BD Onclarity™ HPV Assay

IVD

bd.com/e-labeling

℞ Only

8089894(08)
2024-xx
English

REF 441990 REF 444074 REF 444075 REF 444083 REF 444087 REF 444089

TABLE OF CONTENTS

BD Onclarity™ HPV Assay

IVD bd.com/e-labeling Rx Only

8089894(08)
2024-XX
English

REF 441990 REF 444074 REF 444075 REF 444083 REF 444087 REF 444089

INTENDED USE

The BD Onclarity HPV Assay is a qualitative in vitro test for the detection of high-risk (HR) Human Papillomavirus. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 HR HPV types in a single analysis. The test specifically identifies types 16, 18, 31, 45, 51, and 52 while reporting the other HR HPV types in groups (33/58, 35/39/68, and 56/59/66) in the specimens listed below.

Clinician-collected cervical specimens should be obtained using an endocervical brush/spatula combination or broom and placed in a BD SurePath vial or placed in ThinPrep Pap Test PreservCyt Solution.

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

The BD Onclarity HPV Assay is indicated for use for routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (or adjunctive screen) with cytology, and HPV primary screening of individuals with a cervix to assess the risk for cervical precancer and cancer. Patients should be followed-up in accordance with professional medical guidelines, results from prior screening, medical history, and other risk factors.

CONTRAINDICATIONS: None

WARNINGS

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

The BD Onclarity HPV Assay is NOT intended:

- For use in determining the need for treatment (i.e., excisional or ablative treatment of the cervix) in the absence of high-grade cervical dysplasia. Patients who are HPV 16, 18 and 45 positive should be assessed for the development of high-grade cervical intraepithelial neoplasia according to current practice guidelines.
- For women who have undergone hysterectomy with removal of the cervix.
- For use with cervical specimens other than those collected by a clinician using an endocervical brush/spatula combination or broom and placed in the BD SurePath Preservative Fluid Collection Vial or placed in PreservCyt Solution.
- For use with self-collected vaginal specimens other than those collected with collection devices specifically FDA-approved or cleared for use with the BD Onclarity HPV Assay.

HPV-negative cancers of the cervix do occur infrequently.[1,2] In addition, HPV screening is not 100% sensitive for HPV-associated cervical cancer. Use of this device for primary cervical cancer screening should be undertaken after carefully considering the performance characteristics put forth in this label, as well as recommendations of professional guidelines.

The use of this test has not been evaluated for the management of women with prior ablative or excisional therapy, or who are pregnant, or below age 21, or for the management of transgender individuals.

SUMMARY AND EXPLANATION OF THE TEST

HPV is a double-stranded DNA virus with a circular genome of approximately 8,000 base pairs and encodes 8 open reading frames (ORFs). Its ORFs are divided into early and late genes involved in replication (i.e., E1 and E2) and packaging (i.e., L1 and L2) with the remaining genes (E6, E7, E5, and E4) playing roles in driving cell cycle entry, immune evasion, and virus release.[6]

There are more than 170 different genotypes of human papillomavirus (HPV), of which 14 are considered high-risk for cervical cancer and its precursor lesions. It is one of the most common sexually transmitted viruses in the world: The majority of sexually active men and women will be exposed to HPV at some point in their lives. More than 90% of the infected individuals eventually clear the infection.[3] According to the World Health Organization (WHO), cervical cancer is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020.[4] It is estimated that in 2020 there were 14,100 cases of cervical cancer and 4,280 deaths in the United States, which correspond, respectively, to an age-adjusted rate of 7.4 and 2.3 per 100,000 women, annually.[5]

A persistent infection of one of the fourteen sexually transmitted HPV genotypes considered high risk (genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) can lead to the development of cervical cancer and its precursor lesions, although HPV66 was recently categorized as “possibly carcinogenic” based on its relatively low prevalence in invasive cervical carcinomas.[7] Of the fourteen high-risk HPV genotypes, 16 and 18 cause 60–70% of cervical cancer worldwide.[8] Although HPV45 is not one of the most prevalent genotypes in cervical cancers overall, it is disproportionately responsible for aggressive forms of adenocarcinoma, where, together with HPV genotypes 16 and 18, it can account for up to 94% of all cases.[8,9]

Following high-risk HPV infection, the risk of progression to high-grade cervical intraepithelial neoplasia and cancer is strongly associated with HPV genotype and genotype-specific persistence. Each HPV genotype has an associated risk for cervical cancer precursors and for cervical cancer. Under the principle of similar management for similar risk, genotype information can be utilized to support optimal risk-based management of patients.

The identification of the HPV virus' relationship to cervical cancer disease has resulted in a rich volume of scientific activity in this field. These activities range from the development of vaccines designed to prevent infection with HPV viruses to in vitro diagnostic tests for use as aids in cervical cancer screening and clinical patient management. Today, Pap tests (cervical cytology-based screening) can inform a clinician if there are changes to the cervical cells. If that assessment determines that there is a low-grade abnormality, an HPV test may be done to determine if those cervical changes are due to a high risk strain of HPV which can lead to cervical cancer. The BD Onclarity™ HPV Assay provides qualitative results and detects HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and allows discrete identification of the high-risk types 16, 18, 31, 45, 51, and 52, and three HR HPV groups (33/58, 35/39/68, and 56/59/66).

The BD Onclarity™ HPV Assay should be used for cervical cancer screening to assess the risk of cervical intraepithelial neoplasia and cancer. Women who test positive or negative by this assay should be followed up in accordance with the clinician's assessment of patient screening results, past medical history, other risk factors, and clinical practice guidelines. The results of this test are not intended to prevent women from proceeding to colposcopy.

PRINCIPLES OF THE PROCEDURE

The BD Onclarity™ HPV Assay is based on two major processing steps: 1) automated specimen preparation to homogenize the matrix, lyse cells, and extract cellular DNA; and 2) PCR amplification of target DNA sequences using primers and fluorescently-labeled detector probes for both HPV and human beta globin. The human beta globin serves as an internal control of the entire test by concurrently assessing specimen processing, extraction, and amplification. The BD Onclarity™ HPV Assay uses HPV target regions for primers and probes (E6/E7 oncogenes) that provide robust detection of HPV genotypes reducing the potential risk for lack of detection due to nucleic acid deletions and/or mutations.[10,11] Testing on the BD COR™ System allows for automated sample aliquoting from BD SurePath™ vials or PreservCyt® Solution to sample diluent tubes.

The automated specimen preparation for the BD Onclarity™ HPV Assay is completed by the BD COR™ PX Instrument or by the BD Pre-Warm Heater and the BD Viper™ LT System. Cervical specimens collected in BD SurePath™ Collection Vials or PreservCyt® Solution are extracted using BD FOX™ Extraction to release cellular DNA. The purified cellular DNA solution from each extracted specimen is transferred into PCR tubes containing reagents which are then sealed to prevent contamination.

The BD Onclarity™ HPV Assay reagents are dried in three individual PCR tubes that are capable of detecting 14 high risk HPV genotypes and a specimen-derived internal control consisting of a fragment of DNA from the human beta globin gene. These genotypes are reported either individually (16, 18, 31, 45, 51, 52) or as a genotype group (33/58, 56/59/66, and 35/39/68). Each of the three PCR tubes contains specific oligonucleotide sets to detect HPV genotype DNA and an oligonucleotide set to detect a region of the human beta globin gene.

The BD Onclarity™ HPV Assay uses real-time PCR technology.[12] The detection of the target DNA is accomplished using TaqMan® DNA probes that include a fluorescent dye at the 5' end and a quenching molecule at the 3' end of the oligonucleotide. The BD Onclarity™ HPV Assay utilizes fifteen probes labeled with one of four fluorescent dyes. Each dye is paired with one of two Black Hole Quencher molecules (BHQ® Dye). Fluorescent detection of amplification occurs in four separate optical channels on the BD Viper™ LT System and the BD COR™ System.

REAGENTS

BD COR™ Reagents

BD Onclarity™ HPV Assay Reagent Pack (576 tests) Catalog Number 444075		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV PCR Plate	18 x 32 tests	BD Onclarity™ HPV PCR Plates contain the following ingredients. G1, G2 and G3 tubes each contain unique primers and probes. Tris Buffer, Glycerol, Trehalose <1.00% Upstream and downstream HPV primers <0.06% Upstream and downstream beta-globin primers <0.62% Fluorescent-labeled HPV probes <0.12% Fluorescent-labeled beta globin probes <1.97% Hot Gold Star polymerase (microbial)
BD FOX™ PCR Extraction Tubes	18 x 32 tests	Iron Oxide in dissolvable film
Safety and Warnings N/A		

BD Onclarity™ HPV Assay Diluent for BD COR™ Catalog Number 444083		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV Assay Diluent for BD COR™	4 x 750 mL	<0.9% Detergent <0.05% Proclin <4.0% Tris HCl <5.0% Tris Base <1.5% Sodium Chloride
Safety and Warnings  **WARNING** **H317** May cause an allergic skin reaction. **H319** Causes serious eye irritation. **H411** Toxic to aquatic life with long lasting effects. **P261** Avoid breathing dust/fume/gas/mist/vapors/spray. **P272** Contaminated work clothing should not be allowed out of the workplace. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P273** Avoid release to the environment. **P302+P352** IF ON SKIN: Wash with plenty of soap and water. **P333+P313** If skin irritation or rash occurs: Get medical advice/attention. **P363** Wash contaminated clothing before reuse. **P391** Collect spillage. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P337+P313** If eye irritation persists: Get medical advice/attention. **P501** Dispose of contents/container to an approved facility in accordance with local, regional, national and international regulations.		

BD Onclarity™ HPV Extraction Reagent Trough Catalog Number 444074		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV Extraction Reagent Trough for BD COR™	2 troughs	Sodium Phosphate, Monobasic Proclin 300 <0.109% Detergent <22.0% Sulfuric Acid <38.0% Potassium Hydroxide <0.3% Tris Base <2.9% Tris HCl
Safety and Warnings  **DANGER** **H314** Causes severe skin burns and eye damage. **H350** May cause cancer. **P201** Obtain special instructions before use. **P202** Do not handle until all safety precautions have been read and understood. **P260** Do not breathe dust/fume/gas/mist/vapors/spray. **P264** Wash face, hands and any exposed skin thoroughly after handling. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P301+P330+P331** IF SWALLOWED: Rinse mouth. Do NOT induce vomiting. **P303+P361+P353** IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water [or shower]. **P304+P340** IF INHALED: Remove person to fresh air and keep comfortable for breathing. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P310** Immediately call a POISON CENTER/doctor. **P363** Wash contaminated clothing before reuse. **P405** Store locked up. **P501** Dispose of contents/container to an approved facility in accordance with local, regional, national and international regulations.		

BD Control Set for the BD Onclarity™ HPV Assay (372 sets) Catalog Number 445025		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV Positive Control	372 x 0.05 mL (dried)	<1.178% Nonspecific DNA (biological) <0.077% Non-infectious plasmid DNA (microbial) containing HPV-16, 18, 56 sequences <0.013% Non-infectious plasmid DNA (microbial) containing human beta-globin sequence
BD Onclarity™ HPV Negative Control	372 x 0.05 mL (dried)	<1.182% Nonspecific DNA (biological)
Safety and Warnings N/A		

BD Viper™ LT Reagents

BD Onclarity™ HPV Assay Reagent Pack (192 tests) Catalog Number 441990		
Components	**Quantity per kit**	**Ingredients**
HPV Assay G1 PCR tubes	2 x 96 tests	Tris Buffer, Glycerol, Trehalose <0.75% Upstream and downstream HPV primers <0.06% Upstream and downstream beta-globin primers <0.37% Fluorescent-labeled HPV probes <0.12% Fluorescent-labeled beta-globin probes <1.97% Hot Gold Star polymerase (microbial)
HPV Assay G2 PCR tubes	2 x 96 tests	Tris Buffer, Glycerol, Trehalose <1.00% Upstream and downstream HPV primers <0.06% Upstream and downstream beta-globin primers <0.62% Fluorescent-labeled HPV probes <0.12% Fluorescent-labeled beta-globin probes <1.97% Hot Gold Star polymerase (microbial)
HPV Assay G3 PCR tubes	2 x 96 tests	Tris Buffer, Glycerol, Trehalose <1.00% Upstream and downstream HPV primers <0.06% Upstream and downstream beta-globin primers <0.50% Fluorescent-labeled HPV probes <0.12% Fluorescent-labeled beta-globin probes <1.97% Hot Gold Star polymerase (microbial)
Safety and Warnings N/A		

BD Viper™ PCR Extraction Reagent Trough with Piercing Tool (96 tests) Catalog Number 444087		
Components	**Quantity per kit**	**Ingredients**
BD Viper™ PCR Extraction Reagent Trough with Piercing Tool	12 troughs	Sodium Phosphate, Monobasic Proclin 300 <0.109% Detergent <22.0% Sulfuric Acid <38.0% Potassium Hydroxide <0.3% Tris Base <2.9% Tris HCl
Safety and Warnings  **DANGER** **H314** Causes severe skin burns and eye damage. **H350** May cause cancer. **P260** Do not breathe dust/fume/gas/mist/vapors/spray. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P264** Wash face, hands and any exposed skin thoroughly after handling. **P201** Obtain special instructions before use. **P202** Do not handle until all safety precautions have been read and understood. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P310** Immediately call a POISON CENTER/doctor. **P303+P361+P353** IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water [or shower]. **P304+P340** IF INHALED: Remove person to fresh air and keep comfortable for breathing. **P301+P330+P331** IF SWALLOWED: Rinse mouth. Do NOT induce vomiting. **P363** Wash contaminated clothing before reuse. **P405** Store locked up. **P501** Dispose of contents/container to an approved facility in accordance with local, regional, national and international regulations.		

BD Control Set for the BD Onclarity™ HPV Assay (24 sets) Catalog Number 444088		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV Positive Control	24 x 0.05 mL (dried)	<1.178% Nonspecific DNA (biological) <0.077% Non-infectious plasmid DNA (microbial) containing HPV-16, 18, 56 sequences <0.013% Non-infectious plasmid DNA (microbial) containing human beta-globin sequence
BD Onclarity™ HPV Negative Control	24 x 0.05 mL (dried)	<1.182% Nonspecific DNA (biological)
Safety and Warnings N/A		

BD FOX™ PCR Extraction Tubes (384 tubes) Catalog Number 444089		
Components	**Quantity per kit**	**Ingredients**
PCR Extraction Tubes	48 x 8	Iron Oxide in dissolvable film
Safety and Warnings N/A		

BD COR™ and BD Viper™ LT Reagents

BD Onclarity™ HPV SurePath™ Diluent Tubes (400 tubes) Catalog Number 445329 For use with BD SurePath™ specimens		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV SurePath™ Diluent	400 x 1.7 mL	<0.9% Detergent <0.05% Proclin <4.0% Tris HCl <5.0% Tris Base <1.5% Sodium Chloride
Safety and Warnings  **WARNING** **H317** May cause an allergic skin reaction. **H319** Causes serious eye irritation. **H411** Toxic to aquatic life with long lasting effects. **P261** Avoid breathing dust/fume/gas/mist/vapors/spray. **P272** Contaminated work clothing should not be allowed out of the workplace. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P273** Avoid release to the environment. **P302+P352** IF ON SKIN: Wash with plenty of soap and water. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P333+P313** If skin irritation or rash occurs: Get medical advice/attention. **P337+P313** If eye irritation persists: Get medical advice/attention. **P363** Wash contaminated clothing before reuse. **P391** Collect spillage. **P501** Dispose of contents/container to an approved facility in accordance with local, regional, national and international regulations.		

BD Onclarity™ HPV LBC Diluent Tubes (400 tubes) Catalog Number 445328 For use with PreservCyt® specimens		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV LBC Diluent	400 x 1.7 mL	<0.9% Detergent <0.05% Proclin <4.0% Tris HCl <5.0% Tris Base <1.5% Sodium Chloride
Safety and Warnings  **WARNING** **H317** May cause an allergic skin reaction. **H319** Causes serious eye irritation. **H411** Toxic to aquatic life with long lasting effects. **P261** Avoid breathing dust/fume/gas/mist/vapors/spray. **P272** Contaminated work clothing should not be allowed out of the workplace. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P273** Avoid release to the environment. **P302+P352** IF ON SKIN: Wash with plenty of soap and water. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P333+P313** If skin irritation or rash occurs: Get medical advice/attention. **P337+P313** If eye irritation persists: Get medical advice/attention. **P363** Wash contaminated clothing before reuse. **P391** Collect spillage. **P501** Dispose of contents/container to an approved facility in accordance with local, regional, national and international regulations.		

BD Onclarity™ HPV Self Collection Diluent Tube (400 tubes) Catalog Number 445416 For use with Self-Collected Vaginal Specimens		
Components	**Quantity per kit**	**Ingredients**
BD Onclarity™ HPV Self Collection Diluent Tube	400 x 3.0 mL	<0.9% Detergent <0.05% Proclin <4.0% Tris HCl <5.0% Tris Base <1.5% Sodium Chloride

WARNING

H317 May cause an allergic skin reaction. **H319** Causes serious eye irritation. **H411** Toxic to aquatic life with long lasting effects. **P261** Avoid breathing dust/fume/gas/mist/vapors/spray. **P272** Contaminated work clothing should not be allowed out of the workplace. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P273** Avoid release to the environment. **P302+P352** IF ON SKIN: Wash with plenty of soap and water. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P333+P313** If skin irritation or rash occurs: Get medical advice/attention. **P337+P313** If eye irritation persists: Get medical advice/attention. **P363** Wash contaminated clothing before reuse. **P391** Collect spillage. **P501** Dispose of contents/container to an approved facility in accordance with local, regional, national and international regulations.

WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic use. For Use by Trained Laboratory Personnel.
2. For warnings, precautions and cleaning procedures related to automated instrumentation, consult the BD Viper™ LT or BD COR™ System User's Manuals.
3. Pathogenic microorganisms, including hepatitis viruses and Human Immunodeficiency Virus, may be present in clinical specimens. "Standard Precautions"[13-16] and institutional guidelines should be followed in handling all items contaminated with blood and other body fluids. For additional specific warnings, cautions and notes specific to the BD Viper™ LT or BD COR™ System, consult the appropriate system user's manual.

Specimen

4. The BD Onclarity™ HPV Assay has been validated for use with cervical specimens collected using either an endocervical broom or a brush/spatula combination and placed in the BD SurePath™ Vial or PreservCyt® Solution (as described in their respective instructions for use). An aliquot of specimen is removed prior to or after processing for the BD SurePath™ Liquid-Based Pap test or ThinPrep® Pap Test and must be diluted in the appropriate BD Onclarity™ HPV diluent tube prior to testing with the BD Onclarity™ HPV Assay on the BD Viper™ LT or BD COR™ System.
5. The BD Onclarity™ HPV Assay has been validated for use with self-collected vaginal specimens collected in a healthcare environment using a vaginal swab, transported dry to the laboratory, and placed in a BD Onclarity™ HPV Self Collection Diluent Tube before being processed on the BD Viper™ LT or BD COR™ System. Self-collected vaginal specimens placed in a BD Onclarity™ HPV Self Collection Diluent Tube may be collected utilizing the Copan FLOQSwabs® catalog number 5C188S.BD (5C188S.BD is the same swab as 5E089N utilized in clinical study regarding vaginal specimen).
6. BD SurePath™ specimens must be diluted into BD Onclarity™ HPV SurePath™ Diluent Tubes, and PreservCyt® specimens must be diluted into BD Onclarity™ HPV LBC Diluent Tubes to ensure accuracy of results. Refer to section above (Reagents) for further information on the BD Onclarity™ HPV SurePath™ Diluent Tubes and BD Onclarity™ HPV LBC Diluent Tubes.
7. Self-collected vaginal specimens must be diluted in BD Onclarity™ HPV Self Collection Diluent Tubes.
8. Optimal performance of the BD Onclarity™ HPV Assay requires proper specimen collection, handling and testing within the expiration dating of the BD Onclarity™ HPV SurePath™ Diluent Tube, the BD Onclarity™ HPV LBC Diluent Tube and the BD Onclarity™ HPV Self Collection Diluent Tube.
9. Take care to avoid cross-contamination during the specimen handling steps. Ensure that specimen containers do not contact one another, and discard used materials without passing over open containers. If gloves come in contact with specimen, change gloves to avoid contamination.
10. Under- or over-dispensing of LBC specimen into the appropriate BD Onclarity™ HPV diluent tube may affect assay performance. Over filling the tubes may also result in liquid overflow on the BD Viper™ LT deck and could cause contamination.
11. Use only polypropylene aerosol-resistant pipette tips to transfer specimens to the BD Onclarity™ HPV SurePath™ Diluent Tubes and BD Onclarity™ HPV LBC Diluent Tubes.
12. The BD COR™ Tube Tray Cover is single use only. Discard after use.
13. Vaginal specimens should be self-collected in a healthcare environment.
14. Do not test the BD Onclarity™ HPV Self Collection Diluent Tube without a collection device present. A false negative test result may occur.
15. When processing specimens on the BD Viper™ LT, select the appropriate test type from the Rack Login Display dropdown menu. Processing with the incorrect test type may result in downstream processing errors or inaccurate results.

Assay/Reagent

16. Use only sample and control tubes with pierceable caps on the BD Viper™ LT and BD COR™ Systems. For the BD COR™ System, use only BD Molecular Aliquot Tubes with pierceable caps. Do not remove pierceable caps prior to running the instrument. Post pre-warm samples with punctured caps are stable at 2–30 °C for 7 days without re-capping. Please refer to the specimen transport and storage table for further information.
17. For the BD COR™ System, PCR plates come pre-assembled. Do not remove tubes from the tray. If tubes become dislodged, do not use.
18. Reagent pouches containing unused PCR tubes MUST be carefully resealed after opening. Verify that desiccant is present prior to resealing the reagent pouches.
19. Use only the 1,000 µL BD Pipette tips specified for the system you are using (BD Viper™ LT or the BD COR™ System).
20. Do not use reagents after their expiration dates.
21. The Positive and Negative Controls are intended to monitor for substantial system failure and ensures reagent functionality. Quality control requirements must be performed in conformance with local, state and/or federal regulations or accreditation requirements and your laboratory's standard Quality Control procedures.
22. Although dedicated work areas are not required because the BD Viper™ LT and BD COR™ System designs reduce the possibility of amplicon contamination in the testing environment, other precautions for controlling contamination, particularly to avoid contamination of specimens during manipulation, are necessary.
23. CHANGE GLOVES if they come in contact with specimen or appear to be wet, to avoid contaminating other specimens. Change gloves before leaving work area and upon entry into work area.
24. Safety Data Sheets (SDS) are available at bd.com or by contacting BD Technical Service and Support.
25. Contact BD Technical Service and Support in the event of an unusual situation, such as a spill into the BD Viper™ LT or BD COR™ System or DNA contamination that cannot be removed by cleaning.

STORAGE AND HANDLING REQUIREMENTS

1. Do not freeze reagents.
2. All reagents may be stored at 2–33 °C until the indicated expiration date.
3. Once a PCR tube pouch is opened, the PCR tubes are stable for 4 weeks at 2–33 °C, if properly sealed or until the expiration date, whichever comes first.

Reagents and Materials Provided

BD Viper™ LT Reagents and Materials

Contents	Quantity
BD Onclarity™ HPV Assay Reagent Pack Catalog Number 441990	192 Tests
BD FOX™ PCR Extraction Tubes Catalog Number 444089	384 Tubes
BD Viper™ PCR Extraction Reagent Trough with Piercing Tool Catalog Number 444087	12 Troughs
Control Set for the BD Onclarity™ HPV Assay Catalog Number 444088	24 Sets
BD Viper™ XTR Neutralization Pouch Catalog Number 441354	12 Pouches
BD Viper™ LT Pipette Tips Catalog Number 440330	3,840 Tips
BD Viper™ Waste Liners Catalog Number 442968	100 Liners
BD Viper™ LT PCR Accessory Kit Catalog Number 442967	80 Pieces
BD Viper™ LT PCR Tube/Tray Kit Catalog Number 442957	20 Pieces
BD Viper™ LT System Catalog Number 442839	1 System
BD Key Card Catalog Number 443747 1000	Each

BD COR™ Reagents and Materials

Contents	Quantity
BD Onclarity™ HPV Assay Reagent Pack Catalog Number 444075	576 Tests
BD Onclarity™ HPV Assay Diluent for BD COR™ Catalog Number 444083	4 Bottles
BD Onclarity™ HPV Extraction Reagent Trough Catalog Number 444074	2 Troughs
Control Set for the BD Onclarity™ HPV Assay Catalog Number 445025	372 Sets
BD Molecular Aliquot Tubes (For use with non-manual aliquoting of BD SurePath™ or PreservCyt® specimens on the BD COR™ System) Catalog Number 444080	24 x 63 Tubes
BD COR™ Neutralization Pouch Catalog Number 444820	12 Pouches
BD Pipette Tips 1000 µL, Filtered, Conductive Catalog Number 443996	4,800 Tips
BD COR™ PX Waste Biohazard Bags Catalog Number 444816	50 Bags
BD COR™ GX Waste Biohazard Bags Catalog Number 444834	50 Bags
BD COR™ Molecular Aliquot Rack Cover Catalog Number 444745	40 Covers
BD COR™ System BD COR™ PX Instrument Catalog Number 443988 BD COR™ GX Instrument Catalog Number 443990	1 System

BD COR™ and BD Viper™ LT Reagents and Materials

Contents	Quantity
BD Pierceable Caps Catalog Number 440295	200 Caps
BD Pierceable Caps(Pink) Catalog Number 440331	200 Caps
BD Onclarity™ HPV SurePath™ Diluent Tubes (For use with BD SurePath™ specimens) Catalog Number 445329	400 Tubes
BD Onclarity™ HPV LBC Diluent Tubes (For use with PreservCyt® specimens) Catalog Number 445328	400 Tubes
BD Onclarity™ HPV Self Collection Diluent Tube Catalog Number 445416	400 Tubes

Materials Required but Not Provided

- Vortex Mixer
- Nitrile gloves
- Displacement pipettes and polypropylene aerosol-resistant tips capable of delivering 0.5 ± 0.05 mL
- 0.5% or 1.0% (v/v) sodium hypochlorite
- 3% (v/v) hydrogen peroxide
- Isopropyl alcohol
- Molecular biology-grade nuclease free water

SPECIMEN COLLECTION, TRANSPORT AND STORAGE
PRECAUTION: Handle all specimens as if they are capable of transmitting infectious agents.

Specimen Collection

BD SurePath™ or PreservCyt® Solution specimens must be collected using either an endocervical broom or a brush/spatula combination as described in the BD SurePath™ or PreservCyt® Solution product insert. Self-collected vaginal specimens should be collected using the collection devices approved for BD Onclarity HPV Assay including Copan Floqswab®. Please refer to Appendix I for vaginal self-collection instruction.

Specimen Transport and Storage

Specimen transport should comply with applicable regulations for the transport of etiological agents.

For use in the BD Onclarity™ HPV Assay, cervical specimen-collected in BD SurePath™ or PreservCyt® vials and self-collected vaginal specimens shipped dry may be stored according to the conditions listed, up to the specified timeframe

Specimen Type	2–8 °C	2–30 °C	-20 °C
Specimen in BD SurePath™ vial (after collection)	180 days	30 days	180 days
Specimen in PreservCyt® vial (after collection)	180 days	30 days	180 days
Self-collected vaginal specimen [a]	30 days	30 days	30 days
Specimen in appropriate BD Onclarity™ HPV diluent tube[a] (after dilution)	15 days	15 days	90 days
Sample in BD Onclarity™ HPV Self Collection Diluent Tube (after specimen transfer and prior to pre-warm)	15 days	15 days	15 days
Specimen in appropriate BD Onclarity™ HPV diluent tube[a], post-prewarm and capped (after dilution and prewarm)	7 days	7 days	180 days
Sample in BD Onclarity™ HPV Self Collection Diluent Tube, capped post pre-warm (after specimen transfer and sample pre-warm)	7 days	7 days	7 days
Specimen in appropriate BD Onclarity™ HPV diluent tube[a], **punctured cap** post prewarm (after specimen transfer and sample pre-warm with punctured cap)	7 days	7 days	N/A
Specimen in BD Onclarity™ HPV Self Collection Diluent Tube, **punctured cap** post prewarm (after specimen transfer and sample pre-warm with punctured cap)	7 days	7 days	N/A

[a]BD Onclarity™ HPV SurePath™ Diluent Tubes are for use with BD SurePath™ specimens. BD Onclarity™ HPV LBC Diluent Tubes are for use with PreservCyt® specimens. BD Onclarity™ HPV Self Collection Diluent Tubes are for use with self-collected vaginal specimens.

Specimen Transfer

BD COR™ System Automated Specimen Transfer

BD SurePath™ vials, PreservCyt® vials and BD Onclarity™ HPV Self Collection Diluent Tubes can be loaded directly onto the BD COR™ PX Instrument. Automated transfer into the Molecular Aliquot Tubes will occur for BD SurePath™ or PreservCyt® vials. See BD COR™ System User's Manual for instructions to load the system. If necessary for BD SurePath™ or PreservCyt® vials, follow the Specimen Transfer to BD SurePath™ Diluent Tubes or BD Onclarity™ HPV LBC Diluent Tubes.

Specimen Transfer to BD SurePath™ Diluent Tubes or BD Onclarity™ HPV LBC Diluent Tubes

NOTE: BD SurePath™ or PreservCyt® specimens may be manually transferred to appropriate BD SurePath™ Diluent Tubes or BD Onclarity™ HPV LBC Diluent Tubes off the BD COR™ System, however it is not required. See the BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube product insert for additional information.

A 0.5 mL aliquot of the LBC specimen may be manually transferred from the original LBC vial to the appropriate BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube. Wear gloves when handling the BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube and the LBC specimen vial. If gloves come in contact with the specimen, immediately change them to prevent contamination of other specimens and handle one specimen at a time for processing.

A. Manual BD SurePath™ Specimen Transfer Prior to or after Processing for the BD SurePath™ Test

NOTE: Refer to the BD PrepStain™ Slide Processor of BD Totalys™ SlidePrep product insert for instructions on removing an aliquot from the BD SurePath™ specimen vial prior to performing the BD SurePath™ liquid-based Pap test.

NOTE: Handle one specimen at a time for processing.

1. Label a BD Onclarity™ HPV SurePath™ Diluent Tube with patient identification information.

   NOTE: Do not cover the diluent tube product label barcode, as it is required for processing.

2. Remove the cap from the BD Onclarity™ HPV SurePath™ Diluent Tube.
3. In order to ensure a homogenous mixture, vortex the BD SurePath™ specimen vial for 10–20 seconds.
4. Quickly transfer 0.5 mL from the specimen vial using an aerosol-resistant tip to the BD Onclarity™ HPV SurePath™ Diluent Tube within 1 minute of vortexing.
5. Discard pipette tip.

   NOTE: A separate pipette tip must be used for each specimen.
6. Tightly recap the BD Onclarity™ HPV SurePath™ Diluent Tube.

   NOTE: Bubbles may be seen upon recapping. To prevent bubbles, the user may discard the cap removed in Step 2 and replace with a new pierceable cap.
7. Invert the BD Onclarity™ HPV SurePath™ Diluent Tube 3 to 4 times to ensure that the specimen and diluent are well mixed.
8. Load into the appropriate sample rack as indicated in the BD Viper™ LT or BD COR™ System User's Manual.

B. Automated BD SurePath™ Specimen Transfer Using BD Totalys™ MultiProcessor, Prior to or after Processing for the BD SurePath™ Test

1. Refer to the BD Totalys™ MultiProcessor User's Manual for instructions on removing an aliquot from the BD SurePath™ vial.
2. Refer to the BD Onclarity™ HPV SurePath™ Diluent Tube product insert for instructions on loading the BD Onclarity™ HPV SurePath™ Diluent Tube in the MultiProcessor for automated aliquot transfer.
3. Load into the appropriate sample rack as indicated in the BD Viper™ LT or BD COR™ System User's Manual.

C. Manual PreservCyt® Specimen Transfer Prior to or after Processing for the ThinPrep® Pap Test

NOTE: Refer to the ThinPrep® 2000 System Operator's Manual Addendum for instructions on removing an aliquot from the PreservCyt® specimen vials prior to performing the ThinPrep® test.

NOTE: Handle one specimen at a time for processing.

1. Label a BD Onclarity™ HPV LBC Diluent Tube with patient identification information.

   NOTE: Do not cover the diluent tube product label barcode, as it is required for processing.
2. Remove the cap from the BD Onclarity™ HPV LBC Diluent Tube.
3. In order to ensure a homogenous mixture, vortex the PreservCyt® specimen vial at high speed for 8–12 seconds.
4. Immediately transfer 0.5 mL from the specimen vial using an aerosol-resistant tip to the BD Onclarity™ HPV LBC Diluent Tube.
5. Discard pipette tip.

   NOTE: A separate pipette tip must be used for each specimen.
6. Tightly recap the BD Onclarity™ HPV LBC Diluent Tube.

   NOTE: Bubbles may be seen upon recapping. To prevent bubbles, the user may discard the cap removed in Step 2 and replace with a new pierceable cap.
7. Invert the BD Onclarity™ HPV LBC Diluent Tube 3 to 4 times to ensure that the specimen and diluent are well mixed.
8. Load into the appropriate sample rack as indicated in the BD Viper™ LT or BD COR™ System User's Manuals.

D. Specimen Transfer to BD Onclarity™ HPV Self Collection Diluent Tube

1. Uncap a BD Onclarity™ HPV Self Collection Diluent Tube.
2. Hold the test tube in one hand with the test tube opening facing away from your face.
3. Grip the end of the shaft with the thumb and forefinger of the other hand.
4. Align the breakpoint (red area with indent) with the edge of the tube.
5. Bend the swab shaft to an angle of 180° so that it breaks at the breakpoint. If necessary, gently turn the swab shaft until it is completely broken off. Discard the broken off part of the swab.

   NOTE: Breaking or cutting the shaft at the wrong location could result in downstream processing errors, delaying test results.
6. Tightly recap the BD Onclarity™ HPV Self Collection Diluent Tube.

   NOTE: Bubbles may be seen upon recapping. To prevent bubbles, the user may discard the cap removed in Step 1 and replace with a new pierceable cap.
7. If sample is to be processed on the BD Viper™ LT, use a vortex mixer to mix the tube at high speed for 5 seconds to ensure that the specimen and diluent are well mixed. Vortexing is not required for samples to be processed on the BD COR™ System.
8. Load into the appropriate sample rack as indicated in the BD Viper™ LT or BD COR™ System User's Manual.

QUALITY CONTROL

The HPV Positive Control will monitor for substantial reagent failure. The BD Onclarity™ HPV Negative Control monitors for reagent and/or environmental contamination.

BD COR™ System

Controls must be loaded onto the BD COR™ System according to the BD COR™ System User's Manual. One BD Onclarity™ HPV Positive and one BD Onclarity™ HPV Negative Control are included automatically with each assay sample set.

BD Viper™ LT System

One BD Onclarity™ HPV Positive and one BD Onclarity™ HPV Negative Control must be included in each assay run and for each new reagent kit lot number. Controls must be positioned according to the BD Viper™ LT System User's Manual. Additional controls may be tested according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations.

General QC Information for the BD Viper™ LT System

The location of the PCR tubes is shown in a color-coded plate layout screen on the LCD Monitor. The plus symbol (+) within the tube indicates the positive QC sample. The minus symbol (-) within the tube indicates the negative QC sample. A QC pair must be logged in for each reagent kit lot number. If QC pairs have not been properly logged in, a message box appears that prevents saving the rack and proceeding with the run until complete. Additional (optional) QC tubes for testing may be logged in if desired. These tubes are tested as regular samples and do not affect the Pass/Fail status of the run. Refer to the BD Viper™ LT System User’s Manual HPV Addendum for instructions.

NOTE: BD Onclarity™ HPV Controls must be manually hydrated prior to loading them into the BD Viper™ LT Specimen Rack.

INSTRUCTIONS FOR USE WITH THE BD COR™ SYSTEM

Quality Control Processing

1. The control set for the BD Onclarity™ HPV Assay is provided separately and loaded directly on the BD COR™ System. There is no preparation of controls necessary when run on the BD COR™ System.
2. Load a BD COR™ Control Rack with BD Onclarity™ HPV Negative Controls and BD Onclarity™ HPV Positive Controls as instructed in the BD COR™ System User's Manual.
3. Controls may be stored on the instrument until product expiration, or once rehydrated for up to 7 days prior to pre-warming. After pre-warming, the controls may be stored for up to 7 days.

   NOTE: Once controls have been rehydrated and removed from the system they can no longer be used.

Processing Procedure for All Specimens

NOTE: If previously prepared specimens are frozen, make sure they are thawed completely at room temperature and mixed by inversion prior to proceeding.

Load specimens into the appropriate rack type for the sample container type to be tested as indicated in the BD COR™ System User's Manual.

Test Procedure

NOTE: Refer to the BD COR™ System User's Manual for detailed instructions for operating and maintaining the components of the system.

NOTE: If a specimen returns an "HR" result of POS (Positive for High Risk HPV types) and extended genotype results are ordered, then a second test of the specimen is required. Refer to the Specimen Transport and Storage section to ensure that appropriately stored specimens are utilized for the second test. Discordant initial and second test results may be obtained, and both test results should be reported to an ordering physician.

INSTRUCTIONS FOR USE WITH THE BD VIPER™ SYSTEM

Quality Control Preparation

1. Uncap a BD Onclarity™ HPV Negative Control and a BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube.
2. Pour the entire contents of the BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube into the BD Onclarity™ HPV Negative Control.
3. Re-cap the rehydrated BD Onclarity™ HPV Negative Control. Re-cap and discard the empty BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube.
4. Uncap a BD Onclarity™ HPV Positive Control and a BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube.
5. Pour the entire contents of the BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube into the BD Onclarity™ HPV Positive Control.
6. Re-cap the rehydrated BD Onclarity™ HPV Positive Control. Re-cap and discard the empty BD SurePath™ Diluent Tube or BD Onclarity™ HPV LBC Diluent Tube.
7. Using the Tube Layout Report, place the rehydrated BD Onclarity™ HPV Positive and Negative Controls into the appropriate positions in the BD Viper™ LT Specimen Rack.
8. Controls are ready to be pre-warmed with the specimens. Once hydrated, unpunctured controls may be stored at 2–33 °C for up to 7 days prior to pre-warming. Post pre-warm, unpunctured controls may be stored at 2–33 °C for an additional 7 days prior to testing.

Processing Procedure for All Specimens

NOTE: If previously prepared specimens are frozen, make sure they are thawed completely at room temperature and mixed by inversion prior to proceeding.

1. Using the Tube Layout Report, place the specimens in order in the BD Viper™ LT Specimen Rack and lock into place.
2. Specimens are ready to be pre-warmed.
3. Change gloves prior to proceeding to avoid contamination.

Pre-warm Procedure

NOTE: The pre-warm procedure must be applied to all specimens to ensure that the specimen matrix is homogeneous prior to loading on the BD Viper™ LT System. Failure to pre-warm specimens may have an adverse impact on performance of the BD Onclarity™ HPV Assay and/or BD Viper™ LT System.

1. Insert the BD Viper™ LT Specimen Rack into the BD Pre-Warm Heater and select the BD Onclarity™ HPV Assay pre-warm protocol on the BD Viper™ LT Instrument.
2. The BD Pre-warm heater will automatically pre-warm the specimens and controls according to the BD Onclarity™ HPV Assay pre-warm protocol.
3. After the BD Onclarity™ HPV Assay pre-warm protocol is complete, remove the rack from the heater and load into the BD Viper™ LT instrument.
4. After pre-warming, specimens may be stored for up to 7 days at 2–30 °C without additional pre-warming prior to testing on the BD Viper™ LT System.
5. After pre-warming, controls may be stored for up to 24 hours at 2–30 °C without additional pre-warming prior to testing on the BD Viper™ LT System.

Test Procedure

NOTE: Refer to the BD Viper™ LT Instrument User's Manual for detailed instructions for operating and maintaining the components of the system.

1. The BD Onclarity™ HPV Assay may be used to run 1 to 30 specimens plus one Positive Control and one Negative Control.
2. Perform the system startup and maintenance procedures by following the instructions in the appropriate BD Viper™ LT User's Manual.
3. Access the Rack Login Display on the Viper LT instrument to log in the rack barcode and select the test type to be run.

Specimen Type	Test Type
BD SurePath™ Preservative Fluid	HPV-BD SurePath
PreservCyt® Solution	HPV ThinPrep
Vaginal Self-Collection	HPV Self Collect

4. Log in the Positive and Negative Control tubes in the first two positions (A1 and B1) as well as the BD SurePath™ Diluent Tubes, BD Onclarity™ HPV LBC Diluent Tubes, or BD Onclarity™ HPV Self Collection Diluent Tubes.
5. Log in specimen tubes by typing in or scanning each accession number/barcode in the Specimen Login window.
6. Log in Extraction tube QC information by tapping the "extraction lot" button and load extraction tubes where indicated on the Extraction Tube Lot Login display.
7. Tap the plate layout button to view the Plate Layout Display.
8. Load the PCR tubes into PCR Plate as shown on the display. PCR tubes are color-coded as follows:
   a. Blue=G1
   b. Green=G2
   c. Orange=G3

   NOTE: Use empty PCR tubes to completely fill the PCR Plates if less than a full plate of tubes is required/logged in.
9. BD SurePath™ LBC samples and Positive and Negative Control tubes must be pre-warmed prior to extraction on the BD Viper™ LT.
10. To prepare the BD Viper™ LT instrument for specimen processing and testing, follow the steps outlined in the BD Viper™ LT System User's Manual.
11. After specimens have been logged in, pre-warmed, and the BD Viper™ LT instrument has been prepared, then the run can be initiated by tapping the "start run" button on the Main status display.

INTERPRETATION OF TEST RESULTS FOR THE BD VIPER™ SYSTEM

The BD Onclarity™ HPV Assay uses the real-time polymerase chain reaction to detect the presence of Human Papillomavirus (HPV) in clinical specimens. All calculations are performed automatically by the BD Viper™ LT software. The presence or absence of clinically relevant HPV DNA is determined by the PCR cycle (Ct) at which the signal crosses a pre-established threshold. The assay will extract, amplify and detect a fragment of the human beta globin gene as an internal control to assess specimen processing, extraction, amplification, and to indicate the presence of PCR inhibitors. If the HPV-specific signal is greater than a cycle threshold, the internal control is utilized by the algorithm in the interpretation of the result. If the HPV-specific signal is less than or equal to a cycle threshold, the internal control is ignored by the algorithm. The BD SurePath™ or PreservCyt® specimen types as well as the different high risk HPV genotypes, have different Ct threshold cutoff values.

For HPV specimens, an "HR" result (the combination of all genotypes) appears on the Tube Results Report. A positive symbol in this column indicates that the HPV assay detected one or more genotypes for unmasking.

Specific genotypes and combined genotypes appear in columns. If the results for a genotype have been unmasked, those results are reported as explained below. If any genotype results have not been configured for automatic unmasking, those results are masked by a "key" icon.

The instrument can be configured to unmask/report specific genotypes when the run is complete. See the BD Viper™ LT System User's Manual HPV Addendum for instructions on authorizing automatic genotype reporting.

If assay control results are not as expected, patient results are not reported. See the Quality Control section for expected control values. Reported results are determined as follows.

Table 1: Interpretation of High Risk HPV Genotype HPV Test Results for the BD Onclarity™ HPV Assay

High Risk HPV Result	Interpretation	Result	Report
HR ⊕←	Positive for High Risk HPV types	HPV HR Positive	HPV DNA detected by PCR.
HR ⊖	Negative for High Risk HPV types	HPV HR Negative	HPV DNA not detected by PCR.
~~IC~~	HPV DNA, if present, is not detectable	Internal Control Failure	Internal Control Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
~~ET~~	HPV DNA, if present, is not detectable	Extraction Transfer Failure	Extraction Transfer Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.

	HPV DNA, if present, is not detectable.	Liquid Level Failure	Liquid Level Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
	HPV DNA, if present, is not detectable.	Error	Error. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.

[a] BD Onclarity™ HPV SurePath™ Diluent Tubes are for use with BD SurePath™ specimens. BD Onclarity™ HPV LBC Diluent Tubes are for use with PreservCyt® specimens. BD Onclarity™ HPV Self Collection Diluent Tubes are for use with self-collected vaginal specimens.

Table 2: Interpretation of Specific HPV Genotype Test Results for the BD Onclarity™ HPV Assay

HPV Genotype Result	Interpretation	Result
16 ⊕←	Positive for HPV type 16	HPV type 16 Positive
16 ⊖	Negative for HPV type 16	HPV type 16 Negative
18 ⊕←	Positive for HPV type 18	HPV type 18 Positive
18 ⊖	Negative for HPV type 18	HPV type 18 Negative
45 ⊕←	Positive for HPV type 45	HPV type 45 Positive
45 ⊖	Negative for HPV type 45	HPV type 45 Negative
P1 ⊕←	Positive for HPV types 33 and/or 58	HPV type 33 and/or 58 Positive
P1 ⊖	Negative for HPV types 33 and/or 58	HPV type 33 and/or 58 Negative
31 ⊕←	Positive for HPV type 31	HPV type 31 Positive
31 ⊖	Negative for HPV type 31	HPV type 31 Negative
P2 ⊕←	Positive for HPV types 56, 59 and/or 66	HPV type 56, 59 and/or 66 Positive
P2 ⊖	Negative for HPV types 56, 59 and/or 66	HPV type 56, 59 and/or 66 Negative
51 ⊕←	Positive for HPV type 51	HPV type 51 Positive
51 ⊖	Negative for HPV type 51	HPV type 51 Negative
52 ⊕←	Positive for HPV type 52	HPV type 52 Positive
52 ⊖	Negative for HPV type 52	HPV type 52 Negative
P3 ⊕←	Positive for HPV types 35, 39 and/or 68	HPV type 35, 39 and/or 68 Positive
P3 ⊖	Negative for HPV types 35, 39 and/or 68	HPV type 35, 39 and/or 68 Negative
	HPV genotype result is available for purchase	Genotype result is locked
- -	HPV genotype result is not available for purchase	HPV Negative result, Internal Control failure, Liquid Level failure or Extraction Transfer failure.

See the BD Viper™ LT System User's Manual HPV Addendum for additional information on results reporting.

Interpretation of Quality Control Results

If assay control results are not as expected, patient results are not reported. If either of the controls does not provide the expected result, repeat the entire run using a new set of controls. If either of the controls is consistently invalid, contact BD Technical Service and Support for technical assistance.

Table 3: Interpretation of Quality Control Results

Control Type	Tube Result Report Symbol	QC Disposition
BD Onclarity™ HPV Positive Control	OK	QC Pass
BD Onclarity™ HPV Positive Control	OK	QC Failure
BD Onclarity™ HPV Positive Control	INT	QC Failure
BD Onclarity™ HPV Positive Control		QC Failure
BD Onclarity™ HPV Negative Control	OK	QC Pass
BD Onclarity™ HPV Negative Control	OK	QC Failure
BD Onclarity™ HPV Negative Control	INT	QC Failure
BD Onclarity™ HPV Negative Control		QC Failure

Refer to the Interpretation of Test Results for a description of Tube Result Report symbols.

INTERPRETATION OF TEST RESULTS FOR BD COR™

The BD Onclarity™ HPV Assay uses the real-time polymerase chain reaction to detect the presence of Human Papillomavirus (HPV) in clinical specimens. All calculations are performed automatically by the BD COR™ System software. The presence or absence of clinically relevant HPV DNA is determined by the PCR cycle (Ct) at which the signal crosses a pre-established threshold. The assay will extract, amplify and detect a fragment of the human beta globin gene as an internal control to assess specimen processing, extraction, amplification, and to indicate the presence of PCR inhibitors. If the HPV-specific signal is greater than a cycle threshold, the internal control is utilized by the algorithm in the interpretation of the result. If the HPV-specific signal is less than or equal to a cycle threshold, the internal control is ignored by the algorithm.

For HPV specimens, an "HR" result (the combination of all genotypes) appears on the Tube Results Report. A positive result in this column indicates that the HPV assay detected one or more genotypes. Further results descriptions are outlined in Table 4. The "Positive Genotypes" column displays the positive genotype(s) detected.

Specific and combined genotypes appear in columns as displayed in Table 5. Genotype results will remain blank if your system is configured for "HR" result only.

If assay control results are not as expected, patient results are not reported. See the Quality Control section for expected control values. Reported results are determined as follows.

Table 4: Interpretation of High Risk HPV Genotype Test Results for the BD Onclarity™ HPV Assay

High Risk HPV Result	Interpretation	Result	Report
POS	Positive for High Risk HPV types	HPV HR Positive	HPV DNA detected by PCR.
NEG	Negative for High Risk HPV types	HPV HR Negative	HPV DNA not detected by PCR.
ICF	HPV DNA, if present, is not detectable	Internal Control Failure	Internal Control Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
ETF	HPV DNA, if present, is not detectable	Extraction Transfer Failure	Extraction Transfer Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
LLF	HPV DNA, if present, is not detectable.	Liquid Level Failure	Liquid Level Failure. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
INC	Aborted sample set or sample	Incomplete	Sample processing is incomplete. No results are available for controls or samples. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.
QCF	Positive or Negative Control Failure	Quality Control Failure	No results are available for samples. Repeat test from appropriate BD Onclarity™ HPV diluent tube[a] or obtain another specimen for testing.

[a] BD Onclarity™ HPV SurePath™ Diluent Tubes are for use with BD SurePath™ specimens. BD Onclarity™ HPV LBC Diluent Tubes are for use with PreservCyt® specimens. BD Onclarity™ HPV Self Collection Diluent Tubes are for use with vaginal self-collection specimens.

Table 5: Interpretation of Specific HPV Genotype Test Results for the BD Onclarity™ HPV Assay

HPV Genotype Result	Interpretation	Result
16 POS	Positive for HPV type 16	HPV type 16 Positive
16 NEG	Negative for HPV type 16	HPV type 16 Negative
18 POS	Positive for HPV type 18	HPV type 18 Positive
18 NEG	Negative for HPV type 18	HPV type 18 Negative
45 POS	Positive for HPV type 45	HPV type 45 Positive
45 NEG	Negative for HPV type 45	HPV type 45 Negative
P1 POS	Positive for HPV types 33 and/or 58	HPV types 33 and/or 58 Positive
P1 NEG	Negative for HPV types 33 and/or 58	HPV types 33 and/or 58 Negative
31 POS	Positive for HPV type 31	HPV type 31 Positive
31 NEG	Negative for HPV type 31	HPV type 31 Negative
P2 POS	Positive for HPV types 56, 59, and/or 66	HPV types 56, 59, and/or 66 Positive
P2 NEG	Negative for HPV types 56, 59, and/or 66	HPV types 56, 59, and/or 66 Negative
51 POS	Positive for HPV type 51	HPV type 51 Positive
51 NEG	Negative for HPV type 51	HPV type 51 Negative
52 POS	Positive for HPV type 52	HPV type 52 Positive
52 NEG	Negative for HPV type 52	HPV type 52 Negative
P3 POS	Positive for HPV types 35, 39, and/or 68	HPV types 35, 39, and/or 68 Positive
P3 NEG	Negative for HPV types 35, 39, and/or 68	HPV types 35, 39, and/or 68 Negative
ICF	HPV DNA, if present, is not detectable	Internal Control Failure
- -	No result reported	Liquid Level failure or Extraction Transfer failure

Interpretation of Quality Control Results

If assay control results are not as expected, patient results are not reported. If either of the controls does not provide the expected result, repeat the entire run (a new set of controls will be assigned to the sample set when re-processed by the BD COR™ System). If either of the controls is consistently invalid, contact BD Technical Service and Support for technical assistance.

Table 6: Interpretation of Quality Control Results

Control Type	Tube Result Report	QC Disposition
BD Onclarity™ HPV Positive Control	PASS	QC Pass
BD Onclarity™ HPV Positive Control	FAIL	QC Failure
BD Onclarity™ HPV Positive Control	ETF	QC Failure
BD Onclarity™ HPV Positive Control	LLF	QC Failure
BD Onclarity™ HPV Positive Control	INC	QC Failure
BD Onclarity™ HPV Negative Control	PASS	QC Pass
BD Onclarity™ HPV Negative Control	FAIL	QC Failure
BD Onclarity™ HPV Negative Control	ETF	QC Failure
BD Onclarity™ HPV Negative Control	LLF	QC Failure
BD Onclarity™ HPV Negative Control	INC	QC Failure

Refer to the Interpretation of Test Results for a description of Tube Result Report acronyms.

Monitoring for the Presence of DNA Contamination

Consult the BD Viper™ LT System User's Manual or BD COR™ System User's Manual for more information on Environmental Monitoring and Cleaning Procedures. If a contamination event does not resolve, contact BD Technical Service and Support for additional information.

LIMITATIONS

1. The BD Onclarity™ HPV Assay detects DNA of the high-risk types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, and does not detect DNA of HPV low-risk types (e.g., 6, 11, 42, 43, 44) since there is no clinical utility for testing of low-risk HPV types for cervical cancer screening.[17]
2. The BD Onclarity™ HPV Assay is not recommended for evaluation of suspected sexual abuse.
3. Optimal performance of the test requires adequate specimen collection, transport, storage and processing. Follow the procedures in this product insert and the BD Viper™ LT or the BD COR™ System User's Manual.
4. A negative test result does not exclude the possibility of infection because test results may be affected by improper specimen collection, technical error, specimen mix-up, or the number of organisms in the specimen which may be below the limit of detection of the test.
5. The BD Onclarity™ HPV Assay provides qualitative results. Any reported Ct value should only be used for the purposes of laboratory quality control trending and research. The Ct value is not to be used to overrule or change the reported test results. The instrument and assay shall be used in a manner consistent with applicable labeling.
6. Use of the BD Onclarity™ HPV Assay is limited to personnel who have been trained in the assay procedure and the BD Viper™ LT or the BD COR™ System.
7. The BD Onclarity™ HPV Assay has been validated for use with cervical specimens collected by a clinician using an endocervical brush/spatula combination or broom and placed in a BD SurePath™ Preservative Fluid Collection Vial or PreservCyt® vial. BD SurePath™ cell pellets obtained after processing on the BD PrepStain™ Slide Processor have not been evaluated with the BD Onclarity™ HPV Assay.
8. Use only validated self-collection devices.
9. Cervical Specimens often show visibly detectable levels of blood as a pink or light brown coloration. If blood concentrations exceed 4% (v/v) in BD SurePath™ Preservative fluid and 5% (v/v) in PreservCyt® prior to dilution in the BD Onclarity™ HPV SurePath™ Diluent Tube or BD Onclarity™ HPV Diluent Tube, there is a likelihood of obtaining a false-negative HPV result. Self-collected vaginal specimens may show visibly detectable levels of blood as a pink or light brown coloration. If blood concentrations exceed 1% (v/v) after dilution in the BD Onclarity™ HPV Self-Collection Diluent Tube, there is a likelihood of obtaining a false-negative HPV result.
10. The following may interfere with the performance of the assay in clinician collected cervical specimens when present at concentrations greater than those specified (see table 83 for complete information): Mucin, Zovirax® (Acyclovir) Cream, Monistat (miconazole), and clindamycin vaginal cream. The following may interfere with the performance of the assay in self-collected vaginal specimens when present at concentrations greater than those specific (see table 83 for complete information: Preparation H, Summer's Eve Deodorant, KY Jelly Personal Lubricant, Bovine mucin, Replens, Nonoxynol-9 Contraceptive Gel.
11. The effects of other potential variables such as vaginal discharge, use of tampons, douching, etc. and specimen collection variables have not been evaluated.
12. The BD Onclarity™ HPV Assay was not evaluated in women with acetic acid, iodine, spermicide, douche, or anti-fungal medications applied to the cervical area within 24 hours of specimen collection in the BD SurePath™ clinical study. In the PreservCyt® study, the BD Onclarity™ HPV Assay was not evaluated in women treated with acetic acid.
13. 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.
14. Prevalence of HPV infection in a population may affect predictive values. Positive predictive values decrease when testing populations with low prevalence or individuals with no risk of infection.

15. A negative high-risk HPV result does not exclude the possibility of future or underlying CIN2-3 or cancer but indicates a low likelihood of CIN2-3 or cancer.
16. Infection with HPV is not an indicator of cytologic HSIL or underlying high-grade CIN, nor does it imply that CIN2-3 or cancer will develop. Most women infected with one or more high-risk HPV types do not develop CIN2-3 or cancer. Women who are positive for high risk HPV by the BD Onclarity HPV™ Assay from a clinician-collected cervical specimen or a self-collected vaginal specimen should follow up with a clinician to determine management.
17. Human beta globin amplification and detection is included in the BD Onclarity™ HPV Assay to differentiate HPV negative specimens from those that do not exhibit HPV signal due to insufficient cell mass in the specimen. An HPV negative specimen must have a valid beta globin signal within a pre-defined range to generate a negative result on the BD Viper™ LT and BD COR™ Systems. The beta globin control does not differentiate between targeted (cervical) and non-targeted nucleated cell types.
18. A 0.7% cross-contamination rate was observed when BD SurePath™ specimens were aliquoted using the BD Totalys™ MultiProcessor.

PERFORMANCE CHARACTERISTICS OF CERVICAL SPECIMENS IN BD SUREPATH™

BD SurePath™ Clinical Study

A total of 33,858 women were enrolled in the study across 31 collection sites, and cervical samples were tested at 4 testing sites in the US. Of these, 33,634 (99.3%) women were eligible to participate in the study. Eligible women were ≥21 years, provided informed consent, satisfied study inclusion/exclusion criteria, had not enrolled in a cervical disease diagnostic trial since 2007, and had not withdrawn authorization before undergoing study procedures.

The median age of the eligible women was 37, with 28.0% of women in age group 21–29 years, 28.3 % in age group 30–39, and 43.7% of women in age group ≥40 years. A total of 90.6% of women had NILM cytology, and 5.8% of women had ASC-US cytology, 3.3% of women had >ASC-US cytology, and only 0.2% of women had unsatisfactory cytology.

The percent of final non-reportable BD Onclarity™ assay results was 0.24% (79/33,570). Not included in this calculation are specimens that did not yield a result (64/33,634) due to specimen labeling, processing and volume issues.

A total of 1,960 ASC-US women ≥21 years were enrolled in the study of which 1,953 were evaluable; evaluable women had an ASC-US cytology result and valid results from the BD Onclarity™ HPV Assay.

A total of 22,383 NILM women ≥30 years were enrolled in the study of which 22,284 were evaluable; evaluable women had a NILM cytology result and valid results from the BD Onclarity™ HPV Assay.

A total of 29,633 women ≥25 years were enrolled in the study of which 29,513 were evaluable; evaluable women had valid cytology and BD Onclarity™ HPV Assay results.

Table 7 shows HPV positivity of the BD Onclarity™ HPV Assay by testing site and study population. HPV prevalence was 39.1% in the ASC-US ≥21 years) population, 7.9% in the NILM (≥30 years) population and 12.7% in the Primary Screening ≥25 years) population.

Table 7: Summary of HPV Positivity of the BD Onclarity™ HPV Assay by Testing Sites and Study Population

	BD Onclarity™ HPV HR Positivity Rate		
Testing Site	**ASC-US ≥21 years)**	**NILM ≥30 years)**	**Primary Screening ≥25 years)**
1	39.5% (234/592)	9.3% (644/6,921)	14.2% (1,306/9,167)
2	36.7% (126/343)	7.4% (369/4,962)	12.0% (757/6,300)
3	33.3% (259/778)	7.1% (372/5,219)	12.7% (941/7,434)
4	60.0% (144/240)	7.3% (376/5,182)	11.3% (744/6,612)
Total	39.1% (763/1,953)	7.9% (1,761/22,284)	12.7% (3,748/29,513)

Table 8 shows HPV prevalence by the BD Onclarity™ HPV Assay by age and study population. HPV prevalence decreased with age in each study population.

Table 8: Summary of HPV Positivity of the BD Onclarity™ HPV Assay by Age and Study Population

	BD Onclarity™ HPV HR Positivity Rate		
Age Group	**ASC-US ≥21 years)**	**NILM ≥30 years)**	**Screening ≥25 years)**
21–29	54.6% (398/729)	N/A	22.4% (1,216/5,432)
30–39	39.2% (204/521)	10.3% (889/8,663)	13.8% (1,310/9,477)
≥40	22.9% (161/703)	6.4% (872/13,621)	8.4% (1,222/14,604)
Total	39.1% (763/1,953)	7.4% (1,761/22,284)	12.7% (3,748/29,513)

The BD Onclarity™ HPV Assay results, stratified into three groups by age is outlined in Table 9 for the ASC-US population ≥21 years), in Table 10 for the NILM population (≥30 years) and in Table 11 for the Screening population ≥25 years).

In all populations, the other 11 HPV HR positive results were more frequent than HPV16, HPV18 and HPV45 positive results in general and within age groups. HPV prevalence for each category decreases with age in all three populations.

NOTE: In Tables 9–11, women with mixed genotype HPV infections were counted for each of their positive HPV genotypes.

Table 9: BD Onclarity™ HPV Assay Result by Age Group for ASC-US ≥21 Years) Population

BD Onclarity™ HPV Assay Result					
Age Group	**HPV16+**	**HPV18+**	**HPV45+**	**11 Other HPV HR+**	**HPV-**
21–29	10.6% (77/729)	3.4% (25/729)	3.2% (23/729)	45.8% (334/729)	45.4% (331/729)
30–39	7.7% (40/521)	2.5% (13/521)	2.1% (11/521)	31.1% (162/521)	60.8% (317/521)
≥40	3.8% (27/703)	1.4% (10/703)	1.8% (13/703)	18.9% (133/703)	77.1% (542/703)
Total	7.4% (144/1,953)	2.5% (48/1,953)	2.4% (47/1,953)	32.2% (629/1,953)	60.9% (1,190/1,953)

Table 10: BD Onclarity™ HPV Assay Result by Age Group for NILM ≥30 Years) Population

BD Onclarity™ HPV Assay Result					
Age Group	**HPV16+**	**HPV18+**	**HPV45+**	**11 Other HPV HR+**	**HPV-**
30–39	2.0% (173/8,663)	0.5% (45/8,663)	0.8% (68/8,663)	7.7% (671/8,663)	89.7% (7,774/8,663)
≥40	1.2% (157/13,621)	0.4% (53/13,621)	0.4% (56/13,621)	4.9% (671/13,621)	93.6% (12,749/13,621)
Total	1.5% (330/22,284)	0.4% (98/22,284)	0.6% (124/22,284)	6.0% (1,342/22,284)	92.1% (20,523/22,284)

Table 11: BD Onclarity™ HPV Assay Result by Age Group for Screening (≥25 Years) Population

BD Onclarity™ HPV Assay Result				
Age Group	**HPV16+**	**HPV18+**	**12 Other HPV HR+**	**HPV-**
25–29	4.5% (246/5,432)	1.2% (63/5,432)	18.9% (1,025/5,432)	77.6% (4,216/5,432)
30–39	2.9% (274/9,477)	0.8% (78/9,477)	11.2% (1,063/9,477)	86.2% (8,167/9,477)
≥40	1.5% (223/14,604)	0.6% (84/14,604)	6.9% (1,010/14,604)	91.6% (13,382/14,604)
Total	2.5% (743/29,513)	0.8% (225/29,513)	10.5% (3,098/29,513)	87.3% (25,765/29,513)

CLINICAL PERFORMANCE OF CERVICAL SPECIMENS IN BD SUREPATH™

Baseline Phase

A multicenter, prospective study was conducted to evaluate the performance of the BD Onclarity™ HPV Assay as a triage test to stratify women with ASC-US cytology results for referral to colposcopy, as an adjunctive test to cervical cytology to guide management decisions, and also as a primary cervical cancer screening test. The study consisted of a Baseline Phase and a 3 year Follow-up Phase. In the Baseline Phase, women ≥21 years old undergoing routine cervical cancer screening were invited to participate in the study. In total, 33,858 women were enrolled from August 2013 to June 2015 at 31 clinical sites in the Baseline Phase. Following written informed consent, demographic information and gynecologic histories were obtained. Two cervical specimens were collected from each woman and preserved in liquid based cytology (LBC) media. Cytology testing was performed on the first vial collected, at three different laboratories, and results were classified according to the 2001 Bethesda System criteria. HPV testing with the BD Onclarity™ HPV Assay was performed using the BD Viper™ LT System at one of four laboratories, from a pre-cytology aliquot of the first vial collected and performance results are shown below.

The second cervical specimen collected was tested with the BD Onclarity™ HPV Assay and an FDA-approved HPV test, according to the manufacturer's instructions.

Those women ≥21 years old with ≥ASC-US cytology and women ≥25 years old with unsatisfactory cytology were invited to undergo colposcopy. In addition, all women ≥25 years old with a positive high-risk HPV test result (positive by the BD Onclarity™ HPV Assay and/or the FDA-approved HPV test), as well as a randomly selected subset of women (approximately 5%) with NILM (negative for intraepithelial lesions or malignancy) cytology and negative high-risk HPV DNA (by both the BD Onclarity™ HPV Assay and the FDA-approved HPV DNA test), were invited to proceed to colposcopy. In order to avoid observation bias, both study participants and colposcopists were blinded to all HPV tests and cytology results until after the colposcopy was completed.

Colposcopy was conducted according to a standardized protocol in which biopsies were obtained on all visible lesions or acetowhite areas; endocervical curettage was performed in all patients, and a single random cervical biopsy at the squamocolumnar junction was obtained if no lesions or acetowhite areas were visible. All biopsies were examined by a Central Pathology Review Panel (CPR) consisting of three expert pathologists. Discordant results were adjudicated according to a pre-defined protocol. For all analyses, the clinical performance of the BD Onclarity™ HPV Assay was measured against CPR histopathology results using both conventional H&E staining and H&E with p-16 assisted immunohistochemical staining, in alignment with the consensus recommendations of The 2012 Lower Anogenital Squamous Terminology Standardization Project for HPV- Associated Lesions (LAST).[18] Clinical performance for the BD Onclarity™ HPV Assay is expressed using p-16- assisted H&E for purposes of consistency, especially in the histopathologic category of CIN2. Overall, there are no statistically significant differences in clinical performance of the BD Onclarity™ HPV Assay with both histology reference methods for each of the three intended use populations.

Follow-Up Phase

All women who were biopsied at baseline and not treated and approximately 10% of NILM women (≥25 years) with HPV HR negative results and no baseline biopsy or treatment were invited to participate in a 3 year longitudinal study. Approximately 8,900 women were eligible for the follow-up study. All women invited into this 3 year longitudinal study undergo annual visits for cervical sampling for cytology and HPV DNA testing with the BD Onclarity™ HPV Assay. All women with ≥ASC-US are invited to proceed to colposcopy. Colposcopy and biopsies are performed in a standardized manner as described above. All cervical tissue is examined by the Central Pathology Review Panel. An exit colposcopy with biopsy and endocervical curettage (ECC) is collected from all women in Year 3. All women, regardless of histology result, will be followed through the duration of the study with the exception of those who receive treatment procedures; they will exit the study.

STUDY DESIGNS

Study Design to Demonstrate Clinical Sensitivity and Specificity for Screening Patients with ASC-US Cytology Results to Determine the Need for Referral to Colposcopy

Those women ≥21 years old with ASC-US cytology, regardless of HPV results, were invited to undergo colposcopy. Both study participants and colposcopists were blinded to all HPV tests and cytology results until after the colposcopy was completed. Colposcopy was conducted according to a standardized protocol and all biopsies were read by the CPR, as described above. The clinical performance of the BD Onclarity™ HPV Assay was measured against histology results of ≥CIN2 and ≥CIN3 by CPR.

Study Design to Demonstrate Clinical Performance of the HPV Assay as an Adjunct to Cervical Cytology in Women ≥30 Years

All women ≥30 years old with NILM cytology and a positive result for HR HPV DNA (BD Onclarity™ HPV Assay and/or the FDA approved HPV test), as well as a randomly selected subset of women (approximately 5%) with NILM cytology/negative HR HPV DNA (BD Onclarity™ HPV Assay and the FDA approved HPV test), were invited to proceed to colposcopy. The analyses were performed for histology results of ≥CIN2 and ≥CIN3 by CPR.

Study Design to Demonstrate Clinical Performance of the HPV Assay as a First-Line Primary Test for Cervical Cancer Screening

Women ≥25 years with ≥ASC-US cytology and/or a positive result for HR HPV DNA (BD Onclarity™ HPV Assay and/or the FDA approved HPV test) were invited to proceed to colposcopy in the baseline phase. All women who were invited to colposcopy in the baseline phase and a portion (approximately 10%) of women ≥25 years with NILM cytology and HR HPV negative results, who did not have baseline biopsy and were not treated are eligible to participate in a 3 year longitudinal study for the BD Onclarity™ HPV Assay. All women with follow-up cytology ≥ASC-US are invited to proceed to colposcopy; colposcopy and biopsies are performed in a standardized manner as describe above. All cervical biopsies are examined by the CPR. Exit colposcopy with biopsy and ECC are performed on all women. The objectives of the follow-up phase of the study are to determine the 3-year risk (cumulative incidence rates, CIRs) of developing ≥CIN2 and ≥CIN3 in different study sub-populations defined by baseline HPV status and cytology. Baseline data were evaluated for all evaluable women 25 years and older. The clinical performance of the primary screening indication for the BD Onclarity™ HPV Assay was measured against histology results of ≥CIN2 and ≥CIN3 by CPR and compared to the performance of cytology alone.

EVALUATION OF CO-INFECTIONS AND HIERARCHAL RISK FROM BD ONCLARITY™ HPV ASSAY CLINICAL STUDIES

The BD Onclarity™ HPV Assay result is categorized hierarchically based on genotype risks in the relevant tables below (e.g., Table 18) in the order of HPV 16, 18, 45, 31, 33/58, 52, 51, 35/39/68, 56/59/66, and HPV negative for assessing risk from co-infections (i.e., risk is categorized by the risk of the highest risk genotype); e.g., women positive for HPV16 and HPV18 are categorized as HPV16. The order of genotypes is based in part on CIN3+ risk from data collected in this study as well as data from other published studies evaluating the attributable fraction of each genotype to CIN2, CIN3, and cervical cancer. In particular, the placement of HPV45 prior to the 11 other genotypes is in alignment with studies[8,20] indicating its high prevalence relative to the 11 other genotypes when using cervical cancer as the endpoint (particularly adenocarcinoma), as opposed to an endpoint of CIN2+/CIN3+. The underrepresentation of HPV45 in results based on CIN2+/CIN3+ is likely due to its rapid clinical progression to cancer.

The hierarchical ordering used in relevant tables below does not strictly represent the results of studies with the BD Onclarity™ HPV Assay. Ordering of risk by genotype may differ across published papers or in professional recommendations reflecting the specific clinical/pathological endpoint(s) used for analysis, grouping of genotypes (e.g., certain low risk genotypes may not be individually identified in all studies), the number of proposed risk strata, increased understanding of the clinical course infection associated with different HPV genotypes, as well as other factors such as vaccination status. Application of the risk estimates in the table below to clinical care should always occur in the context of a broad understanding of the risks associated with infection by HPV genotype, and recommendations from professional guidelines.

PERFORMANCE CHARACTERISTICS IN THE ASC-US POPULATION (≥21 YEARS)

A total of 1,960 ASC-US women ≥21 years were enrolled in the study of which 1,953 were evaluable. Evaluable women had an ASC-US cytology result and valid results from the BD Onclarity™ HPV Assay. Of the 1,953 evaluable ASC-US women, 1,607 completed the colposcopy procedure with a valid CPR result. The results of the BD Onclarity™ HPV Assay reported as (HPV HR) Positive or (HPV HR) Negative together with the CPR diagnosis are presented in Table 12. Of the 1,607 ASC-US women with a valid CPR panel diagnosis and BD Onclarity™ HPV result, 105 women were ≥CIN2 (prevalence of 6.5%), and 35 women were ≥CIN3 (prevalence of 2.2%).

Table 12: Results of the BD Onclarity™ HPV Assay and Central Pathology Review Panel Diagnosis in the ASC-US Population

	Central Pathology Review Panel Diagnosis					
BD Onclarity™ HPV Assay Result	**NEG**	**CIN1**	**CIN2**	**≥CIN3**	**Unknown Disease Status**	**Total**
Positive	423	116	58	32	134	763
Negative	888	75	12	3	212	1,190
Invalid/Missing[a]	6	0	0	0	1	7
Total	1,317	191	70	35	347[b]	1,960

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results

[b] 341 women did not return or were no longer eligible for a colposcopy procedure. Three women had unsatisfactory histology results and three women had biopsy specimen collection errors.

The performance of the BD Onclarity™ HPV Assay in detecting high-grade cervical disease (≥CIN2 and ≥CIN3 is presented in Table 13. The sensitivity and the specificity of the test for detecting ≥CIN2 histology were 85.7% (90/105) and 64.1% (963/1,502), respectively. The positive likelihood ratio (PLR) was estimated as 2.4, which indicates a positive BD Onclarity™ HPV Assay result is 2.4 times more likely in women with ≥CIN2 than in women with <CIN2. The negative likelihood ratio (NLR) was estimated as 0.2, which indicates that a negative BD Onclarity™ HPV Assay result is 5 (1/0.2) times more likely in women with <CIN2 than in women with ≥CIN2.

The sensitivity and specificity of the BD Onclarity™ HPV Assay for detecting ≥CIN3 histology were 91.4% (32/35) and 62.0% (975/1,572), respectively.

Table 13: Performance of the BD Onclarity™ HPV Assay in the ASC-US Population (≥21 Years)

Performance	**≥CIN2**	**≥CIN3**
	Central Pathology Review Panel Diagnosis	
Sensitivity (%) (95% CI)	85.7 90/105[a] (77.8, 91.1)	91.4 32/35[b] (77.6, 97.0)
Specificity (%) (95% CI)	64.1 963/1,502 (61.7, 66.5)	62.0 975/1,572 (59.6, 64.4)
PPV (%) (95% CI)	14.3 90/629 (13.0, 15.5)	5.1 32/629 (4.3, 5.6)
NPV (%) (95% CI)	98.5 963/978 (97.6, 99.0)	99.7 975/978 (99.2, 99.9)
PLR (95% CI)	2.39 (2.13, 2.63)	2.41 (2.03, 2.64)
NLR (95% CI)	0.22 (0.14, 0.35)	0.14 (0.05, 0.36)
Disease Prevalence (%)	6.5 105/1,607	2.2 35/1,607

[a] 12 of the 15 BD Onclarity™ HPV Assay negative, ≥CIN2 subjects were also negative by the FDA approved HPV test. Three of the subjects were positive by the FDA approved HPV test and were identified as low risk HPV types 67 and/or 82 by a sequencing method.

[b] 2 of the 3 BD Onclarity™ HPV Assay negative ≥CIN3 subjects were also negative by the FDA approved HPV test. One subject was positive by the FDA approved HPV test and was identified as low risk HPV type 67 by a sequencing method.

The performance of the BD Onclarity™ HPV Assay in detecting high-grade cervical disease ≥CIN2 and ≥CIN3) and the performance of the FDA approved HPV test is presented in Table 14. The sensitivity for detecting ≥CIN2 histology was 85.7% (90/105) for the BD Onclarity™ HPV Assay and 82.9% (87/105) for the FDA approved HPV test. The specificity for detecting ≥CIN2 histology was 64.1% (959/1,496) for the BD Onclarity™ HPV Assay and 61.4% (919/1,496) for the FDA approved HPV test.

The sensitivity for detecting ≥CIN3 histology was 91.4% (32/35) for the BD Onclarity™ HPV Assay and 85.7% (30/35) for the FDA approved HPV test. The specificity for detecting ≥CIN3 histology was 62.0% (971/1,566) for the BD Onclarity™ HPV Assay and 59.5% (932/1,566) for the FDA approved HPV test.

Table 14: Comparison of the Performance of the BD Onclarity™ HPV Assay and an FDA Approved HPV Test in the ASC-US Population (≥21 Years)

Performance Metrics	BD Onclarity™ HPV Assay		FDA Approved HPV Test	
	Estimate	95% CI	Estimate	95% CI
≥CIN2; Prevalence 6.6% (105/1,601)				
Sensitivity (%)	85.7 (90/105)	(77.8, 91.1)	82.9 (87/105)	(74.5, 88.9)
Specificity (%)	64.1 (959/1,496)	(61.6, 66.5)	61.4 (919/1,496)	(58.9, 63.9)
PPV (%)	14.4 (90/627)	(13.0, 15.6)	13.1 (87/664)	(11.8, 14.3)
NPV (%)	98.5 (959/974)	(97.6, 99.0)	98.1 (919/937)	(97.2, 98.7)
PLR	2.39	(2.13, 2.63)	2.15	(1.90, 2.37)
NLR	0.22	(0.14, 0.35)	0.28	(0.18, 0.42)
≥CIN3; Prevalence 2.2% (35/1,601)				
Sensitivity (%)	91.4 (32/35)	(77.6, 97.0)	85.7 (30/35)	(70.6, 93.7)
Specificity (%)	62.0 (971/1,566)	(59.6, 64.4)	59.5 (932/1,566)	(57.1, 61.9)
PPV (%)	5.1 (32/627)	(4.3, 5.6)	4.5 (30/664)	(3.7, 5.0)
NPV (%)	99.7 (971/974)	(99.2, 99.9)	99.5 (932/937)	(98.9, 99.8)
PLR	2.41	(2.03, 2.64)	2.12	(1.73, 2.37)
NLR	0.14	(0.05, 0.36)	0.24	(0.11, 0.49)

NOTE: This table is a paired analysis of specimens with a valid BD Onclarity™ HPV Assay and FDA approved HPV test result. Six women (<CIN2) with a BD Onclarity™ result but no FDA approved HPV test result were excluded from this analysis.

The performance of the BD Onclarity™ HPV Assay and the FDA approved HPV test for detecting ≥CIN2 and ≥CIN3 evaluated by age group is presented in Table 15. The sensitivity of the BD Onclarity™ HPV Assay and the FDA approved HPV test ranged from 68.8% to 93.6% for ≥CIN2. The specificity of the BD Onclarity™ HPV Assay ranged from 49.5% to 78.2% and from 45.9% to 76.3% for the FDA approved HPV test.

The sensitivity of the BD Onclarity™ HPV Assay for detecting ≥CIN3 histology ranged from 85.7% to 92.9% and from 71.4% to 92.9% for the FDA approved HPV test. The specificity of the BD Onclarity™ HPV Assay ranged from 47.0% to 77.0% and from 43.7% to 75.6% for the FDA approved HPV test.

Table 15: Performance of the BD Onclarity™ HPV Assay and an FDA Approved HPV Test by Age Group in the ASC-US (≥21 Years Population

Performance Metrics	BD HPV	FDA Approved HPV Test	BD HPV	FDA Approved HPV Test	BD HPV	FDA Approved HPV Test
	21–29 Years		30–39 Years		≥40 Years	
≥CIN2						
Sensitivity (%) (95% CI)	93.6 (44/47) (82.8, 97.8)	91.5 (43/47) (80.1, 96.6)	83.3 (35/42) (69.4, 91.7)	78.6 (33/42) (64.1, 88.3)	68.8 (11/16) (44.4, 85.8)	68.8 (11/16) (44.4, 85.8)
Specificity (%) (95% CI)	49.5 (260/525) (45.3, 53.8)	45.9 (241/525) (41.7, 50.2)	63.2 (254/402) (58.4, 67.8)	60.7 (244/402) (55.8, 65.3)	78.2 (445/569) (74.6, 81.4)	76.3 (434/569) (72.6, 79.6)
PPV (%) (95% CI)	14.2 (44/309) (12.6, 15.6)	13.1 (43/327) (11.5, 14.4)	19.1 (35/183) (16.0, 21.9)	17.3 (33/191) (14.2, 20.0)	8.1 (11/135) (5.3, 10.6)	7.5 (11/146) (4.9, 9.7)
NPV (%) (95% CI)	98.9 (260/263) (97.0, 99.6)	98.4 (241/245) (96.2, 99.4)	97.3 (254/261) (95.2, 98.6)	96.4 (244/253) (94.1, 98.0)	98.9 (445/450) (98.0, 99.5)	98.9 (434/439) (98.0, 99.5)
PLR (95% CI)	1.85 (1.61, 2.06)	1.69 (1.46, 1.88)	2.26 (1.82, 2.69)	2.00 (1.59, 2.39)	3.15 (1.99, 4.20)	2.90 (1.83, 3.84)
NLR (95% CI)	0.13 (0.04, 0.35)	0.19 (0.07, 0.44)	0.26 (0.13, 0.49)	0.35 (0.19, 0.60)	0.40 (0.18, 0.71)	0.41 (0.19, 0.73)

Performance Metrics	BD HPV	FDA Approved HPV Test	BD HPV	FDA Approved HPV Test	BD HPV	FDA Approved HPV Test
	21–29 Years		30–39 Years		≥40 Years	
	≥CIN3					
Sensitivity (%) (95% CI)	92.9 (13/14) (68.5, 98.7)	92.9 (13/14) (68.5, 98.7)	92.9 (13/14) (68.5, 98.7)	85.7 (12/14) (60.1, 96.0)	85.7 (6/7) (48.7, 97.4)	71.4 (5/7) (35.9, 91.8)
Specificity (%) (95% CI)	47.0 (262/558) (42.8, 51.1)	43.7 (244/558) (39.7, 47.9)	60.5 (260/430) (55.8, 65.0)	58.4 (251/430) (53.7, 62.9)	77.7 (449/578) (74.1, 80.9)	75.6 (437/578) (71.9, 78.9)
PPV (%) (95% CI)	4.2 (13/309) (3.1, 4.7)	4.0 (13/327) (2.9, 4.4)	7.1 (13/183) (5.3, 8.1)	6.3 (12/191) (4.4, 7.4)	4.4 (6/135) (2.5, 5.5)	3.4 (5/146) (1.7, 4.6)
NPV (%) (95% CI)	99.6 (262/263) (98.3, 99.9)	99.6 (244/245) (98.2, 99.9)	99.6 (260/261) (98.3, 99.9)	99.2 (251/253) (97.8, 99.8)	99.8 (449/450) (99.2, 100.0)	99.5 (437/439) (99.0, 99.9)
PLR (95% CI)	1.75 (1.28, 1.96)	1.65 (1.21, 1.84)	2.35 (1.71, 2.72)	2.06 (1.42, 2.45)	3.84 (2.15, 4.80)	2.93 (1.45, 3.99)
NLR (95% CI)	0.15 (0.03, 0.67)	0.16 (0.03, 0.72)	0.12 (0.02, 0.52)	0.24 (0.07, 0.69)	0.18 (0.03, 0.66)	0.38 (0.11, 0.85)

ASC-US ≥21 Years) Population-Likelihood Ratios and Risk Estimates

Table 16 presents all possible BD Onclarity™ HPV Assay results in the ASC-US evaluable population together with CPR panel diagnosis.

Table 16: Summary of BD Onclarity™ HPV Assay Results and Adjudicated Histology Diagnosis in the ASC-US Population ≥21 Years

BD Onclarity™ HPV Assay Genotyping Results	Central Pathology Review Panel Diagnosis					
	NEG	CIN1	CIN2	≥CIN3	Undetermined	Total
HPV16 Pos, HPV18 Pos, HPV45 Neg, Other HPV Pos	1	2	0	0	1	4
HPV16 Pos, HPV18 Pos, HPV45 Neg, Other HPV Neg	1	0	0	0	1	2
HPV16 Pos, HPV18 Neg, HPV45 Pos, Other HPV Pos	0	1	0	0	0	1
HPV16 Pos, HPV18 Neg, HPV45 Pos, Other HPV Neg	1	0	0	0	0	1
HPV16 Pos, HPV18 Neg, HPV45 Neg, Other HPV Pos	29	8	4	5	13	59
HPV16 Pos, HPV18 Neg, HPV45 Neg, Other HPV Neg	31	5	11	13	17	77
HPV16 Neg, HPV18 Pos, HPV45 Neg, Other HPV Pos	5	5	3	0	2	15
HPV16 Neg, HPV18 Pos, HPV45 Neg, Other HPV Neg	17	3	2	1	4	27
HPV16 Neg, HPV18 Neg, HPV45 Pos, Other HPV Pos	9	6	1	1	1	18
HPV16 Neg, HPV18 Neg, HPV45 Pos, Other HPV Neg	18	4	1	0	4	27
HPV16 Neg, HPV18 Neg, HPV45 Neg, Other HPV Pos	311	82	36	12	91	532
HPV16 Neg, HPV18 Neg, HPV45 Neg, Other HPV Neg	888	75	12	3	212	1,190
Total	1,311	191	70	35	346[a]	1,953

[a]**NOTE:** 340 women did not return or were no longer eligible for a colposcopy procedure. Three women had unsatisfactory histology results and three women had biopsy specimen collection errors.

Likelihood ratios (LRs) for the BD Onclarity™ HPV Assay (HPV HR 16 positive/18 positive/45 positive, 11 other HPV HR positives, and HR HPV negatives) are presented in Table 17 for the ASC-US ≥21 Years) population.

The BD Onclarity™ HPV result is categorized hierarchically based on genotype positivity in the order of HPV16, HPV18, HPV45, 11 Other HPV HR, and HPV negative. Women with multiple genotypes detected were categorized in the earliest genotype listed (e.g., women positive for HPV16 and HPV18 were categorized as HPV16).

The likelihood of HPV HR positive results to be associated with ≥CIN2 or ≥CIN3 was 2.39 and 2.41 respectively, indicating an overall increase of probability of disease.

For ≥CIN2 histology, a positive HPV16 result had the highest positive LR of 5.98, indicating that a positive result is 5.98 times more likely to come from a subject with disease ≥CIN2) than without disease. The LR of a HPV HR negative result was 0.22, indicating that the negative result was approximately 4.55 times more likely to come from a subject without disease (<CIN2), than with disease. Similar likelihood ratios were observed for disease ≥CIN3.

Table 17: Likelihood Ratios by BD Onclarity™ HPV Assay Result in the ASC-US Population (≥21 Years)

BD Onclarity™ HPV Assay Test Results	Likelihood Ratio (95% CI)	
	≥CIN2 vs. <CIN2	≥CIN3 vs. <CIN3
HPV HR Positive	2.39 (2.13, 2.63)	2.41 (2.03, 2.64)
HPV16 Positive	5.98 (4.15, 8.42)	8.60 (5.69, 12.08)
HPV18 Positive	2.86 (1.24, 6.45)	1.28 (0.22, 6.74)
HPV45 Positive	1.16 (0.38, 3.42)	1.15 (0.20, 6.03)
HPV16 and/or HPV18 and/or HPV45 Positive	4.12 (3.07, 5.38)	5.35 (3.72, 7.07)
11 Other HPV HR Positive	1.75 (1.38–2.15)	1.26 (0.76–1.88)
HPV HR Negative	0.22 (0.14, 0.35)	0.14 (0.05, 0.36)

ASC-US ≥21 Years) Population-Absolute and Relative Risk Estimates

Risk of disease is the probability of having disease given a HPV test outcome. The risk of disease among ASC-US ≥21 women with positive HPV HR results was 14.3% ≥CIN2 and 5.1% ≥CIN3 ; the HPV HR negative risk was 1.5% ≥CIN2) and 0.3% (≥CIN). The risk of disease was highest for HPV16 for both ≥CIN2 (29.5%) and ≥CIN3 (16.1%). The remaining genotypes decreased in risk for ≥CIN2 in the following order: HPV31, HPV18, HPV 33/58, HPV52, HPV51, HPV45, HPV 39/68/35, and HPV 56/59/66.

Table 18: Baseline Absolute Risk of Disease by BD Onclarity™ HPV Assay Result in the ASC-US Population (≥21 Years)

BD Onclarity™ HPV Assay Test Result[a]	Absolute Risk of Disease (%) (95% CI)	
	≥CIN2	≥CIN3
HPV HR Positive	14.3 90/629 (13.0, 15.5)	5.1 32/629 (4.3, 5.6)
HPV16 Positive	29.5 33/112 (22.5, 37.0)	16.1 18/112 (11.2, 21.2)
HPV18 Positive	16.7 6/36 (7.9, 31.1)	2.8 1/36 (0.5, 13.0)
HPV45 Positive	7.5 3/40 (2.6, 19.3)	2.5 1/40 (0.4, 11.8)
HPV31 Positive	26.4 14/53 (16.7, 38.5)	7.5 4/53 (3.0, 16.3)
HPV 33/58 Positive	16.0 8/50 (8.4, 27.7)	0.0 0/50 (0.0, 6.5)
HPV52 Positive	13.0 12/92 (7.8, 20.6)	4.3 4/92 (1.7, 9.6)

BD Onclarity™ HPV Assay Test Result[a]	Absolute Risk of Disease (%) (95% CI)	
	≥CIN2	≥CIN3
HPV51 Positive	12.3 7/57 (6.1, 22.5)	3.5 2/57 (1.0, 10.9)
HPV 35/39/68 Positive	4.9 5/103 (2.1, 10.5)	1.9 2/103 (0.5, 6.1)
HPV 56/59/66 Positive	2.3 2/86 (0.6, 7.8)	0.0 0/86 (0.0, 3.9)
HPV HR Negative	1.5 15/978 (1.0, 2.4)	0.3 3/978 (0.1, 0.8)

[a]Genotypes assigned hierarchically in cases of co-infection.

The relative risk of disease given one reported BD Onclarity™ HPV Assay result compared to another result is summarized in Table 19. The relative risks for women with HPV positive results vs. HPV negative results were 9.33 (≥CIN2) and 16.59 ≥CIN3 .

Positive results for HPV 16, 18, or 45 had the highest relative risk increase when compared to a negative result. Women who have a positive result for any combination of the differentiated genotypes reported by the BD Onclarity™ HPV Assay have a 14.57 (≥CIN2 or 34.68 (≥CIN3) higher risk of disease, relative to a HPV negative result.

Table 19: Relative Risk of Disease by BD Onclarity™ HPV Assay Result in the ASC-US Population ≥21 Years)

BD Onclarity™ HPV Assay Test Results	Relative Risk of Disease (95% CI)	
	≥CIN2	≥CIN3
HPV HR Positive vs. HPV HR Negative	9.33 (5.49, 15.88)	16.59 (5.42, 50.86)
HPV 16/18/45 Positive vs. HPV HR Negative	14.57 (8.30, 25.52)	34.68 (11.09, 108.53)
HPV 16/18/45 Positive vs. 11 Other HPV HR Positive	2.05 (1.41, 2.98)	3.91 (1.98, 7.73)
11 Other HPV HR Positive vs. HPV HR Negative	7.10 (4.05, 12.45)	8.87 (2.70, 29.14)

The relative risk of disease was calculated between women with different BD Onclarity™ HPV Assay results for different age groups. Similar patterns of increased risk were observed as presented in Table 20. The greatest increase in risk of ≥CIN2 is observed in the 21–29 ASC-US population (21.32) for an HPV 16, 18 and 45 positive result compared to a HPV negative result. For ≥CIN3, the greatest increase in risk is observed for the ≥40 population (43.05) given a HPV 16, 18 and 45 positive result compared to a negative HPV result.

Table 20: Relative Risk of Disease by BD Onclarity™ HPV Assay Result by Age in ASC-US Population ≥21 Years)

Age (years)	BD Onclarity™ HPV Assay Test Results	Relative Risk of Disease (95% CI)	
		≥CIN2	≥CIN3
21–29	HPV HR Positive vs. HPV HR Negative	12.54 (4.20, 37.85)	11.11 (1.89, 66.16)
	HPV 16/18/45 Positive vs. HPV HR Negative	21.32 (6.96, 65.83)	24.37 (4.01, 148.82)
	HPV 16/18/45 Positive vs. 11 Other HPV HR Positive	2.34 (1.37, 3.96)	4.10 (1.44, 11.61)
	11 Other HPV HR Positive vs. HPV HR Negative	9.11 (2.97, 28.26)	5.94 (0.93, 38.22)
30–39	HPV HR Positive vs. HPV HR Negative	7.13 (3.32, 15.45)	18.54 (3.15, 110.21)
	HPV 16/18/45 Positive vs. HPV HR Negative	10.11 (4.44, 22.90)	35.39 (5.84, 215.31)
	HPV 16/18/45 Positive vs. 11 Other HPV HR Positive	1.77 (0.98, 3.14)	3.36 (1.20, 9.39)
	11 Other HPV HR Positive vs. HPV HR Negative	5.71 (2.53, 12.95)	10.52 (1.65, 67.52)
≥40	HPV Positive vs. HPV HR Negative	7.31 (2.69, 19.82)	19.94 (3.18, 125.42)
	HPV 16/18/45 Positive vs. HPV HR Negative	10.76 (3.40, 33.10)	43.05 (6.54, 281.50)
	HPV 16/18/45 Positive vs. 11 Other HPV HR Positive	1.87 (0.63, 5.42)	4.48 (0.99, 20.27)
	11 Other HPV HR Positive vs. HPV HR Negative	5.77 (1.89, 17.40)	9.62 (1.27, 72.82)

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY (NILM)

NILM (≥30 Years) Population

A total of 22,383 NILM women ≥30 years were enrolled in the study. Women with a NILM cytology result and an HPV positive result (1,991) and a random subset of women (1,228) with negative HPV results (from both the BD Onclarity™ HPV Assay and FDA-approved HPV test) were assigned to colposcopy for a histological diagnosis. Of the 3,219 women identified for colposcopy, 2,591 completed the procedure with a valid CPR and BD Onclarity™ HPV result. In order to account for the different rates of selection in the HPV positive and HPV negative groups, verification bias adjusted (VBA) performance estimates were calculated. Adjustment was made by calculating the likely number of diseased cases that would have been found if all women had colposcopy.

The results of the BD Onclarity™ HPV Assay in the NILM ≥30 years) population reported as HPV HR Positive or HPV HR Negative together with the CPR panel diagnosis are summarized in Table 21.

Table 21: BD Onclarity™ HPV Assay Result and CPR Panel Diagnosis in the NILM Population (≥30 Years)

	Central Pathology Review Panel Diagnosis				Unknown Disease Status	Total
BD Onclarity™ HPV Assay Test Results	Neg	CIN1	CIN2	≥CIN3		
Positive	1,198	93	27	43	400	1,761
Negative	1,184	36	7	3	19,293	20,523
Invalid/Missing[a]	5	1	0	0	93	99
Total	2,387	130	34	46	19,786[b]	22,383

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results

[b] 19,164 women were not identified for colposcopy. 609 women did not return or were no longer eligible for a colposcopy procedure. Six women had unsatisfactory histology results and seven women had biopsy specimen collection errors.

NILM ≥30 years) Population-Performance Evaluation

The performance of the BD Onclarity™ HPV Assay in detecting high grade cervical disease is presented in Table 22. The unadjusted estimates of sensitivity and specificity for detection of ≥CIN2 histology are 87.5% (78.5, 93.1) and 48.6% (46.6, 50.5), respectively. The positive likelihood ratio for the detection of ≥CIN2 was 5.86 (adjusted estimates), indicating a strong probability that a positive result is truly positive. The negative likelihood ratio for the detection of ≥CIN2 was 0.26 (crude estimates) and 0.60 (adjusted estimates), indicating a strong likelihood that a negative result was associated with the absence of disease.

Verification bias adjusted (VBA) sensitivity and specificity for ≥CIN2 are 44.4% (27.2, 76.2) and 92.4% (92.1, 92.8), respectively.

Unadjusted estimates of sensitivity and specificity for the detection of ≥CIN3 are 93.5% (82.5, 97.8) and 48.2% (46.3, 50.2), respectively. The positive likelihood ratio for the detection of ≥CIN3 was 9.02 (adjusted estimates) indicating that an HPV positive result is nearly 9 times more likely to occur in a subject with ≥CIN3 histology than in a subject with <CIN3. Negative likelihood ratio was 0.3 (adjusted estimates), indicating a strong likelihood that a negative result was associated with the absence of disease.

VBA sensitivity and specificity for the detection of ≥CIN3 are 69.3% (42.0, 100) and 92.3% (92.0, 92.7), respectively.

Table 22: Performance of the BD Onclarity™ HPV Assay in the NILM Population (≥30 Years)

Performance	Central Pathology Review Panel Diagnosis			
	≥CIN2		≥CIN3	
	Unadjusted Estimate	Adjusted Estimate (%, 95% CI)	Unadjusted Estimate	Adjusted Estimate (%, 95% CI)
Sensitivity (%) (95% CI)	87.5 70/80 (78.5, 93.1)	44.4 (27.7, 76.2)	93.5 43/46 (82.5, 97.8)	69.3 (42.0, 100)
Specificity (%) (95% CI)	48.6 1,220/2,511 (46.6, 50.5)	92.4 (92.1, 92.8)	48.2 1,227/2,545 (46.3, 50.2)	92.3 (92.0, 92.7)
PPV (%) (95% CI)	5.1 70/1,361 (4.6, 5.5)	5.1 (3.9, 6.3)	3.2 43/1,361 (2.8, 3.4)	3.0 (2.1, 3.9)
NPV (%) (95% CI)	99.2 1,220/1,230 (98.6, 99.5)	99.5 (99.0, 99.9)	99.8 1,227/1,230 (99.3, 99.9)	99.9 (99.7, 100)
PLR (95% CI)	1.70 (1.52, 1.83)	5.86 (3.63, 10.11)	1.81 (1.59, 1.92)	9.02 (5.48, 13.21)
NLR (95% CI)	0.26 (0.14, 0.44)	0.60 (0.26, 0.78)	0.14 (0.05, 0.36)	0.33 (0.0, 0.63)
Disease Prevalence (%)	3.1 80/2,591	0.9 (0.5, 1.4)	1.8 46/2,591	0.3 (0.2, 0.6)

The performance of the BD Onclarity™ HPV Assay as well as the FDA approved HPV test for detecting ≥CIN2 and ≥CIN3 is presented in Table 23.

Table 23: Performance of the BD Onclarity™ HPV Assay and an FDA Approved HPV Assay in the NILM Population ≥30 Years

Performance	Central Pathology Review Panel Diagnosis			
	Unadjusted Estimates		Adjusted Estimates	
	BD HPV	FDA Approved HPV Test	BD HPV	FDA Approved HPV Test
≥CIN2; unadjusted prevalence 3.1%, adjusted prevalence 0.9%				
Sensitivity (%) (95% CI)	87.5 70/80 (78.5, 93.1)	82.5 66/80 (72.7, 89.3)	44.1 (27.7, 77.8)	40.3 (25.2, 69.0)
Specificity (%) (95% CI)	48.6 1,220/2,508 (46.7, 50.6)	52.3 1,312/2,508 (50.4, 54.3)	92.4 (92.1, 92.8)	93.4 (93.1, 93.8)
PPV (%) (95% CI)	5.2 70/1,358 (4.6, 5.5)	5.2 66/1,262 (4.6, 5.7)	5.0 (3.9, 6.1)	5.3 (4.1, 6.5)
NPV (%) (95% CI)	99.2 1,220/1,230 (98.6, 99.5)	98.9 1,312/1,326 (98.4, 99.4)	99.5 (98.9, 99.9)	99.4 (98.9, 99.8)
PLR (95% CI)	1.70 (1.52, 1.84)	1.73 (1.52, 1.90)	5.82 (3.65, 10.19)	6.14 (3.83, 10.59)
NLR (95% CI)	0.26 (0.14, 0.44)	0.33 (0.20, 0.52)	0.61 (0.24, 0.78)	0.64 (0.33, 0.80)
≥CIN3; unadjusted prevalence 1.8%, adjusted prevalence 0.3%				
Sensitivity (%) (95% CI)	93.5 43/46 (82.5, 97.8)	87.0 40/46 (74.3, 93.9)	69.5 (42.8, 100.0)	63.3 (38.7, 94.9)
Specificity (%) (95% CI)	48.3 1,227/2,542 (46.3, 50.2)	51.9 1,320/2,542 (50.0, 53.9)	92.3 (92.0, 92.7)	93.3 (93.0, 93.7)
PPV (%) (95% CI)	3.2 43/1,358 (2.8, 3.4)	3.2 40/1,262 (2.7, 3.5)	3.0 (2.2, 4.0)	3.2 (2.3, 4.2)
NPV (%) (95% CI)	99.8 1,227/1,230 (99.3, 99.9)	99.5 1,320/1,326 (99.1, 99.8)	99.9 (99.7, 100.0)	99.9 (99.7, 100.0)
PLR (95% CI)	1.81 (1.59, 1.92)	1.81 (1.54, 1.98)	9.05 (5.52, 13.19)	9.49 (5.82, 14.42)
NLR (95% CI)	0.14 (0.05, 0.36)	0.25 (0.12, 0.49)	0.33 (0.0, 0.62)	0.39 (0.06, 0.66)

NOTE: This table is a paired analysis of specimens with a valid BD Onclarity™ HPV Assay and FDA approved HPV test result. Three women with BD Onclarity™ results but without FDA approved test results were not included in the analysis.

NILM ≥30 years) Population-Likelihood Ratios and Risk Estimates

Table 24 presents all possible BD Onclarity™ HPV Assay results in the NILM ≥30 years evaluable population together with the CPR panel diagnosis.

Table 24: BD Onclarity™ HPV Assay Results and CPR Panel Diagnosis in the NILM Population (≥30 Years)

BD Onclarity™ HPV Assay Genotyping Result	Central Pathology Review Panel Diagnosis					
	NEG	CIN1	CIN2	≥CIN3	Undetermined	Total
HPV16 Pos, HPV18 Pos, HPV45 Pos, Other HPV Pos	0	0	0	0	1	1
HPV16 Pos, HPV18 Pos, HPV45 Neg, Other HPV Pos	0	0	0	0	1	1
HPV16 Pos, HPV18 Pos, HPV45 Neg, Other HPV Neg	1	2	0	0	0	3
HPV16 Pos, HPV18 Neg, HPV45 Pos, Other HPV Pos	1	0	0	0	1	2
HPV16 Pos, HPV18 Neg, HPV45 Pos, Other HPV Neg	3	0	0	0	0	3
HPV16 Pos, HPV18 Neg, HPV45 Neg, Other HPV Pos	45	2	1	4	8	60
HPV16 Pos, HPV18 Neg, HPV45 Neg, Other HPV Neg	103	5	3	14	135	260
HPV16 Neg, HPV18 Pos, HPV45 Pos, Other HPV Pos	0	0	0	0	1	1
HPV16 Neg, HPV18 Pos, HPV45 Pos, Other HPV Neg	2	0	0	0	0	2
HPV16 Neg, HPV18 Pos, HPV45 Neg, Other HPV Pos	17	0	0	1	6	24
HPV16 Neg, HPV18 Pos, HPV45 Neg, Other HPV Neg	51	5	1	1	8	66
HPV16 Neg, HPV18 Neg, HPV45 Pos, Other HPV Pos	24	1	1	0	4	30
HPV16 Neg, HPV18 Neg, HPV45 Pos, Other HPV Neg	65	1	0	1	18	85
HPV16 Neg, HPV18 Neg, HPV45 Neg, Other HPV Pos	886	77	21	22	217	1,223
HPV16 Neg, HPV18 Neg, HPV45 Neg, Other HPV Neg	1,184	36	7	3	19,293	20,523
Total	2,382	129	34	46	19,693[a]	22,284

[a] 19,073 women were not identified for colposcopy. 607 women did not return or were no longer eligible for a colposcopy procedure. Six women had unsatisfactory histology results and seven women had biopsy specimen collection errors.

Unadjusted and adjusted estimates of likelihood ratio along with 95% CIs for HPV HR 16,18 and 45 positive, 11 other HR and HPV HR negative for the NILM (≥30 years population is presented in Table 25.

The BD Onclarity™ HPV Assay result is categorized hierarchically based on genotype positivity in the order of HPV16, HPV18, HPV45, 11 Other HPV HR, and HPV negative. Women with multiple genotypes detected were categorized in the earliest genotype listed (e.g., Women positive for HPV16 and HPV18 were categorized as HPV16).

The likelihood of HPV HR positive results to be associated with ≥CIN2 was 5.86 by VBA estimates. For ≥CIN2 histology, a positive HPV16 result had the highest positive LR of 11.27, indicating that a positive result is 11 times more likely to come from a subject with disease ≥CIN2) than without. The LR of a HPV HR negative result was 0.60 for ≥CIN2, indicating that the negative result was more likely to come from a subject without disease than with disease. Larger positive likelihood ratios and smaller negative likelihood ratios were observed for ≥CIN3.

Table 25: Likelihood Ratio by BD Onclarity™ HPV Assay Result in the NILM Population ≥30 Years)

BD Onclarity™ HPV Assay Test Results (%, 95% CI)	Central Pathology Review Panel Diagnosis			
	≥CIN2 (%)		≥CIN3 (%)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HPV HR Positive	1.70 (1.52, 1.83)	5.86 (3.63, 10.11)	1.81 (1.59, 1.92)	9.02 (5.48, 13.21)
HPV16 Positive	4.26 (2.85, 6.12)	11.27 (5.92, 21.08)	6.00 (3.95, 8.52)	21.42 (11.10, 38.33)
HPV18 Positive	1.26 (0.42, 3.58)	4.41 (0.0, 11.90)	1.46 (0.40, 4.97)	7.64 (0.0, 22.64)
HPV45 Positive	0.69 (0.19, 2.43)	2.42 (0.0, 7.18)	0.60 (0.11, 3.17)	3.16 (0.0, 12.28)
HPV 16/18/45 Positive	2.58 (1.84, 3.49)	8.06 (4.48, 14.46)	3.48 (2.42, 4.66)	14.92 (8.19, 25.88)
11 Other HPV HR Positive	1.40 (1.11, 1.69)	4.92 (3.00, 8.51)	1.24 (0.88, 1.61)	6.49 (3.59, 10.98)
HPV HR Negative	0.26 (0.14, 0.44)	0.60 (0.26, 0.78)	0.14 (0.05, 0.36)	0.33 (0.0, 0.63)

NILM ≥30 years) Population-Absolute Risk and Relative Risk Estimates

Estimates of absolute risk of ≥CIN2 and ≥CIN3 for the BD Onclarity™ HPV Assay are presented in Table 26. The estimates were calculated with and without adjusting for verification bias; verification bias adjustment mainly affects the risks for HPV negative women because only a fraction of the HPV negative women were assigned to colposcopy.

Table 26: Baseline Absolute Risk of Disease by BD Onclarity™ HPV Assay Result in the NILM Population (≥30 Years)

HPV HR Positive	5.1 70/1,361 (4.6, 5.5)	5.1 (3.9, 6.3)	3.2 43/1,361 (2.8, 3.4)	3.0 (2.1, 3.9)
HPV16 Positive	12.0 22/184 (8.3, 16.3)	9.3 (5.5, 13.7)	9.8 18/184 (6.7, 13.3)	6.9 (3.9, 9.9)
HPV18 Positive	3.8 3/78 (1.3, 10.2)	3.9 (0.0, 8.4)	2.6 2/78 (0.7, 8.2)	2.6 (0.0, 6.4)
HPV45 Positive	2.2 2/93 (0.6, 7.2)	2.2 (0.0, 5.5)	1.1 1/93 (0.2, 5.4)	1.1 (0.0, 3.4)
HPV31 Positive	12.0 18/150 (8.0, 17.1)	12.0 (7.0, 17.8)	8.7 13/150 (5.4, 12.9)	8.7 (4.5, 13.3)
HPV 33/58 Positive	4.0 5/126 (1.7, 8.5)	4.0 (0.8, 8.0)	2.4 3/126 (0.8, 6.2)	2.4 (0.0, 5.4)
HPV52 Positive	4.5 7/155 (2.2, 8.6)	4.5 (1.6, 8.2)	1.3 2/155 (0.4, 4.2)	1.3 (0.0, 3.6)
HPV51 Positive	4.8 3/62 (1.7, 12.7)	4.8 (0.0, 10.5)	1.6 1/62 (0.3, 8.0)	1.6 (0.0, 5.4)
HPV 39/68/35 Positive	1.8 5/275 (0.8, 4.0)	1.8 (0.4, 3.5)	0.7 2/275 (0.2, 2.4)	0.7 (0.0, 1.9)
HPV 56/59/66 Positive	2.1 5/238 (0.9, 4.6)	2.1 (0.5, 4.0)	0.4 1/238 (0.1, 2.2)	0.4 (0.0, 1.4)
HPV HR Negative	0.8 10/1,230 (0.5, 1.4)	0.5 (0.1, 1.0)	0.2 3/1,230 (0.1, 0.7)	0.1 (0.0, 0.3)

[a]Genotypes assigned hierarchically in cases of co-infection.

The relative risk of disease given one reported BD Onclarity™ HPV Assay result compared to another result is summarized in Table 27. The adjusted relative risks for women with HPV positive results vs. HPV negative results were 9.3 ≥CIN2) or 26.4 (≥CIN3 .

Positive results for HPV 16, 18, or 45 had the highest relative risk increase when compared to a negative result. Women who have a positive result for any combination of the differentiated genotypes reported by the BD Onclarity™ HPV Assay have a 12.56 (≥CIN2 or 42.78 (≥CIN3) larger risk of disease, relative to a HPV negative result.

Table 27: Relative Risk of Disease by BD Onclarity™ HPV Assay Result in the NILM Population (≥30 Years)

BD Onclarity™ HPV Assay Test Results (%, 95% CI)	Central Pathology Review Panel Diagnosis			
	Unadjusted Estimates		Adjusted Estimates	
	≥CIN2	≥CIN3	≥CIN2	≥CIN3
HPV HR Positive vs. HPV HR Negative	6.33 (3.32, 12.09)	12.95 (4.28, 39.33)	9.31 (4.50, 38.03)	26.36 (8.51, Inf)
HPV 16/18/45 Positive vs. HPV HR Negative	9.35 (4.64, 18.86)	24.25 (7.76, 75.94)	12.56 (5.62, 49.57)	42.78 (13.16, Inf)
HPV 16/18/45 Positive vs. 11 Other HPV HR Positive	1.78 (1.12, 2.82)	2.70 (1.52, 4.81)	1.59 (0.97, 2.57)	2.24 (1.22, 4.05)
11 Other HPV HR Positive vs. HPV HR Negative	5.26 (2.69, 10.29)	8.97 (2.87, 28.07)	7.88 (3.81, 32.06)	19.14 (5.83, Inf)

AGREEMENT WITH A COMPOSITE COMPARATOR FOR THE ASC-US (≥21 YEARS) AND NILM ≥30) POPULATION

A random subset of cervical samples from women ≥21 years who had ASC-US cytology results (n=1,120) and a stratified random sample of women ≥30 years with NILM cytology results (n=1,118) were analyzed by a composite comparator. The composite comparator determined the presence or absence of HPV using the FDA- approved HPV test and bi-directional sequencing.

The BD Onclarity™ HPV Assay was evaluated by estimating the positive percent agreement (PPA) and the negative percent agreement (NPA) compared with the composite comparator (Table 28) or genotype specific HPV DNA sequencing results alone (Tables 29 and 30). The composite comparator result was indeterminate if results were discordant between the HPV DNA sequencing result and the FDA approved HPV test result, or if the result from the FDA approved test was indeterminate, or if the HPV DNA sequencing result was invalid. The indeterminate and invalid results are presented in the table but not included in the calculation of percent agreement.

Table 28: Percent Agreement of the BD Onclarity™ HPV Assay vs. the Composite Comparator

Composite Comparator Results									
Population	**BD Onclarity™ HPV Assay**	**Positive**	**Negative**	**Indeterminate**	**Total**	**Unadjusted PPA (%) (95% CI)**	**Unadjusted NPA (%) (95% CI)**	**Adjusted PPA (%) (95% CI)**	**Adjusted NPA (%) (95% CI)**
ASC-US ≥21 Years	Positive	417	9	25	451	97.4 417/428 (95.5, 98.6)	98.5 578/587 (97.1, 99.2)	N/A	
	Negative	11	578	80	669				
	Total	428	587	105	1,120				
NILM ≥30 Years	Positive	448	46	182	676	92.2 448/486 (89.4, 94.3)	87.4 320/366 (83.6, 90.4)	92.0 (89.8, 94.0)	99.4 (99.3, 99.6)
	Negative	38	320	84	442				
	Total	486	366	266	1,118				

In the HPV Sequencing Result Tables 29 and 30, the “Negative” BD Onclarity™ HPV Results are further divided into “Negative, Virus Not Detected” and “Negative, Virus Detected.”

Table 29: Percent Agreement of the BD Onclarity™ HPV Assay Result vs. the HPV Sequencing Result in the ASC-US Population (>21 Years)

HPV HR Genotype	**BD Onclarity™ HPV Assay**	**Sequencing Results**					
	ASC-US ≥21 Years	**Positive**	**Negative**	**Invalid**	**Total**	**PPA (%) (95% CI)**	**NPA (%) (95% CI)**
HPV16	Positive	78	11	0	89	98.7 78/79 (93.2, 99.8)	98.9 1,030/1,041 (98.1, 99.4)
	Negative	1	1,030	0	1,031		
	Negative, Virus Not Detected	1	1,028	0	1,029		
	Negative, Virus Detected	0	2	0	2		
	Total	79	1,041	0	1,120		
HPV18	Positive	22	2	0	24	88.0 22/25 (70.0, 95.8)	99.8 1,093/1,095 (99.3, 99.9)
	Negative	3	1,093	0	1,096		
	Negative, Virus Not Detected	1	1,089	0	1,090		
	Negative, Virus Detected	2	4	0	6		
	Total	25	1,095	0	1,120		
HPV45	Positive	23	0	0	23	76.7 23/30 (59.1, 88.2)	100.0 1,090/1,090 (99.6, 100)
	Negative	7	1,090	0	1,097		
	Negative, Virus Not Detected	0	1,087	0	1,087		
	Negative, Virus Detected	7	3	0	10		
	Total	30	1,090	0	1,120		
HPV31	Positive	44	1	0	45	88.0 44/50 (76.2, 94.4)	99.9 1,068/1,069 (99.5, 100)
	Negative	6	1,068	0	1,074		
	Negative, Virus Not Detected	3	1,062	0	1,065		
	Negative, Virus Detected	3	6	0	9		
	Total	50	1,069	0	1,119		
HPV 33/58	Positive	40	2	0	42	78.4 40/51 (65.4, 87.5)	99.8 1,066/1,068 (99.3, 99.9)
	Negative	11	1,066	0	1,077		
	Negative, Virus Not Detected	5	1,063	0	1,068		
	Negative, Virus Detected	6	3	0	9		
	Total	51	1,068	0	1,119		

HPV HR Genotype	BD Onclarity™ HPV Assay	Sequencing Results					
	ASC-US ≥21 Years	Positive	Negative	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)
HPV 39/68/35	Positive	118	2	0	120	78.1 118/151 (70.9, 84.0)	99.8 966/968 (99.2, 99.9)
	Negative	33	966	0	999		
	Negative, Virus Not Detected	12	948	0	960		
	Negative, Virus Detected	21	18	0	39		
	Total	151	968	0	1,119		
HPV51	Positive	60	3	0	63	85.7 60/70 (75.7, 92.1)	99.7 1,046/1,049 (99.2, 99.9)
	Negative	10	1,046	0	1,056		
	Negative, Virus Not Detected	4	1,038	0	1,042		
	Negative, Virus Detected	6	8	0	14		
	Total	70	1,049	0	1,119		
HPV52	Positive	83	6	0	89	94.3 83/88 (87.4, 97.5)	99.4 1,025/1,031 (98.7, 99.7)
	Negative	5	1,025	0	1,030		
	Negative, Virus Not Detected	4	1,019	0	1,023		
	Negative, Virus Detected	1	6	0	7		
	Total	88	1,031	0	1,119		
HPV 56/59/66	Positive	116	4	0	120	79.5 116/146 (72.2, 85.2)	99.6 969/973 (98.9, 99.8)
	Negative	30	969	0	999		
	Negative, Virus Not Detected	12	952	0	964		
	Negative, Virus Detected	18	17	0	35		
	Total	146	973	0	1,119		

Table 30: Percent Agreement of the BD Onclarity™ HPV Assay Result vs. the HPV Sequencing Result in the NILM Population (≥30 Years)

HPV HR Genotype	BD Onclarity™ HPV Assay	Sequencing Results				Percent Agreement			
						Unadjusted		Adjusted	
	NLIM ≥30 Years	Pos.	Neg.	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)	PPA (%) (95% CI)	NPA (%) (95% CI)
HPV16	Positive	72	17	0	89	96.0 72/75 (88.9, 98.6)	98.4 1,026/1,043 (97.4, 99.0)	86.5 (59.4, 97.3)	99.6 (99.5, 99.8)
	Negative	3	1,026	0	1,029				
	Negative, Virus Not Detected	1	1,023	0	1,024				
	Negative, Virus Detected	2	3	0	5				
	Total	75	1,043	0	1,118				
HPV18	Positive	34	5	0	39	79.1 34/43 (64.8, 88.6)	99.5 1,070/1,075 (98.9, 99.8)	61.9 (30.4, 81.7)	99.9 (99.9, 100)
	Negative	9	1,070	0	1,079				
	Negative, Virus Not Detected	3	1,062	0	1,065				
	Negative, Virus Detected	6	8	0	14				
	Total	43	1,075	0	1,118				
HPV45	Positive	51	2	0	53	89.5 51/57 (78.9, 95.1)	99.8 1,059/1,061 (99.3, 99.9)	72.2 (39.3, 89.6)	100 (99.9, 100)
	Negative	6	1,059	0	1,065				
	Negative, Virus Not Detected	2	1,056	0	1,058				
	Negative, Virus Detected	4	3	0	7				
	Total	57	1,061	0	1,118				

HPV HR Genotype	BD Onclarity™ HPV Assay	Sequencing Results				Percent Agreement			
						Unadjusted		Adjusted	
	NLIM ≥30 Years	Pos.	Neg.	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)	PPA (%) (95% CI)	NPA (%) (95% CI)
HPV31	Positive	64	1	0	65	84.2 64/76 (74.4, 90.7)	99.9 1,040/1,041 (99.5, 100)	53.2 (30.0, 77.1)	100 (99.9, 100)
	Negative	12	1,040	0	1,052				
	Negative, Virus Not Detected	7	1,030	0	1,037				
	Negative, Virus Detected	5	10	0	15				
	Total	76	1,041	0	1,117				
HPV 33/58	Positive	68	11	0	79	81.9 68/83 (72.3, 88.7)	98.9 1,023/1,034 (98.1, 99.4)	56.1 (31.3, 77.7)	99.9 (99.8, 99.9)
	Negative	15	1,023	0	1,038				
	Negative, Virus Not Detected	13	1,019	0	1,032				
	Negative, Virus Detected	2	4	0	6				
	Total	83	1,034	0	1,117				
HPV 39/68/35	Positive	149	8	0	157	77.6 149/192 (71.2, 82.9)	99.1 918/926 (98.3, 99.6)	55.4 (38.5, 71.0)	99.9 (99.8, 100)
	Negative	43	918	0	961				
	Negative, Virus Not Detected	4	902	0	906				
	Negative, Virus Detected	39	16	0	55				
	Total	192	926	0	1,118				
HPV51	Positive	32	3	0	35	69.6 32/46 (55.2, 80.9)	99.7 1,069/1,072 (99.2, 99.9)	58.0 (31.0, 76.0)	100 (99.9, 100)
	Negative	14	1,069	0	1,083				
	Negative, Virus Not Detected	5	1,056	0	1,061				
	Negative, Virus Detected	9	13	0	22				
	Total	46	1,072	0	1,118				

PRIMARY SCREENING POPULATION (≥25 YEARS)

A total of 29,633 women ≥25 years were enrolled in the study of which 29,513 were evaluable. Evaluable women had valid cytology and BD Onclarity™ HPV Assay results.

The median age of enrolled women in the primary screening population was 39 years with 18% of women 25–29, 32% of women 30–39, and 50% of women ≥40 years old. Approximately 79% of women were white and 18% were Black or African American.

A total of 5,534 women ≥25 years completed the colposcopy procedure with a valid CPR and BD Onclarity™ HPV result. The number of women with adjudicated histology results for each combination of BD Onclarity™ HPV and cytology results is shown in Table 31.

A correction of verification bias was applied due to the different rate of disease adjudication in each category, in particular the NILM HPV negative category. Cases of disease were imputed for the women without histology results from the women with histology diagnoses in different categories defined by HPV results, cytology result, and age.

Table 31: Number of Subjects in Primary Screening Population ≥25 Years) with Adjudicated Histology Results

BD Onclarity™ HPV Result	Subjects	Cytology			Total
		>ASC-US	ASC-US	NILM	
HPV 16/18 Pos	Total	199	140	609	948
	Total With Adjudicated Histology	164	116	382	662
12 Other HPV HR Pos	Total	434	420	1,946	2,800
	Total With Adjudicated Histology	360	358	1,596	2,314
HPV HR Neg	Total	223	1,060	24,482	25,765
	Total With Adjudicated Histology	180	881	1,497	2,558
Total	Total	856	1,620	27,037	29,513
	Total With Adjudicated Histology	704	1,355	3,475	5,534

Baseline and 3-Year Cumulative Risks of High Grade Cervical Disease in the Primary Screening Population ≥25 years

The baseline and 3-Year risks of high grade cervical disease ≥CIN2 and ≥CIN3) were calculated in the primary screening population (≥25 years) for women with different BD Onclarity™ HPV Assay results.

Women positive for HPV16 had the highest baseline (21.3%) and 3-year risk (29.7%) for ≥CIN2, followed by HPV31, HPV18, HPV 33/58, HPV52, HPV51 (note HPV51 is slightly higher than HPV52 at Year 3), HPV45, HPV 39/68/35, HPV 56/59/66. The ≥CIN2 risk level for HPV negative women was 0.31% at baseline and 0.88% after 3 years.

Table 32: Baseline and 3-Year Cumulative Risks of Disease for Categories in the Primary Screening Population ≥25 Years)

Subgroup[a]	% With Result (at baseline)	≥CIN2 Risk (95% CI)		≥CIN3 Risk (95% CI)	
		Baseline	3-Year	Baseline	3-Year
HPV HR+	12.7	10.4 (9.3, 11.4)	15.5 (14.2,16.8)	5.3 (4.5, 6.1)	7.5 (6.5, 8.5)
HPV16	2.5	21.3 (18.2, 24.7)	29.7 (26.1, 34.3)	14.2 (11.8, 16.6)	18.7 (15.6, 22.2)
HPV18	0.7	11.4 (6.9, 16.4)	17.7 (11.2, 23.2)	5.2 (2.2, 9.1)	8.0 (3.5, 12.0)
HPV45	0.8	5.9 (3.0, 9.1)	11.5 (6.3, 16.7)	2.7 (0.6, 5.1)	4.2 (1.2, 7.3)
HPV31	1.2	17.3 (12.6, 21.1)	25.0 (18.7, 30.3)	9.8 (6.3, 13.2)	13.2 (9.0, 17.9)
HPV 33/58	1.1	9.6 (6.4, 13.6)	14.4 (9.7, 18.4)	4.2 (2.1, 7.8)	5.5 (2.9, 8.8)
HPV52	1.4	8.5 (5.8, 11.6)	12.0 (8.7, 16.4)	3.2 (1.5, 5.4)	4.9 (2.7, 7.8)
HPV51	0.8	7.9 (4.7, 12.1)	13.0 (8.2, 19.8)	1.6 (0.4, 4.1)	4.3 (1.3, 8.7)
HPV 39/68/35	2.3	4.8 (3.1, 6.4)	9.5 (6.8, 11.9)	1.4 (0.5, 2.4)	3.0 (1.5, 4.6)
HPV 56/59/66	1.9	2.5 (1.2, 3.7)	3.4 (1.8, 4.9)	0.2 (0.0, 0.7)	0.2 (0.0, 0.7)
hrHPV NEG	87.3	0.3 (0.2, 0.5)	0.9 (0.6, 1.2)	0.1 (0.0, 0.2)	0.2 (0.1, 0.3)

[a]Genotypes assigned hierarchically in cases of co-infection.

Baseline and 3-Year Cumulative Risks of High Grade Cervical Disease by Age Group in the Primary Screening Population

≥25 years

The baseline and 3-Year cumulative risks of ≥CIN2 and ≥CIN3 by age group for the Primary Screening Algorithm are presented in Tables 33–35. The risk of ≥CIN2 ranges from 6.2–22.8% at baseline and 8.6–38.9% at Year 3 for women positive for HPV 16/18 and women positive for 12 other HPV and ≥ASC-US cytology. The risk of ≥CIN3 ranges from 0.0–0.30% at baseline and Year 3 for women with a negative HPV result.

Table 33: Baseline and 3-Year Cumulative Risk of Disease for Categories in the Primary Screening Algorithm (25–29 Years)

Subgroup[a]	% With Result (at baseline)	≥CIN2 Risk (95% CI)		≥CIN3 Risk (95% CI)	
		Baseline	3-Year	Baseline	3-Year
HPV HR+	22.4	11.4 (9.4, 13.6)	18.7 (16.4, 22.3)	5.2 (4.0, 6.7)	8.0 (6.4, 10.2)
HPV16	4.5	24.9 (18.2, 31.9)	42.0 (33.9, 51.4)	15.2 (10.0, 20.5)	22.2 (16.6, 29.5)
HPV18	1.0	11.8 (2.1, 23.5)	24.9 (8.4, 43.1)	4.7 (0.0, 11.5)	8.4 (0.0, 18.4)
HPV45	1.5	3.4 (0.0, 9.4)	6.2 (0.0, 14.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
HPV31	1.9	20.6 (12.5, 29.0)	27.7 (16.2, 38.5)	8.3 (3.0, 14.9)	11.8 (3.7, 19.7)
HPV 33/58	1.9	12.0 (5.1, 19.1)	16.8 (7.5, 25.2)	4.7 (1.2, 9.6)	8.4 (2.4, 15.3)
HPV52	2.7	8.8 (4.7, 14.1)	15.7 (8.6, 24.2)	3.2 (0.8, 7.1)	4.4 (1.6, 8.9)
HPV51	2.0	7.2 (2.3, 13.3)	14.8 (7.3, 22.7)	2.1 (0.0, 5.5)	7.6 (2.2, 15.3)
HPV 39/68/35	3.6	4.4 (1.3, 7.5)	9.7 (4.3, 15.4)	1.2 (0.0, 3.0)	2.5 (0.0, 5.7)
HPV 56/59/66	3.3	2.9 (0.7, 6.1)	3.6 (0.8, 6.9)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
hrHPV NEG	77.61	0.4 (0.1, 0.9)	1.7 (0.6, 2.8)	0.3 (0.0, 0.8)	0.3 (0.0, 0.8)

[a]Genotypes assigned hierarchically in cases of co-infection.

Table 34: Baseline and 3-Year Cumulative Risk of Disease for Categories in the Primary Screening Algorithm (30–39 Years)

Subgroup[a]	% With Result (at baseline)	≥CIN2 Risk (95% CI)		≥CIN3 Risk (95% CI)	
		Baseline	3-Year	Baseline	3-Year
HPV HR+	13.8	13.2 (11.1, 15.4)	18.2 (15.9, 20.7)	6.9 (5.4, 8.4)	9.3 (7.6, 11.0)
HPV16	2.9	25.7 (20.1, 32.6)	30.6 (23.8, 37.8)	17.3 (13.0, 22.1)	22.2 (17.0, 28.4)
HPV18	0.8	11.5 (4.3, 19.9)	18.8 (9.3, 29.1)	5.0 (0.0, 10.9)	10.6 (1.7, 19.3)
HPV45	0.9	10.3 (4.5, 16.5)	17.1 (9.4, 26.7)	4.5 (0.0, 9.8)	6.8 (1.6, 14.0)
HPV31	1.6	23.8 (16.4, 30.4)	32.0 (22.8, 40.5)	14.6 (8.3, 21.2)	16.6 (9.6, 22.9)
HPV 33/58	1.2	10.4 (5.2, 17.1)	19.8 (10.6, 29.6)	3.2 (0.0, 7.1)	3.2 (0.0, 7.1)
HPV52	1.4	11.9 (6.5, 17.8)	15.8 (8.7, 23.3)	3.7 (0.8, 7.7)	7.4 (2.5, 13.8)
HPV51	0.8	10.0 (3.1, 18.1)	15.5 (7.1, 26.6)	1.7 (0.0, 6.4)	1.7 (0.0, 6.4)
HPV 39/68/35	2.3	4.4 (1.4, 7.9)	8.4 (4.2, 12.9)	1.6 (0.0, 3.6)	2.8 (0.5, 5.4)
HPV 56/59/66	2.0	2.5 (0.6, 4.5)	2.5 (0.6, 4.5)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
hrHPV NEG	86.2	0.4 (0.1, 0.7)	1.0 (0.6, 1.5)	0.1 (0.0, 0.4)	0.3 (0.1, 0.5)

[a]Genotypes assigned hierarchically in cases of co-infection.

Table 35: Baseline and 3-Year Cumulative Risk of Disease for Categories in the Primary Screening Algorithm (≥40 Years)

Subgroup[a]	% With Result (at baseline)	≥CIN2 Risk (95% CI)		≥CIN3 Risk (95% CI)	
		Baseline	3-Year	Baseline	3-Year
HPV HR+	8.4	6.2 (4.8, 7.6)	9.3 (7.6, 11.2)	3.5 (2.5, 4.9)	4.8 (3.5, 6.3)
HPV16	1.5	11.5 (7.3, 17.0)	14.5 (9.1, 20.4)	8.3 (4.6, 12.4)	9.9 (5.9, 15.1)
HPV18	0.6	11.2 (4.2, 19.0)	12.8 (5.0, 20.8)	5.6 (0.0, 12.2)	5.6 (0.0, 12.2)
HPV45	0.5	3.0 (0.0, 7.4)	9.6 (2.3, 18.5)	3.0 (0.0, 7.4)	5.0 (0.0, 10.4)
HPV31	0.8	5.3 (1.2, 10.8)	13.7 (6.2, 22.7)	4.2 (0.0, 9.1)	9.8 (3.4, 18.7)
HPV 33/58	0.7	5.9 (1.8, 11.3)	7.4 (2.6, 13.5)	4.6 (1.1, 9.2)	4.6 (1.1, 9.2)
HPV52	0.9	4.4 (0.9, 8.7)	4.4 (0.9, 8.7)	2.6 (0.0, 6.0)	2.6 (0.0, 6.0)
HPV51	0.3	6.3 (0.0, 17.2)	6.3 (0.0, 17.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
HPV 39/68/35	1.8	5.3 (2.4, 8.6)	10.4 (6.3, 14.7)	1.4 (0.0, 3.3)	3.6 (1.0, 6.3)
HPV 56/59/66	1.4	2.3 (0.5, 4.4)	3.7 (1.2, 6.8)	0.6 (0.0, 1.9)	0.6 (0.0, 1.9)
hrHPV NEG	91.6	0.2 (0.1, 0.4)	0.6 (0.2, 0.9)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)

[a]Genotypes assigned hierarchically in cases of co-infection.

Table 36: Likelihood Ratio by BD Onclarity™ HPV Assay Result in the Screening Population at Baseline ≥25 Years)

BD Onclarity™ HPV Assay Test Results[a]	Central Pathology Review Panel Diagnosis			
	≥CIN2 vs. <CIN2		≥CIN3 vs. <CIN3	
	Unadjusted	Adjusted	Unadjusted	Adjusted
HPV HR Positive	1.8 (1.7, 1.8)	6.1 (5.0, 7.3)	1.8 (1.7, 1.9)	6.5 (5.1, 8.0)
HPV16 Positive	5.0 (4.2, 6.0)	14.4 (11.2, 18.4)	6.5 (5.4, 7.7)	19.3 (14.2, 25.5)
HPV18 Positive	1.9 (1.2, 3.0)	6.8 (3.9, 10.6)	1.7 (0.9, 3.2)	6.3 (2.8, 11.6)
HPV45 Positive	0.9 (0.5, 1.6)	3.3 (1.5, 5.7)	0.8 (0.4, 1.9)	3.2 (0.7, 6.7)
HPV31 Positive	3.1 (2.3, 4.0)	11.0 (7.6, 15.2)	3.3 (2.4, 4.7)	12.7 (8.1, 19.0)
HPV 33/58 Positive	1.6 (1.0, 2.3)	5.6 (3.4, 8.4)	1.4 (0.8, 2.4)	5.0 (2.2, 8.7)
HPV52 Positive	1.4 (1.0, 2.0)	4.8 (3.2, 7.0)	1.0 (0.6, 1.8)	3.8 (1.8, 6.6)
HPV51 Positive	1.3 (0.8, 2.1)	4.5 (2.3, 7.3)	0.5 (0.2, 1.4)	1.9 (0.0, 4.7)
HPV 39/68/35 Positive	0.7 (0.5, 1.0)	2.6 (1.6, 3.8)	0.5 (0.2, 0.9)	1.7 (0.7, 3.2)
HPV 56/59/66 Positive	0.4 (0.2, 0.7)	1.4 (0.6, 2.3)	0.1 (0.0, 0.4)	0.2 (0.0, 0.8)
HPV HR Negative	0.2 (0.2, 0.3)	0.3 (0.2, 0.5)	0.1 (0.1, 0.2)	0.2 (0.0, 0.4)

[a]Genotypes assigned hierarchically in cases of co-infection.

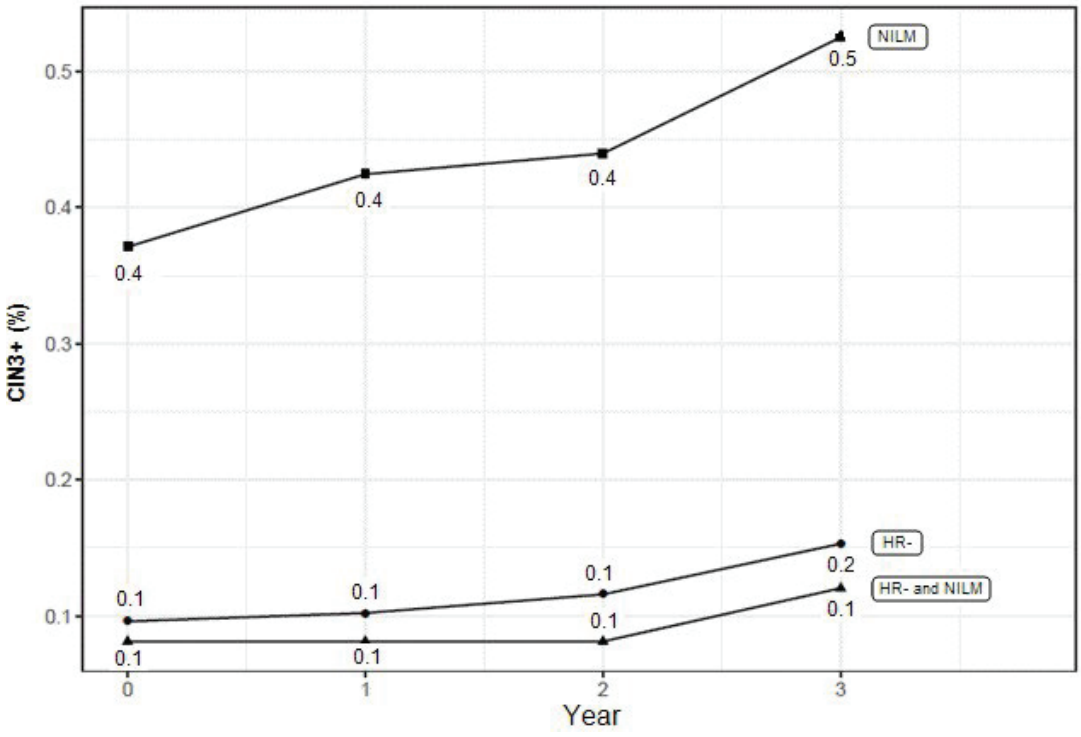
Baseline and 3-Year Cumulative Risk of Disease for Women with NILM Cytology and Negative BD Onclarity™ HPV Test Results

The baseline and Year 3 risks of disease were compared in the primary screening population between women with a NILM cytology result and women with a negative BD Onclarity™ HPV result. Women with a negative BD Onclarity™ HPV result had a baseline risk of 0.1% and a 3-year cumulative risk of 0.2% for ≥CIN3 compared to a baseline risk of 0.4% and a 3-year cumulative risk of 0.5% for women with NILM cytology. The addition of a NILM cytology result to a negative BD Onclarity™ HPV result had similar ≥CIN3 risk at baseline (0.1%) and marginally decreased ≥CIN3 risk at 3 years (0.2% vs. 0.1%).

Table 37: Baseline and 3-Year Cumulative Risk of Disease for Women with NILM Cytology and Negative BD Onclarity™ HPV Test Results in the Primary Screening (≥25 Years) Population

Subgroup	% With Result (at baseline)	≥CIN3 Risk (95% CI)		≥CIN2 Risk (95% CI)	
		Baseline	3-Year	Baseline	3-Year
NILM	91.61	0.4 (0.3, 0.5)	0.5 (0.4, 0.7)	0.8 (0.6, 1.0)	1.6 (1.3, 1.9)
HPV HR NEG	87.30	0.1 (0.0, 0.2)	0.2 (0.1, 0.3)	0. 3 (0.2, 0.5)	0.9 (0.6, 1.2)
HPV HR NEG and NILM	82.95	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.2 (0.1, 0.4)	0.7 (0.4, 1.1)

Figure 1: Cumulative Risk of Disease ≥CIN3 for Women with NILM Cytology, Negative BD Onclarity™ HPV Results in the Primary Screening (≥25 Years Population



Performance In Unvaccinated and Vaccinated Women

The clinical sites enrolled both HPV vaccinated and unvaccinated women, with a vaccinated enrollment limit of approximately 10%. The final vaccinated rate in the study was 9.1%, with an additional 1.4% unknown or missing vaccination status; vaccination status was self-reported.

The first HPV vaccine was introduced in 2006 and the clinical study occurred from 2013 to 2015, thus a majority of the vaccinated women in the study were under the age of 30 (3,064 vaccinated subjects overall, 2,625 under 30). The performance of the BD Onclarity™ HPV Assay in vaccinated and unvaccinated women (excluding women with unknown or missing vaccination status) is shown below for women with ASC-US cytology (21–29 years old) and a subset of the primary screening population (25–29 years old).

Table 38: BD Onclarity™ HPV Assay Performance in Unvaccinated and Vaccinated Women with ASC-US Cytology (21–29 Years Old)

Performance Metrics	≥CIN2			
	Unvaccinated (prevalence 7.8%)		Vaccinated (prevalence 9.7%)	
	Estimate	95% CI	Estimate	95% CI
Sensitivity	100% (31/31)	(89.0%, 100%)	80.0% (12/15)	(54.8%, 93.0%)
Specificity	48.9% (180/368)	(43.8%, 54.0%)	52.1% (73/140)	(43.9%, 60.2%)
PPV	14.2% (31/219)	(13.3%, 15.5%)	15.2% (12/79)	(10.7%, 18.8%)
NPV	100% (180/180)	(98.1%, 100%)	96.1% (73/76)	(91.3%, 98.6%)
PLR	1.96	(1.82, 2.17)	1.67	(1.11, 2.16)
NLR	0.0	(0.0, 0.23)	0.38	(0.13, 0.89)
Performance Metrics	**≥CIN3**			
	Unvaccinated (prevalence 2.0%)		Vaccinated (prevalence 3.2%)	
	Estimate	95% CI	Estimate	95% CI
Sensitivity	100% (8/8)	(67.6%, 100%)	80.0% (4/5)	(37.6%, 96.4%)
Specificity	46.0% (180/391)	(41.2%, 51.0%)	50.0% (75/150)	(42.1%, 57.9%)
PPV	3.7% (8/219)	(3.6%, 4.0%)	5.1% (4/79)	(2.4%, 6.6%)
NPV	100% (180/180)	(98.6%, 100%)	98.7% (75/76)	(95.9%, 99.8%)
PLR	1.85	(1.82, 2.04)	1.60	(0.74, 2.12)
NLR	0.0	(0.0, 0.71)	0.40	(0.07, 1.28)

Table 39: BD Onclarity™ HPV Assay Performance in Unvaccinated and Vaccinated Women in the Primary Screening Population (25–29 Years Old)

Performance	Unadjusted Estimate		Adjusted Estimate	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
		≥CIN2		
Sensitivity (%) (95% CI)	67.05 59/88 (56.69, 75.97)	60.00 15/25 (40.74, 76.60)	58.85 (41.92, 76.31)	59.26 (39.57, 76.83)
Specificity (%) (95% CI)	68.86 690/1,002 (65.93, 71.65)	79.64 223/280 (74.54, 83.94)	89.39 (88.39, 90.33)	93.78 (92.35, 95.43)
PPV (%) (95% CI)	15.90 59/371 (13.54, 18.15)	20.83 15/72 (14.46, 27.29)	15.97 (12.11, 19.79)	20.18 (10.83, 30.54)
NPV (%) (95% CI)	95.97 690/719 (94.75, 97.03)	95.71 223/233 (93.74, 97.45)	98.45 (97.00, 99.27)	98.86 (98.07, 99.44)
PLR (95% CI)	2.15 (1.78, 2.53)	2.95 (1.89, 4.20)	5.54 (3.80, 7.43)	9.53 (6.04, 14.24)
NLR (95% CI)	0.48 (0.35, 0.63)	0.50 (0.29, 0.75)	0.46 (0.26, 0.65)	0.43 (0.25, 0.65)
Colpo Rate (95% CI)			12.21 (11.24, 13.23)	7.59 (5.84, 9.11)
Prevalence (95% CI)			3.31 (2.39, 4.67)	2.58 (1.65, 3.69)

Performance	Unadjusted Estimate		Adjusted Estimate	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
		≥CIN3		
Sensitivity (%) (95% CI)	81.58 31/38 (66.58, 90.78)	61.54 8/13 (35.52, 82.29)	58.48 (31.62, 92.66)	61.35 (34.93, 86.50)
Specificity (%) (95% CI)	67.68 712/1,052 (64.79, 70.44)	78.08 228/292 (72.99, 82.45)	88.59 (87.57, 89.54)	93.17 (91.77, 94.93)
PPV (%) (95% CI)	8.36 31/371 (6.83, 9.54)	11.11 8/72 (6.51, 15.54)	8.12 (5.43, 11.07)	11.20 (4.58, 19.77)
NPV (%) (95% CI)	99.03 712/719 (98.24, 99.51)	97.85 228/233 (96.44, 99.00)	99.20 (97.80, 99.90)	99.42 (98.87, 99.88)
PLR (95% CI)	2.52 (2.03, 2.92)	2.81 (1.57, 4.13)	5.12 (2.68, 8.28)	8.98 (4.86, 14.76)
NLR (95% CI)	0.27 (0.14, 0.49)	0.49 (0.23, 0.83)	0.47 (0.08, 0.77)	0.41 (0.14, 0.69)
Colpo Rate (95% CI)			12.21 (11.24, 13.23)	7.59 (5.84, 9.11)
Prevalence (95% CI)			1.70 (0.92, 2.97)	1.39 (0.68, 2.25)

Comparison of Results from the BD Onclarity™ HPV Assay for PreQuot vs. PostQuot BD SurePath™ Cervical Samples
An equivalence study design was employed to compare the performance of the BD Onclarity™ HPV Assay with a cervical specimen tested prior to (PreQuot) or after (PostQuot) normal cytology processing.

A total of 3,879 subjects were enrolled in the PreQuot vs. PostQuot study. During the Baseline Study, 0.5 mL of the cervical specimen stored in BD SurePath™ was manually transferred into a BD Onclarity™ HPV LBC Diluent Tube (PreQuot). After normal processing per the BD PrepMate™ labeling, 0.5 mL of the residual specimen in BD SurePath™ was manually transferred into a BD Onclarity™ HPV LBC Diluent Tube (PostQuot). The comparative performance of the PreQuot to the PostQuot sample when tested with the BD Onclarity™ HPV Assay is shown in Tables 40 and 41.

Table 40: Agreement Results of the BD Onclarity™ HPV Assay PreQuot vs. PostQuot

Population	Positive Percent Agreement (%, 95% CI)	Negative Percent Agreement (%, 95% CI)	Overall Percent Agreement (%, 95% CI)
NILM ≥30 yrs	86.0 (80.3, 90.3)	99.3 (98.8, 99.5)	98.3 (97.8, 98.8)
ASC-US ≥21 yrs	100 (95.0, 100)	97.7 (93.5, 99.2)	98.5 (95.8, 99.5)
>ASC-US ≥21 yrs	97.6 (91.8, 99.4)	100 (83.2, 100)	98.1 (93.3, 99.5)
Screening Population ≥25 yrs	91.0 (87.7, 93.4)	99.0 (98.6, 99.3)	98.1 (97.6, 98.5)

Table 41: BD Onclarity™ HPV Assay PreQuot vs. PostQuot Results

BD Onclarity™ HPV Assay PostQuot Result	BD Onclarity™ HPV Assay PreQuot Result							
	ASC-US ≥21		>ASC-US ≥21		NILM ≥30		All Subjects ≥25	
	POS	NEG	POS	NEG	POS	NEG	POS	NEG
Positive	73	3	83	0	160	18	353	30
Negative	0	129	2	19	26	2,431	35	3,052
Total	73	132	85	19	186	2,449	388	3,082

BD COR™ SYSTEM PERFORMANCE CHARACTERISTICS
The performance of the BD Onclarity™ HPV Assay on the BD COR™ System with BD SurePath™ and PreservCyt® specimens was evaluated in an agreement study by comparing the assay results obtained on the BD Viper™ LT System to the BD COR™ System. Remnant BD SurePath™ and PreservCyt® specimens were used for each agreement study. Clinical panels were created either with individual specimens, pooled positive clinical specimens, or negative clinical specimens spiked with a positive clinical specimen. Contrived panels were created by spiking HPV containing cell lines into HPV negative clinical matrix.

Percent Agreement between the BD Onclarity™ HPV Assay Performed on the BD Viper™ LT System and the BD COR™ System with BD SurePath™ Cervical Specimens

The percent agreement between the BD Onclarity™ HPV Assay performed on the BD Viper™ LT System and the BD COR™ System was evaluated. The panels were prepared with HPV genotypes16, 18, 45, 31, 33/58, 35/39/68, 51, 52, and 56/59/66 where the majority of the specimens were at levels close to the cutoff. Each panel member was divided into three aliquots, where each aliquot was tested twice, once with the BD Viper™ LT System and once with the BD COR™ System at three different sites (two external sites, one in-house). All BD Viper™ LT testing occurred internally and results served as the reference.

The agreement study with BD SurePath™ included 317 independent panel members of which 297 were clinical and 20 were contrived. Out of the 317 panel members, 315 (201 positive and 114 negative) had paired results (both BD COR™ and BD Viper™ LT results) and were considered evaluable in the study. Each panel member had three replicate aliquots tested on both systems, resulting in a total of 1,092 samples tested of which 1,032 were clinical and 60 were contrived. Out of the 1,092 BD SurePath™ samples, 940 (581 positive and 359 negative) had paired results (both BD COR™ and BD Viper™ LT results) and were considered evaluable in the study.

The positive and negative agreement between results on the BD Viper™ LT and BD COR™ Systems were calculated for each of the three sites where BD COR™ testing occurred using the majority result on the BD Viper™ LT (two of three evaluable BD Viper™ LT system replicates for each panel member) as the comparator for each panel member. A total of 315 evaluable panel members were included. PPA and NPA were calculated separately for genotypes 16, 18, 45, 31, 33/58, 52, 51, 39/68/35, and 56/59/66. PPA and NPA estimates were also averaged across the three test sites. The positive and negative percent agreement results for BD SurePath™ panel members at each site and averaged across all sites are summarized in Tables 42–50 for each result readout.

For each of the following tables, the denominator for PPA and NPA also included the reference comparator result for the samples with non-evaluable replicates and final equivocal results, as indicated in the footnotes. Equivocal results noted in Table 43 are defined as one BD Viper™ LT (VLT) Positive, one negative, and one non-evaluable.

Table 42: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV16)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV16	1	BD COR™ Result	Positive	71	3	1	1
			Negative	1	3	2	228
			Total	72	6	3	229
		PPA: 94.9% (75/79), 95% CI: (87.7, 98.0) NPA: 99.1% (233/235), 95% CI: (97.0, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 3 (BD COR™ Negative)				
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	72	3	0	1
			Negative	0	3	3	228
			Total	72	6	3	229
		PPA: 96.2% (76/79), 95% CI: (89.4, 98.7) NPA: 99.6% (235/236), 95% CI: (97.6, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)				
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	72	4	0	0
			Negative	0	2	3	229
			Total	72	6	3	229
		PPA: 97.4% (76/78), 95% CI: (91.1, 99.3) NPA: 100% (233/233), 95% CI: (98.4, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)				
Average PPA: 96.2% Bootstrap 95% CI: (92.4, 99.1) Average NPA: 99.6% CI:(N/A[a])							

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Table 43: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV18)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV18	1	BD COR™ Result	Positive	31	2	2	1
			Negative	0	2	0	272
			Total	31	4	2	273
		PPA: 94.3% (33/35), 95% CI: (81.4, 98.4) NPA: 98.6% (275/279), 95% CI: (96.4, 99.4) Number of VLT equivocal results: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 3 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	31	4	1	2
			Negative	0	0	1	271
			Total	31	4	2	273
		PPA: 100% (35/35), 95% CI: (90.1, 100) NPA: 98.6% (276/280), 95% CI: (96.4, 99.4) Number of VLT equivocal results: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	31	4	1	2
			Negative	0	0	1	271
			Total	31	4	2	273
		PPA: 100% (35/35), 95% CI: (90.1, 100) NPA: 98.9% (273/276), 95% CI: (96.9, 99.6) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)					
Average PPA: 98.1% Bootstrap 95% CI: (95.1, 100) Average NPA: 98.7% Bootstrap 95% CI: (97.5, 99.8)							

Table 44: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV31)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV31	1	BD COR™ Result	Positive	16	2	0	0
			Negative	0	0	0	291
			Total	16	2	0	291
		PPA: 100% (18/18), 95% CI: (82.4, 100) NPA: 100% (296/296), 95% CI: (98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	16	2	0	0
			Negative	0	0	0	291
			Total	16	2	0	291
		PPA: 100% (18/18), 95% CI: (82.4, 100) NPA: 100% (297/297), 95% CI: (98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	16	1	0	1
			Negative	0	1	0	290
			Total	16	2	0	291
		PPA: 94.4% (17/18), 95% CI: (74.2, 99.0) NPA: 99.7% (292/293), 95% CI: (98.1, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 98.1% Bootstrap 95% CI: (93.8, 100) Average NPA: 99.9% CI:(N/A[a])							

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Table 45: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV 33/58)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV 33/58	1	BD COR™ Result	Positive	20	0	1	0
			Negative	0	0	1	287
			Total	20	0	2	287
		PPA: 100% (20/20), 95% CI: (83.9, 100) NPA: 99.7% (293/294), 95% CI: (98.1, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	20	0	1	1
			Negative	0	0	1	286
			Total	20	0	2	287
		PPA: 100% (20/20), 95% CI: (83.9, 100) NPA: 99.3% (293/295), 95% CI: (97.6, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	20	0	0	0
			Negative	0	0	2	287
			Total	20	0	2	287
		PPA: 100% (20/20), 95% CI: (83.9, 100) NPA: 100% (291/291), 95% CI: (98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 100% CI:(N/A[a]) Average NPA: 99.7% CI:(N/A[a])							

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Table 46: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV 39/68/35)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV 39/68/35	1	BD COR™ Result	Positive	23	1	1	1
			Negative	0	0	2	282
			Total	23	1	3	283
		PPA: 100% (24/24), 95% CI: (86.2, 100) NPA: 99.3% (288/290), 95% CI: (97.5, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	22	0	1	0
			Negative	1	1	2	283
			Total	23	1	3	283
		PPA: 91.7% (22/24), 95% CI: (74.2, 97.7) NPA: 99.7% (290/291), 95% CI: (98.1, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	23	1	1	0
			Negative	0	0	2	283
			Total	23	1	3	283
		PPA: 100% (24/24), 95% CI: (86.2, 100) NPA: 99.7% (286/287), 95% CI: (98.1, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)					
Average PPA: 97.2% Bootstrap 95% CI: (92.6, 100) Average NPA: 99.5% Bootstrap 95% CI: (99.1, 99.9)							

Table 47: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV45)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV45	1	BD COR™ Result	Positive	36	3	0	0
			Negative	0	1	0	270
			Total	36	4	0	270
		PPA: 97.5% (39/40), 95% CI: (87.1, 99.6) NPA: 100% (274/274), 95% CI: (98.6, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	36	3	0	0
			Negative	0	1	0	270
			Total	36	4	0	270
		PPA: 97.5% (39/40), 95% CI: (87.1, 99.6) NPA: 100% (275/275), 95% CI: (98.6, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	36	3	0	1
			Negative	0	1	0	269
			Total	36	4	0	270
		PPA: 97.5% (39/40), 95% CI: (87.1, 99.6) NPA: 99.6% (270/271), 95% CI: (97.9, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)					
Average PPA: 97.5% Bootstrap 95% CI: (94.4, 100) Average NPA: 99.9% CI:(N/A[a])							

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Table 48: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV51)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV51	1	BD COR™ Result	Positive	17	0	2	0
			Negative	0	1	0	290
			Total	17	1	2	290
		PPA: 94.4% (17/18), 95% CI: (74.2, 99.0) NPA: 99.3% (294/296), 95% CI: (97.6, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	17	1	0	0
			Negative	0	0	2	290
			Total	17	1	2	290
		PPA: 100% (18/18), 95% CI: (82.4, 100) NPA: 100% (297/297), 95% CI: (98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	17	0	0	1
			Negative	0	1	2	289
			Total	17	1	2	290
		PPA: 94.4% (17/18), 95% CI: (74.2, 99.0) NPA: 99.7% (292/293), 95% CI: (98.1, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)					
Average PPA: 96.3% Bootstrap 95% CI: (88.1, 100) Average NPA: 99.7% CI:(N/A[a])							

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Table 49: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV52)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV52	1	BD COR™ Result	Positive	16	0	2	0
			Negative	0	1	2	289
			Total	16	1	4	289
		PPA: 94.1% (16/17), 95% CI: (73.0, 99.0) NPA: 99.3% (295/297), 95% CI: (97.6, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	16	0	0	0
			Negative	0	1	4	289
			Total	16	1	4	289
		PPA: 94.1% (16/17), 95% CI: (73.0, 99.0) NPA: 100% (298/298), 95% CI: (98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	16	0	2	0
			Negative	0	1	2	289
			Total	16	1	4	289
		PPA: 94.1% (16/17), 95% CI: (73.0, 99.0) NPA: 99.3% (292/294), 95% CI: (97.6, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)					
Average PPA: 94.1% Bootstrap 95% CI: (80.0, 100) Average NPA: 99.5% Bootstrap 95% CI: (99.1, 99.9)							

Table 50: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using BD SurePath™ Cervical Specimens (HPV 59/56/66)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV 59/56/66	1	BD COR™ Result	Positive	37	1	3	2
			Negative	2	0	4	260
			Total	39	1	7	262
		PPA: 95.0% (38/40), 95% CI: (83.5, 98.6) NPA: 98.2% (269/274), 95% CI: (95.8, 99.2) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	38	0	1	1
			Negative	1	1	6	261
			Total	39	1	7	262
		PPA: 95.0% (38/40), 95% CI: (83.5, 98.6) NPA: 99.3% (273/275), 95% CI: (97.4, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	37	1	2	4
			Negative	2	0	5	258
			Total	39	1	7	262
		PPA: 95.0% (38/40), 95% CI: (83.5, 98.6) NPA: 97.8% (265/271), 95% CI: (95.3, 99.0) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 95.0% Bootstrap 95% CI: (88.4, 100) Average NPA: 98.4% Bootstrap 95% CI: (97.1, 99.4)							

Table 51 is a summary table of the PPA and NPA averaged across the three sites for each result readout.

Table 51: Percent Agreement by Genotype of the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Using BD SurePath™ Cervical Specimens

			Positive Percent Agreement		Negative Percent Agreement	
Specimen Type	Genotype	Total Panel Members	Percent	95% CI	Percent	95% CI
BD SurePath™	16	315	96.2	(92.4, 99.1)	99.6	N/A[a]
	18		98.1	(95.1, 100)	98.7	(97.5, 99.8)
	45		97.5	(94.4, 100)	99.9	N/A[a]
	31		98.1	(93.8, 100)	99.9	N/A[a]
	33/58		100	N/A[a]	99.7	N/A[a]
	52		94.1	(80.0, 100)[b]	99.5	(99.1, 99.9)
	51		96.3	(88.1, 100)[b]	99.7	N/A[a]
	39/68/35		97.2	(92.6, 100)	99.5	(99.1, 99.9)
	56/59/66		95.0	(88.4, 100)[b]	98.4	(97.1, 99.4)
	HPV HR		96.8	(94.9, 98.6)	94.4	(90.9, 97.2)

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.
[b]All discordant results occurred in samples that were close to the clinical cutoff.

Using the Ct values generated for each panel member on the BD Viper™ LT and BD COR™ Systems, Deming regression analyses were conducted to determine whether a systematic bias in signal output existed between the two systems. The slope and intercept of the regression lines for each of the result readouts is illustrated in Table 52.

Table 52: Deming Regression Line Statistics for the BD Onclarity™ HPV Assay Tested on the BD Viper™ LT and BD COR™ Systems Using BD SurePath™ Cervical Specimens

HPV Result Readout	Parameter	Estimate	95% CI
HPV16	slope	1.01	(0.98, 1.03)
	intercept	-0.45	(-1.24, 0.35)
HPV18	slope	0.99	(0.97, 1.02)
	intercept	-0.15	(-0.97, 0.67)
HPV45	slope	1.02	(0.98, 1.05)
	intercept	-0.79	(-1.87, 0.29)
HPV31	slope	0.95	(0.88, 1.02)
	intercept	1.45	(-0.43, 3.32)
HPV 33/58	slope	1.00	(0.97, 1.03)
	intercept	0.09	(-0.84, 1.02)
HPV51	slope	1.03	(0.98, 1.09)
	intercept	-1.27	(-2.71, 0.17)
HPV52	slope	0.97	(0.90, 1.05)
	intercept	0.94	(-1.53, 3.41)
HPV 39/68/35	slope	1.00	(0.96, 1.04)
	intercept	-0.16	(-1.42, 1.11)
HPV 59/56/66	slope	1.00	(0.97, 1.02)
	intercept	0.06	(-0.58, 0.71)

The systematic bias estimates between two systems using the slope and intercept from the regression lines are depicted in Table 53 for different Ct value bins. The data indicate that no significant systematic bias exists in the BD COR™ System.

Table 53: Systematic Bias Estimates Using BD SurePath™ Cervical Specimens

HPV Result Readout	Ct value	Bias Estimate at Ct	95% CI
HPV16	32.3 (High Positive)	-0.18	(-0.29, -0.07)
	35.3 (Low positive)	-0.16	(-0.31, -0.00)
	38.3 (cutoff)	-0.13	(-0.35, 0.08)
	40 (negative)	-0.12	(-0.37, 0.14)
HPV18	28.2 (High Positive)	-0.33	(-0.46, -0.20)
	31.2 (Low positive)	-0.35	(-0.47, -0.22)
	34.2 (cutoff)	-0.36	(-0.52, -0.21)
	40 (negative)	-0.40	(-0.69, -0.12)
HPV45	28.2 (High Positive)	-0.30	(-0.44, -0.15)
	31.2 (Low positive)	-0.24	(-0.37, -0.12)
	34.2 (cutoff)	-0.19	(-0.36, -0.02)
	40 (negative)	-0.09	(-0.44, 0.26)
HPV31	28.2 (High Positive)	0.07	(-0.18, 0.32)
	31.2 (Low positive)	-0.08	(-0.42, 0.27)
	34.2 (cutoff)	-0.22	(-0.73, 0.29)
	40 (negative)	-0.51	(-1.38, 0.37)
HPV 33/58	28.2 (High Positive)	0.15	(-0.03, 0.32)
	31.2 (Low positive)	0.15	(-0.05, 0.36)
	34.2 (cutoff)	0.16	(-0.11, 0.42)
	40 (negative)	0.17	(-0.26, 0.59)
HPV51	28.2 (High Positive)	-0.32	(-0.46, -0.17)
	31.2 (Low positive)	-0.21	(-0.46, 0.03)
	34.2 (cutoff)	-0.11	(-0.50, 0.28)
	40 (negative)	0.08	(-0.60, 0.76)

HPV Result Readout	Ct value	Bias Estimate at Ct	95% CI
HPV52	28.2 (High Positive)	0.23	(-0.11, 0.58)
	31.2 (Low positive)	0.16	(-0.10, 0.41)
	34.2 (cutoff)	0.08	(-0.27, 0.43)
	40 (negative)	-0.06	(-0.80, 0.68)
HPV 39/68/35	28.2 (High Positive)	-0.09	(-0.23, 0.05)
	31.2 (Low positive)	-0.08	(-0.20, 0.03)
	34.2 (cutoff)	-0.07	(-0.27, 0.12)
	40 (negative)	-0.06	(-0.48, 0.36)
HPV 59/56/66	28.2 (High Positive)	-0.07	(-0.22, 0.08)
	31.2 (Low positive)	-0.09	(-0.25, 0.07)
	34.2 (cutoff)	-0.10	(-0.30, 0.09)
	40 (negative)	-0.13	(-0.42, 0.16)

PERFORMANCE CHARACTERISTICS OF CERVICAL SPECIMENS IN PRESERVCYT® SOLUTION

Clinical Performance in PreservCyt® Solution

A retrospective study was conducted to provide data to support the performance of the BD Onclarity™ HPV Assay with specimens collected in PreservCyt® Solution. In this retrospective clinical study, disease status was established using routine clinical care. The retrospective study used residual specimens and associated clinical data from the New Mexico HPV Pap Registry (NMHPVPR).[21]

The study cohort was constructed by stratified random sampling, with the size of each stratus informed by the observed cytology prevalence in the USA multi-site BD SurePath™ prospective clinical study with strata sizes constructed to model a screening population of women aged 21 to 65 years. The inclusion/exclusion criteria were selected for each stratus such that women who met the criteria had adequate follow-up according to current medical practice. All specimens in the cohort represented baseline screening cervical collection obtained from a residual PreservCyt® LBC samples between August 2013 and October 2016. The study cohort follow-up time was up to 5 years after the baseline cytology sampling. To be included in the study cohort, women with NILM and ASC-US cytology required follow up biopsy/ECC or negative follow up (last cytology = NILM, and last HPV test negative or unavailable). Negative follow-up of subjects indicates low risk of disease and was assumed to be ≤CIN1. Subjects with baseline >ASC-US cytology were only included in the study if a cervical biopsy follow-up was available. For subjects with available biopsy evaluation(s), disease status was calculated as the worst available histological diagnosis over the follow-up period (≤CIN1, CIN2, ≥CIN3).

The retrospective de-identified data from 19,879 women in the NMHPVPR were included in the study cohort. All specimens from women with baseline cytology ≥ASC-US, with available follow-up biopsy, and a random subset of 5% NILM without available follow-up biopsy were selected for HPV testing. A total of 4,820 residual samples were randomly assigned to two laboratories to be tested with the BD Onclarity™ HPV Assay on the BD Viper™ LT system and an FDA approved HPV assay as a comparator for the performance comparison. The percent of final non-reportable BD Onclarity™ HPV Assay results in the retrospective study was 0.5% (26/4,820).

In order to account for the NILM selection rate, adjusted performance estimates were calculated. The tables below summarize the adjusted data obtained for the NILM ≥30 years old), Screening ≥25 years old), and ASC-US (≥21 years old) populations.

NOTE: Estimates of the performance can be biased due to the study design and should be used only for the comparison of two HPV tests.

Table 54 shows the positivity rate of the BD Onclarity™ HPV assay in the clinical study as well as the adjusted positivity rate.

Table 54: Summary of HPV Positivity of the BD Onclarity™ HPV Assay by Testing Sites and Study Population

	BD Onclarity™ HPV HR Positivity Rate		
Testing Site	**ASC-US ≥21 years)**	**NILM ≥30 years)**	**Primary Screening ≥25 years)**
1	40.8% (248/608)	11.7% (140/1,194)	26.3% (548/2,082)
2	42.0% (241/574)	11.0% (131/1,190)	26.6% (554/2,086)
Total	41.4% (489/1,182)	11.4% (271/2,384)	26.4% (1,102/4,168)
HPV Test Invalid[a]	5	17	23
HPV Test not performed	0	11,248	13,352
Adjusted Positivity Rate	41.3%	5.1%	10.1%

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results.

PERFORMANCE CHARACTERISTICS IN THE ASC-US POPULATION (≥21 YEARS)

A total of 1,187 residual samples from women with ASC-US baseline cytology results ≥21 years old) were tested with both the BD Onclarity™ and FDA approved HPV assays. There were 1,175 samples with paired results for the ASC-US (≥21 years old) population. The results of the BD Onclarity™ HPV Assay, (HPV HR) Positive or (HPV HR) Negative, together with the pathology diagnosis are presented in Table 55.

Table 55: Results of the BD Onclarity™ HPV Assay and Pathology Diagnosis in the ASC-US Population (≥21 Years)

	Pathology Diagnosis					
BD Onclarity™ HPV Assay Result	**Negative Follow-up**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**Total**
Positive	157	124	144	38	26	489
Negative	512	115	57	9	0	693
Invalid/Missing[a]	2	2	1	0	0	5
Total	671	241	202	47	26	1,187

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results.

The performance of the BD Onclarity™ HPV Assay in detecting high-grade cervical disease ≥CIN2 and ≥CIN3) and the performance of the FDA approved HPV test is presented in Table 56. The sensitivity for detecting ≥CIN2 histology was 87.7% (64/73) for the BD Onclarity™ HPV Assay and the FDA approved HPV test. The specificity for detecting ≥CIN2 histology was 61.1% (679/1,102) for the BD Onclarity™ HPV Assay and 59.7% (658/1,102) for the FDA approved HPV test.

The sensitivity for detecting ≥CIN3 histology was 100% (26/26) for the BD Onclarity™ HPV Assay and the FDA approved HPV test. The specificity for detecting ≥CIN3 histology was 59.9% (688/1,149) for the BD Onclarity™ HPV Assay and 58.1% (667/1,149) for the FDA approved HPV test.

Table 56: Comparison of the Performance of the BD Onclarity™ HPV Assay and an FDA Approved HPV Test in the ASC-US Population (≥21 Years)

Performance Metrics	**BD Onclarity™ HPV Assay**		**FDA Approved Test**	
	Estimate	**95% CI**	**Estimate**	**95% CI**
≥CIN2; Prevalence 6.2% (73/1,175)				
Sensitivity (%)	87.7 (64/73)	(78.2, 93.4)	87.7 (64/73)	(78.2, 93.4)
Specificity (%)	61.1 (679/1,102)	(58.7, 64.4)	59.7 (658/1,102)	(56.8, 62.6)
PPV (%)	13.1 (64/487)	(11.7, 14.4)	12.6 (64/508)	(11.2, 13.8)
1-NPV (%)	1.3 (9/688)	(0.7, 2.3)	1.3 (9/667)	(0.7, 2.4)
PLR	2.28	(2.00, 2.53)	2.18	(1.91, 2.41)
NLR	0.20	(0.11, 0.35)	0.21	(0.11, 0.37)
≥CIN3; Prevalence 2.2% (26/1,175)				
Sensitivity (%)	100 (26/26)	(87.1, 100)	100 (26/26)	(87.1, 100)
Specificity (%)	59.9 (688/1,149)	(57.0, 62.7)	58.1 (667/1,149)	(55.2, 60.9)
PPV (%)	5.3 (26/487)	(5.2, 5.7)	5.1 (26/508)	(5.0, 5.5)
1-NPV (%)	0.0 (0/688)	(-0.0, 0.5)	0.0 (0/667)	(0.0, 0.5)
PLR	2.49	(2.41, 2.68)	2.38	(2.31, 2.56)
NLR	0.0	(0.00, 0.22)	0.0	(0.00, 0.22)

NOTE: Estimates of the performance can be biased due to the study design and should be used only for the comparison of two HPV tests.

ASC-US ≥21 Years) Population-Absolute Risk Estimates

Risk of disease is the probability of having disease given an HPV test outcome. The risk of disease among ASC-US (≥21 women with positive HPV HR results at 1 and 3 years was 7.3% and 11.7%, ≥CIN2) and 2.7% and 5.2% (≥CIN3 ; the HPV HR negative risk at 1 and 3 years was 0.4% and 0.9%, ≥CIN2) and 0.0% for all years ≥CIN3). The risk of disease was highest for HPV16 for both ≥CIN2 (20.2%, 30.0%) and ≥CIN3 (11.4%, 19.6% .

Table 57: Risk of ≥CIN2 at 1 and 3 Years According to Baseline HPV Result in ASC-US Subjects Age 21 and Above

BD Onclarity™ HPV Assay Test Results	Absolute Risk of Disease (%) (95% CI)		
	% With Result	≥ CIN2 1-year	≥ CIN2 3-year
HPV HR Positive	41.3	7.3 (5.0, 9.6)	11.7 (8.8, 14.6)
HPV16 Positive	6.3	20.2 (10.5, 28.8)	30.0 (18.6, 39.8)
HPV18 Positive	2.2	11.5 (0.0, 22.9)	16.1 (0.2, 29.4)
HPV45 Positive	3.0	5.5 (0.0, 12.7)	5.5 (0.0, 12.7)
HPV31 Positive	3.6	4.8 (0.0, 11.0)	7.8 (0.0, 16.0)
HPV 33/58 Positive	4.0	8.3 (0.2, 15.8)	14.7 (4.0, 24.2)
HPV52 Positive	4.8	7.0 (0.1, 13.4)	8.7 (1.1, 15.8)
HPV51 Positive	3.5	2.4 (0.0, 7.0)	4.9 (0.0, 11.2)
HPV 35/39/68 Positive	7.3	3.5 (0.0, 7.3)	6.0 (0.7, 10.9)
HPV 56/59/66 Positive	6.7	2.5 (0.0, 5.9)	8.8 (2.4, 14.9)
HPV HR Negative	58.7	0.4 (0.0, 0.9)	0.9 (0.2, 1.6)

Table 58: Risk of ≥CIN3 at 1 and 3 Years According to Baseline HPV Result in ASC-US Subjects Age 21 and Above

BD Onclarity™ HPV Assay Test Results	Absolute Risk of Disease (%) (95% CI)		
	% With Result	≥ CIN3 1-year	≥ CIN3 3-year
HPV HR Positive	41.3	2.7 (1.3, 4.2)	5.2 (3.2, 7.3)
HPV16 Positive	6.3	11.4 (3.6, 18.6)	19.6 (9.3, 28.6)
HPV18 Positive	2.2	0.0 (0.0, 0.0)	5.2 (0.0, 14.7)
HPV45 Positive	3.0	2.9 (0.0, 8.2)	2.9 (0.0, 8.2)
HPV31 Positive	3.6	2.4 (0.0, 6.9)	5.5 (0.0, 12.7)
HPV 33/58 Positive	4.0	4.3 (0.0, 10.0)	6.6 (0.0, 13.5)
HPV52 Positive	4.8	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
HPV51 Positive	3.5	0.0 (0.0, 0.0)	2.5 (0.0,7.2)
HPV 35/39/68 Positive	7.3	1.2 (0.0, 3.5)	2.4 (0.0, 5.6)
HPV 56/59/66 Positive	6.7	0.0 (0.0, 0.0)	1.4 (0.0, 4.0)
HPV HR Negative	58.7	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

NILM (≥30 Years Old) Population

The retrospective de-identified data from 13,649 women with NILM baseline cytology results (≥30 years old) were included in this study set. From this group, 2,401 were tested with both the BD Onclarity™ and FDA approved HPV assays. There were 2,288 samples with paired results for the NILM (≥30 years old) population. The results of the BD Onclarity™ HPV Assay, (HPV HR) Positive or (HPV HR) Negative, together with the pathology diagnosis are presented in Table 59.

Table 59: Results of the BD Onclarity™ HPV Assay and Pathology Diagnosis in the NILM Population (≥30 Years)

	Pathology Diagnosis					
BD Onclarity™ HPV Assay Result	**Negative Follow-up**	**Negative**	**CIN1**	**CIN2**	**>=CIN3**	**Total**
Positive	21	142	65	18	25	271
Negative	567	1,403	114	16	13	2,113
Invalid/Missing[a]	4	12	1	0	0	17
Not selected for Testing	11,248	0	0	0	0	11,248
Total	11,840	1,557	180	34	38	13,649

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results.

The unadjusted and adjusted performance estimates of the BD Onclarity™ HPV Assay as well as the FDA approved HPV test for detecting ≥CIN2 and ≥CIN3 in the NILM population ≥30 years) is presented in Table 60. The BD Onclarity™ adjusted sensitivity was 59.7% for ≥CIN2 and 65.8% for ≥CIN3.

Table 60: Performance of the BD Onclarity™ HPV Assay and an FDA Approved HPV Assay in the NILM Population ≥30 Years

Performance	**Pathology Diagnosis**			
	Unadjusted Estimates		**Adjusted Estimates**	
	BD HPV	**FDA Approved HPV Test**	**BD HPV**	**FDA Approved HPV Test**
≥CIN2; unadjusted prevalence 3.0%, adjusted prevalence 0.5%				
Sensitivity (%) (95% CI)	63.2 43/68 (51.4, 73.7)	64.7 44/68 (52.8, 75.0)	59.7 (48.8, 70.8)	61.8 (50.5, 72.7)
Specificity (%) (95% CI)	89.8 1,993/2,220 (88.4, 91.0)	86.8 1,927/2,220 (85.3, 88.1)	95.2 (93.7, 96.5)	92.7 (91.0, 94.3)
PPV (%) (95% CI)	15.9 43/270 (13.0, 18.8)	13.1 44/337 (10.7, 15.3)	6.1 (4.0, 9.3)	4.3 (2.9, 6.0)
1-NPV (%) (95% CI)	1.2 25/2,018 (0.9, 1.6)	1.2 24/1,951 (0.9, 1.6)	0.2 (0.2, 0.3)	0.2 (0.1, 0.3)
PLR (95% CI)	6.2 (4.9, 7.6)	4.9 (3.9, 5.9)	12.3 (8.8, 17.7)	8.4 (6.2, 11.6)
NLR (95% CI)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)
≥CIN3; unadjusted prevalence 1.5%, adjusted prevalence 0.3%				
Sensitivity (%) (95% CI)	71.4 25/35 (54.9, 83.7)	71.4 25/35 (54.9, 83.7)	65.8 (50.0, 80.0)	66.6 (51.2, 82.1)
Specificity (%) (95% CI)	89.1 2,008/2,253 (87.8, 90.3)	86.2 1,941/2,253 (84.7, 87.5)	95.0 (93.6, 96.4)	92.6 (90.9, 94.2)
PPV (%) (95% CI)	9.3 25/270 (7.1, 11.1)	7.4 25/1,337 (5.7, 8.9)	3.6 (2.0, 5.7)	2.4 (1.4, 3.7)
1-NPV (%) (95% CI)	0.5 10/2,018 (0.3, 0.8)	0.5 10/1,951 (0.3, 0.8)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
PLR (95% CI)	6.6 (4.9, 8.1)	5.2 (3.9, 6.3)	13.2 (9.1, 19.1)	8.9 (6.4, 12.2)
NLR (95% CI)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.4 (0.2, 0.5)	0.4 (0.2, 0.5)

NOTE: Estimates of the performance can be biased due to the study design and should be used only for the comparison of two HPV tests.

Risks of Cervical Disease by HPV Genotype for the BD Onclarity™ HPV Assay

NILM (≥30 years Population-Absolute Risk Estimates

Adjusted estimates of absolute risk of ≥CIN2 and ≥CIN3 for the BD Onclarity™ HPV Assay are presented in Table 61. The adjustment of estimates is necessary as only a portion of the NILM women were selected for testing.

Table 61: Risk of ≥CIN2 at 1 and 3 Years According to Baseline HPV Result in NILM Subjects Age 30 and Above

BD Onclarity™ HPV Assay Test Results	Absolute Risk of Disease (%) (95% CI)		
	% With Result	≥ CIN2 1-year	≥ CIN2 3-year
HPV HR Positive	6.1	0.6 (0.1, 1.1)	3.4 (2.2, 4.7)
HPV16 Positive	0.8	3.6 (0.1, 7.1)	7.3 (2.2, 12.2)
HPV18 Positive	0.2	0.0 (0.0, 0.0)	12.4 (0.0, 23.3)
HPV45 Positive	0.5	0.0 (0.0, 0.0)	4.6 (0.0, 9.6)
HPV31 Positive	0.6	0.0 (0.0, 0.0)	4.1 (0.0, 8.7)
HPV 33/58 Positive	0.5	0.0 (0.0, 0.0)	2.8 (0.0, 6.6)
HPV52 Positive	0.6	1.2 (0.0, 3.5)	4.8 (0.0, 9.3)
HPV51 Positive	0.5	0.0 (0.0, 0.0)	1.5 (0.0, 4.4)
HPV 35/39/68 Positive	1.2	0.0 (0.0, 0.0)	1.3 (0.0, 3.2)
HPV 56/59/66 Positive	1.2	0.0 (0.0, 0.0)	0.7 (0.0, 1.9)
HPV HR Negative	93.9	0.0 (0.0, 0.1)	0.2 (0.1, 0.2)

Table 62: Risk of ≥CIN3 at 1 and 3 Years According to Baseline HPV Result in NILM Subjects Age 30 and Above

BD Onclarity™ HPV Assay Test Results	Absolute Risk of Disease (%) (95% CI)		
	% With Result	≥ CIN3 1-year	≥ CIN3 3-year
HPV HR Positive	6.1	0.2 (0.0, 0.6)	1.7 (0.8, 2.6)
HPV16 Positive	0.8	1.8 (0.0, 4.3)	4.7 (0.5, 8.6)
HPV18 Positive	0.2	0.0 (0.0, 0.0)	6.6 (0.0, 15.1)
HPV45 Positive	0.5	0.0 (0.0, 0.0)	1.5 (0.0, 4.4)
HPV31 Positive	0.6	0.0 (0.0, 0.0)	4.1 (0.0, 8.7)
HPV 33/58 Positive	0.5	0.0 (0.0, 0.0)	1.4 (0.0, 4.1)
HPV52 Positive	0.6	0.0 (0.0, 0.0)	1.2 (0.0, 3.6)
HPV51 Positive	0.5	0.0 (0.0, 0.0)	1.5 (0.0, 4.4)
HPV 35/39/68 Positive	1.2	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
HPV 56/59/66 Positive	1.2	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
HPV HR Negative	93.9	0.0 (0.0, 0.0)	0.1 (0.0, 0.1)

Primary Screening (≥25 Years Old) Population

The retrospective de-identified data from 17,543 women ≥25 years old were included in the study set, of which 4,191 residual samples were tested with both the BD Onclarity™ and FDA approved HPV assays. The results of the BD Onclarity™ HPV Assay, (HPV HR) Positive or (HPV HR) Negative, together with the pathology diagnosis are presented in Table 63.

Table 63: Results of the BD Onclarity™ HPV Assay and Pathology Diagnosis in the Screening Population (≥25 Years)

	Pathology Diagnosis					
BD Onclarity™ HPV Assay Result	**Negative Follow-up**	**Negative**	**CIN1**	**CIN2**	**≥CIN3**	**Total**
Positive	128	390	351	120	113	1,102
Negative	1,094	1,666	251	34	21	3,066
Invalid/Missing[a]	6	15	2	0	0	23
Not selected for Testing	13,352	0	0	0	0	13,352
Total	14,580	2,071	604	154	134	17,543

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results.

The 1 and 3 Year adjusted risks of high grade cervical disease ≥CIN2 and ≥CIN3 were calculated in the primary screening population (≥25 years) for women with different BD Onclarity™ HPV Assay results.

Table 64: Risk of ≥CIN2 at 1 and 3 Years According to Baseline HPV Result Baseline and 3-Year Cumulative Risks of Disease for Categories in the Primary Screening Population (≥25 Years)

BD Onclarity™ HPV Assay Test Results	**Absolute Risk of Disease (%) (95% CI)**		
	% With Result	**≥ CIN2 1-year**	**≥ CIN2 3-year**
HPV HR Positive	10.2	6.7 (5.5, 7.9)	11.3 (9.8, 12.8)
HPV16 Positive	1.7	19.4 (14.7, 23.9)	28.4 (22.8, 33.6)
HPV18 Positive	0.5	7.1 (1.4, 12.5)	15.8 (7.3, 23.4)
HPV45 Positive	0.8	5.8 (1.8, 9.7)	9.5 (4.3, 14.4)
HPV31 Positive	0.9	5.8 (1.9, 9.5)	13.0 (7.1, 18.4)
HPV 33/58 Positive	0.9	5.2 (1.6, 8.6)	12.5 (7.0, 17.8)
HPV52 Positive	0.9	4.9 (1.4, 8.2)	9.9 (4.9, 14.6)
HPV51 Positive	0.9	2.6 (0.1, 5.1)	4.0 (0.8, 7.1)
HPV 35/39/68 Positive	1.8	4.1 (1.9, 6.3)	6.4 (3.6, 9.1)
HPV 56/59/66 Positive	1.8	1.6 (0.2, 3.0)	3.0 (1.0, 4.7)
HPV HR Negative	89.8	0.1 (0.0, 0.1)	0.3 (0.2, 0.3)

Table 65: Risk of ≥CIN3 at 1 and 3 Years According to Baseline HPV Result in the Primary Screening Population ≥25 Years

BD Onclarity™ HPV Assay Test Results	**Absolute Risk of Disease (%) (95% CI)**		
	% With Result	**≥ CIN3 1-year**	**≥ CIN3 3-year**
HPV HR Positive	10.2	3.0 (2.2, 3.8)	5.4 (4.3, 6.5)
HPV16 Positive	1.7	11.8 (7.9, 15.5)	18.5 (13.6, 23.1)
HPV18 Positive	0.5	2.4 (0.0, 5.7)	7.8 (1.5, 13.6)
HPV45 Positive	0.8	1.5 (0.0, 3.6)	2.3 (0.0, 4.8)
HPV31 Positive	0.9	2.0 (0.0, 4.2)	6.9 (2.5, 11.0)

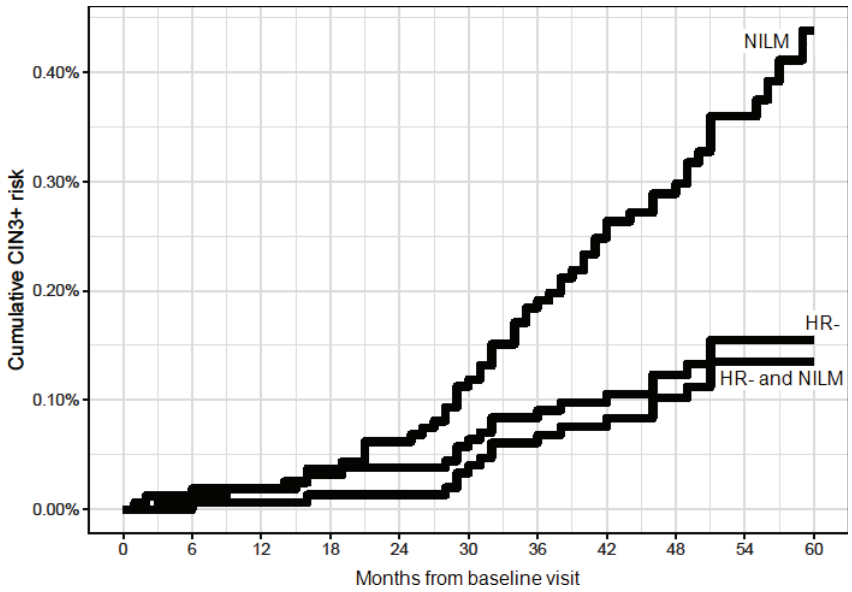
BD Onclarity™ HPV Assay Test Results	Absolute Risk of Disease (%) (95% CI)		
	% With Result	≥ CIN3 1-year	≥ CIN3 3-year
HPV 33/58 Positive	0.9	2.6 (0.0, 5.1)	6.1 (2.1, 10.0)
HPV52 Positive	0.9	1.2 (0.0, 2.9)	3.3 (0.3, 6.1)
HPV51 Positive	0.9	1.3 (0.0, 3.1)	2.7 (0.0, 5.3)
HPV 35/39/68 Positive	1.8	1.3 (0.0, 2.5)	1.3 (0.0, 2.5)
HPV 56/59/66 Positive	1.8	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
HPV HR Negative	89.8	0.0 (0.0, 0.0)	0.1 (0.0, 0.1)

1 and 3 Year Cumulative Risks of Disease for Women with NILM Cytology and Negative BD Onclarity™ HPV Test Results
The 1 and 3 year risks of disease were compared in the primary screening population between women with a NILM cytology result and women with a negative BD Onclarity™ HPV result. Women with a negative BD Onclarity™ HPV result had a 1 year risk of 0.02% and a 3-year cumulative risk of 0.09% for ≥CIN3 compared to a 1 and 3 year risks of 0.02% and 0.19%, for women with NILM cytology. The addition of a NILM cytology result to a negative BD Onclarity™ HPV result had similar ≥CIN3 risks at 1 (0.01%) and 3 (0.07%) years.

Table 66: 1 and 3-Year Cumulative Risk of Disease for Women (≥25 Years) with NILM Cytology and Negative BD Onclarity™ HPV Test Results

Subgroup	% With Result (at baseline)	≥CIN3 Risk (95% CI)		≥CIN2 Risk (95% CI)	
		1-Year	3-Year	1-Year	3-Year
NILM	91.74	0.02 (0.00, 0.04)	0.19 (0.12, 0.26)	0.06 (0.02, 0.09)	0.42 (0.32, 0.52)
HPV HR NEG	89.84	0.02 (0.00, 0.04)	0.09 (0.04, 0.14)	0. 07 (0.03, 0.11)	0.26 (0.18, 0.34)
HPV HR NEG and NILM	85.82	0.01 (0.00, 0.02)	0.07 (0.03, 0.11)	0.02 (0.00, 0.04)	0.18 (0.11, 0.24)

Figure 2: Cumulative Risk of Disease ≥CIN3 for Women with NILM Cytology, Negative BD Onclarity™ HPV Results in the Primary Screening (≥25 Years Population



Comparison of Results from the BD Onclarity™ HPV Assay for PreQuot vs. PostQuot Cervical Specimens in PreservCyt® Solution

A study was conducted to compare the performance of the BD Onclarity™ HPV Assay with PreservCyt® Solution prior to (PreQuot) or after (PostQuot) normal cytology processing. Remnant HPV negative PreservCyt® specimens that were collected during the prospective clinical study were retrieved from storage and used to create negative and positive panel members. Positive panel members were made by co-spiking HPV negative PreservCyt® specimens with HPV16 and HPV45 cell lines to achieve the required analyte levels. A panel of 250 samples containing 125 HPV negative and 125 HPV16 and HPV45 positive were created for this study. The HPV concentrations within the panel cover the full range of the assay, including levels close to the cutoff, and moderate and high positive. The technicians running the study were blinded to the panel composition. At the clinical laboratory, each panel member was aliquoted for the BD Onclarity™ HPV Assay (PreQuot), processed on the T2000 ThinPrep® Processor, and then another aliquot for the BD Onclarity™ HPV Assay was taken (PostQuot). One BD Viper™ LT and one T2000 ThinPrep® Processor were used in the study.

Table 67: Percent Agreement of the BD Onclarity™ HPV Assay PreQuot versus PostQuot Result (PreservCyt® specimens)

BD Onclarity™ HPV Assay PostQuot Result	BD Onclarity™ HPV Assay PreQuot Result					
	Overall		HPV16		HPV45	
	POS	NEG	POS	NEG	POS	NEG
POS	201	1[b]	125	0	76	0
NEG	3[a]	170	0	0	0	49
Total	204	171	125	0	76	49
PPA	98.5% (95.8%, 99.5%)		100% (97.0%, 100%)		100% (95.2%, 100%)	
NPA	99.4% (96.8%, 99.9%)		N/A		N/A	
OPA	98.9% (97.3%, 99.6%)		N/A		N/A	

All discordant specimens were analytically negative for HPV16 and HPV45.

[a] Two specimens tested positive for HPV genotype group 39/68/35 in the PreQuot and tested negative in the PostQuot. One specimen tested positive for HPV genotype group 33/58 in the PreQuot and tested negative in the PostQuot.

[b] One specimen tested negative for HPV genotype group 39/68/35 in the PreQuot and tested positive in the PostQuot.

Percent Agreement between the BD Onclarity™ HPV Assay Performed on the BD Viper™ LT System and the BD COR™ System with PreservCyt® Cervical Specimens

The percent agreement between the BD Onclarity™ HPV Assay performed on the BD Viper™ LT System and the BD COR™ System was evaluated. The panels were prepared with HPV genotypes 16, 18, 45, 31, 33/58, 35/39/68, 51, 52, and 56/59/66 where the majority of the specimens were at levels close to the cutoff. Each panel member was divided into three aliquots, where each aliquot was tested twice, once with the BD Viper™ LT System and once with the BD COR™ System at three different sites (two external sites, one in-house). All BD Viper™ LT testing occurred internally and results served as the reference.

The agreement study with PreservCyt® specimens included 312 independent panel members (221 HR HPV positive, 91 HR HPV negative) of which 306 were clinical and 6 were contrived. The 312 panel members were tested in three different sites, and samples were considered evaluable if both BD COR™ and BD Viper™ LT had reportable results. Out of 312, 306 panel members had evaluable results from all three sites, and 6 panel members had evaluable results from two sites only, resulting in 930 evaluable samples (915 clinical, 15 contrived).

The positive and negative agreement between results on the BD Viper™ LT and BD COR™ Systems were calculated for each of the three sites where BD COR™ testing occurred using the majority result on the BD Viper™ LT (two of three evaluable BD Viper™ LT system replicates for each panel member) as the comparator for each panel member. A total of 312 evaluable panel members were included. PPA and NPA were calculated separately for genotypes 16, 18, 45, 31, 33/58, 52, 51, 39/68/35, and 56/59/66. PPA and NPA estimates were also averaged across the three test sites. The positive and negative percent agreement results for PreservCyt® panel members at each site and averaged across all sites are summarized in Tables 68-76 for each result readout.

For each of the following tables, the denominator for PPA and NPA also included the reference comparator result for the samples with non-evaluable replicates and final equivocal results, as indicated in the footnotes. Equivocal results noted in the tables below are defined as one BD Viper™ LT (VLT) Positive, one negative, and one non-evaluable.

Table 68: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV16)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV16	1	BD COR™ Result	Positive	81	2	2	1
			Negative	0	1	2	217
			Total	81	3	4	218
		PPA: 98.8% (83/84), 95% CI: (93.6, 99.8) NPA: 98.2% (222/226), 95% CI: (95.5, 99.3) Number of VLT equivocal results: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 3 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	80	3	2	0
			Negative	1	0	2	218
			Total	81	3	4	218
		PPA: 98.8% (84/85), 95% CI: (93.6, 99.8) NPA: 98.7% (224/227), 95% CI: (96.2, 99.5) Number of VLT equivocal results: 1 (BD COR™ Positive) Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	80	3	2	2
			Negative	1	0	2	216
			Total	81	3	4	218
		PPA: 98.8% (84/85), 95% CI: (93.6, 99.8) NPA: 98.2% (219/223), 95% CI: (95.5, 99.3) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 1 (BD COR™ Negative)					
Average PPA: 98.8%, Bootstrap 95% CI: (97.3, 100) Average NPA: 98.4%, Bootstrap 95% CI: (96.8, 99.6)							

Table 69: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV18)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV18	1	BD COR™ Result	Positive	35	2	4	0
			Negative	0	0	4	261
			Total	35	2	8	261
		PPA: 100% (38/38), 95% CI: (90.8, 100) NPA: 98.5% (268/272), 95% CI: (96.3, 99.4) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 3 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	34	1	1	0
			Negative	1	1	7	261
			Total	35	2	8	261
		PPA: 94.7% (36/38), 95% CI: (82.7, 98.5) NPA: 99.6% (278/279), 95% CI: (98.0, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	34	2	2	0
			Negative	1	0	6	261
			Total	35	2	8	261
		PPA: 97.3% (36/37), 95% CI:(86.2, 99.5) NPA: 99.3% (269/271), 95% CI:(97.3 ,99.8) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 0 Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 97.3%, Bootstrap 95% CI: (94.1, 100) Average NPA: 99.1%, Bootstrap 95% CI: (98.3, 99.9)							

Table 70: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV31)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV31	1	BD COR™ Result	Positive	22	1	0	0
			Negative	1	0	0	280
			Total	23	1	0	280
		PPA: 95.8% (23/24), 95% CI:(79.8, 99.3) NPA: 100% (286/286), 95% CI:(98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	22	1	0	0
			Negative	1	0	0	280
			Total	23	1	0	280
		PPA: 95.8% (23/24), 95% CI:(79.8, 99.3) NPA: 100% (287/287), 95% CI:(98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 7 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	23	1	0	0
			Negative	0	0	0	280
			Total	23	1	0	280
		PPA: 100% (24/24), 95% CI:(86.2, 100) NPA: 100% (284/284), 95% CI:(98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
Average PPA: 97.2%, Bootstrap 95% CI: (90.5, 100) Average NPA: 99.9%[a]							

[a]Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Table 71: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV 33/58)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV 33/58	1	BD COR™ Result	Positive	23	0	2	1
			Negative	1	1	1	275
			Total	24	1	3	276
		PPA: 92.0% (23/25), 95% CI:(75.0, 97.8) NPA: 98.9% (282/285), 95% CI:(97.0, 99.6) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	24	1	1	0
			Negative	0	0	2	276
			Total	24	1	3	276
		PPA: 100% (25/25), 95% CI:(86.7, 100) NPA: 99.7% (285/286), 95% CI:(98.0, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 7 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	24	0	0	0
			Negative	0	1	3	276
			Total	24	1	3	276
		PPA: 96.0% (24/25), 95% CI:(80.5, 99.3) NPA: 100% (283/283), 95% CI:(98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
Average PPA: 96.0%, Bootstrap 95% CI: (89.3, 100) Average NPA: 99.4% Bootstrap 95% CI: (98.7, 99.9)							

Table 72: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV 39/68/35)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV 39/68/35	1	BD COR™ Result	Positive	29	3	1	0
			Negative	0	0	2	269
			Total	29	3	3	269
		PPA: 100% (33/33), 95% CI:(89.6, 100) NPA: 99.6% (275/276), 95% CI:(98.0, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	29	2	1	0
			Negative	0	1	2	270
			Total	29	3	3	270
		PPA: 96.9% (31/32), 95% CI:(84.3, 99.4) NPA: 99.6% (278/279), 95% CI:(98.0, 99.9) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	28	0	0	0
			Negative	1	3	3	270
			Total	29	3	3	270
		PPA: 87.9% (29/33), 95% CI:(72.7, 95.2) NPA: 100% (275/275), 95% CI:(98.6, 100) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 93.9%, Bootstrap 95% CI: (88.2, 98.7) Average NPA: 99.6%, Bootstrap 95% CI: (99.2, 100)							

Table 73: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV45)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV45	1	BD COR™ Result	Positive	35	2	2	0
			Negative	0	0	3	264
			Total	35	2	5	264
		PPA: 100% (38/38), 95% CI:(90.8, 100) NPA: 99.3% (270/272), 95% CI:(97.4, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 3 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	35	1	3	1
			Negative	0	1	2	263
			Total	35	2	5	264
		PPA: 97.4% (37/38), 95% CI:(86.5, 99.5) NPA: 98.5% (270/274), 95% CI:(96.3, 99.4) Number of VLT equivocal results: 0 Number of 2 VLT Positive, 1 non-evaluable: 1 (BD COR™ Positive) Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	33	2	0	0
			Negative	2	0	5	264
			Total	35	2	5	264
		PPA: 94.6% (35/37), 95% CI:(82.3, 98.5) NPA: 100% (271/271), 95% CI:(98.6, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 97.3%, Bootstrap 95% CI: (94.2, 100) Average NPA: 99.3%, Bootstrap 95% CI: (98.5, 99.9)							

Table 74: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV51)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV51	1	BD COR™ Result	Positive	16	1	0	0
			Negative	1	0	3	283
			Total	17	1	3	283
		PPA: 94.4% (17/18), 95% CI:(74.2, 99.0) NPA: 100% (291/291), 95% CI:(98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	17	1	2	1
			Negative	0	0	1	283
			Total	17	1	3	284
		PPA: 100% (18/18), 95% CI:(82.4, 100) NPA: 99.0% (290/293), 95% CI:(97.0, 99.7) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 6 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	16	1	0	0
			Negative	1	0	3	284
			Total	17	1	3	284
		PPA: 94.4% (17/18), 95% CI:(74.2, 99.0) NPA: 100% (290/290), 95% CI:(98.7, 100) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 3 (BD COR™ Negative)					
Average PPA: 96.3%, Bootstrap 95% CI: (90.5, 100) Average NPA: 99.4%, Bootstrap 95% CI: (98.9, 99.9)							

Table 75: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV52)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV52	1	BD COR™ Result	Positive	24	1	2	0
			Negative	0	1	4	272
			Total	24	2	6	272
		PPA: 96.2% (25/26), 95% CI:(81.1, 99.3) NPA: 99.3% (281/283), 95% CI:(97.5, 99.8) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	24	2	3	0
			Negative	0	0	3	273
			Total	24	2	6	273
		PPA: 96.3% (26/27), 95% CI:(81.7, 99.3) NPA: 98.9% (281/284), 95% CI:(96.9, 99.6) Number of VLT equivocal results: 1 (BD COR™ Negative) Number of 2 VLT Negative, 1 non-evaluable: 5 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	24	2	1	0
			Negative	0	0	5	273
			Total	24	2	6	273
		PPA: 96.3% (26/27), 95% CI:(81.7, 99.3) NPA: 99.6% (280/281), 95% CI:(98.0, 99.9) Number of VLT equivocal results: 1 (BD COR™ Negative) Number of 2 VLT Negative, 1 non-evaluable: 2 (BD COR™ Negative)					
Average PPA: 96.2%, Bootstrap 95% CI: (89.7, 100) Average NPA: 99.1%, Bootstrap 95% CI: (98.3, 99.8)							

Table 76: Percent Agreement of Results for the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Tested Using PreservCyt® Cervical Specimens (HPV 59/56/66)

HPV Result Output	Site			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
HPV 59/56/66	1	BD COR™ Result	Positive	36	1	3	1
			Negative	0	0	8	255
			Total	36	1	11	256
		PPA: 100% (37/37), 95% CI:(90.6, 100) NPA: 98.5% (269/273), 95% CI:(96.3, 99.4) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 7 (BD COR™ Negative)					
	2			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	36	1	5	1
			Negative	0	0	6	255
			Total	36	1	11	256
		PPA: 100% (37/37), 95% CI:(90.6, 100) NPA: 97.8% (268/274), 95% CI:(95.3, 99.0) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 7 (BD COR™ Negative)					
	3			BD Viper™ LT (VLT) Result			
				3 Positive	2 Positive, 1 Negative	2 Negative, 1 Positive	3 Negative
		BD COR™ Result	Positive	36	1	5	0
			Negative	0	0	6	256
			Total	36	1	11	256
		PPA: 100% (37/37), 95% CI:(90.6, 100) NPA: 98.2% (266/271), 95% CI:(95.8, 99.2) Number of VLT equivocal results: 0 Number of 2 VLT Negative, 1 non-evaluable: 4 (BD COR™ Negative)					
Average PPA: 100% Average NPA: 98.0%, Bootstrap 95% CI: (96.9, 99.1)							

Table 77 is a summary table of the PPA and NPA averaged across the three sites for each result readout.

Table 77: Percent Agreement by Genotype of the BD Onclarity™ HPV Assay between the BD Viper™ LT System and the BD COR™ System Using PreservCyt® Cervical Specimens

			Positive Percent Agreement		Negative Percent Agreement	
Specimen Type	**Genotype**	**Total Panel Members**	**Percent**	**95% CI**	**Percent**	**95% CI**
PreservCyt®	16	312	98.8	(97.3, 100)	98.4	(96.8, 99.6)
	18		97.3	(94.1, 100)	99.1	(98.3, 99.9)
	45		97.3	(94.2, 100)	99.3	(98.5, 99.9)
	31		97.2	(90.5, 100)	99.9	N/A[a]
	33/58		96.0	(89.3, 100)	99.4	(98.7, 99.9)
	52		96.2	(89.7, 100)	99.1	(98.3, 99.8)
	51		96.3	(90.5, 100)	99.4	(98.9, 99.9)
	39/68/35		93.9	(88.2, 98.7)	99.6	(99.2, 100)
	56/59/66		100	N/A[a]	98	(96.9, 99.1)
	HPV HR		98.6	(97.5, 99.5)	92.6	(88.3, 96.4)

[a] Confidence intervals for point estimates close to 100% have not been included, as suggested by FDA guidance for assay migration studies.

Using the Ct values generated for each panel member on the BD Viper™ LT and BD COR™ Systems, Deming regression analyses were conducted to determine whether a systematic bias in signal output existed between the two systems. The slope and intercept of the regression lines for each of the result readouts is illustrated in Table 78.

Table 78: Deming Regression Line Statistics for the BD Onclarity™ HPV Assay Tested on the BD Viper™ LT and BD COR™ Systems Using PreservCyt® Cervical Specimens

HPV Result Readout	Parameter	Estimate	95% CI
HPV16	slope	0.94	(0.90, 0.98)
	intercept	1.81	(0.51, 3.10)
HPV18	slope	1.00	(0.96, 1.04)
	intercept	0.11	(-0.96, 1.18)
HPV45	slope	1.00	(0.95, 1.04)
	intercept	-0.16	(-1.58, 1.26)
HPV31	slope	1.02	(0.76, 1.29)
	intercept	-0.41	(-8.15, 7.33)
HPV 33/58	slope	0.97	(0.87, 1.07)
	intercept	1.33	(-1.77, 4.43)
HPV51	slope	1.02	(0.91, 1.12)
	intercept	-0.43	(-3.39, 2.53)
HPV52	slope	0.98	(0.92, 1.04)
	intercept	0.56	(-1.14, 2.26)
HPV 39/68/35	slope	0.97	(0.90, 1.05)
	intercept	0.60	(-1.70, 2.89)
HPV 59/56/66	slope	0.97	(0.86, 1.07)
	intercept	1.08	(-2.35, 4.51)

The systematic bias estimates between the two systems using the slope and intercept from the regression lines are depicted in Table 79 for different Ct value bins. The data indicate that no significant systematic bias exists in the BD COR™ System.

Table 79: Systematic Bias Estimates Using PreservCyt® Cervical Specimens

HPV Result Readout	Ct value	Bias Estimate at Ct	95% CI
HPV16	32.3 (High Positive)	-0.23	(-0.35, -0.10)
	35.3 (Low Positive)	-0.41	(-0.59, -0.23)
	38.5 (High Negative)	-0.62	(-0.90, -0.33)
	40 (Negative)	-0.71	(-1.05, -0.37)
HPV18	29.2 (High Positive)	0.06	(-0.16, 0.29)
	32.2 (Low Positive)	0.06	(-0.21, 0.32)
	36.2 (High Negative)	0.05	(-0.32, 0.42)
	40 (Negative)	0.04	(-0.44, 0.53)
HPV45	29.2 (High Positive)	-0.24	(-0.41, -0.08)
	32.2 (Low Positive)	-0.25	(-0.45, -0.06)
	36.2 (High Negative)	-0.26	(-0.61, 0.08)
	40 (Negative)	-0.28	(-0.78, 0.23)
HPV31	29.2 (High Positive)	0.32	(-0.02, 0.66)
	32.2 (Low Positive)	0.4	(-0.40, 1.20)
	36.2 (High Negative)	0.5	(-1.31, 2.30)
	40 (Negative)	0.59	(-2.21, 3.39)
HPV 33/58	29.2 (High Positive)	0.34	(0.04, 0.65)
	32.2 (Low Positive)	0.24	(-0.07, 0.55)
	36.2 (High Negative)	0.11	(-0.52, 0.73)
	40 (Negative)	-0.02	(-1.01, 0.96)
HPV31	29.2 (High Positive)	0.06	(-0.21, 0.32)
	32.2 (Low Positive)	0.11	(-0.41, 0.62)
	36.2 (High Negative)	0.17	(-0.75, 1.09)
	40 (Negative)	0.24	(-1.08, 1.55)
HPV52	29.2 (High Positive)	-0.02	(-0.23, 0.18)
	32.2 (Low Positive)	-0.08	(-0.42, 0.25)
	36.2 (High Negative)	-0.17	(-0.71, 0.38)
	40 (Negative)	-0.24	(-1.01, 0.53)
HPV 39/68/35	29.2 (High Positive)	-0.21	(-0.45, 0.04)
	32.2 (Low Positive)	-0.29	(-0.57, -0.01)
	36.2 (High Negative)	-0.4	(-0.90, 0.11)
	40 (Negative)	-0.5	(-1.27, 0.27)
HPV 59/56/66	29.2 (High Positive)	0.06	(-0.31, 0.44)
	32.2 (Low Positive)	-0.04	(-0.36, 0.28)
	36.2 (High Negative)	-0.18	(-0.80, 0.45)
	40 (Negative)	-0.31	(-1.32, 0.70)

Performance with Self-Collected Vaginal Specimens

The performance of the BD Onclarity™ HPV assay using vaginal swab samples (FLOQSwab 5E089N, Copan Italia Spa, Brescia, Italy) was evaluated in a study as part of the VALHUDES framework, which enrolled 300 women from two Italian colposcopy centers.[20] All women were referred to colposcopy because of a recent history of abnormal cervical cytology. Each woman provided Self-collected Vaginal (SV) FLOQSwab prior to undergoing colposcopy. A standard of care Clinician-collected Cervical (CC) sample was also taken at colposcopy using a Cervex-Brush (Rovers Medical Devices, The Netherlands) which was transferred into 20 mL of PreservCyt liquid-based-cytology (LBC) medium (Hologic Inc., Bedford, MA, USA). The vaginal samples were transported to the laboratory where they were resuspended in 3 mL BD Onclarity HPV Self Collection diluent. The cervical samples and the vaginal samples were tested on the BD Viper LT platform. In the study, there were 286 patients with both valid CC and valid SV results. Data are presented in the table 80 and Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) were calculated along with two-sided 95% confidence intervals (95% CI).

Table 80: Concordance between SV and CC

Total		CC			
		HPV16 or 18	12 Other HR HPV	HR HPV Negative	Total
SV	HPV16 or 18	76	12	3	91
	12 Other HR HPV	0	93	20	113
	HR HPV Negative	2	5	75	82
	Total	78	110	98	286
PPA (HR HPV) (%): 96.3 (181/188); 95% CI: (92.5, 98.2) PPA (HPV 16 or 18) (%): 97.4 (76/78); 95% CI: (91.1, 99.3) PPA (12 Other HR HPV) (%): 84.5 (93/110); 95% CI: (76.6, 90.1) NPA (HR HPV) (%): 76.5 (75/98); 95% CI: (67.2, 83.8)					

The absolute sensitivity, specificity and ratio of sensitivity and specificity (SV:CC) are presented in Table 81.

Table 81: The absolute sensitivity, specificity and ratio of sensitivity and specificity (SV:CC)

Sensitivity for ≥CIN2			Sensitivity for ≥CIN3			Specificity for ≤CIN1		
SV (%), (95% CI)	CC (%), (95% CI)	Ratio, (95% CI)	SV (%), (95% CI)	CC (%), (95% CI)	Ratio, (95% CI)	SV (%), (95% CI)	CC (%), (95% CI)	Ratio, (95% CI)
90.4, (82.1, 95.0)	89.2, (80.7, 94.2)	1.01 (0.97,1.06)	91.7 (80.4, 96.7)	91.7 (80.4, 96.7)	1.00 (0.94, 1.06)	36.3 (30.0, 43.1)	43.2 (36.6, 50.0)	0.83 (0.73, 0.94)

Limit of Detection at the Clinical Cutoff

The limit of detection (LoD) at the HPV clinical cutoff was determined for the BD Onclarity™ HPV Assay using HPV positive cell lines: SiHa (HPV16), HeLa (HPV18) and MS751 (HPV45) and cloned plasmid DNA containing the sequences for the following HPV genotypes: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 in BD SurePath™ Preservative Fluid and PreservCyt® Solution using a HPV-negative cell line (C33A) background. Plasmids and cell lines were diluted to concentrations below, above and at the expected LoD levels. A minimum of forty-five replicates were tested for each HPV cell line and plasmid for HPV16, HPV18 and HPV45. Twenty replicates were tested for each HPV plasmid of the other 11 high risk HPV genotypes. A minimum of three lots of reagents were utilized across three BD Viper™ LT Systems. The LoD is the level of HPV DNA in the specimen that has positive results below the clinical cutoff at least 95% of the time. The maximum LoD value which was produced from the most conservative reagent lot is in Table 80. HPV positive samples were also prepared by spiking SiHa (HPV16), HeLa (HPV18) and MS751 (HPV45) cell lines in clinical vaginal matrix. In addition, the assay sensitivity for HPV 16, 18 and 45 was found to be equivalent between the clinical vaginal matrix and simulated C33A cell background matrix.

The LoDs for the remaining 11 HR HPV genotypes in C33A background are presented in Table 82.

Table 82: Limit of Detection

Media	Target	LOD (Cells or Copies/mL)[a]	95% Confidence Interval	Media
			Lower	Upper
BD SurePath™	SiHa (HPV16)	50	37	67
	HeLa (HPV18)	199	154	256
	MS751 (HPV45)	862	669	1,111
	HPV16	251	193	326
	HPV18	1,083	1,000	1,267
	HPV45	1,261	1,154	1,358
	HPV31	830	718	879
	HPV33	1,665	1,495	2,030
	HPV35	1,550	1,472	1,655
	HPV39	1,794	1,617	1,862
	HPV51	1,522	1,315	1,613
	HPV52	814	776	951
	HPV56	1,090	937	1,185
	HPV58	2,369	2,231	6,631
	HPV59	1,000	942	1,152
	HPV66	862	823	916
	HPV68	2,392	2,227	2,646
PreservCyt®	SiHa (HPV16)	156	114	239
	HeLa (HPV18)	158	105	290
	MS751 (HPV45)	701	497	1,146
	HPV16	132	93	168
	HPV18	419	355	486
	HPV45	482	405	559
	HPV31	333	294	372
	HPV33	581	373	769
	HPV35	529	463	592
	HPV39	633	470	786
	HPV51	439	372	503
	HPV52	416	260	607
	HPV56	329	280	375
	HPV58	891	784	1,003
	HPV59	302	141	438
	HPV66	264	222	304
	HPV68	753	340	1,099
	SiHa (HPV16)	9.7	7.7	13.4
	HeLa (HPV18)	51	46	56
	MS751 (HPV45)	305	284	343
	HPV31	692	650	817
	HPV33	1,376	1272	1451
	HPV35	1,552	1317	1780

BD Onclarity HPV Self Collection Diluent	HPV39	1,531	1419	1685
	HPV51	1,229	1155	1353
	HPV52	833	744	934
	HPV56	836	737	911
	HPV58	2,990	2656	7818
	HPV59	772	722	899
	HPV66	701	646	767
	HPV68	2,079	1995	2125

[a] Concentrations are provided in cells/mL (for HPV 16, 18 and 45) or copies/mL (for 11 other hrHPV genotypes) in the 2.2 mL sample input tube (1.7 mL diluent tube after specimen addition) for SurePath™ Preservative Fluid and PreservCyt® Solution. For self-collected vaginal samples, concentrations are provided and in cells/mL (for HPV 16, 18 and 45) or copies/mL (for 11 other hrHPV genotypes) in the 3.0 mL sample input tube for BD Onclarity HPV Self Collection Diluent.

Analytical equivalence of the BD Onclarity™ HPV Assay with BD SurePath™, PreservCyt®, and vaginal specimens was confirmed between the BD COR™ System and the BD Viper™ LT System. SurePath™ and PreservCyt® panels were created using low positive and moderate positive levels. For the vaginal samples, only the low positive level (C95) was tested. Panel members were prepared with HPV positive cell lines: SiHa (HPV16) or MS751 (HPV45) diluted in HPV negative matrix. For BD SurePath™ and PreservCyt® HPV negative clinical matrix was used. For vaginal samples, an HPV-negative cell line (C33A) matrix was used.

Each panel member in BD SurePath™ and PreservCyt® had pre-analytical sample dilution performed by the BD COR™ System, hand pipetting (manual) or MultiProcessor (BD SurePath™ only) (Table 83). Each panel was tested for the presence or absence of the HPV targets on the BD COR™ System. As a reference, manually diluted panels were tested on the BD Viper™ LT System. Table 83 depicts the Ct values for each of the pre-processing steps on the BD COR™ as well as manual processing on the BD Viper™ LT for each of the panel members. Analytical equivalence of the BD Onclarity™ HPV Assay with BD SurePath™ and PreservCyt® specimens was also verified for BD COR™ Dual GX System.

Table 83: Confirmation of Limit of Detection for cervical samples on the BD COR™ System, Mean Differences and Percent Correct, by Target and Level

Media	Target	Target Level[c]	Platform-Conversion	N (Amplification results)	Mean Ct	Difference in Mean Ct (90% CI)	N	N Positive	Percent Positive (95% CI)
BD SurePath™	HPV16	Low Positive (220 cells/mL)	COR-COR	90	35.55	-0.06 (-0.20, 0.07)	90	90	100 (95.91, 100)
			COR-Manual	89	35.72	0.11 (-0.03, 0.25)	89[a]	89	100 (95.86, 100)
			COR-MultiProcessor	90	35.55	-0.06 (-0.20, 0.07)	90	90	100 (95.91, 100)
			VLT-Manual	90	35.61	–	90	90	100 (95.91, 100)
	HPV45	Low Positive (3,793 cells/mL)	COR-COR	90	32.58	-0.40 (-0.49, -0.31)	90	90	100 (95.91, 100)
			COR-Manual	90	32.75	-0.23 (-0.33, -0.13)	90	90	100 (95.91, 100)
			COR-MultiProcessor	90	32.56	-0.42 (-0.51, -0.33)	90	90	100 (95.91, 100)
			VLT-Manual	90	32.98	–	90	89	98.89 (93.97, 99.80)
	HPV16	Moderate Positive (660 cells/mL)	COR-COR	90	33.93	-0.15 (-0.27, -0.03)	90	90	100 (95.91, 100)
			COR-Manual	90	33.97	-0.11 (-0.22, 0.00)	90	90	100 (95.91, 100)
			COR-MultiProcessor	90	33.77	-0.31 (-0.41, -0.21)	90	90	100 (95.91, 100)
			VLT-Manual	90	34.08	–	90	90	100 (95.91, 100)
	HPV45	Moderate Positive (11,379 cells/mL)	COR-COR	90	31.01	-0.33 (-0.39, -0.26)	90	90	100 (95.91, 100)
			COR-Manual	91	31.24	-0.10 (-0.17, -0.03)	91[b]	91	100 (95.95, 100)
			COR-MultiProcessor	90	31.12	-0.22 (-0.31, -0.14)	90	90	100 (95.91, 100)
			VLT-Manual	90	31.34	–	90	90	100 (95.91, 100)
PreservCyt®	HPV16	Low Positive (717 cells/mL)	COR-COR	90	35.28	-0.12 (-0.26, 0.03)	90	90	100 (95.9, 100)
			COR-Manual	90	35.04	-0.36 (-0.49, -0.22)	90	90	100 (95.9, 100)
			VLT-Manual	90	35.40	N/A	90	90	100 (95.9, 100)
	HPV45	Low Positive (5,425 cells/mL)	COR-COR	90	32.09	-0.38 (-0.48, -0.29)	90	90	100 (95.9, 100)
			COR-Manual	90	31.88	-0.59 (-0.68, -0.50)	90	90	100 (95.9, 100)
			VLT-Manual	89	32.47	N/A	90	89	98.9 (94.0, 99.8)
	HPV16	Moderate Positive (2,151 cells/mL)	COR-COR	90	33.41	-0.39 (-0.52, -0.24)	90	90	100 (95.9, 100)
			COR-Manual	90	33.32	-0.48 (-0.59, -0.37)	90	90	100 (95.9, 100)
			VLT-Manual	89	33.80	N/A	90	89	98.9 (94.0, 99.8)
	HPV45	Moderate Positive (16,275 cells/mL)	COR-COR	90	30.68	-0.30 (-0.37, -0.24)	90	90	100 (95.9, 100)
			COR-Manual	90	30.49		90	90	100 (95.9, 100)
			VLT-Manual	90	30.98	N/A	90	90	100 (95.9, 100)

[a] A sample with an extraction error was not repeated.
[b] One sample was repeated due to an extraction error and the whole run was repeated due to aliquot issues, which resulted in 2 valid results for the same sample.

[c] Concentrations are provided as cells/mL in the BD SurePath™ or PreservCyt® vial (undiluted).

Table 84: Confirmation of Limit of Detection for Vaginal Samples on the BD COR system

Media	Target	Target Level[a]	Platform-Conversion	N (Amplification results)	Mean Ct	Difference in Mean Ct (90% CI)	N	N Positive	Percent Positive (95% CI)
BD Onclarity HPV Self Collection Diluent	HPV 16	Low Positive (9.7)	COR	90	36.39	-0.11 (-0.27, 0.05)	90	90	100% (95.9, 100)
			VLT	89	36.50		90	85	94.4% (87.7, 97.6)
	HPV 45	Low Positive (305)	COR	90	32.83	-0.16 (-0.23,-0.08)	90	90	100% (95.9, 100)
			VLT	90	32.99		90	89	98.9% (94.0, 99.8)

[a] Concentrations are provided as cells/mL in the 3.0 mL sample input tube for BD Onclarity HPV Self Collection Diluent.

Analytical Specificity

A panel of bacteria, yeast and cultured viruses, including those found in female urogenital specimens along with cloned plasmid DNA containing high-risk and low-risk HPV target sequences was used to evaluate the analytical specificity of the BD Onclarity™ HPV Assay on the BD Viper™ LT System. Each potential cross-reactant was tested in BD SurePath™ Preservative Fluid and PreservCyt® containing a HPV-negative cell line (C33A). The microorganisms are described in Table 85. Bacteria and yeast were tested at ≥ $1x10^6$ CFU/mL, HPV plasmid DNA were tested at ≥ $1x10^6$ copies/mL and non-HPV viruses were tested at ≥ $1x10^6$ vp/mL. The BD Onclarity™ HPV Assay did not cross-react with any of the microorganisms tested.

Table85: Microorganisms Tested for Analytical Specificity

Actinomyces israelii	*Proteus vulgaris*	HPV56
Atopobium vaginae	*Providencia stuartii*	HPV58
Bacteroides fragilis	*Pseudomonas aeruginosa*	HPV59
Bacteroides ureolyticus	*Staphylococcus aureus*	HPV66
Bifidobacterium adolescentis	*Staphylococcus epidermidis*	HPV68
Bifidobacterium breve	*Streptococcus agalactiae*	HPV16
Bifidobacterium longum ssp. *longum*	*Streptococcus pyogenes*	HPV6
Chlamydia trachomatis	*Ureaplasma urealyticum*	HPV11
Clostridium perfringens	*Candida albicans*	HPV26
Corynebacterium genitalium	*Trichomonas vaginalis*	HPV30
Enterobacter cloacae ssp. *cloacae*	Adenovirus, type 5	HPV34
Enterococcus faecalis	HCMV, AD169 Strain	HPV53
Enterococcus faecium	HSV1	HPV67
Escherichia coli	HSV2	HPV69
Fusobacterium nucleatum ssp. *Nucleatum*	EBV-1, B95-8 Strain	HPV70
Gardnerella vaginalis	HIV-1	HPV73
Klebsiella pneumoniae ssp. *ozaenae*	HPV16	HPV82
Lactobacillus acidophilus	HPV18	HPV97
Mycobacterium smegmatis	HPV31	
Mycoplasma genitalium	HPV33	
Neisseria gonorrhoeae	HPV35	
Peptostreptococcus anaerobius	HPV39	
Prevotella bivia	HPV45	
Prevotella disiens	HPV51	
Proteus mirabilis	HPV52	

Interfering Substances

Contrived HPV negative and positive specimens were tested in the presence or absence of each potential interfering substance that may be present in clinical cervical or self-collected vaginal specimens. The concentrations of exogenous and endogenous substances tested in this study represent concentrations that could potentially occur during specimen collection. Substances tested are described in Table 86.

The concentrations tested represent the highest level of a substance assessed with the BD Onclarity™ HPV Assay that did not result in interference.

Table 86: Potential Interfering Substances

	BD SurePath™	PreservCyt®	Vaginal Self-Collection
Potential Interfering Substance	**Concentration Tested**	**Concentration Tested**	**Concentration Tested**
KY® Vaginal Lubricant [a]	6% (w/v)	10% (w/v)	8% (w/v)
VCF® Vaginal Contraceptive Film	10% (w/v)	10% (w/v)	3% (w/v)
VCF® Vaginal Contraceptive Foam	10% (w/v)	10% (w/v)	10% (w/v)
Nonoxynol-9 Contraceptive Gel, 4%	10% (w/v)	10% (w/v)	1% (w/v)
Monistat® 3[a]	2% (w/v)	1.4% (w/v)	1.8% (w/v)
Clotrimazole 7	10% (w/v)	10% (w/v)	10% (w/v)
Tioconazole Ointment, 6.5%	2% (w/v)	2% (w/v)	1% (w/v)
Clindamycin Vaginal Cream	8% (w/v)	10% (w/v)	9% (w/v)
Summer's Eve® Douche	10% (v/v)	10% (v/v)	10% (v/v)
Zovirax® (Acyclovir) Cream [a]	7% (w/v)	10% (w/v)	10% (w/v)
Vandazole™ Gel (Metronidazole Vaginal Gel, 0.75%)	10% (w/v)	10% (w/v)	10% (w/v)
Summer's Eve Deodorant	3% (w/v)	2% (w/v)	1% (w/v)
Replens™ Moisturizer [a]	10% (w/v)	10% (w/v)	2.8% (w/v)
Bovine Mucin [a]	8% (v/v)	8% (v/v)	7.8% (w/v)
Progesterone	20 ng/mL	20 ng/mL	20 ng/mL
Estradiol	1.2 ng/mL	1.2 ng/mL	1.2 ng/mL
Whole Blood[a]	4% (v/v)	5% (v/v)	1% (v/v)
Leukocytes	$1x10^6$ cells/mL	$1x10^6$ cells/mL	$1x10^6$ cells/mL
Semen	10% (v/v)	10% (v/v)	10% (v/v)
Acetic Acid Wash[b]		5% (v/v)	
Blood + Acetic Acid Wash[b]		5% Blood (v/v) 2.5% Acetic Acid Wash (v/v)	
Estrace [a], 0.01%			7% (w/v)
Crinone[a], 4%			2% (w/v)
Preparation H [a]			6% (w/v)

[a] This sub-set of substances was tested on the BD COR™ System because they may most challenge the pipetting system, e.g., gels, salves and mucins. Those substances that are soluble were not included because the assay chemistry remains unchanged.

[b] Acetic Acid Wash consists of 1 part Glacial Acetic Acid: 9 parts CytoLyt® solution.

BD Viper™ LT System Precision

An in-house precision study was performed utilizing panels consisting of HPV negative cervical clinical specimen matrix spiked with HPV cell lines (SiHa or MS751), and pooled negative and positive cervical clinical specimens. Tables 87 to 90 show the outcome for the HPV positive and negative panel members with the BD Onclarity™ HPV Assay on the BD Viper™ LT System. The overall CV (%) for contrived samples ranged from 0.90% to 1.84% in BD SurePath™ and from 1.10% to 1.53% in PreservCyt®. The overall CV (%) for pooled HPV positive clinical specimens ranged from 2.01% to 5.63% in BD SurePath™ and from 3.64% to 6.45% in PreservCyt®.

Table 87: Summary of BD Viper™ LT Precision Panel (Contrived Specimens in cervical matrix) and Agreement Rates for BD Onclarity™ HPV Assay Precision Study

Media	HPV Genotype	HPV Target Source	HPV Panel Level[a] (cells/mL)	Total Tested	Total Positive	Percent Positive	95% CI	
							Lower	Upper
BD SurePath™	HPV16	SiHa cells	50	216	207	95.83%	92.27%	97.79%
			150	215	213	99.07%	96.67%	99.74%
	HPV45	MS751 cells	862	216	214	99.07%	96.69%	99.75%
			2,586	216	216	100%	98.25%	100%
PreservCyt®	HPV16	SiHa cells	163	216	216	100%	98.25%	100%
			489	216	216	100%	98.25%	100%
	HPV45	MS751 cells	1,233	216	216	100%	98.25%	100%
			3,699	216	216	100%	98.25%	100%

[a] Concentrations are provided in cells/mL in the 2.2 mL sample input tube (1.7 mL diluent tube after specimen addition).

Table 88: Summary of BD Viper™ LT Precision Panel (Clinical Cervical Specimens) and Agreement Rates for BD Onclarity™ HPV Assay Precision Study

Media	HPV Genotype	HPV Target Source	HPV Panel Level	Mean HPV Ct	Total Tested	Total Correct	Percent Agreement	95% CI	
								Lower	Upper
BD SurePath™	HPV16	Pooled Clinical	Negative	N/A	216	216	100% Negative	98.25%	100%
	HPV18	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV31	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV 33/58	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV 39/68/35	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV45	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV51	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV52	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV 59/56/66	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV16	Pooled Clinical HPV16	Positive	34.75	216	216	100% Positive	98.25%	100%
	HPV18	Pooled Clinical HPV18		30.60	216	216	100% Positive	98.25%	100%
	HPV31	Pooled Clinical HPV31		32.92	216	182	84.26% Positive	78.81%	88.51%
	HPV 33/58	Pooled Clinical HPV 33/58		30.34	216	216	100% Positive	98.25%	100%
	HPV45	Pooled Clinical HPV45		32.48	216	173	80.09% Positive	74.26%	84.87%
	HPV52	Pooled Clinical HPV52		31.58	216	216	100% Positive	98.25%	100%

Media	HPV Genotype	HPV Target Source	HPV Panel Level	Mean HPV Ct	Total Tested	Total Correct	Percent Agreement	95% CI	
								Lower	Upper
PreservCyt®	HPV16	Pooled Clinical	Negative	N/A	216	216	100% Negative	98.25%	100%
	HPV18	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV31	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV 33/58	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV 39/68/35	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV45	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV51	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV52	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV 59/56/66	Pooled Clinical		N/A	216	216	100% Negative	98.25%	100%
	HPV16	Pooled Clinical HPV16	Positive	35.45	216	212	98.15% Positive	95.34%	99.28%
	HPV18	Pooled Clinical HPV18		30.16	216	216	100% Positive	98.25%	100%
	HPV31	Pooled Clinical HPV31		30.21	216	216	100% Positive	98.25%	100%
	HPV 33/58	Pooled Clinical HPV 33/58		30.81	216	216	100% Positive	98.25%	100%
	HPV45	Pooled Clinical HPV45		30.57	216	216	100% Positive	98.25%	100%
	HPV52	Pooled Clinical HPV52		30.47	216	215	99.54% Positive	97.43%	99.92%

Table 89: Variance Component Analysis Results for Contrived Specimens in cervical matrix in BD Onclarity™ HPV Assay on BD Viper™ LT Precision Study

Media	HPV Cell Line	Level[a]	Mean Ct	Between-Operator		Between-Instrument		Between-Reagent		Between-Day		Between-Run		Within-run		Total	
				SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
BD SurePath™	SiHa (HPV16)	Low Positive (50 cells/mL)	36.59	0.10	0.28	0.11	0.30	0.08	0.22	0.00	0.00	0.00	0.00	0.65	1.78	0.67	1.84
		Moderate Positive (150 cells/mL)	34.98	0.00	0.00	0.12	0.33	0.03	0.09	0.00	0.00	0.17	0.50	0.55	1.56	0.59	1.68
	MS751 (HPV45)	Low Positive (862 cells/mL)	32.02	0.00	0.00	0.09	0.27	0.03	0.09	0.00	0.00	0.16	0.51	0.27	0.84	0.33	1.02
		Moderate Positive (2,586 cells/mL)	30.54	0.00	0.00	0.08	0.27	0.00	0.00	0.00	0.00	0.12	0.38	0.23	0.77	0.27	0.90
PreservCyt®	SiHa (HPV16)	Low Positive (163 cells/mL)	34.51	N/A	N/A	0.02	0.06	0	0	0.17	0.50	0.18	0.53	0.47	1.35	0.53	1.53
		Moderate Positive (489 cells/mL)	33.22	N/A	N/A	0	0	0.04	0.13	0.08	0.23	0.13	0.39	0.34	1.02	0.37	1.13
	MS751 (HPV45)	Low Positive (1,233 cells/mL)	31.93	N/A	N/A	0.10	0.30	0.09	0.28	0.04	0.13	0.15	0.46	0.36	1.13	0.41	1.29
		Moderate Positive (3,699 cells/mL)	30.19	N/A	N/A	0.12	0.39	0.05	0.18	0.09	0.31	0.14	0.45	0.26	0.85	0.33	1.10

[a] Concentrations are provided in cells/mL in the 2.2 mL sample input tube (1.7 mL diluent tube after specimen addition).

Table 90: Variance Component Analysis Results for Clinical Cervical Specimens in BD Onclarity™ HPV Assay on BD Viper™ LT Precision Study

Media	HPV Panel Member	Mean Ct	Between-Operator		Between-Instrument		Between-Reagent Lot		Between-Day		Between-Run		Within-Run		Total	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
BD SurePath™	Clinical Positive HPV16	34.75	0.00	0.00	0.25	0.72	0.00	0.00	0.00	0.00	0.00	0.00	1.56	4.49	1.58	4.54
	Clinical Positive HPV18	30.60	0.00	0.00	0.00	0.00	0.12	0.38	0.13	0.42	0.00	0.00	1.16	3.78	1.17	3.83
	Clinical Positive HPV31	32.92	0.06	0.18	0.12	0.36	0.18	0.54	0.00	0.00	0.00	0.00	1.68	5.09	1.69	5.13
	Clinical Positive HPV 33/58	30.34	0.00	0.00	0.04	0.12	0.00	0.00	0.12	0.38	0.00	0.00	0.60	1.97	0.61	2.01
	Clinical Positive HPV45	32.48	0.23	0.69	0.35	1.07	0.18	0.56	0.00	0.00	0.00	0.00	1.77	5.46	1.83	5.63
	Clinical Positive HPV52	31.58	0.24	0.76	0.09	0.28	0.00	0.00	0.19	0.61	0.00	0.00	1.39	4.40	1.43	4.51
PreservCyt®	Clinical Positive HPV16	35.45	N/A	N/A	0.25	0.72	0.00	0.00	0.60	1.68	0.00	0.00	1.79	5.05	1.90	5.37
	Clinical Positive HPV18	30.16	N/A	N/A	0.00	0.00	0.00	0.00	0.50	1.65	0.00	0.00	1.88	6.24	1.95	6.45
	Clinical Positive HPV31	30.21	N/A	N/A	0.08	0.25	0.00	0.00	0.43	1.43	0.00	0.00	1.01	3.34	1.10	3.64
	Clinical Positive HPV 33/58	30.81	N/A	N/A	0.00	0.00	0.19	0.62	0.72	2.34	0.00	0.00	1.34	4.35	1.53	4.98
	Clinical Positive HPV45	30.57	N/A	N/A	0.00	0.00	0.17	0.54	0.00	0.00	0.00	0.00	1.20	3.93	1.21	3.96
	Clinical Positive HPV52	30.47	N/A	N/A	0.00	0.00	0.00	0.00	0.67	2.21	0.00	0.00	1.44	4.74	1.59	5.23

BD COR™ System Precision

An in-house precision study was performed utilizing panels consisting of HPV negative cervical clinical specimen matrix spiked with HPV cell lines (SiHa or MS751), and pooled negative and positive cervical clinical specimens. The positive cervical clinical panel members were prepared with pooled high risk positive specimens (HPV16, HPV18, HPV45, HPV31, HPV 33/58, and HPV52) in BD SurePath™ and PreservCyt®. Tables 91 and 92 show the outcome for the HPV positive and negative panel members with the BD Onclarity™ HPV Assay on the BD COR™ System. The overall CV (%) for contrived samples ranged from 0.66% to 1.57% in BD SurePath™ and from 0.63% to 1.43% in PreservCyt®. The overall CV (%) for pooled HPV positive cervical clinical specimens ranged from 2.11% to 7.76% in BD SurePath™ and from 2.69% to 8.90% in PreservCyt®.

Table 91: Summary of Precision Panel (Contrived Specimens in cervical matrix) and Agreement Rates for BD Onclarity™ HPV Assay on the BD COR™ System

Media	HPV Cell Line	Level[a]	Percent Positive	95% Confidence Interval		Mean Ct	Within-Run		Between-Run		Total	
				Lower	Upper		SD	%CV	SD	%CV	SD	%CV
BD SurePath™	SiHa cells (HPV16)	Low Positive (220 cells/mL)	100 (72/72)	94.9	100	35.70	0.44	1.22	0.25	0.71	0.56	1.57
		Moderate Positive (660 cells/mL)	100 (72/72)	94.9	100	33.92	0.40	1.17	0.14	0.42	0.44	1.28
	MS751 cells (HPV45)	Low Positive (3,793 cells/mL)	100 (72/72)	94.9	100	32.64	0.32	0.97	0.10	0.31	0.37	1.14
		Moderate Positive (11,379 cells/mL)	100 (72/72)	94.9	100	31.04	0.18	0.56	0.08	0.26	0.20	0.66
PreservCyt®	SiHa cells (HPV16)	Low Positive (717 cells/mL)	100 (72/72)	94.9	100	35.26	0.50	1.43	0.00	0.00	0.50	1.43
		Moderate Positive (2,151 cells/mL)	100 (72/72)	94.9	100	33.34	0.30	0.89	0.00	0.00	0.33	0.99
	MS751 cells (HPV45)	Low Positive (5,425 cells/mL)	100 (72/72)	94.9	100	31.99	0.26	0.80	0.00	0.00	0.28	0.88
		Moderate Positive (16,275 cells/mL)	100 (72/72)	94.9	100	30.53	0.15	0.50	0.07	0.23	0.19	0.63

[a] Concentrations are provided as cells/mL in the BD SurePath™ or PreservCyt® vial (undiluted).

Table 92: Summary of Precision Panel (Cervical Clinical Specimens) and Agreement Rates for BD Onclarity™ HPV Assay on the BD COR™ System

Media	HPV Genotype	HPV Target Source	Level	Percent Agreement	95% Confidence Interval		Mean Ct	Within-Run		Between-Run		Total	
					Lower	Upper		SD	%CV	SD	%CV	SD	%CV
BD SurePath™	NA	Pooled Clinical	Negative	100 (72/72)	94.9	100	NA	NA	NA	NA	NA	NA	NA
	HPV16	Pooled Clinical HPV16	Positive	95.8 (69/72)	88.5	98.6	34.83	1.95	5.61	0.16	0.46	2.08	5.98
	HPV18	Pooled Clinical HPV18	Positive	97.2 (70/72)	90.4	99.2	32.12	2.46	7.67	0.00	0.00	2.49	7.76
	HPV31	Pooled Clinical HPV31	Positive	100 (72/72)	94.9	100	30.48	0.64	2.10	0.05	0.16	0.64	2.11
	HPV 33/58	Pooled Clinical HPV 33/58	Positive	100 (72/72)	94.9	100	31.42	1.57	5.01	0.00	0.00	1.57	5.01
	HPV45	Pooled Clinical HPV45	Positive	100 (72/72)	94.9	100	31.33	0.94	2.99	0.33	1.07	1.05	3.36
	HPV52	Pooled Clinical HPV52	Positive	91.7 (66/72)	83.0	96.1	31.83	1.86	5.84	0.00	0.00	1.91	6.00

Media	HPV Genotype	HPV Target Source	Level	Percent Agreement	95% Confidence Interval		Mean Ct	Within-Run		Between-Run		Total	
					Lower	Upper		SD	%CV	SD	%CV	SD	%CV
PreservCyt®	NA	Pooled Clinical	Negative	95.8 (69/72)	88.5	98.6	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	HPV16	Pooled Clinical HPV16	Positive	95.8 (69/72)	88.5	98.6	36.58	1.01	2.76	0.00	0.00	1.01	2.76
	HPV18	Pooled Clinical HPV18	Positive	80.6 (58/72)	70.0	88.1	33.64	2.99	8.88	0.00	0.00	2.99	8.90
	HPV31	Pooled Clinical HPV31	Positive	100 (72/72)	94.9	100	31.29	1.67	5.32	0.00	0.00	1.67	5.32
	HPV 33/58	Pooled Clinical HPV 33/58	Positive	97.2 (69/71)[a]	90.3	99.2	33.11	2.04	6.17	1.07	3.23	2.30	6.96
	HPV45	Pooled Clinical HPV45	Positive	100 (72/72)	94.9	100	31.14	0.84	2.69	0.00	0.00	0.84	2.69
	HPV52	Pooled Clinical HPV52	Positive	100 (72/72)	94.9	100	31.69	1.57	4.96	0.74	2.35	1.86	5.88

[a] There was one unresolved result that was excluded.

BD Viper™ LT System Reproducibility

Panels consisting of HPV negative BD SurePath™ cervical clinical specimen matrix spiked with HPV cell lines (SiHa or MS751), and pooled negative and positive cervical clinical specimens were tested for reproducibility at three sites.

Two operators per site tested one panel per day, over a total of nine days. This reproducibility study utilized three reagent lots for a total of eighteen runs performed at each site.

All valid test results were included for calculation of negativity or positivity rates. The number of replicates per panel member ranged from 156 to 159 due to excluded data from operator error, a negative control failure, and an extraction error on the BD Viper™ LT system. There were no false positive results in 158 tests performed on the pooled negative clinical panel member (See Table 93). Percent positive results along with 95% confidence intervals for the positive panel members are shown in Table 93.

Analysis of variance of the Ct scores from valid tests performed on positive panel members (see Table 94) yielded overall CV (%) for contrived samples ranging from of 1.7% to 1.8%. The overall CV (%) for pooled HPV positive clinical specimens ranged from 2.9% to 5.6%.

Table 93: Results by Sample Type and Panel Member for Lot and Site

Sample Type	Level[a]	Lot	Percent Agreement	Site	Percent Agreement	95% CI	
						Lower	Upper
Pooled negative clinical sample	Negative	1	100 (51/51)	1	100 (53/53)		
		2	100 (53/53)	2	100 (54/54)		
		3	100 (54/54)	3	100 (51/51)		
		All	100 (158/158)	All	100 (158/158)	97.6	100
SiHa (HPV16)	Low Positive (50 cells/mL)	1	100 (51/51)	1	100 (54/54)		
		2	98.1 (53/54)	2	98.1 (53/54)		
		3	100 (54/54)	3	100 (51/51)		
		All	99.4 (158/159)	All	99.4 (158/159)	96.5	99.9
SiHa (HPV16)	Moderate Positive (150 cells/mL)	1	100 (50/50)	1	100 (53/53)		
		2	100 (54/54)	2	100 (54/54)		
		3	100 (54/54)	3	100 (51/51)		
		All	100 (158/158)	All	100 (158/158)	97.6	100
MS751 (HPV45)	Low Positive (862 cells/mL)	1	96.3 (52/54)	1	94.4 (51/54)		
		2	96.1 (49/51)	2	94.1 (48/51)		
		3	94.1 (48/51)	3	98.0 (50/51)		
		All	95.5 (149/156)	All	95.5 (149/156)	91.0	97.8
MS751 (HPV45)	Moderate Positive (2,586 cells/mL)	1	98.1 (53/54)	1	100 (54/54)		
		2	100 (51/51)	2	98.0 (50/51)		
		3	100 (51/51)	3	100 (51/51)		
		All	99.4 (155/156)	All	99.4 (155/156)	96.5	99.9

Sample Type	Level[a]	Lot	Percent Agreement	Site	Percent Agreement	95% CI	
						Lower	Upper
Pooled HPV16 clinical sample	Positive	1	100 (51/51)	1	98.1 (53/54)		
		2	100 (54/54)	2	96.3 (52/54)		
		3	94.4 (51/54)	3	100 (51/51)		
		All	98.1 (156/159)	All	98.1 (156/159)	94.6	99.4
Pooled HPV18 clinical sample	Positive	1	100 (54/54)	1	100 (54/54)		
		2	100 (51/51)	2	100 (51/51)		
		3	100 (51/51)	3	100 (51/51)		
		All	100 (156/156)	All	100 (156/156)	97.6	100
Pooled HPV45 clinical sample	Positive	1	57.4 (31/54)	1	55.6 (30/54)		
		2	66.7 (34/51)	2	68.6 (35/51)		
		3	60.8 (31/51)	3	60.8 (31/51)		
		All	61.5 (96/156)	All	61.5 (96/156)	53.7	68.8
Pooled HPV31 clinical sample	Positive	1	64.8 (35/54)	1	74.1 (40/54)		
		2	74.5 (38/51)	2	76.5 (39/51)		
		3	76.5 (39/51)	3	64.7 (33/51)		
		All	71.8 (112/156)	All	71.8 (112/156)	64.3	78.3
Pooled HPV 33/58 clinical sample	Positive	1	96.3 (52/54)	1	96.3 (52/54)		
		2	100 (51/51)	2	96.1 (49/51)		
		3	96.1 (49/51)	3	100 (51/51)		
		All	97.4 (152/156)	All	97.4 (152/156)	93.6	99.0
Pooled HPV52 clinical sample	Positive	1	100 (54/54)	1	100 (54/54)		
		2	100 (51/51)	2	100 (51/51)		
		3	100 (51/51)	3	100 (51/51)		
		All	100 (156/156)	All	100 (156/156)	97.6	100

[a] Concentrations are provided in cells/mL in the 2.2 mL Diluent Tube (1.7 mL diluent tube after specimen addition).

Table 94: Overall Mean, Standard Deviation, and Coefficients of Variation (%) for Cycle Threshold

				Stand Deviation (SD) and Percent Coefficient of Variation (% CV)													
				Within-Run		Between-Run		Between-Operator		Between-Site		Between-Lot		Between-Day		Total	
Sample Type	Level[a]	N	Mean	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
SiHa (HPV16)	Low Positive (50 cells/mL)	159	36.36	0.6	1.7	0.0	0.0	0.1	0.4	0.2	0.6	0.1	0.2	0.0	0.0	0.6	1.8
	Moderate Positive (150 cells/mL)	158	35.03	0.6	1.6	0.0	0.0	0.0	0.0	0.1	0.3	0.1	0.4	0.0	0.0	0.6	1.7
MS751 (HPV45)	Low Positive (862 cells/mL)	156	32.90	0.5	1.6	0.1	0.2	0.0	0.0	0.3	0.8	0.1	0.4	0.0	0.0	0.6	1.8
	Moderate Positive (2,586 cells/mL)	156	31.41	0.5	1.6	0.0	0.0	0.2	0.7	0.1	0.1	0.0	0.0	0.0	0.0	0.6	1.7
Pooled HPV16 clinical sample	Positive	159	35.22	1.5	4.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.8	0.3	0.9	1.6	4.5
Pooled HPV18 clinical sample	Positive	156	30.47	1.1	3.5	0.0	0.0	0.1	0.3	0.3	1.0	0.0	0.0	0.0	0.0	1.1	3.6
Pooled HPV45 clinical sample	Positive	156	33.35	1.8	5.3	0.3	1.0	0.0	0.0	0.3	0.8	0.0	0.0	0.0	0.0	1.8	5.5
Pooled HPV31 clinical sample	Positive	156	33.21	1.8	5.4	0.0	0.0	0.0	0.0	0.0	0.0	0.5	1.5	0.0	0.0	1.9	5.6
Pooled HPV 33/58 clinical sample	Positive	156	30.73	1.4	4.5	0.2	0.7	0.0	0.0	0.1	0.4	0.2	0.6	0.0	0.0	1.4	4.6
Pooled HPV52 clinical sample	Positive	156	30.08	0.8	2.6	0.2	0.8	0.0	0.0	0.3	1.1	0.0	0.0	0.0	0.0	0.9	2.9

[a] Concentrations are provided in cells/mL in the 2.2 mL Diluent Tube (1.7 mL diluent tube after specimen addition).

NOTE: Only replicates with detected viral load were included in the variance components analysis.

BD COR™ System Reproducibility

Site-to-Site and Lot-to-Lot Reproducibility

Panels consisting of BD SurePath™ or PreservCyt® HPV negative cervical clinical specimen matrix spiked with HPV cell lines (SiHa, HeLa, or MS751), and pooled negative and positive clinical cervical specimens were tested for evaluation of reproducibility at three sites.

The Site-to-Site Reproducibility design included two operators per site testing one panel per day, over a total of five days. This reproducibility study utilized one reagent lot for a total of ten runs performed at each site.

The Lot-to-Lot Reproducibility design included two operators testing one panel per day, over a total of five days per lot. This reproducibility study utilized three reagent lots for a total of ten runs per lot. All valid test results were included for calculation of negativity or positivity rates. The number of replicates per panel member ranged from 89 to 90 due to excluded data from operator error, a negative control failure, and an extraction error on the BD COR™ System. Percent negative and positive results along with 95% confidence intervals are shown in Tables 95 and 97.

Site-to-Site

Analysis of variance of the Ct score results from valid tests performed on BD SurePath™ positive panel members (see Table 96) yielded overall CV (%) for contrived samples ranging from 0.92% to 1.43%. The overall CV (%) for pooled HPV positive cervical clinical specimens ranged from 2.38% to 6.95%.

Analysis of variance of the Ct score results from valid tests performed on PreservCyt® positive panel members (see Table 96) yielded overall CV (%) for contrived samples ranging from 0.71% to 1.53%. The overall CV (%) for pooled HPV positive cervical clinical specimens ranged from 2.89% to 9.21%.

Lot-to-Lot

Analysis of variance of the Ct score results from valid tests performed on BD SurePath™ positive panel members (see Table 98) yielded overall CV (%) for contrived samples ranging from 0.58% to 1.56%. The overall CV (%) for pooled HPV positive cervical clinical specimens ranged from 2.10% to 7.67%.

Analysis of variance of the Ct score results from valid tests performed on PreservCyt® positive panel members (see Table 98) yielded overall CV (%) for contrived samples ranging from 0.66% to 1.69%. The overall CV (%) for pooled HPV positive cervical clinical specimens ranged from 3.59% to 7.81%.

Table 95: Results by Sample Type and Panel Member for Site-to-Site Reproducibility

BD SurePath™	Pooled negative clinical sample	Negative	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	SiHa (HPV16)	Low Positive (220 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	SiHa (HPV16)	Moderate Positive (660 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	MS751 (HPV45)	Low Positive (3,793 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	MS751 (HPV45)	Moderate Positive (11,378 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV16 clinical sample	Positive	1	100 (30/30)		
			2	96.7 (29/30)		
			3	100 (30/30)		
			All	98.9 (89/90)	94.0	99.8
	Pooled HPV18 clinical sample	Positive	1	96.7 (29/30)		
			2	96.7 (29/30)		
			3	96.7 (29/30)		
			All	96.7 (87/90)	90.7	98.9
	Pooled HPV45 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV31 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV 33/58 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV52 clinical sample	Positive	1	90.0 (27/30)		
			2	100 (30/30)		
			3	96.7 (29/30)		
			All	95.6 (86/90)	89.1	98.3

Media	Sample Type	Level[a]	Site	Percent Agreement	95% CI	
					Lower	Upper
PreservCyt®	Pooled negative clinical sample	Negative	1	100 (30/30)		
			2	100 (30/30)		
			3	90.0 (27/30)		
			All	96.7 (87/90)	90.7	98.9
	SiHa (HPV16)	Low Positive (717 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	SiHa (HPV16)	Moderate Positive (2,151 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	MS751 (HPV45)	Low Positive (5,425 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	MS751 (HPV45)	Moderate Positive (16,275 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV16 clinical sample	Positive	1	96.7 (29/30)		
			2	93.3 (28/30)		
			3	100 (30/30		
			All	96.7 (87/90)	90.7	98.9
	Pooled HPV18 clinical sample	Positive	1	86.7 (26/30)		
			2	90.0 (27/30)		
			3	90.0 (27/30)		
			All	88.9 (80/90)	80.7	93.9
	Pooled HPV45 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV31 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV 33/58 clinical sample	Positive	1	96.6 (28/29)[b]		
			2	90.0 (27/30)		
			3	93.3 (28/30)		
			All	93.3 (83/89)	80.1	96.9
	Pooled HPV52 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100

[a] Concentrations are provided as cells/mL in the BD SurePath™ or PreservCyt® vial (undiluted).

[b] There was one unresolved result that was excluded.

Table 96: Overall Mean, Standard Deviation, and Coefficients of Variation (%) for Cycle Threshold for Site-to-Site Reproducibility on the BD COR™ System

Media	Sample Type	Level[a]	N	Mean Ct	Within-Run		Between-Run		Between-Site		Total	
					SD	%CV	SD	%CV	SD	%CV	SD	%CV
BD SurePath™	SiHa cells (HPV16)	Low Positive (220 cells/mL)	90	35.47	0.45	1.28	0.23	0.64	0.00	0.00	0.51	1.43
		Moderate Positive (660 cells/mL)	90	33.86	0.34	1.00	0.16	0.47	0.00	0.00	0.37	1.10
	MS751 cells (HPV45)	Low Positive (3,793 cells/mL)	90	32.62	0.26	0.78	0.10	0.32	0.13	0.41	0.31	0.94
		Moderate Positive (11,378 cells/mL)	90	31.08	0.17	0.56	0.10	0.33	0.19	0.60	0.29	0.92
	Pooled HPV16 Clinical Sample	Positive	90	35.13	2.02	5.76	0.48	1.36	0.75	2.13	2.22	6.32
	Pooled HPV18 Clinical Sample	Positive	90	32.43	2.16	6.65	0.00	0.00	0.61	1.88	2.25	6.95
	Pooled HPV31 Clinical Sample	Positive	90	30.38	0.70	2.32	0.00	0.00	0.16	0.53	0.72	2.38
	Pooled HPV 33/58 Clinical Sample	Positive	90	31.35	1.44	4.59	0.56	1.77	0.00	0.00	1.54	4.92
	Pooled HPV45 Clinical Sample	Positive	90	31.13	1.22	3.92	0.00	0.00	0.00	0.00	1.22	3.92
	Pooled HPV52 Clinical Sample	Positive	90	31.74	1.53	4.82	0.21	0.65	0.00	0.00	1.56	4.90
PreservCyt®	SiHa cells (HPV16)	Low Positive (717 cells/mL)	90	35.28	0.53	1.49	0.00	0.00	0.02	0.04	0.54	1.53
		Moderate Positive (2,151 cells/mL)	90	33.33	0.29	0.88	0.07	0.22	0.14	0.42	0.33	1.00
	MS751 cells (HPV45)	Low Positive (5,425 cells/mL)	90	32.01	0.24	0.75	0.00	0.00	0.17	0.53	0.29	0.91
		Moderate Positive (16,275 cells/mL)	90	30.54	0.15	0.48	0.06	0.19	0.12	0.40	0.22	0.71
	Pooled HPV16 Clinical Sample	Positive	90	36.46	1.24	3.39	0.00	0.00	0.00	0.00	1.24	3.39
	Pooled HPV18 Clinical Sample	Positive	90	33.50	3.08	9.21	0.00	0.00	0.00	0.00	3.08	9.21
	Pooled HPV31 Clinical Sample	Positive	90	31.19	1.84	5.90	0.00	0.00	0.00	0.00	1.84	5.90
	Pooled HPV 33/58 Clinical Sample	Positive	89	33.12	2.04	6.16	0.83	2.50	0.22	0.65	2.21	6.68
	Pooled HPV45 Clinical Sample	Positive	90	31.03	0.80	2.58	0.00	0.00	0.00	0.00	0.90	2.89
	Pooled HPV52 Clinical Sample	Positive	90	31.39	1.87	5.95	0.00	0.00	0.47	1.49	1.92	6.13

[a] Concentrations are provided as cells/mL in the BD SurePath™ or PreservCyt® vial (undiluted).

Table 97: Results by Sample Type and Panel Member for Lot-to-Lot Reproducibility

BD SurePath™	Pooled Clinical Sample	Negative	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	SiHa cells (HPV16)	Low Positive (220 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
		Moderate Positive (660 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	MS751 cells (HPV45)	Low Positive (3,793 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
		Moderate Positive (11,378 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV16 clinical sample	Positive	1	100 (30/30)		
			2	90.0 (27/30)		
			3	96.7 (29/30)		
			All	95.6 (86/90)	89.1	98.3
	Pooled HPV18 clinical sample	Positive	1	96.7 (29/30)		
			2	96.7 (29/30)		
			3	76.7 (23/30)		
			All	90.0 (81/90)	82.1	94.7
	Pooled HPV31 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV 33/58 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV45 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV52 clinical sample	Positive	1	96.7 (29/30)		
			2	96.7 (29/30)		
			3	100 (30/30)		
			All	97.8 (88/90)	92.3	99.4

Media	Sample Type	Level[a]	Lot	Percent Agreement	95% CI	
					Lower	Upper
PreservCyt®	Pooled Clinical Sample	Negative	1	100 (30/30)		
			2	93.3 (28/30)		
			3	96.7 (29/30)		
			All	96.7 (87/90)	90.7	98.9
	SiHa cells (HPV16)	Low Positive (717 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
		Moderate Positive (2,151 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	MS751 cells (HPV45)	Low Positive (5,425 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
		Moderate Positive (16,275 cells/mL)	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV16 clinical sample	Positive	1	96.7 (29/30)		
			2	93.3 (28/30)		
			3	96.7 (29/30)		
			All	95.6 (86/90)	89.1	98.3
	Pooled HPV18 clinical sample	Positive	1	83.3 (25/30)		
			2	93.3 (28/30)		
			3	86.7 (26/30)		
			All	87.8 (79/90)	79.4	93
	Pooled HPV31 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV 33/58 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	96.7 (29/30)		
			All	98.9 (89/90)	94.0	99.8
	Pooled HPV45 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100
	Pooled HPV52 clinical sample	Positive	1	100 (30/30)		
			2	100 (30/30)		
			3	100 (30/30)		
			All	100 (90/90)	95.9	100

[a] Concentrations are provided as cells/mL in the BD SurePath™ or PreservCyt® vial (undiluted).

Table 98: Overall Mean, Standard Deviation, and Coefficients of Variation (%) for Cycle Threshold for Lot-to-Lot Reproducibility on the BD COR™ System

Media	Sample Type	Level[a]	N	Mean Ct Score	Within-Run		Between-Run		Between-Lot		Total	
					SD	%CV	SD	%CV	SD	%CV	SD	%CV
BD SurePath™	SiHa cells (HPV16)	Low Positive (220 cells/mL)	90	35.55	0.49	1.38	0.00	0.00	0.00	0.00	0.56	1.56
		Moderate Positive (660 cells/mL)	90	33.93	0.46	1.36	0.00	0.00	0.00	0.00	0.46	1.36
	MS751 cells (HPV45)	Low Positive (3,793 cells/mL)	90	32.58	0.28	0.87	0.07	0.20	0.06	0.18	0.30	0.91
		Moderate Positive (11,378 cells/mL)	90	31.01	0.16	0.52	0.08	0.25	0.03	0.08	0.18	0.58
	Pooled HPV16 clinical sample	Positive	87	35.36	2.14	6.06	0.00	0.00	0.00	0.00	2.20	6.22
	Pooled HPV18 clinical sample	Positive	90	32.42	2.39	7.38	0.00	0.00	0.60	1.84	2.49	7.67
	Pooled HPV31 clinical sample	Positive	90	30.3	0.62	2.06	0.00	0.00	0.13	0.43	0.64	2.10
	Pooled HPV 33/58 clinical sample	Positive	90	31.19	1.36	4.37	0.32	1.02	0.52	1.67	1.50	4.79
	Pooled HPV45 clinical sample	Positive	90	31.09	0.93	2.99	0.43	1.38	0.10	0.33	1.03	3.32
	Pooled HPV52 clinical sample	Positive	90	31.78	1.65	5.21	0.39	1.23	0.00	0.00	1.70	5.35
PreservCyt®	SiHa cells (HPV16)	Low Positive (717 cells/mL)	90	35.28	0.57	1.60	0.00	0.00	0.08	0.24	0.57	1.62
		Moderate Positive (2,151 cells/mL)	90	33.41	0.55	1.64	0.12	0.35	0.07	0.22	0.56	1.69
	MS751 cells (HPV45)	Low Positive (5,425 cells/mL)	90	32.09	0.29	0.92	0.00	0.00	0.09	0.29	0.31	0.96
		Moderate Positive (16,275 cells/mL)	90	30.68	0.13	0.43	0.00	0.00	0.08	0.26	0.20	0.66
	Pooled HPV16 clinical sample	Positive	90	36.06	1.99	5.52	0.00	0.00	0.24	0.66	2.01	5.56
	Pooled HPV18 clinical sample	Positive	90	33.88	2.50	7.37	0.87	2.57	0.00	0.00	2.65	7.81
	Pooled HPV31 clinical sample	Positive	90	31.47	1.57	4.99	0.00	0.00	0.33	1.06	1.61	5.10
	Pooled HPV 33/58 clinical sample	Positive	90	32.78	1.94	5.92	0.94	2.86	0.00	0.00	2.15	6.57
	Pooled HPV45 clinical sample	Positive	90	31.08	1.10	3.53	0.00	0.00	0.00	0.00	1.12	3.59
	Pooled HPV52 clinical sample	Positive	90	31.48	2.03	6.46	0.00	0.00	0.00	0.00	2.03	6.46

[a] Concentrations are provided as cells/mL in the BD SurePath™ or PreservCyt® vial (undiluted).

Cross-Contamination

BD Viper™ LT System

A study was performed to evaluate the risk of producing a false positive result in either the same run (within run cross-contamination) or in a subsequent run (between run carryover contamination) on the BD Viper™ LT System. Multiple runs were performed across three instruments comprising a total of 225 HPV negative replicates. Each run consisted of specimens containing an HPV negative cell line (C33A) with and without CaSki cells spiked at a target level higher than 95% of HPV16 target levels observed in cervical clinical samples. HPV positive and negative specimens were arranged in an alternating checkerboard pattern. The overall contamination rate for the BD SurePath™ Preservative Fluid was 0.44% (0.08%, 2.47%) and for PreservCyt® was 0.00%.

BD COR™ System

A study was performed to evaluate the risk of producing a false positive result in either the same run (within run cross-contamination) or in a subsequent run (between run carryover contamination) on the BD COR™ System. At least thirty runs were tested for each sample type: BD SurePath™ and PreservCyt®. Each run, arranged in an alternating checkerboard pattern, consisted of specimens containing an HPV negative cell line (C33A) with and without CasKi cells spiked at a target level higher than 95% of HPV16 target levels observed in cervical clinical samples. The overall contamination rate for the BD SurePath™ Preservative Fluid and PreservCyt® specimens was 0.00%. The overall contamination rates for BD COR™ Dual GX System were 0.22% for the BD SurePath™ Preservative Fluid and 0.00% for PreservCyt® specimens.

In a BD PrepMate™ contamination study, the potential contamination rate contributed by the BD PrepMate™ System was calculated as 0.00%.

In a T2000 ThinPrep® Processor study, the potential contamination rate contributed by the T2000 ThinPrep® Processor was calculated to be 0.00%.

INTERPRETATION OF TABLES

Symbols and Abbreviations

Symbols

(+)	Positive
(-)	Negative
#	Number
%	Percentage

Abbreviations

ASC-US	Atypical squamous cells of undetermined significance
BHQ	Black Hole Quencher
CFU	Colony Forming Units
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIR	Cumulative Incidence Rates
CPR	Central Pathology Review
Ct	Cycle Threshold
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
GT	Genotype
H&E	Hematoxylin and Eosin
HPV	Human Papillomavirus HR High Risk
INF	Infinity
LAST	Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions
LBC	Liquid Based Cytology
LCD	Liquid Crystal Display
LR	Likelihood Ratios
mL	milliliter
NA	Not applicable
NEG	Negative
ng	nanogram
NILM	Negative for intraepithelial lesion or malignancy
NLR	Negative Likelihood Ratio
NPA	Negative Percent Agreement
NPV	Negative Predictive Value
p16	Immunohistochemical stain for the qualitative detection of the $p16^{INK4a}$ protein
PCR	Polymerase Chain Reaction
PLR	Positive Likelihood Ratio
POS	Positive
PPA	Positive Percent Agreement
PPV	Positive Predictive Value
QC	Quality Control
SD	Standard Deviation
SDS	Safety Data Sheet
UNSAT	Unsatisfactory

Appendix I Vaginal Self-Collection Instruction

R_x Only

IVD

Self-Collection with the BD Onclarity™ HPV Assay

The Copan Floqswab® to be used for the collection of vaginal specimens for use with the BD Onclarity™ HPV Assay. Users should read and carefully follow instructions. If you have any questions or difficulties with the collection process described below, please contact your healthcare provider for more information.
Should unexpected events not described in these instructions occur during self-collection, inform your healthcare provider.

WARNINGS
Inform your healthcare provider if you have used any substances such as vaginal creams, gels, lubricants, etc. within 24 hours prior to collection.
If swab is dropped/touched in the area below the red mark, discard and request a new swab. The swab should not touch any other surface prior to inserting into vagina.

DO NOT USE:

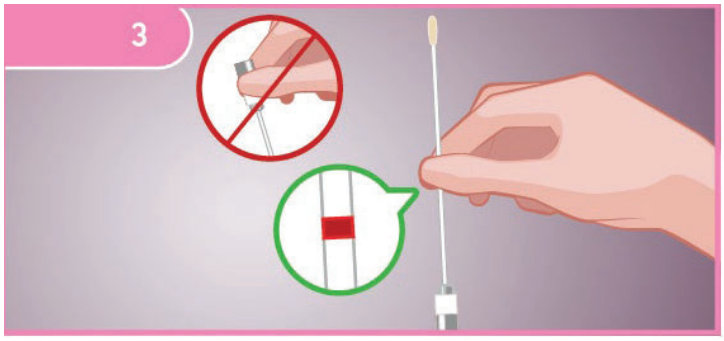
- During pregnancy or within three months after giving birth
- If recently undergone gynecological surgery
- In case of unusual bleeding or pelvic pain

INSTRUCTIONS

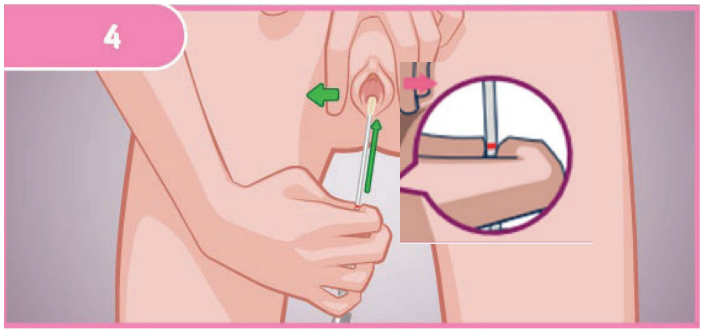
1. **Wash your hands with soap and water.**

2. **Twist cap to break seal. Carefully pull cap off the tube to remove the swab. Do not touch the soft swab tip or lay the swab down. If swab is dropped or touched in the area below the red mark, discard and request a new swab. The swab should not touch any other surface prior to inserting into the vagina.**

3. **Hold the swab at the red mark with your dominant hand (the hand that you write with).**

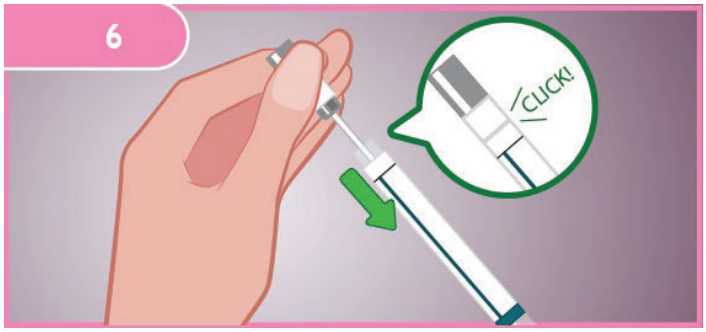


4. **Standing in a comfortable position, use the free hand to spread the skin of the vaginal opening while carefully inserting the swab up to the red mark.**



5. **Gently rotate swab for 10-30 seconds and carefully withdraw the swab.**

6. **Place swab back into the tube and securely recap.**



7. **After collection, return the recapped swab to the healthcare provider.**

REFERENCES

1. Pirog EC, Kleter B, Olgac S, Bobkiewicz P, Lindeman J, Quint WG, et al. (2000). Prevalence of human papillomavirus DNA in different histological subtypes of cervical adenocarcinoma. *The American Journal of Pathology*, 157(4): 1055–1062.
2. Rodríguez-Carunchio L, Soveral I, Steenbergen RDM, Torné A, Martinez S, Fusté P, et al. (2015). HPV-negative carcinoma of the uterine cervix: a distinct type of cervical cancer with poor prognosis. BJOG, 122(1): 119–127.
3. CDC. (2016). Genital HPV Infection - Fact Sheet. http://www.cdc.gov/std/hpv/stdfact-hpv.htm
4. WHO. (2015). Human papillomavirus (HPV) and cervical cancer. Fact sheet N°380 http://www.who.int/mediacentre/factsheets/fs380/en/.
5. National Cancer Institute. (2018). Surveillance, Epidemiology, and End Results Program-Cervical Cancer.https://seer.cancer.gov/statfacts/html/cervix.html
6. Doorbar J, Egawa N, Griffin H, Kranjec C & Murakami I. (2015). Human papillomavirus molecular biology and disease association. *Reviews in Medical Virology*, 25 Suppl 1, 2–23.
7. Kjær SK, Frederiksen K, Munk C, Iftner T. (2010). Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst.,102(19): 1478–88.
8. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, et al. (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *The Lancet Oncology*, 11(11): 1048–56.
9. Li N, Franceschi S, Howell-Jones R, Snijders P J & Clifford GM. (2011). Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: Variation by geographical region, histological type and year of publication. *International Journal of Cancer*, 128(4): 927–35.
10. Tjalma WA & Depuydt CE. (2013). Cervical cancer screening: which HPV test should be used-L1 or E6/E7? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 170(1): 45–46.
11. Tjalma WA & Depuydt CE. (2014). Cervical atypical glandular cells and false negative HPV testing: a dramatic reality of the wrong test at the right place. *European Journal of Gynaecological Oncology*, 35(2): 117–20.
12. Higuchi R, Fockler C, Dollinger G & Watson R. (1993). Kinetic PCR analysis: real-time monitoring of DNA amplification reactions. *Biotechnology* (NY), 11(9): 1026–30.
13. Clinical and Laboratory Standards Institute. 2005. Approved Guideline M29-A3. Protection of laboratory workers from occupationally acquired infections, 3rd ed., CLSI, Wayne, PA.
14. Garner JS. (1996). Hospital Infection Control Practices Advisory Committee, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Guideline for isolation precautions in hospitals. *Infect. Control Hosp. Epidemiol.* 17: 53–80.
15. US Department of Health and Human Services. (2007). “Biosafety in microbiological and biomedical laboratories.” HHS Publication (CDC), 5th ed. US Government Printing Office, Washington, DC.
16. Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC). Official Journal L262, 17/10/2000, p. 0021–0045.
17. Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, et al. (2007). 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *American Journal of Obstetrics and Gynecology*, 197 (4): 346–55.
18. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC, for members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med 2012;136: 1266–1297 Available at http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.LGT200570?code=coap-site (Accessed 12/28/16)
19. Massad LS, Einstein MH, Huh WK, Katki HA, et al. (2013). 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Percursors: for the 2012 ASCCP Consensus Guidelines Conference. *Journal of Lower Genital Tract Disease*. 17 (5). S1-S27.
20. Extended VALHUDES study (NCT04788849). Martinelli, M., A. Latsuzbaia, J. Bonde, H. Pedersen, A. D. Iacobone, F. Bottari, A. F. Piana*, et al.* "Performance of BD Onclarity HPV Assay on Floqswabs Vaginal Self-Samples." [In eng]. *Microbiol Spectr* (Feb 7 2024): e0287223. https://doi.org/10.1128/spectrum.02872-23.

Technical Service and Support: In the United States contact BD at 1.800.638.8663 or bd.com.

For regions outside of the United States, contact your local BD representative or bd.com.

Change History

Revision	Date	Change Summary
06	2023-03	Added claim for use of PreservCyt® Solution. Removed catalog numbers 443837 and 444072 and added 445328 and 445329. Replaced catalog number 441996 with 440330. Added a note to perform a second test on any specimen with a positive result for high risk HPV types in the Instructions for Use with the BD COR™ System section. Removed all references to “GT” results. Updated Symbols Glossary. Made typographical and formatting updates.
07	2023-05	Made typographical and formatting updates.
08	2024-XX	Added claim for self-collected vaginal specimens collected in a healthcare environment. Updated Symbols Glossary. Added clarification about usage of Ct values and/or curves in Limitations of the Procedure section. Added catalog number 445416 Made typographical and formatting updates. Updated Symbols glossary

SYMBOLS GLOSSARY

Please refer to product labeling for applicable symbols.

Symbol	Meaning
	Manufacturer
	Authorized representative in the European Community
	Authorised representative in Switzerland
	Date of manufacture
	Use-by date
	Batch code
	Catalogue number
	Serial number
	Sterile
	Sterilized using aseptic processing techniques
	Sterilized using ethylene oxide
	Sterilized using irradiation
	Sterilized using steam or dry heat
	Do not resterilize
	Non-sterile
	Do not use if package is damaged and consult *instructions for use*
	Sterile fluid path
	Sterile fluid path (ethylene oxide)
	Sterile fluid path (irradiation)
	Fragile, handle with care
	Keep away from sunlight
	Keep dry
	Lower limit of temperature
	Upper limit of temperature
	Temperature limit
	Humidity limitation
	Biological risks
	Do not re-use
	Consult *instructions for use* or consult electronic *instructions for use*
	Caution
	Contains or presence of natural rubber latex
	In vitro diagnostic medical device
	Negative control
	Positive control
	Contains sufficient for <n> tests
	For IVD performance evaluation only
	Non-pyrogenic
	Patient number
	This way up

Symbol	Meaning
	Do not stack
	Single sterile barrier system
	Contains or presence of phthalate: combination of bis(2-ethylhexyl) phthalate (DEHP) and benzyl butyl phthalate (BBP)
	Collect separately Indicates separate collection for waste of electrical and electronic equipment required.
	CE marking: Signifies European technical conformity
	Device for near-patient testing
	Device for self-testing
	This only applies to US: "Caution: Federal Law restricts this device to sale by or on the order of a licensed practitioner."
	Country of manufacture "CC" shall be replaced by either the two letter or the three letter country code.
	Collection time
	Cut
	Peel here
	Collection date
	Keep away from light
	Hydrogen gas is generated
	Perforation
	Start panel sequence number
	End panel sequence number
	Internal sequence number
	<Box #> / <Total Boxes>
	Medical device
	Contains hazardous substances
	Ukrainian conformity mark
	Meets FCC requirements per 21 CFR Part 15
	UL product certification for US and Canada
	Unique device identifier
	Importer
	Place patient label in framed area only
	Magnetic resonance (MR) safe
	Magnetic resonance (MR) conditional
	Magnetic resonance (MR) unsafe
	This Product Contains Dry Natural Rubber
	For Export Only

Note: Text layout in symbols is determined by label design.

Becton, Dickinson and Company
7 Loveton Circle
Sparks, Maryland 21152 USA