel and RepHresh™ Clean Balance™ Kit has been associated with false-negative results.
- Use of Metronidazole Vaginal Gel has been associated with false-negative 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.[13]
- **cobas**® HPV 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. Women who are positive for high-risk HPV by the cobas® HPV Test from a clinician-collected cervical specimen or a self-collected vaginal specimen should follow-up with a clinician to determine management.
- A negative high-risk HPV result does not exclude the possibility of future cytologic HSIL or underlying CIN2-3 or cancer.
- Human 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 **cobas**® HPV must be limited to personnel trained in the techniques of PCR and the use of the **cobas**® 5800 System 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.
- HPV negative results are not intended to prevent women from proceeding to colposcopy.
- Positive test results indicate 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.
- Use of tubes other than those recommended in Table 9 must be verified by user prior to implementation into **cobas**® HPV workflow in the laboratory.
- Use of barcodes other than those recommended in Table 9 must be verified by user prior to implementation into **cobas**® HPV workflow in the laboratory.
- Residual post-cytology specimens evaluated were processed on the ThinPrep® 2000 Processor.

Non-clinical performance evaluation

Key performance characteristics

Limit of Detection (LoD) in cervical specimens at the clinical cutoff

The LoD at the clinical cutoff for HPV16 and HPV18 was assessed using SiHa and HeLa cell lines in the background of pooled HPV negative cervical specimens. 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 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 DNA in the sample that has positive test results at least 95% of the time with concentration above the clinical cutoff.

The LoD for SiHa and HeLa was 16 cells/mL. Table 16 and Table 17 contain results from the reagent lot producing the most conservative (highest) LoD in the analysis for HPV16 and HPV18.

Table 16 Limit of Detection levels for HPV16 (SiHa Cell Line) in Cervical Specimens

SiHa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	24 / 24	100%	86.2% - 100%
16	**24 / 24**	**100%**	**86.2% - 100%**
8	22 / 24	91.7%	74.2% - 97.7%

Table 17 Limit of Detection levels for HPV18 (HeLa Cell Line) in Cervical Specimens

HeLa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	24 / 24	100%	86.2% - 100%
16	**24 / 24**	**100%**	**86.2% - 100%**
8	22 / 24	91.7%	74.2% - 97.7%

Limit of Detection (LoD) in self-collected vaginal specimens at the clinical cutoff

The LoD at the clinical cutoff for HPV16 and HPV18 was assessed using SiHa and HeLa cell lines in the background of pooled HPV negative self-collected vaginal specimens. Cell lines were diluted to concentrations targeting below, above and at the expected LoD levels. A minimum of 27 replicates were tested for each cell line level using 2 reagent lots with an equal number tests on the **cobas**® 5800, **cobas**® 6800 and the **cobas**® 8800 Systems. The LoD was defined as the level of HPV DNA in the sample that has positive test results at least 95% of the time with concentration above the clinical cutoff.

The LoD for SiHa and HeLa was 16 cells/mL and 32 cells/mL, respectively. Table 18 and Table 19 contain results from the reagent lot producing the most conservative (highest) LoD in the analysis for HPV16 and HPV18.

Table 18 Limit of Detection levels for HPV16 (SiHa Cell Line) in Vaginal Specimens

SiHa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	27 / 27	100%	87.2% - 100%
16	**27 / 27**	**100%**	**87.2% - 100%**
8	22 / 27	81.5%	61.9% - 93.7%

Table 19 Limit of Detection levels for HPV18 (HeLa Cell Line) in Vaginal Specimens

HeLa Concentration (cells/mL)	Number of Positive/Tested	% Positive	95% Confidence Interval
32	**27 / 27**	**100%**	**87.2% - 100%**
16	25 / 27	92.6%	75.7% - 99.1%
8	27 / 27	100%	87.2% - 100%

Equivalency of the cobas® 5800 System to the cobas® 6800/8800 Systems at cobas® HPV LoD levels

The equivalency of the **cobas®** 5800 System to the **cobas®** 6800/8800 Systems was confirmed with **cobas®** HPV using panels prepared at levels around the LoD. Dilutions of SiHa and HeLa cell lines in pooled HPV negative clinical specimens were tested across three **cobas®** 5800 Systems and two **cobas®** 6800/8800 Systems using three reagent lots. There were at least 65 replicates for each level tested on both the **cobas®** 5800 System and **cobas®** 6800/8800 Systems. Table 20 and Table 21 show the HPV positive rates and 95% confidence intervals for HPV16 and HPV18, respectively.

Table 20 cobas® 5800 System vs. cobas® 6800/8800 Systems performance at Limit of Detection levels for HPV16 (SiHa Cell Line)

HPV16 Level Tested	cobas® 5800 System			cobas® 6800/8800 Systems		
	Number of Positive/Tested	% Positive	95% Confidence Interval	Number of Positive/Tested	% Positive	95% Confidence Interval
2x LoD	66 / 66	100%	94.5% - 100%	66 / 66	100%	94.5% - 100%
1x LoD	62 / 66	93.9%	85.4% - 97.6%	66 / 66	100%	94.5% - 100%
0.5x LoD	51 / 66	77.3%	65.8% - 85.7%	51 / 65	78.5%	67.0% - 86.7%
0.25x LoD	40 / 66	60.6%	48.5% - 71.5%	34 / 66	52.3%	40.4% - 64.0%
0.125x LoD	19 / 66	28.8%	19.3% - 40.6%	18 / 66	27.3%	18.0% - 39.0%

Table 21 cobas® 5800 System vs. cobas® 6800/8800 Systems performance at Limit of Detection levels for HPV18 (HeLa Cell Line)

HPV18 Level Tested	cobas® 5800 System			cobas® 6800/8800 Systems		
	Number of Positive/Tested	% Positive	95% Confidence Interval	Number of Positive/Tested	% Positive	95% Confidence Interval
2x LoD	66 / 66	100%	94.5% - 100%	66 / 66	100%	94.5% - 100%
1x LoD	66 / 66	100%	94.5% - 100%	65 / 66	98.5%	91.9% - 99.7%
0.5x LoD	59 / 66	89.4%	79.7% - 94.8%	57 / 65	87.7%	77.5% - 93.6%
0.25x LoD	38 / 66	57.6%	45.6% - 68.8%	40 / 65	61.5%	49.4% - 72.4%
0.125x LoD	27 / 66	40.9%	29.9% - 53.0%	26 / 66	39.4%	28.5% - 51.5%

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 cervical specimens. All 12 of the high risk genotypes tested close to the LoD at the clinical cutoff were detected by the assay.

Plasmid for high risk genotypes 45 was tested in the background of pooled HPV negative self-collected vaginal specimens as a representative type to demonstrate performance in vaginal specimens. Testing of HPV45 close to the LoD at the clinical cutoff was detected by the assay.

Precision

Within-laboratory precision was examined using a panel composed of either HPV cell lines or HPV positive clinical samples diluted into a pool of negative cervical specimen matrix. Additionally, a "zero concentration" HPV negative sample composed of HCT-15 cells in PreservCyt Solution was also included.

The precision panel was designed to include members with high negative, very low (< LoD), low (~ LoD) and moderate (> LoD) concentrations of HPV as well as an HPV negative. 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 22.

All panel members exhibited the expected hit rates when tested using **cobas**® HPV.

Analysis of Ct values variability in positive panel members yielded overall CV (%) ranges from 4.32% to 6.19% for Other High Risk HPV (Table 23), 1.09% to 4.61% for HPV16 (Table 24) and 1.23% to 3.76% for HPV18 (Table 25).

Table 22 Summary of within laboratory precision

Panel Level	Target Source	HPV Concentration	Target Channel	N Tested	N Positive	Hit Rate	Hit Rate 95% CI	
							LL	UL
Negative	N/A	N/A	Other HR HPV	72	0	0%	0%	5%
Negative	N/A		HPV16	72	0	0%	0%	5%
Negative	N/A		HPV18	72	0	0%	0%	5%
High Negative	Clinical sample	N/A	Other HR HPV	72	0	0%	0%	5%
High Negative	Clinical sample		HPV16	72	0	0%	0%	5%
High Negative	Clinical sample		HPV18	72	5	7%	3%	15%
< 1 x LoD	Clinical sample	N/A	Other HR HPV	72	30	42%	31%	53%
< 1 x LoD	Clinical sample	N/A	HPV16	71	33	47%	35%	58%
< 1 x LoD	Clinical sample	N/A	HPV18	72	49	68%	57%	78%
< 1 x LoD	SiHa cell line	4.8 cells/mL	HPV16	72	44	61%	50%	72%
< 1 x LoD	HeLa cell line	4.8 cells/mL	HPV18	72	49	68%	57%	78%
~ 1 x LoD	Clinical sample	N/A	Other HR HPV	72	72	100%	95%	100%
~ 1 x LoD	SiHa cell line	16 cells/mL	HPV16	72	72	100%	95%	100%
~ 1 x LoD	HeLa cell line	16 cells/mL	HPV18	72	72	100%	95%	100%
> 1 x LoD	Clinical sample	N/A	Other HR HPV	72	72	100%	95%	100%
> 1 x LoD	SiHa cell line	48 cells/mL	HPV16	72	72	100%	95%	100%
> 1 x LoD	HeLa cell line	48 cells/mL	HPV18	72	72	100%	95%	100%

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

Table 23 Overall mean, standard deviations and coefficients of variation (%) for cycle threshold – 12 Other High Risk HPV

Level	Hit Rate	Mean Ct	Between-Day		Between-Instrument		Between-Operator		Between-Lot		Between-Run		Within-Run		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
< LoD[1]	41.7%	33.2	0	0	0	0	0	0	0	0	0.47	1.43	1.72	5.18	1.78	5.37
~ LoD[1]	100%	32.4	0	0	0	0	0.49	1.50	0.16	0.51	0	0	1.94	5.98	2.01	6.19
> LoD[1]	100%	30.7	0	0	0	0	0	0	0.27	0.88	0	0	1.30	4.23	1.33	4.32

1 12 Other HR HPV positive clinical sample diluted in pooled negative cervical specimen matrix

Table 24 Overall mean, standard deviations and coefficients of variation (%) for cycle threshold – HPV16

Level	Hit Rate	Mean Ct	Between-Day		Between-Instrument		Between-Operator		Between-Lot		Between-Run		Within-Run		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
< LoD[1]	46.5%	35.7	0.84	2.34	0.29	0.80	0.85	2.39	0	0	0	0	1.10	3.07	1.65	4.61
< LoD[2]	61.1%	36.1	0.44	0.67	0	0	0.16	0.45	0.21	0.57	0	0	0.49	1.36	0.61	1.68
~ LoD[2]	100%	35.0	0	0	0.02	0.06	0.02	0.07	0.38	1.09	0	0	0.45	1.28	0.59	1.69
> LoD[2]	100%	34.0	0.03	0.09	0.04	0.12	0	0	0.27	0.78	0	0	0.25	0.74	0.37	1.09

[1] HPV16 positive clinical sample diluted in pooled negative cervical specimen matrix.

[2] HPV16 cell line diluted in pooled negative cervical specimen matrix.

Table 25 Overall mean, standard deviations and coefficients of variation (%) for cycle threshold – HPV18

Level	Hit Rate	Mean Ct	Between-Day		Between-Instrument		Between-Operator		Between-Lot		Between-Run		Within-Run		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
< LoD[1]	68.1%	35.9	0	0	0.55	1.52	0	0	0.18	0.51	0.17	0.49	1.21	3.37	1.35	3.76
< LoD[2]	68.1%	35.3	0.19	0.54	0	0	0.02	0.06	0	0	0	0	0.97	2.75	0.99	2.80
~ LoD[2]	100%	33.8	0	0	0	0	0	0	0.37	1.11	0	0	0.73	2.17	0.82	2.44
> LoD[2]	100%	32.2	0	0	0	0	0	0	0.22	0.68	0.03	0.10	0.33	1.02	0.39	1.23

[1] HPV18 positive clinical sample diluted in pooled negative cervical specimen matrix.

[2] HPV18 cell line diluted in pooled negative cervical specimen matrix.

Analytical specificity

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 26 were spiked at concentrations of approximately 1 x 10^6 units*/mL for bacteria and approximately 1 x 10^5 units*/mL for viruses (except Adenovirus Type 40 which was tested at 2.82 x 10^4 units*/mL) into pools of HPV negative cervical specimens. Testing was performed with each potential interfering organism alone as well as with each organism mixed with HPV31 plasmid, SiHa (HPV16) and HeLa (HPV18) cell lines at approximately 3 x LoD of **cobas**® HPV. Results indicated that none of these organisms interfered with detection of Other High Risk HPV, 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 *Chlamydia trachomatis* which was quantified as Inclusion Forming Units (IFU). *Trichomonas vaginalis* was quantified as cells/mL. All viruses were quantified as units/mL as determined by $TCID_{50}$ Endpoint Dilution Assay except Epstein Barr virus which was in copies/mL.

Table 26 Microorganisms tested for analytical specificity

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

*Formerly *Peptostreptococcus magnus*

Interference

Testing in cervical specimens

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 3 x LoD of **cobas®** HPV in HPV negative samples.

Endogenous substances tested were cervical mucus, peripheral blood mononuclear cells and whole blood. Levels of endogenous substances tolerated by the assay are shown in Table 27. Exogenous substance testing included 18 over-the-counter (OTC) feminine hygiene and prescription products that are listed in Table 28. Of OTC feminine hygiene and prescription products tested, Metronidazole Vaginal Gel, Replens™, RepHresh™ Odor Eliminating Vaginal Gel and RepHresh™ Clean Balance™ Feminine Freshness Kit produced false negative results.

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

Table 27 Summary of endogenous substance concentrations in cervical specimens that do not interfere with performance

Endogenous Substance	PreservCyt®
Mucus	Presence*
Peripheral Blood Mononuclear Cells (PBMCs as cells/mL)	1.00E+06
Whole Blood (% v/v)	10%

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

Table 28 List of substances with concentrations that do not interfere with performance in cervical specimens

Product Name	Concentration
Clindamycin Phosphate Vaginal Cream	1.40 mg/mL
CVS Tioconazole 1 (Equate™ tioconazole 1)	8.02 mg/mL
Equate™ Vagicaine Anti-Itch Cream	5.87 mg/mL
Estrace® Cream	4.38 mg/mL
K-Y® Ultra Gel	6.59 mg/mL
Metronidazole Vaginal Gel§	*
Monistat® 3 Vaginal Antifungal Combination Pack	1.57 mg/mL
Monistat® Complete Care Itch Relief Cream	4.76 mg/mL
Gyne-Lotrimin® 7	3.13 mg/mL
Norforms® Suppositories	1.10 mg/mL
Premarin® Vaginal Cream	3.65 mg/mL
Replens™ Long-Lasting Vaginal Moisturizer§	†
RepHresh™ Odor Eliminating Vaginal Gel§	‡
RepHresh™ Clean Balance™ Feminine Freshness Kit§	‡
Summer's Eve® Feminine Deodorant Spray	0.90 mg/mL
VCF® - Vaginal Contraceptive Foam	1.42 mg/mL
Yeast Gard Advanced®	3.04 mg/mL
ZOVIRAX® (acyclovir) Cream 5%	10.37 mg/mL
Glacial acetic acid	5% (v/v)

* Concentration of product that did not cause interference with test performance was 0.20 mg/mL.

† Concentration of product that did not cause interference with test performance was 0.96 mg/mL.

‡ Concentrations of product that did not interfere with test performance were not determined.

§ Products containing carbomer(s) have been shown to cause interference.

Testing in self-collected vaginal specimens

The effects of endogenous and exogenous substances that may be present in vaginal 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 3 x LoD in pools of HPV negative self-collected vaginal specimens.

Endogenous substances tested were beta estradiol, biotin, mucin, peripheral blood mononuclear cells, progesterone, seminal fluid and whole blood. Levels of endogenous substances tolerated by the assay are shown in Table 29. Exogenous substance testing included 6 over-the-counter (OTC) feminine hygiene products that are listed in Table 30. Of OTC feminine hygiene products tested, Dove Advanced Care Antiperspirant Dry Spray and RepHresh™ Odor Eliminating Vaginal Gel produced false negative results.

Table 29 Summary of endogenous substance concentrations in vaginal specimens that do not interfere with performance

Endogenous Substance	PreservCyt®
Beta Estradiol	0.07 mg/mL
Biotin	3.87 µg/mL
Mucin	0.80% w/v
Peripheral Blood Mononuclear Cells (PBMCs as cells/mL)	1.00E+06
Progesterone	0.07 mg/mL
Seminal fluid (% v/v)	5%
Whole Blood (% v/v)	10%

Table 30 List of substances with concentrations that do not interfere with performance in vaginal specimens

Product Name	Concentration
Abreva® Cold Sore Cream	0.25% w/v
Dove Advanced Care Clear Finish Antiperspirant Dry Spray (0% alcohol)	*
Preparation H® Hemorrhoidal Ointment	0.25% w/v
Summer's Eve® Povidone-Iodine Medicated Douche	0.25% w/v
Summer's Eve® Cleansing Wash	0.40% w/v
RepHresh™ Odor Eliminating Vaginal Gel†	*

* Concentrations of product that did not cause interference with test performance were not determined.

† Products containing carbomer(s) have been shown to cause interference.

Competitive inhibition

Competitive inhibition of HPV16 and HPV18 detection was assessed by testing samples containing low concentrations of HPV16 and HPV18 along with high concentration of non-targeted low risk HPV and targeted other high risk HPV. The HPV16 and HPV18 were spiked to concentrations close to ~1 x LoD; each of the 25 low risk and 12 other high risk HPV tested were at a concentration were spiked to a concentration 1000-fold ($3\log_{10}$) higher than that of HPV16 and HPV18.

Results confirmed that **cobas**® HPV can detect low concentrations of HPV16 and HPV18 in the presence of any of the 25 non-targeted low risk and 12 other high risk HPV at a concentration that is 1000-fold ($3\log_{10}$) higher in concentration.

Cross contamination

cobas® 6800/8800 Systems

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% (0/288, 95% CI= 0.00% – 1.27%) 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% (0/187, 95% CI= 0.00% – 1.95%).

cobas® 5800 System

Studies were performed to evaluate potential cross contamination on the **cobas**® 5800 Systems using **cobas**® HPV. In this performance study the sample to sample cross-contamination rate of **cobas**® HPV has been determined to be 0% (0/72, 1-sided upper 95% CL= 4.08%) 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% (0/22, 1-sided upper 95% CL= 12.73%).

Clinical performance evaluation

Expected results

A multicenter, prospective study (IMPACT trial, IMproved Primary screening And Colposcopy Triage) was conducted to evaluate the performance of **cobas®** HPV performed on the **cobas®** 6800/8800 Systems (Roche Molecular Systems, Inc., hereafter referred to as **cobas®** 6800/8800 HPV test) as a triage test to stratify women with ASC-US Pap cytology results for colposcopy, as an adjunctive test to cervical cytology to guide management decisions in women with NILM Pap cytology, and as a first-line primary test for cervical cancer screening.

In total, 35,263 women 25-65 years were enrolled from September 2017 to October 2018 at 32 clinical sites in the United States. A total of 34,914 women met study eligibility criteria. One woman was excluded due to insufficient sample volume for HPV testing (eligible n=34,913). The percent of invalid **cobas®** 6800/8800 HPV test results was 0.04% (13/34,913) with 95% CI: 0.02% to 0.06%.

Table 31 shows HPV positivity by the **cobas®** 6800/8800 HPV test by testing site and study population. The overall HPV positivity was 35.20% in the ASC-US (25-65 years) population, 10.16% in the NILM (30-65 years) population and 15.08% in the Primary Screening (25-65 years) population.

Table 31 HPV positivity by the cobas® 6800/8800 HPV test by testing sites and study population

Testing Site	Evaluable ASC-US Population (25-65 Years)	Evaluable NILM Population (30-65 Years)	Evaluable Primary Screening Population (25-65 Years)
1	38.28% (116/303)	8.83% (454/5,139)	13.29% (910/6,846)
2	39.53% (204/516)	10.47% (636/6,074)	15.10% (1,229/8,138)
3	32.40% (335/1,034)	10.78% (902/8,364)	16.85% (2,051/12,171)
4	34.53% (144/417)	10.10% (580/5,745)	13.85% (1,060/7,652)
Overall	35.20% (799/2,270)	10.16% (2,572/25,322)	15.08% (5,250/34,807)

Table 32 shows HPV positivity of the **cobas®** 6800/8800 HPV test by age and study population. HPV positivity decreased with age in each study population. In the ASC-US population, HPV positivity decreased from 52.15% in 25-29 year olds to 38.20% in 30-39 year olds and remained ~24% in women 40-65 years old. In the NILM population, HPV positivity was 12.67% in 30-39 year old women and remained about 8% in 40-65 year old women. In the primary screening population, HPV positivity decreased from 24.01% in 25-29 year olds to 16.44% in 30-39 year olds and remained relatively constant at ~10-11% in 40-65 year old women.

Table 32 HPV positivity by the cobas® 6800/8800 HPV test by age and study population

Age Group (Years)	cobas® 6800/8800 HPV Test Result ASC-US Population (25-65 Years)	cobas® 6800/8800 HPV Test Result NILM Population (30-65 Years)	cobas® 6800/8800 HPV Test Result Primary Screening Population (25-65 Years)
25-29	52.15% (267/512)	Not Applicable	24.01% (1,568/6,530)
30-39	38.20% (288/754)	12.67% (1,328/10,482)	16.44% (1,944/11,826)
40-49	24.00% (129/538)	8.54% (632/7,397)	11.05% (914/8,271)
50-65	24.68% (115/466)	8.22% (612/7,443)	10.07% (824/8,180)
Overall	35.20% (799/2,270)	10.16% (2,572/25,322)	15.08% (5,250/34,807)

cobas® 6800/8800 HPV test results stratified by age for the ASC-US, NILM, and primary screening populations are presented in Table 33. In all populations, 12 Other HR HPV positive results were more frequent than HPV16 and HPV18 positive results in general and within age groups.

Table 33 cobas® 6800/8800 HPV test results by age group for the evaluable populations

cobas® 6800/8800 HPV Test Result					
Age Group (Years)	**HPV16 Positive n (%)**	**HPV18 Positive n (%)**	**12 Other HR HPV Positive n (%)**	**HPV Negative n (%)**	**Total N**
ASC-US Population (25-65 Years)					
Overall	6.34% (144/2,270)	2.78% (63/2,270)	26.08% (592/2,270)	64.80% (1,471/2,270)	2,270
25-29	8.01% (41/512)	2.34% (12/512)	41.80% (214/512)	47.85% (245/512)	512
30-39	7.43% (56/754)	3.18% (24/754)	27.59% (208/754)	61.80% (466/754)	754
40-49	5.02% (27/538)	2.42% (13/538)	16.54% (89/538)	76.02% (409/538)	538
50-65	4.29% (20/466)	3.00% (14/466)	17.38% (81/466)	75.32% (351/466)	466
NILM Population (30-65 Years)					
Overall	2.20% (556/25,322)	1.21% (306/25,322)	6.75% (1,710/25,322)	89.84% (22750/25,322)	25,322
30-39	2.57% (269/10,482)	1.43% (150/10,482)	8.67% (909/10,482)	87.33% (9,154/10,482)	10,482
40-49	2.16% (160/7,397)	1.04% (77/7,397)	5.34% (395/7,397)	91.46% (6,765/7,397)	7,397
50-65	1.71% (127/7,443)	1.06% (79/7,443)	5.45% (406/7,443)	91.78% (6,831/7,443)	7,443
Primary Screening Population (25-65 Years)					
Overall	3.06% (1,064/34,807)	1.42% (493/34,807)	10.61% (3,693/34,807)	84.92% (29557/34,807)	34,807
25-29	3.61% (236/6,530)	1.23% (80/6,530)	19.17% (1,252/6,530)	75.99% (4,962/6,530)	6,530
30-39	3.57% (422/11,826)	1.70% (201/11,826)	11.17% (1,321/11,826)	83.56% (9,882/11,826)	11,826
40-49	2.88% (238/8,271)	1.27% (105/8,271)	6.90% (571/8,271)	88.95% (7,357/8,271)	8,271
50-65	2.05% (168/8,180)	1.31% (107/8,180)	6.71% (549/8,180)	89.93% (7,356/8,180)	8,180

Clinical performance

The study enrolled 35,263 women aged 25–65 years undergoing routine cervical cancer screening in the US from September 2017 to October 2018 at 32 clinical sites in the Baseline Phase. A total of 34,914 women were eligible to participate in the study.

Following written informed consent, demographic information and gynecologic histories were obtained. All women had one cervical sample collected using a brush/spatula for approximately half of the subjects and a broom-type device for the other half. Cervical samples were collected for HPV testing and ThinPrep® Pap Test™ liquid based cytology (LBC). Two HPV tests were used: the FDA-approved HPV Test and **cobas**® 6800/8800 HPV test, performed according to manufacturer's instructions. HPV testing was performed on pre-aliquoted samples in secondary vials prior to cytology processing at four testing laboratories. LBC testing was conducted at the same four laboratories. Cytology samples were classified according to the criteria of the 2001 Bethesda System. Pap cytology, FDA approved HPV Test, and **cobas**® 6800/8800 HPV test results were used to inform referral to colposcopy.

To determine the clinical study endpoint, a subset of non-pregnant women identified at the enrollment visit was selected to undergo colposcopy and biopsy/endocervical curettage (ECC). The subset included women aged 25-65 years with ≥ASC-US cytology and women aged 25-65 years with positive **cobas**® HPV Test results (positive by the FDA-approved HPV Test and/or **cobas**® 6800/8800 HPV test). In addition, 59 women with unsatisfactory Pap cytology and HPV-negative results (negative by both the FDA-approved HPV Test and **cobas**® 6800/8800 HPV test), and a randomly selected subset of subjects with NILM Pap cytology and HPV-negative results (negative by both the FDA-approved HPV Test and **cobas**® 6800/8800 HPV test) were referred to colposcopy (approximately 1:50). In order to avoid bias, study participants and colposcopists were blinded to all HPV test and cytology results until after the colposcopy was completed.

Colposcopy was conducted according to a standardized protocol following the principles recommended by the American Society for Colposcopy and Cervical Pathology (ASCCP) as follows: 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 Central Pathology Review (CPR) process consisting of three expert pathologists, and discordant results adjudicated according to a pre-defined protocol. The slides that were prepared from the biopsies were stained using conventional hematoxylin and eosin (H&E) staining, and H&E with p16 IHC assay (CINtec Histology, Ventana Medical Systems, Inc.). The expert pathologist first evaluated H&E-stained slides to establish the $CPR_{H\&E}$ reference diagnosis, then evaluated both H&E- and p16 histology-stained slides for that case to establish the $CPR_{H\&E+p16}$ reference diagnosis. Additionally, CPR results were derived using results from $CPR_{H\&E}$ and $CPR_{H\&E+p16}$ diagnoses, where diagnosis was based on the H&E-stained slides with adjunctive interpretation of the p16-stained slides only when a case met LAST (Lower Anogenital Squamous Terminology) criteria (excluding ASC-US/HPV16+ as a LAST criterion).

Clinical performance of the **cobas**® 6800/8800 HPV test is presented using interpretation of H&E-stained slides with adjunctive use of p16-stained slides in accordance with the 2012 Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions (LAST)[30] excluding ASC-US/HPV16+ as a LAST criterion ($CPR_{H\&E+p16\ per\ LAST}$) at the clinical endpoints ≥CIN2 and ≥CIN3.

ASC-US (25-65 years) population – performance evaluation

In IMPACT, all women 25-65 years old with ≥ASC-US Pap cytology, regardless of HPV results, were invited to undergo colposcopy. The clinical performance of **cobas®** 6800/8800 HPV test was measured against histology results of ≥CIN2 and ≥CIN3 by CPR.

Eligible women in IMPACT who had an ASC-US Pap cytology result and valid **cobas®** 6800/8800 HPV test results were considered evaluable for the analyses of the ASC-US objectives. Of the 34,807 evaluable women in the overall population, 2,270 women had an ASC-US Pap cytology (6.5%) and valid **cobas®** 6800/8800 HPV test result. The results of the **cobas®** 6800/8800 HPV test reported as HPV Positive or HPV Negative by CPR histologic diagnosis are presented in Table 34. Of the 1,814 women with ASC-US and valid CPR diagnosis, 124 women were diagnosed with ≥CIN2 (prevalence of 6.8%) and 36 women were diagnosed with ≥CIN3 (prevalence of 2.0%).

Table 34 cobas® 6800/8800 HPV test results and central pathology review diagnoses in the evaluable ASC-US population (25-65 years)

cobas® 6800/8800 HPV Test Result	Central Pathology Review Diagnoses Undetermined[1]	Central Pathology Review Diagnoses Normal[2]	Central Pathology Review Diagnoses CIN1	Central Pathology Review Diagnoses CIN2	Central Pathology Review Diagnoses ≥CIN3	Total
HPV Positive	42	440	84	75	32	673
HPV Negative	66	1,101	65	13	4	1,249
Total	108	1,541	149	88	36	1,922

[1] Undetermined includes: biopsy sample inadequate for analysis, subject/colposcopist unblinded to HPV or Pap cytology result at colposcopy visit or biopsy sample taken out of window.

[2] Normal includes: Negative or normal histology and atypical squamous cells or glandular changes indefinite for neoplasia.

The performance of **cobas®** 6800/8800 HPV test and the FDA-approved HPV Test in detecting high grade cervical disease (≥CIN2 and ≥CIN3) is presented in Table 35. The sensitivity for detecting ≥CIN2 was 86.29% (95% CI: 79.14, 91.26) for the **cobas®** 6800/8800 HPV test, similar to the performance of the FDA-approved HPV Test (86.18%, 95% CI: 78.98, 91.19). The specificity for detecting ≥CIN2 was 68.99% (95% CI: 66.75, 71.15) for the **cobas®** 6800/8800 HPV test and 69.47% (95% CI: 67.23, 71.62) for the FDA-approved HPV Test.

The sensitivity for detecting ≥CIN3 was 88.89% (95% CI: 74.69, 95.59) for the **cobas®** 6800/8800 HPV test, and 86.11% (95% CI: 71.34, 93.92) for the FDA-approved HPV Test. The specificity for detecting ≥CIN3 was 66.31% (95% CI: 64.08, 68.47) for the **cobas®** 6800/8800 HPV test, and 66.74% (95% CI: 64.52, 68.89) for the FDA-approved HPV Test.

Table 35 Performance of the cobas® 6800/8800 HPV test and the FDA-approved HPV Test in the evaluable ASC-US population (25-65 years)

Performance Parameters	≥CIN2 Prevalence (95% CI)=6.84% (124/1814) (5.76, 8.09) cobas® 6800/8800 HPV Test	≥CIN2 Prevalence (95% CI)=6.84% (124/1814) (5.76, 8.09) FDA-approved HPV Test	≥CIN3 Prevalence (95% CI)=1.98% (36/1814) (1.44, 2.74) cobas® 6800/8800 HPV Test	≥CIN3 Prevalence (95% CI)=1.98% (36/1814) (1.44, 2.74) FDA-approved HPV Test
Sensitivity (%) (95% CI)	86.29 (107/124) (79.14, 91.26)	86.18 (106/123) (78.98, 91.19)	88.89 (32/36) (74.69, 95.59)	86.11 (31/36) (71.34, 93.92)
Specificity (%) (95% CI)	68.99 (1166/1690) (66.75, 71.15)	69.47 (1174/1690) (67.23, 71.62)	66.31 (1179/1778) (64.08, 68.47)	66.74 (1186/1777) (64.52, 68.89)
PPV (%) (95% CI)	16.96 (107/631) (15.60, 18.41)	17.04 (106/622) (15.66, 18.52)	5.07 (32/631) (4.47, 5.75)	4.98 (31/622) (4.33, 5.73)
NPV (%) (95% CI)	98.56 (1166/1183) (97.78, 99.07)	98.57 (1174/1191) (97.80, 99.08)	99.66 (1,179/1,183) (99.15, 99.87)	99.58 (1,186/1,191) (99.06, 99.81)
PLR (95% CI)	2.78 (107/124) / (524/1690) (2.52, 3.08)	2.82 (106/123) / (516/1690) (2.55, 3.12)	2.64 (32/36) / (599/1778) (2.31, 3.01)	2.59 (31/36) / (591/1777) (2.24, 3.00)
NLR (95% CI)	0.20 (17/124) / (1166/1690) (0.13, 0.31)	0.20 (17/123) / (1174/1690) (0.13, 0.31)	0.17 (4/36) / (1179/1778) (0.07, 0.42)	0.21 (5/36) / (1186/1777) (0.09, 0.47)

PPV=Positive predictive value; NPV=Negative predictive value; PLR=Positive likelihood ratio; NLR=Negative likelihood ratio

The performance of the **cobas®** 6800/8800 HPV test and the FDA-approved HPV Tests for detecting high grade cervical disease (≥CIN2 and ≥CIN3) stratified by age group is presented in Table 36. The sensitivity for detecting ≥CIN2 ranged from 80.77% to 89.36% for the **cobas®** 6800/8800 HPV test and from 84.62% to 89.36% for the FDA-approved HPV Test; the specificity ranged from 51.35% to 77.72% for the **cobas®** 6800/8800 HPV test and from 52.25% to 78.43% for the FDA-approved HPV Test.

The sensitivity for ≥CIN3 of both the **cobas®** 6800/8800 HPV test and the FDA-approved HPV Test ranged from 66.67% to 93.33%; the specificity ranged from 47.95% to 76.22% for the **cobas®** 6800/8800 HPV test and from 48.77% to 76.79% for the FDA-approved HPV Test.

Table 36 Performance of the cobas® 6800/8800 HPV test and the FDA-approved HPV Test in detecting ≥CIN2 and ≥CIN3 in the evaluable ASC-US population, stratified by age group

Statistic	cobas® 6800/8800 HPV Test	FDA-approved HPV Test	cobas® 6800/8800 HPV Test	FDA-approved HPV Test	cobas® 6800/8800 HPV Test	FDA-approved HPV Test
	25–29 Years		30–39 Years		40–65 Years	
≥CIN2						
Prevalence (%) (95% CI)	12.37 (47/380) (9.43, 16.06)		8.63 (51/591) (6.62, 11.17)		3.08 (26/843) (2.11, 4.48)	
Sensitivity (%) (95% CI)	89.36 (42/47) (77.41, 95.37)	89.36 (42/47) (77.41, 95.37)	86.27 (44/51) (74.28, 93.19)	84.00 (42/50) (71.49, 91.66)	80.77 (21/26) (62.12, 91.49)	84.62 (22/26) (66.47, 93.85)
Specificity (%) (95% CI)	51.35 (171/333) (46.00, 56.67)	52.25 (174/333) (46.89, 57.56)	66.67 (360/540) (62.59, 70.51)	66.54 (360/541) (62.46, 70.39)	77.72 (635/817) (74.74, 80.44)	78.43 (640/816) (75.48, 81.12)
PPV (%) (95% CI)	20.59 (42/204) (18.27, 23.11)	20.90 (42/201) (18.53, 23.47)	19.64 (44/224) (17.21, 22.32)	18.83 (42/223) (16.38, 21.56)	10.34 (21/203) (8.42, 12.65)	11.11 (22/198) (9.20, 13.36)
NPV (%) (95% CI)	97.16 (171/176) (93.69, 98.75)	97.21 (174/179) (93.79, 98.77)	98.09 (360/367) (96.27, 99.03)	97.83 (360/368) (95.96, 98.84)	99.22 (635/640) (98.30, 99.64)	99.38 (640/644) (98.48, 99.75)
≥CIN3						
Prevalence (%) (95% CI)	3.95 (15/380) (2.41, 6.41)		2.54 (15/591) (1.54, 4.15)		0.71 (6/843) (0.33, 1.54)	
Sensitivity (%) (95% CI)	93.33 (14/15) (70.18, 98.81)	93.33 (14/15) (70.18, 98.81)	93.33 (14/15) (70.18, 98.81)	86.67 (13/15) (62.12, 96.26)	66.67 (4/6) (30.00, 90.32)	66.67 (4/6) (30.00, 90.32)
Specificity (%) (95% CI)	47.95 (175/365) (42.87, 53.07)	48.77 (178/365) (43.68, 53.88)	63.54 (366/576) (59.53, 67.37)	63.54 (366/576) (59.53, 67.37)	76.22 (638/837) (73.22, 78.98))	76.79 (642/836) (73.81, 79.53)
PPV (%) (95% CI)	6.86 (14/204) (5.87, 8.01)	6.97 (14/201) (5.95, 8.14)	6.25 (14/224) (5.31, 7.34)	5.83 (13/223) (4.71, 7.20)	1.97 (4/203) (1.11, 3.46))	2.02 (4/198) (1.14, 3.55)
NPV (%) 95% CI (%)	99.43 (175/176) (96.33, 99.91)	99.44 (178/179) (96.39, 99.92)	99.73 (366/367) (98.22, 99.96)	99.46 (366/368) (98.05, 99.85)	99.69 (638/640) (99.04, 99.90)	99.69 (642/644) (99.04, 99.90)

PPV=Positive predictive value; NPV=Negative predictive value.

Table 37 presents CPR diagnosis by all possible **cobas®** 6800/8800 HPV test results in the evaluable ASC-US women who completed colposcopy.

Table 37 All possible cobas® 6800/8800 HPV test results and central pathology review diagnoses in the evaluable ASC-US population (25-65 years)

cobas® 6800/8800 HPV Test Result (12 Other HR HPV; HPV16; HPV18)	Central Pathology Review Diagnoses Undetermined[1]	Central Pathology Review Diagnoses Normal[2]	Central Pathology Review Diagnoses CIN1	Central Pathology Review Diagnoses CIN2	Central Pathology Review Diagnoses ≥CIN3	Total
12 Other HR HPV Negative; HPV16 Negative; HPV18 Negative	66	1,101	65	13	4	1,249
12 Other HR HPV Negative; HPV16 Negative; HPV18 Positive	1	18	5	2	1	27
12 Other HR HPV Negative; HPV16 Positive; HPV18 Negative	3	31	4	10	9	57
12 Other HR HPV Negative; HPV16 Positive; HPV18 Positive	0	1	0	1	0	2
12 Other HR HPV Positive; HPV16 Negative; HPV18 Negative	31	344	67	49	13	504
12 Other HR HPV Positive; HPV16 Negative; HPV18 Positive	2	15	3	3	0	23
12 Other HR HPV Positive; HPV16 Positive; HPV18 Negative	5	28	4	10	9	56
12 Other HR HPV Positive; HPV16 Positive; HPV18 Positive	0	3	0	0	0	3
12 Other HR HPV Positive; Invalid; Invalid	0	0	1	0	0	1
Overall	108	1,541	149	88	36	1,922

[1]Undetermined includes: biopsy sample inadequate for analysis, subject/colposcopist unblinded to HPV or Pap cytology result at colposcopy visit or biopsy sample taken out of window.

[2]Normal includes: Negative or normal histology and atypical squamous cells or glandular changes indefinite for neoplasia.

Likelihood ratios (LRs) for the **cobas®** 6800/8800 HPV test are presented in Table 38 for the ASC-US (25-65 years) population.

Likelihood ratio of 14 HR HPV positive results associated with ≥CIN2 and ≥CIN3 was 2.78 and 2.64, respectively, indicating an overall increased probability of disease in women with HPV positive results.

For ≥CIN2, the LR of HPV16 positive and/or HPV18 positive was 5.48, indicating that an HPV16 positive and/or an HPV18 positive result is ~5.5 times more likely to occur in a subject with ≥CIN2 than in a subject without. The LR of a negative **cobas®** 6800/8800 HPV test result was 0.20, indicating that a negative result was 5 times more likely to occur in a subject without <CIN2 than in a subject with ≥CIN2.

For ≥CIN3, LR of HPV16 positive and/or HPV18 positive was 6.80, and the LR of an HPV negative result was 0.17.

Table 38 Likelihood ratios of disease (≥CIN2 and ≥CIN3) by the cobas® 6800/8800 HPV test results in the evaluable ASC-US population (25-65 years)

cobas® 6800/8800 HPV Test Result	Likelihood Ratio (95% CI) ≥CIN2 vs <CIN2	Likelihood Ratio (95% CI) ≥CIN3 vs <CIN3
HPV Positive	2.78 (2.52, 3.08)	2.64 (2.31, 3.01)
HPV16 Positive	7.49 (5.30, 10.58)	9.66 (6.59, 14.17)
HPV18 Positive	1.99 (0.86, 4.61)	1.07 (0.15, 7.57)
HPV16/18 Positive	5.48 (4.08, 7.35)	6.80 (4.80, 9.63)
12 Other HR HPV Positive	2.05 (1.69, 2.49)	1.39 (0.90, 2.17)
HPV Negative	0.20 (0.13, 0.31)	0.17 (0.07, 0.42)

ASC-US (25-65 years) population – absolute and relative risk estimates

The absolute risk of disease among women with positive HPV results was 16.96% and 5.07% for ≥CIN2 and ≥CIN3, respectively (Table 39). For both ≥CIN2 and ≥CIN3, the risk of disease was highest for women with HPV positive results, HPV16 and/or HPV18 positive results, and 12 Other HR HPV positive results and lowest for an HPV negative result.

The absolute risk of disease (≥CIN2 and ≥CIN3) by **cobas®** 6800/8800 HPV test results stratified by age group in the evaluable ASC-US population is presented in Table 40. For all age groups, absolute risks were higher for women with any HPV positive results, and lowest for an HPV negative result.

Table 39 Absolute risk of disease (≥CIN2 and ≥CIN3) by HPV genotype from the cobas® 6800/8800 HPV test in the evaluable ASC-US population (25-65 years)

cobas® 6800/8800 HPV Test Result	Absolute Risk % (n/N) (95% CI) ≥CIN2	Absolute Risk % (n/N) (95% CI) ≥CIN3
HPV Positive	16.96 (107/631) (14.23, 20.08)	5.07 (32/631) (3.61, 7.07)
HPV16/18 Positive	28.66 (45/157) (22.17, 36.18)	12.10 (19/157) (7.89, 18.13)
HPV16 Positive	35.45 (39/110) (27.14, 44.75)	16.36 (18/110) (10.61, 24.39)
HPV18 Positive	12.77 (6/47) (5.98, 25.17)	2.13 (1/47) (0.38, 11.11)
12 Other HR HPV Positive	13.08 (62/474) (10.34, 16.41)	2.74 (13/474) (1.61, 4.64)
HPV Negative	1.44 (17/1183) (0.90, 2.29)	0.34 (4/1183) (0.13, 0.87)

Table 40 Absolute risk of disease (≥CIN2 and ≥CIN3) by HPV Genotype from the cobas® 6800/8800 HPV test in the evaluable ASC-US population (25-65 years), stratified by age group

cobas® 6800/8800 HPV Test Result	Absolute Risk,% (95% CI) ≥CIN2	Absolute Risk,% (95% CI) ≥CIN3
25–29 Years		
HPV Positive	20.59 (15.61, 26.66)	6.86 (4.13, 11.19)
HPV16/18 Positive	34.21 (21.21, 50.11)	15.79 (7.44, 30.42)
HPV16 Positive	38.71 (23.73, 56.18)	19.35 (9.19, 36.28)
HPV18 Positive	14.29 (2.57, 51.31)	0.00 (0.00, 35.43)
12 Other HR HPV Positive	17.47 (12.45, 23.96)	4.82 (2.46, 9.22)
HPV Negative	2.84 (1.22, 6.48)	0.57 (0.10, 3.15)
30–39 Years		
HPV Positive	19.64 (14.97, 25.34)	6.25 (3.76, 10.22)
HPV16/18 Positive	40.00 (28.57, 52.63)	18.33 (10.56, 29.92)
HPV16 Positive	46.51 (32.51, 61.08)	23.26 (13.15, 37.74)
HPV18 Positive	23.53 (9.55, 47.26)	5.88 (1.05, 26.98)
12 Other HR HPV Positive	12.20 (8.03, 18.09)	1.83 (0.62, 5.24)
HPV Negative	1.91 (0.93, 3.88)	0.27 (0.05, 1.53)
40–65 Years		
HPV Positive	10.34 (6.87, 15.30)	1.97 (0.77, 4.96)
HPV16/18 Positive	13.56 (7.03, 24.54)	3.39 (0.93, 11.54)
HPV16 Positive	19.44 (9.75, 35.03)	5.56 (1.54, 18.14)
HPV18 Positive	4.35 (0.77, 20.99)	0.00 (0.00, 14.31)
12 Other HR HPV Positive	9.03 (5.35, 14.83)	1.39 (0.38, 4.92)
HPV Negative	0.78 (0.33, 1.82)	0.31 (0.09, 1.13)

The relative risk (RR) of disease (≥CIN2 and ≥CIN3) by **cobas**® 6800/8800 HPV test results in the evaluable ASC-US population is presented in Table 41.

The RRs of ≥CIN2 and ≥CIN3 for women with positive vs. negative **cobas**® 6800/8800 HPV test results were 11.78 (95% CI: 7.14, 19.50) and 14.91 (95% CI: 5.33, 42.22), respectively, indicating that women with a positive HPV result were ~12 times more likely to have ≥CIN2 and ~15 times more likely to have ≥CIN3 than women with a HPV negative test result.

Similarly, women who were HPV16 and/or HPV18 positive were significantly more likely to have ≥CIN2 than women with (i) a positive result for 12 Other HR HPV types (2.19), or (ii) a HPV negative result (19.90). Women with a positive 12 Other HR HPV result were significantly more likely to have ≥CIN2 than women with a HPV negative result (9.08). Similar results were observed for ≥CIN3 histology i.e. women with HPV positive results were more likely to have ≥CIN3 compared to HPV negative results (8.06).

Table 41 Relative risk of disease (≥CIN2 and ≥CIN3) by HPV genotype from the cobas® 6800/8800 HPV test in the evaluable ASC-US population (25-65 years)

cobas® 6800/8800 HPV Test Result	Relative Risk (95% CI) ≥CIN2	Relative Risk (95% CI) ≥CIN3
HPV Positive vs HPV Negative	11.78 (7.14, 19.50)	14.91 (5.33, 42.22)
HPV16/18 Positive vs HPV Negative	19.90 (11.71, 33.97)	35.59 (12.33, 103.86)
HPV16/18 Positive vs 12 Other HR HPV Positive	2.19 (1.56, 3.07)	4.42 (2.23, 8.73)
12 Other HR HPV Positive vs HPV Negative	9.08 (5.38, 15.40)	8.06 (2.66, 24.75)

The relative risk of disease (≥CIN2 and ≥CIN3) by **cobas**® 6800/8800 HPV test results stratified by age group in the evaluable ASC-US population is presented in Table 42 . For all age groups, similar patterns of increased risks associated with any HPV positive results were observed as those presented for the overall population in Table 42.

Table 42 Relative risk of disease (≥CIN2 and ≥CIN3) by HPV Genotype from the cobas® 6800/8800 HPV test in the evaluable ASC-US population (25-65 years), stratified by age group

cobas® 6800/8800 HPV Test Result	Relative Risk (95% CI) ≥CIN2	Relative Risk (95% CI) ≥CIN3
25-29 Years		
HPV Positive vs HPV Negative	7.25 (2.93, 17.92)	12.04 (1.60, 90.94)
HPV16/18 Positive vs HPV Negative	12.05 (4.56, 31.77)	27.70 (3.44, 224.18)
HPV16/18 Positive vs 12 Other HR HPV Positive	1.96 (1.13, 3.40)	3.28 (1.21, 8.89)
12 Other HR HPV Positive vs HPV Negative	6.15 (2.44, 15.51)	8.46 (1.07, 67.09)
30-39 Years		
HPV Positive vs HPV Negative	10.28 (4.72, 22.47)	23.15 (3.04, 173.25)
HPV16/18 Positive vs HPV Negative	20.94 (9.46, 46.51)	67.89 (8.85, 511.73)
HPV16/18 Positive vs 12 Other HR HPV Positive	3.28 (1.96, 5.49)	10.02 (2.89, 34.70)
12 Other HR HPV Positive vs HPV Negative	6.39 (2.76, 14.82)	6.78 (0.70, 64.06)
40-65 Years		
HPV Positive vs HPV Negative	13.26 (5.06, 34.67)	6.35 (1.16, 34.17)
HPV16/18 Positive vs HPV Negative	17.38 (5.86, 51.37)	10.94 (1.56, 75.62)
HPV16/18 Positive vs 12 Other HR HPV Positive	1.50 (0.66, 3.43)	2.44 (0.35, 16.92)
12 Other HR HPV Positive vs HPV Negative	11.58 (4.19, 31.90)	4.48 (0.63, 31.29)

Use of the cobas® 6800/8800 HPV test in ASC-US triage of women 21-24 years

In order to evaluate the performance of the **cobas®** 6800/8800 HPV test in 21- to 24–year old women with ASC-US Pap cytology, 140 refrigerated residual cervical samples collected in PreservCyt® were identified from participants in the ATHENA trial who were 21-24 years old and diagnosed with ASC-US Pap cytology. Samples were tested in 2018 using both **cobas®** 6800/8800 HPV test and the FDA-approved HPV Test (Table 43). One sample had invalid result by the FDA-approved HPV test and the number of evaluable samples was 139. Agreements for HPV16, HPV18, and 12 Other HR HPV are shown in Table 43, respectively.

Table 43 Cross-tabulation of cobas® 6800/8800 HPV test results and the FDA-approved HPV Test results using residual ATHENA samples

cobas® 6800/8800 HPV Test Result	FDA-approved HPV Test Result HPV16 Positive	FDA-approved HPV Test Result HPV18 Positive	FDA-approved HPV Test Result 12 Other HR HPV Positive	FDA-approved HPV Test Result HPV Negative	Total
HPV16 Positive	33	0	2	0	35
HPV18 Positive	0	8	3	1	12
12 Other HR HPV Positive	0	0	81	0	81
HPV Negative	0	0	2	9	11
Total	33	8	88	10	139
Genotype Specific PPA (95% CI)	100.00% (33/33) (89.57, 100.00)	100.00% (8/8) (67.55, 100.00)	92.05% (81/88) (84.48, 96.09)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA: 98.45% (127/129) (94.52, 99. 57)	PPA: 98.45% (127/129) (94.52, 99. 57)	NPA: 90.00% (9/10) (59.50, 98.21)	NPA: 90.00% (9/10) (59.50, 98.21)	-

PPA: Positive percent agreement; NPA: Negative percent agreement.

Note: HPV16 positive implies HPV16 positive, HPV18 positive or negative and 12 Other HR HPV positive or negative.

HPV18 positive implies HPV16 negative, HPV18 Positive and 12 Other HR HPV positive or negative.

12 Other HR HPV positive implies HPV16 negative, HPV18 negative and 12 Other HR HPV positive.

NILM population (30-65 years) - performance characteristics

Of the 34,807 evaluable women in the overall population, 25,322 had NILM Pap cytology and were 30-65 years of age. Among these, a total of 3,335 (13.17%) were selected or randomized for colposcopy for histologic diagnosis. Of those identified for colposcopy, 2,805 completed the procedure, and thereof 2,632 had a valid CPR and **cobas®** 6800/8800 HPV test result. Table 44 summarizes the distribution of verified and unverified CPR diagnoses by the **cobas®** 6800/8800 HPV test results. A total of 151 subjects were diagnosed with ≥CIN2 by CPR including 54 cases with ≥CIN3.

Table 44 cobas® 6800/8800 HPV test results and central pathology review diagnoses in the evaluable NILM population (30-65 years)

cobas® 6800/8800 HPV Test Result	Central Pathology Review Diagnoses				Unknown Disease Status[2]	Total
	Normal[1]	CIN1	CIN2	≥CIN3		
HPV Positive	1,797	100	94	54	527	2,572
HPV Negative	571	13	3	0	22,163	22,750
Total	2,368	113	97	54	22,690	25,322

[1]Normal includes: Negative or normal histology, and atypical squamous cells or glandular changes indefinite for neoplasia.

[2]Unknown disease status includes: biopsy sample inadequate for analysis or subject/colposcopist unblinded to HPV or Pap cytology result at colposcopy visit or biopsy sample taken out of window or subjects not selected for colposcopy.

Unadjusted and adjusted performance characteristics for the NILM (30-65) population are shown in Table 45. The unadjusted estimates of sensitivity and specificity for detection of ≥CIN2 were 98.01% (95% CI: 94.32, 99.32) and 23.54% (95% CI: 21.91, 25.25) respectively; for detection of ≥CIN3 estimates were 100% (95% CI: 93.36, 100) and 22.77% (95% CI: 21.19, 24.43). The verification bias adjusted sensitivities for ≥CIN2 and ≥CIN3 were 72.51% and 100%, respectively; adjusted specificities were 90.48% and 90.08%, respectively. The adjusted estimates of PPV for ≥CIN2 and ≥CIN3 were 7.20% and 2.61%, respectively; NPVs were 99.69% and 100%, respectively.

The adjusted estimates of prevalence for ≥CIN2 and ≥CIN3 were 1.01% and 0.27%, respectively.

Table 45 Performance of the cobas® 6800/8800 HPV test in the evaluable NILM population (30–65 years)

Performance Parameters	Central Pathology Review Diagnoses			
	≥CIN2		≥CIN3	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Sensitivity (%) (95% CI)	98.01 (148/151) (94.32, 99.32)	72.51 (44.28, 100.00)	100.00 (54/54) (93.36, 100.00)	100.00 (93.36, 100.00)
Specificity (%) (95% CI)	23.54 (584/2481) (21.91, 25.25)	90.48 (90.10, 90.85)	22.77 (587/2578) (21.19, 24.43)	90.08 (89.72, 90.45)
PPV (%) (95% CI)	7.24 (148/2045) (6.19, 8.44)	7.20 (6.10, 8.34)	2.64 (54/2045) (2.03, 3.43)	2.61 (1.93, 3.30)
NPV (%) (95% CI)	99.49 (584/587) (98.51, 99.83)	99.69 (99.02, 100.00)	100.00 (587/587) (99.35, 100.00)	100.00 (99.35, 100.00)
Prevalence (%) (95% CI)	5.74 (151/2632) (4.91, 6.69)	1.01 (0.65, 1.62)	2.05 (54/2632) (1.58, 2.67)	0.27 (0.19, 0.34)

PPV=Positive predictive value; NPV=Negative predictive value.

NILM (30–65 years) population – likelihood ratios

Table 46 shows the **cobas**® 6800/8800 HPV test results in the evaluable NILM (30-65) population by CPR diagnoses.

Table 46 All possible cobas® 6800/8800 HPV test results and central pathology review diagnoses in the evaluable NILM population (30–65 years)

cobas® 6800/8800 HPV Test Result (12 Other HR HPV; HPV16; HPV18)	Central Pathology Review Diagnoses Undetermined[1]	Central Pathology Review Diagnoses Normal[2]	Central Pathology Review Diagnoses CIN1	Central Pathology Review Diagnoses CIN2	Central Pathology Review Diagnoses ≥CIN3	Total
12 Other HR HPV Negative; HPV16 Negative; HPV18 Negative	22,163	571	13	3	0	22,750
12 Other HR HPV Negative; HPV16 Negative; HPV18 Positive	45	189	5	5	5	249
12 Other HR HPV Negative; HPV16 Positive; HPV18 Negative	98	304	13	6	20	441
12 Other HR HPV Negative; HPV16 Positive; HPV18 Positive	3	9	1	0	0	13
12 Other HR HPV Positive; HPV16 Negative; HPV18 Negative	351	1,193	73	70	22	1,709
12 Other HR HPV Positive; HPV16 Negative; HPV18 Positive	10	39	4	3	1	57
12 Other HR HPV Positive; HPV16 Positive; HPV18 Negative	19	56	4	10	6	95
12 Other HR HPV Positive; HPV16 Positive; HPV18 Positive	0	7	0	0	0	7
12 Other HR HPV Positive ; Invalid; Invalid	1	0	0	0	0	1
Overall	22,690	2,368	113	97	54	25,322

[1]Undetermined includes: biopsy sample inadequate for analysis, or subject/colposcopist unblinded to HPV or Pap cytology result at colposcopy visit or biopsy sample taken out of window and subjects not identified for colposcopy

[2]Normal includes: Negative or normal histology and atypical squamous cells or glandular changes indefinite for neoplasia.

Table 47 presents the likelihood ratio (LR) of disease (≥CIN2 and ≥CIN3) in women 30-65 years old with NILM Pap cytology by the **cobas**® 6800/8800 HPV test results. Adjusted likelihood ratios of HR HPV positive results associated with ≥CIN2 and ≥CIN3 were 7.62 and 10.08, respectively, indicating an overall increased probability of disease associated with HPV positive result.

For ≥CIN3, positive HPV16 results had the highest positive LR of 23.78 (adjusted), indicating that a positive HPV16 result is approximately 23 times more likely to come from those with ≥CIN3 than without. There were no cases of ≥CIN3 observed among women with a negative **cobas**® 6800/8800 HPV test result. Similar patterns of high positive likelihood associated with HPV positive results and low negative likelihoods associated with HPV negative results were observed for ≥CIN2.

Table 47 Likelihood ratios of disease (≥CIN2 and ≥CIN3) by the cobas® 6800/8800 HPV test results in the evaluable NILM population (30-65 years)

cobas® 6800/8800 HPV Test Result	Likelihood Ratio (95% CI)			
	≥CIN2 vs <CIN2		≥CIN3 vs <CIN3	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HPV Positive	1.28 (1.24 ,1.32)	7.62 (4.63, 10.78)	1.29 (1.27, 1.32)	10.08 (9.64, 10.50)
HPV16 Positive	1.75 (1.33, 2.30)	10.14 (5.34, 16.58)	3.03 (2.26, 4.05)	23.78 (13.94, 30.90)
HPV18 Positive	0.97 (0.58, 1.62)	5.78 (2.19, 11.65)	1.17 (0.54, 2.51)	8.82 (1.44, 16.05)
HPV16/18 Positive	1.46 (1.17, 1.81)	8.55 (5.07, 12.89)	2.33 (1.85, 2.94)	18.34 (12.49, 22.22)
12 Other HR HPV Positive	1.19 (1.04, 1.36)	7.15 (4.37, 11.05)	0.79 (0.57,1.09)	6.05 (4.02, 8.95)
HPV Negative	0.08 (0.03, 0.24)	0.30 (0.00, 0.60)	0.00* (0.00, 0.29)	0.00* (0.00, 0.29)

*No ≥CIN3 cases observed among women with negative **cobas®** 6800/8800 HPV test results

NILM (30-65 years) population – absolute risk and relative risk estimates

The adjusted absolute risk (AR) of disease (≥CIN2 and ≥CIN3) in the NILM 30-65 population by the **cobas®** 6800/8800 HPV test results are presented in Table 48. The adjusted AR of ≥CIN2 was 7.19% among women with a positive HPV test result; highest in women with a positive HPV16 result (9.35%), followed by women with a positive 12 Other HR HPV result (6.78%), and women with an HPV18 positive result (5.56%). The adjusted AR of ≥CIN3 was 2.60% among women with a positive HPV test result; highest in women with a positive HPV16 result (5.94%), followed by women with a positive HPV18 result (2.29%), and women with a positive 12 Other HR HPV result (1.58%).

The risks of ≥CIN2 and ≥CIN3 were low among women with HPV negative results (adjusted ARs: 0.31%, and 0.15%, respectively). Age stratified absolute risks are presented in Table 49 and Table 50.

Table 48 Absolute risk of disease (≥CIN2 and ≥CIN3) by HPV genotype from the cobas® 6800/8800 HPV test in the evaluable NILM population (30-65 years)

cobas® 6800/8800 HPV Test Result	Absolute Risk % (95% CI)			
	≥CIN2		≥CIN3	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HPV Positive	7.24 (148/2045) (6.19, 8.44)	7.19 (6.10, 8.33)	2.64 (54/2045) (2.03, 3.43)	2.60 (1.93, 3.31)
HPV16 Positive	9.63 (42/436) (7.21, 12.77)	9.35 (6.66, 12.09)	5.96 (26/436) (4.10, 8.59)	5.94 (3.60, 8.19)
HPV18 Positive	5.58 (14/251) (3.35, 9.14)	5.56 (2.68, 8.40)	2.39 (6/251) (1.10, 5.12)	2.29 (0.63, 4.38)
HPV16/18 Positive	8.15 (56/687) (6.33, 10.44)	8.00 (5.99, 10.06)	4.66 (32/687) (3.32, 6.50)	4.64 (3.11, 6.29)
12 Other HR HPV Positive	6.77 (92/1358) (5.56, 8.24)	6.78 (5.54, 8.21)	1.62 (22/1358) (1.07, 2.44)	1.58 (0.96, 2.30)
HPV Negative	0.51 (3/587) (0.17, 1.49)	0.31 (0.00, 0.98)	0.09 (0.5*/587) (0.01, 0.81)	0.15 (0.00; 0.18)

*No ≥CIN3 cases observed among women with negative **cobas®** 6800/8800 HPV test results, 0.5 case was used in order to estimate risk.

Table 49 Absolute risk of disease (≥CIN2 and ≥CIN3) by HPV genotype from the cobas® 6800/8800 HPV test in the evaluable NILM population (30-39 years)

cobas® 6800/8800 HPV Test Result	Absolute Risk % (95% CI)			
	≥CIN2		≥CIN3	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HPV Positive	9.44 (98/1038) (7.81, 11.37)	9.26 (7.64,10.93)	3.47 (36/1038) (2.52, 4.76)	3.39 (2.31,4.44)
HPV16 Positive	16.27 (34/209) (11.88, 21.87)	15.61 (11.21,20.38)	9.57 (20/109) (6.28, 14.32)	9.29 (5.55,13.25)
HPV18 Positive	5.74 (7/122) (2.81, 11.37)	5.33 (2.03,9.83)	1.64 (2/122) (0.45, 5.78)	1.33 (0.00,4.21)
HPV16/18 Positive	12.39 (41/331) (9.26, 16.37)	11.93 (8.95,15.35)	6.65 (22/331) (4.43, 9.86)	6.44 (4.00,9.10)
12 Other HR HPV Positive	8.06 (57/707) (6.27, 10.30)	8.03 (6.11,9.95)	1.98 (14/707) (1.18, 3.30)	1.98 (1.04,2.96)
HPV Negative	0.42 (1/236) (0.07, 2.36)	0.74 (0.00,2.55)	0.21(0.5/236) (0.02, 2.00)	0.37 (0.00,0.43)

Table 50 Absolute risk of disease (≥CIN2 and ≥CIN3) by HPV genotype from the cobas® 6800/8800 HPV test in the evaluable NILM population (40-65 years)

cobas® 6800/8800 HPV Test Result	Absolute Risk % (95% CI)			
	≥CIN2		≥CIN3	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HPV Positive	4.97 (50/1007) (3.79, 6.49)	4.98 (3.78,6.43)	1.79 (18/1007) (1.13, 2.81)	1.85 (0.97,2.65)
HPV16 Positive	3.52 (8/227) (1.80, 6.80)	3.48 (1.44,6.11)	2.64 (6/227) (1.22, 5.65)	2.79 (0.66,5.03)
HPV18 Positive	5.43 (7/129) (2.65, 10.78)	5.77 (1.95,9.90)	3.10 (4/129) (1.21, 7.70)	3.21 (0.56,6.62)
HPV16/18 Positive	4.21 (15/356) (2.57, 6.83)	4.29 (2.23,6.47)	2.81 (10/356) (1.53, 5.09)	2.93 (1.12,4.59)
12 Other HR HPV Positive	5.38 (35/651) (3.89, 7.39)	5.37 (3.83,7.08)	1.23 (8/651) (0.62, 2.41)	1.25 (0.50,2.11)
HPV Negative	0.57 (2/351) (0.16, 2.05)	0.02 (0.00,0.05)	0.14 (0.5/351) (0.01, 1.35)	0.01 (0.00,0.01)

The relative risk (RR) of ≥CIN2 and ≥CIN3 is shown in Table 51. Relative risk of ≥CIN2 and ≥CIN3 for women with HPV positive result compared with HPV negative result was 14.21 and 29.33, respectively. Women with HPV16 and/or HPV18 positive results had the highest relative risk compared to women with HPV negative results (≥CIN2: 15.98 and ≥CIN3: 51.78).

Table 51 Relative risk of disease (≥CIN2 and ≥CIN3) by HPV genotype from the cobas® 6800/8800 HPV test in the evaluable NILM population (30-65 years)

cobas® 6800/8800 HPV Test Result	Central Pathology Review Diagnoses ≥CIN2	Central Pathology Review Diagnoses ≥CIN3
HPV Positive vs. Negative	14.20 (4.53, 44.25)	29.33 (1.92, 501.27)
HPV16/18 Positive vs. Negative	15.98 (5.02, 50.69)	51.78 (3.35, 891.43)
12 Other HR HPV Positive vs. Negative	13.27 (4.21, 41.69)	18.00 (1.15, 313.24)
HPV16/18 Positive vs. 12 Other HR HPV positive	1.20 (0.87, 1.66)	2.88 (1.68, 4.91)

Note: Unadjusted estimates shown

Agreement between the cobas® 6800/8800 HPV test results and the FDA-approved HPV Test results for women 25-65 years

The analytical agreement of the **cobas®** 6800/8800 HPV test was also evaluated by estimating the percent agreements, along with 95% confidence intervals (CIs), for different results of the FDA-approved HPV Test in pre-quot samples (Table 52 and Table 53). Genotype specific percent agreements were: PPA for HPV16 positive was 97.07% (95% CI: 95.64, 98.04); PPA for HPV18 positive was 97.21% (95% CI: 94.60, 98.658), PPA for 12 Other HR HPV positive was 85.96% (95% CI: 84.8, 87.00) and NPA for HPV negative was 97.73% (95% CI: 97.55, 97.89).

Table 52 Cross-tabulation of the cobas® 6800/8800 HPV test results and the FDA-approved HPV test results

cobas® 6800/8800 HPV Test Result	FDA-approved HPV Test Result HPV16 Positive	FDA-approved HPV Test Result HPV18 Positive	FDA-approved HPV Test Result 12 Other HR HPV Positive	FDA-approved HPV Test Result HPV Negative	Total
HPV16 Positive	762	6	46	250	1,064
HPV18 Positive	2	279	47	165	493
12 Other HR HPV Positive	13	1	3,409	260	3,683
HPV Negative	8	1	464	29,011	29,484
Total	785	287	3,966	29,686	34,724

Note: HPV16 positive implies HPV16 positive, HPV18 positive or negative and 12 Other HR HPV positive or negative.

HPV18 positive implies HPV16 negative, HPV18 Positive and 12 Other HR HPV positive or negative.

12 Other HR HPV positive implies HPV16 negative, HPV18 negative and 12 Other HR HPV positive.

Table 53 Agreement between the cobas® 6800/8800 HPV test results and the FDA Approved HPV test results for the detection of HPV genotypes

HPV Genotypes	Positive Percent Agreement % (n/N; 95% CI)	Negative Percent Agreement % (n/N; 95% CI)
HPV16 Positive	97.07% (762/785; 95.64%, 98.04%)	99.11% (33,637/33,939; 99.00%, 99.20%)
HPV18 Positive	97.21% (279/287; 94.60%, 98.58%)	99.38% (34,223/34,437; 99.29%, 99.46%)
12 Other HR HPV Positive	85.96% (3,409/3,966; 84.84%, 87.00%)	99.11% (30,484/30,758; 99.00%, 99.21%)
HPV Positive	90.61% (4,565/5,038; 89.77%, 91.39%)	97.73% (29,011/29,686; 97.55%, 97.89%)

Note: HPV16 positive implies HPV16 positive, HPV18 positive or negative and 12 Other HR HPV positive or negative.

HPV18 positive implies HPV16 negative, HPV18 Positive and 12 Other HR HPV positive or negative.

12 Other HR HPV positive implies HPV16 negative, HPV18 negative and 12 Other HR HPV positive.

Agreement with a composite comparator for the ASC-US (25-65 years) and the NILM (30-65 years) populations

The agreement of the **cobas**® 6800/8800 HPV test was evaluated by comparing results from the test with a composite comparator composed of HPV DNA sequencing and an FDA-approved HR HPV DNA test.

Representative cervical samples were selected from 2 subsets of women from the IMPACT study: women ≥25 years who had ASC-US Pap cytology results (n=590), and women 30-65 years with NILM Pap cytology results (n=3,167).

The analytical agreement of the **cobas**® 6800/8800 HPV test results were compared with the composite comparator for the detection of 14 HR HPV genotypes and the positive percent agreement (PPA), negative percent agreement (NPA) and 95% confidence intervals (CIs) were calculated. The composite comparator for the detection of 14 HR HPV was indeterminate if results were discordant between HPV DNA sequencing result and the FDA-approved HR HPV DNA test result. All results including the indeterminate results for the composite comparator for the detection of 14 HR HPV are presented in Table 54.

Table 54 Agreement between the cobas® 6800/8800 HPV test results and the composite comparator for the detection of 14 HR HPV

Population	cobas® 6800/8800 HPV Test Result	HPV Composite Comparator Positive	HPV Composite Comparator Negative	HPV Composite Comparator Indeterminate	Total	Agreement (%) (95% CI)
ASC-US ≥25 Years	Positive	420	0	12	432	PPA: 98.36% (420/427) (96.66%, 99.20%)
ASC-US ≥25 Years	Negative	7	134	17	158	NPA: 100.0% (134/134) (97.21%, 100.00%)
ASC-US ≥25 Years	Total	427	134	29	590	-
NILM ≥30 Years	Positive	1153	31	79	1263	PPA: 90.57% (1153/1273) (88.84%, 92.06%)
NILM ≥30 Years	Negative	120	1635	149	1904	NPA: 98.14% (1635/1666) (97.37%, 98.69%)
NILM ≥30 Years	Total	1273	1666	228	3167	-

PPA=positive percent agreement, NPA=negative percent agreement.

The analytical agreement of the **cobas**® 6800/8800 HPV test results were compared with the composite comparator for HPV genotyping and the corresponding percent agreements (PA) along with 95% confidence intervals (CIs) were calculated: PA for HPV16 positive, PA for HPV18 positive, PA for 12 Other HR HPV positive and PA for HPV negative. The composite comparator for HPV genotyping was indeterminate if results were discordant between HPV DNA sequencing result and the FDA-approved HR HPV DNA test result. All results including the indeterminate results for the composite comparator for HPV genotyping are presented in Table 55 and Table 56 for ASC-US 25-65 years and NILM 30-65 years, respectively.

Table 55 Agreement between the cobas® 6800/8800 HPV test results and composite comparator in the ASC-US population (25-65 years)

cobas® 6800/8800 HPV Test Result	**Composite Comparator for HPV Genotyping**					**Total**
	FDA-approved= HPV16 Positive, DNA Sequencing= HPV16 Positive	FDA-approved= HPV18 Positive, DNA Sequencing= HPV18 Positive	FDA-approved= 12 Other HR HPV Positive, DNA Sequencing= 12 Other HR HPV Positive	FDA-approved= HPV Negative DNA Sequencing= HPV Negative	Indeterminate	
HPV16 Positive	68	0	2	0	6	76
HPV18 Positive	0	21	2	0	8	31
12 Other HR HPV Positive	0	0	317	0	8	325
HPV Negative	0	0	7	134	17	158
Total	68	21	328	134	39	590
Percent Agreement (95% CI)	100.0% (68/68) (94.65%, 100.0%)	100.0% (21/21) (84.54%, 100.0%)	96.65% (317/328) (94.10%, 98.12%)	100.0% (134/134) (97.21%, 100.0%)	-	-

Note: Indeterminate includes results where FDA approved and DNA Sequencing results are discordant.

Table 56 Agreement between the cobas® 6800/8800 HPV test results and composite comparator in the NILM population (30-65 years)

cobas® 6800/8800 HPV Test Result	**Composite Comparator for HPV Genotyping**					**Total**
	FDA-approved= HPV16 Positive, DNA Sequencing= HPV 16 Positive	FDA-approved= HPV18 Positive, DNA Sequencing= HPV18 Positive	FDA-approved=12 Other HR HPV Positive, DNA Sequencing=12 Other HR HPV Positive	FDA-approved= HPV Negative, DNA Sequencing= HPV Negative	Indeterminate	
HPV16 Positive	171	1	13	19	30	234
HPV18 Positive	0	74	11	5	15	105
12 Other HR HPV Positive	0	0	853	7	64	924
HPV Negative	1	1	113	1635	154	1904
Total	172	76	990	1666	263	3167
Percent Agreement (95% CI)	99.42% (171/172) (96.78%, 99.90%)	97.37% (74/76) (90.90%, 99.28%)	86.16% (853/990) (83.87%, 88.17%)	98.14% (1635/1666) (97.37%, 98.69%)	-	-

Note: Indeterminate includes results where FDA approved and DNA Sequencing results are discordant.

Primary screening population (25-65 years) - performance evaluation

Among the 35,263 women enrolled in the study, 34,914 met study eligibility criteria. One woman was excluded due to insufficient sample volume for **cobas®** 6800/8800 HPV testing and from the 34,913 eligible women, a total of 34,807 were evaluable for the analyses of the primary screening population. To be evaluable, women must have been eligible for study at enrollment and have a valid **cobas®** 6800/8800 HPV test result. The percent of invalid **cobas®** 6800/8800 HPV test results was 0.04% (13/34,913) with 95% CI: 0.02% to 0.06%.

The median age of the evaluable women in the primary screening population was 39 years with 18.8% women in the age group 25-29 years and 34% in the age group 30-39 years; the remaining 47.2% women were 40-65 years old. Approximately 12% self-reported that they had received the HPV vaccine, 91.5% reported Pap cytology screening within the previous 5 years, and 8.4% reported having colposcopy procedure within 5 years prior to study enrollment. Among the evaluable women 42.4% reported having an HPV screening test in the previous 5 years and among them 12.7% reported having a positive HPV result.

A total of 6,826 women proceeded to colposcopy and of these 6,776 subjects completed colposcopy. Thereof, biopsy samples for 3 subjects were lost/misplaced during transport. Diagnosis of ≥CIN2 was observed in 595 of 6,773 (8.8%) women who went to colposcopy and had valid CPR results at colposcopy.

The number of women with colposcopy results for each combination of the **cobas**® 6800/8800 HPV test and Pap cytology results is shown in Table 57. A correction for verification bias was applied due to the different rate of colposcopy in each category. Disease status was imputed for those women without histology results from the women who went to colposcopy based on their HPV result (from both **cobas**® 6800/8800 HPV test and FDA-approved HPV Test), Pap cytology, and age.

Table 57 Number of subjects with adjudicated histology and pap cytology and cobas® 6800/8800 HPV test results in the evaluable primary screening population (25-65 years)

cobas® 6800/8800 HPV Test Result	Number of Subjects	Pap Cytology NILM	Pap Cytology ASC-US	Pap Cytology >ASC-US	Pap Cytology Unsatisfactory	Total
HPV16/18 Positive	Total	1,061	207	270	19	1,557
HPV16/18 Positive	With adjudicated colposcopy	884	168	230	12	-
12 Other HR HPV Positive	Total	2,518	592	545	38	3,693
12 Other HR HPV Positive	With adjudicated colposcopy	2,099	506	447	26	-
HPV Negative	Total	27,326	1,471	323	437	29,557
HPV Negative	With adjudicated colposcopy	804	1,250	285	65	-
Total	-	30,905	2,270	1,138	494	34,807

Screening algorithms

The use of the **cobas**® 6800/8800 HPV test as a first line screening method was evaluated by comparing the Primary Screening algorithm (Figure 7) with the Cytology Alone algorithm (Figure 8).

Figure 7 Primary screening algorithm

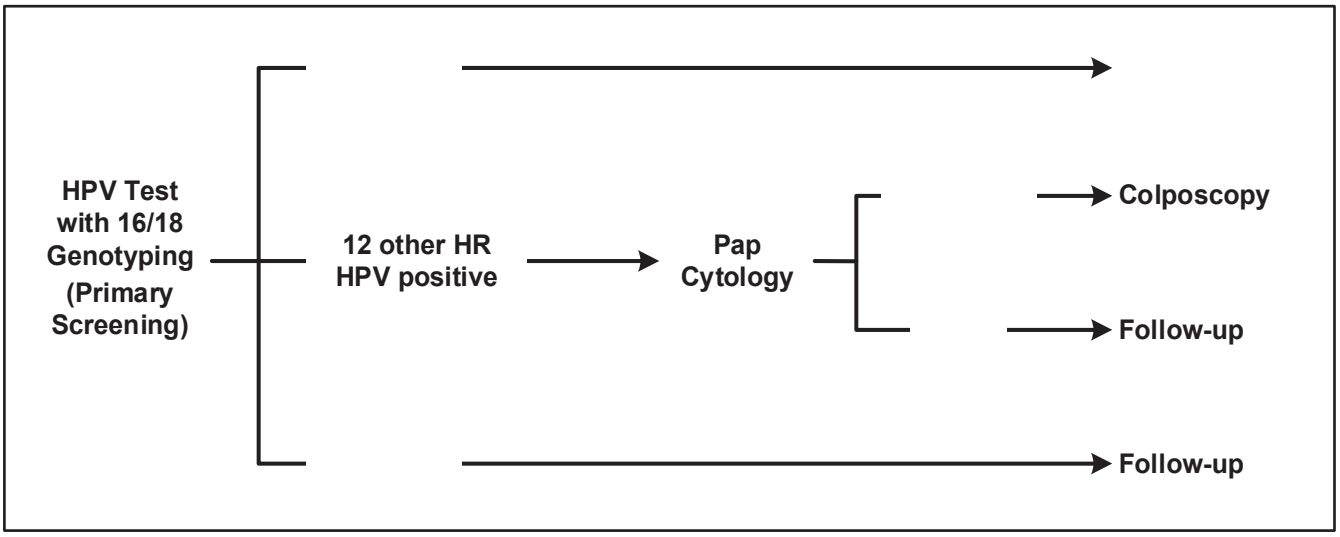
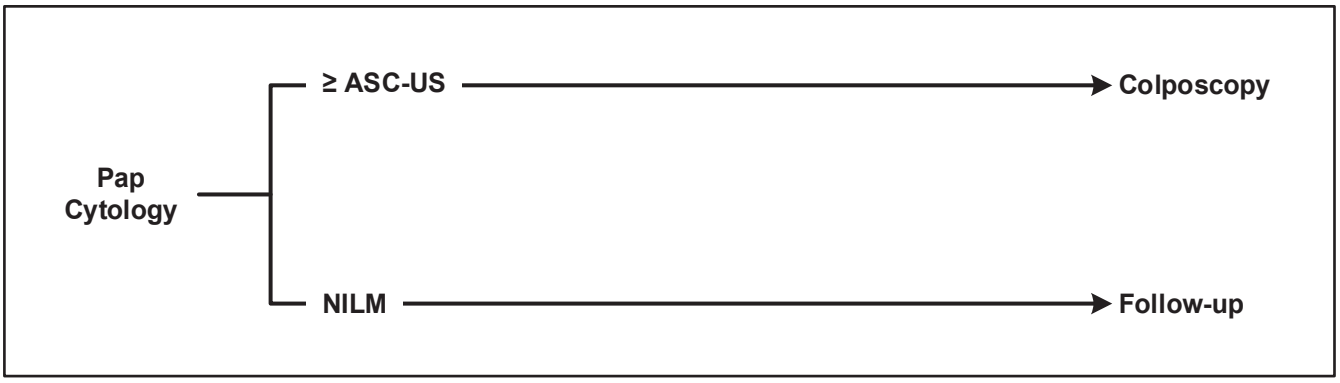
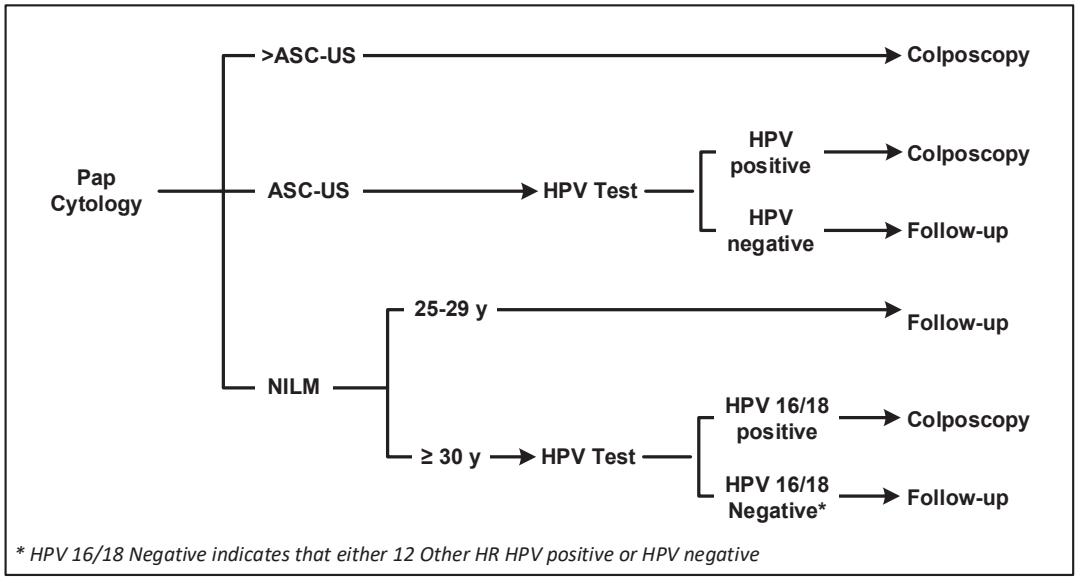


Figure 8 Cytology alone algorithm



The performance of the **cobas**® 6800/8800 HPV test as a first line screening method was also evaluated by comparing the Primary Screening algorithm with the ASC-US Triage/Co-testing algorithm which represents the screening strategy endorsed by the 2012 American Society of Colposcopy and Cervical Pathology guidelines.[15] According to these guidelines, women 25-29 years of age with >ASC-US Pap cytology results or ASC-US and high risk HPV positive results are referred to colposcopy, as are women ≥30 years with >ASC-US Pap cytology results or ASC-US and high risk HPV positive results, as well as those with NILM Pap cytology and HPV16 and/or HPV18 positive results (Figure 9).

Figure 9 ASC-US triage/co-testing algorithm



Performance of the Primary Screening algorithm and the Cytology Alone algorithm was evaluated by estimating the sensitivity, specificity, PLR, NLR, prevalence, PPV, and NPV in the identification of high-grade cervical disease (≥CIN2 and ≥CIN3); results of the comparison are presented in Table 58.

The performance of the Primary Screening algorithm was significantly better than the Cytology Alone algorithm for both ≥CIN2 and ≥CIN3 clinical endpoints in that the Primary Screening algorithm had significantly higher sensitivity, specificity, PPV, NPV and PLR, and also significantly lower NLR compared with the Cytology Alone algorithm. Also, the Primary Screening algorithm improved disease detection (13.82% increase in ≥CIN3 sensitivity) and required 2.05% fewer colposcopy referrals compared to the Cytology Alone algorithm.

Table 58 Adjusted performance of the primary screening and cytology alone algorithms in the evaluable primary screening population (25-65 years)

Performance Parameters	≥CIN2 Prevalence (95% CI)=2.34 (2.03, 2.83)			≥CIN3 Prevalence (95% CI)=0.87 (0.77, 0.98)		
	Primary Screening Algorithm	Cytology Alone Algorithm	Difference	Primary Screening Algorithm	Cytology Alone Algorithm	Difference
Sensitivity (%)	62.41	56.39	6.02	79.93	66.12	13.82
(95% CI)	(52.39, 70.24)	(47.27, 64.21)	(2.85, 9.21)	(74.36, 84.80)	(59.71, 72.37)	(8.42, 19.46)
Specificity (%)	93.57	91.32	2.24	92.90	90.71	2.19
(95% CI)	(93.31, 93.85)	(91.04, 91.63)	(1.93, 2.54)	(92.62, 93.19)	(90.41, 91.00)	(1.89, 2.50)
PPV (%)	18.86	13.47	5.39	9.02	5.90	3.12
(95% CI)	(17.15, 20.55)	(12.13, 14.85)	(4.35, 6.23)	(7.90, 10.20)	(5.06, 6.81)	(2.51, 3.81)
NPV (%)	99.05	98.87	0.18	99.81	99.67	0.14
(95% CI)	(98.57, 99.32)	(98.39, 99.16)	(0.09, 0.25)	(99.75, 99.86)	(99.60, 99.74)	(0.09, 0.19)
PLR	9.70	6.50	3.20	11.25	7.11	4.14
(95% CI)	(8.09, 11.11)	(5.38, 7.47)	(2.51, 3.86)	(10.35, 12.12)	(6.42, 7.83)	(3.37, 4.92)
NLR	0.40	0.48	-0.08	0.22	0.37	-0.16
(95% CI)	(0.32, 0.51)	(0.39, 0.58)	(-0.11, -0.04)	(0.16, 0.28)	(0.31, 0.44)	(-0.22, -0.10)
Colposcopy Referral (%)	7.74	9.79	-2.05	7.74	9.79	-2.05
(95% CI)	(7.45, 8.02)	(9.48, 10.09)	(-2.35, -1.74)	(7.45, 8.02)	(9.48, 10.09)	(-2.35, -1.74)

PPV=Positive predictive value; NPV=Negative predictive value; PLR=Positive likelihood ratio; NLR= Negative likelihood ratio.

The comparisons of the Primary Screening algorithm to the ASC-US Triage/Co-testing algorithm are shown in Table 59. For both ≥CIN2 and ≥CIN3 clinical endpoints, Primary Screening algorithm had significantly higher specificity, PPV and PLR compared with the ASC-US Triage/Co-testing algorithm. Also, the Primary Screening algorithm required 0.35% fewer colposcopy referrals compared to the ASC-US Triage/Co-testing algorithm. For detecting ≥CIN2 and ≥CIN3, sensitivity, NPV, and NLRs were similar between the two algorithms.

Table 59 Adjusted performance of the primary screening algorithm and the ASC-US triage/co-testing algorithm in the evaluable primary screening population (25-65 years)

Performance Parameters	≥CIN2 Prevalence (95% CI)=2.34% (2.03, 2.83)			≥CIN3 Prevalence (95% CI)=0.87% (0.77, 0.98)		
	Primary Screening Algorithm	ASC-US Triage /Co-testing Algorithm	Difference	Primary Screening Algorithm	ASC-US Triage /Co-testing Algorithm	Difference
Sensitivity (%)	62.41	62.53	-0.12	79.93	77.63	2.30
(95% CI)	(52.39, 70.24)	(52.65, 70.78)	(-2.18, 1.55)	(74.36, 84.80)	(71.90, 82.69)	(-0.96, 5.95)
Specificity (%)	93.57	93.21	0.36	92.90	92.52	0.37
(95% CI)	(93.31, 93.85)	(92.96, 93.50)	(0.21, 0.48)	(92.62, 93.19)	(92.25, 92.80)	(0.24, 0.50)
PPV (%)	18.86	18.08	0.78	9.02	8.38	0.64
(95% CI)	(17.15, 20.55)	(16.51, 19.83)	(0.14, 1.26)	(7.90, 10.20)	(7.34, 9.57)	(0.27, 1.05)
NPV (%)	99.05	99.05	0.00	99.81	99.79	0.02
(95% CI)	(98.57, 99.32)	(98.57, 99.33)	(-0.05, 0.04)	(99.75, 99.86)	(99.72, 99.84)	(-0.01, 0.06)
PLR	9.70	9.21	0.49	11.25	10.38	0.87
(95% CI)	(8.09, 11.11)	(7.71, 10.56)	(0.09, 0.81)	(10.35, 12.12)	(9.52, 11.20)	(0.36, 1.40)
NLR	0.40	0.40	-0.00	0.22	0.24	-0.03
(95% CI)	(0.32, 0.51)	(0.31, 0.51)	(-0.02, 0.02)	(0.16, 0.28)	(0.19, 0.30)	(-0.07, 0.01)
Colposcopy Referral (%)	7.74	8.09	-0.35	7.74	8.09	-0.35
(95% CI)	(7.45, 8.02)	(7.80, 8.38)	(-0.48, -0.22)	(7.45, 8.02)	(7.80, 8.38)	(-0.48, -0.22)

PPV=Positive predictive value; NPV=Negative predictive value; PLR=Positive likelihood ratio; NLR= Negative likelihood ratio.

Table 60 presents the performance of the Primary Screening algorithm, Cytology Alone algorithm and the ASC-US Triage/Co-testing algorithm stratified by age groups for detection of ≥CIN3.

Table 60 Adjusted performance of the primary screening algorithm, cytology alone algorithm and ASC-US triage/co-testing algorithm for detection of ≥CIN3, stratified by age group

Performance Parameters	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	PLR (95% CI)	NLR (95% CI)	Colposcopy Referral (%) (95% CI)
25–29 Years Prevalence (%) (95% CI)=1.50 (1.19,1.87)							
Primary Screening Algorithm	76.53 (65.77, 85.86)	89.60 (88.81,90.35)	10.08 (7.55, 12.71)	99.60 (99.38, 99.78)	7.36 (6.18, 8.42)	0.26 (0.16, 0.38)	11.39 (10.64,12.20)
Cytology Alone Algorithm	65.31 (54.12, 75.77)	87.66 (86.87, 88.49)	7.46 (5.54, 9.56)	99.40 (99.15, 99.61)	5.29 (4.36, 6.22)	0.40 (0.28, 0.52)	13.14 (12.33, 13.97)
ASC-US Triage/Co-Testing Algorithm	64.29 (52.94, 73.96)	91.45 (90.73, 92.15)	10.28 (7.61, 13.27)	99.41 (99.15, 99.61)	7.52 (6.04, 8.99)	0.39 (0.28, 0.52)	9.39 (8.68, 10.11)

Performance Parameters	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	PLR (95% CI)	NLR (95% CI)	Colposcopy Referral (%) (95% CI)
30–39 Years Prevalence (%) (95% CI)=1.23 (1.02, 1.44)							
Primary Screening Algorithm	84.14 (77.23, 90.48)	92.30 (91.78, 92.79)	11.94 (9.70, 14.29)	99.79 (99.69, 99.88)	10.92 (9.84, 12.12)	0.17 (0.10, 0.25)	8.64 (8.15, 9.17)
Cytology Alone Algorithm	68.28 (59.41, 76.34)	90.75 (90.24, 91.27)	8.39 (6.62, 10.02)	99.57 (99.42, 99.70)	7.38 (6.31, 8.40)	0.35 (0.26, 0.45)	9.98 (9.46, 10.51)
ASC-US Triage/Co-Testing Algorithm	86.21 (79.43, 92.39)	91.30 (90.76, 91.80)	10.96 (8.90, 13.05)	99.81 (99.71, 99.90)	9.91 (8.95, 10.85)	0.15 (0.08, 0.23)	9.65 (9.13, 10.19)
40–65 Years Prevalence (%) (95% CI)=0.37 (0.27, 0.47)							
Primary Screening Algorithm	77.05 (64.81, 87.67)	94.62 (94.27, 94.95)	5.06 (3.66, 6.58)	99.91 (99.85, 99.95)	14.33 (11.91, 16.67)	0.24 (0.13, 0.37)	5.64 (5.32, 6.00)
Cytology Alone Algorithm	62.30 (50.75, 76.36)	91.87 (91.46, 92.30)	2.77 (1.96, 3.79)	99.85 (99.78, 99.91)	7.67 (6.22, 9.53)	0.41 (0.26, 0.54)	8.33 (7.89, 8.75)
ASC-US Triage/Co-Testing Algorithm	80.33 (68.94, 90.65)	93.82 (93.47, 94.17)	4.61 (3.39, 6.02)	99.92 (99.87, 99.97)	13.00 (11.09, 15.00)	0.21 (0.10, 0.33)	6.46 (6.11, 6.83)

PPV=Positive predictive value; NPV=Negative predictive value; PLR=Positive likelihood ratio; NLR= Negative likelihood ratio.

Primary Screening Population (25-65 years) – risk estimates

The risks of high-grade cervical disease using the Primary Screening algorithm are presented in Table 61. Women positive for HPV16 and/or HPV18 (4.47%) and 12 Other HR HPV positive with ≥ASC-US cytology (3.27%) are referred for immediate colposcopy by the Primary Screening algorithm. The risks of ≥CIN2 were 18.63% (95% CI: 16.60, 20.70) for HPV16 and/or HPV18 positive, and 19.09% (95% CI: 16.60, 21.69) for 12 Other HR HPV positive with ≥ASC-US cytology (Table 61).

Women with 12 Other HR HPV positive and NILM cytology had a risk of 7.47% for ≥CIN2. The majority of women (84.92%) were HPV-negative and had a risk of 0.39% for ≥CIN2.

Table 61 Adjusted risk of disease in HPV and cytology categories by the primary screening algorithm (25-65 years)

cobas® 6800/8800 HPV Test Result	Proportion of women with Result (%)	Risk of ≥CIN2 (%) (95% CI)	Risk of ≥CIN3 (%) (95% CI)
HPV Positive	15.08	13.30 (12.26, 14.39)	5.56 (4.91, 6.18)
HPV16/18 Positive	4.47	18.63 (16.60, 20.70)	10.85 (9.27, 12.44)
HPV16 Positive	3.06	22.65 (19.99, 25.41)	14.00 (11.78, 16.09)
HPV18 Positive	1.42	9.94 (7.25, 12.99)	4.06 (2.42, 6.22)
12 Other HR HPV Positive and ≥ASC-US	3.27	19.09 (16.60, 21.69)	6.60 (5.11, 8.31)
12 Other HR HPV Positive and NILM Cytology	7.34	7.47 (6.25, 8.71)	1.88 (1.27, 2.52)
HPV Negative	84.92	0.39 (0.15, 0.88)	0.05 (0.02, 0.08)

The risks of high-grade cervical disease using the Primary Screening algorithm stratified by age group are presented in Table 62. The risks of ≥CIN2 were all above 10% in each age group for women with HPV16 and/or HPV18 positive results and women with 12 Other HR HPV positive result and ≥ASC-US cytology. The risk of ≥CIN3 was no more than 0.10% in each age group for women with a HPV negative test result (ranged from 0.03 to 0.10%).

Table 62 Risk of disease in HPV and cytology categories by the primary screening algorithm, stratified by age group

cobas® 6800/8800 HPV Test Result	Proportion of women with Result (%)	Risk of ≥CIN2 (%) (95% CI)	Risk of ≥CIN3 (%) (95% CI)
25-29 Years			
HPV Positive	24.01	15.18 (13.30, 17.26)	5.99 (4.71, 7.41)
HPV16/18 Positive	4.84	22.15 (17.49, 27.60)	12.97 (8.87, 17.33)
HPV16 Positive	3.61	27.12 (20.80, 34.03)	16.95 (11.60, 22.68)
HPV18 Positive	1.23	7.50 (1.39, 15.79)	1.25 (0.00, 5.59)
12 Other HR HPV Positive and ≥ASC-US	6.55	22.43 (17.81, 26.97)	7.94 (5.09, 11.23)
12 Other HR HPV Positive and NILM Cytology	12.62	8.74 (6.65, 11.02)	2.31 (1.13, 3.55)
HPV Negative	75.99	0.40 (0.22, 0.61)	0.10 (0.02, 0.22)
30-39 Years			
HPV Positive	16.44	15.74 (13.86, 17.65)	7.25 (6.04, 8.58)
HPV16/18 Positive	5.27	24.08 (20.45, 28.09)	14.93 (11.92, 18.15)
HPV16 Positive	3.57	29.62 (25.00, 35.02)	19.19 (15.10, 23.65)
HPV18 Positive	1.70	12.44 (7.23, 17.47)	5.97 (2.78, 9.61)
12 Other HR HPV Positive and ≥ASC-US	3.37	20.30 (15.97, 24.68)	7.27 (4.45, 10.26)
12 Other HR HPV Positive and NILM Cytology	7.80	8.24 (6.29, 10.25)	2.06 (1.10, 3.14)
HPV Negative	83.56	0.82 (0.13, 2.26)	0.04 (0.00, 0.08)
40-65 Years			
HPV Positive	10.56	8.86 (7.46, 10.34)	3.28 (2.42, 4.17)
HPV16/18 Positive	3.76	11.33 (8.67, 13.84)	5.66 (3.90, 7.75)
HPV16 Positive	2.47	12.81 (9.48, 16.23)	6.90 (4.40, 9.77)
HPV18 Positive	1.29	8.49 (4.52, 12.53)	3.30 (0.91, 5.97)
12 Other HR HPV Positive and ≥ASC-US	1.88	12.90 (9.10,17.47)	3.87 (1.84, 6.46)
12 Other HR HPV Positive and NILM Cytology	4.92	5.31 (3.74, 7.21)	1.23 (0.50, 2.12)
HPV Negative	89.44	0.10 (0.05, 0.17)	0.03 (0.01, 0.07)

Primary screening population (25-65 years) – risks of disease in women with NILM cytology and negative cobas® 6800/8800 HPV test results

Table 63 presents the absolute risks (AR) of disease (≥CIN2 and ≥CIN3) for women with NILM Pap cytology, HPV-negative, and NILM with HPV-negative results. Risk of ≥CIN3 in women with NILM Pap cytology was 0.33% compared with 0.05% among women with negative **cobas®** 6800/8800 HPV test results. This indicates that women with NILM Pap cytology have 6.6 (0.33/0.05) times higher risk of ≥CIN3 compared with women with HPV-negative results. The addition of a NILM cytology result to a negative **cobas®** 6800/8800 HPV test result marginally decreased ≥CIN3 risk.

Table 63 Adjusted risk of disease in women with NILM cytology and negative cobas® 6800/8800 HPV test results

Cytology and cobas® 6800/8800 HPV Test Result	Proportion of women with Result (%)	Risk of ≥CIN2 (%) (95% CI)	Risk of ≥CIN3 (%) (95% CI)
NILM	90.21% (31,399/34,807)	1.13 (0.84, 1.61)	0.33 (0.26, 0.40)
HPV Negative	84.92% (29,557/34,807)	0.39 (0.15, 0.88)	0.05 (0.02, 0.08)
NILM and HR HPV Negative	79.76% (27,763/34,807)	0.25 (0.01, 0.76)	0.00 (0.00, 0.01)

Primary screening population (25-65 years) – benefit and risk per 10,000 women

Benefits and risks per 10,000 women using the Primary Screening, Cytology Alone, and ASC-US Triage/Co-testing algorithms are presented in Table 64. Per 10,000 women, the Primary Screening algorithm correctly identified the highest number of true positive ≥CIN3 cases (70) compared to the Cytology Alone algorithm (58) and ASC-US Triage/Co-testing algorithm (68). The Primary Screening algorithm was associated with fewer colposcopies compared to the Cytology Alone algorithm and the ASC-US Triage/Co-testing algorithm (775 vs. 980 and 810, respectively). Fewer cases of ≥CIN3 high grade disease were missed by the Primary Screening algorithm (17 vs. 29 and 19) as well as fewer false positive CIN2 (<CIN2) were identified with the Primary Screening algorithm compared with Cytology Alone, and ASC-US Triage/Co-testing algorithms (628 vs. 848 and 663, respectively).

Table 64 Benefit and risk of using the primary screening, cytology alone, and ASC-US triage/co-testing algorithms in the primary screening population (25-65 years) per 10,000 women

Algorithm	Number of Tests and Procedures Pap Cytology	Number of Tests and Procedures cobas® 6800/8800 HPV	Number of Tests and Procedures Colposcopy	Benefit True Positives ≥CIN3	Benefit True Positives CIN2	Risk False Negatives ≥CIN3	Risk False Negatives CIN2	False Positives <CIN2
Primary Screening	1,061	10,000	775	70	77	17	70	628
Cytology Alone	10,000	0	980	58	74	29	73	848
ASC-US Triage/Co-testing	10,000	8,043	810	68	79	19	68	663

Primary screening population (25–65 years) – benefits and risk per 100 colposcopy procedures

Benefits and risks per 100 colposcopy procedures when using the Primary Screening, Cytology Alone, and ASC-US Triage/Co-testing algorithms are presented in Table 65. For the Primary Screening algorithm, the number of screening tests that had to be performed to select 100 women for colposcopy was 1,427 (137+1,290); 1,020 were required for the Cytology alone algorithm, while 2,228 (1,235+993) were required for the ASC-US Triage/Co-testing algorithm. The number of true positives (≥CIN2) by the Primary Screening algorithm was 19 per 100 colposcopies compared to 14 for Cytology alone, and 18 for the ASC-US Triage/Co-testing algorithm. The probability of ≥CIN3 among women not referred to colposcopy was 0.17% (2/1,190) by the Primary Screening algorithm, 0.30% (3/920) by the Cytology alone algorithm and 0.18% (2/1,135) by the ASC-US Triage/Co-testing algorithm.

Table 65 Benefit and risks of the primary screening, cytology alone and ASC-US triage/co-testing algorithms in the primary screening population (25–65 years) per 100 colposcopy procedures

Algorithm	Number of Tests and Procedures Pap Cytology	Number of Tests and Procedures cobas® 6800/8800 HPV	Number of Tests and Procedures Colposcopy	Benefit True Positives ≥CIN3	Benefit True Positives CIN2	Risk False Negatives ≥CIN3	Risk False Negatives CIN2	False Positives <CIN2
Primary Screening	137	1,290	100	9	10	2	9	81
Cytology Alone	1,020	0	100	6	8	3	7	86
ASC-US Triage/Co-testing	1,235	993	100	8	10	2	8	82

Performance by vaccination status

The performance of the **cobas**® 6800/8800 HPV test was also evaluated by self-reported vaccination status in the 25-29 year age group. Among the 25-29 year participants, 39% self-reported having received the HPV vaccine. The performance of **cobas**® 6800/8800 HPV in unvaccinated and vaccinated women with ASC-US cytology (25-29 years old) is presented in Table 66. Results in a subset of the primary screening population (25-29 years old) stratified by self-reported vaccination status is presented in Table 67.

Table 66 Performance of the cobas® 6800/8800 HPV test in detecting disease, stratified by HPV vaccination status in the ASC-US population (25–29 years)

Statistic	Overall	Vaccinated	Unvaccinated
≥CIN2			
Sensitivity (%) (95% CI)	89.13 (41/46) (76.96, 95.27)	78.57 (11/14) (52.41, 92.43)	93.75 (30/32) (79.85, 98.27)
Specificity (%) (95% CI)	51.35 (171/333) (46.00, 56.67)	52.76 (67/127) (44.12, 61.23)	50.49 (104/206) (43.71, 57.24)
PPV (%) (95% CI)	20.20 (41/203) (15.25, 26.25)	15.49 (11/71) (8.88, 25.65)	22.73 (30/132) (16.41, 30.59)
NPV (%) (95% CI)	97.16 (171/176) (93.52, 98.78)	95.71 (67/70) (88.14, 98.53)	98.11 (104/106) (93.38, 99.48)
Prevalence (%) (95% CI)	12.14 (46/379) (9.22 ,15.81)	9.93 (14/141) (6.01 ,15.98)	13.45 (32/238) (9.69 ,18.36)

Statistic	Overall	Vaccinated	Unvaccinated
≥CIN3			
Sensitivity (%) (95% CI)	93.33 (14/15) (70.18, 98.81)	83.33 (5/6) (43.65, 96.99)	100.00 (9/9) (70.09, 100.00)
Specificity (%) (95% CI)	48.08 (175/364) (42.99, 53.20)	51.11 (69/135) (42.77, 59.40)	46.29 (106/229) (39.94, 52.75)
PPV (%) (95% CI)	6.90 (14/203) (4.15, 11.24)	7.04 (5/71) (3.05, 15.45)	6.82 (9/132) (3.63, 12.45)
NPV (%) (95% CI)	99.43 (175/176) (96.85, 99.90)	98.57 (69/70) (92.34, 99.75)	100.00 (106/106) (96.50, 100.00)
Prevalence (%) (95% CI)	3.96 (15/379) (2.41 ,6.43)	4.26 (6/141) (1.96 ,8.97)	3.78 (9/238) (2.00 ,7.03)

PPV=Positive predictive value; NPV=Negative predictive value.

Table 67 Performance of the cobas® 6800/8800 HPV test in detecting disease, stratified by HPV vaccination status in the primary screening population (25-29 years)

Statistics	Unadjusted Vaccinated	Unadjusted Unvaccinated	Adjusted Vaccinated	Adjusted Unvaccinated
≥CIN2				
Sensitivity (%) (95% CI)	55.17 (32/58) (42.45, 67.25)	69.12 (94/136) (60.92, 76.27)	54.67 (42.22, 68.01)	68.51 (60.98, 76.60)
Specificity (%) (95% CI)	75.56 (405/536) (71.75, 79.01)	64.21(531/827) (60.88, 67.40)	93.04 (91.99, 94.06)	89.29 (88.24, 90.39)
PPV (%) (95% CI)	19.63 (32/163) (15.64, 24.35)	24.10 (94/390) (21.55, 26.85)	19.07 (13.67, 25.44)	23.48 (19.60, 27.86)
NPV (%) (95% CI)	93.97 (405/431) (92.10, 95.41)	92.67 (531/573) (90.73, 94.23)	98.56 (97.98, 99.07)	98.34 (97.85, 98.82)
PLR (95% CI)	2.26 (32/58)/(131/536) (1.71, 2.97)	1.93 (94/136)/(296/827) (1.67, 2.23)	7.85 (5.87, 10.51)	6.40 (5.51, 7.47)
NLR (95% CI)	0.59 (26/58)/(405/536) (0.44, 0.79)	0.48 (42/136)/(531/827) (0.37, 0.62)	0.49 (0.34, 0.62)	0.35 (0.26, 0.44)
Colposcopy Referral (%) (95% CI)	27.44 (163/594) (24.01, 31.17)	40.50 (390/963) (37.44, 43.63)	8.35 (7.34, 9.42)	13.35 (12.29, 14.48)
Prevalence (%) (95% CI)	9.76 (58/594) (7.63, 12.42)	14.12 (136/963) (12.07, 16.46)	2.91 (2.25, 3.65)	4.58 (3.88, 5.36)
≥CIN3				
Sensitivity (%) (95% CI)	65.38 (17/26) (46.22, 80.59)	81.63 (40/49) (68.64, 90.02)	66.67 (45.83, 83.87)	80.00 (69.78, 92.91)
Specificity (%) (95% CI)	74.30 (422/568) (70.55, 77.72)	61.71 (564/914) (58.51, 64.80)	92.41 (91.32, 93.42)	87.76 (86.68, 88.90)
PPV (%) (95% CI)	10.43 (17/163) (7.85, 13.73)	10.26 (40/390) (8.90, 11.79)	10.23 (5.94, 15.23)	9.85 (7.24, 13.19)
NPV (%) (95% CI)	97.91 (422/431) (96.50, 98.76)	98.43 (564/573) (97.20, 99.13)	99.53 (99.15, 99.79)	99.62 (99.39, 99.88)

Statistics	Unadjusted Vaccinated	Unadjusted Unvaccinated	Adjusted Vaccinated	Adjusted Unvaccinated
		≥CIN2		
PLR (95% CI)	2.54 (17/26)/(146/568) (1.86, 3.48)	2.13 (40/49)/(350/914) (1.82, 2.49)	8.78 (5.85, 11.63)	6.54 (5.62, 7.77)
NLR (95% CI)	0.47 (9/26)/(422/568) (0.27, 0.79)	0.30 (9/49)/(564/914) (0.16, 0.54)	0.36 (0.17, 0.59)	0.23 (0.08, 0.34)
Colposcopy Referral (%) (95% CI)	27.44 (163/594) (24.01, 31.17)	40.50 (390/963) (37.44, 43.63)	8.35 (7.34, 9.42)	13.35 (12.29, 14.48)
Prevalence (%) (95% CI)	4.38 (26/594) (3.00, 6.34)	5.09 (49/963) (3.87, 6.66)	1.28 (0.85, 1.83)	1.64 (1.21, 2.10)

Comparison of results from the cobas® 6800/8800 HPV test for pre-quot vs. post-quot clinical samples

Within IMPACT, a sub-study was designed to compare the performance of the **cobas®** 6800/8800 HPV test on cervical specimens tested prior to Pap cytology processing (pre-quot) and after Pap cytology processing (post-quot) on the ThinPrep® 2000 Processor (Hologic Inc.). The **cobas®** 6800/8800 HPV test was performed on 3,753 paired pre-quot and post-quot samples.

Agreement between the **cobas®** 6800/8800 HPV test results of pre-quot samples and post-quot samples for any HPV and for genotype-specific results are presented in Table 68 , Table 69, and Table 70 for each of the three study populations (ASC-US 25-65 years, NILM 30-65 years, and the primary screening population 25-65 years).

Table 68 Agreement of cobas® 6800/8800 HPV test results in pre-quot vs. post-quot samples in the ASC-US population (25-65 years), stratified by CPR diagnosis

Pre-quot Cytology Samples					
≥CIN2					
Post-quot Cytology Samples	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	3	0	0	0	3
HPV18 Positive	0	0	0	0	0
12 Other HR HPV Positive	0	0	2	0	2
HPV Negative	0	0	0	2	2
Total	3	0	2	2	7
Genotype Specific PPA (95% CI)	100.0% (3/3) (43.85%, 100.0%)	NC	100.0% (2/2) (34.24%, 100.0%)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA=100.0% (5/5) (56.55%, 100.0%)	PPA=100.0% (5/5) (56.55%, 100.0%)	PPA=100.0% (5/5) (56.55%, 100.0%)	NPA=100.0% (2/2) (34.24%, 100.0%)	-
<CIN2					
Post-quot Cytology Samples	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	6	0	1	1	8
HPV18 Positive	0	3	0	0	3
12 Other HR HPV Positive	0	0	32	0	32
HPV Negative	0	0	4	121	125
Total	6	3	37	122	168
Genotype Specific PPA (95% CI)	100.0% (6/6) (60.97%, 100.0%)	100.0% (3/3) (43.85%, 100.0%)	86.49% (32/37) (72.02%, 94.09%)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA=91.30% (42/46) (79.68%, 96.57%)	PPA=91.30% (42/46) (79.68%, 96.57%)	PPA=91.30% (42/46) (79.68%, 96.57%)	NPA=99.18% (121/122) (95.50%, 99.86%)	-

NC=not calculable

Table 69 Agreement of cobas® 6800/8800 HPV test results in pre-quot vs. post-quot samples in the NILM population (30-65 years), stratified by CPR diagnosis

Pre-quot Cytology Samples					
≥CIN2					
Post-quot Cytology Samples	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	6	0	0	0	6
HPV18 Positive	0	0	0	0	0
12 Other HR HPV Positive	0	0	8	0	8
HPV Negative	0	0	0	1	1
Total	6	0	8	1	15
Genotype Specific PPA (95% CI)	100.00% (6/6) (60.97%, 100.0%)	NC	100.0% (8/8) (67.56%, 100.0%)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA=100.0% (14/14) (78.47%, 100.0%)	PPA=100.0% (14/14) (78.47%, 100.0%)	PPA=100.0% (14/14) (78.47%, 100.0%)	NPA=100.0% (1/1) (20.65%, 100.0%)	-
<CIN2					
Post-quot Cytology Samples	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	41	0	0	2	43
HPV18 Positive	0	17	1	0	18
12 Other HR HPV Positive	1	0	107	5	113
HPV Negative	8	2	19	58	87
Total	50	19	127	65	261
Genotype Specific PPA (95% CI)	82.00% (41/50) (69.20%, 90.23%)	89.47% (17/19) (68.61%, 97.06%)	84.25% (107/127) (76.92%, 89.57%)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA=85.20% (167/196) (79.56%, 89.50%)	PPA=85.20% (167/196) (79.56%, 89.50%)	PPA=85.20% (167/196) (79.56%, 89.50%)	NPA=89.23% (58/65) (79.40%, 94.68%)	-

NC=not calculable

Table 70 Agreement of cobas® 6800/8800 HPV test results in pre-quot vs. post-quot samples in the primary screening population (25-65 years), stratified by CPR diagnosis

Pre-quot Cytology Samples					
≥CIN2					
Post-quot Cytology Samples	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	18	0	0	0	18
HPV18 Positive	0	5	0	0	5
12 Other HR HPV Positive	0	0	30	1	31
HPV Negative	0	0	0	5	5
Total	18	5	30	6	59
Genotype Specific PPA (95% CI)	100.0% (18/18) (82.41%, 100.0%)	100.0% (5/5) (56.55%, 100.0%)	100.0% (30/30) (88.65%, 100.0%)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA=100.0% (53/53) (93.24%, 100.0%)	PPA=100.0% (53/53) (93.24%, 100.0%)	PPA=100.0% (53/53) (93.24%, 100.0%)	NPA=83.33% (5/6) (43.65%, 96.99%)	-
<CIN2					
Post-quot Cytology Samples	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	67	0	2	4	73
HPV18 Positive	0	28	1	0	29
12 Others Positive	1	0	218	7	226
HPV Negative	8	2	26	237	273
Total	76	30	247	248	601
Genotype Specific PPA (95% CI)	88.16% (67/76) (79.00%, 93.64%)	93.33% (28/30) (78.68%, 98.15%)	88.26% (218/247) (83.65%, 91.70%)	-	-
14 HR HPV Percent Agreement (95% CI)	PPA=89.80% (317/353) (86.20%, 92.54%)	PPA=89.80% (317/353) (86.20%, 92.54%)	PPA=89.80% (317/353) (86.20%, 92.54%)	NPA=95.56% (237/248) (92.23%, 97.51%)	-

Agreement of cobas® HPV results between the cobas® 5800 System and the cobas® 6800/8800 Systems

The study was performed to compare agreement between the **cobas®** 5800 System and **cobas®** 6800/8800 Systems for **cobas®** HPV qualitative nucleic acid test (**cobas®** HPV).

A total of 2,571 paired clinical samples were tested on both the **cobas®** 5800 System and **cobas®** 6800/8800 Systems. All 2,571 paired specimens were tested on three **cobas®** 6800/8800 Systems at one site and three cobas® 5800 Systems across three sites.

Analysis population included 2,501 samples with valid test results for both systems (**cobas®** 5800 and **cobas®** 6800/8800).

The positive and negative percent agreement between **cobas®** HPV results on **cobas®** 5800 and **cobas®** 6800/8800 Systems were calculated separately for each channel (genotypes HPV16, HPV18, and 12 Other HR HPV) and shown in Table 71.

Table 71: Percent agreement of results for **cobas®** HPV on the **cobas®** 5800 and the **cobas®** 6800/8800 Systems

cobas® HPV Results: cobas® 5800 System	**cobas® HPV Results: cobas® 6800/8800 Systems**				
	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	HPV Negative	Total
HPV16 Positive	322	2	11	8	343
HPV18 Positive	0	153	4	4	161
12 Other HR HPV Positive	6	8	1136	32	1182
HPV Negative	8	2	33	772	815
Total	336	165	1184	816	2501
Genotype Specific Agreement (%) [95%CI]	PPA =322/336 (95.83%) [93.1%, 97.5%] NPA = 2144/2165 (99.03%) [98.52%, 99.36%]	PPA =153/165 (92.73%) [87.7%, 95.8%] NPA= 2328/2336 (99.66%) [99.33%, 99.83%]	PPA = 1136/1184 (95.95%) [94.7%, 96.9%] NPA = 1271/1317 (96.51%) [95.4%, 97.4%]	-	-
14 HR HPV Agreement (%) [95%CI]	PPA = 1643/1685 (97.45%) [96.58%, 98.10%]	PPA = 1643/1685 (97.45%) [96.58%, 98.10%]	PPA = 1643/1685 (97.45%) [96.58%, 98.10%]	NPA = 772/816 (94.61%) [92.8%, 96%]	-

Deming Regression Analysis

Using the cycle threshold values (Ct) generated for each genotype on the **cobas**® 5800 and **cobas**® 6800/8800 Systems, Deming regression analyses were conducted to determine whether a systematic bias in signal output existed between the two systems. The slope and intercept of the regression lines for each genotype is illustrated in Table 72. For each genotype, relationship of the Ct values for **cobas**® HPV on the **cobas**® 5800 System and the **cobas**® 6800/8800 Systems was found to be linear.

Table 72: Deming Regression Line Statistics for cobas® HPV on the cobas® 5800 and the cobas® 6800/8800 Systems

HPV Genotype	No. of Paired Samples	Parameter	Parameter Estimate	Standard Error	95% CI
HPV16	324	Intercept	-0.16	0.30	(-0.75, 0.43)
		Slope	1.01	0.01	(0.98, 1.03)
HPV18	171	Intercept	0.11	0.52	(-0.91, 1.12)
		Slope	0.99	0.02	(0.96, 1.03)
12 Other HR HPV	1,520	Intercept	0.03	0.21	(-0.38, 0.44)
		Slope	1.0	0.01	(0.98, 1.01)

The systematic bias estimates between the **cobas**® 5800 System and the **cobas**® 6800/8800 Systems using the slope and intercept from the regression lines are depicted in Table 73 for each genotype. The data indicate that no significant systematic bias exists in the **cobas**® Systems.

Table 73: Systematic Bias Estimates at Assay Cutoff

HPV Channel	No. of Paired Samples	Bias Estimate at (Ct)	95% CI of Bias
HPV16	324	0.07	(-0.22, 0.36)
HPV18	171	-0.08	(-0.52, 0.35)
12 Other HR HPV	1,520	-0.08	(-0.25, 0.09)

Site-to-site reproducibility

cobas® 6800/8800 Systems

To evaluate site-to-site reproducibility testing was performed at three testing sites, using one reagent lot and four **cobas®** Systems (three **cobas®** 6800 Systems at all three testing sites and one **cobas®** 8800 System at one of those site). Each panel member was tested for five days, three replicates per run, on the four Systems. Two operators performed one run per day for five days for each System. A 13-member panel composed of pools made from clinical samples collected into PreservCyt® Solution, and from samples derived from SiHa and HeLa cell lines was tested for reproducibility.

Table 74 summarizes results for the negative panel members by site/instrument, operator/run, and day on the three **cobas®** 6800 Systems and one **cobas®** 8800 System. All negative panel members were correctly identified as negative across site/instrument, operator/run and testing day.

Percent of positive results for the positive panel members are presented in Table 75. Analysis of variance of the Ct values from tests performed on positive panel members yielded total CV(%) ranging from 1.1% to 5.6% across all panel members. The CV(%) ranged from 1.1% to 2.7% for the cell line panel members and 2.1% to 5.6% for the pooled clinical panel members. The largest component of variance observed (1.71 for Pooled HPV45 Low Positive at 1 x LoD) among all positive panel members was for within-run (Table 76).

Table 74 Agreement and variability for negative panel member for site/instrument, operator/run, and day on the cobas® 6800/8800 Systems

			Number of Negatives/Total Number of Valid Results								
			Between-Site/Instrument			Between-Operator/Run			Between-Day		
Panel Member	Ct SD	Ct CV%	ID	Negative Agreement (%)	Negative/ Valid	ID*	Negative Agreement (%)	Negative/ Valid	ID	Negative Agreement (%)	Negative/ Valid
Negative background cell line	n/a	n/a	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
Negative background cell line			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
Negative background cell line			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
Negative background cell line			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
Negative background cell line						5	100.0	30/30	5	100.0	24/24
Negative background cell line						6	100.0	30/30			
Negative pooled clinical samples	n/a	n/a	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
Negative pooled clinical samples			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
Negative pooled clinical samples			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24

			Number of Negatives/Total Number of Valid Results								
			Between-Site/Instrument			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**	**ID***	**Negative Agreement (%)**	**Negative/ Valid**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**
Negative pooled clinical samples			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
Negative pooled clinical samples						5	100.0	30/30	5	100.0	24/24
Negative pooled clinical samples						6	100.0	30/30		-	-

*Note: Operators 1 and 2 were at testing site 1; Operators 3 and 4 were at testing site 2; Operators 5 and 6 were at testing site 3.

Table 75 Agreement and variability for positive panel members for site/instrument, operator/run, and day on the cobas® 6800/8800 Systems

			Number of Positive Results/Total Number of Valid Results								
			Between-Site/Instrument			Between-Operator/Run			Between-Day		
Panel Member	Ct SD	Ct CV%	ID	Positive Agreement (%)	Positive/ Valid	ID[1]	Positive Agreement (%)	Positive/ Valid	ID	Positive Agreement (%)	Positive/ Valid
Positive Cell Line Panel Members: HPV16/18 Weak Positive (0.3 x LoD)											
HPV16 Weak Positive (0.3 x LoD)	0.76	2.1	11	66.7	20/30	1	60.0	9/15	1	58.3	14/24
			21	76.7	23/30	2	73.3	11/15	2	54.2	13/24
			31	46.7	14/30	3	93.3	14/15	3	62.5	15/24
			32	60.0	18/30	4	60.0	9/15	4	83.3	20/24
						5	53.3	16/30	5	54.2	13/24
						6	53.3	16/30			
HPV18 Weak Positive (0.3 x LoD)	0.96	2.7	11	53.3	16/30	1	40.0	6/15	1	70.8	17/24
			21	60.0	18/30	2	66.7	10/15	2	66.7	16/24
			31	60.0	18/30	3	60.0	9/15	3	45.8	11/24
			32	70.0	21/30	4	60.0	9/15	4	70.8	17/24
						5	73.3	22/30	5	50.0	12/24
						6	56.7	17/30		-	-
Positive Cell Line Panel Members: HPV16/18 Low Positive (1 x LoD)											
HPV16 Low Positive (1 x LoD)	0.47	1.3	11	96.7	29/30	1	100.0	15/15	1	95.8	23/24
			21	96.7	29/30	2	93.3	14/15	2	100.0	24/24
			31	100.0	30/30	3	93.3	14/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	95.8	23/24
						6	100.0	30/30			
HPV18 Low Positive (1 x LoD)	0.63	1.9	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	96.7	29/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	95.8	23/24
						5	96.7	29/30	5	100.0	24/24
						6	100.0	30/30			
Positive Cell Line Panel Members: HPV16/18 Positive (3 x LoD)[2]											
HPV16 Positive (3 x LoD)	0.37	1.1	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	29/29	4	100.0	15/15	4	100.0	23/23
						5	100.0	30/30	5	100.0	24/24
						6	100.0	29/29			
HPV18 Positive (3 x LoD)	0.40	1.2	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	29/29	4	100.0	15/15	4	100.0	23/23
						5	100.0	30/30	5	100.0	24/24
						6	100.0	29/29			

			Number of Positive Results/Total Number of Valid Results								
			Between-Site/Instrument			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**	**ID[1]**	**Positive Agreement (%)**	**Positive/ Valid**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**
Positive Clinical Panel Members											
Pooled HPV16 Low Positive (1 x LoD)	1.07	3.2	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			
Pooled HPV16 Positive (3 x LoD)	0.89	2.7	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			
Pooled HPV18 Low Positive (1 x LoD)	0.74	2.1	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	96.7	29/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	93.3	14/15	4	95.8	23/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			
Pooled HPV18 Positive (3 x LoD)	0.92	2.7	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			
Pooled HPV45 Low Positive (1 x LoD)	1.80	5.6	11	96.7	29/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	93.3	14/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	95.8	23/24
						6	100.0	30/30			
Pooled HPV45 Positive (3 x LoD)	1.54	5.2	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			
Pooled HPV39 Low Positive (1 x LoD)	1.04	3.1	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			

			Number of Positive Results/Total Number of Valid Results								
			Between-Site/Instrument			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**	**ID[1]**	**Positive Agreement (%)**	**Positive/ Valid**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**
Pooled HPV39 Positive (3 x LoD)	1.45	4.6	11	100.0	30/30	1	100.0	15/15	1	100.0	24/24
			21	100.0	30/30	2	100.0	15/15	2	100.0	24/24
			31	100.0	30/30	3	100.0	15/15	3	100.0	24/24
			32	100.0	30/30	4	100.0	15/15	4	100.0	24/24
						5	100.0	30/30	5	100.0	24/24
						6	100.0	30/30			

Note: [1]Operators 1 and 2 were at testing site 1; Operators 3 and 4 were at testing site 2; Operators 5 and 6 were at testing site 3.

[2]One replicate failed due to processing error and excluded from analysis.

Table 76 Overall mean, standard deviation, and coefficients of variation (%) for cycle threshold, estimated from positive panel members

			Standard Deviation, Coefficient of Variation (%)				
Panel Member	**N**	**Mean Ct**	**Between-Site/Instrument**	**Between-Operator/ Run**	**Between-Day**	**Within-Run**	**Total CV**
Positive Cell Line Panel Members							
HPV16/18 Weak Positive (0.3 x LoD)							
HPV16 Weak Positive (0.3 x LoD)	77	36.6	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.76, (2.08%)	2.1
HPV18 Weak Positive (0.3 x LoD)	74	35.3	0.00, (0.00%)	0.00, (0.00%)	0.12, (0.34%)	0.95, (2.69%)	2.7
HPV16/18 Low Positive (1 x LoD)							
HPV16 Low Positive (1 x LoD)	118	35.6	0.10, (0.27%)	0.00, (0.00%)	0.15, (0.43%)	0.43, (1.22%)	1.3
HPV18 Low Positive (1 x LoD)	119	34.1	0.00, (0.00%)	0.09, (0.28%)	0.00, (0.00%)	0.63, (1.83%)	1.9
HPV16/18 Positive (3 x LoD)							
HPV16 Positive (3 x LoD)	119	34.7	0.05, (0.16%)	0.00, (0.00%)	0.11, (0.31%)	0.35, (1.01%)	1.1
HPV18 Positive (3 x LoD)	119	32.9	0.05, (0.16%)	0.08, (0.25%)	0.00, (0.00%)	0.39, (1.19%)	1.2
Positive Clinical Panel Members							
Pooled HPV16 Low Positive (1 x LoD)	120	33.6	0.25, (0.73%)	0.00, (0.00%)	0.00, (0.00%)	1.05, (3.11%)	3.2
Pooled HPV16 Positive (3 x LoD)	120	33.1	0.30, (0.90%)	0.00, (0.00%)	0.00, (0.00%)	0.84, (2.53%)	2.7
Pooled HPV18 Low Positive (1 x LoD)	119	35.1	0.00, (0.00%)	0.00, (0.00%)	0.11, (0.31%)	0.74, (2.09%)	2.1
Pooled HPV18 Positive (3 x LoD)	120	34.0	0.56, (1.64%)	0.00, (0.00%)	0.21, (0.62%)	0.70, (2.06%)	2.7
Pooled HPV45 Low Positive (1 x LoD)	120	31.9	0.56, (1.74%)	0.00, (0.00%)	0.00, (0.00%)	1.71, (5.37%)	5.6
Pooled HPV45 Positive (3 x LoD)	120	29.7	0.00, (0.00%)	0.00, (0.00%)	0.60, (2.04%)	1.42, (4.79%)	5.2
Pooled HPV39 Low Positive (1 x LoD)	120	33.4	0.20, (0.61%)	0.00, (0.00%)	0.33, (0.98%)	0.97, (2.90%)	3.1
Pooled HPV39 Positive (3 x LoD)	120	31.5	0.00, (0.00%)	0.00, (0.00%)	0.62, (1.95%)	1.31, (4.15%)	4.6

Notes: Ct=Cycle Threshold; CV=Coefficient of Variation

cobas® 5800 System

To evaluate site-to-site reproducibility testing with the **cobas®** 5800 System, testing was completed with three **cobas®** 5800 Systems across three sites. The panel was composed of HPV cell lines (SiHa and HeLa) diluted into a pool of HPV-negative cervical specimen collected into PreservCyt® Solution and a "zero concentration" HPV negative sample composed of HCT-15 cells in PreservCyt Solution. Each panel member was tested for five days, two runs per day, three replicates per run.

Table 77 summarizes results for the negative panel members by site/instrument, run, and day on the three **cobas®** 5800 Systems. All negative panel members were correctly identified as negative across site/instrument, run and testing day.

Percent of positive results for the positive panel members are presented in Table 78. Analysis of variance of the Ct values from tests performed on positive panel members yielded total CV(%) ranging from 1.9 to 2.6% across all panel members. The largest component of variance observed (0.79 for HPV16 Low Positive at 1.5 x LoD) among positive panel members was for within-run (Table 79).

Table 77 Agreement and variability for negative panel member for site/instrument, run, and day on the cobas® 5800 System

			Number of Negatives/Total Number of Valid Results								
			Between-Site/Instrument			Between-Run			Between-Day		
Panel Member	Ct SD	Ct CV%	ID	Negative Agreement (%)	Negative/ Valid	ID	Negative Agreement (%)	Negative/ Valid	ID	Negative Agreement (%)	Negative/ Valid
Negative background cell line	n/a	n/a	1	100.0	30/30	1	100.0	15/15	1	100.0	18/18
			2	100.0	30/30	2	100.0	15/15	2	100.0	18/18
			3	100.0	30/30	3	100.0	15/15	3	100.0	18/18
						4	100.0	15/15	4	100.0	18/18
						5	100.0	15/15	5	100.0	18/18
						6	100.0	15/15			

Table 78 Agreement and variability for positive panel members for site/instrument, run, and day on the cobas® 5800 System

			Number of Positive Results/Total Number of Valid Results								
			Between-Site/Instrument			Between-Run			Between-Day		
Panel Member	Ct SD	Ct CV%	ID	Positive Agreement (%)	Positive/ Valid	ID	Positive Agreement (%)	Positive/ Valid	ID	Positive Agreement (%)	Positive/ Valid
Positive Cell Line Panel Members: HPV16/18 Low Positive (1.5 x LoD)											
HPV16 Low Positive (1.5 x LoD)	0.9	2.6	1	100.0	30/30	1	100.0	15/15	1	100.0	18/18
			2	100.0	30/30	2	100.0	15/15	2	100.0	18/18
			3	96.7	29/30	3	100.0	15/15	3	100.0	18/18
						4	100.0	15/15	4	100.0	18/18
						5	93.3	14/15	5	94.4	17/18
						6	100.0	15/15			
HPV18 Low Positive (1.5 x LoD)	0.7	2.1	1	100.0	30/30	1	100.0	15/15	1	100.0	18/18
			2	100.0	30/30	2	100.0	15/15	2	100.0	18/18
			3	100.0	30/30	3	100.0	15/15	3	100.0	18/18
						4	100.0	15/15	4	100.0	18/18
						5	100.0	15/15	5	100.0	18/18
						6	100.0	15/15			
Positive Cell Line Panel Members: HPV16/18 Positive (3 x LoD)											
HPV16 Positive (3 x LoD)	0.7	2.1	1	100.0	30/30	1	100.0	15/15	1	100.0	18/18
			2	100.0	29/29	2	100.0	15/15	2	100.0	18/18
			3	100.0	30/30	3	100.0	14/14	3	100.0	18/18
						4	100.0	15/15	4	100.0	18/18
						5	100.0	15/15	5	100.0	17/17
						6	100.0	15/15			
HPV18 Positive (3 x LoD)	0.6	1.9	1	100.0	30/30	1	100.0	15/15	1	100.0	18/18
			2	100.0	29/29	2	100.0	15/15	2	100.0	18/18
			3	100.0	30/30	3	100.0	14/14	3	100.0	18/18
						4	100.0	15/15	4	100.0	18/18
						5	100.0	15/15	5	100.0	17/17
						6	100.0	15/15			

Table 79 Overall mean, standard deviation, and coefficients of variation (%) for cycle threshold, estimated from positive panel members

			Standard Deviation, Coefficient of Variation (%)				
Panel Member	**N**	**Mean Ct**	**Between-Site/Instrument**	**Between-Day**	**Between-Run**	**Within-Run**	**Total CV**
Positive Cell Line Panel Members							
HPV16/18 Low Positive (1.5 x LoD)							
HPV16 Low Positive (1.5 x LoD)	89	34.0	0.14, (0.42%)	0.19, (0.57%)	0.28, (0.84%)	0.79, (2.33%)	2.6
HPV18 Low Positive (1.5 x LoD)	90	32.7	0.11, (0.33%)	0.16, (0.48%)	0.18, (0.56%)	0.62, (1.89%)	2.1
HPV16/18 Positive (3 x LoD)							
HPV16 Positive (3 x LoD)	89	33.6	0.11, (0.33%)	0.16, (0.47%)	0.17, (0.51%)	0.66, (1.96%)	2.1
HPV18 Positive (3 x LoD)	89	32.2	0.09, (0.29%)	0.16, (0.50%)	0.09, (0.27%)	0.58, (1.79%)	1.9

A separate study was conducted to assess the precision of **cobas**® HPV on the **cobas**® 5800 System with a panel member detected in the 12 Other HR HPV channel. The precision of **cobas**® HPV on the **cobas**® 5800 System was found to be acceptable as compared to the **cobas**® 6800/8800 Systems.

Lot-to-lot variability

Lot-to-lot variability was evaluated at one testing site, using three reagent lots for each of the two Systems separately (**cobas®** 6800 and **cobas®** 8800). This study used the same panel as described in the site-to-site reproducibility study. Each panel member was tested for 15 days (5 days per lot), three replicates per run, for each of the two **cobas®** Systems. Two operators performed one run per day for 5 days for each reagent lot.

Table 80 and Table 81 show results for the negative panel member by reagent lot, operator/run and day on the **cobas®** 6800 System and on the **cobas®** 8800 System, respectively. In both Systems all negative panel members were correctly identified as negative across reagent lot, operator/run and testing day.

Table 80 Agreement and variability for negative panel members by lot, operator/run, and day on the cobas® 6800 System

			Number Negative/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**
Negative background cell line	n/a	n/a	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Negative pooled clinical samples	n/a	n/a	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18

Table 81 Agreement and variability for negative panel members by lot, operator/run, and day on the cobas® 8800 System

			Number of Negatives/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**	**ID**	**Negative Agreement (%)**	**Negative/ Valid**
Negative background cell line	N/A	N/A	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Negative pooled clinical samples	N/A	N/A	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18

Table 82 presents the percent of positive results for the positive panel members by reagent lot, operator/run and day on the **cobas®** 6800 System. Analysis of variance of the Ct values from valid tests performed on positive panel members yielded total CV(%) ranging of 0.9% to 5.0% across all panel members. The CV(%) ranged from 0.9% to 2.2% for the cell line panel members and 1.7% to 5.0% for the pooled clinical panel members (Table 82). The largest component of variance observed (1.55 for Pooled HPV45 Low Positive at 1 x LoD) among all positive panel members on the **cobas®** 6800 System was for within-run (Table 83).

Table 84 presents the percent of positive results for the positive panel members by reagent lot, operator/run and day on the **cobas®** 8800 System. Analysis of variance of the Ct values from valid tests performed on positive panel members yielded total CV(%) ranging of 1.1% to 7.4% across all panel members. The CV(%) ranged from 1.1% to 3.0% for the cell line panel members and 2.0% to 7.4% for the pooled clinical panel members (Table 85). The largest component of variance observed (2.16 for Pooled HPV45 Low Positive at 1 x LoD) among all positive panel members on the **cobas®** 8800 System was for within-run (Table 85).

Table 82 Agreement and variability for positive panel members for lot, operator, and day on the cobas® 6800 System

			Number of Positives/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	Ct SD	Ct CV%	ID	Positive Agreement (%)	Positive/ Valid	ID*	Positive Agreement (%)	Positive/ Valid	ID	Positive Agreement (%)	Positive/ Valid
Positive Cell Line Panel Members: HPV16/18 Weak Positive (0.3 x LoD)											
HPV16 Weak Positive (0.3 x LoD)	0.75	2.0	1	46.7	14/30	5	57.8	26/45	1	61.1	11/18
			2	46.7	14/30	6	53.3	24/45	2	44.4	8/18
			3	73.3	22/30				3	38.9	7/18
									4	77.8	14/18
									5	55.6	10/18
HPV18 Weak Positive (0.3 x LoD)	0.77	2.2	1	60.0	18/30	5	62.2	28/45	1	66.7	12/18
			2	60.0	18/30	6	66.7	30/45	2	66.7	12/18
			3	73.3	22/30				3	66.7	12/18
									4	66.7	12/18
									5	55.6	10/18
Positive Cell Line Panel Members: HPV16/18 Low Positive (1 x LoD)											
HPV16 Low Positive (1 x LoD)	0.50	1.4	1	100.0	30/30	5	97.8	44/45	1	94.4	17/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	96.7	29/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
HPV18 Low Positive (1 x LoD)	0.67	2.0	1	96.7	29/30	5	97.8	44/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	94.4	17/18
									5	100.0	18/18

			Number of Positives/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**	**ID***	**Positive Agreement (%)**	**Positive/ Valid**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**
Positive Cell Line Panel Members: HPV16/18 Positive (3 x LoD)											
HPV16 Positive (3 x LoD)	0.31	0.9	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
HPV18 Positive (3 x LoD)	0.39	1.2	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Positive Clinical Panel Members											
Pooled HPV16 Low Positive (1 x LoD)	1.13	3.4	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV16 Positive (3 x LoD)	1.00	3.0	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV18 Low Positive (1 x LoD)	0.60	1.7	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV18 Positive (3 x LoD)	0.86	2.5	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
	1.60	5.0	1	100.0	30/30	5	97.8	44/45	1	100.0	18/18

			Number of Positives/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**	**ID***	**Positive Agreement (%)**	**Positive/ Valid**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**
Pooled HPV45 Low Positive (1 x LoD)			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	96.7	29/30				3	100.0	18/18
									4	94.4	17/18
									5	100.0	18/18
Pooled HPV45 Positive (3 x LoD)	1.46	4.9	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV39 Low Positive (1 x LoD)	0.75	2.3	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV39 Positive (3 x LoD)	0.84	2.6	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18

*Note: Operators 5 and 6 were at testing site 3.

Table 83 Overall mean, standard deviation, and coefficients of variation (%) for cycle threshold, estimated from positive panel members on the cobas® 6800 System

			Standard Deviation, Coefficient of Variation (%)				
Panel Member	**N**	**Mean Ct**	**Between-Lot**	**Between-Operator/Run**	**Between-Day**	**Within-Run**	**Total CV**
Positive Cell Line Panel Members							
HPV16/18 Weak Positive (0.3 x LoD)							
HPV16 Weak Positive (0.3 x LoD)	52	36.5	0.07, (0.20%)	0.00, (0.00%)	0.28, (0.78%)	0.69, (1.88%)	2.0
HPV18 Weak Positive (0.3 x LoD)	58	35.4	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.77, (2.19%)	2.2
HPV16/18 Low Positive (1 x LoD)							
HPV16 Low Positive (1 x LoD)	89	35.6	0.09, (0.24%)	0.04, (0.13%)	0.00, (0.00%)	0.49, (1.37%)	1.4
HPV18 Low Positive (1 x LoD)	89	34.1	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.67, (1.97%)	2.0
HPV16/18 Positive (3 x LoD)							
HPV16 Positive (3 x LoD)	90	34.6	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.31, (0.88%)	0.9
HPV18 Positive (3 x LoD)	90	32.9	0.00, (0.00%)	0.00, (0.00%)	0.13, (0.41%)	0.36, (1.10%)	1.2
Positive Clinical Panel Members							
Pooled HPV16 Low Positive (1 x LoD)	90	33.5	0.11, (0.32%)	0.00, (0.00%)	0.00, (0.00%)	1.12, (3.35%)	3.4
Pooled HPV16 Positive (3 x LoD)	90	33.1	0.11, (0.33%)	0.00, (0.00%)	0.00, (0.00%)	1.00, (3.01%)	3.0
Pooled HPV18 Low Positive (1 x LoD)	90	35.1	0.14, (0.41%)	0.00, (0.00%)	0.00, (0.00%)	0.58, (1.67%)	1.7
Pooled HPV18 Positive (3 x LoD)	90	33.7	0.00, (0.00%)	0.26, (0.76%)	0.14, (0.43%)	0.81, (2.39%)	2.5
Pooled HPV45 Low Positive (1 x LoD)	90	32.0	0.00, (0.00%)	0.00, (0.00%)	0.42, (1.31%)	1.55, (4.84%)	5.0
Pooled HPV45 Positive (3 x LoD)	90	29.7	0.18, (0.62%)	0.00, (0.00%)	0.00, (0.00%)	1.45, (4.89%)	4.9
Pooled HPV39 Low Positive (1 x LoD)	90	33.3	0.00, (0.00%)	0.00, (0.00%)	0.23, (0.69%)	0.71, (2.14%)	2.3
Pooled HPV39 Positive (3 x LoD)	90	31.6	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.84, (2.65%)	2.6

Notes: Ct=Cycle Threshold; CV=Coefficient of Variation

Table 84 Agreement and variability for positive panel member by lot, operator/run, and day on the cobas® 8800 System

			Number of Positives/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**	**ID[1]**	**Positive Agreement (%)**	**Positive/ Valid**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**
Positive Cell Line Panel Members: HPV16/18 Weak Positive (0.3 x LoD)											
HPV16 Weak Positive (0.3 x LoD)	0.67	1.8	1	60.0	18/30	5	57.8	26/45	1	66.7	12/18
			2	63.3	19/30	6	68.9	31/45	2	61.1	11/18
			3	66.7	20/30				3	72.2	13/18
									4	66.7	12/18
									5	50.0	9/18
HPV18 Weak Positive (0.3 x LoD)	1.07	3.0	1	70.0	21/30	5	73.3	33/45	1	77.8	14/18
			2	70.0	21/30	6	64.4	29/45	2	72.2	13/18
			3	66.7	20/30				3	72.2	13/18
									4	72.2	13/18
									5	50.0	9/18
Positive Cell Line Panel Members: HPV16/18 Low Positive (1 x LoD)											
HPV16 Low Positive (1 x LoD)	0.44	1.2	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	96.7	29/30	6	95.6	43/45	2	100.0	18/18
			3	96.7	29/30				3	94.4	17/18
									4	100.0	18/18
									5	94.4	17/18
HPV18 Low Positive (1 x LoD)	0.74	2.2	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Positive Cell Line Panel Members: HPV16/18 Positive (3 x LoD)[2]											
HPV16 Positive (3 x LoD)	0.38	1.1	1	100.0	29/29	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	44/44	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	17/17
									5	100.0	18/18
HPV18 Positive (3 x LoD)	0.41	1.2	1	100.0	29/29	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	44/44	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	17/17
									5	100.0	18/18
Positive Clinical Panel Members											
	0.91	2.7	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18

			Number of Positives/Total Number Valid Results								
			Between-Lot			Between-Operator/Run			Between-Day		
Panel Member	**Ct SD**	**Ct CV%**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**	**ID[1]**	**Positive Agreement (%)**	**Positive/ Valid**	**ID**	**Positive Agreement (%)**	**Positive/ Valid**
Pooled HPV16 Low Positive (1 x LoD)			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV16 Positive (3 x LoD)	0.88	2.7	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV18 Low Positive (1 x LoD)	0.70	2.0	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV18 Positive (3 x LoD)	1.02	3.0	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV45 Low Positive (1 x LoD)	2.32	7.4	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV45 Positive (3 x LoD)	1.74	5.9	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV39 Low Positive (1 x LoD)	1.06	3.2	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18
Pooled HPV39 Positive (3 x LoD)	1.52	4.8	1	100.0	30/30	5	100.0	45/45	1	100.0	18/18
			2	100.0	30/30	6	100.0	45/45	2	100.0	18/18
			3	100.0	30/30				3	100.0	18/18
									4	100.0	18/18
									5	100.0	18/18

[1] Operators 5 and 6 were at testing site 3.

[2] One replicate failed due to processing error and excluded from analysis.

Table 85 Overall mean, standard deviation, and coefficients of variation (%) for cycle threshold, estimated from positive panel members on the cobas® 8800

			Standard Deviation, Coefficient of Variation (%)				
Panel Member	**N**	**Mean Ct**	**Between-Lot**	**Between-Operator/Run**	**Between-Day**	**Within-Run**	**Total CV**
Positive Cell Line Panel Members							
HPV16/18 Weak Positive (0.3 x LoD)							
HPV16 Weak Positive (0.3 x LoD)	58	36.6	0.00, (0.00%)	0.16, (0.45%)	0.16, (0.44%)	0.63, (1.72%)	1.8
HPV18 Weak Positive (0.3 x LoD)	63	35.5	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	1.07, (3.01%)	3.0
HPV16/18 Low Positive (1 x LoD)							
HPV16 Low Positive (1 x LoD)	88	35.6	0.00, (0.00%)	0.00, (0.00%)	0.14, (0.40%)	0.42, (1.18%)	1.2
HPV18 Low Positive (1 x LoD)	90	34.2	0.00, (0.00%)	0.16, (0.46%)	0.30, (0.86%)	0.66, (1.94%)	2.2
HPV16/18 Positive (3 x LoD)							
HPV16 Positive (3 x LoD)	89	34.6	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.38, (1.10%)	1.1
HPV18 Positive (3 x LoD)	89	32.7	0.00, (0.00%)	0.00, (0.00%)	0.00, (0.00%)	0.41, (1.24%)	1.2
Positive Clinical Panel Members							
Pooled HPV16 Low Positive (1 x LoD)	90	33.6	0.07, (0.21%)	0.00, (0.00%)	0.00, (0.00%)	0.91, (2.71%)	2.7
Pooled HPV16 Positive (3 x LoD)	90	32.9	0.00, (0.00%)	0.00, (0.00%)	0.13, (0.39%)	0.87, (2.64%)	2.7
Pooled HPV18 Low Positive (1 x LoD)	90	35.0	0.00, (0.00%)	0.05, (0.15%)	0.16, (0.47%)	0.68, (1.94%)	2.0
Pooled HPV18 Positive (3 x LoD)	90	33.6	0.24, (0.70%)	0.25, (0.75%)	0.18, (0.54%)	0.94, (2.80%)	3.0
Pooled HPV45 Low Positive (1 x LoD)	90	31.2	0.40, (1.27%)	0.00, (0.00%)	0.74, (2.37%)	2.16, (6.93%)	7.4
Pooled HPV45 Positive (3 x LoD)	90	29.5	0.00, (0.00%)	0.41, (1.40%)	0.59, (2.00%)	1.59, (5.39%)	5.9
Pooled HPV39 Low Positive (1 x LoD)	90	33.1	0.00, (0.00%)	0.00, (0.00%)	0.30, (0.92%)	1.02, (3.07%)	3.2
Pooled HPV39 Positive (3 x LoD)	90	31.4	0.00, (0.00%)	0.00, (0.00%)	0.59, (1.88%)	1.40, (4.46%)	4.8

Notes: Ct=Cycle Threshold; CV=Coefficient of Variation

Performance with Self-Collected Vaginal Specimens

Comparison of Self-Collected Sample Vaginal Specimens Using Evalyn® Brush and Clinician-Collected Cervical Specimens A comparison of results from self-collected vaginal specimens and clinician-collected cervical specimens was performed using paired samples from 556 screening-eligible women.

Each woman first collected her vaginal sample using an Evalyn® Brush (Rovers® Medical Devices, Netherlands) which was suspended by a healthcare provider into a methanol-based medium after collection. A second sample (cervical sample) was collected by a clinician during the same visit using the standard of care protocol; the clinician-collected cervical sample was suspended in the same medium type as that of the self-collected vaginal sample.

A total of 532 valid paired results were evaluable for the purposes of agreements calculation.

The correlation results and calculated positive percent agreements for 14 high risk HPV, HPV16/18, and 12 other high risk HPV, and, negative percent agreement along with 95% confidence intervals are shown in Table 86.

The rate of invalid results for the self-collected and clinician-collected results were 4.3% and 0.0%, respectively.

Table 86 Agreements between self-collected vaginal specimens using		Clinician-collected cervical sample			
		HPV 16/18 Positive	12 other HPV HR Positive	Negative	Total
Self-collected vaginal sample	HPV 16/18 Positive	26	1	8	35
	12 other HPV HR Positive	0	97	27	124
	Negative	0	21	352	373
	Total	26	119	387	532

		Result (%)	95% Confidence Interval
HPV 16/18 Positive	Positive Percent Agreement	100.0%	87.1%-100.0%
12 other HPV HR Positive	Positive Percent Agreement	81.5%	73.6%-87.5%
14 HPV HR	Positive Percent Agreement	85.5%	78.9%-90.3%
	Negative Percent Agreement	91.0%	87.7%-93.4%

Comparison of Self-Collected Vaginal Specimens Using FLOQSwab® 552C.RM and Clinician-Collected Cervical Specimens

A comparison of results from self-collected vaginal specimens and clinician-collected cervical specimens was performed using paired samples from 511screening-eligible women.

Each woman first collected her vaginal sample using a FLOQSwab® #552C.RM (Copan, Italy) which was suspended by a healthcare provider into a methanol-based medium after collection. A second sample (cervical samples) was collected by a clinician during the same visit using the standard of care protocol; the clinician-collected cervical sample was suspended in the same medium type as that of the self-collected vaginal sample.

A total of 487 valid paired results were evaluable for the purposes of agreements calculation.

The correlation results and calculated positive percent agreements for 14 high risk HPV, HPV16/18, and 12 other high risk HPV, and negative percent agreement along with 95% confidence intervals are shown in Table 87.

The rate of invalid results for the self-collected and clinician-collected results were 4.3% and 0.4%, respectively.

Table 87 Agreement between self-collected vaginal specimens using FLOQSwab® 552C.RM and clinician-collected cervical specimens

		Clinician-collected cervical sample			
		HPV 16/18 Positive	**12 other HPV HR Positive**	**Negative**	**Total**
Self-collected vaginal sample	**HPV 16/18 Positive**	14	0	3	17
	12 other HPV HR Positive	0	78	30	108
	Negative	1	22	339	362
	Total	15	100	372	487

		Result (%)	**95% Confidence Interval**
HPV 16/18 Positive	**Positive Percent Agreement**	93.3%	70.2%-98.8%
12 other HPV HR Positive	**Positive Percent Agreement**	78.0%	68.9%-85.0%
14 HPV HR	**Positive Percent Agreement**	80.0%	71.8%-86.3%
	Negative Percent Agreement	91.1%	87.8%-93.6%

Additional information

Key assay features

Sample types	Cervical specimen collected in PreservCyt® Solution Self-collected vaginal specimen
Amount of sample processed	≥1000 µL required in sample tube for PreservCyt® samples, instrument processes 400 µL Maximum volume of 4 mL in sample tube for PreservCyt® samples On the **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 88 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 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 US Only: 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:
https://www.roche.com/about/business/roche_worldwide.htm

Manufacturer and distributor

Table 89 Manufacturer and distributor

Roche Molecular Systems, Inc.
1080 US Highway 202 South
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Made in USA

Distributed by Roche Diagnostics
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Document revision

Document Revision Information	
Doc Rev. 1.0 11/2023	First Publishing.
Doc Rev. X.X XX/XXXX	Updated the **Intended use** section. Updated the **Warning** section. Updated the **Background and rationale for HPV testing** section. Updated the **Additional materials required for sample collection for cobas® HPV** section. Updated the **Warnings and precautions** section. Updated the **Specimen collection, transport, and storage** section. Updated the **Instructions for use** section. Addition of suspension instructions for samples collected with FLOQSwabs® 552C.RM and Evalyn® brush Updated the **Running cobas® HPV on the cobas® 5800 System** section. Updated the **Running cobas® HPV on the cobas® 6800/8800 Systems** section. Updated the **Interpretation of results** section. Updated the **Procedural limitations** section. Addition of data to support the testing of vaginal samples collected with FLOQSwabs® 552C.RM suspended in PreservCyt® Solution. Addition of data to support the testing of vaginal samples collected with Evalyn® brush suspended in PreservCyt® Solution. Updated the **Additional information** section. Please contact your local Roche Representative if you have any questions.