

**WHO Prequalification of In Vitro Diagnostics
PUBLIC ASSESSMENT REPORT**

**Product: cobas 4800 HPV Test
WHO reference number: PQDx 0466-046-00**

cobas 4800 HPV Test with product codes 05235804190, 05235782190, 05235910190, 05235901190, 05235855190, 05235839190, 05235812190, 05235871190 and 05235863190, manufactured by Roche Molecular Systems, Inc., CE-mark regulatory version, was accepted for the WHO list of prequalified in vitro diagnostics and was listed on 25 July 2024.

Summary of WHO’s Prequalification Assessment for the cobas 4800 HPV Test

	Date	Outcome
Prequalification listing	25 July 2024	Listed
TSS-4 gap analysis	24 May 2023	MR
Product performance evaluation	Quarter (Q) 4 2023 to Q1 2024	MR

MR: Meet Requirements

Report amendments and product changes

This public report has since been amended. Amendments may have arisen because of changes to the prequalified product, for which the WHO has been notified and has undertaken a review. The amendments to the report are summarized in the following table, and details of each amendment are provided below.

Version	Summary of amendment and change request reference, where applicable.	Date of report amendment
2.0	Addition of self-collected vaginal sample (PQC-IVD-2024-0050)	17 February 2026

Intended use:

According to the claim of intended use from Roche Molecular Systems, Inc., *“The cobas 4800 Human Papillomavirus (HPV) Test is a qualitative in vitro test for the detection of Human Papillomavirus in patient specimens. The test utilizes amplification of target DNA by the*

Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies HPV16 and HPV18 while concurrently detecting the other high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels. Specimens are limited to cervical cells collected in Roche Cell Collection Medium (Roche Molecular Systems, Inc.), PreservCyt Solution (Hologic Corp.) and SurePath™ Preservative Fluid (BD Diagnostics-TriPath). Indications for use of the cobas 4800 HPV Test are:

(a) The cobas 4800 HPV Test is indicated for use in screening patients with ASC-US (atypical squamous cells of undetermined significance) cervical cytology results to determine the need for referral to colposcopy.

(b) The cobas 4800 HPV Test is indicated for use in screening patients with ASC-US cervical cytology results to assess the presence or absence of high-risk HPV genotypes 16 and 18.

(c) The cobas 4800 HPV Test is indicated for use adjunctively with cervical cytology to assess the presence or absence of high risk HPV types.

(d) The cobas 4800 HPV Test is indicated for use adjunctively with cervical cytology to assess the presence or absence of HPV genotypes 16 and 18.

(e) The cobas 4800 HPV Test is indicated for use as a first-line primary screening test to identify women at increased risk for the development of cervical cancer or presence of high-grade disease.

(f) The cobas 4800 HPV Test is indicated for use as a first-line primary screening test to assess the presence or absence of HPV genotypes 16 and 18.

The cobas 4800 HPV Test can also be used with healthcare worker–instructed self-collected vaginal specimens collected in Roche Cell Collection Medium or PreservCyt Solution. The results from the cobas HPV Test, together with the physician’s assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. The results of the cobas HPV Test are not intended to prevent women from proceeding to colposcopy.”

Test kit contents:

cobas 4800 System Sample Preparation Kit	05235782190 (240 Tests)
MGP (cobas 4800 System Magnetic Glass Particles)	10 x 4.5 mL
EB (cobas 4800 System Elution Buffer)	10 x 18 mL
cobas 4800 System Sample Preparation Kit (c4800 SMPL PREP)	05235804190 (960 Tests)
MGP (cobas 4800 System Magnetic Glass Particles)	10 x 13.5 mL
EB (cobas 4800 System Elution Buffer)	10 x 18 mL
cobas 4800 System Wash Buffer Kit (c4800 WB)	05235863190 (240 Tests)
WB (cobas 4800 System Wash Buffer)	10 x 55 mL

cobas 4800 System Wash Buffer Kit (c4800 WB)	05235871190 (960 Tests)
WB (cobas 4800 System Wash Buffer)	10 x 200 mL
cobas 4800 System Liquid Cytology Preparation Kit (c4800 LIQ CYT)	05235812190 (240 Tests)
PK (cobas 4800 Proteinase K)	10 x 0.9 mL
SDS (cobas 4800 System SDS Reagent)	10 x 3 mL
LYS (cobas 4800 System Lysis Buffer)	10 x 10 mL
cobas 4800 System Liquid Cytology Preparation Kit (c4800 LIQ CYT)	05235839190 (960 Tests)
PK(cobas 4800 Proteinase K)	20 x 1.2 mL
SDS (cobas 4800 System SDS Reagent)	10 x 9 mL
LYS (cobas 4800 System Lysis Buffer)	10 x 36 mL
cobas 4800 HPV Amplification/Detection Kit (c4800 HPV AMP/DET)	5235901190 (240 Tests)
HPV MMX (cobas 4800 HPV Master Mix)	10 x 0.5 mL
HPV Mg/Mn (cobas 4800 HPV Mg/Mn Solution)	10 x 1.0 mL
cobas 4800 HPV Amplification/Detection Kit (c4800 HPV AMP/DET)	05235910190 (960 Tests)
HPV MMX (cobas 4800 HPV Master Mix)	20 x 1.0 mL
HPV Mg/Mn (cobas 4800 HPV Mg/Mn Solution)	10 x 1.0 mL
cobas 4800 HPV Controls Kit (c4800 HPV CTLs)	05235855190 (10 Sets)
cobas 4800 HPV Positive Control	10 x 0.5 mL
cobas 4800 System Negative Control)	10 x 0.5 mL

Items required but not provided:

Specimen and Reagent Handling

- Roche Cell Collection Medium (Roche P/N 07994745190, optional)
- Roche Cell Collection Medium Replacement Caps (Roche P/N 08037230190, optional)
- Cervical Collection Brush (Roche P/N 08399832190, optional)
- Cervical Collection Brush, sterile (Roche P/N 08779040190, optional)
- Copan FLOQSwabs for vaginal self-collection, 552C.80 (Roche P/N 09032932190)
- Rovers Evalyn Brush (Roche P/N 09032959190)
- Sample suspension instructions for Copan FLOQSwabs for vaginal self-collection, 552C.80 (Roche P/N 09652671001)
- Sample suspension instructions for Evalyn Brush (Roche P/N 09907238001)

- CO-RE Tips, 1000 µL, rack of 96 (Roche P/N 04639642001 or Hamilton P/N 235905)
- 50 mL Reagent Reservoir (Roche P/N 05232732001)
- 200 mL Reagent Reservoir (Roche P/N 05232759001)
- For HPV ASAP v2.0.1 use cobas 4800 System Extraction (deep well) plate 1.6 mL (Roche P/N 05232716001)
- For HPV ASAP v2.1 use cobas 4800 System Extraction (deep well) plate 2.0 mL (Roche P/N 06884008001)
- cobas 4800 System AD (microwell) plate 0.3 mL and Sealing Film (Roche P/N 05232724001)
- Solid waste bag [Roche P/N 05530873001 (small) or 04691989001 (large)]
- Hamilton STAR Plastic Chute (Roche P/N 04639669001)
- Tubes 13 mL Round Base (Roche: P/N 07958048190) for use as secondary sample tubes
- Caps, neutral color (Roche P/N 07958056190; for recapping post-run specimens in 13 mL Round Base tubes)
- Disposable gloves, powderless

Instrumentation and Software

- **cobas x** 480 instrument,
- **cobas z** 480 analyzer,
- **cobas** 4800 System Control Unit with System Software version 2.2 or higher,
- **cobas** 4800 System cobas HPV AP software version 2.0. or higher.

Optional Equipment and Materials

- **cobas** Sample Prep Buffer (Roche P/N 06526985190; Tris buffered detergent)*
- Pipettes: capable of delivering 1000 µL
- Aerosol barrier DNase-free tips: capable of delivering 1000 µL
- Centrifuge equipped with a swinging bucket rotor with minimum RCF of 1500
- Stand-alone magnetic plate (Roche P/N 05440777001)
- Vortex Mixer (single tube)
- Multi-tube vortexer [e.g. VWR P/N 58816-116]
- Heat-resistant barcode labels (RACO Industries; Cat # RAC-225075-9501)
- Thermometer -20/150°C (VWR Cat# 89095-600) or equivalent
- Digital Heater Block 120V (VWR Cat# 75838-294) or equivalent
- 12-Hole Heat Block Module 16mm (VWR Cat# 13259-162) or equivalent

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

Storage:

- Do not freeze reagents.
- Store MGP, EB, PK, SDS, LYS, HPV MMX, HPV Mg/Mn, HPV (+) C and (-) C at 2-8°C. These reagents are stable until the expiration date indicated.
- Store WB at 15-25°C. This reagent is stable until the expiration date indicated.

Shelf-life upon manufacture¹:

18 months.

Note: The manufacturer provided an additional summary of the Limit of Detection (LoD) for HPV Targets in Roche Cell Collection Medium (RCCM) and PreservCyt (PROBIT and Hit Rate Values) that were not included in the attached IFU (below). The goal of the study was to demonstrate the comparable performance between RCCM and PreservCyt as sample collection media in a side-by-side testing scenario. Comparability is shown in the data set below with the overlapping confidence intervals of all presented LoD values.

Summary of LOD for HPV Targets in RCCM and PreservCyt (PROBIT and Hit Rate Values)

Target	PreservCyt LOD			RCCM LOD		
	LOD	PROBIT		LOD	PROBIT	
		95% Lower Confidence Limit	95% Upper Confidence Limit		95% Lower Confidence Limit	95% Upper Confidence Limit
HPV31	967 copies/mL	804 copies/mL	1258 copies/mL	830 copies/mL	690 copies/mL	1071 copies/mL
HPV16	106 cells/mL	72 cells/mL	317 cells/mL	98 cells/mL	80 cells/mL	129 cells/mL
HPV18	64 cells/mL	53 cells/mL	83 cells/mL	57 cells/mL	46 cells/mL	77 cells/mL

Product dossier assessment

Roche Molecular Systems, Inc. submitted a gap analysis for cobas 4800 HPV Test as per the requirements of TSS-4 (2018). The information (data and documentation) submitted in the

¹ The assigned device shelf-life is based on stability data generated from the date of manufacture. The finished goods shelf-life, calculated from the date of packaging completion, may be shorter depending on the time elapsed between manufacture and final packaging of the device.

gap analysis was reviewed by WHO staff and external technical experts (assessors) appointed by WHO. The manufacturer's responses to the discrepancies found during assessment were accepted on 24 May 2023.

Based on the gap analysis assessment findings, the gap analysis documentation for cobas 4800 HPV Test meets WHO prequalification requirements.

Manufacturing site assessment

The inspection of the manufacturing site(s) was conducted to assess whether the manufacturer’s quality management system (QMS) and manufacturing practices are in alignment with:

- (i) applicable international standards, such as ISO 13485 (Medical devices – Quality management systems – Requirements for regulatory purposes);
- (ii) the manufacturer’s own documented procedures and quality requirements; and
- (iii) other relevant international standards and guidelines applicable to in vitro diagnostic (IVD) medical devices. The WHO’s Public Inspection Reports are accessible at:

<https://extranet.who.int/pgweb/vitro-diagnostics/who-public-inspection-reports>

Product performance evaluation

The cobas 4800 HPV Test was evaluated by the Scottish HPV Reference Laboratory, United Kingdom of Great Britain and Northern Ireland, in collaboration with the TCD Molecular Pathology Research Laboratory, Coombe Hospital, Dublin, Ireland on behalf of WHO in the 4th quarter of 2023 and 1st quarter of 2024, according to protocol PQDx_255 v2.0.

Analytical performance evaluation

Analytical performance characteristics	
Limit of detection (LoD)	The LoD was estimated at 5746 IU/mL (95% CI: 3362-9281) for HPV Type 16; 1963 IU/mL (95% CI: 1264-3046) for HPV Type 18; and 1429 IU/mL (95% CI: 859-2380) for HPV Type 31.
Reproducibility	The hit rates for detection of HPV 16, HPV 18 and HPV 31 at approx. 10 ⁴ IU/mL were all 100%.
Genotype detection	The following genotypes from the genotype detection panel were detected: HPV types 16, 18, 31, 33, 45, 52, 58, in agreement with manufacturer’s claim; HPV types 6 and 11 were not detected in agreement with the manufacturer’s claim.

Cross-contamination / carry-over	No cross-contamination was observed when high positive and negative specimens were tested alternatively.
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Operational characteristics and ease of use

This assay requires laboratory equipment and cannot be performed in laboratories with limited facilities or in non-laboratory settings. The instrument requires a stable source of electricity and significant physical space. Furthermore, training and implementation of good laboratory practice is essential to obtaining accurate results.

The assay was found easy to use by the operators performing the evaluation.

Key operational characteristics	
Time to result for one run	270 minutes
Operator hands-on time for one run	60 minutes
Level of automation	Semi-automated: plates must be removed from cobas x 480 after extraction, manually sealed, and then placed on cobas z 480 within 90 minutes after extraction.
Quality controls	QCs are provided by the manufacturer and should be purchased separately.
Operating temperature	15- 30°C.
Result display and connectivity	Results are displayed on the computer connected to the instrument. They may be printed using a standard printer. The results can be exported to the laboratory information system and other health information systems.
Power sources	Main power The use of a UPS is recommended, as stable electricity is required.
Biosafety (<i>outside of infectious specimen handling</i>)	Operators reported biosafety considerations, based on the product IFU. Specimens, reagents and waste must be handled according to the manufacturer’s instruction. Reagents contain components that may cause skin irritation, skin allergy, eye irritation or damage, or explosions.
Waste	The volume of liquid waste is approx. 1ml per test. The volume of solid waste is approx. 2122g per run. Waste disposal does not require specific measures in addition to usual laboratory biohazard waste disposal procedures.
Calibration	Not required.

	Calibration is checked during system maintenance by manufacturer as a contractor service.
Maintenance	Daily and weekly maintenance is required with a 6-month preventative maintenance conducted by the manufacturer.
Other specific requirements	NA

** Steps for one specimen: each action required to obtain a result for one specimen (excluding specimen collection, instrument management, maintenance/calibration), e.g. add specimen to the cartridge, close the cartridge, scan/type specimen ID, load the cartridge on the instrument, press start (5 steps) OR scan/type specimen ID, load the specimen collection tube into the instrument, press start (3 step)*

*** Steps for instrument management: each action required daily or per run to set up and shut down the instrument, e. g. switch on instrument, log in, maintain supplies, maintain reagents, discard liquid waste, discard solid waste, archive results, switch off instrument (8 steps)*

Based on these results, the performance evaluation of the cobas 4800 HPV Test meets the WHO prequalification requirements.

Labelling review

The labelling submitted for cobas 4800 HPV Test was reviewed by WHO staff and external technical experts appointed by WHO. The review evaluated the labelling for clarity and consistency with the information submitted in the product dossier, alignment with international guidance and standards, and suitability for the intended users and settings in WHO Member States, including low- and middle-income countries.

The table below provides traceability of the labelling documents reviewed during the assessment, including document titles, version numbers, approval dates, and control identifiers.

Controlled Labelling References

Document Type	Document Title	Version / Revision	Date Approved	Controlled Document No.
Outer box artwork	ART5641144001	v04	20-Jan-2022	1010006503010
Outer box artwork	ART5641152001	V04	14-Jan-2022	1010006502971
Outer box artwork	ART5641047001	V09	05-Nov-2021	1010006503008

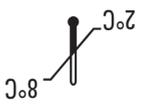
Document Type	Document Title	Version / Revision	Date Approved	Controlled Document No.
Outer box artwork	ART5641055001	V09	29-Nov-2021	1010006502932
Outer box artwork	ART5641098001	V05	17-Oct-2024	1010006503009
Outer box artwork	ART5641101001	V06	18-Nov-2024	1010006502933
Outer box artwork	ART5641063001	V11	04-Nov-2024	1010006503011
Outer box artwork	ART5641071001	V11	18-Nov-2024	1010006502975
Outer box artwork	ART5641179001	V07	20-Jan-2022	1010006502974
Instructions for Use (IFU)	ART5641225001EN	V24	24-Aug-2024	1010007503627

Labels

cobas®

c4800 SMPL PREP

Rx Only



IVD



REF 05235782190

cobas® 4800 System Sample Preparation Kit

NOTICE
The instructions for use of this kit are contained in the target-specific cobas® 4800 test package insert.

WIKES
Die Gebrauchsanleitung für dieses Produkt finden Sie in der testspezifischen Packungsbegleite des jeweiligen cobas® 4800-Tests.

INDICATION
Les instructions d'utilisation de ce produit sont contenues dans la notice relative au test cobas® 4800 correspondant.

AVISO
Le istruzioni per l'uso di questo prodotto sono contenute nel foglio illustrativo del test cobas® 4800 specifico per il target.

AVISO
Las instrucciones de uso de este producto figuran en el boletín técnico de la prueba cobas® 4800 específica para el objetivo.

AVISO
As instruções de utilização deste produto encontram-se no folheto informativo do teste cobas® 4800 específico do alvo.

BEMERKUNG
Brauchsanleitung für dieses Produkt finden Sie in der testspezifischen Packungsbegleite des jeweiligen cobas® 4800-Tests.

MEDELÄNDE
Bruksanvisningen för den här produkten finns i den target-specifika bifogat med testet cobas® 4800.

UWAGA
Instrukcje dotyczące stosowania tego produktu umieszczone są w książeczce dla docelowych organizmów ulotce testu cobas® 4800.

OZNÁMENIE
Návod na použitie pre tento produkt nájdete v cieľovo špecifickom prílohovom listku testov cobas® 4800.

CONTENT

cobas® 4800 System Sample Preparation Reagents

For USA*

MGP 10 x 4.5 mL
EB 10 x 18 mL

CONTENT

MGP 10 x 4.5 mL
Magnetic Glass Particles
93% Isopropanol

EB 10 x 18 mL
Tris buffer
0.09% Sodium azide

* Composition information required by US only.

DANGER/GEFAHR/PERICOLO/PELIGRO/PERIGO/FARE/FARV/NIEBEZPIECZENSTWO/NEBEZPEČENSTVO



H225, H319, H336, P210, P233, P261, P280, P303 + P361 + P353, P370 + P378

For US Only:
Refer to the product specific Instructions For Use for detailed information regarding hazards.

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876 USA

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany
EC Importer¹



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Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247²)

¹ Symbol text required by USA only.
² For USA only.

Made in USA

cobas® 4800 System Sample Preparation Kit



c4800 SMPL PREP

cobas®

EC REP

Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany



Comp/lot label affixed here when necessary

UDI Label Here

cobas

c4800 SMPL PREP

Rx Only



IVD



REF 05235804190

cobas® 4800 System Sample Preparation Kit

NOTICE
The instructions for use of this kit are contained in the target-specific cobas® 4800 test package insert.

HINWIS
Die Gebrauchsanleitung für dieses Produkt finden Sie in der testpezifischen Packungsbegleite des jeweiligen cobas® 4800-Tests.

AVERTISSEMENT
Les instructions d'utilisation de ce produit sont contenues dans la notice relative au test cobas® 4800 spécifique pour le target.

AVISO
Le istruzioni per l'uso di questo prodotto sono contenute nel foglio illustrativo del test cobas® 4800 specifico per il target.

AVISO
Las instrucciones de uso de este producto figuran en el boletín técnico de la prueba cobas® 4800 específica para el objetivo.

AVISO
As instruções de utilização deste produto encontram-se no folheto informativo do teste cobas® 4800 específico do alvo.

BEMERKUNG
Brauchföhrungsanleitung für dieses Produkt, inkl. target-spezifische Packungsbegleite für cobas® 4800-Tests.

MEDELÄNDE
Bruksanvisningen för den test som är avsett för cobas® 4800-testet.

UWAGA
Instrukcje dotyczące stosowania tego produktu umieszczone są w książeczce dla docelowych organizmów ulotce testu cobas® 4800.

OZNÁMENIE
Návod na použitie pre tento produkt nájdete v cieľovo špecifickom príbalovom listku testov cobas® 4800.

CONTENT

cobas® 4800 System Sample Preparation Reagents

For USA*

MGP 10 x 13.5 mL
EB 10 x 18 mL

CONTENT

MGP 10 x 13.5 mL
Magnetic Glass Particles
93% Isopropanol

EB 10 x 18 mL
Tris buffer
0.09% Sodium azide

* Composition information required by US only.

DANGER/ GEFAHR/ PELIGRO/ PERICOLO/ PERIGO/
FARE/ FARA/ NIEBEZPIECZENSTWO/ NEBEZPEČENSTVO



H225, H319, H336, P210, P233, P261, P370 + P378
P280, P303 + P361 + P353

For US Only:
Refer to the product specific Instructions For Use for detailed information regarding hazards.

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876 USA

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany



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toll-free: 1-800-526-1247)¹

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² For USA only.

Made in USA

cobas® 4800 System Sample Preparation Kit



c4800 SMPL PREP

cobas®

EC REP

Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany



Comp/lot label affixed here when necessary

UDI Label Here

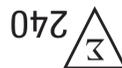
cobas

c4800 LIQ CYT

Rx Only



IVD



REF 05235812190

cobas® 4800 System Liquid Cytology Preparation Kit

NOTICE
The instructions for use for this product are contained in the target-specific **cobas® 4800** test package insert.

HINWEIS
Die Gebrauchsanleitung für dieses Produkt ist in der test-spezifischen Packungsbeilage des jeweiligen **cobas® 4800** Tests.

AVERTISSEMENT
Les instructions d'utilisation de ce produit sont contenues dans la notice relative au test **cobas® 4800** correspondant.

AVISO
Le istruzioni per l'uso di questo prodotto sono contenute nel foglio illustrativo del test **cobas® 4800** specifico per il target.

AVISO
Las instrucciones de uso de este producto figuran en el boletín técnico de la prueba **cobas® 4800** específica para el objetivo.

AVISO
As instruções de utilização deste produto encontram-se no díptico informativo do teste **cobas® 4800** específico do alvo.

BEWERKING
Brugsvejledningen til dette produkt findes på det target-specifikke pakningsindlæg til **cobas® 4800**-testet.

MEDELANDE
Bruksanvisningen för den här produktens finns på den target-specifika typsäcksläp till **cobas® 4800**-testet.

UWAGA
Instrukcje dotyczące stosowania tego produktu umieszczone są w właściwym dla docelowych organizmów ulotce testu **cobas® 4800**.

OZNAČENIE
Návod na použitie pre tento produkt nájdeš v príslušnej špecifickom prílohu testu **cobas® 4800**.

CONTENT

PK 10 x 0.9 mL
SDS 10 x 3 mL
LYS 10 x 10 mL

cobas® 4800 System Liquid Cytology Sample Preparation Reagents

For USA*

CONTENT

PK 10 x 0.9 mL
Tris buffer
< 0.05% EDTA
Calcium chloride
Calcium acetate
Glycerol
< 2% Proteinase K

SDS 10 x 3 mL
Tris-HCl buffer
0.2% SDS
0.05% Sodium azide

LYS 10 x 10 mL
Tris-HCl buffer
3% Guanidine HCl
< 5% Polydocanol

DANGER/ GEFAHR/ PERICOLO/ PELIGRO/ PERIGO/ FARE/ FARA/ NIEBEZPIECZENSTWO/ NEBEZPEČENSTVO



H302, H315, H317, H318, H334, P261, P264, P280, P304 + P340, P305 + P351 + P338 + P310, P342 + P311

For US Only:
Refer to the product specific Instructions For Use for detailed information regarding hazards.

* Composition information required by US only.

c4800 LIQ CYT

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Branchburg, NJ 08876 USA

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68305 Mannheim, Germany



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toll-free: 1-800-526-1247)¹

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² For USA only.

Made in USA



cobas® 4800 System Liquid Cytology Preparation Kit

c4800 LIQ CYT

cobas

EC REP Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany



Comp/lot label affixed here when necessary

UDI Label Here

cobas

c4800 LIQ CYT

Rx Only



IVD



REF 05235839190

cobas® 4800 System Liquid Cytology Preparation Kit

NOTICE
The instructions for use for this product are contained in the target-specific cobas® 4800 test package insert.

HINWEIS
Die Gebrauchsanleitung für dieses Produkt finden Sie in der testspezifischen Packungshilfslage des jeweiligen cobas® 4800-T-Tests.

AVERTISSEMENT
Les instructions d'utilisation de ce produit sont dans le notice relative au test cobas® 4800 correspondant.

AVISO
Le istruzioni per l'uso di questo prodotto sono contenute nel foglio illustrativo del test cobas® 4800 specifico per il target.

AVISO
Las instrucciones de uso de este producto figuran en el boletín técnico de la prueba cobas® 4800 específica para el objetivo.

AVISO
As instruções de utilização deste produto encontram-se no folheto informativo do teste cobas® 4800 específico do alvo.

BEZMĚKNÍK
Brugvejledningen til dette produkt findes på det targetspecifikke pakningsindlæg til cobas® 4800-testen.

MEDELÄGGE
Bruksanvisningen för den här produkten finns på den targetspecifika påckningsstället för cobas® 4800-testet.

UWAGA
Instrukcje dotyczące stosowania tego produktu umieszczone są wkleścewce dla docelowych organizmów, które są testu cobas® 4800.

OZNAČENIE
Návod na použitie pre tento produkt nájdete v celovo špecifickom príbalnom listku testu cobas® 4800.

CONTENT

PK 20 x 1.2 mL
 SDS 10 x 9 mL
 LYS 10 x 36 mL

cobas® 4800 System Liquid Cytology Sample Preparation Reagents

For USA*

CONTENT

PK 20 x 1.2 mL
 Tris buffer
 < 0.05% EDTA
 Calcium chloride
 Calcium acetate
 Glycerol
 < 2% Proteinase K

SDS 10 x 9 mL
 Tris-HCl buffer
 0.2% SDS
 0.05% Sodium azide

LYS 10 x 36 mL
 Tris-HCl buffer
 37% Guanidine HCl
 < 5% Polyoxydant

* Composition information required by US only.

DANGER/ GEFAHR/ PERICOLO/ PELIGRO/ PERIGO/ FARE/ FARVA/ NIEBEZPIECZENSTWO/ NEBEZPEČENSTVO



H302, H315, H317, H318, H334, P261, P264, P280, P304 + P340, P305 + P351 + P338, P310, P342 + P311

For US Only: Refer to the product specific Instructions For Use for detailed information regarding hazards.

c4800 LIQ CYT

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876, USA

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany
EC Importer*

Roche COBAS is a trademark of Roche. ©2024 Roche Molecular Systems, Inc.

Distributed by
Roche Diagnostics
3115 Hague Road
Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247)[†]

[†] Symbol text required by USA only.
[‡] For USA only.

Made in USA

cobas® 4800 System Liquid Cytology Preparation Kit

c4800 LIQ CYT



cobas®

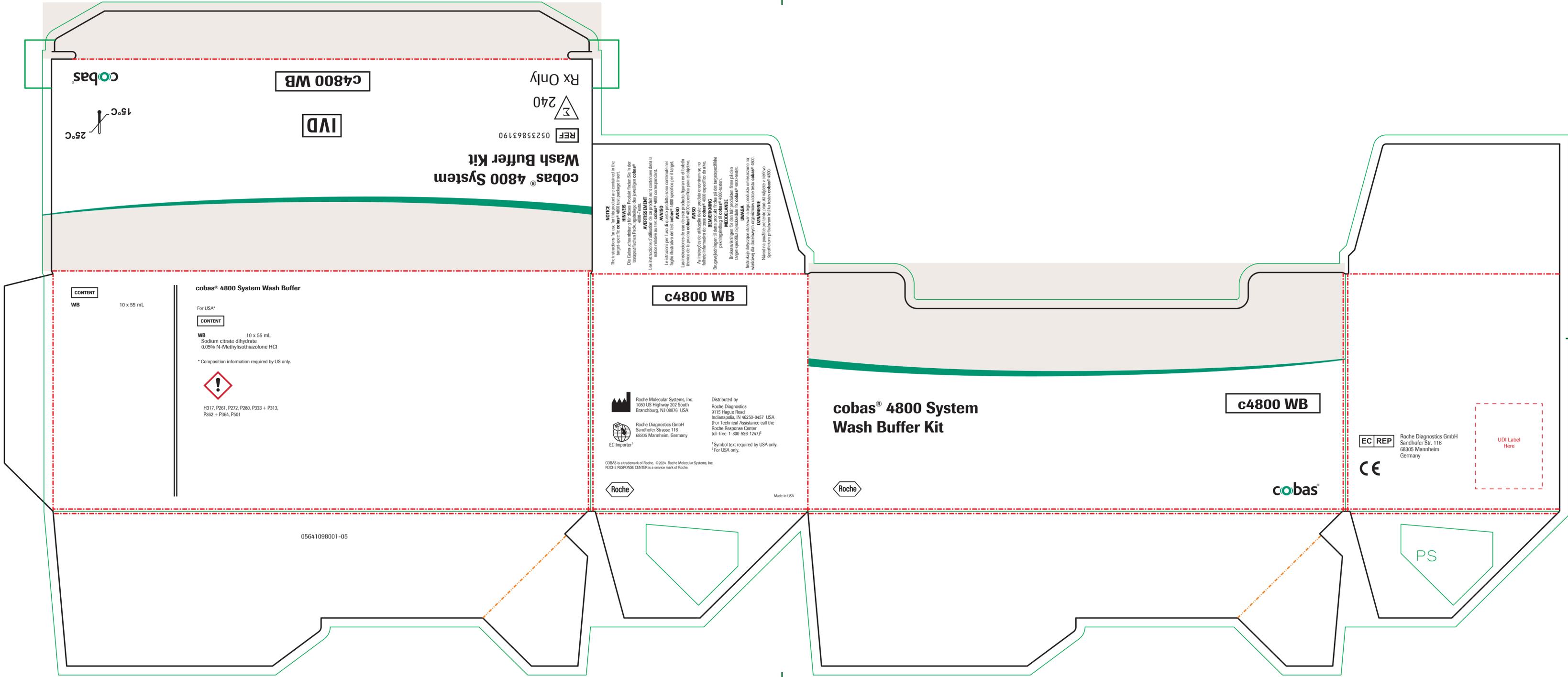
EC REP

Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany



Comp/lot label affixed here when necessary

UDI Label Here





cobas

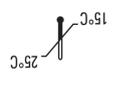
c4800 WB

Rx Only

IVD

REF 05235871190

cobas® 4800 System Wash Buffer Kit



NOTICE
The instructions for use for this product are contained in the larger specific cobas® 4800 product package insert.
Die Gebrauchsanleitung für dieses Produkt finden Sie in der entsprechenden Packung des jeweiligen cobas® 4800 Tests.

AVVERTIMENTO
Le istruzioni per l'uso di questo prodotto sono contenute nel foglio illustrativo del test cobas® 4800 specifico per il target. Le istruzioni di uso del test prodotto figurano in el foglio tecnico di la prima cobas® 4800 specifica per el objetivo. Al momento de utilizar el test, consulte el manual de instrucciones de información de uso respectivo de este kit.

BEWAARINGSINSTRUKTIES
Bij gebruik van dit kit moet u eerst de gebruiksaanwijzing raadplegen voor de juiste gebruiksaanwijzing van het product.

MEGLYKLEND
Brauchungsanleitung für dieses Produkt finden Sie im größeren spezifischen Packungsbeleg für das jeweilige cobas® 4800 Testkit.

UWAGA
Instrukcje dotyczące użytkowania produktu znajdują się w ulotkach dołączonych do konkretnych zestawów testów cobas® 4800. Manual do użytku. OZWIENIENIE
Specyfikacja produktu znajduje się w zestawie testów cobas® 4800.

CONTENT
WB 10 x 200 mL

cobas® 4800 System Wash Buffer

For USA*

CONTENT

WB 10 x 200 mL
Sodium citrate dihydrate
0.05% N-Methylisothiazolone HCl

* Composition information required by US only.



H317, P261, P272, P280, P333 + P313,
P362 + P364, P501

c4800 WB

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08879, USA

Distributed by
Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247)¹



Made in USA

cobas® 4800 System Wash Buffer Kit

c4800 WB



cobas

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Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany

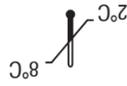


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UDI Label Here

05641101001-06

cobas



cobas® 4800 HPV Amplification/Detection Kit

REF 05235901190

Rx Only

IVD

NOTICE
The purchase of this product allows the purchaser to use it for amplification and detection of nucleic acid sequences by polymerase chain reaction (PCR) and related processes for human *in vitro* diagnostic purposes. This product is not intended for use in any other diagnostic setting.

AVERTISSEMENT
L'achat de ce produit permet à l'acheteur de l'utiliser pour procéder à une amplification et une détection des séquences d'acides nucléiques par réaction en chaîne par polymérisation (PCR) et autres méthodes en vue d'un diagnostic *in vitro* chez l'homme. Aucun brevet général ou licence autre que le droit d'utilisation spécifique délivré lors de l'achat ne sera autorisé.

HINWEIS
Mit dem Kauf dieses Produkts wird der Käufer des Recht, das Produkt für die Amplifikation und den Nachweis von Nukleinsäuresequenzen mittels Polymerase-Kettenreaktion (PCR) und für verwandte Verfahren in der *In-vitro*-Humandagnostik zu benutzen, erworben. Kein allgemeines Recht oder Lizenz wird durch den Kauf dieses Produkts übertragen.

AVISO
La adquisición de este producto permite que el comprador lo utilice para la amplificación y detección de secuencias de ácido nucleico mediante la reacción en cadena de la polimerasa (PCR) y otros procesos relacionados en el diagnóstico *in vitro*. La adquisición de este producto no confiere ningún derecho específico de uso de este documento.

AVISO
L'acquisto di questo prodotto ne consente l'uso al fine di amplificare e rilevare le sequenze di acidi nucleici tramite reazione polimerasica a catena (PCR) e processi associati per la diagnostica umana *in vitro*. L'acquisto non comporta la concessione di alcun brevetto generale né di altra licenza o qualsiasi altro diritto di specifico uso.

AVISO
Aquisição deste produto permite ao comprador utilizá-lo para a amplificação e detecção de sequências de ácidos nucleicos por reação de polimerização em cadeia (PCR) e procedimentos relacionados para diagnóstico *in vitro* no ser humano. Não se concede qualquer direito de uso específico de este documento.

AVISO
L'acquisto di questo prodotto ne consente l'uso al fine di amplificare e rilevare le sequenze di acidi nucleici tramite reazione polimerasica a catena (PCR) e processi associati per la diagnostica umana *in vitro*. L'acquisto non comporta la concessione di alcun brevetto generale né di altra licenza o qualsiasi altro diritto di specifico uso.

CONTENT

HPV MMX 10 x 0.5 mL
HPV Mg/Mn 10 x 1.0 mL

c4800 HPV AMP/DET

c4800 HPV AMP/DET

cobas® 4800 HPV Amplification/Detection Kit

c4800 HPV AMP/DET

UDI Label Here

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876 USA

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany

EC Importer¹

Distributed by
Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247)²

¹ Symbol text required by USA only.
² For USA only.

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Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany



2797

05641144001-04

PS

cobas **4800 HPV** Amplification/Detection Kit

REF 05235910190

Rx Only

IVD

8°C 2°C

96

CONTENT

HPV MMX 20 x 1.0 mL

HPV Mg/Mn 10 x 1.0 mL

05641152001-04

NOTICE
The purchase of this product gives the purchaser the right to use it for amplification and detection of human papillomavirus (HPV) by polymerase chain reaction (PCR) for the detection of HPV DNA in clinical specimens. No general patent or other license is granted hereby. The specific right of use from purchase is granted hereby.

AVERTISSEMENT
L'achat de ce produit confère au client le droit d'utiliser ce produit pour l'amplification et la détection de l'ADN du papillomavirus humain (ADN HPV) par réaction en chaîne par polymérisation (PCR) pour la détection de l'ADN HPV dans des échantillons cliniques. Aucune licence générale ou autre licence n'est accordée par la présente. Le droit spécifique d'utilisation est accordé par l'achat de ce produit.

HINWEIS
Mit dem Kauf dieses Produkts erhält der Käufer das Recht, das Produkt für die Amplifikation und die Detektion von HPV-DNA in klinischen Proben durch Polymerase-Kettenreaktion (PCR) und Nukleinsäure-Amplifikation (NA) zu verwenden. Es wird keine allgemeine Lizenz oder andere Lizenz erteilt. Das spezifische Nutzungsrecht wird durch den Kauf dieses Produkts erworben.

AVISO
La adquisición de este producto otorga al comprador el derecho de amplificar y detectar el ADN del papillomavirus humano (ADN HPV) mediante la reacción en cadena por polimerización (PCR) y otros métodos de amplificación de ácido nucleico (NA) en muestras clínicas. No se concede ninguna licencia general ni otra licencia. El derecho específico de uso se adquiere al comprar este producto.

c4800 HPV AMP/DET

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876 USA

Distributed by
Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247[†])

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany

EC Importer¹

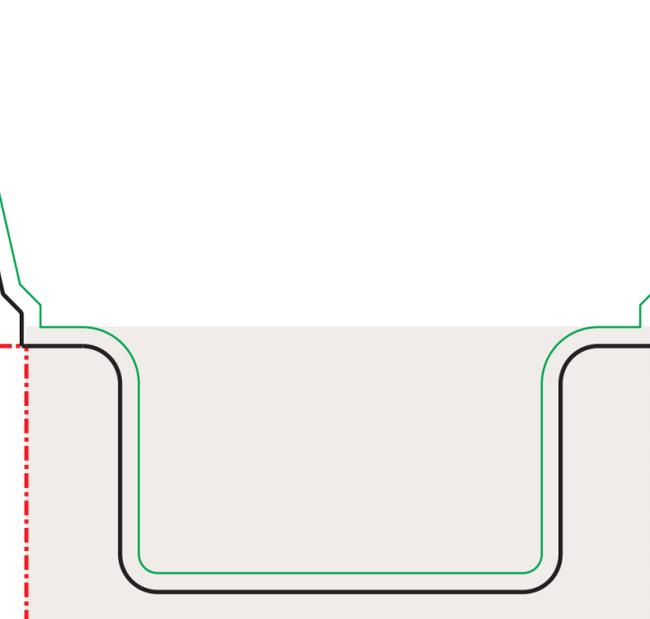
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Roche

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PS



cobas[®] 4800 HPV
Amplification/Detection Kit

c4800 HPV AMP/DET

Roche

cobas[®]

05641152001-04

AVISO
A aquisição deste produto, o comprador adquire o direito de amplificação e detecção de sequências de ácidos nucleicos por reação em cadeia por polimerização (PCR) e procedimentos de amplificação de ácido nucleico (NA) para a detecção de DNA de papillomavirus humano (DNA HPV) em amostras clínicas. Não é concedida nenhuma licença geral ou outra licença. O direito específico de utilização é adquirido com a compra deste produto.

OBRA
Kupem ovaj proizvod dobijate pravo na amplifikaciju i detekciju DNK papiloma virusa (DNA HPV) u kliničkim uzorcima. Ne dobijate nikakvu opću ili drugu licencu. Specifično pravo korišćenja dobijate kupovinom ovog proizvoda.

BEZPEČENOST
Kupem el dēdē produktu gūvājam tiesības tālā amavēdēt detēlā polimēras ķēdes reakcijā (PCR) un citos nukleinskābes amplifikācijas (NA) metodes, lai atklātu cilvēka papilomas vīrusa (HPV) DNS klīniskajos paraugos. Neatļauju jebkādu vispārēju vai citādu licenču. Konkrēto izmantošanas tiesību iegūst, iegādājoties šo produktu.

POWISZ
Zakup niniejszego produktu umożliwia nabywcy uzyskanie prawa do amplifikacji i detekcji sekwencji kwasów nukleinowych za pomocą reakcji łańcuchowej polimeracji (PCR) i innych metod amplifikacji kwasów nukleinowych (NA) w celu wykrycia DNA wirusa papillomawirusa (DNA HPV) w próbkach klinicznych. Nie otrzymuje żadnych licencji ogólnych ani innych. Prawo do konkretnego sposobu wykorzystania produktu jest nabywane poprzez zakup niniejszego produktu.

SLOVAK
Nákup tohto produktu oprávňuje kupujúceho použiť tento produkt na amplifikáciu a detekciu sekvenci ľudského kľúčového vírusu (DNA HPV) v klinických vzorkách. Neobdrža žiadnu všeobecnú ani inú licenciu. Konkrétne právo na používanie výrobku získava sa nákupom tohto produktu.

UDI Label Here

Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany

EC REP

CE 2797

05641152001-04

cobas

IVD

8°C
2°C

Rx Only

10

REF 05235855190

cobas® 4800 HPV Controls Kit

NOTICE
The instructions for use for this product are contained in the target-specific cobas® 4800 test package insert.

HINWEIS
Die Gebrauchsanleitung für dieses Produkt finden Sie in der target-spezifischen Packung des jeweiligen cobas® 4800-Testes.

AVERTISSEMENT
Les instructions d'utilisation de ce produit sont contenues dans la notice relative au test cobas® 4800 correspondant.

AVISO
Os instruções de utilização deste produto encontram-se no folheto informativo do teste cobas® 4800 específico para o alvo.

AVISO
Las instrucciones de uso de este producto figuran en el boletín técnico de la prueba cobas® 4800 específica para el objetivo.

AVISO
As instruções de utilização deste produto encontram-se no folheto informativo do teste cobas® 4800 específico do alvo.

BEMERKUNG
Brugvejledningen af dette produkt findes på det target-specifikke pakningsmateriale til cobas® 4800-testet.

MEDELÄNDE
Bruksanvisningen för den här produkten finns på den target-specifika bipackningen för cobas® 4800-testet.

UWAGA
Instrukcje dotyczące sposobu użytkowania produktu umieszczone są w ulotkach do docelowych komponentów, ulotce testu cobas® 4800.

OZNAČENIE
Návod na použitie pre tento produkt nájdete v cieľovo špecifickom príbalnom listiku testu cobas® 4800.

CONTENT

HPV (+) C 10 x 0.5 mL
(-) C 10 x 0.5 mL

Non-infectious HPV Positive DNA Control and Negative Control

For USA*

CONTENT

HPV (+) C 10 x 0.5 mL
Tris-HCl buffer
EDTA
< 0.00001% Poly rA RNA (synthetic)
< 0.00001% Non-infectious plasmid DNA (microbial) containing HPV 16 sequence
< 0.00001% Non-infectious plasmid DNA (microbial) containing HPV 18 sequence
< 0.00001% Non-infectious plasmid DNA (microbial) containing HPV 39 sequence
< 0.00001% Non-infectious plasmid DNA (microbial) containing human β -globin sequences
0.05% Sodium azide

(-) C 10 x 0.5 mL
Tris-HCl buffer
EDTA
< 0.00001% Poly rA RNA (synthetic)
0.05% Sodium azide

* Composition information required by US only.

c4800 HPV CTLS

 Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876 USA

Distributed by
Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247)²

 Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany

EC Importer¹

¹ Symbol text required by USA only.
² For USA only.

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Made in USA

cobas® 4800 HPV Controls Kit

c4800 HPV CTLS



cobas

EC REP

Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany



2797

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here when necessary

UDI
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05641179001-07

PS

Instructions for use²

² English version of the IFU was the one that was assessed by WHO. It is the responsibility of the manufacturer to ensure correct translation into other languages.

FOR IN VITRO DIAGNOSTIC USE.

cobas [®] 4800 System Sample Preparation Kit	c4800 SMPL PREP	960 Tests 240 Tests	P/N: 05235804190 P/N: 05235782190
cobas [®] 4800 HPV Amplification/Detection Kit	c4800 HPV AMP/DET	960 Tests 240 Tests	P/N: 05235910190 P/N: 05235901190
cobas [®] 4800 HPV Controls Kit	c4800 HPV CTLS	10 Sets	P/N: 05235855190
cobas [®] 4800 System Liquid Cytology Preparation Kit	c4800 LIQ CYT	960 Tests 240 Tests	P/N: 05235839190 P/N: 05235812190
cobas [®] 4800 System Wash Buffer Kit	c4800 WB	960 Tests 240 Tests	P/N: 05235871190 P/N: 05235863190

NOTICE: The purchase of this product allows the purchaser to use it for amplification and detection of nucleic acid sequences by polymerase chain reaction (PCR) and related processes for human in vitro diagnostics. No general patent or other license of any kind other than this specific right of use from purchase is granted hereby.

INTENDED USE

The cobas[®] 4800 Human Papillomavirus (HPV) Test is a qualitative in vitro test for the detection of Human Papillomavirus in patient specimens. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies HPV16 and HPV18 while concurrently detecting the other high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) at clinically relevant infection levels. Specimens are limited to cervical cells collected in Roche Cell Collection Medium (Roche Molecular Systems, Inc.), PreservCyt[®] Solution (Hologic Corp.) and SurePath[™] Preservative Fluid (BD Diagnostics-TriPath).

Indications for use of the cobas[®] 4800 HPV Test are:

- The cobas[®] 4800 HPV Test is indicated for use in screening patients with ASC-US (atypical squamous cells of undetermined significance) cervical cytology results to determine the need for referral to colposcopy.
- The cobas[®] 4800 HPV Test is indicated for use in screening patients with ASC-US cervical cytology results to assess the presence or absence of high-risk HPV genotypes 16 and 18.
- The cobas[®] 4800 HPV Test is indicated for use adjunctively with cervical cytology to assess the presence or absence of high risk HPV types.
- The cobas[®] 4800 HPV Test is indicated for use adjunctively with cervical cytology to assess the presence or absence of HPV genotypes 16 and 18.
- The cobas[®] 4800 HPV Test is indicated for use as a first-line primary screening test to identify women at increased risk for the development of cervical cancer or presence of high-grade disease.
- The cobas[®] 4800 HPV Test is indicated for use as a first-line primary screening test to assess the presence or absence of HPV genotypes 16 and 18.

The cobas[®] 4800 HPV Test can also be used with healthcare worker-instructed self-collected vaginal specimens collected in Roche Cell Collection Medium or PreservCyt[®] Solution.

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

SUMMARY AND EXPLANATION OF THE TEST

Persistent infection with human papillomavirus (HPV) is the cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN)¹⁻³. The presence of HPV has been implicated in greater than 99% of cervical cancers, worldwide³. HPV is a small, non-enveloped, double-stranded DNA virus, with a genome of approximately 8000 nucleotides. There are more than 118 different types of HPV^{4,5}, and approximately 40 different HPV types that can infect the human anogenital mucosa^{6,7}. However, only a subset of 13 to 18 of these types is considered high-risk for the development of cervical cancer and its precursor lesions^{3,8-13}. In an analysis of data from the International Agency of Research on Cancer (IARC) multi-center case-control study, the pooled OR (Odds Ratio) for squamous-cell cervical cancer with HPV infection was 158.2 when the analysis was restricted to studies using well validated HPV detection techniques¹². In this study, the odds ratios for cervical cancer ranged from 109 to 276 in studies from different parts of the world¹².

Although persistent infection with high-risk (HR) HPV is a necessary cause of cervical cancer and its precursor lesions, a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women experiencing exposure to HPV at some point¹⁴. However, > 90% of infected women will mount an effective immune response and clear the infection in 6 to 24 months without any long term health consequences¹⁵⁻²⁰. An infection with any HPV type can produce cervical intraepithelial neoplasia (CIN) although this also usually resolves once the HPV infection has been cleared²¹.

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 requires interpretation by highly trained cytopathologists and is a relatively inaccurate test with a high rate of false negatives. Cytological abnormalities observed in the Pap smear are primarily due to infection with HPV; however, various inflammatory or sampling variations can result in false positive Pap results. Triage of an abnormal Pap smear involves repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed in order to prevent the development of invasive cervical cancer.

Papillomavirus is extremely difficult to culture in vitro, and not all patients infected with HPV have a demonstrable antibody response. Nucleic acid (DNA) testing by PCR is a non-invasive method for determining the presence of a cervical HPV infection. The implementation of HPV DNA testing has increased the efficiency of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with NILM cytology and by reducing the need for unnecessary colposcopy and treatment in patients 21 and older with ASC-US cytology. Furthermore, the superior sensitivity of HPV

testing over Pap smears for the detection of high grade disease in a screening population has been well documented^{22,23}. With superior sensitivity established, HPV DNA testing as a first-line primary screening test has been proposed and adopted in some screening programs.

PRINCIPLES OF THE PROCEDURE

The **cobas**[®] 4800 HPV Test is based on two major processes: (1) automated specimen preparation to simultaneously extract HPV and cellular DNA; (2) PCR amplification²⁴ of target DNA sequences using both HPV and β -globin specific complementary primer pairs and real-time detection of cleaved fluorescent-labeled HPV and β -globin specific oligonucleotide detection probes. The concurrent extraction, amplification and detection of β -globin in the **cobas**[®] 4800 HPV Test monitors the entire test process.

The Master Mix reagent for the **cobas**[®] 4800 HPV Test contains primer pairs and probes specific for the 14 high-risk HPV types and β -globin DNA. The detection of amplified DNA (amplicon) is performed during thermal cycling using oligonucleotide probes labeled with four different fluorescent dyes. 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.

Specimen Preparation

Specimen preparation for the **cobas**[®] 4800 HPV Test is automated with the use of the **cobas**[®] x 480 instrument. Cervical specimens collected in Roche Cell Collection Medium, PreservCyt[®] Solution or SurePath[™] Preservative Fluid are digested under denaturing conditions at elevated temperatures and then lysed in the presence of chaotropic reagent. Released HPV nucleic acids, along with the β -globin DNA serving as process control, are purified through absorption to magnetic glass particles, washed and finally separated from these particles, making them ready for PCR amplification and detection.

PCR Amplification

Target Selection

The **cobas**[®] 4800 HPV Test uses primers to define a sequence of approximately 200 nucleotides within the polymorphic L1 region of the HPV genome. A pool of HPV primers present in the Master Mix is designed to amplify HPV DNA from 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68)^{3,8-13,25}. Fluorescent oligonucleotide probes bind to polymorphic regions within the sequence defined by these primers.

An additional primer pair and probe target the human β -globin gene (330 bp amplicon) to provide a process control.

Target Amplification

EagleZ05 DNA Polymerase²⁶, a chemically modified version of *Thermus species* Z05 DNA polymerase²⁷, is utilized for "hot start" amplification of the HPV targets and the β -globin control. First, the PCR reaction mixture is heated to activate EagleZ05 DNA Polymerase, to denature the viral DNA and genomic DNA and to expose the primer target sequences. As the mixture cools, the upstream and downstream primers anneal to the target DNA sequences. The EagleZ05 DNA Polymerase, in the presence of divalent metal ion and excess dNTPs, extends the primer(s), and a second DNA strand is synthesized. This completes the first cycle of PCR, yielding a double-stranded DNA copy of the target region of the HPV genome and β -globin gene. The DNA Polymerase extends the annealed primers along the target templates to produce an approximately 200 -base pair double-stranded HPV target DNA molecule or a 330 base pair β -globin DNA molecule termed an amplicon. This process is repeated for a number of cycles, each cycle effectively doubling the amount of amplicon DNA. Amplification occurs only in the region of the HPV genome and/or β -globin gene between the appropriate primer pair. The entire genome is not amplified.

Automated Real-time Detection

The **cobas**[®] 4800 HPV Test utilizes real-time^{29,30} PCR technology. Each oligonucleotide probe in the reaction is labeled with a fluorescent dye that serves as a reporter, and with a quencher that quenches fluorescent emissions from the dye in an intact probe. As amplification progresses, probes that are complementary to the amplicon bind to specific single-stranded DNA sequences and are cleaved by the 5' to 3' nuclease activity of the EagleZ05 DNA Polymerase. Once the reporter dye is separated from the quencher by this nuclease activity, it emits fluorescence of a characteristic wavelength when excited by the proper spectrum of light. This characteristic wavelength for each dye allows HPV16 amplicon, HPV18 amplicon, other HPV amplicons (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and the β -globin control to be measured independently because the probes specific for these sequences are labeled with different dyes.

Selective Amplification

Selective amplification of target nucleic acid from the clinical specimen is achieved in the **cobas**[®] 4800 HPV Test by the use of AmpErase[®] (uracil-N-glycosylase) enzyme and deoxyuridine triphosphate (dUTP). AmpErase enzyme recognizes and catalyzes the destruction of DNA strands containing deoxyuridine, but not DNA containing deoxythymidine. Deoxyuridine is not present in naturally occurring DNA, but is always present in amplicon due to the use of deoxyuridine triphosphate in place of thymidine triphosphate as one of the dNTPs in the Master Mix reagent. Therefore, only amplicon contain deoxyuridine. Deoxyuridine renders contaminating amplicon susceptible to destruction by AmpErase enzyme prior to amplification of the target DNA. AmpErase enzyme, which is included in the Master Mix reagent, catalyzes the cleavage of deoxyuridine-containing DNA at the deoxyuridine residues by opening the deoxyribose chain at the C1-position. When heated in the first thermal cycling step, the amplicon DNA chain breaks at the position of the deoxyuridine, thereby rendering the DNA non-amplifiable. AmpErase enzyme is inactive at temperatures above 55°C, i.e., throughout the thermal cycling steps, and therefore does not destroy target amplicon. AmpErase enzyme in the **cobas**[®] 4800 HPV Test has been demonstrated to inactivate at least 10⁶ copies of deoxyuridine-containing HPV amplicon per PCR.

REAGENTS

cobas® 4800 System Sample Preparation Kit (c4800 SMPL PREP) 240 Tests (P/N: 05235782190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
MGP (cobas® 4800 System Magnetic Glass Particles)	Magnetic glass particles 93% Isopropanol ^b	10 x 4.5 mL	 <p>DANGER</p> <p>H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. H336: May cause drowsiness or dizziness. P210: Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. P233: Keep container tightly closed. P261: Avoid breathing mist or vapours. P280: Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection. P303 + P361 + P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water. P370 + P378: In case of fire: Use dry sand, dry chemical or alcohol-resistant foam to extinguish. 67-63-0 Propan-2-ol</p>
EB (cobas® 4800 System Elution Buffer)	Tris buffer 0.09% Sodium azide	10 x 18 mL	N/A

^a Product safety labeling primarily follows EU GHS guidance

^b Hazardous substance

cobas® 4800 System Sample Preparation Kit (c4800 SMPL PREP) 960 Tests (P/N: 05235804190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
MGP (cobas® 4800 System Magnetic Glass Particles)	Magnetic glass particles 93% Isopropanol ^b	10 x 13.5 mL	 <p>DANGER</p> <p>H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. H336: May cause drowsiness or dizziness. P210: Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. P233: Keep container tightly closed. P261: Avoid breathing mist or vapours. P280: Wear protective gloves/ protective clothing / eye protection/ face protection/ hearing protection. P303 + P361 + P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water. P370 + P378: In case of fire: Use dry sand, dry chemical or alcohol-resistant foam to extinguish. 67-63-0 Propan-2-ol</p>
EB (cobas® 4800 System Elution Buffer)	Tris buffer 0.09% Sodium azide	10 x 18 mL	N/A

^a Product safety labeling primarily follows EU GHS guidance

^b Hazardous substance

cobas® 4800 System Wash Buffer Kit (c4800 WB) 240 Tests (P/N:05235863190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
WB (cobas® 4800 System Wash Buffer)	Sodium citrate dihydrate 0.05% N-Methyl-isothiazolone HCl	10 x 55 mL	 <p>WARNING</p> <p>H317: May cause an allergic skin reaction.</p> <p>P261: Avoid breathing mist or vapours.</p> <p>P272: Contaminated work clothing should not be allowed out of the workplace.</p> <p>P280: Wear protective gloves.</p> <p>P333 + P313: If skin irritation or rash occurs: Get medical attention.</p> <p>P362 + P364: Take off contaminated clothing and wash it before reuse.</p> <p>P501: Dispose of contents/ container to an approved waste disposal plant.</p> <p>2617254-3 2-methyl-2H-isothiazol-3-one hydrochloride</p>

^a Product safety labeling primarily follows EU GHS guidance

^b Hazardous substance

cobas® 4800 System Wash Buffer Kit (c4800 WB) 960 Tests (P/N:05235871190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
WB (cobas® 4800 System Wash Buffer)	Sodium citrate dihydrate 0.05% N-Methyl-isothiazolone HCl	10 x 200 mL	 <p>WARNING</p> <p>H317: May cause an allergic skin reaction.</p> <p>P261: Avoid breathing mist or vapours.</p> <p>P272: Contaminated work clothing should not be allowed out of the workplace.</p> <p>P280: Wear protective gloves.</p> <p>P333 + P313: If skin irritation or rash occurs: Get medical attention.</p> <p>P362 + P364: Take off contaminated clothing and wash it before reuse.</p> <p>P501: Dispose of contents/ container to an approved waste disposal plant.</p> <p>2617254-3 2-methyl-2H-isothiazol-3-one hydrochloride</p>

^a Product safety labeling primarily follows EU GHS guidance

^b Hazardous substance

cobas® 4800 System Liquid Cytology Preparation Kit (c4800 LIQ CYT) 240 Tests (P/N:05235812190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
PK (cobas® 4800 Proteinase K)	Tris buffer < 0.05% EDTA Calcium chloride Calcium acetate Glycerol < 2% Proteinase K	10 x 0.9 mL	 <p>DANGER</p> <p>H317: May cause an allergic skin reaction.</p> <p>H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.</p> <p>P261: Avoid breathing mist or vapours.</p> <p>P280: Wear protective gloves.</p> <p>P284: Wear respiratory protection.</p> <p>P304 + P340: IF INHALED: Remove person to fresh air and keep comfortable for breathing.</p>

cobas® 4800 System Liquid Cytology Preparation Kit (c4800 LIQ CYT) 240 Tests (P/N: 05235812190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
			P333 + P313: If skin irritation or rash occurs: Get medical attention. P342 + P311: If experiencing respiratory symptoms: Call a POISON CENTER/doctor. 3945001-6 Proteinase, Tritirachium album serine
SDS (cobas® 4800 System SDS Reagent)	Tris buffer 0.2% SDS 0.09% Sodium azide	10 x 3 mL	N/A
LYS (cobas® 4800 System Lysis Buffer)	Tris buffer 37% (w/w) Guanidine HCl < 5% Polidocanol ^b	10 x 10 mL	 <p>DANGER</p> <p>H302: Harmful if swallowed. H315: Causes skin irritation. H318: Causes serious eye damage. P264: Wash skin thoroughly after handling. P270: Do not eat, drink or smoke when using this product. P280: Wear protective gloves/ eye protection/ face protection. P301 + P312 + P330: IF SWALLOWED: Call a POISON CENTER/doctor if you feel unwell. Rinse mouth. 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. P501: Dispose of contents/ container to an approved waste disposal plant. 50-01-1 Guanidinium chloride 9002-92-0 Polidocanol</p>

^a Product safety labeling primarily follows EU GHS guidance

^b Hazardous substance

cobas® 4800 System Liquid Cytology Preparation Kit (c4800 LIQ CYT) 960 Tests (P/N: 05235839190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning ^a
PK (cobas® 4800 Proteinase K)	Tris buffer < 0.05% EDTA Calcium chloride Calcium acetate Glycerol < 2% Proteinase K	20 x 1.2 mL	 <p>DANGER</p> <p>H317: May cause an allergic skin reaction. H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.</p> <p>P261: Avoid breathing dust or vapours. P280: Wear protective gloves. P284: Wear respiratory protection. P304 + P340: IF INHALED: Remove person to fresh air and keep comfortable for breathing. P333 + P313: If skin irritation or rash occurs: Get medical attention. P342 + P311: If experiencing respiratory symptoms: Call a POISON CENTER or doctor. 3945001-6 Proteinase, Tritirachium album serine</p>
SDS (cobas® 4800 System SDS Reagent)	Tris buffer 0.2% SDS 0.09% Sodium azide	10 x 9mL	N/A
LYS (cobas® 4800 System Lysis Buffer)	Tris buffer 37% (w/w) Guanidine HCl < 5% Polidocanol ^b	10 x 36 mL	 <p>DANGER</p> <p>H302: Harmful if swallowed. H315: Causes skin irritation. H318: Causes serious eye damage.</p> <p>P264: Wash skin thoroughly after handling. P270: Do not eat, drink or smoke when using this product. P280: Wear protective gloves/ eye protection/ face protection. P301 + P312 + P330: IF SWALLOWED: Call a POISON CENTER or doctor if you feel unwell. Rinse mouth. 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 or doctor. P501: Dispose of contents/ container to an approved waste disposal plant. 50-01-1 Guanidinium chloride 9002-92-0 Polidocanol</p>

^a Product safety labeling primarily follows EU GHS guidance

^b Hazardous substance

cobas® 4800 HPV Amplification/Detection Kit (c4800 HPV AMP/DET) 240 Tests (P/N: 05235901190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning
HPV MMX (cobas® 4800 HPV Master Mix)	Tricine buffer Potassium acetate Potassium hydroxide Glycerol < 0.13% dATP, dCTP, dGTP, dUTP < 0.01% Upstream and downstream HPV primers < 0.01% Upstream and downstream β-globin primers < 0.01% Fluorescent-labeled HPV probes < 0.01% Fluorescent-labeled β-globin probes < 0.10% EagleZ05 DNA polymerase (microbial) < 0.10% AmpErase (uracil-N-glycosylase) enzyme (microbial) 0.09% Sodium azide	10 x 0.5 mL	N/A
HPV Mg/Mn (cobas® 4800 HPV Mg/Mn Solution)	Magnesium acetate Manganese acetate < 0.02% Glacial acetic acid 0.09% Sodium azide	10 x 1.0 mL	N/A

cobas® 4800 HPV Amplification/Detection Kit (c4800 HPV AMP/DET) 960 Tests (P/N: 05235910190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning
HPV MMX (cobas® 4800 HPV Master Mix)	Tricine buffer Potassium acetate Potassium hydroxide Glycerol < 0.13% dATP, dCTP, dGTP, dUTP < 0.01% Upstream and downstream HPV primers < 0.01% Upstream and downstream β-globin primers < 0.01% Fluorescent-labeled HPV probes < 0.01% Fluorescent-labeled β-globin probes < 0.10% EagleZ05 DNA polymerase (microbial) < 0.10% AmpErase (uracil-N-glycosylase) enzyme (microbial) 0.09% Sodium azide	20 x 1.0 mL	N/A
HPV Mg/Mn (cobas® 4800 HPV Mg/Mn Solution)	Magnesium acetate Manganese acetate < 0.02% Glacial acetic acid 0.09% Sodium azide	10 x 1.0 mL	N/A

cobas® 4800 HPV Controls Kit (c4800 HPV CTLs) 10 Sets (P/N: 05235855190)			
Kit components	Reagent ingredients	Quantity per kit	Safety symbol and warning
HPV (+) C (cobas® 4800 HPV Positive Control)	Tris buffer EDTA 0.05% Sodium azide < 0.00001% Poly rA RNA (synthetic) < 0.00001% Noninfectious plasmid DNA (microbial) containing HPV6, 18, 39 sequences < 0.00001% Noninfectious plasmid DNA (microbial) containing human β -globin sequences	10 x 0.5 mL	N/A
(-) C (cobas® 4800 System Negative Control)	Tris buffer EDTA 0.05% Sodium azide < 0.00001% Poly rA RNA (synthetic)	10 x 0.5 mL	N/A

NOTE: Product safety labeling primarily follows EU GHS guidance.

WARNINGS AND PRECAUTIONS

A. FOR IN VITRO DIAGNOSTIC USE.

- B. Self-collected vaginal specimens must be suspended in Roche Cell Collection Medium or PreservCyt® Solution after sample is collected.
- C. False negative or invalid results may occur with self-collected samples if samples are not suspended in medium after collection.
- D. Do not pipette by mouth.
- E. Do not eat, drink or smoke in laboratory work areas. Wear protective disposable gloves, laboratory coats and eye protection when handling specimens and kit reagents. Wash hands thoroughly after handling specimens and test reagents.
- F. Avoid microbial and DNA contamination of reagents.
- G. Dispose of unused reagents and waste in accordance with country, federal, state and local regulations.
- H. Do not use reagents after their expiration dates.
- I. Do not pool reagents.
- J. Material Safety Data Sheets (MSDS) are available on request from your local Roche office.
- K. Gloves must be worn and must be changed between handling specimens and cobas® 4800 reagents to prevent contamination.
- L. Specimens should be handled as infectious using safe laboratory procedures such as those outlined in *Biosafety in Microbiological and Biomedical Laboratories*³¹ and in the CLSI Document M29-A3³².
- M. **LYS** contains guanidine hydrochloride. **Do not allow direct contact between guanidine hydrochloride and sodium hypochlorite (bleach) or other highly reactive reagents such as acids or bases. These mixtures can release a noxious gas.** If liquid containing guanidine hydrochloride is spilled, clean with suitable laboratory detergent and water. If a spill occurs with potentially infectious agents, **FIRST** clean the affected area first with laboratory detergent and water, and then with 0.5% sodium hypochlorite.
- N. **MGP** contains isopropanol and is highly flammable. Keep away from open flames and potential spark producing environments.
- O. **EB SDS HPV MMX, HPV Mg/Mn, (-) C, and HPV (+) C** contain sodium azide. 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.
- P. Wear eye protection, laboratory coats and disposable gloves when handling any reagents. Avoid contact of these materials with skin, eyes or mucous membranes. If contact does occur, immediately wash with large amounts of water. Burns can occur if untreated. If spills occur, dilute with water before wiping dry.
- Q. All disposable items are for one time use. Do not reuse.
- R. Do not use sodium hypochlorite solution (bleach) for cleaning the cobas® x 480 instrument or cobas® z 480 analyzer. Clean the cobas® x 480 instrument or cobas® z 480 analyzer according to procedures described in the cobas® 4800 System User Assistance.
- S. For additional warnings, precautions and procedures to reduce the risk of contamination for the cobas® x 480 instrument or cobas® z 480 analyzer, consult the cobas® 4800 System User Assistance.
- T. Do not use reagents or containers that are visibly damaged or show signs of leakage.
- U. Inform your local competent authority and manufacturer about any serious incidents which may occur when using this assay.

STORAGE AND HANDLING REQUIREMENTS

- A. **Do not freeze reagents.**
- B. Store **MGP, EBPK, SDS, LYS, HPV MMX, HPV Mg/Mn, HPV (+) C and (-) C** at 2-8°C. These reagents are stable until the expiration date indicated.
- C. Store **WB** at 15-25°C. This reagent is stable until the expiration date indicated.

MATERIALS PROVIDED

<p>A. cobas® 4800 System Sample Preparation Kit (P/N: 05235782190)</p>	<p>c4800 SMPL PREP</p>	<p>240 Tests</p>
<p>MGP (cobas® 4800 System Magnetic Glass Particles) EB (cobas® 4800 System Elution Buffer)</p>		
<p>B. cobas® 4800 System Sample Preparation Kit (P/N: 05235804190)</p>	<p>c4800 SMPL PREP</p>	<p>960 Tests</p>
<p>MGP (cobas® 4800 System Magnetic Glass Particles) EB (cobas® 4800 System Elution Buffer)</p>		
<p>C. cobas® 4800 System Wash Buffer Kit (P/N: 05235863190)</p>	<p>c4800 WB</p>	<p>240 Tests</p>
<p>WB (cobas® 4800 System Wash Buffer)</p>		
<p>D. cobas® 4800 System Wash Buffer Kit (P/N: 05235871190)</p>	<p>c4800 WB</p>	<p>960 Tests</p>
<p>WB (cobas® 4800 System Wash Buffer)</p>		
<p>E. cobas® 4800 HPV Amplification/Detection Kit (P/N: 05235901190)</p>	<p>c4800 HPV AMP/DET</p>	<p>240 Tests</p>
<p>HPVMMX (cobas® 4800 HPV Master Mix) HPV Mg/Mn (cobas® 4800 HPV Mg/Mn Solution)</p>		
<p>F. cobas® 4800 HPV Amplification/Detection Kit (P/N: 05235910190)</p>	<p>c4800 HPV AMP/DET</p>	<p>960 Tests</p>
<p>HPVMMX (cobas® 4800 HPV Master Mix) HPV Mg/Mn (cobas® 4800 HPV Mg/Mn Solution)</p>		
<p>G. cobas® 4800 System Liquid Cytology Preparation Kit (P/N: 05235812190)</p>	<p>c4800 LIQ CYT</p>	<p>240 Tests</p>
<p>PK (cobas® 4800 Proteinase K) SDS (cobas® 4800 System SDS Reagent) LYS (cobas® 4800 System Lysis Buffer)</p>		
<p>H. cobas® 4800 System Liquid Cytology Preparation Kit (P/N: 05235839190)</p>	<p>c4800 LIQ CYT</p>	<p>960 Tests</p>
<p>PK (cobas® 4800 Proteinase K) SDS (cobas® 4800 System SDS Reagent) LYS (cobas® 4800 System Lysis Buffer)</p>		
<p>I. cobas® 4800 HPV Controls Kit (P/N: 05235855190)</p>	<p>c4800 HPV CTLS</p>	<p>10 Sets</p>
<p>HPV(+) C (cobas® 4800 HPV Positive Control) (-) C (cobas® 4800 System Negative Control)</p>		

MATERIALS REQUIRED BUT NOT PROVIDED

Specimen and Reagent Handling

- Roche Cell Collection Medium (Roche P/N 07994745190, optional)
- Roche Cell Collection Medium Replacement Caps (Roche P/N 08037230190, optional)
- Cervical Collection Brush (Roche P/N 08399832190, optional)
- Cervical Collection Brush, sterile (Roche P/N 08779040190, optional)
- Copan FLOQSwabs[®] for vaginal self-collection, 552C.80 (Roche P/N 09032932190)
- Rovers Evalyn[®] Brush (Roche P/N 09032959190)
- Sample suspension instructions for Copan FLOQSwabs[®] for vaginal self-collection, 552C.80 (Roche P/N 09652671001)
- Sample suspension instructions for Evalyn[®] Brush (Roche P/N 09907238001)
- CO-RE Tips, 1000 µL, rack of 96 (Roche P/N 04639642001 or Hamilton P/N 235905)
- 50 mL Reagent Reservoir (Roche P/N 05232732001)
- 200 mL Reagent Reservoir (Roche P/N 05232759001)
- For HPV ASAP v2.0.1 use **cobas**[®] 4800 System Extraction (deep well) plate 1.6 mL (Roche P/N 05232716001)
- For HPV ASAP v2.1 use **cobas**[®] 4800 System Extraction (deep well) plate 2.0 mL (Roche P/N 06884008001)
- **cobas**[®] 4800 System AD (microwell) plate 0.3 mL and Sealing Film (Roche P/N 05232724001)
- Solid waste bag [Roche P/N 05530873001 (small) or 04691989001 (large)]
- Hamilton STAR Plastic Chute (Roche P/N 04639669001)
- Tubes 13 mL Round Base (Roche: P/N 07958048190) for use as secondary sample tubes
- Caps, neutral color (Roche P/N 07958056190; for recapping post-run specimens in 13 mL Round Base tubes)
- Disposable gloves, powderless

Instrumentation and Software

- **cobas**[®] x 480 instrument
- **cobas**[®] z 480 analyzer
- **cobas**[®] 4800 System Control Unit with System Software version 2.2 or higher
- **cobas**[®] 4800 System **cobas**[®] HPV AP software version 2.0. or higher

Optional Equipment and Materials

- **cobas**[®] Sample Prep Buffer (Roche P/N 06526985190; Tris buffered detergent)*
- Pipettes: capable of delivering 1000 µL
- Aerosol barrier DNase-free tips: capable of delivering 1000 µL
- Centrifuge equipped with a swinging bucket rotor with minimum RCF of 1500
- Stand-alone magnetic plate (Roche P/N 05440777001)
- Vortex Mixer (single tube)
- Multi-tube vortexer [e.g. VWR P/N 58816-116]
- Heat-resistant barcode labels (RACO Industries; Cat # RAC-225075-9501)
- Thermometer -20/150°C (VWR Cat# 89095-600) or equivalent
- Digital Heater Block 120V (VWR Cat# 75838-294) or equivalent
- 12-Hole Heat Block Module 16mm (VWR Cat# 13259-162) or equivalent

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

SPECIMEN COLLECTION, TRANSPORT AND STORAGE

NOTE: Handle all specimens as if they are capable of transmitting infectious agents.

A. Specimen Collection

Cervical specimens collected in Roche Cell Collection Medium, PreservCyt[®] Solution and SurePath[™] Preservative Fluid have been validated for use with the **cobas**[®] 4800 HPV Test.

Vaginal specimens collected with FLOQSwabs[®] for vaginal self-collection and suspended in Roche Cell Collection Medium and PreservCyt[®] Solution have been validated for use with the **cobas**[®] 4800 HPV Test.

Vaginal specimens collected with Evalyn[®] brush and suspended in Roche Cell Collection Medium and PreservCyt[®] Solution have been validated for use with the **cobas**[®] 4800 HPV Test.

Follow the manufacturer's instructions for collecting specimens.

B. Specimen Transport

Specimens collected in Roche Cell Collection Medium, PreservCyt[®] Solution and SurePath[™] Preservative Fluid can be transported at 2-30°C. Transportation of HPV specimens must comply with country, federal, state and local regulations for the transport of etiologic agents³³.

C. Specimen Storage

Specimens collected in Roche Cell Collection Medium and PreservCyt[®] Solution may be stored at 2-30°C for up to 6 months after the date of collection. Cervical specimens collected in SurePath[™] Preservative Fluid may be stored at 28°C for up to 6 months or may be stored at 15-30°C for up to 6 weeks after the date of collection provided that SurePath[™] Preservative Fluid matrix-induced crosslinks are reversed through treatment with **cobas[®]** Sample Prep Buffer prior to HPV testing.

INSTRUCTIONS FOR USE

Sample suspension instructions for

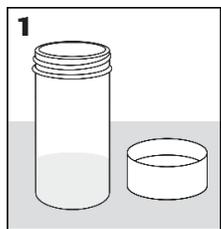
Copan FLOQSwab[®] for vaginal selfcollection (552C.80)

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

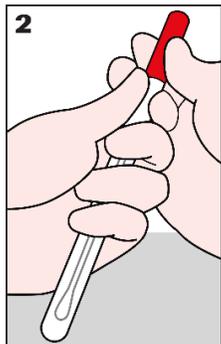
Self-collected sample must be placed into medium after sample has been collected.

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

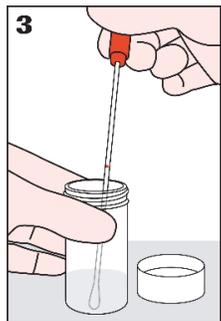
Handle the collected sample with care .



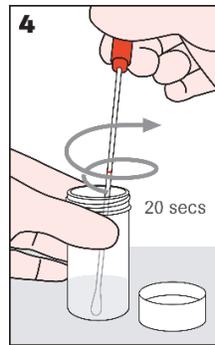
1. Carefully uncap the vial containing medium and place it on a stable, flat surface.



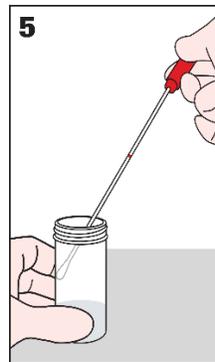
2. Slowly pull the FLOQSwab cap off to remove the swab from the tube. **Minimize touching the inner walls of the tube as you remove the FLOQSwab.**



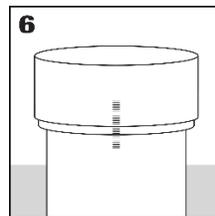
3. Hold the vial with one hand then with the other hand place the FLOQSwab tip into the vial until the FLOQSwab **tip is fully immersed in the medium** and **touching the bottom** of the vial.



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



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



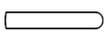
6. Re-cap the vial and tighten until **the lines on the cap and vial meet or slightly overlap** to prevent leakage. Store upright.

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

Glossary



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



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



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

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

Sample suspension instructions for

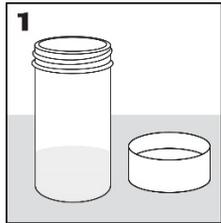
Rovers Evalyn® Brush

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

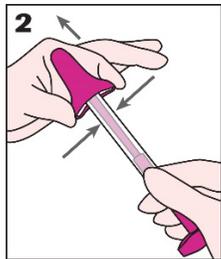
Self-collected sample must be placed into medium after sample has been collected.

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

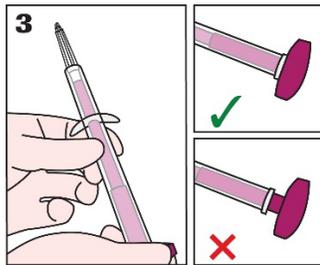
Handle the collected sample with care .



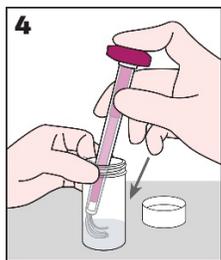
1. Carefully uncap the vial containing medium and place it on a stable, flat surface.



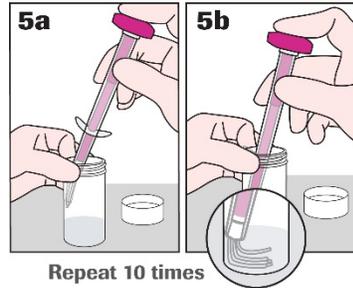
2. Remove the pink cap from the Evalyn Brush **taking care not to touch the exposed end.**



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



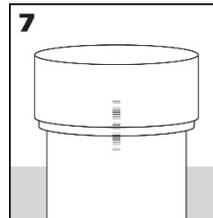
4. Hold the vial with one hand then with the other hand place the white brush into the vial so that the **bristles are fully immersed in the medium and the wings are past the opening of the vial.**



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



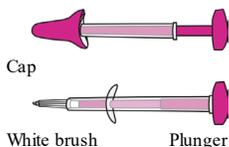
6. Remove the white brush by carefully drawing the brush up along the inner wall of the primary vial until the brush is no longer submerged in the medium. **Hold the brush against the inner vial wall to drain fluid** off the brush. Place the Evalyn brush back inside the packaging and discard.



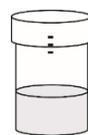
7. Re-cap the vial and tighten until **the lines on the cap and vial meet or slightly overlap** to prevent leakage. Store upright.

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

Glossary



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



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

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

NOTE: All reagents except HPV MMX and HPV Mg/Mn must be at ambient temperature prior to loading on the cobas® x 480 instrument. The HPV MMX and HPV Mg/Mn may be taken directly from 2 -8°C storage as they will equilibrate to ambient temperature on board the cobas® x 480 instrument by the time they are used in the process

NOTE: Specimens in Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid must be at ambient temperature before loading on the cobas® x 480 instrument.

NOTE: Refer to the cobas® 4800 System- User Assistance for detailed operating instructions.

Run Size:

The cobas® 4800 System is designed to support the cobas® 4800 HPV Test with run sizes from 1 to 94 specimens plus controls (up to 96 assays per run). Each cobas® 4800 System Sample Preparation Kit, cobas® 4800 System Liquid Cytology Preparation Kit and cobas® 4800 System Wash Buffer Kit contains reagents sufficient for 10 runs of either 24 tests (240 tests per kit) or 96 tests (960 tests per kit). Each cobas® 4800 HPV Amplification/Detection Kit contains reagents sufficient for 10 runs of either 24 tests (240 tests per kit) or 96 tests (960 tests per kit); multiple 240 Test Kits can be used to optimize reagent usage for 48 or 72 tests. The cobas® 4800 HPV Controls Kit contains reagents sufficient for a total of 10 runs (10 sets per kit). The minimum run size on the cobas® 4800 System is 1 specimen plus controls. One replicate of the cobas® 4800 System Negative Control (–) C] and one replicate of the cobas® 4800 HPV Positive Control HPV (+) C] are required to perform each test run (see "Quality Control" section).

Workflow:

NOTE: Although not an optimal use of reagents, a System Sample Preparation 960 Test Kit can be used for a 24 sample run and an HPV Amplification/Detection 960 Test Kit can be used for a 24, 48, or 72 sample run.

The cobas® 4800 HPV Test can be run using either of two workflows, referred to as "Full Workflow" or "Recovery Workflow" with the cobas® 4800 Software.

HPV Full Workflow:

The "HPV Full Workflow" consists of sample preparation on the cobas® x 480 instrument followed by amplification/detection on the cobas® z 480 analyzer. Run size can be a 24 test format (from 1 to 22 specimens plus 2 controls) or a 96 test format (from 1 to 94 specimens plus 2 controls). Refer to the "Performing a Full Workflow" section below and the cobas® 4800 System- User Assistance for details.

HPV Recovery Workflow:

The "HPV Recovery Workflow" consists of manual PCR plate setup using eluate from the processed deep well plate followed by amplification/detection on the cobas® z 480 analyzer. Refer to the "Performing a Recovery Workflow" section below and the cobas® 4800 System- User Assistance for details.

Specimens:

The following are specimen types that can be assayed using the cobas® 4800 HPV Test:

- cervical specimens in Roche Cell Collection Medium
- cervical specimens in PreservCyt® Solution
- cervical specimens in SurePath™ Preservative Fluid (See Treatment of SurePath™ primary specimens section)
- self-collected vaginal specimens using FLOQSwab® 552C.80 and suspended in Roche Cell Collection Medium
- self-collected vaginal specimens using FLOQSwab® 552C.80 and suspended in PreservCyt® Solution
- self-collected vaginal specimens using Evalyn® brush and suspended in Roche Cell Collection Medium
- self-collected vaginal specimens using Evalyn® brush and suspended in PreservCyt® Solution

Roche Cell Collection Medium and PreservCyt® Solution specimens may be processed directly out of their primary containers with a proper barcode or out of a properly barcoded 13 mL round-based tube on the cobas® x 480 instrument. SurePath™ specimens must be transferred into a properly barcoded 13 mL round-based tube for specimen treatment (See Treatment of SurePath™ primary specimens section) and processing on the cobas® x 480 instrument. Consult the cobas® 4800 System- User Assistance for proper barcoding procedures and the list of acceptable barcodes for the cobas® 4800 System.

NOTE: SurePath™ specimens must be treated with cobas® Sample Prep Buffer to reverse matrix-induced cross-links prior to HPV testing on the cobas® 4800 System.

Treatment of SurePath™ primary specimens with cobas® Sample Prep Buffer to reverse matrix-induced crosslinks

NOTE: Heat-resistant barcodes are required for tubes used to reverse matrix -induced cross -links (see the Optional Equipment and Materials section).

NOTE: It is recommended that steps B, C, G and H below are done in a biological hood to minimize possible cross contamination.

- Prepare a barcoded 13 mL round-based tube with 0.5 mL of cobas® Sample Prep Buffer for each SurePath™ specimen to be tested. An open bottle of cobas® Sample Prep Buffer (CSPB) may be stored at ambient temperature (15-30°C) for up to 21 days and up to 4 separate uses for the pre-analytic treatment of SurePath™ samples.
- Vortex SurePath™ specimens for 10 seconds prior to transfer. Transfer 0.5 mL of each SurePath™ specimen into a 13 mL round-based tube prepared in step A. Re-cap each tube before moving to the next. Always change pipet tips for each specimen.
- Vortex each tube for 1 second.
- Transfer tubes to the heating unit set at 120°C (see Optional Equipment and Materials section). Up to 48 tubes can be processed per batch.
- Heat for 20 minutes.
- After heating, remove tubes to a collection rack and cool at ambient temperature for 10 minutes.
- Vortex each tube for 5 seconds.
- Transfer tubes to 24 position cobas® 4800 specimen racks, discard caps and process on the cobas® 4800 System for HPV testing

SurePath™ specimens treated with cobas® Sample Prep Buffer can be stored for future HPV testing if, for example, cytology evaluation is required first. The following procedure should be followed:

- A. Follow the treatment procedure above to step G.
- B. Store tubes with SurePath™ specimens treated with **cobas**® Sample Prep Buffer at 2-30°C for up to 4 weeks prior to HPV testing on the **cobas**® 4800 System

NOTE: The minimum volume required in the Roche Cell Collection Medium and PreservCyt® Solution primary containers is 3.0 mL. When using 13 mL round-based secondary tubes, fill to a minimum volume of 1.0 mL and a maximum volume of 10 mL.

NOTE: Use only Roche Cell Collection Medium, PreservCyt® Solution and SurePath™ Preservative Fluid to collect cervical specimens for the **cobas**® 4800 HPV Test. The **cobas**® 4800 HPV Test has not been validated with other media types. Using the **cobas**® 4800 HPV Test with other media types could lead to false negative, false positive and/or invalid results

NOTE: To avoid cross-contamination of processed specimens, additional caps for vials (see Materials Required But Not Provided section) should be used to recap specimens after processing. Recap tightly. Store and ship the vials in upright orientation.

NOTE: It may be necessary to aliquot specimens into barcoded 13 mL round-based tubes for processing on the **cobas**® x 480 instrument. Use pipettors with aerosol barrier or positive-displacement tips to handle specimens. To avoid cross contamination of processed specimens, additional caps for these tubes in an alternate color (see Materials Required But Not Provided section) should be used to recap these specimens after processing

NOTE: Use caution when transferring specimens from primary containers to 13 mL round-based secondary tubes. Vortex primary specimens prior to transfer. Change pipet tips after each specimen.

NOTE: Do not process specimens which appear bloody or have a dark brown color

A single run can have any combination of specimens (Roche Cell Collection Medium, PreservCyt® Solution and/or SurePath™ Preservative Fluid) and each specimen can be tested with either the HPV High Risk or HPV High Risk Plus Genotyping sub-tests.

Workflows

Performing a Full Workflow:

- A. The **cobas**® 4800 HPV Test may be used for 1 to 94 specimens plus one **cobas**® 4800 System negative control and one **cobas**® 4800 HPV positive control.
- B. Perform the system startup and maintenance procedures by following the instructions in the **cobas**® 4800 System - User Assistance.
- C. Start a new run by clicking the “New run” button.
- D. In the Selection test window, select Workflow type “Full” then select the Test “HPV”.
- E. Enter a run name or leave as the default run name, then click “OK” to proceed.
- F. Follow the software wizard guide to load specimens.

NOTE: Specimens can be loaded in barcoded primary or secondary tubes in any order

NOTE: If primary containers for Roche Cell Collection Medium, and PreservCyt® Solution specimens are used for processing, vortex prior to loading.

- G. Select a Specimen type for each specimen.
 - Choose “PC” for ordering Roche Cell Collection Medium, PreservCyt® Solution specimens.
 - Choose “SP” for ordering SurePath™ Preservative Fluid specimens.

NOTE: Test orders may be annotated to identify self-collected samples using the instrument software and users are encouraged to do so. Refer to the **cobas**® 4800 System- User Assistance for annotation instructions.

- H. Select the Request result for each specimen.
 - Choose Requested result “HPV High Risk Panel” to report any one of, or combination of high risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 test results.
 - Choose Requested result “HPV High Risk Panel Plus Genotyping” to report any one of, or combination of high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and to separately report high risk HPV Type 16 and high risk HPV Type 18 test results.
- I. Follow the software wizard guide to load all consumables.
- J. Follow the software wizard guide to load all reagents.

NOTE: Controls [HPV (+) C and (-) C] are not loaded together with specimens. They are loaded onto the reagent carrier during reagent loading. Two positions (A1 and B1) on each of the Extraction plate and microwell plate are reserved for the HPV (+) and (-) controls, respectively.

NOTE: The **cobas**® 4800 System has an internal clock to monitor the length of time the reagents are on-board. Once the WB is scanned, 1 hour is allowed to complete the loading process and click on the Start button. A countdown timer is displayed on the Workplace Tab. The system will not allow the run to start if the on-board time has expired.

NOTE: To assure the accurate transfer of MGP, vortex or vigorously shake the MGP vial prior to dispensing into the reagent reservoir.

- K. Load the sample preparation reagents (WB, MGP, EB, SDS and LYS) into the barcoded reagent reservoirs using the “scan-scan-pour-place” method:
 - Scan the reagent bottle barcode
 - Scan the reagent reservoir barcode
 - Pour the reagent into the reservoir
 - Place the filled reagent reservoir into the designated position on the reagent carrier
- L. The reagent reservoirs are available in two sizes: 200 mL and 50 mL. Follow the software wizard guide to select the appropriate reagent reservoir sizes. The reagent reservoir barcodes must face to the right of the carrier.

NOTE: Amplification/detection reagents (HPV MMX and HPV Mg/Mn), Controls [HPV (+) C and (-) C] and PK are loaded directly onto the reagent carrier and scanned by the *cobas*[®] x 480 instrument automatically

NOTE: All reagents and reagent reservoirs are barcoded and designed for one time use. The *cobas*[®] 4800 Software tracks the use of the reagents and reagent reservoirs and rejects previously used reagents or reagent reservoirs. The software also verifies sufficient reagents are loaded on the instrument.

NOTE: The *cobas*[®] 4800 Software tracks the expiration date of all reagents. Reagents that are beyond their expiration date will not be accepted for use on the *cobas*[®] 4800 System

M. Start sample preparation by clicking on “Start Run”.

N. After successful completion of sample preparation, click “Unload” to unload the plate carrier.

** The status of sample preparation can be reviewed at this point, prior to clicking “Unload”. See the *cobas*[®] 4800 System- User Assistance.

O. Follow the instructions in the *cobas*[®] 4800 System- User Assistance to seal the microwell plate, transport the plate to the *cobas*[®] z 480 analyzer and start the amplification and detection run.

NOTE: The *cobas*[®] 4800 System has an internal clock to monitor the length of time after addition of the prepared samples to working master mix. Amplification and detection should be started as soon as possible but no later than 90 minutes after the end of the *cobas*[®] x 480 instrument run. A countdown timer is displayed on the Workplace Tab.

P. When the amplification and detection run is completed, unload the microwell plate from the *cobas*[®] z 480 analyzer.

Q. Follow the instructions in the *cobas*[®] 4800 System- User Assistance to review and accept results.

Performing a Recovery Workflow

NOTE: The Recovery Workflow is available as a recovery option in the event that the full workflow cannot be completed due to circumstances beyond the user's control (e.g. power failure during amplification/detection run).

NOTE: Only samples successfully processed on the *cobas*[®] x 480 instrument can be amplified/detected using the Recovery run. System surveillance for reagents and consumables is limited during the Recovery run. No sample position tracking is provided when using the Recovery workflow – the end user must ensure that the actual position of a sample on the microwell plate corresponds to the one designated in the Recovery Plate Layout Report Work Order file. Extreme care must be exercised while preparing the microwell plate to ensure proper PCR setup and to avoid contamination.

NOTE: Samples processed on the *cobas*[®] x 480 instrument have limited stability. They must be amplified/detected using the Recovery workflow within 24 hours if stored at 2C to 30°C.

A. Start a Recovery run by clicking the New run button.

B. In the Test Selection window, select “Recovery” then select test type “HPV”.

C. Enter a run name or leave as the default run name, then click OK to proceed.

D. Select a run to recover.

E. If using HPV ASAP v2.1, scan the original DWP ID from the full workflow.

F. Enter the new MWP ID.

G. Enter the Master Mix and Metal Ions IDs for all Amplification/Detection reagent vials in the kit.

H. Prepare the *cobas*[®] 4800 HPV working master mix:

1. For a 240 Test Kit, add 240 µL of HPV Mg/Mn to one vial of HPV MMX (0.5 mL vial from 240 Test Kit).

2. For a 960 Test Kit, add 450 µL of HPV Mg/Mn to each of the two vials of HPV MMX (1.0 mL vials from 960 Test Kit).

NOTE: The Recovery run must be started within 90 minutes of addition of HPV Mg/Mn to the HPV MMX. The system does not monitor the length of time after addition of the prepared samples to working master mix in the Recovery workflow. The end user must ensure that amplification and detection is started within the allotted time.

I. Thoroughly mix working master mix by carefully inverting the vial(s). Do not vortex the working master mix.

J. Transfer 25 µL of working Master Mix to the required wells in the microwell plate.

K. Place the Extraction plate from the run to be repeated onto the stand-alone magnetic plate.

L. Manually transfer 25 µL of eluate from the Extraction plate wells to the corresponding wells in the microwell plate. Ensure that well positions are maintained (e.g. eluate in A1 well in Extraction plate is transferred to A1 on the microwell plate). Ensure that no MGP is carried over to the microwell plate.

M. Follow the instructions in the *cobas*[®] 4800 System- User Assistance to seal the microwell plate.

N. Centrifuge the microwell plate using a swinging bucket rotor for at least 5 seconds at 1500 RCF.

O. Transport the plate to the *cobas*[®] z 480 analyzer and start the amplification and detection run.

P. When the amplification and detection run is completed, unload the microwell plate from the *cobas*[®] z 480 analyzer.

Q. Follow the instructions in the *cobas*[®] 4800 System- User Assistance to review and accept results.

Interpretation of Results

NOTE: All assay and run validation is performed by the cobas® 4800 Software.

NOTE: A valid run may include both valid and invalid specimen results.

For a valid run, specimen results are interpreted as shown in Tables 1 and 2:

Table 1
Result Interpretation of the cobas® 4800 HPV Test for Presence of HPV DNA

cobas® 4800 HPV Test	Result Report and Interpretation
Requested Result "HPV High Risk Panel":	
POS HR HPV	High Risk HPV Positive 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, 68.
NEG HR HPV	High Risk 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 HR HPV	High Risk HPV Invalid The results for HR HPV are invalid. For PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens the original specimen should be retested if sufficient volume remains. If the results are still invalid a new specimen should be obtained.
Failed	No Result for Specimen Consult the cobas® 4800 System User Assistance for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid result.
Requested Result "HPV High Risk Panel Plus Genotyping":	
POS Other HR HPV	Other High Risk HPV Positive 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, 68.
NEG Other HR HPV	Other High Risk HPV Negative* HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold.
Invalid Other HR HPV	Invalid Other High Risk HPV The result for Other HR HPV is Invalid. For PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens the original specimen should be retested if sufficient volume remains. If the results are still invalid a new specimen should be obtained.
POS HPV16	HPV16 Positive Specimen is positive for HPV type 16 DNA.
NEG HPV16	HPV16 Negative* HPV type 16 DNA was undetectable or below the pre-set threshold.
Invalid HPV16	Invalid HPV16 The result for HPV16 is Invalid. For PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens the original specimen should be retested if sufficient volume remains. If the results are still invalid a new specimen should be obtained.
POS HPV18	HPV18 Positive Specimen is positive for HPV type 18 DNA.
NEG HPV18	HPV18 Negative* HPV type 18 DNA was undetectable or below the pre-set threshold.
Invalid HPV18	Invalid HPV18 The result for HPV18 is Invalid. For PreservCyt® specimens, the original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained. For SurePath™ specimens the original specimen should be retested if sufficient volume remains. If the results are still invalid a new specimen should be obtained.
Failed	No Result for Specimen Consult the cobas® 4800 System User Assistance for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid results.

* A negative result does not preclude the presence of HPV infection because results depend on adequate specimen collection, absence of inhibitors, and sufficient DNA to be detected.

Table 2
Result Interpretation of the cobas® 4800 HPV Test for Patients with Cytological Abnormalities

Results	Interpretation
NEG Other HR HPV*, NEG HPV16, NEG HPV18	Very low likelihood of underlying \geq CIN2.
POS Other HR HPV*, NEG HPV16, NEG HPV18	Increased likelihood that underlying \geq CIN2 will be detected at colposcopy.
POS HPV16 and/or POS HPV18	Highest likelihood that underlying \geq CIN2 will be detected at colposcopy ^{34,35} .

*Other HR HPV DNA includes the following types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

NOTE: HPV negativereults are not intended to prevent women from proceeding to colposcopy.

NOTE: In addition to the results tabulated above, invalid results for one or more combinations is also possible. If such a result is obtained, for example:

Other HR HPV NEG, HPV16 POS, HPV18 Invalid

The positive and negative results should be interpreted as shown in Table 1. In this example HPV 18 results are invalid. 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.

NOTE: Negative results indicate HPV DNA concentrations are undetectable or below the pre-set threshold.

NOTE: Positive test results indicates the presence of any one or more of the high risk types, but since patients are often co-infected with low-risk types it does not rule out the presence of low-risk types in patients with mixed infections.

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

LIST OF RESULT FLAGS

The following table lists common flags for the cobas® 4800 HPV Test which are relevant for result interpretation. Refer to the cobas® 4800 System - User Assistance for a full list of flags.

Table 3
List of flags for cobas® 4800 HPV Test

Flag code	Description	Recommended action
R20	Positive control is invalid.	Positive control values were invalid. 1. Repeat entire run with fresh reagents. 2. If the problem persists, contact Roche Service.
R21	Negative control is invalid.	Negative control values were invalid. To avoid carryover, use Good Laboratory Practice. 1. Repeat entire run with fresh reagents. 2. If the problem persists, contact Roche Service.
X3	Error: Clot was detected. Sample was not processed.	Make sure that the samples were handled according to the workflow description. 1. Check the sample for clots. 2. Rerun the sample.
X4	Error: Pipetting error occurred. Sample was not processed.	Insufficient sample volume or mechanical error during pipetting is the most likely reason. 1. Make sure that there is enough sample volume. 2. Check whether the tip eject plate is placed correctly. 3. Rerun the sample.

QUALITY CONTROL

One set of cobas® 4800 HPV Test Positive and Negative Controls are included in each run. For any run, valid results must be obtained for both the Positive and Negative Control for the cobas® 4800 Software to display the reportable cobas® 4800 HPV Test results from that run.

Positive Control

The HPV(+) Control result must be 'Valid'. If the HPV(+) Control results are consistently invalid, contact your local Roche office for technical assistance.

Negative Control

The (-) Control result must be 'Valid'. If the (-) Control results are consistently invalid, contact your local Roche office for technical assistance.

PROCEDURAL PRECAUTIONS

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

PROCEDURAL LIMITATIONS

1. The **cobas**[®] 4800 HPV Test 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 types³⁶.
2. The **cobas**[®] 4800 HPV Test for detection of human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 is not recommended for evaluation of suspected sexual abuse.
3. The performance of the **cobas**[®] 4800 HPV Test has not been adequately established for HPV vaccinated individuals³⁷.
4. 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.
5. 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.
6. A negative high-risk HPV result does not exclude the possibility of future cytologic HSIL or underlying CIN2-3 or cancer.
7. Test only the indicated specimen type. The **cobas**[®] 4800 HPV Test has only been validated for use with:
 - cervical specimens collected in Roche Cell Collection Medium,
 - cervical specimens collected in PreservCyt[®] Solution
 - cervical specimens collected in SurePath[™] Preservative Fluid
 - vaginal specimens collected with FLOQSwabs[®] 552C.80 and suspended in Roche Cell Collection Medium
 - vaginal specimens collected with FLOQSwabs[®] 552C.80 and suspended in PreservCyt[®] Solution
 - vaginal specimens collected with Evalyn[®] Brush and suspended in Roche Cell Collection Medium
 - vaginal specimens collected with Evalyn[®] Brush and suspended in PreservCyt[®] SolutionAssay performance has not been validated for use with other collection media and/or collection devices. Use of other collection media and/or collection devices may lead to false positive, false negative or invalid results.
8. 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.
9. Beta-globin amplification and detection is included in the **cobas**[®] 4800 HPV Test 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 Beta-globin signal within a pre-defined range to be identified as valid negatives by the **cobas**[®] 4800 System.
10. Reliable results are dependent on adequate specimen collection, transport, storage and processing. Follow the procedures in this Package Insert and the **cobas**[®] 4800 System - User Assistance.
11. The addition of AmpErase enzyme into the **cobas**[®] 4800 HPV Master Mix enables selective amplification of target DNA; however, good laboratory practices and careful adherence to the procedures specified in this Package Insert are necessary to avoid contamination of reagents.
12. Use of this product must be limited to personnel trained in the techniques of PCR and the use of the **cobas**[®] 4800 System.
13. Only the **cobas**[®] x 480 instrument and **cobas**[®] z 480 analyzer have been validated for use with this product. No other sample preparation instrument or PCR system can be used with this product.
14. 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.
15. The effects of other potential variables such as vaginal discharge, use of tampons, douching, etc. and specimen collection variables have not been evaluated.
16. Though rare, mutations within the highly conserved regions of the genomic DNA of Human papillomavirus covered by the **cobas**[®] 4800 HPV Test's primers and/or probes may result in failure to detect the presence of the viral DNA.
17. The presence of PCR inhibitors may cause false negative or invalid results.
18. Cervical specimens often show visibly detectable levels of whole blood as a pink or light brown coloration. These specimens are processed normally on the **cobas**[®] 4800 System. If concentrations of whole blood exceeds 2% (dark red or brown coloration) in Roche Cell Collection Medium, or PreservCyt[®] Solution, or above 4% in SurePath[™] Preservative Fluid treated with **cobas**[®] Sample Prep Buffer, there is a likelihood of obtaining a false-negative result. See Interference results for details.
19. Use of the vaginal moisturizer Replens[®] has been associated with false-negative results in SurePath[™] Preservative Fluid.
20. Use of the RepHresh[®] vaginal hygiene products has been associated with false-negative results in Roche Cell Collection Medium and PreservCyt[®] Solution.
21. Removal of red blood cells from Roche Cell Collection Medium, PreservCyt[®], or SurePath[™] specimens through treatment with glacial acetic acid (GAA) has not been validated with the **cobas**[®] 4800 HPV Test. Any use of GAA treatments with the **cobas**[®] 4800 HPV Test must be validated by the testing laboratory.

CLINICAL PERFORMANCE USING CLINICAL SPECIMENS

Performance Comparison to a CE Mark Comparator HPV Test

Clinical sensitivity and specificity to disease status (\geq CIN2) was determined for the **cobas**[®] 4800 HPV Test and a CE Mark comparator HPV test³⁸ in a population of women at least 21 years old with ASC-US cytology results, determined through routine cervical cancer screening. All testing was carried out using PreservCyt[®] Solution cervical specimens. A total of 1578 subjects with an initial ASC-US cytology result underwent colposcopy and had valid HPV tests and cervical biopsy results. Disease status of the subjects was ascertained by a central pathology review panel from the biopsy specimens obtained at colposcopy. The results for an ASC-US population are summarized in Table 4 and indicate that the **cobas**[®] 4800 HPV Test performance was comparable to the comparator test.

Table 4
Comparison of the Performance of the cobas[®] 4800 HPV Test and a CE Mark Comparator HPV test in Detecting \geq CIN2 and \geq CIN3 in the ASC-US Population

	cobas [®] 4800 HPV Test		CEMarked HPV Test	
	Point Estimate	95% CI	Point Estimate	95% CI
\geq CIN2				
Sensitivity (%)	90.0 (72/80)	(81.5, 94.8)	87.2 (68/78) ¹	(78.0, 92.9)
Specificity (%)	70.5 (1,056/1,498)	(68.1, 72.7)	71.1 (1,056/1,485) ²	(68.8, 73.4)
PPV (%)	14.0 (72/514)	(12.8, 15.3)	13.7 (68/497)	(12.4, 15.1)
NPV (%)	99.2 (1,056/1,064)	(98.6, 99.6)	99.1 (1,056/1,066)	(98.3, 99.5)
Prevalence (%)	5.1 (80/1578)	(4.1, 6.3)	5.0 (78/1563)	(4.0, 6.2)
\geq CIN3				
Sensitivity (%)	93.5 (43/46)	(82.5, 97.8)	91.3 (42/46)	(79.7, 96.6)
Specificity (%)	69.3 (1,053/1,517)	(66.9, 71.5)	70.0 (1,062/1,517)	(67.7, 72.3)
PPV (%)	8.4 (43/514)	(7.6, 9.2)	8.5 (42/497)	(7.6, 9.4)
NPV (%)	99.7 (1,061/1,064)	(99.2, 99.9)	99.6 (1,062/1,066)	(99.0, 99.9)
Prevalence (%)	2.9 (43/1578)	(2.2, 3.9)	3.0 (46/1563)	(2.2, 3.9)

¹ Results for two subjects with a \geq CIN2 diagnosis could not be determined by the CE Mark Comparator HPV Test due to insufficient volume resulting from repeated testing.

² Results for thirteen subjects with a $<$ CIN2 diagnosis could not be determined by the CE Mark Comparator HPV Test due to insufficient volume resulting from repeated testing.

In women \geq 30 years with normal cytology, the risk of cervical disease (\geq CIN2) is 7.29 fold higher with a High Risk positive **cobas**[®] 4800 HPV Test result than with a negative **cobas**[®] 4800 HPV Test result. Relative risk estimates and their 95% confidence intervals are presented in Table 5.

In women 30 years or older, the **cobas**[®] 4800 HPV Test can be used to assess the presence or absence of HPV genotypes 16 and 18. The risk of cervical disease (\geq CIN2) is 13.71 fold higher with an HPV16 and/or HPV18 positive **cobas**[®] 4800 HPV Test result than with a negative result and the risk is 2.51 fold higher with an HPV16 and/or HPV18 positive **cobas**[®] 4800 HPV Test result compared to a positive **cobas**[®] 4800 HPV Test result for the 12 other high risk types. In all cases, the lower bound of the 95% confidence interval exceeds 1, suggesting a statistically higher risk of developing cervical disease with a positive HPV test result.

Table 5
Relative Risk for Cervical Disease (\geq CIN2 by Central Pathology Review) in Women \geq 30 Years with Normal Cytology*

HPV Result	Relative Risk Estimate	95% CI*
Pos vs. Neg	7.29	(3.99, 22.11)
16+/18+ vs. Neg	13.71	(7.31, 41.92)
16+/18+ vs. 12 other HR+	2.51	(1.73, 3.61)

Note: 0.5 was added to a zero cell of the estimated number of diseased subjects in any of the 1000 bootstrap samples
*95% CI is 2.5 and 97.5 percentile of bootstrap CI based on 1000 bootstrap samples

NILM (\geq 30 Years) Population – Performance Evaluation

For the NILM (\geq 30 years) population, estimates of sensitivity and specificity along with 95% CIs for HR HPV positive vs. HR HPV negative are presented in Table 6 for unadjusted results.

The unadjusted sensitivity and the specificity of the test for \geq CIN2 histology were 83.2% (109/131) with 95% CI: 75.9% to 88.6% and 60.4% (2492/4127) with 95% CI: 58.9% to 61.9%, respectively. The unadjusted sensitivity and specificity of the **cobas**[®] HPV Test for detecting \geq CIN3 histology were 90.0% (72/80) with 95% CI: 81.5% to 94.8% and 60.0% (2506/4178) with 95% CI: 58.5% to 61.5%, respectively.

Table 6
Performance of **cobas[®] 4800 HPV Test in the NILM (\geq 30 years) Population (Unadjusted Estimates)**

CPR Diagnosis	Performance	Estimate	95% CI
\geq CIN2	Sensitivity (%)	83.2 (109/131)	(75.9, 88.6)
	Specificity (%)	60.4 (2492/4127)	(58.9, 61.9)
	PPV(%)	6.3 (109/1744)	(5.8, 6.8)
	NPV(%)	99.1 (2492/2514)	(98.7, 99.4)
	Prevalence (%)	3.1 (131/4258)	(2.6, 3.6)
\geq CIN3	Sensitivity (%)	90.0 (72/80)	(81.5, 94.8)
	Specificity (%)	60.0 (2506/4178)	(58.5, 61.5)
	PPV(%)	4.1 (72/1744)	(3.8, 4.5)
	NPV(%)	99.7 (2506/2514)	(99.4, 99.8)
	Prevalence (%)	1.9 (80/4258)	(1.5, 2.3)

Overall (\geq 25 Years) Population – Comparison of Performance of HPV testing vs. Cytology

Clinical performance of the **cobas**[®] HPV Test and liquid based cytology (PreservCyt[®]) was determined in a population of 40,901 women 25 years and older, independent of cytology status (Overall Population). For the Overall (\geq 25 Years) population, estimates of sensitivity and specificity for the **cobas**[®] HPV Test vs. cytology for the detection of \geq CIN2 and \geq CIN3 are presented³⁸ in Table 7. The unadjusted sensitivities of the **cobas**[®] HPV Test and cytology for detection of \geq CIN2 were 88.2% (380/431) with 95% CI 84.8-90.9% and 51.5% (222/431) with CI 46.8-56.2%, respectively. The unadjusted sensitivities of the **cobas**[®] HPV Test and cytology for detection of \geq CIN3 were 92.0% (252/274) with 95% CI 88.1-94.6 and 53.3% (146/274) with CI 47.4-59.1%, respectively. Verification bias adjusted specificities of the **cobas**[®] HPV Test and cytology for detection of \geq CIN2 were 90.5% (36343/40163) with CI 90.2-90.8% and 94.1% (37811/40163) with CI 93.9-94.4%, respectively.

Table 7
Comparison of performance of the cobas® 4800
HPV Test and Cytology for the detection of ≥ CIN2 and ≥ CIN3 in the Overall (≥ 25 years) Population

	Cytology		cobas® HPV Test	
	% (n)	95% CI	% (n)	95% CI
≥CIN2				
Sensitivity	51.5 (222/431)	(46.8–56.2)	88.2 (380/431)	(84.8–90.9)
Specificity	73.4 (5428/7392)	(72.4–74.4)	57.8 (4270/7392)	(56.6–58.9)
PPV	10.2 (222/2186)	(9.3–11.1)	10.9 (380/3502)	(10.4–11.3)
NPV	96.3 (5428/5637)	(95.9–96.6)	98.8 (4270/4321)	(98.5–99.1)
≥CIN3				
Sensitivity	53.3 (146/274)	(47.4–59.1)	92.0 (252/274)	(88.1–94.6)
Specificity	73.0 (5509/7549)	(72.0–74.0)	56.9 (4299/7549)	(55.8–58.1)
PPV	6.7 (146/2186)	(6.0–7.4)	7.2 (252/3502)	(6.9–7.5)
NPV	97.7 (5509/5637)	(97.4–98.0)	99.5 (4299/4321)	(99.2–99.7)

Limit of Detection: PreservCyt® Solution and SurePath™ Preservative Fluid

The limit of detection (LOD) of high risk HPV genotypes HPV16, HPV18 and HPV31 was determined for the cobas® 4800 HPV Test. The LODs were assessed using 1) plasmids of HPV31, HPV16 and HPV18 in the background of pooled HPV negative patient specimens collected in PreservCyt® Solution and SurePath™ Preservative Fluid, and 2) HPV positive cell lines SiHa (HPV16) and HeLa (HPV18) in PreservCyt® Solution and SurePath™ Preservative Fluid containing an HPV negative cell line (HCT-15) background. Plasmid and cell lines were diluted to concentrations below, above and at the expected LOD levels. A minimum of 60 replicates were tested for each plasmid or cell line level in both PreservCyt® Solution and SurePath™ Preservative Fluid for each of 3 reagent lots. All testing in SurePath™ specimen background was done using treatment with cobas® Sample Prep Buffer. The LOD is the level of HPV DNA in the sample that has positive test results at least 95% of the time. Tables 8 and 9 contain results from the reagent lot producing the most conservative (highest) LOD in the analysis for PreservCyt® Solution and SurePath™ Preservative Fluid, respectively.

Table 8
Limit of Detection Levels for HPV Types 31, 16, 18 and Cell Lines SiHa (HPV16) and HeLa (HPV18) in PreservCyt® Solution

HPV Type	Titer (copies or cells/mL)	Number of Positive/Tested	% Positives	95% Confidence Interval	
				Lower	Upper
31	600	60/60	100%	94%	100%
31	300	59/61	97%	89%	100%
31	150	49/60	82%	70%	90%
16	1500	60/60	100%	94%	100%
16	600	60/60	100%	94%	100%
16	300	55/61	90%	80%	96%
18	1,500	60/60	100%	94%	100%
18	600	60/60	100%	94%	100%
18	300	42/61	69%	56%	80%
SiHa (HPV 16)	200	66/66	100%	95%	100%
SiHa (HPV 16)	100	64/65	98%	92%	100%
SiHa (HPV 16)	50	57/60	95%	86%	99%
HeLa (HPV 18)	80	60/60	100%	94%	100%
HeLa (HPV 18)	40	60/60	100%	94%	100%
HeLa (HPV 18)	20	56/60	93%	84%	98%

Table 9
Limit of Detection Levels for HPV Types 31, 16, 18 and Cell Lines SiHa (HPV16) and HeLa (HPV18) in SurePath™ Preservative Fluid

HPV Type	Titer (copies or cells/mL)	Number of Positive/Tested	% Positives	95% Confidence Interval	
				Lower	Upper
31	600	60/60	100%	94%	100%
31	300	59/59	100%	94%	100%
31	150	54/60	90%	80%	96%
16	600	60/60	100%	94%	100%
16	300	59/60	98%	91%	100%
16	150	40/60	67%	53%	78%
18	1,500	60/60	100%	94%	100%
18	600	60/60	100%	94%	100%
18	300	55/59	93%	84%	98%
SiHa (HPV 16)	400	60/60	100%	94%	100%
SiHa (HPV 16)	200	60/60	100%	94%	100%
SiHa (HPV 16)	100	55/60	92%	82%	97%
HeLa (HPV 18)	80	60/60	100%	94%	100%
HeLa (HPV 18)	40	59/60	98%	91%	100%
HeLa (HPV 18)	20	43/60	72%	59%	83%

Limit of Detection: Roche Cell Collection Medium

Dilution panels of HPV31 plasmid, HPV16 and HPV18 cell lines in the background of pooled HPV negative patient specimens collected in Roche Cell Collection Medium and PreservCyt® Solution were tested side-by-side. The limit of detection for the **cobas®** 4800 HPV Test was comparable.

Inclusivity Verification

To verify that the **cobas®** 4800 HPV Test is capable of accurately detecting all HPV high risk genotypes, the limit of detection (LOD) was determined (Tables 10 and 11) for genotypes 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The sensitivity of the **cobas®** 4800 HPV Test for HPV genotypes 16, 18 and 31 was determined in the Limit of Detection Study described above in this Package Insert. Quantified plasmid stocks of each HPV genotype were diluted into either PreservCyt® Solution or SurePath™ Preservative Fluid containing HPV-negative HCT-15 cells to concentrations below, above and at the expected LOD levels. One lot of reagents was used to produce a minimum of 48 replicates for each positive level in each media. For testing in SurePath™ Preservative Fluid using treatment with **cobas®** Sample Prep Buffer (Table 11), background material was prepared from cervical specimens collected in SurePath™ Preservative Fluid and tested as 24 replicates each with two lots of reagents. For each HPV type, the reported LOD was defined as the lowest testing concentration having a ≥ 95% positive hit rate with all higher concentrations having at least a 95% hit rate.

Table 10
Summary of High Risk Genotype Limit of Detection for cobas® 4800 HPV Genotype Inclusivity Study (PreservCyt® Solution)

HPV DNA Type	LOD (copies/mL)	Number of Positive/Tested	Hit Rate	95% Confidence Interval	
				Lower	Upper
33	190	46/48	96%	86%	99%
35	480	48/48	100%	93%	100%
39	80	48/48	100%	93%	100%
45	190	46/48	96%	86%	99%
51	100	46/48	96%	86%	99%
52	2400	48/48	100%	93%	100%
56	1400	48/48	100%	93%	100%
58	480	47/48	98%	89%	100%
59	190	46/48	96%	86%	99%
66	640	48/48	100%	93%	100%
68	450	48/48	100%	93%	100%

Table 11
Summary of High Risk Genotype Limit Of Detection for cobas® 4800 HPV Genotype Inclusivity Study
(SurePath™ Preservative Fluid)

HPV DNA Type	LOD (copies/mL)	Number of Positive/Tested	Hit Rate	95% Confidence Interval	
				Lower	Upper
33	300	48/48	100%	93%	100%
35	600	47/48	100%	89%	100%
39	150	48/48	100%	93%	100%
45	300	48/48	100%	93%	100%
51	600	46/48	96%	86%	99%
52	4800	48/48	100%	93%	100%
56	1200	46/48	96%	86%	99%
58	600	48/48	100%	93%	100%
59	600	48/48	100%	93%	100%
66	1200	48/48	100%	93%	100%
68	300	48/48	100%	93%	100%

Precision: PreservCyt® Solution and SurePath™ Preservative Fluid

In-house Precision was examined using panel members prepared for the Limit of Detection Study described in this Package Insert. Levels at and above the limit of detection were used for the precision analysis. Panels were prepared by spiking plasmids of HPV31, HPV16 and HPV18 into the background of pooled HPV negative patient specimens collected in PreservCyt® Solution and SurePath™ Preservative Fluid. All testing in SurePath™ specimen background was done using treatment with cobas® Sample Prep Buffer.

The positive hit rates for panel members (PreservCyt® Solution and SurePath™ Preservative Fluid) at and above the LOD are shown in Tables 12 and 13, respectively. Hit rates were above 95% for all plasmid panel levels. The variance in Ct value for the test was analyzed, and contribution from reagent lot, systems, run-to-run, and within-run random factors were calculated and summarized in Table 14 for PreservCyt® Solution and Table 15 for SurePath™ Preservative Fluid. Table 16 shows the Ct value SD and %CV of components of variation in PreservCyt® Solution. Table 17 shows the Ct value SD and %CV of components of variation in SurePath™ Preservative Fluid.

Table 12
Summary of Hit Rates for cobas® 4800 HPV Precision Study At or Above LOD (in PreservCyt® Solution)

Target	Panel Level	Concentration (copies or cells/mL)	N Tests	N Pos	Hit Rate	95% CI for Hit Rate	
						Lower	Upper
HPV31	> LOD	600	186	186	100%	98%	100%
	= LOD	300	187	184	98%	95%	100%
HPV16	> LOD	1,500	186	186	100%	98%	100%
	= LOD	600	186	186	100%	98%	100%
HPV18	> LOD	1,500	186	186	100%	98%	100%
	= LOD	600	186	186	100%	98%	100%

Table 13
Summary of Hit Rates for cobas® 4800 HPV Precision Study At or Above LOD (in SurePath™ Preservative Fluid)

Target	Panel Level	Concentration (copies or cells/mL)	N Tests	N Pos	Hit Rate	95% CI for Hit Rate	
						Lower	Upper
HPV31	> LOD	300	180	180	100%	98%	100%
	= LOD	150	180	175	97%	94%	99%
HPV16	> LOD	600	180	180	100%	98%	100%
	= LOD	300	180	180	100%	98%	100%
HPV18	> LOD	1,500	180	180	100%	98%	100%
	= LOD	600	180	180	100%	98%	100%

Table 14

Analysis of Ct Value Variance Components for cobas® 4800 HPV Precision StudyPanel Levels Prepared in PreservCyt® Solution

Target	Panel Level	N	Mean Elbow	Variance Components/Percent Contribution				
				Rgt Lot	System	Run	Random	Total
HPV16	> LOD	186	36.3	0.038	0	0.111	0.079	0.228
				17%	0%	49%	35%	100%
	= LOD	186	37.5	0.025	0	0.042	0.161	0.228
				11%	0%	18%	71%	100%
HPV18	> LOD	186	36.6	0.043	0	0.149	0.067	0.259
				16%	0%	58%	26%	100%
	= LOD	186	37.8	0.027	0	0.050	0.184	0.261
				10%	0%	19%	71%	100%
HPV31	> LOD	186	36.5	0.003	0.002	0.105	0.187	0.297
				1%	1%	35%	63%	100%
	= LOD	187	37.6	0.020	0	0.157	0.489	0.666
				3%	0%	24%	73%	100%

Table 15

Analysis of Ct Value Variance Components for cobas® 4800 HPV Precision StudyPanel Levels Prepared in SurePath™ Preservative Fluid

Target	Panel Level	N	Mean Elbow	Variance Components/Percent Contribution				
				Rgt Lot	System	Run	Random	Total
HPV16	> LOD	180	37.2	0.014	0	0.039	0.157	0.209
				7%	0%	18%	75%	100%
	= LOD	180	38.2	0	0	0.090	0.316	0.405
				0%	0%	22%	78%	100%
HPV18	> LOD	180	36.3	0.011	0	0.119	0.073	0.204
				5%	0%	58%	36%	100%
	= LOD	180	37.7	0	0	0.148	0.219	0.366
				0%	0%	40%	60%	100%
HPV31	> LOD	180	37.2	0	0	0.099	0.393	0.493
				0%	0%	20%	80%	100%
	= LOD	180	38.1	0.026	0.015	0.038	0.684	0.764
				3%	2%	5%	90%	100%

Table 16

Analysis of Ct Value SD and %CV for cobas® 4800 HPV Precision StudyPanel Levels Prepared in PreservCyt® Solution

Target	Panel Level	N	Mean Elbow	SD Components/%CV				
				Rgt Lot	System	Run	Random	Total
HPV16	> LOD	186	36.3	0.19	0	0.33	0.28	0.48
				0.50%	0.00%	0.90%	0.80%	1.30%
	= LOD	186	37.5	0.16	0	0.20	0.40	0.48
				0.40%	0.00%	0.50%	1.10%	1.30%
HPV18	> LOD	186	36.6	0.21	0	0.39	0.26	0.51
				0.60%	0.00%	1.10%	0.70%	1.40%
	= LOD	186	37.8	0.16	0	0.22	0.43	0.51
				0.40%	0.00%	0.60%	1.10%	1.30%
HPV31	> LOD	186	36.5	0.05	0.05	0.32	0.43	0.54
				0.10%	0.10%	0.90%	1.20%	1.50%
	= LOD	187	37.6	0.14	0	0.40	0.70	0.82
				0.40%	0.00%	1.10%	1.90%	2.20%

Table 17

Analysis of Ct Value SD and %CV for cobas® 4800 HPV Precision Study Panel Levels Prepared in SurePath™ Preservative Fluid

Target	Panel Level	N	Mean Elbow	SD Components/%CV				
				Rgt Lot	System	Run	Random	Total
HPV16	> LOD	180	37.2	0.12	0	0.20	0.40	0.46
				0.30%	0.00%	0.50%	1.10%	1.20%
	= LOD	180	38.2	0	0	0.30	0.56	0.64
				0.00%	0.00%	0.80%	1.50%	1.70%
HPV18	> LOD	180	36.3	0.11	0	0.34	0.27	0.45
				0.30%	0.00%	1.00%	0.70%	1.20%
	= LOD	180	37.7	0	0	0.38	0.47	0.61
				0.00%	0.00%	1.00%	1.20%	1.60%
HPV31	> LOD	180	37.2	0	0.02	0.32	0.63	0.70
				0.00%	0.10%	0.80%	1.70%	1.90%
	= LOD	180	38.1	0.16	0.12	0.20	0.83	0.87
				0.40%	0.30%	0.50%	2.20%	2.30%

Precision: Roche Cell Collection Medium

Panels were prepared by spiking HPV16 cell line DNA and HPV18 cell line DNA into a background of pooled HPV negative patient specimens collected in Roche Cell Collection Medium at and above the LOD. Testing of the panels prepared in Roche Cell Collection Medium demonstrated precision comparable to the precision with panels prepared in PreservCyt® Solution.

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 the cobas® 4800 HPV Test to assess analytical specificity. The organisms listed in Table 18 were spiked at high concentrations ($\geq 1 \times 10^3$ units/reaction) into HPV negative PreservCyt® Solution specimen background and into HPV negative PreservCyt® Solution specimen spiked with HPV 31, HPV16 and HPV18 plasmid DNA at 3 times the LOD. Organisms with an asterisk were also tested in SurePath™ Preservative Fluid specimen background under the same conditions. Organisms with a double asterisk were tested only in SurePath™ specimen background. All testing in SurePath™ specimen background was done using treatment with cobas® Sample Prep Buffer. Results indicated that none of these organisms interfered with detection of HPV31, HPV16 and HPV18 plasmid DNA or produced a false positive result in the HPV negative specimen.

Table 18
Microorganisms Tested for Analytical Specificity

<i>Achromobacter xerosis</i>	<i>Haemophilus ducreyi</i>	<i>Streptococcus agalactiae</i> *
<i>Acinetobacter calcaceticus</i>	Hepatitis B virus (HBV)	<i>Streptococcus anginosus</i>
<i>Acinetobacter Iwoffii</i>	Herpes simplex virus 1*	<i>Streptococcus faecalis</i> **
<i>Acinetobacter sp. Genospecies 3</i>	Herpes simplex virus 2*	<i>Streptococcus pyogenes</i> *
<i>Actinomyces israelii</i>	Human immunodeficiency virus (HIV-1)	<i>Streptococcus sanguis</i>
Adenovirus*	<i>Kingella kingae</i>	SV40
<i>Aerococcus viridans</i>	<i>Klebsiella pneumoniae ss ozaenae</i> *	<i>Treponema pallidum</i>
<i>Alcaligenes faecalis</i>	<i>Lactobacillus acidophilus</i> *	<i>Trichomonas vaginalis</i> *
<i>Bacillus thuringiensis</i>	<i>Lactobacillus crispus</i>	<i>Ureaplasma urealyticum</i>
<i>Bacteroides caccae</i> **	<i>Lactobacillus delbrueckii s. lactis</i>	<i>Veillonella parvula</i>
<i>Bacteroides fragilis</i>	<i>Lactobacillus jensenii</i>	<i>Vibrio parahaemolyticus</i>
<i>Bacteroides ureolyticus</i>	<i>Lactobacillus vaginalis</i>	<i>Weissella paramesenteroides</i>
<i>Bifidobacterium longum</i>	<i>Lactococcus lactis cremoris</i>	<i>Yersinia enterocolitica</i>
<i>Bifidobacterium adolescentis</i> *	<i>Legionella pneumophila</i>	HPV 6*
<i>Bifidobacterium brevi</i>	<i>Micrococcus luteus</i>	HPV 11*
<i>Campylobacter jejuni</i>	<i>Mobiluncus curtisii s. curtisii</i>	HPV 26*
<i>Candida albicans</i> *	<i>Moraxella osloensis</i>	HPV 30**
<i>Chlamydia trachomatis</i> *	<i>Morganella morganii</i>	HPV 34**
<i>Chromobacter violaceum</i>	<i>Mycobacterium avium</i>	HPV 40
<i>Citrobacter braakii</i>	<i>Mycobacterium smegmatis</i>	HPV 42
<i>Clostridium adolescentis</i>	<i>Mycoplasma genitalium</i>	HPV 53**
<i>Clostridium beijerinckii</i> **	<i>Mycoplasma hominis</i>	HPV 54
<i>Clostridium perfringens</i>	<i>Neisseria gonorrhoeae</i> *	HPV 55B
<i>Corynebacterium genitalium</i> **	<i>Neisseria meningitidis Serogroup A</i>	HPV 61
<i>Corynebacterium glutamicum</i>	<i>Pasteurella multocida</i>	HPV 62
Cytomegalovirus*	<i>Pediococcus acidilactici</i>	HPV 64
<i>Eikenella corrodens</i>	<i>Peptostreptococcus anaerobius</i> *	HPV 67*
<i>Enterobacter aerogenes</i> **	<i>Propionibacterium acnes</i>	HPV 69*
<i>Enterobacter cloacae</i>	<i>Proteus mirabilis</i> *	HPV 70*
<i>Enterococcus faecalis</i>	<i>Proteus vulgaris</i>	HPV 71
<i>Enterococcus faecium</i> *	<i>Providencia stuartii</i>	HPV 72
Epstein Barr Virus*	<i>Pseudomonas aeruginosa</i>	HPV 73*
<i>Erysipelothrix rhusiopathiae</i>	<i>Pseudomonas fluorescens</i> **	HPV 81
<i>Escherichia coli</i> *	<i>Ruminococcus productus</i>	HPV 82*
<i>Ewingella americana</i>	<i>Salmonella minnesota</i>	HPV 83
<i>Fusobacterium nucleatum</i>	<i>Serratia marcescens</i>	HPV 84
<i>Fusobacterium varium</i> **	<i>Staphylococcus aureus</i> *	HPV 85**
<i>Gemella morbillorum</i>	<i>Staphylococcus epidermidis</i> *	HPV 89 (CP6108)
<i>Gardnerella vaginalis</i>	<i>Staphylococcus saprophyticus</i>	-

*Tested in both PreservCyt® and SurePath™ specimen background

**Tested only in SurePath™ specimen background

Interfering Substances

HPV positive and HPV negative cervical specimens as well as contrived specimens were used to assess the effects of endogenous and exogenous interfering substances that could potentially be present in cervical specimens. Testing materials used in these studies are described in Table 19. The concentrations of endogenous and exogenous substances tested represent conditions that could occur during specimen collection.

Whole blood, Peripheral Blood Mononuclear Cells (PBMC) and cervical mucus were tested as potential endogenous interfering substances found in cervical specimens. All testing in SurePath™ specimen background was done using treatment with cobas® Sample Prep Buffer. Levels of each potential interfering substance tested and performance observations are described in Table 20. No interference was seen for PBMC or cervical mucus at all levels tested. Whole blood showed no interference when present in visually detectable amounts of up to 2% in Roche Cell Collection Medium and PreservCyt® Solution. Whole blood showed no interference when present in visually detectable amounts up to 4% in SurePath™ Preservative Fluid.

Table 19
Interference Testing Sample Descriptions

Sample type	Description
HPV Positive Cervical Specimens	10 individual HPV positive PreservCyt® Solution specimens were aliquoted for testing with and without endogenous interfering substances.
HPV Negative Cervical Specimens	10 individual HPV negative PreservCyt® Solution specimens were aliquoted for testing with and without endogenous interfering substances.
Contrived HPV Positive Cervical Specimen	HPV positive (channel 1) PreservCyt® Solution specimens were diluted with HPV negative specimen to an approximate level of 3 x LOD. HPV types 16 (channel 2) and 18 (channel 3) plasmids were then added at ~ 3 x LOD. HPV31 plasmid, HPV16 cell line DNA, and HPV18 cell line DNA were added at ~ 3X LOD to HPV negative specimens collected in Roche Cell Collection Medium.
3x LOD PreservCyt® Solution and SurePath™ Preservative Fluid pools	HPV types 31, 16, 18 plasmids were each diluted to 3 x LOD in pools of PreservCyt® Solution and SurePath™ Preservative Fluid negative specimen.

Table 20
Interference Testing Results with Endogenous Interferents

Interferent Tested	Concentrations Tested	Interference Observed	
		PreservCyt®	SurePath™
Whole Blood	1%, 1.5%, 2%, 3%, 4%, 6%, 8% v/v	Above 2%	Above 4%
PBMC	10 ⁴ , 10 ⁵ , 10 ⁶ cells/mL	None	None
Cervical Mucus	Mucus obtained from standard cervical cleaning procedure	None	None

A total of 18 over-the-counter (OTC) feminine hygiene and contraceptive products were tested as potential interfering substances. Types of potential interferents tested and performance observations in Roche Cell Collection Medium, PreservCyt® Solution, and SurePath™ Preservative Fluid 3 x LOD pools are described in Table 21.

Table 21
Interference Testing Results with Exogenous Interferents

Interferent Description	Interference Observed
Contraceptive Gels, Foams	None
Vaginal Lubricants	*Yes
Vaginal Douche	None
Anti-fungal creams containing 1% clotrimazole, Phenazopyridine Hydrochloride, 1% Hydrocortisone, 2% Miconazole nitrate, 6.5% Tiocnazole Ointment, 20% Benzocaine	None

* Replens® (topical anti-dryness gel) produced negative results in replicates of the SurePath™ Preservative Fluid 3 x LOD pool. This interference was also seen when SurePath™ material was treated with cobas® Sample Prep Buffer. RepHresh® vaginal hygiene products produced negative results in replicates of the 3 x LOD pools of Roche Cell Collection Medium and PreservCyt® Solution.

SurePath™ Specimen Stability for 6 Weeks at 2-30°C using Treatment with cobas® Sample Prep Buffer

Three SurePath™ HPV negative specimen pools were spiked with HPV Type 51 positive SurePath™ specimen material to produce positive, high positive and low positive specimen pools. The low positive pool was at ~ Limit of Detection (LOD) for the test at Day 0 prior to treatment with cobas® Sample Prep Buffer. These pools were stored at 32°C and tested at intervals up to 6 weeks. Pooled materials were treated to reverse matrix-induced crosslinks followed by analysis with the cobas® 4800 HPV Test at each timepoint. All three pools maintained Ct averages below the clinical cutoff for HPV type 51 (40.0 for channel 1) through the 6 week storage period (see Table 22).

Table 22
SurePath™ Specimen Stability Results for 6 Weeks with Treatment using cobas® Sample Prep Buffer

SurePath™ Pools	Average Ct Values*				
	Day 0	Week 1	Week 3	Week 4	Week 6
High Positive	28.7	30.1	30.3	30.6	31.1
Positive	32.9	33.5	34.1	33.9	34.6
Low Positive (~LOD)	36.9	37.9	38.0	38.8	38.7

*Low Positive timepoints tested as 40 replicates; Positive timepoints as 30 replicates; High Positive timepoints as 20 replicates

Correlation of Results from Self-Collected Sample Using FLOQSwab® 552C.80 and Clinician-Collected Specimens

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

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

The rate of invalid results for the self-collected and clinician-collected results were 4.6% and 0.3%, respectively. A total of 708 valid paired results were used for correlation analysis. Specimens positive for any of the 14 high risk HPV genotypes detected by the test (HPV -HR) were considered positive; specimens with negative results for all of the 14 high risk HPV genotypes detected by the test were considered negative.

The correlation results and calculated positive, negative and overall percent agreements along with 95% confidence intervals are shown in Table 23.

Table 23
Correlation of Results for Self-Collected Vaginal Specimens using FLOQSwabs® 552C.80 and Clinician-Collected Cervical Specimens

		Clinician-collected cervical sample 14 HR Result		Total
		Positive	Negative	
Self-collected vaginal sample using FLOQSwabs® #552C.80 14 HR Result	Positive	161	48	209
	Negative	22	477	499
Total		183	525	708

	Result (%)	95% Confidence Interval
Positive Percent Agreement	88.0%	82.5% - 91.9%
Negative Percent Agreement	90.8%	88.1% - 93.0%
Overall Percent Agreement	90.1%	87.7% - 92.1%

Correlation of Results from Self-Collected Sample Using Evalyn® Brush and Clinician-Collected Specimens

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

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

The rate of invalid results for the self-collected and clinician-collected results were 4.7% and 0.4%, respectively. A total of 742 valid paired results were used for correlation analysis. Specimens positive for any of the 14 high risk HPV genotypes detected by the test (HPV -HR) were considered positive; specimens with negative results for all of the 14 high risk HPV genotypes detected by the test were considered negative.

The correlation results and calculated positive, negative and overall percent agreements along with 95% confidence intervals are shown in Table 24.

Table 24
Correlation of Results for Self-Collected Vaginal Specimens using Evalyn® Brush and Clinician-Collected Cervical Specimens

		Clinician-collected cervical sample 14 HR Result		Total
		Positive	Negative	
Self-collected vaginal sample using Evalyn® Brush 14 HR Result	Positive	195	37	232
	Negative	25	485	510
Total		220	522	742

	Result (%)	95% Confidence Interval
Positive Percent Agreement	88.6%	83.8% - 92.2%
Negative Percent Agreement	92.9%	90.4% - 94.8%
Overall Percent Agreement	91.6%	89.4% - 93.4%

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Document Revision Information	
Doc Rev23.0 11/2023	<p>Correction to Table 23</p> <p>Corrected formatting throughout, as needed.</p> <p>Updated cobas® branding.</p> <p>Please contact your local Roche Representative if you have any questions.</p>
Doc Rev24.0 08/2024	<p>Updated Sample Preparation kits hazard information.</p> <p>Updated Liquid Cytology Preparation Kit and Wash Buffer Kits hazard information.</p> <p>Updated competent authority statement.</p> <p>Removed material number and versioning above EC REP symbol to avoid redundant information.</p> <p>Removed Rx Only from front page.</p> <p>Updated the harmonized symbol page.</p> <p>Please contact your local Roche Representative if you have any questions</p>

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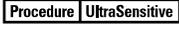
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