BD Onclarity™ HPV Assay

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TABLE OF CONTENTS

INTENDED USE

The **BD Onclarity™** HPV Assay is a qualitative *in vitro* test for the detection of Human Papillomavirus in cervical specimens collected by a clinician using an endocervical brush/spatula combination or broom and placed in a **BD SurePath™** vial. The test utilizes amplification of target DNA by Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types 16, 18 and 45 while concurrently detecting the other HR HPV types that include 31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68.

The **BD Onclarity** HPV Assay is indicated:

(a) In women 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results, the **BD Onclarity** HPV Assay can be used to determine the need for referral to colposcopy.

(b) In women 21 years and older with ASC-US cervical cytology test results, the **BD Onclarity** HPV assay can be used to detect high-risk HPV genotypes 16, 18 and 45. This information together with physician's assessment of screening history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy.

(c) In women 30 years and older, the **BD Onclarity** HPV Assay can be used together with cervical cytology to adjunctively screen to detect high risk HPV types. This information, together with the physician's assessment of screening history, other factors, and professional guidelines, may be used to guide patient management.

(d) In women 30 years and older, the **BD Onclarity** HPV Assay can be used to detect high-risk HPV genotypes 16, 18 and 45. This information, together with the physician's assessment of screening history, other factors, and professional guidelines, may be used to guide patient management.

(e) In women 25 years and older, the **BD Onclarity** HPV Assay can be used as a first-line primary cervical cancer screening test to detect high risk HPV, including 16 and 18. Women who test negative for the high risk HPV types by the **BD Onclarity** HPV Assay should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the **BD Onclarity** HPV Assay should be referred to colposcopy. Women who test high risk HPV positive and 16 and 18 negative by the **BD Onclarity** HPV Assay (12 other HR HPV Positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

WARNING

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 monitored for the development of high-grade cervical dysplasia according to current practice guidelines.
- For women who have undergone hysterectomy.
- For use with samples other than those collected by a clinician using an endocervical brush/spatula combination or broom and placed in the **BD SurePath** Preservative Fluid Collection Vial.

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

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

SUMMARY AND EXPLANATION OF THE TEST

There are more than 100 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: nearly all sexually active men and women will get HPV at some point in their lives.[3] According to the World Health Organization (WHO), cervical cancer is the fourth largest contributor to female cancer mortality worldwide, claiming an estimated 270,000 lives annually.[4] It is estimated that in 2017 there were 12,820 cases of cervical cancer and 4,210 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] In many cases, HPV infections are transient, and the body will clear the virus on its own.

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]

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.[7] Of the fourteen high-risk HPV genotypes, 16 and 18 cause 60–70% of cervical cancer worldwide.[8] Although HPV 45 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]

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 therapeutic 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 can inform a clinician if there are changes to the cervical cells. If those cells are abnormal, 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. Not all molecular assays can distinguish among the different types of HPV. The **BD Onclarity** HPV Assay detects HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and allows simultaneous, discrete identification of the high-risk types 16, 18, and 45.

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]

The automated specimen preparation for the **BD Onclarity** HPV Assay is completed by the **BD** Pre-Warm Heater and the **BD Viper™** LT System. Cervical specimens collected in **BD SurePath** Collection Vials 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, 45) or as a genotype group (31, 51, 52, 33/58, 59/56/66, 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.

REAGENTS

BD Onclarity HPV Assay Reagent Pack (192 tests) Cat # 441990			
Components	**Quantity per kit**	**Ingredients**	**Safety and Warnings**
HPV Assay G1 PCR tubes	2 x 96 tests	Tris Buffer Magnesium Acetate 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)	**N/A**
HPV Assay G2 PCR tubes	2 x 96 tests	Tris Buffer Magnesium Acetate 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)	**N/A**
HPV Assay G3 PCR tubes	2 x 96 tests	Tris Buffer Magnesium Acetate 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)	**N/A**

Control Set for the BD Onclarity HPV Assay (24 sets) Cat #444088			
Components	**Quantity per kit**	**Ingredients**	**Safety and Warnings**
HPV Positive Control	24 x 0.05 mL	< 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	**N/A**
HPV Negative Control	24 x 0.05 mL	< 1.182% Nonspecific DNA (biological)	**N/A**

BD Onclarity HPV Liquid Based Cytology Specimen (LBC) Diluent (400 tubes) Cat # 443837			
Components	**Quantity per kit**	**Ingredients**	**Safety and Warnings**
Liquid Based Cytology Specimen (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	 **WARNING** **H315+H320** Causes skin and eye irritation. **H335** May cause respiratory irritation. **P261** Avoid breathing dust/fume/gas/mist/vapors/spray. **P280** Wear protective gloves/protective clothing/eye protection/face protection. **P264** Wash thoroughly after handling. **P271** Use only outdoors or in a well-ventilated area. **P305+P351+P338** IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P304+P340** IF INHALED: Remove person to fresh air and keep comfortable for breathing. **P332+P313** If skin irritation occurs: Get medical advice/attention. **P337+P313** If eye irritation persists: Get medical advice/attention. **P302+P352** IF ON SKIN: Wash with plenty of soap and water. **P403+P233** Store in a well-ventilated place. Keep container tightly closed. **P501** Dispose of contents/container in accordance with local/regional/national/international regulations.
			The **BD Onclarity** HPV LBC Diluent Tube should be stored upright at 2–25 °C.

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

BD Viper PCR Extraction Reagent Trough with Piercing Tool (96 tests) Cat# 444087			
Components	**Quantity per kit**	**Ingredients**	**Safety and Warnings**
PCR Extraction Reagent Trough with Piercing Tool	96 tests	Sodium Phosphate, Monobasic Proclin 300 < 0.109% Detergent < 22.0% Sulfuric Acid < 38.0% Potassium Hydroxide < 0.3% Tris Base < 2.9% Tris HCl	 **DANGER** **H302** Harmful if swallowed. **H314** Causes severe skin burns and eye damage. **H318** Causes serious eye damage. **H350** May cause cancer. **P260** Do not breathe dust/fume/gas/mist/ vapors/spray. **P270** Do not eat, drink or smoke when using this product. **P280** Wear protective gloves/protective clothing/ eye protection/face protection. **P264** Wash thoroughly after handling. **P201** Obtain special instructions before use. **P202** Do not handle until all safety precautions have been read and understood. **P301+P312 IF SWALLOWED:** Call a POISON CENTER or doctor/physician if you feel unwell. **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 or doctor/physician. **P303+P361+P353** IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower. **P304+P340** IF INHALED: Remove person to fresh air and keep comfortable for breathing. **P308+P313** IF exposed or concerned: Get medical advice/attention. **P301+P330+P331** IF SWALLOWED: rinse mouth. Do NOT induce vomiting. **P321** Specific treatment (see on this label). **P363** Wash contaminated clothing before reuse. **P405** Store locked up. **P501** Dispose of contents/container in accordance with local/regional/national/ international regulations.

WARNINGS AND PRECAUTIONS

1. For *In Vitro* Diagnostic Use.
2. For warnings, precautions and cleaning procedures related to automated instrumentation, consult the **BD Viper** LT System User's Manual.
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, consult the **BD Viper** LT 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 with the **BD SurePath** Preservative Fluid Collection Vial (as described in the **BD SurePath** Preservative Fluid Collection Vial product insert). An aliquot is removed prior to or after processing for the **BD SurePath** Liquid-based Pap test and must be diluted in the **BD Onclarity** HPV LBC Diluent tube prior to testing with the **BD Onclarity** HPV Assay on the **BD Viper** LT System.
5. Optimal performance of the **BD Onclarity** HPV Assay requires proper specimen collection, handling and testing within the expiration dating of the **BD Onclarity** HPV LBC Diluent tube
6. 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.
7. Under- or over-dispensing of LBC specimen into the **BD Onclarity** HPV LBC 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.
8. Use only polypropylene aerosol-resistant pipette tips to transfer specimens to the **BD Onclarity** HPV LBC Diluent tubes.

Assay/Reagent:

9. Use only sample and control tubes with pierceable caps on the **BD Viper** LT System. Do not remove pierceable caps prior to running the instrument. Be sure to replace any punctured pierceable caps with new pierceable caps prior to running the instrument.
10. Reagent pouches containing unused PCR tubes MUST be carefully resealed after opening. Verify that desiccant is present prior to resealing the reagent pouches.
11. Do not use reagents after their expiration dates.
12. 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 you laboratory's standard Quality Control procedures.
13. Although dedicated work areas are not required because the **BD Viper** LT design reduces the possibility of amplicon contamination in the testing environment, other precautions for controlling contamination, particularly to avoid contamination of specimens during manipulation, are necessary.
14. 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.
15. Safety Data Sheets (SDS) are available at www.bd.com or by contacting BD Technical Service and Support.
16. Contact BD Technical Service and Support in the event of an unusual situation, such as a spill into the **BD Viper** LT System or DNA contamination that cannot be removed by cleaning.

STORAGE AND HANDLING REQUIREMENTS

A. Do not freeze reagents.
B. The **BD Onclarity** HPV LBC Diluent Tube should be stored upright at 2–25 °C until the indicated expiration date.
C. The **BD Onclarity** HPV Assay Reagent Pack should be stored at 2–8 °C until the indicated expiration date.
D. All other reagents may be stored at 2–33 °C until the indicated expiration date.
E. Once a PCR tube pouch is opened, the PCR tubes are stable for 4 weeks at 2–8 °C, if properly sealed or until the expiration date, whichever comes first.

REAGENTS AND MATERIALS PROVIDED

Contents	Quantity
BD Onclarity HPV Assay Reagent Pack Cat# 441990	192 Tests
Control Set for the **BD Onclarity** HPV Assay Cat# 444088	24 Sets
BD Onclarity HPV Liquid Based Cytology Specimen (LBC) Diluent Cat# 443837	400 Tubes
BD FOX PCR Extraction Tubes Cat# 444089	384 Tubes
BD Viper PCR Extraction Reagent Trough with Piercing Tool Cat# 444087	96 Tests
BD Viper XTR Neutralization Pouch Cat# 441354	12 Pouches
BD Viper LT Pipette Tips Cat# 441996	3,840 Tips
BD Viper Waste Liners Cat# 442968	100 Liners
BD Viper LT PCR Accessory Kit Cat# 442967	80 Pieces
Pierceable Caps for the **BD Viper** XTR System (Black) Cat# 441359	400 Caps
BD Viper LT PCR Tube/Tray Kit Cat# 442957	20 Pieces
BD Viper LT System Cat# 442839	1 System
BD Key Card Cat# 443747 1000 Cat# 443748 500 Cat# 443430 100	Each

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 AND TRANSPORT

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

A. Specimen Collection

Cervical specimens collected in a **BD SurePath** Preservative Fluid Collection Vial using an endocervical brush/spatula or broom device (LBC Specimen) have been validated for use with the **BD Onclarity** HPV Assay. Follow the manufacturer's instructions for collecting cervical specimens.

Specimen Transfer to BD Onclarity HPV LBC Diluent Tubes

NOTE: See the **BD Onclarity** HPV LBC Diluent tube Package Insert for additional information.

A 0.5 mL aliquot of the LBC specimen must be manually transferred from the original LBC vial to the **BD Onclarity** HPV LBC Diluent Tube. Wear gloves when handling the **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

BD SurePath Specimen Transfer Prior to or After Processing for the BD SurePath test

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

NOTE: A separate pipette tip must be used for each specimen.

6. Tighten the cap on the **BD Onclarity** HPV LBC Diluent Tube securely.
7. Invert the **BD Onclarity** HPV LBC Diluent Tube 3–4 times to ensure that the specimen and diluent are well mixed.

B. Specimen Transport

Once collected, cervical specimens can be transported in their original vials at 2–30 °C. Specimen transport should comply with applicable country, federal, state, and local regulations for the transport of etiological agents.

C. Specimen Storage

For use in the **BD Onclarity** HPV Assay, cervical specimens collected in a **BD SurePath** Preservative Fluid Collection Vial may be stored at 2–30 °C for up to 30 days, at 2–8 °C for 180 days, or at -20 °C for 180 days prior to transfer to **BD Onclarity** HPV LBC Diluent tube. See **BD SurePath** Preservative Fluid Collection Vial labeling for storage requirements prior to cytology processing.

After transfer to a **BD Onclarity** HPV LBC Diluent tube, the diluted specimen can be stored at 2–30 °C for up to 15 days, or up to 90 days when stored at -20 °C.

QUALITY CONTROL

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

QUALITY CONTROL PREPARATION

1. Uncap a **BD Onclarity** HPV Negative Control and a **BD Onclarity** HPV LBC Diluent tube.
2. Pour the entire contents of the **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 Onclarity** HPV LBC Diluent tube.
4. Uncap a **BD Onclarity** HPV Positive Control and a **BD Onclarity** HPV LBC Diluent tube.
5. Pour the entire contents of the **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 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, controls may be stored at 2–30 °C for up to 24 h prior to pre-warming.

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 to log in the rack barcode and select the test type to be run.
4. Log in the Positive and Negative Control tubes in the first two positions (A1 and B1) as well as the HPV LBC 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. SurePath LBC samples and Positive and Negative Control tubes must be prewarmed prior to extraction on the Viper LT.
10. To prepare the **BD Viper** LT instrument for specimen processing and testing, follow the steps outlined in the Viper LT 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

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.

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. The "GT" column is used to report results for genotypes that are not available in your region.

These results cannot be unmasked.

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.
	HPV DNA, if present, is not detectable	Internal Control Failure	Internal Control Failure. Repeat test from initial specimen tube or obtain another specimen for testing.
	HPV DNA, if present, is not detectable	Extraction Transfer Failure	Extraction Transfer Failure. Repeat test from initial specimen tube or obtain another specimen for testing.
	HPV DNA, if present, is not detectable.	Liquid Level Failure	Liquid Level Failure. Repeat test from initial specimen tube or obtain another specimen for testing.
	HPV DNA, if present, is not detectable.	Error	Error. Repeat test from initial specimen tube or obtain another specimen for testing.

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
GT ⊕←	Positive HPV Genotype result(s) for HPV 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, and/or 68	Positive HPV Genotype result(s) other than HPV 16, 18, or 45
GT ⊖	Negative HPV Genotype result(s) for HPV 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, and/or 68	Negative HPV Genotype result(s) masked
	HPV genotype result is available for unmasking	Genotype result is masked
	HPV genotype result is not available for unmasking	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		QC Failure
BD Onclarity HPV Positive Control		QC Failure
BD Onclarity HPV Positive Control		QC Failure
BD Onclarity HPV Negative Control	OK	QC Pass
BD Onclarity HPV Negative Control		QC Failure
BD Onclarity HPV Negative Control		QC Failure
BD Onclarity HPV Negative Control		QC Failure

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

Monitoring for the Presence of DNA Contamination

At least monthly, the following test procedure should be performed to monitor the work area and equipment surfaces for the presence of DNA contamination. Environmental monitoring is essential to detect contamination prior to the development of a problem.

1. For each area to be tested, use a clean collection swab from the **BD ProbeTec** *Chlamydia trachomatis/Neisseria gonorrhoeae* (CT/GC) Amplified DNA Assay Endocervical Specimen Collection and DRY TRANSPORT Kit.
2. Pour off some molecular biology grade nuclease-free water into a small clean container.
3. Dip the swab into the molecular biology grade nuclease-free water and wipe the first area using a broad sweeping motion.
4. Remove the cap of a **BD Onclarity** HPV LBC Diluent tube and insert the swab into the Diluent. Mix by swirling the swab in the **BD Onclarity** HPV Diluent for 5–10 s.
5. Express the swab along the inside of the tube so that liquid runs back into the bottom of the tube.
6. Remove the swab carefully from the **BD Onclarity** HPV LBC Diluent tube to avoid splashing. Discard the swab.

7. Tightly recap the **BD Onclarity** HPV LBC Diluent tube with the black pierceable cap.
8. Repeat for each desired area.
9. After all swabs have been collected and expressed, process them according to the Pre-warming Procedure and then follow the Test Procedure.

Consult the **BD Viper** LT 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.

PROCEDURAL 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. This test does not detect DNA of HPV low-risk types (e.g. 6, 11, 42, 43, 44) since there is no clinical utility for testing of low-risk HPV types 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 Package insert and the **BD Viper** LT 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 sensitivity of the test.
5. The **BD Onclarity** HPV Assay provides qualitative results.
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 System.
7. The **BD Onclarity** HPV Assay has only 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. In the clinical study, the Cytobrush® Plus GT Gentle Touch and Pap Perfect® Plastic Spatula (CooperSurgical, Inc.) and Rovers® Cervex-Brush® (Rovers Medical Devices B.V.) were used. **BD SurePath** cell pellets obtained after processing on the **BD PrepStain™** Slide Processor have not been evaluated with the **BD Onclarity** HPV Assay.
8. Cervical Specimens often show visibly detectable levels of blood as a pink or light brown coloration. If concentrations exceed 4% (v/v) in SurePath Preservative fluid prior to dilution in the **BD Onclarity** HPV Diluent tube, there is a likelihood of obtaining a false-negative HPV result.
9. False negatives may occur for specimens containing > 8% (v/v) mucin, >7% (w/v) Zovirax® (Acyclovir) Cream, and > 8% (w/v) clindamycin vaginal cream.
10. The effects of other potential variables such as vaginal discharge, use of tampons, douching, etc. and specimen collection variables have not been evaluated.
11. 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.
12. 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.
13. Prevalence of HPV infection in a population may affect performance. Positive predictive values decrease when testing populations with low prevalence or individuals with no risk of infection.
14. A negative high-risk HPV result does not exclude the possibility of future cytologic High-grade squamous intraepithelial lesion (HSIL) or underlying CIN2-3 or cancer, but indicates a low likelihood of CIN2-3 or cancer.
15. 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.
16. 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 System. The beta globin control does not differentiate between targeted (cervical) and non-targeted nucleated cell types.
17. Residual post-cytology specimens evaluated in the **BD Onclarity** HPV Assay were processed on the **BD PrepMate™** system.

EXPECTED RESULTS

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 4 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 4: 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 5 shows HPV prevalence by the **BD Onclarity** HPV Assay by age and study population. HPV prevalence decreased with age in each study population.

Table 5: 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 6** for the ASC-US population (≥ 21 years), in **Table 7** for the NILM population (≥ 30 years) and in **Table 8** 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 6–8**, women with mixed genotype HPV infections were counted for each of their positive HPV genotypes.

Table 6: 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 7: 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 8: BD Onclarity HPV Assay Result by Age Group for Screening (≥ 25 years) Population

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)

PERFORMANCE CHARACTERISTICS

Clinical Performance

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 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 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 BD ONCLARITY 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 BD ONCLARITY 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.

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 9**. 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 9: 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

NOTE:
[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 10**. 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 10: 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 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 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 11**. 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 11: 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 12**. The sensitivity of the **BD Onclarity** HPV Assay and the FDA approved HPV test ranged from 68.8–93.6% for ≥CIN2. The specificity of the **BD Onclarity** HPV Assay ranged from 49.5–78.2% and from 45.9–76.3% for the FDA approved HPV test.

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

Table 12: 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)
≥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 13 presents all possible **BD Onclarity** HPV assay results in the ASC-US evaluable population together with CPR panel diagnosis.

Table 13: 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 14** for the ASC-US (≥ 21 Years) population.

The **BD Onclarity** HPV result is categorized hierarchically based on genotype positivity in the order of HPV 16, HPV 18, HPV 45, 11 Other HPV HR, and HPV negative. Women with multiple genotypes detected were categorized in the earliest genotype listed (e.g. women positive for HPV 16 and HPV 18 were categorized as HPV 16).

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 HPV 16 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. 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 14: 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)
HPV 16 Positive	5.98 (4.15, 8.42)	8.60 (5.69, 12.08)
HPV 18 Positive	2.86 (1.24, 6.45)	1.28 (0.22, 6.74)
HPV 45 Positive	1.16 (0.38, 3.42)	1.15 (0.20, 6.03)
HPV 16 and/or HPV 18 and/or HPV 45 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 women with positive HPV HR results was 14.3% (≥CIN2) and 5.1% (≥CIN3) in the ASC-US (≥21) population. The risk of disease was significantly increased for the test results of HPV16 positive/HPV18 positive/HPV45 positive and 11 Other HPV HR positive and significantly decreased for an HPV HR negative result.

Table 15: Absolute Risk of Disease by BD Onclarity HPV Assay Result in the ASC-US Population (≥21 years)

BD Onclarity HPV Assay Test Results	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)
HPV 16 Positive	29.5 33/112 (22.5, 37.0)	16.1 18/112 (11.2, 21.2)
HPV 18 Positive	16.7 6/36 (7.9, 31.1)	2.8 1/36 (0.5, 13.0)
HPV 45 Positive	7.5 3/40 (2.6, 19.3)	2.5 1/40 (0.4, 11.8)
HPV 16 and/or HPV 18 and/or HPV 45 Positive	22.3 42/188 (17.7, 27.3)	10.6 20/188 (7.7, 13.6)
11 Other HPV HR Positive	10.9 48/441 (8.8, 13.1)	2.7 12/441 (1.7, 4.0)
HPV HR Negative	1.5 15/978 (1.0, 2.4)	0.3 3/978 (0.1, 0.8)

The relative risk of disease given one reported **BD Onclarity** HPV Assay result compared to another result is summarized in **Table 16**. 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 16: 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 17**. 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 17: 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)

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 18**.

Table 18: 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 19**. 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, 100.0) and 92.3% (92.0, 92.7), respectively.

Table 19: 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, 100.0)
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, 100.0)
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, 0.63)
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 20**.

Table 20: 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, 0.62)	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 21 presents all possible **BD Onclarity** HPV assay results in the NILM ≥30 years evaluable population together with the CPR panel diagnosis.

Table 21: 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] Note: 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 22**.

The **BD Onclarity** HPV Assay result is categorized hierarchically based on genotype positivity in the order of HPV 16, HPV 18, HPV 45, 11 Other HPV HR, and HPV negative. Women with multiple genotypes detected were categorized in the earliest genotype listed (e.g. Women positive for HPV 16 and HPV 18 were categorized as HPV 16).

Likelihood of HPV HR positive results to be associated with ≥CIN2 was 5.86 by VBA estimates. For ≥CIN2 histology, a positive HPV 16 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 22: 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 vs. < CIN2		≥ CIN3 vs. < 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)
HPV 16 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)
HPV 18 Positive	1.26 (0.42, 3.58)	4.41 (0, 11.90)	1.46 (0.40, 4.97)	7.64 (0, 22.64)
HPV 45 Positive	0.69 (0.19, 2.43)	2.42 (0, 7.18)	0.60 (0.11, 3.17)	3.16 (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, 0.63)

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 23**. 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. The adjusted risks of ≥CIN2 and ≥CIN3 were 6.8% and 4.9% for a NILM subject with a HPV 16/18/45 positive result. The adjusted risks of ≥CIN2 and ≥CIN3 were 0.5% and 0.1%, respectively, for a NILM subject with a HPV HR negative result.

Table 23: Absolute 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			
	≥CIN2 (%)		≥CIN3 (%)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
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)
HPV 16 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)
HPV 18 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)
HPV 45 Positive	2.2 2/93 (0.6, 7.2)	2.2 (0.0, 5.4)	1.1 1/93 (0.2, 5.4)	1.1 (0.0, 3.4)
HPV 16/18/45 Positive	7.6 27/355 (5.5, 10.0)	6.8 (4.4, 9.7)	5.9 21/355 (4.2, 7.8)	4.9 (3.0, 6.9)
11 Other HPV HR Positive	4.3 43/1,006 (3.4, 5.1)	4.3 (3.1, 5.5)	2.2 22/1,006 (1.6, 2.8)	2.2 (1.4, 3.2)
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)

The relative risk of disease given one reported **BD Onclarity** HPV Assay result compared to another result is summarized in **Table 24**. 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 24: 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 YEARS) 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 25**) or genotype specific HPV DNA sequencing results alone (**Tables 26, 27, and 28**). 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 25: 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	98.5	N/A	
	Negative	11	578	80	669	417/428	578/587		
	Total	428	587	105	1,120	(95.5,98.6)	(97.1,99.2)		
NILM ≥30 Years	Positive	448	46	182	676	92.2	87.4	92.0	99.4
	Negative	38	320	84	442	448/486	320/366		
	Total	486	366	266	1,118	(89.4,94.3)	(83.6,90.4)	(89.8,94.0)	(99.3,99.6)

In the HPV Sequencing Result **Tables 26–29**, the “Negative” **BD Onclarity** HPV Results are further divided into “Negative, Virus Not Detected” and “Negative, Virus Detected.”

Table 26: Percent Agreement of the BD Onclarity HPV Assay Result vs the HPV Sequencing Result (HPV 16)

BD Onclarity HPV Assay Positive		HPV 16 Sequencing Results					
		Positive	**Negative**	**Invalid**	**Total**	**PPA (%) (95% CI)**	**NPA (%) (95% CI)**
ASC-US ≥21 Years	**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		

BD Onclarity HPV Assay		HPV 16 Sequencing Results				Percent Agreement			
						Unadjusted		Adjusted	
		Pos.	**Neg.**	**Invalid**	**Total**	**PPA (%) (95% CI)**	**NPA (%) (95% CI)**	**PPA (%) (95% CI)**	**NPA (%) (95% CI)**
NILM ≥30 Years	**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				

Table 27: Percent Agreement of the BD Onclarity HPV Assay Result vs the HPV Sequencing Result (HPV18)

BD Onclarity HPV Assay		HPV 18 Sequencing Results					
		Positive	Negative	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)
ASC-US ≥21 Years	Positive	22	2	0	24		
	Negative	3	1,093	0	1,096	88.0	99.8
	Negative, Virus Not Detected	1	1,089	0	1,090	22/25	1,093/1,095
	Negative, Virus Detected	2	4	0	6	(70.0, 95.8)	(99.3, 99.9)
	Total	25	1,095	0	1,120		

BD Onclarity HPV Assay		HPV 18 Sequencing Results				Percent Agreement			
						Unadjusted		Adjusted	
		Pos.	Neg.	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)	PPA (%) (95% CI)	NPA (%) (95% CI)
NILM ≥30 Years	Positive	34	5	0	39				
	Negative	9	1,070	0	1,079	79.1	99.5	61.9	99.9
	Negative, Virus Not Detected	3	1,062	0	1,065	34/43	1,070/1,075		
	Negative, Virus Detected	6	8	0	14	(64.8, 88.6)	(98.9, 99.8)	(30.4, 81.7)	(99.9, 100.0)
	Total	43	1,075	0	1,118				

Table 28: Percent Agreement of the BD Onclarity HPV Assay Result vs the HPV Sequencing Result (HPV45)

BD Onclarity HPV Assay		HPV 45 Sequencing Results					
		Positive	Negative	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)
ASC-US ≥21 Years	Positive	23	0	0	23		
	Negative	7	1,090	0	1,097	76.7	100.0
	Negative, Virus Not Detected	0	1,087	0	1,087	23/30	1,090/1,090
	Negative, Virus Detected	7	3	0	10	(59.1, 88.2)	(99.6, 100.0)
	Total	30	1,090	0	1,120		

BD Onclarity HPV Assay		HPV 45 Sequencing Results				Percent Agreement			
						Unadjusted		Adjusted	
		Pos.	Neg.	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)	PPA (%) (95% CI)	NPA (%) (95% CI)
NILM ≥30 Years	Positive	51	2	0	53				
	Negative	6	1,059	0	1,065	89.5	99.8	72.2	100.0
	Negative, Virus Not Detected	2	1,056	0	1,058	51/57	1,059/1,061		
	Negative, Virus Detected	4	3	0	7	(78.9, 95.1)	(99.3, 99.9)	(39.3, 89.6)	(99.9, 100.0)
	Total	57	1,061	0	1,118				

Table 29: Percent Agreement of the BD Onclarity HPV Assay Result vs the HPV Sequencing Result (11 Other HPV HR)

BD Onclarity HPV Assay		11 Other HPV HR Sequencing Results					
		Positive	Negative	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)
ASC-US ≥21 Years	Positive	371	9	0	380		
	Negative	46	694	0	740	89.0	98.7
	Negative, Virus not Detected	21	666	0	687	371/417	694/703
	Negative, Virus Detected	25	28	0	53	(85.6, 91.6)	(97.6, 99.3)
	Total	417	703	0	1,120		

BD Onclarity HPV Assay		11 Other HPV HR Sequencing Results				Percent Agreement			
						Unadjusted		Adjusted	
		Pos.	Neg.	Invalid	Total	PPA (%) (95% CI)	NPA (%) (95% CI)	PPA (%) (95% CI)	NPA (%) (95% CI)
NILM ≥30 Years	Positive	507	38	0	545				
	Negative	64	509	0	573	88.8	93.1	61.6	99.6
	Negative, Virus Not Detected	23	478	0	501	507/571	509/547		
	Negative, Virus Detected	41	31	0	72	(85.9, 91.1)	(90.6, 94.9)	(50.4, 72.7)	(99.5, 99.7)
	Total	571	547	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 30**.

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 30:Number of Subjects in Primary Screening Population (≥25) 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

Screening Algorithms

The use of the **BD Onclarity** HPV Assay as a first line screening method was evaluated by comparing the Primary Screening algorithm with the Cytology algorithm, shown in **Figures 1 and 2**.

Figure 1: Primary Screening Algorithm

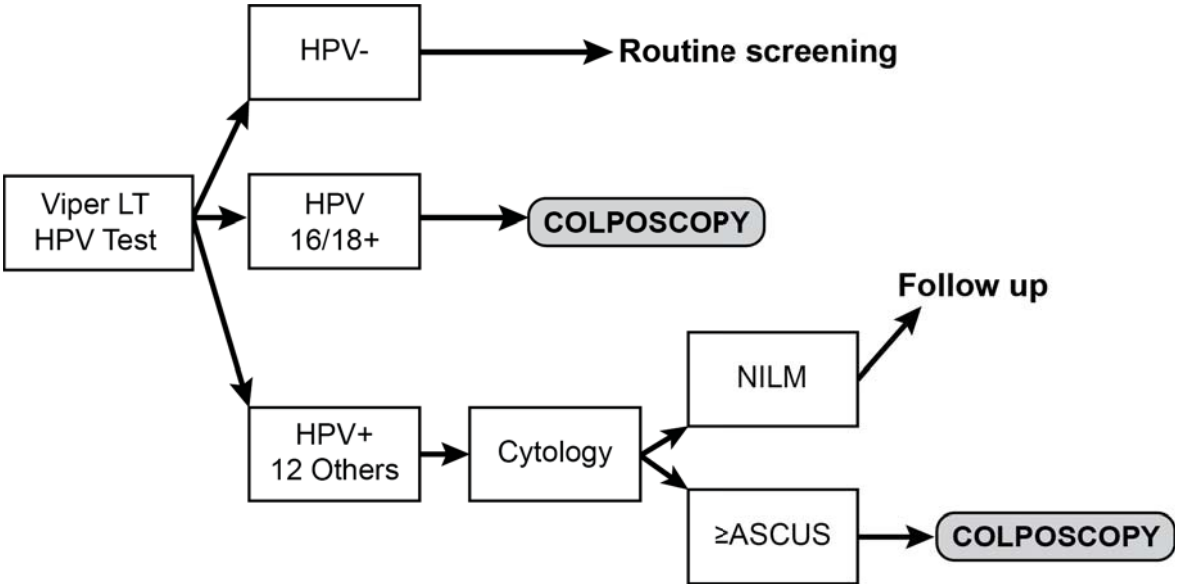
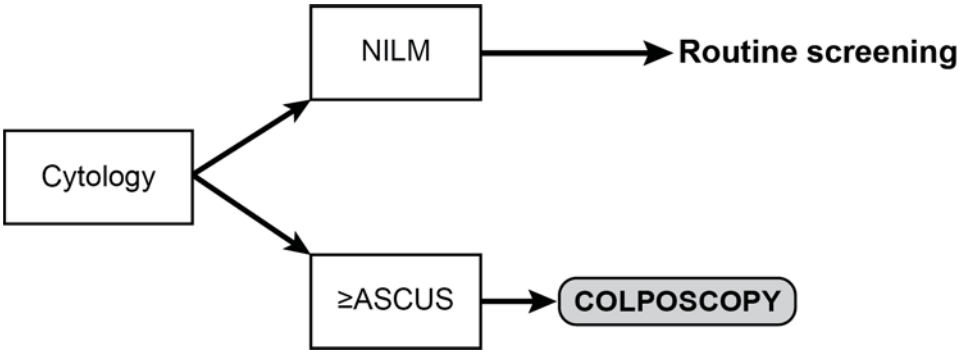


Figure 2: Cytology Algorithm



The performance of the Primary Screening algorithm with HPV 16 and 18 genotyping with reflex to cytology, and the Cytology algorithm (cytology alone) was evaluated and compared in the primary screening population by estimating the sensitivity, specificity, PPV, NPV, PLR, and NLR for the identification of ≥CIN2 and ≥CIN3.

Results are presented in **Table 31**. As compared to cytology alone, the primary screening algorithm improves disease detection, while also reducing the number of colposcopies: 15.0% increase in ≥CIN3 sensitivity, 2.3% reduction in colposcopy rates (27.2% relative reduction).

Table 31: Performance Comparison of the Primary Screening Algorithm and Cytology Algorithm

Performance Metrics	≥CIN2; Prevalence (Adjusted) = 1.9%			≥CIN3; Prevalence (Adjusted) = 0.8%		
	Primary Screening Algorithm	Cytology Screening Algorithm	Difference	Primary Screening Algorithm	Cytology Screening Algorithm	Difference
Sensitivity (%) (95% CI)	53.72 (44.18, 65.52)	47.42 (39.31, 57.77)	6.30[a] (2.39, 10.51)	64.24 (50.59, 79.65)	49.20 (38.31, 62.64)	15.05[a] (9.12, 22.26)
Specificity (%) (95% CI)	94.80 (94.53, 95.06)	92.36 (92.03, 92.67)	2.45[a] (2.17, 2.74)	94.39 (94.11, 94.66)	91.96 (91.63, 92.27)	2.43[a] (2.15, 2.72)
PPV (%) (95% CI)	16.48 (14.58, 18.48)	10.59 (9.34, 12.00)	5.89[a] (4.67, 7.16)	8.98 (7.70, 10.49)	5.00 (4.09, 5.98)	3.97[a] (3.14, 4.88)
NPV (%) (95% CI)	99.08 (98.66, 99.41)	98.92 (98.53, 99.27)	0.15[a] (0.07, 0.24)	99.68 (99.44, 99.85)	99.53 (99.28, 99.71)	0.15[a] (0.09, 0.20)
PLR (95% CI)	10.34 (8.36, 12.76)	6.20 (5.06, 7.62)	4.13[a] (3.18, 5.50)	11.46 (8.99, 14.22)	6.12 (4.74, 7.82)	5.34[a] (4.00, 7.09)
NLR (95% CI)	0.49 (0.36, 0.59)	0.57 (0.46, 0.66)	-0.08[a] (-0.12, -0.04)	0.38 (0.22, 0.52)	0.55 (0.41, 0.67)	-0.17[a] (-0.25, -0.11)
Colposcopy Rate (95% CI)	6.11 (5.83, 6.38)	8.39 (8.08, 8.72)	-2.28[a] (-2.58, -2.00)	6.11 (5.83, 6.38)	8.39 (8.08, 8.72)	-2.28[a] (-2.58, -2.00)

[a] Indicates statistically significant difference at the 0.05 level

The performance of the Primary Screening algorithm with HPV 16 and 18 genotyping with reflex to cytology, was also compared to an algorithm corresponding to the 2012 American Society for Colposcopy and Cervical Pathology guidelines.[19] In this algorithm, women 25–29 years old with a >ASCUS cytology result or with an ASCUS and HR HPV positive result are directed to colposcopy. Women 30 years and older with a >ASCUS cytology result or with an ASCUS and HR HPV positive result as well as those with a NILM cytology result and HPV 16 and/or 18 positive result are sent to colposcopy. Results comparing the Primary Screening algorithm to the ASCUS triage/co-testing algorithm are presented in **Table 32**. As compared to the ASCUS triage/co-testing algorithm, the Primary Screening algorithm improves disease detection (6.5% increase in ≥CIN3 sensitivity), with a similar rate of colposcopy.

Table 32: Performance Comparison of the Primary Screening Algorithm and ASCUS Triage/Co-testing Algorithm

Performance Metrics	≥CIN2; Prevalence (Adjusted) = 1.9%			≥CIN3; Prevalence (Adjusted) = 0.8%		
	Primary Screening Algorithm	ASCUS Triage /Co-Testing Algorithm	Difference	Primary Screening Algorithm	ASCUS Triage /Co-Testing Algorithm	Difference
Sensitivity (%) (95% CI)	53.72 (44.18, 65.52)	50.33 (41.32, 61.17)	3.38[a] (1.00, 6.00)	64.24 (50.59, 79.65)	57.72 (45.19, 72.41)	6.53[a] (3.06, 10.93)
Specificity (%) (95% CI)	94.80 (94.53, 95.06)	94.61 (94.34, 94.88)	0.19[a] (0.05, 0.32)	94.39 (94.11, 94.66)	94.21 (93.94, 94.49)	0.18[a] (0.05, 0.30)
PPV (%) (95% CI)	16.48 (14.58, 18.48)	15.13 (13.39, 17.07)	1.35[a] (0.58, 2.13)	8.98 (7.70, 10.49)	7.90 (6.63, 9.39)	1.07[a] (0.56, 1.61)
NPV (%) (95% CI)	99.08 (98.66, 99.41)	99.01 (98.61, 99.34)	0.07[a] (0.02, 0.12)	99.68 (99.44, 99.85)	99.62 (99.38, 99.80)	0.06[a] (0.03, 0.09)
PLR (95% CI)	10.34 (8.36, 12.76)	9.34 (7.59, 11.49)	1.00[a] (0.42, 1.62)	11.46 (8.99, 14.22)	9.97 (7.84, 12.61)	1.49[a] (0.79, 2.37)
NLR (95% CI)	0.49 (0.36, 0.59)	0.52 (0.41, 0.62)	-0.04[a] (-0.06, -0.01)	0.38 (0.22, 0.52)	0.45 (0.29, 0.58)	-0.07[a] (-0.12, -0.03)
Colposcopy Rate (95% CI)	6.11 (5.83, 6.38)	6.23 (5.94, 6.53)	-0.13 (-0.24, 0.02)	6.11 (5.83, 6.38)	6.23 (5.94, 6.53)	-0.13 (-0.24, 0.02)

[a] Indicates statistically significant difference at the 0.05 level

The **BD Onclarity** HPV Assay performance for the Primary Screening algorithm, Cytology Screening algorithm, and ASCUS Triage/Co-testing algorithm is shown below by age group for ≥CIN3.

Table 33: Performance of the BD Onclarity HPV Assay by Age Group in the Primary Screening Algorithm, Cytology Screening Algorithm, and ASCUS Triage/Co-testing Algorithm (≥CIN3)

Performance Metrics for ≥CIN3	Primary Screening Algorithm	Cytology Screening Algorithm	ASCUS Triage Co-Testing Algorithm	Primary Screening Algorithm	Cytology Screening Algorithm	ASCUS Triage /Co-Testing Algorithm
Subgroup	**25–29 Years**			**30–39 Years**		
Sensitivity (%) (95% CI)	60.42 (37.66, 87.52)	41.76 (24.38, 65.31)	40.40 (23.23, 62.78)	60.95 (40.74, 81.29)	47.36 (30.52, 66.09)	60.95 (40.74, 81.29)
Specificity (%) (95% CI)	89.62 (88.81, 90.38)	87.98 (87.13, 88.79)	91.72 (91.02, 92.45)	93.97 (93.50, 94.41)	91.89 (91.36, 92.42)	93.15 (92.68, 93.62)
PPV (%) (95% CI)	8.77 (6.29, 11.43)	5.43 (3.56, 7.49)	7.46 (4.89, 10.55)	11.03 (8.44, 13.62)	6.68 (5.01, 8.26)	9.85 (7.62, 12.20)
NPV (%) (95% CI)	99.28 (98.32, 99.83)	98.92 (97.98, 99.55)	98.94 (98.02, 99.53)	99.49 (98.94, 99.81)	99.30 (98.74, 99.66)	99.49 (98.93, 99.81)
PLR (95% CI)	5.82 (3.49, 8.68)	3.48 (1.99, 5.56)	4.88 (2.78, 7.80)	10.10 (6.81, 13.76)	5.84 (3.77, 8.24)	8.90 (5.99, 12.07)
NLR (95% CI)	0.44 (0.14, 0.70)	0.66 (0.39, 0.86)	0.65 (0.41, 0.84)	0.42 (0.20, 0.63)	0.57 (0.37, 0.75)	0.42 (0.20, 0.64)
Colposcopy Rate (95% CI)	11.19 (10.38, 11.98)	12.50 (11.65, 13.33)	8.80 (8.06, 9.54)	6.70 (6.23, 7.15)	8.59 (8.05, 9.15)	7.50 (7.02, 7.99)
Subgroup	**40–49 Years**			**≥50 Years**		
Sensitivity (%) (95% CI)	77.98 (60.40, 92.63)	66.72 (47.02, 86.30)	81.63 (64.32, 95.61)	82.40 (58.14, 100.00)	65.74 (32.98, 91.01)	82.40 (58.14, 100.00)
Specificity (%) (95% CI)	95.72 (95.28, 96.18)	92.44 (91.84, 93.03)	95.03 (94.54, 95.53)	97.12 (96.76, 97.50)	94.50 (94.00, 95.02)	96.58 (96.20, 96.99)
PPV (%) (95% CI)	7.39 (4.20, 10.90)	3.73 (1.99, 5.52)	6.72 (3.93, 9.83)	5.14 (2.25, 8.38)	2.21 (0.76, 3.65)	4.36 (1.87, 7.16)
NPV (%) (95% CI)	99.90 (99.81, 99.97)	99.84 (99.73, 99.95)	99.92 (99.83, 99.98)	99.97 (99.91, 100.00)	99.93 (99.85, 99.98)	99.97 (99.91, 100.00)
PLR (95% CI)	18.21 (13.74, 22.56)	8.83 (6.19, 11.54)	16.42 (12.89, 19.82)	28.62 (19.36, 37.40)	11.95 (6.08, 17.11)	24.08 (16.25, 31.24)
NLR (95% CI)	0.23 (0.08, 0.41)	0.36 (0.15, 0.57)	0.19 (0.05, 0.37)	0.18 (0.00, 0.43)	0.36 (0.10, 0.71)	0.18 (0.00, 0.44)
Colposcopy Rate (95% CI)	4.60 (4.11, 5.06)	7.82 (7.21, 8.45)	5.31 (4.79, 5.83)	3.03 (2.64, 3.39)	5.61 (5.09, 6.11)	3.57 (3.15, 3.96)

Baseline Risks of High Grade Cervical Disease for the Primary Screening Algorithm (≥ 25 years)

Women positive for HPV16 and/or 18 (3.21%) and women who are 12 other HPV positive with ≥ASC-US cytology (2.89%) are referred to immediate colposcopy by the Primary Screening Algorithm. The high ≥CIN2 risk estimates of these two groups (19.35% and 13.30%) justify the referral to colposcopy. The ≥CIN2 risk level for women positive for 12 other HPV with NILM cytology was 4.76%, while the ≥CIN2 risk level for women with negative HPV was 0.63%.

Table 34: Baseline Risk of Disease for Categories in the Primary Screening Algorithm (≥ 25 years)

Subgroup	Percentage with result	≥CIN3 Risk (95% CI)	≥CIN2 Risk (95% CI)
HPV HR POS	12.70	5.32 (4.60, 6.13)	10.40 (9.35, 11.46)
HPV 16/18	3.21	12.25 (10.05, 14.54)	19.35 (16.37, 22.32)
HPV 16+	2.52	14.20 (11.50, 17.21)	21.54 (18.08, 25.18)
HPV 18+	0.69	5.16 (2.27, 8.82)	11.42 (7.10, 16.27)
HPV 12 Other HPV HR + and ≥ASC-US	2.89	5.35 (3.70, 7.15)	13.30 (10.98, 15.78)
HPV 12 Other HPV HR + and NILM	6.59	1.94 (1.27, 2.65)	4.76 (3.76, 5.73)
HPV HR NEG (adjusted)	87.30	0.20 (0.03, 0.45)	0.63 (0.29, 1.07)

Baseline Risks of High Grade Cervical Disease by Age Group for the Primary Screening Algorithm (≥ 25 years)

The risks of ≥CIN2 and ≥CIN3 by age group for the Primary Screening Algorithm are presented in **Table 35**. The risk of ≥CIN2 ranges from 6.25–23.16% for women positive for HPV 16/18 and women positive for 12 other HPV and ≥ASC-US cytology. The risk of ≥CIN3 ranges from 0.02–0.60% for women with a negative HPV result.

Table 35: Baseline Risk of Disease for Categories in the Primary Screening Algorithm by Age Group

Subgroup	Central Pathology Review Panel Diagnosis 25–29 years			Central Pathology Review Panel Diagnosis 30–39 years		
	% with Result	≥CIN2 Risk (95% CI)	≥CIN3 Risk (95% CI)	% with Result	≥CIN2 Risk (95% CI)	≥CIN3 Risk (95% CI)
HPV HR+	22.39	11.44 (9.50, 13.45)	5.19 (3.79, 6.67)	13.82	13.32 (11.33, 15.26)	6.93 (5.48, 8.25)
HPV 16/18	5.52	22.91 (17.49, 28.71)	13.41 (9.19, 18.16)	3.64	23.16 (17.84, 28.69)	14.79 (10.82, 18.79)
12 Other HPV ≥ASC-US	5.67	10.58 (6.85, 14.28)	4.26 (1.95, 6.93)	3.06	18.20 (13.52, 22.83)	6.55 (3.49, 9.73)
12 Other HPV NILM	11.19	6.23 (4.25, 8.32)	1.60 (0.61, 2.88)	7.12	6.19 (4.31, 8.06)	3.08 (1.74, 4.49)
hrHPV NEG (Adjusted)	77.61	0.72 (0.09, 1.81)	0.60 (0.03, 1.68)	86.18	0.71 (0.16, 1.46)	0.29 (0.01, 0.85)
Subgroup	**Central Pathology Review Panel Diagnosis 40–49 years**			**Central Pathology Review Panel Diagnosis ≥50 years**		
HPV HR+	9.72	7.99 (5.80, 10.21)	4.33 (2.76, 6.17)	6.98	3.68 (1.98, 5.63)	2.47 (1.10, 3.96)
HPV 16/18	2.39	15.50 (9.73, 21.18)	9.47 (4.55, 14.49)	1.75	6.25 (2.17, 11.34)	5.26 (1.74, 9.81)
12 Other HPV ≥ASC-US	2.21	11.76 (6.75, 17.41)	5.16 (1.62, 9.56)	1.28	8.88 (2.90, 15.57)	4.99 (1.08, 10.40)
12 Other HPV NILM	5.12	2.84 (1.07, 4.96)	1.57 (0.32, 3.10)	3.95	0.85 (0.00, 2.17)	0.42 (0.00, 1.39)
hrHPV NEG (Adjusted)	90.28	0.45 (0.07, 1.19)	0.02 (0.00, 0.06)	93.02	0.67 (0.02, 1.65)	0.02 (0.00, 0.05)

Benefit and Risk for Primary Screening (≥25 Years) Population per 10,000 women

The benefit (number of CIN2 or ≥CIN3 cases detected) and risk (number of CIN2 or ≥CIN3 cases missed and number of <CIN2 sent to colposcopy) per 10,000 women in the Primary Screening algorithm, Cytology algorithm, and ASCUS triage/co-testing algorithm was evaluated. The Primary Screening algorithm detected more disease cases (101) compared to the Cytology algorithm (89) and the ASCUS triage/co-testing algorithm (94), with fewer colposcopies (611 vs 839 and 623). Fewer cases of high grade disease were missed by the Primary Screening algorithm (87 vs 98 and 93) as well as fewer negative (<CIN2) women sent to colposcopy (510 vs 750 and 529).

Table 36: Benefit and Risk of the Primary Screening Algorithm, Cytology Algorithm, and ASCUS Triage/Co-testing Algorithm for the Primary Screening Population (per 10,000 Women)

Count	Primary Screening Algorithm	Cytology Algorithm	ASCUS Triage/Co-Testing Algorithm
Cytology tests	949	10,000	10,000
BD Onclarity HPV tests	10,000	0	8,100
Colposcopies	611	839	623
CIN2 detected	46	47	45
≥CIN3 detected	55	42	49
CIN2 missed	56	55	57
≥CIN3 missed	31	43	36
<CIN2 sent to colposcopy	510	750	529

Benefit and Risk for Primary Screening (≥25 Years) Population per 100 Colposcopy Procedures

The benefit (number of CIN2 or ≥CIN3 cases detected) and risk (number of CIN2 or ≥CIN3 cases missed and number of <CIN2 sent to colposcopy) per 100 colposcopies for the Primary Screening algorithm, Cytology algorithm and ASCUS Triage/Co-testing algorithm was evaluated. Per 100 colposcopies performed, the Primary Screening algorithm detected more cases of disease (17) than the Cytology algorithm (11) and the ASCUS triage/Co-testing algorithm (15) with a lower number of <CIN2 women sent to colposcopy (84 vs 89 and 85). The rate of disease in women not referred to colposcopy was lower by the Primary Screening algorithm (0.9%, 14/1,538) compared to the Cytology algorithm (1.1%, 12/1,092) and the ASCUS triage/co-testing algorithm (1.0%, 15/1,505).

Table 37: Benefit and Risk of the Primary Screening Algorithm, Cytology Algorithm and ASCUS Triage/Co-testing Algorithm for the Primary Screening Population (per 100 Colposcopy Procedures)

Count	Primary Screening Algorithm	Cytology Algorithm	ASCUS Triage/Co-Testing Algorithm
Cytology tests	155	1,192	1,605
BD Onclarity HPV tests	1,638	0	1,300
Colposcopies	100	100	100
CIN2 detected	8	6	7
≥CIN3 detected	9	5	8
CIN2 missed	9	7	9
≥CIN3 missed	5	5	6
<CIN2 sent to colposcopy	84	89	85

BASELINE RISK OF DISEASE FOR WOMEN WITH NILM CYTOLOGY AND NEGATIVE BD ONCLARITY HPV TEST RESULTS

The baseline risk of disease was 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 0.20% baseline risk of ≥CIN3 compared to 0.47% for those with NILM cytology. The addition of a NILM cytology result to a negative **BD Onclarity** HPV result marginally decreased the ≥CIN3 risk (0.20 vs 0.19).

Table 38: Baseline Risk of Disease for Women with NILM Cytology and Negative BD Onclarity HPV Test Results in the Primary Screening (≥25 Years) Population

Subgroup	Percentage with result	≥CIN3 Risk (95%CI)	≥CIN2 Risk (95%CI)
NILM	91.61	0.47 (0.29, 0.72)	1.08 (0.73, 1.47)
HPV HR NEG	87.30	0.20 (0.03, 0.45)	0.63 (0.29, 1.07)
HPV HR NEG and NILM	82.95	0.19 (0.01, 0.46)	0.56 (0.20, 1.01)

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 2013–2015, 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 ASCUS cytology (21–29 years old) and a subset of the primary screening population (25–29 years old).

Table 39: BD Onclarity HPV Assay Performance in Unvaccinated and Vaccinated Women with ASCUS Cytology (21–29 years old)

Performance Metrics	≥CIN2			
	Unvaccinated (prevalence 7.8%)		Vaccinated (prevalence 9.7%)	
	Estimate	95% CI	Estimate	95% CI
Sensitivity	100.0% (31/31)	(89.0%, 100.0%)	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	100.0% (180/180)	(98.1%, 100.0%)	96.1% (73/76)	(91.3%, 98.6%)
PLR	1.96	(1.82, 2.17)	1.67	(1.11, 2.16)
NLR	0	(0, 0.23)	0.38	(0.13, 0.89)
Performance Metrics	**≥CIN3**			
	Unvaccinated (prevalence 2.0%)		Vaccinated (prevalence 3.2%)	
	Estimate	95% CI	Estimate	95% CI
Sensitivity	100.0% (8/8)	(67.6%, 100.0%)	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	100.0% (180/180)	(98.6%, 100.0%)	98.7% (75/76)	(95.9%, 99.8%)
PLR	1.85	(1.82, 2.04)	1.60	(0.74, 2.12)
NLR	0	(0, 0.71)	0.40	(0.07, 1.28)

Table 40: 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)
≥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 CLINICAL 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 41 and 42**.

Table 41: 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	100.0 (95.0, 100.0)	97.7 (93.5, 99.2)	98.5 (95.8, 99.5)
>ASC-US ≥21 yrs	97.6 (91.8, 99.4)	100.0 (83.2, 100.0)	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 42: 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

ANALYTICAL PERFORMANCE

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 (HPV 16), HeLa (HPV 18) and MS751 (HPV 45) 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 containing a HPV-negative cell line (C33A). 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 43**.

Table 43: Limit of Detection

Target	LOD (Cells or Copies/mL)	95% Confidence Interval	
		Lower	Upper
SiHa (HPV 16)	50	37	67
HeLa (HPV 18)	199	154	256
MS751 (HPV 45)	862	669	1,111
HPV 16	251	193	326
HPV 18	1,083	1,000	1,267
HPV 45	1,261	1,154	1,358
HPV 31	830	718	879
HPV 33	1,665	1,495	2,030
HPV 35	1,550	1,472	1,655
HPV 39	1,794	1,617	1,862
HPV 51	1,522	1,315	1,613
HPV 52	814	776	951
HPV 56	1,090	937	1,185
HPV 58	2,369	2,231	6,631
HPV 59	1,000	942	1,152
HPV 66	862	823	916
HPV 68	2,392	2,227	2,646

Twenty replicates of each cell line/plasmid diluted to the maximum LOD value were tested using one reagent lot tested on one **BD Viper** LT System. **Table 44** contains results for the confirmation of the maximum LOD for HPV cell lines and plasmid DNA containing various high risk HPV sequences.

Table 44: Confirmation of Limit of Detection

Target	LOD (Cells or Copies/mL)	Ratio POS to Total	Positivity Rate (%)
SiHa cells (HPV 16)	50	20/20	100
HeLa cells (HPV 18)	208	19/20	95
MS751 cells (HPV 45)	862	20/20	100
HPV 16	251	19/20	95
HPV 18	1,083	19/20	95
HPV 45	1,261	19/20	95
HPV 31	830	20/20	100
HPV 33	1,665	20/20	100
HPV 35	1,550	20/20	100
HPV 39	1,794	20/20	100
HPV 51	1,522	20/20	100
HPV 52	814	20/20	100
HPV 56	1,131	19/20	95
HPV 58	2,294	19/20	95
HPV 59	1,000	20/20	100
HPV 66	862	20/20	100
HPV 68	2,367	20/20	100

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 containing a HPV-negative cell line (C33A). The microorganisms are described in **Table 45**. 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.

Table 45: Microorganisms Tested for Analytical Specificity

Actinomyces israelii	*Proteus vulgaris*	HPV 56
Atopobium vaginae	*Providencia stuartii*	HPV 58
Bacteroides fragilis	*Pseudomonas aeruginosa*	HPV 59
Bacteroides ureolyticus	*Staphylococcus aureus*	HPV 66
Bifidobacterium adolescentis	*Staphylococcus epidermidis*	HPV 68
Bifidobacterium breve	*Streptococcus agalactiae*	HPV 16
Bifidobacterium longum ssp. *longum*	*Streptococcus pyogenes*	HPV 6
Chlamydia trachomatis	*Ureaplasma urealyticum*	HPV 11
Clostridium perfringens	*Candida albicans*	HPV 26
Corynebacterium genitalium	*Trichomonas vaginalis*	HPV 30
Enterobacter cloacae ssp. *cloacae*	Adenovirus, type 5	HPV 34
Enterococcus faecalis	HCMV, AD169 Strain	HPV 53
Enterococcus faecium	HSV1	HPV 67
Escherichia coli	HSV2	HPV 69
Fusobacterium nucleatum ssp. *Nucleatum*	EBV-1, B95-8 Strain	HPV 70
Gardnerella vaginalis	HIV-1	HPV 73
Klebsiella pneumonia ssp. *ozaenae*	HPV 16	HPV 82
Lactobacillus acidophilus	HPV 18	HPV 97
Mycobacterium smegmatis	HPV 31	
Mycoplasma genitalium	HPV 33	
Neisseria gonorrhoeae	HPV 35	
Peptostreptococcus anaerobius	HPV 39	
Prevotella bivia	HPV 45	
Prevotella disiens	HPV 51	
Proteus mirabilis	HPV 52	

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

Table 46: Potential Interfering Substances

Potential Interfering Substance	Concentration Tested	Interference Observed
KY* Vaginal Lubricant	6% (w/v)	None
VCF* Vaginal Contraceptive Film	10% (w/v)	None
VCF* Vaginal Contraceptive Foam	10% (w/v)	None
Conceptrol* Contraceptive Gel	10% (w/v)	None
Monistat* 3	2% (w/v)	None
Clotrimazole 7	10% (w/v)	None
Vagistat*-1 Tioconazole	2% (w/v)	None
Clindamycin Vaginal Cream	8% (w/v)	None
Summer's Eve* Douche	10% (v/v)	None
Zovirax* (Acyclovir) Cream	7% (w/v)	None
Vandazole* Gel (Metronidazole) Vaginal Gel, 0.75%)	10% (w/v)	None
Summer's Eve* Deodorant	3% (w/v)	None
Bovine Mucin	8% (v/v)	None
Progesterone	20 ng/mL	None
Estradiol	1.2 ng/mL	None
Whole Blood	4% (v/v)	None
Leukocytes	$1x10^6$ cells/mL	None
Semen	10% (v/v)	None
Replens	10% (w/v)	None

PRECISION:

An in-house precision study was performed utilizing panels consisting of HPV negative clinical specimen matrix spiked with HPV cell lines (SiHa, HeLa, or MS751), and pooled negative and positive clinical specimens. The contrived panel members consisted of HPV target levels below (>94% negative), at (>94% positive) and above (>98% positive) the Limit of Detection of the **BD Onclarity** HPV Assay. The clinical panel members were prepared with pooled high risk positive specimens (HPV16, HPV18, HPV45, HPV31, HPV33/58, and HPV52) in **BD SurePath** Preservative Fluid. **Tables 47 to 50** 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 (%) ranged from 1.41% to 1.84% for SiHa Cells, 0.89% to 2.08% for HeLa cells, 0.90% to 1.53% for MS751 cells. The overall CV (%) for pooled HPV positive clinical specimens ranged from 2.01% to 5.63%.

Table 47: Summary of Precision Panel (Contrived Specimens) and Agreement Rates for BD Onclarity HPV Assay Precision Study

HPV Genotype	HPV Target Source	HPV Panel Level (cells/mL)	Expected Result	Total Tested	Total Correct	Percent Agreement	95% CI	
							Lower	Upper
HPV16	SiHa cells	2	>94% Negative	214	205	95.79% Negative	92.20%	97.77%
HPV16	SiHa cells	50	>94% Positive	216	207	95.83% Positive	92.27%	97.79%
HPV16	SiHa cells	150	>98% Positive	215	213	99.07% Positive	96.67%	99.74%
HPV18	HeLa cells	23	>94% Negative	216	214	99.07% Negative	96.69%	99.75%
HPV18	HeLa cells	208	>94% (Positive)	216	216	100.00% (Positive)	98.25%	100.00%
HPV18	HeLa cells	623	>98% (Positive)	214	214	100.00% (Positive)	98.24%	100.00%
HPV45	MS751 cells	90	>94% (Negative)	214	212	99.07% (Negative)	96.66%	99.74%
HPV45	MS751 cells	862	>94% (Positive)	216	214	99.07% (Positive)	96.69%	99.75%
HPV45	MS751 cells	2,586	>98% (Positive)	216	216	100.00% (Positive)	98.25%	100.00%

Table 48: Summary of Precision Panel (Clinical Specimens) and Agreement Rates for BD Onclarity HPV Assay Precision Study

HPV Genotype	HPV Target Source	HPV Panel Level	Mean HPV Ct Score	Total Tested	Total Correct	Percent Agreement	95% CI	
							Lower	Upper
HPV16	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV18	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV31	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV33/58	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV39/68/35	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV45	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV51	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV52	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV59/56/66	Pooled Clinical	Negative	N/A	216	216	100.00%	98.25%	100.00%
HPV16	Pooled Clinical 16	Positive	34.75	216	216	100.00%	98.25%	100.00%
HPV18	Pooled Clinical 18	Positive	30.60	216	216	100.00%	98.25%	100.00%
HPV31	Pooled Clinical 31	Positive	32.92	216	182	84.26%	78.81%	88.51%
HPV33/58	Pooled Clinical 33/58	Positive	30.34	216	216	100.00%	98.25%	100.00%
HPV45	Pooled Clinical 45	Positive	32.48	216	173	80.09%	74.26%	84.87%
HPV52	Pooled Clinical 52	Positive	31.58	216	216	100.00%	98.25%	100.00%

Table 49: Variance Component Analysis Results for Contrived Specimens in BD Onclarity HPV Assay Precision Study

HPV Cell Lines (cells/mL)	Description	Mean Ct Score	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
SiHa	2 cells/mL >94% Negative	38.42	0.00	0.00	0.29	0.75	0.00	0.00	0.00	0.00	0.23	0.59	0.40	1.04	0.54	1.41
	50 cells/mL >94% Positive	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
	150 cells/mL >98% Positive	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
HeLa	23 cells/mL >94% Negative	35.48	0.00	0.00	0.00	0.00	0.00	0.00	0.09	0.27	0.30	0.85	0.67	1.88	0.74	2.08
	208 cells/mL >94% Positive	32.29	0.00	0.00	0.08	0.26	0.00	0.01	0.00	0.00	0.08	0.26	0.26	0.81	0.29	0.89
	623 cells/mL >98% Positive	30.87	0.00	0.00	0.00	0.00	0.03	0.09	0.00	0.00	0.19	0.62	0.20	0.65	0.28	0.90
MS751	90 cells/mL >94% Negative	35.53	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.19	0.52	0.51	1.44	0.54	1.53
	862 cells/mL >94% Positive	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
	2,586 cells/mL >98% Positive	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

Table 50: Variance Component Analysis Results for Clinical Specimens in BD Onclarity HPV Assay Precision Study

HPV Panel Member	Mean Ct. Score	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
Clinical Positive 16	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 18	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 31	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 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 45	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 52	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

Reproducibility:

Panels consisting of HPV negative clinical specimen matrix spiked with HPV cell lines (SiHa, HeLa, or MS751), and pooled negative and positive 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 156–159 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 51** below). Percent positive results along with 95% confidence intervals for the positive panel members are shown in **Table 52**.

Analysis of variance of the Ct scores from valid tests performed on positive panel members (see **Table 53**) yielded overall CV (%) ranges of 1.7% to 1.8% for SiHa Cells, 1.3% to 1.9% for HeLa cells, and 1.7% to 1.8% for MS751 cells. The overall CV (%) for pooled HPV positive clinical specimens ranged from 2.9% to 5.6%.

Table 51: Results by Sample Type and Negative Panel Member for Lot and Site

Sample Type	Panel Member	Ct SD	Ct %CV	Number Negative/Total Number of Results				
				Lot	Percent Negative	Site	Percent Negative	95% CI
SiHa cell line	HPV 16 High Negative (2 cells/mL)	0.47	1.2	1	96.1 (49/51)	1	92.6 (50/54)	
				2	83.3 (45/54)	2	98.1 (53/54)	
				3	92.6 (50/54)	3	80.4 (41/51)	
				All	90.6 (144/159)	All	90.6 (144/159)	85.0–94.2
HeLa cell line	HPV 18 High Negative (23 cells/mL)	0.95	2.6	1	100.0 (54/54)	1	100.0 (54/54)	
				2	100.0 (51/51)	2	100.0 (51/51)	
				3	100.0 (51/51)	3	100.0 (51/51)	
				All	100.0 (156/156)	All	100.0 (156/156)	97.6–100.0
MS751 cell line	HPV 45 High Negative (90 cells/mL)	0.72	2.0	1	100.0 (54/54)	1	100.0 (54/54)	
				2	100.0 (51/51)	2	100.0 (51/51)	
				3	100.0 (51/51)	3	100.0 (51/51)	
				All	100.0 (156/156)	All	100.0 (156/156)	97.6–100.0
Pooled negative clinical sample	Negative	NA	NA	1	100.0 (51/51)	1	100.0 (53/53)	
				2	100.0 (53/53)	2	100.0 (54/54)	
				3	100.0 (54/54)	3	100.0 (51/51)	
				All	100.0 (158/158)	All	100.0 (158/158)	97.6–100.0

Table 52: Results by Sample Type and Positive Panel Member for Lot and Site

		Number Positive/Total Number of Results				
		Lot		Site		
Sample Type	**Panel Member**	**ID**	**Percent Positive**	**ID**	**Percent Positive**	**95% CI**
SiHa cell line	HPV 16 Low Positive (50 cells/mL)	1	100 (51/51)	1	100.0 (54/54)	
		2	98.1 (53/54)	2	98.1 (53/54)	
		3	100.0 (54/54)	3	100.0 (51/51)	
		All	99.4 (158/159)	All	99.4 (158/159)	96.5–99.9
SiHa cell line	HPV 16 Moderate Positive (150 cells/mL)	1	100.0 (50/50)	1	100.0 (53/53)	
		2	100.0 (54/54)	2	100.0 (54/54)	
		3	100.0 (54/54)	3	100.0 (51/51)	
		All	100.0 (158/158)	All	100.0 (158/158)	97.6 – 100.0
HeLa cell line	HPV 18 Low Positive (208 cells/mL)	1	96.3 (52/54)	1	100.0 (54/54)	
		2	100.0 (51/51)	2	96.1 (49/51)	
		3	98.0 (50/51)	3	98.0 (50/51)	
		All	98.1 (153/156)	All	98.1 (153/156)	94.5–99.3
HeLa cell line	HPV 18 Moderate Positive (623 cells/mL)	1	100.0 (54/54)	1	100.0 (54/54)	
		2	100.0 (51/51)	2	100.0 (51/51)	
		3	100.0 (51/51)	3	100.0 (51/51)	
		All	100.0 (156/156)	All	100.0 (156/156)	97.6–100.0
MS751 cell line	HPV 45 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 cell line	HPV 45 Moderate Positive (2,586 cells/mL)	1	98.1 (53/54)	1	100.0 (54/54)	
		2	100.0 (51/51)	2	98.0 (50/51)	
		3	100.0 (51/51)	3	100.0 (51/51)	
		All	99.4 (155/156)	All	99.4 (155/156)	96.5–99.9
Pooled clinical sample	HPV 16	1	100.0 (51/51)	1	98.1 (53/54)	
		2	100.0 (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 clinical sample	HPV 18	1	100.0 (54/54)	1	100.0 (54/54)	
		2	100.0 (51/51)	2	100.0 (51/51)	
		3	100.0 (51/51)	3	100.0 (51/51)	
		All	100.0 (156/156)	All	100.0 (156/156)	97.6–100.0
Pooled clinical sample	HPV 45	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 clinical sample	HPV 31	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 clinical sample	HPV 33/58	1	96.3 (52/54)	1	96.3 (52/54)	
		2	100.0 (51/51)	2	96.1 (49/51)	
		3	96.1 (49/51)	3	100.0 (51/51)	
		All	97.4 (152/156)	All	97.4 (152/156)	93.6–99.0
Pooled clinical sample	HPV 52	1	100.0 (54/54)	1	100.0 (54/54)	
		2	100.0 (51/51)	2	100.0 (51/51)	
		3	100.0 (51/51)	3	100.0 (51/51)	
		All	100.0 (156/156)	All	100.0 (156/156)	97.6–100.0

Table 53: 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	Panel Member	N	Mean	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
SiHa cell line	HPV 16 Low Positive (50 cells/mL)	159	36.36	0.60	1.7	0.00	0.0	0.13	0.4	0.23	0.6	0.07	0.2	0.00	0.0	0.64	1.8
	HPV 16 Moderate Positive (150 cells/mL)	158	35.03	0.56	1.6	0.00	0.0	0.00	0.0	0.12	0.3	0.13	0.4	0.00	0.0	0.58	1.7
	HPV 16 High Negative (2 cells/mL)	35	38.24	0.36	0.9	0.25	0.7	0.00	0.0	0.13	0.3	0.00	0.0	0.11	0.3	0.47	1.2
HeLa cell line	HPV 18 Low Positive (208 cells/mL)	156	33.16	0.60	1.8	0.00	0.0	0.13	0.4	0.11	0.3	0.01	0.0	0.00	0.0	0.61	1.9
	HPV 18 Moderate Positive (623 cells/mL)	156	31.71	0.34	1.1	0.15	0.5	0.17	0.5	0.13	0.4	0.07	0.2	0.00	0.0	0.42	1.3
	HPV 18 High Negative (23 cells/mL)	153	36.40	0.92	2.5	0.00	0.0	0.00	0.0	0.26	0.7	0.03	0.1	0.00	0.0	0.95	2.6
MS751 cell line	HPV 45 Low Positive (862 cells/mL)	156	32.90	0.54	1.6	0.08	0.2	0.00	0.0	0.26	0.8	0.12	0.4	0.00	0.0	0.60	1.8
	HPV 45 Moderate Positive (2,586 cells/mL)	156	31.41	0.51	1.6	0.00	0.0	0.21	0.7	0.05	0.1	0.00	0.0	0.00	0.0	0.55	1.7
	HPV 45 High Negative (90 cells/mL)	155	36.47	0.64	1.7	0.00	0.0	0.25	0.7	0.29	0.8	0.04	0.1	0.00	0.0	0.72	2.0
Clinical Specimen Pools	HPV 16	159	35.22	1.52	4.3	0.00	0.0	0.00	0.0	0.00	0.0	0.29	0.8	0.32	0.9	1.57	4.5
	HPV 18	156	30.47	1.08	3.5	0.00	0.0	0.08	0.3	0.30	1.0	0.00	0.0	0.00	0.0	1.11	3.6
	HPV 45	156	33.35	1.78	5.3	0.34	1.0	0.00	0.0	0.25	0.8	0.00	0.0	0.00	0.0	1.83	5.5
	HPV 31	156	33.21	1.81	5.4	0.00	0.0	0.00	0.0	0.00	0.0	0.51	1.5	0.00	0.0	1.86	5.6
	HPV 33/58	156	30.73	1.38	4.5	0.20	0.7	0.00	0.0	0.12	0.4	0.19	0.6	0.00	0.0	1.41	4.6
	HPV 52	156	30.08	0.79	2.6	0.24	0.8	0.00	0.0	0.33	1.1	0.00	0.0	0.00	0.0	0.87	2.9

NOTE: Only replicates with detected viral load (Ct score <40.0) were included in the variance components analysis.

Cross Contamination:

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 carry-over contamination) on the **BD Viper** LT System. One run was performed per day over five days on each of three instruments comprising a total of 675 test replicates. Each run, arranged in an alternating checkerboard pattern, consisted of specimens containing an HPV negative cell line (C33A) with and without SiHa cells spiked at 1.0×10^5 cells/mL in **BD SurePath** Preservative Fluid. There were zero false positive results for an overall contamination rate with **BD SurePath** Preservative Fluid of 0% (≤0.43).

In a **BD PrepMate** contamination validation, the potential contamination rate contributed by the **BD PrepMate** System was calculated as 0% (0/72).

INTERPRETATION OF TABLES

Symbols and Abbreviations

Symbols

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

Abbreviations

ASC-US	Atypical squamous cells of undetermined significance
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
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
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
UNSAT	Unsatisfactory

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ГГГГ-ММ-ДД / ГГГГ-ММ (ММ = края на месеца)
RRRR-MM-DD / RRRR-MM (MM = konec měsíce)
ÅÅÅÅ-MM-DD / ÅÅÅÅ-MM (MM = slutning af måned)
JJJJ-MM-TT / JJJJ-MM (MM = Monatsende)
EEEE-MM-HH / EEEE-MM (ΜΜ = τέλος του μήνα)
AAAA-MM-DD / AAAA-MM (MM = fin del mes)
AAAA-KK-PP / AAAA-KK (KK = kuu lõpp)
AAAA-MM-JJ / AAAA-MM (MM = fin du mois)
GGGG-MM-DD / GGGG-MM (MM = kraj mjeseca)
ÉÉÉÉ-HH-NN / ÉÉÉÉ-HH (HH = hónap utolsó napja)
AAAA-MM-GG / AAAA-MM (MM = fine mese)
ЖЖЖЖ-АА-КК / ЖЖЖЖ-АА / (АА = айдың соңы)
YYYY-MM-DD/YYYY-MM(MM = 월말)
MMMM-MM-DD / MMMM-MM (MM = mėnesio pabaiga)
GGGG-MM-DD/GGGG-MM (MM = mēneša beigas)
JJJJ-MM-DD / JJJJ-MM (MM = einde maand)
ÅÅÅÅ-MM-DD / ÅÅÅÅ-MM (MM = slutten av måneden)
RRRR-MM-DD / RRRR-MM (MM = koniec miesiąca)
AAAA-MM-DD / AAAA-MM (MM = fim do mês)
AAAA-LL-ZZ / AAAA-LL (LL = sfârşitul lunii)
ГГГГ-ММ-ДД / ГГГГ-ММ (ММ = конец месяца)
RRRR-MM-DD / RRRR-MM (MM = koniec mesiaca)
GGGG-MM-DD / GGGG-MM (MM = kraj meseca)
ÅÅÅÅ-MM-DD / ÅÅÅÅ-MM (MM = slutet av månaden)
YYYY-AA-GG / YYYY-AA (AA = ayın sonu)
PPPP-ММ-ДД / PPPP-MM (ММ = кінець місяця)
YYYY-MM-DD / YYYY-MM (MM = 月末)

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Temperature limitation / Температурни ограничения / Teplotní omezení / Temperaturbegrænsning / Temperaturbegrenzung / Περιορισμοί θερμοκρασίας / Limitación de temperatura / Temperatuuri piirang / Limites de température / Dozvoljena temperatura / Hőmérsékleti határ / Limiti di temperatura / Температураны шектеу /온도 제한 / Laikymo temperatūra / Temperatūras ierobežojumi / Temperatuurlimiet / Temperaturbegrensning / Ograniczenie temperatury / Limites de temperatura / Limite de temperatură / Ограничение температуры / Ohraničenie teploty / Ograničenje temperature / Temperaturgräns / Sıcaklık sınırlaması / Обмеження температури / 温度限制

Batch Code (Lot) / Код на партидата / Kód (číslo) šarže / Batch-kode (lot) / Batch-Code (Charge) / Κωδικός παρτίδας (παρτίδα) / Código de lote (lote) / Partii kood / Numéro de lot / Lot (kod) / Tétel száma (Lot) / Codice batch (lotto) / Топтама коды / 배치 코드(로트) / Partijos numeris (LOT) / Partijas kods (laidiens) / Lot nummer / Batch-kode (parti) / Kod partii (seria) / Código do lote / Cod de serie (Lot) / Код партии (лот) / Kód série (šarža) / Kod serije / Partinummer (Lot) / Parti Kodu (Lot) / Код партії / 批号（亚批）

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CONTROL

Control / Контролно / Kontrola / Kontrol / Kontrolle / Μάρτυρας / Kontroll / Contrôle / Controllo / Бақылау / 컨트롤 / Kontrolė / Kontrole / Controle / Controlo / Контроль / kontroll / Контроль / 对照

CONTROL +

Positive control / Положителен контрол / Pozitivní kontrola / Positiv kontrol / Positive Kontrolle / Θετικός μάρτυρας / Control positivo / Positiivne kontroll / Contrôle positif / Pozitivna kontrola / Pozitív kontroll / Controllo positivo / Оң бақылау / 양성 컨트롤 / Teigiama kontrolė / Pozitīvā kontrole / Positieve controle / Kontrola dodatnia / Controlo positivo / Control pozitiv / Положительный контроль / Pozitif kontrol / Позитивний контроль / 阳性对照试剂

CONTROL −

Negative control / Отрицателен контрол / Negativní kontrola / Negativ kontrol / Negative Kontrolle / Αρνητικός μάρτυρας / Control negativo / Negatiivne kontroll / Contrôle négatif / Negativna kontrola / Negatív kontroll / Controllo negativo / Неративтік бақылау / 음성 컨트롤 / Neigiama kontrolė / Negatīvā kontrole / Negatieve controle / Kontrola ujemna / Controlo negativo / Control negativ / Отрицательный контроль / Negatif kontrol / Негативний контроль / 阴性对照试剂

STERILE EO

Method of sterilization: ethylene oxide / Метод на стерилизация: етиленов оксид / Způsob sterilizace: etylenoxid / Steriliseringsmetode: ethylenoxid / Sterilisationsmethode: Ethylenoxid / Μέθοδος αποστείρωσης: αιθυλενοξείδιο / Método de esterilización: óxido de etileno / Steriliseerimismeetod: etüleenoksiid / Méthode de stérilisation : oxyde d'éthylène / Metoda sterilizacije: etilen oksid / Sterilizálás módszere: etilén-oxid / Metodo di sterilizzazione: ossido di etilene / Стерилизация әдісі – этилен тотығы / 소독 방법: 에틸렌옥사이드 / Sterilizavimo būdas: etileno oksidas / Sterilizēšanas metode: etilēnoksīds / Gesteriliseerd met behulp van ethyleenoxide / Steriliseringsmetode: etylenoksid / Metoda sterylizacji: tlenek etylu / Método de esterilização: óxido de etileno / Metodă de sterilizare: oxid de etilenă / Метод стерилизации: этиленоксид / Metóda sterilizácie: etylénoxid / Metoda sterilizacije: etilen oksid / Steriliseringsmetod: etenoxid / Sterilizasyon yöntemi: etilen oksit / Метод стерилізації: етиленоксидом / 灭菌方法：环氧乙烷

STERILE R

Method of sterilization: irradiation / Метод на стерилизация: ирадиация / Způsob sterilizace: záření / Steriliseringsmetode: bestråling / Sterilisationsmethode: Bestrahlung / Μέθοδος αποστείρωσης: ακτινοβολία / Método de esterilización: irradiación / Steriliseerimismeetod: kiirgus / Méthode de stérilisation : irradiation / Metoda sterilizacije: zračenje / Sterilizálás módszere: besugárzás / Metodo di sterilizzazione: irradiazione / Стерилизация әдісі – сәуле түсіру / 소독 방법: 방사 / Sterilizavimo būdas: radiacija / Sterilizēšanas metode: apstarošana / Gesteriliseerd met behulp van bestraling / Steriliseringsmetode: bestråling / Metoda sterylizacji: napromienianie / Método de esterilização: irradiação / Metodă de sterilizare: iradiere / Метод стерилизации: облучение / Metóda sterilizácie: ožiarenie / Metoda sterilizacije: ozračavanje / Steriliseringsmetod: strålning / Sterilizasyon yöntemi: irradyasyon / Метод стерилізації: опроміненням / 灭菌方法：辐射

Biological Risks / Биологични рискове / Biologická rizika / Biologisk fare / Biogefährdung / Βιολογικοί κίνδυνοι / Riesgos biológicos / Bioloogilised riskid / Risques biologiques / Biološki rizik / Biológiailag veszélyes / Rischio biologico / Биологиялық тәуекелдер / 생물학적 위험 / Biologinis pavojus / Bioloģiskie riski / Biologisch risico / Biologisk risiko / Zagrożenia biologiczne / Perigo biológico / Riscuri biologice / Биологическая опасность / Biologické riziko / Biološki rizici / Biologisk risk / Biyolojik Riskler / Біологічна небезпека / 生物学风险

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Upper limit of temperature / Горен лимит на температурата / Horní hranice teploty / Øvre temperaturgrænse / Temperaturobergrenze / Ανώτερο όριο θερμοκρασίας / Límite superior de temperatura / Ülemine temperatuuripiir / Limite supérieure de température / Gornja dozvoljena temperatura / Felső hőmérsékleti határ / Limite superiore di temperatura / Температураның руқсат етілген жоғарғы шеги / 상한 온도 / Aukščiausia laikymo temperatūra / Augšējā temperatūras robeža / Hoogste temperatuurlimiet / Øvre temperaturgrense / Górna granica temperatury / Limite máximo de temperatura / Limită maximă de temperatură / Верхний предел температуры / Horná hranica teploty / Gornja granica temperature / Övre temperaturgräns / Sıcaklık üst sınırı / Максимальна температура / 温度上限

Keep dry / Пазете сухо / Skladujte v suchém prostředí / Opbevares tørt / Trocklagern / Φυλάξτε το στεγνό / Mantener seco / Hoida kuivas / Conserver au sec / Držati na suhom / Száraz helyen tartandó / Tenere all'asciutto / Құрғақ күйінде ұста / 건조 상태 유지 / Laikykite sausai / Uzglabāt sausu / Droog houden / Holdes tørt / Przechowywać w stanie suchym / Manter seco / A se feri de umezeală / Не допускать попадания влаги / Uchovávajte v suchu / Držite na suvom mestu / Förvaras torrt / Kuru bir şekilde muhafaza edin / Берегти від вологи / 请保持干燥

Collection time / Време на събиране / Čas odběru / Opsamlingstidspunkt / Entnahmeuhrzeit / Ώρα συλλογής / Hora de recogida / Kogumisaeg / Heure de prélèvement / Sati prikupljanja / Mintavétel időpontja / Ora di raccolta / Жинау уақыты / 수집 시간 / Paėmimo laikas / Savākšanas laiks / Verzameltijd / Tid prøvetaking / Godzina pobrania / Hora de colheita / Ora colectării / Время сбора / Doba odberu / Vreme prikupljanja / Uppsamlingstid / Toplama zamanı / Час забору / 采集时间

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Perforation / Перфорация / Perforace / Perforering / Διάτρηση / Perforación / Perforatsioon / Perforacija / Perforálás / Perforazione / Тесік тесу / 절취선 / Perforacija / Perforācija / Perforatie / Perforacja / Perfuração / Perforare / Перфорация / Perforácia / Perforasyon / Перфорація / 穿孔

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Keep away from heat / Пазете от топлина / Nevystavujte přílišnému teplu / Må ikke udsættes for varme / Vor Wärme schützen / Κρατήστε το μακριά από τη θερμότητα / Mantener alejado de fuentes de calor / Hoida eemal valgusest / Protéger de la chaleur / Držati dalje od izvora topline / Óvja a melegtől / Tenere lontano dal calore / Салқын жерде сақта / 열을 피해야 함 / Laikyti atokiau nuo šilumos šaltinių / Sargāt no karstuma / Beschermen tegen warmte / Må ikke utsettes for varme / Przechowywać z dala od źródeł ciepła / Manter ao abrigo do calor / A se feri de căldură / Не нагревать / Uchovávajte mimo zdroja tepla / Držite dalje od toplote / Får ej utsättas för värme / Isıdan uzak tutun / Берегти від дії тепла / 请远离热源

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Collection date / Дата на събиране / Datum odběru / Opsamlingsdato / Entnahmedatum / Ημερομηνία συλλογής / Fecha de recogida / Kogumiskuupäev / Date de prélèvement / Dani prikupljanja / Mintavétel dátuma / Data di raccolta / Жинаған тізбекүні / 수집 날짜 / Paėmimo data / Savākšanas datums / Verzameldatum / Dato prøvetaking / Data pobrania / Data de colheita / Data colectării / Дата сбора / Dátum odberu / Datum prikupljanja / Uppsamlingsdatum / Toplama tarihi / Дата забору / 采集日期

µL/test / µL/тест / µL/Test / µL/εξέταση / µL/prueba / µL/teszt / µL/테스트 / мкл/тест / µL/tyrimas / µL/pārbaude / µL/teste / мкл/аналіз / µL/检测

Keep away from light / Пазете от светлина / Nevystavujte světlu / Må ikke udsættes for lys / Vor Licht schützen / Κρατήστε το μακριά από το φως / Mantener alejado de la luz / Hoida eemal valgusest / Conserver à l'abri de la lumière / Držati dalje od svjetla / Fény nem érheti / Tenere al riparo dalla luce / Қараңғыланған жерде ұста / 빛을 피해야 함 / Laikyti atokiau nuo šilumos šaltinių / Sargāt no gaismas / Niet blootstellen aan zonlicht / Må ikke utsettes for lys / Przechowywać z dala od źródeł światła / Manter ao abrigo da luz / Feriţi de lumină / Хранить в темноте / Uchovávajte mimo dosahu svetla / Držite dalje od svetlosti / Får ej utsättas för ljus / Işıktan uzak tutun / Берегти від дії світла / 请远离光线

Hydrogen gas generated / Образуван е водород газ / Možnost úniku plynného vodíku / Frembringer hydrogengas / Wasserstoffgas erzeugt / Δημιουργία αερίου υδρογόνου / Producción de gas de hidrógeno / Vesinikgaasi tekitatud / Produit de l'hydrogène gazeux / Sadrži hydrogen vodik / Hidrogén gázt fejleszt / Produzione di gas idrogeno / Газтектес сутеги пайда болды / 수소 가스 생성됨 / Išskiria vandenilio dujas / Rodas ūdeņradis / Waterstofgas gegenereerd / Hydrogengass generert / Powoduje powstawanie wodoru / Produção de gás de hidrogénio / Generare gaz de hidrogen / Выделение водорода / Vyrobené použitím vodíka / Oslobađa se vodonik / Genererad vätgas / Açığa çıkan hidrojen gazı / Реакція з виділенням водню / 会产生氢气

Patient ID number / ИД номер на пациента / ID pacienta / Patientens ID-nummer / Patienten-ID / Αριθμός αναγνώρισης ασθενούς / Número de ID del paciente / Patsiendi ID / No d'identification du patient / Identifikacijski broj pacijenta / Beteg azonosító száma / Numero ID paziente / Пациенттің идентификациялық нөмірі / 환자 ID 번호 / Paciento identifikavimo numeris / Pacienta ID numurs / Identificatienummer van de patiënt / Pasientens ID-nummer / Numer ID pacjenta / Número da ID do doente / Număr ID pacient / Идентификационный номер пациента / Identifikačné číslo pacienta / ID broj pacijenta / Patientnummer / Hasta kimlik numarası / Ідентифікатор пацієнта / 患者标识号

Fragile, Handle with Care / Чупливо, Работете с необходимото внимание. / Křehké. Při manipulaci postupujte opatrně. / Forsigtig, kan gå i stykker. / Zerbrechlich, vorsichtig handhaben. / Εύθραυστο. Χειριστείτε το με προσοχή. / Frágil. Manipular con cuidado. / Õrn, käsitsege ettevaatlikult. / Fragile. Manipuler avec précaution. / Lomljivo, rukujte pažljivo. / Törékeny! Óvatosan kezelendő. / Fragile, maneggiare con cura. / Сынғыш, абайлап пайдаланыңыз. / 조심 깨지기 쉬운 처리 / Trapu, elkitės atsargiai. / Trausls; rīkoties uzmanīgi / Breekbaar, voorzichtig behandelen. / Ømtålig, håndter forsiktig. / Krucha zawartość, przenosić ostrożnie. / Frágil, Manuseie com Cuidado. / Fragil, manipulaţi cu atenţie. / Хрупкое! Обращаться с осторожностью. / Krehké, vyžaduje sa opatrná manipulácia. / Lomljivo - rukujte pažljivo. / Bräckligt. Hantera försiktigt. / Kolay Kırılır, Dikkatli Taşıyın. / Тендітна, звертатися з обережністю / 易碎，小心轻放

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