SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Human Papillomavirus (HPV) DNA detection kit

Device Trade Name: BD Onclarity HPV Assay

Device Procode: MAQ

Applicant's Name and Address: Becton Dickinson and Company
7 Loveton Circle
Sparks, MD 21152

Date(s) of Panel Recommendation: Not applicable

Premarket Approval Application (PMA) Number: P160037

Date of FDA Notice of Approval: February 12, 2018

Priority Review: Not applicable

II. INDICATIONS FOR 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.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BD Onclarity HPV Assay labeling.

V. DEVICE DESCRIPTION

The BD Onclarity HPV Assay is based on two major processing steps: 1) automated specimen preparation to homogenize the matrix, lyse cells, and release 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 gene serves as an internal control for the entire test by concurrently assessing specimen processing, extraction, and amplification. The primers and probes of the BD Onclarity HPV Assay target regions in the E6/E7 oncogenes.

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. 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. These HR HPV 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).

The BD Onclarity HPV Assay uses real-time PCR technology. The detection of the target DNA is accomplished using TaqMan DNA probes, which 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.

Interpretation of Results:

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.

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.

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

HPV Genotype Result	*Interpretation*	*Result*
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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the detection of cervical cancer precursors, including testing by cytology alone, co-testing with HPV alongside or as a follow-up to cytology, or HPV testing as a first line screening test for cervical cancer. Each alternative has its own advantages and disadvantages. A woman should fully discuss these alternatives with her physician to select the method that best meets expectations and lifestyle.

The woman's age, medical history and thorough physical examination will provide further information on the risk of cervical disease, as well as the need for referral to colposcopy. The BD Onclarity HPV Assay should only be used in conjunction with this clinical information in accordance with appropriate clinical patient management guidelines.

VII. MARKETING HISTORY

The BD Onclarity HPV Assay is marketed as an *in vitro* diagnostic assay in the following countries: Australia, New Zealand, India, Korea, Turkey, Saudi Arabia, Brazil, Mexico, Guatemala, and countries within the European Union, including Austria, Belgium, Luxemburg, Denmark, France, Germany, Italy, Poland, Romania, and Spain. It has not been withdrawn from these markets for any reason related to the device's safety or effectiveness.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following section outlines the potential adverse effects (e.g., complications) associated with the use of the BD Onclarity HPV Assay. As with any *in vitro* diagnostic test, the potential adverse effects are associated with incorrect test results or result interpretations. Failure of this device to perform as expected or failure to correctly interpret results may lead to incorrect HPV test results and subsequently, improper patient management decisions in cervical cancer screening. False negative results may lead to delays in the timely diagnosis of cervical cancer, allowing an undetected condition to worsen and potentially increasing morbidity and mortality. False positive

results could lead many women to unnecessarily undergo more frequent screening and potentially invasive procedures such as colposcopy and biopsy.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Clinical Cutoff Determination

The preliminary clinical cutoff determination for the BD Onclarity HPV Assay was established based on a series of studies with remnant clinical specimens from a screening population of patients with normal cytology. Further evaluation of the preliminary cutoff was evaluated with clinical specimens and in independent, published studies designed to compare performance of multiple HPV assays. ROC curves were generated to determine a cutoff allowing for maximal sensitivity and specificity. The methods used for cutoff selection were prioritized to achieve the maximum sensitivity for detecting ≥CIN2 disease while maintaining a clinically acceptable level of specificity. Based on these studies, the clinical cutoff was set at a Ct of 38.3 for HPV16 and 34.2 for all other genotypes.

2. C95 Determination at the Clinical Cutoff

The C95 determination at the clinical cutoff was determined for the BD Onclarity HPV Assay using the following HPV positive cell lines: SiHa (HPV 16), HeLa (HPV 18) and MS751 (HPV 45). The C95 is the level of HPV DNA in the specimen that yields a positive result at least 95% of the time using the clinical cutoff. In addition, cloned plasmid DNA containing the sequences for the following HPV genotypes was also used: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. These cells and plasmids were diluted in BD SurePath media containing an HPV-negative cell line (C33A) for the preparation of at least five dilution levels. Plasmids and cell lines were diluted to concentrations below, above and at the expected C95 levels. A matrix equivalency study was performed between this contrived background and negative clinical matrix to demonstrate equivalent C95s for HPV types 16, 18 and 45 using either background. A minimum of forty-five replicates were tested for each of the HPV positive cell lines and each of the HPV16, HPV18, and HPV45 plasmids. Twenty replicates were tested for each of the remaining 11 other high risk HPV plasmids. Three lots of reagents were utilized across three BD Viper LT Systems. Probit analysis was performed for the determination of C95 for each genotype and each lot. The C95 for each sample was the maximum C95 value which was produced among the three reagent lots. Table 1 lists the C95s determined for the HPV plasmids and cell lines tested.

Table 1: C95 Determination at Clinical Cutoff

Target	C95(Cells or Copies/mL)	95% Confidence Interval	
		Lower	Upper
SiHa cells (HPV 16)	50 (cells/mL)	37	67
HeLa cells (HPV 18)	199 (cells/mL)	154	256
MS751 cells (HPV 45)	862 (cells/mL)	669	1111
HPV 16	251	193	326
HPV 18	1083	1000	1267
HPV 45	1261	1154	1358
HPV 31	830	718	879
HPV 33	1665	1495	2030
HPV 35	1550	1472	1655
HPV 39	1794	1617	1862
HPV 51	1522	1315	1613
HPV 52	814	776	951
HPV 56	1090	937	1185
HPV 58	2369	2231	6631
HPV 59	1000	942	1152
HPV 66	862	823	916
HPV 68	2392	2227	2646

To verify that the BD Onclarity HPV Assay is capable of accurately detecting all target HPV high risk genotypes, the C95 at the HPV clinical cutoff was confirmed using SiHa (HPV 16), HeLa (HPV 18) and MS751 (HPV 45) cell lines as well as 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 media containing an HPV-negative cell line (C33A). Twenty replicates of each cell line/plasmid diluted to the C95 concentrations were tested with one reagent lot on one BD Viper LT System. Table 2 lists the confirmed C95 for each cell line and plasmid.

Table 2: C95 Confirmation

Target	C95 (Cells or Copies/mL)	Ratio POS to Total	Positivity Rate (%)
SiHa cells (HPV 16)	50 (cells/mL)	20/20	100
HeLa cells (HPV 18)	208 (cells/mL)	19/20	95
MS751 cells (HPV 45)	862 (cells/mL)	20/20	100
16	251	19/20	95
18	1083	19/20	95
45	1261	19/20	95
31	830	20/20	100
33	1665	20/20	100
35	1550	20/20	100
39	1794	20/20	100
51	1522	20/20	100
52	814	20/20	100
56	1131	19/20	95
58	2294	19/20	95
59	1000	20/20	100
66	862	20/20	100
68	2367	20/20	100

3. Analytical Specificity

A panel of bacteria, yeast, and cultured viruses, including those found in female urogenital specimens, as well as 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 media containing an HPV-negative cell line (C33A). The microorganisms are described in Table 3. Bacteria and yeast were tested at $\geq 1x10^6$ CFU/mL, HPV plasmid DNA was tested at $\geq 1x10^6$ copies/mL and non-HPV viruses were tested at $\geq 1x10^6$ vp/mL. The BD Onclarity HPV Assay did not exhibit cross-reactivity with any of the microorganisms tested or any non-targetted HPV types.

Table 3: Panel of Potential Cross Reactants for Analytical Specificity Study

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.	*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.	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.	EBV-1, B95-8 Strain	HPV 70

Gardnerella vaginalis	HIV-1	HPV 73
Klebsiella pneumonia ssp.	HPV 16	HPV 82
Lactobacillus acidophilus	HPV 18	HPV 97
Mycobacterium smegmatis	HPV 31	[redacted]
Mycoplasma genitalium	HPV 33	[redacted]
Neisseria gonorrhoeae	HPV 35	[redacted]
Peptostreptococcus anaerobius	HPV 39	[redacted]
Prevotella bivia	HPV 45	[redacted]
Prevotella disiens	HPV 51	[redacted]
Proteus mirabilis	HPV 52	[redacted]

4. Interfering Substances

Endogenous and Exogenous

Contrived HPV negative and positive specimens were tested in the presence or absence of each potential interferent 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. All contrived specimens were prepared from a BD SurePath matrix containing a cellular background of C33A cells. HPV negative contrived specimens contained only the C33A cellular background. HPV positive specimens for this study contained cell lines positive for HPV 16 (SiHa), HPV 18 (HeLa) or HPV 45 (MS751) at 3 x C95. Interfering substances reported in % w/v were weighted and dissolved in the appropriate amount of HPV positive or negative contrived matrix. Vortex and/or incubation in a warm bath were applied as necessary. The potential interfering substances were added to HPV positive or negative contrived matrix and the mixtures were vortexed as necessary. For final sample preparation, a 0.5 mL aliquot from each sample was added to an HPV LBC Diluent tube. Twelve replicates were tested for each interferent.

The tested substances are described in Table 4. The concentrations represent the highest level of substance that did not show any interference in the BD Onclarity HPV Assay:

Table 4: Interference Testing Results with Endogenous and Exogenous 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

There were four substances that yielded false negative results when tested at concentrations higher than described in Table 4: Whole Blood, Mucin, Zovirax Cream (Acyclovir) and Clindamycin Vaginal Cream.

Competing Targets:

A study was performed to test whether high concentrations of HR HPV DNA could interfere with the genotyping capability of HPV types 16, 18 and 45. For the competing target conditions, the appropriate plasmids representing the competing HR genotypes were spiked into positive and negative contrived matrix at a concentration of 1 x 10^6 copies/mL in the SurePath specimen. A 0.5 mL aliquot from each competing target condition was added to 1.7 mL of HPV Diluent. No interference was observed from the competing targets. As a control, a portion of the HPV positive and negative contrived matrix, devoid of any interfering substances or competing target plasmid, was assayed in the same manner as the test conditions. This matrix control was run once per matrix preparation. External negative and positive run controls were included with each run. No competitive interference among any of the targets was identified.

5. Reproducibility

Studies were conducted with panels consisting of contrived samples in negative clinical matrix and pooled clinical specimens. For the contrived panel members, HPV positive cell lines for genotypes 16, 18, and 45 (SiHa, HeLa and MS7541, respectively) were spiked into negative clinical matrix at three different concentrations representing a high negative (i.e., the C5 concentration), low positive (i.e., the C95 concentration), and moderate positive (i.e., 3 x C95). Additionally, six different clinical pools that were positive for either HPV 16, 18, 45, 31, 33/58 or 52 were also tested, as well as a sample containing pooled clinical matrix that was negative for all genotypes. These panels were tested at three clinical sites over the course of nine days for each site. Three reagent lots were utilized (each lot was tested for 3 days). Two runs were performed at each site with 3 replicates per run. Two operators per site participated in the study. The total number of replicates per panel member was 162 (54 replicates per site). Invalid results due operator error, a negative control failure, and an extraction error on the BD Viper LT system were excluded from calculation of negativity and positivity rates and from the analysis of the numeric Ct values, resulting in a total of 156-159 replicates per panel member.

All valid test results were included for calculation of negativity or positivity rates. There were no false positive results in 158 tests performed on the negative panel members. Percent positive

results along with 95% confidence intervals for the negative and positive panel members are shown in Tables 5 and 6, respectively.

Table 5: Results by Sample Type for High Negative and Negative Panel Members for Lot and Site/Instrument:

				Number Negative/Total Number of Results				
				Lot		Site/Instrument		
Sample Type	**Panel Member**	**Ct SD**	**Ct %CV**	**ID**	**Percent Negative**	**ID**	**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 6: Results by Sample Type for Positive Panel Member for Lot and Site/Instrument

		Number Positive/Total Number of Results				
		Lot		Site/Instrument		
Sample Type	**Panel Member**	**ID**	**Percent Positive**	**ID**	**Percent Positive**	**95% CI**
SiHa cell line	HPV 16 Low Positive (50 cells/mL)	1	100.0 (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)	

		Number Positive/Total Number of Results				
		Lot		Site/Instrument		
Sample Type	**Panel Member**	**ID**	**Percent Positive**	**ID**	**Percent Positive**	**95% CI**
		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 (2586 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

		Number Positive/Total Number of Results				
		Lot		Site/Instrument		
Sample Type	Panel Member	ID	Percent Positive	ID	Percent Positive	95% CI
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

The overall mean, standard deviation and coefficients of variation for cycle threshold (Ct) for positive panel members is summarized in Table 7. Analysis of variance of the Ct score from the valid tests performed on positive panel members yielded % 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 7: 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 (2586 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.

6. Precision

An in-house precision study was performed using the same panel members as described in the Reproducibility study. Testing was performed over the course of 12 days with 4 instruments, 3 operators and 3 lots. Each operator tested the panel with two runs per day per lot. Three replicates per panel member were performed for each run. Tables 8 and 9 show the agreement results for the contrived and clinical panel members, respectively, with the BD Onclarity Assay on the BD Viper LT system. The total number of measurments per panel member was 214-216. Tables 10 and 11 summarize the variance component analysis results for the contrived and pooled clinical panel members, respectively. The overall %CV ranged from 1.4% to 1.8% for SiHa cells, 0.9% to 2.1% for HeLa cells, and 0.9% to 1.5% for MS751 cells. The overall %CV for pooled HPV positive clinical specimens ranged from 2.0% to 5.6%.

Table 8: Summary of Precision Panel Contrived Specimens and Agreement Rates

HPV Genotype	HPV Target Source	HPV Panel Level (cells/mL)	Total Tested	Total Correct	Percent Agreement	95% CI	
						Lower	Upper
HPV16	SiHa cells	2	214	205	95.79% Negative	92.20%	97.77%
HPV16	SiHa cells	50	216	207	95.83% Positive	92.27%	97.79%
HPV16	SiHa cells	150	215	213	99.07% Positive	96.67%	99.74%
HPV18	HeLa cells	23	216	214	99.07% Negative	96.69%	99.75%
HPV18	HeLa cells	208	216	216	100.00% (Positive)	98.25%	100.00%
HPV18	HeLa cells	623	214	214	100.00% (Positive)	98.24%	100.00%
HPV45	MS751 cells	90	214	212	99.07% (Negative)	96.66%	99.74%
HPV45	MS751 cells	862	216	214	99.07% (Positive)	96.69%	99.75%
HPV45	MS751 cells	2586	216	216	100.00% (Positive)	98.25%	100.00%

Table 9: Summary of Precision Panel Pooled Clinical Specimens and Agreement Rates

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 10: Variance Component Analysis Results for Contrived Specimens

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
	2586 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 11: Variance Component Analysis Results for Pooled Clinical Specimens

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	0.0	00	0.25	0.72	0.0	0.0	0.0	0.0	0.0	0.0	1.56	4.49	58	4.54
Clinical Positive 18	30.60	0.0	0.0	0.0	0.0	0.12	0.38	0.13	0.42	0.0	0.0	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	0.0	0.0	0.0	0.0	1.68	5.09	1.69	5.13
Clinical Positive 33/58	30.34	0.0	0.0	0.04	0.12	0.0	0.0	0.12	0.38	0.0	0.0	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	0.0	0.0	0.0	0.0	1.77	5.46	1.83	5.63
Clinical Positive 52	31.58	0.24	0.76	0.09	0.28	0.0	0.0	0.19	0.61	0.0	0.0	1.39	4.40	1.43	4.51

7. Carry-over/Cross Contamination

A study was performed to evaluate the risk of producing a false positive result in either the same run (within run carry-over) or in a subsequent run (between run carry-over carry-over) 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 (i.e., an HPV 16 positive cell line) spiked at 1.0 x 10^5 cells/mL in BD SurePath media. There were zero false positive results among 675 results for the HPV negative samples and the contamination rate with BD SurePath media was 0% (0/675) with 95% CI: 0.0% to 0.6%.

Because the BD Onclarity HPV Assay can be run on a post-cytology specimen after processing on the PrepMate Cytology Processor, a carry-over/cross-contamination study was also performed on the PrepMate to ensure no upstream specimen processing events could cause false positive results. An HPV16 positive cell line was spiked in SurePath media containing a background of HPV negative C33A cells. The HPV16 positive cell line was spiked at a concentration that represented the amount of target necessary to achieve an HPV16 Ct in the 5th percentile from the clinical study. For each run, six of these HPV16 high positive samples were run with six HPV16 negative samples in a checkerboard pattern on the PrepMate. Twelve consecutive runs on the PrepMate were performed on one PrepMate system, for a total of 72 replicates. No false positive results among 72 results for the HPV negative samples were found in this study and the contamination rate was 0% (0/72) with 95% CI: 0.0% to 5.1%.

8. Reagent Stability

The BD Onclarity Assay consists of five reagents. Table 12 lists each of the reagents along with their corresponding shelf life and storage temperature, as supported by the results of real time stability studies:

Table 12: Reagent Stability

BD Onclarity HPV Assay Reagents	***Shelf Life Dating in days (approximate months)***	***Storage Temperature***
HPV Reagent Pack	249 (~8 months)	2-8°C
HPV Positive/Negative Control	528 (~18 months)	2-33°C
HPV LBC Diluent Tube	249 (~8 months)	2-25°C
HPV PCR Reagent Trough	249 (~8 months)	2-33°C
HPV Extraction Tube	249 (~8 months)	2-33°C

The change in Ct value between baseline and the maximum storage duration was ≤1 for all temperatures.

9. Specimen Stability

Specimen stability studies demonstrated that for the BD Onclarity HPV Assay, cervical specimens can be stored in SurePath media at 2-30 °C for up to 30 days, 2-8 °C for 180 days, or at -20 °C for 180 days from the date of collection to the time of transfer to the HPV LBC Diluent tube. 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. After pre-warming, the specimens may be stored for up to 7 days at 2-30 °C. The change in Ct value between baseline and the maximum storage duration was ≤1 for all temperatures.

B. Animal Studies

Not Applicable

C. Additional Studies

Not applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of high risk HPV type nucleic acid detection with the BD Onclarity HPV Assay for routine cervical cancer screening in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were enrolled between August 2013 and June 2015. The database for this PMA reflected data collected through June 2015 and included 33,858 women. There were 31 investigational sites. Specific entrance criteria were structured to qualify subjects, specimens, and test results.

The multicenter, prospective clinical study was conducted to evaluate the performance of the BD Onclarity HPV Assay for the following three indications: 1. As a triage test to stratify women aged 21 with ASC-US cytology results for colposcopy; 2. As an adjunctive test to cervical cytology to guide management decisions in women aged ≥30; and 3. As a first-line primary test for cervical cancer screening in women aged ≥25. Women aged ≥21 undergoing routine cervical cancer screening were enrolled from 31 collection sites between August 2013 and June 2015. Following written informed consent, demographic and gynecologic histories were obtained. Two liquid based cytology (LBC) specimens were collected from each woman, the first being collected in SurePath collection media, and the second in PreservCyt collection media. The cytology results from the first collected SurePath specimen were evaluated at one of three central laboratories and classified according to the 2001 Bethesda System. BD Onclarity HPV Assay testing was performed on LBC specimen aliquots removed prior to cytology testing (i.e., "prequots") at one of four testing laboratories. A post-cytology aliquot (i.e., "postquot") was also removed from the first collected SurePath specimen for a subset of randomly selected women and tested with the BD Onclarity Assay. The second collected PreservCyt specimen was tested with the BD Onclarity Assay and an FDA-approved HPV assay. Clinical performance of the BD Onclarity assay was evaluated using the pre-cytology aliquot from the first-collected SurePath specimen.

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 test result for high risk HPV DNA by the BD Onclarity HPV Assay in either SurePath or PreservCyt and/or the FDA-approved HPV test, as well as a randomly selected subset of women (approximately 10%) with NILM cytology and negative HR HPV DNA results (by both the BD Onclarity HPV assay and the FDA-approved HPV DNA test) were invited to

proceed to colposcopy. In order to avoid bias in the evaluation of HPV and cytology testing, both study participants and colposcopists were blinded to all HPV test and cytology results until after the colposcopy procedure 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 was obtained if no lesions or acetowhite areas were visible. All biopsies were examined by a Central Pathology Review (CPR) Panel consisting of three expert pathologists. Discordant histology results were adjudicated according to a pre-defined protocol.

The slides that were prepared from the biopsies and reviewed by the CPR panel were stained with hematoxylin and eosin (H&E). In addition, recommendations outlined in the 2012 Lower Anogenital Squamous Terminology (LAST) guidelines[1] were adapted in selecting certain H&E stained slides to also be evaluated using p16 immunohistochemistry assistance. The criteria in selecting slides to be read with p16 assistance were established based on the LAST committee recommendations, where p16 assistance should be used as a supplement to H&E only for slides where the H&E architecture is equivocal in nature. Based on these recommendations, the following criteria were established for using p16 assistance after the reading of H&E stained slides: 1. at least of one the expert CPR adjudicators reported a CIN2 diagnosis for the histologic specimen, and 2. there was disagreement among the diagnoses of the reviewers, whereby at least one of the reviewers reported a diagnosis of ≥CIN2 and at least one of the reviewers reported a diagnosis of <CIN2. This approach to the evaluation of slides resulted in two sets of clinical diagnoses: 1. diagnoses based on H&E staining alone for all cases (i.e. "H&E alone"), and 2. diagnoses based on H&E+p16 assistance for slides meeting the LAST-adapted criteria and H&E alone for all other slides (i.e., H&E +p16 (LAST)). The clinical performance of the BD Onclarity HPV Assay was evaluated against the CPR histology diagnoses for each histologic endpoint (H&E alone and H&E+p16 assistance(LAST)).

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the BD-USHPV clinical study was limited to patients who met the following inclusion criteria:

- Female subjects who are ≥21 years of age
- Women > 65 years of age may be included following USPSTF recommendations.
- Female subjects who provide informed consent.
- Female subjects who have received the HPV vaccine (approximately 10% of total enrollment)
- Subjects who have the following minimum specimen results:
    - Cytology result from the BD SurePath Collection Vial
    - At least one LBC aliquot for BD Viper LT testing

Patients were not permitted to enroll in the BD-USHPV study if they met any of the following exclusion criteria:

- Subjects known to be pregnant.
- Subjects who had a cervical cytology specimen collected within the last 4 months.

- Subjects with prior complete or partial hysterectomy involving removal of cervix.
- Subjects with an application of chemical compounds to the cervical area 24 hour prior to study entry- acetic acid, iodine, spermicide, douche, or anti-fungal meds.
- Subjects on whom conization, LEEP, cervical laser surgery or cryosurgery on the cervix has been performed in the last twelve months.
- Subjects who have been previously enrolled in a cervical disease diagnostic trial since 2007.

2. Follow-up Schedule

All women with abnormal cytology results (i.e., ≥ASC-US), unsatisfactory cytology results, women who were HPV positive by either the BD Onclarity or FDA-approved HPV assay, as well as a subset of women with normal cytology who were HPV negative by both HPV assays were invited to undergo the colposcopy procedure within approximately three months.

For the primary screening indication, all women aged ≥25 years who had undergone colposcopy and biopsy in the baseline phase but did not receive treatment as well as approximately 10% of NILM women (≥25 years) with HR HPV negative results and no baseline biopsy or treatment were invited to proceed to the three year Follow-up Phase of the study. Approximately 8,900 women from the baseline phase are eligible for the three-year follow-up study, where they will undergo annual cytology and HPV DNA testing with the BD Onclarity HPV Assay. Those women with abnormal cytology will be invited to proceed to colposcopy. Colposcopy and biopsies will be performed in a standardized manner as described above. All cervical tissue will be examined by the Central Pathology Review Panel. An exit colposcopy with biopsy and endocervical curettage (ECC) will be offered to all women in Year 3. All women, regardless of cytology or histology result, will be followed through the duration of the study. Women who receive treatment procedures will exit the study. The three-year follow-up study is currently underway and will be submitted as a post-approval study as a condition of approval for the primary screening claim.

Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, as an *in vitro* diagnostic test, the BD Onclarity HPV Assay involves sampling cells from the cervix using an endocervical brush/spatula or broom. The test, therefore, presents no more safety hazard to an individual being tested than other tests where cervical cells are sampled in this manner (i.e., cervical cytology). Safety issues regarding false positive and negative test results are discussed in section VIII.

With regards to effectiveness, the following are the clinical endpoints for each indication:

ASC-US Triage (≥21 years) indication: The clinical performance of the BD Onclarity HPV Assay was evaluated against CPR panel histology diagnoses, with ≥CIN2 and ≥CIN3 as the disease endpoints for all women aged ≥21 with ASC-US cytology.

Adjunct (NILM ≥30 years) indication: Clinical performance of the BD Onclarity HPV Assay was evaluated against CPR panel histology diagnoses, with ≥CIN2 and ≥CIN3 as the disease endpoints for all women aged ≥30 years with NILM cytology. Baseline risks for both ≥CIN2 and ≥CIN3 were evaluated for each BD Onclarity HPV result.

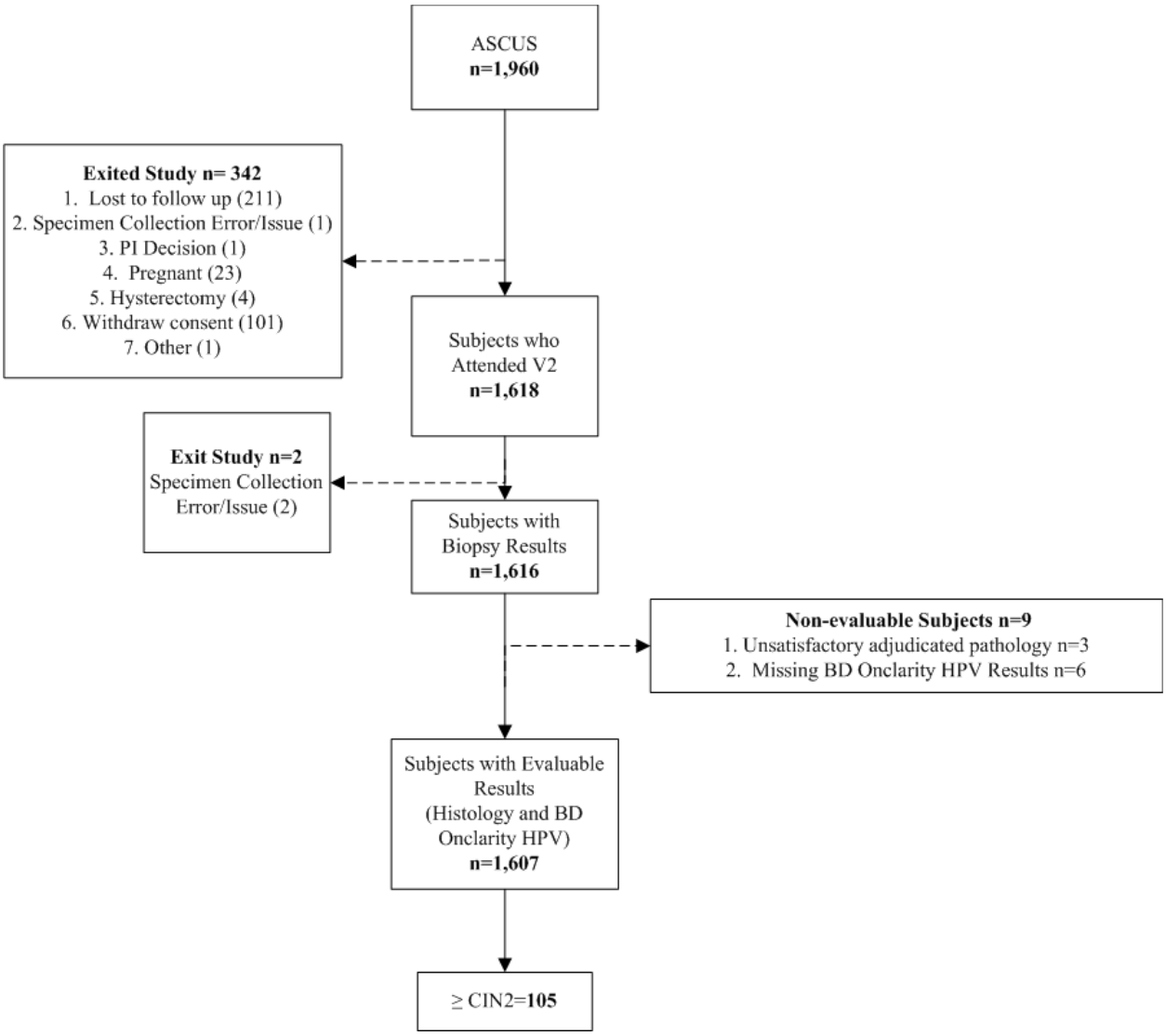
Primary Screening (≥25 years) indication: The clinical performance of the BD Onclarity HPV Assay in the baseline phase was evaluated against CPR panel histology diagnoses, with ≥CIN2 and ≥CIN3 as the disease endpoints for all women aged ≥25 years. The performance of the primary screening algorithm was compared to two different screening algorithms, one based on current practice and the other based on cytology alone. Risks for ≥CIN2 and ≥CIN3 were evaluated according to the baseline HPV status (as determined by the BD Onclarity HPV assay) for each BD Onclarity HPV assay readout as well as different HPV genotype and cytology combinations.

B. Accountability of PMA Cohort

A total of 33,858 subjects were enrolled in this study. Of the enrolled subjects, 33,634 subjects had evaluable cytology. Subject age and cytology result were used to group the enrolled subjects into the following intended use populations:

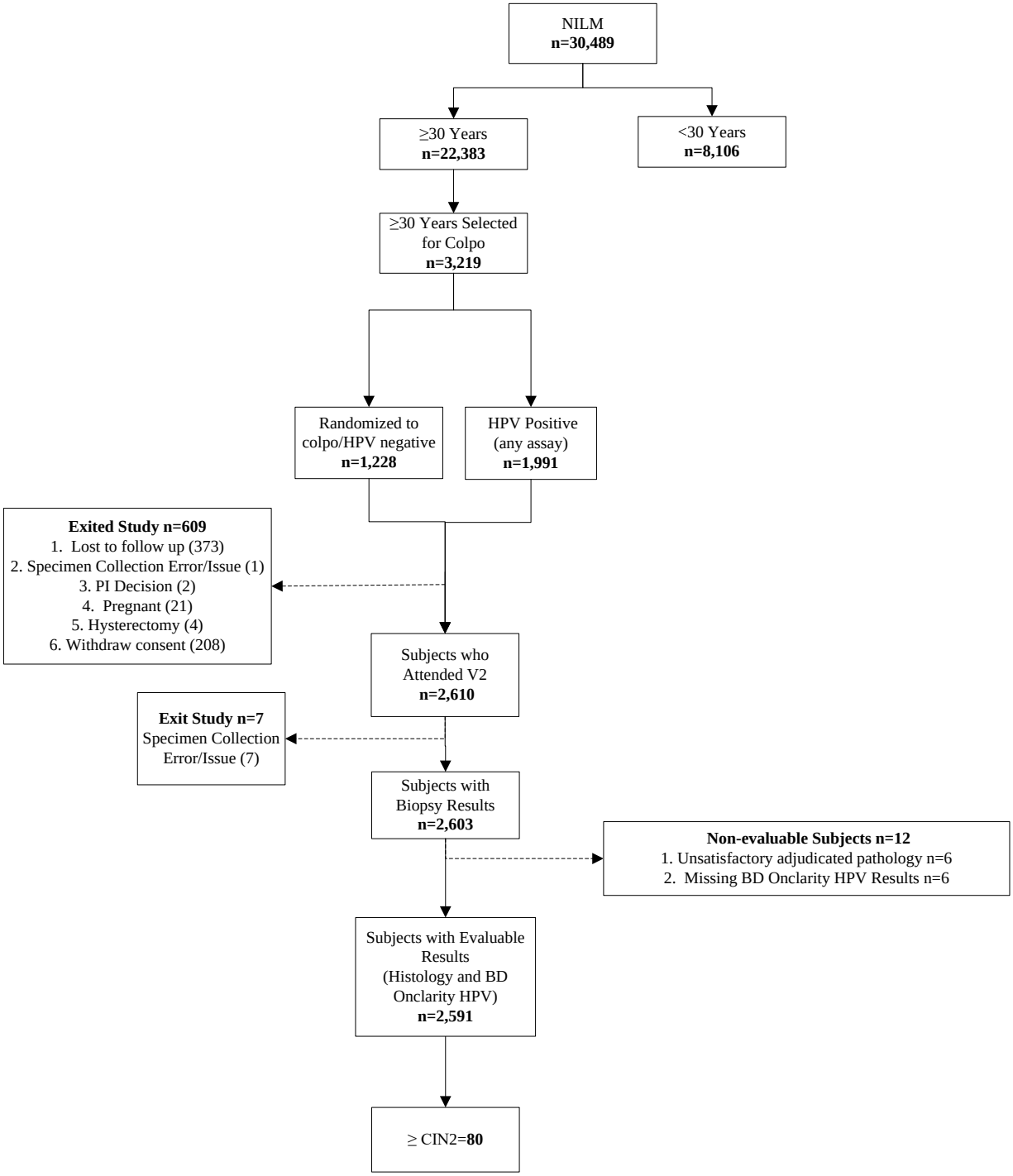
ASC-US Population (≥21 years)

Women ≥21 years with ASC-US cytology were evaluated for the ASC-US triage indication. A total of 1,960 (5.8%) subjects out of 33,634 subjects with evaluable cytology had an ASC-US cytology result and were invited to proceed to the colposcopy/biopsy procedure, of which, 1,618 attended. Out of the 1,618 subjects, two had specimen collection errors/issues, leaving 1,616 subjects with biopsy results. Three of these subjects had unsatisfactory adjudicated results, and six had missing BD Onclarity results, leaving a total of 1,607 evaluable subjects.



Adjunct Population (≥30 years)

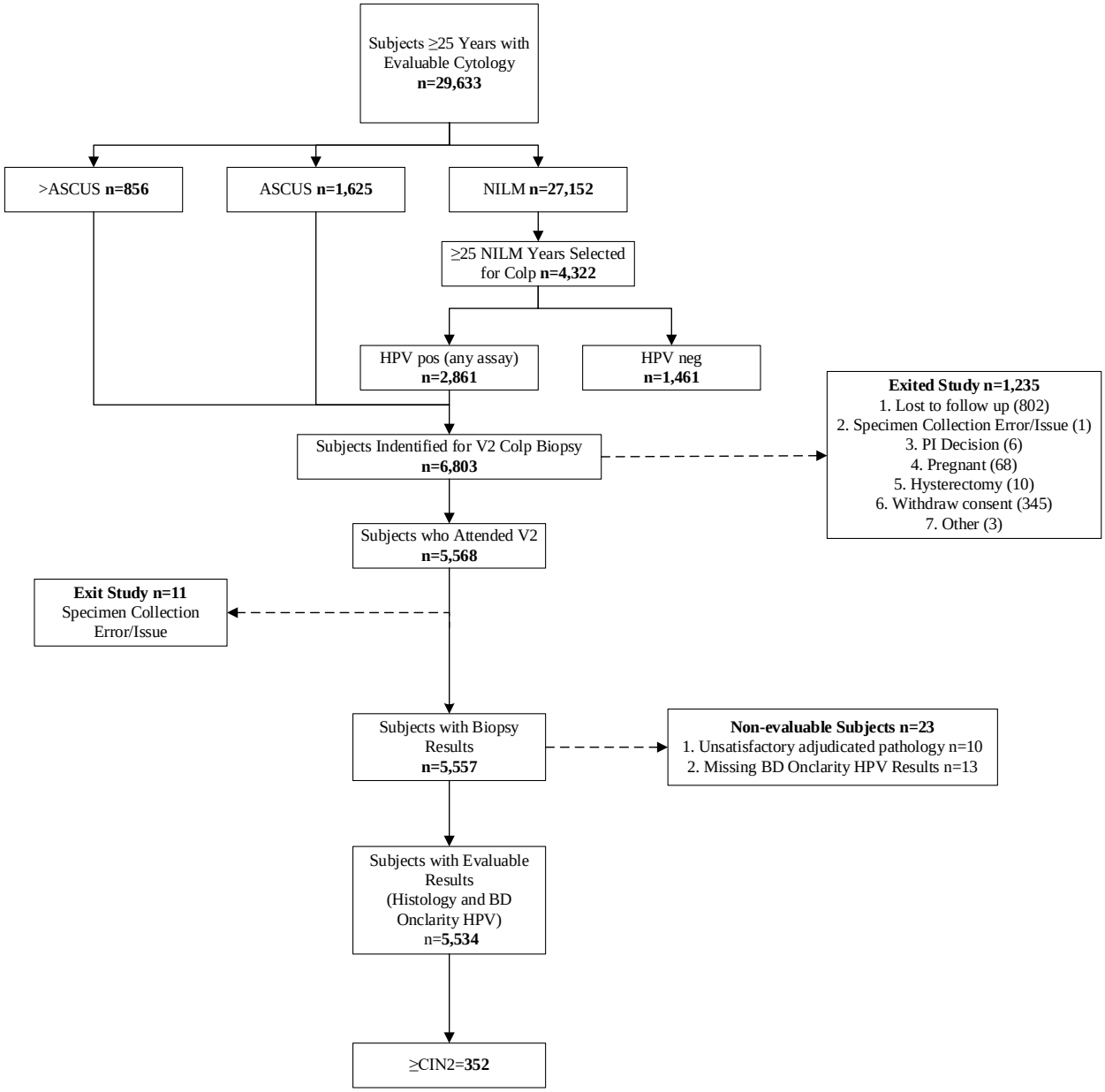
Women ≥30 years with NILM cytology were evaluated for the Adjunct indication. Out of the 33,634 subjects women with evaluable cytology, 30,489 had NILM cytology. Of these, 22,383 subjects were 30 years or older. Of these, 1,991 women with an HPV positive result and 1,228 randomly selected women who were HPV negative by both the Onclarity and FDA approved tests were invited to proceed to the colposcopy/biopsy procedure, for a total of 3,219 subjects. Of these 3,219 women, 2,610 attended the colposcopy visit and 2,603 had biopsy results. Six subjects had adjudicated results of unsatisfactory and were not used in the data analysis, and six had either missing or invalid HPV results. Evaluable histology and HPV results were obtained for 2,591 subjects.



Primary Screening Population (≥25 years)

All women ≥25 years with valid cytology results were evaluated for the primary screening indication. Out of the 33,634 subjects with evaluable cytology, 29,690 were over the age of 25. Fifty-seven of these subjects had unsatisfactory cytology results and were excluded, for a total of 29,633 subjects in the primary screening population. This represented about 88.1% of the

enrolled subjects. Of these, 27,152 subjects had NILM, 1,625 subjects had ASC-US, and 856 subjects had >ASC-US cytology. A total of 6,803 subjects were invited to return for the colposcopy/biopsy procedure because they either had an abnormal cytology result (2,481), were HPV positive NILM (2,861), or were a random selection of HPV negative NILM (1,461). Of these, 5,568 attended the colposcopy visit and 5,557 had biopsy results. Ten subjects had unsatisfactory results and were not included in the data analysis. Of the 5,547 women with evaluable adjudicated results, 13 had missing HPV Onclarity test results, leaving a total of 5,534 women in the primary screening population with evaluable histology and HPV results.



C. Study Population Demographics and Baseline Parameters

The demographics of the study population shown in Table 13 are typical for a cervical cancer screening study performed in the US.

Table 13: Study Demographics for Each Intended Use Population

Demographics		*ASC-US*	*Adjunct*	*Primary Screening*
Age at Consent (years)	*Mean*	36.2	43.9	40.7
	Standard Deviation	11.5	9.6	10.9
	Median	34.0	43.0	39.0
	(Min, Max)	21, 82	30, 83	25, 83
	Total (n)	1960	22383	29633
Ethnicity (%)	*Hispanic or Latino*	15.5 303/1960	20.5 4592/22383	19.9 5887/29633
	Not Hispanic or Latino	84.5 1657/1960	79.5 17789/22383	80.1 23744/29633
	Ethnicity data missing	0 0/1960	0.0 2/22383	0.0 2/29633
Race (%)	*American Indian or Alaskan Native*	0.4 7/1960	0.4 97/22383	0.5 149/29633
	Asian	1.0 20/1960	1.5 336/22383	1.4 416/29633
	Black or African American	23.4 459/1960	16.6 3722/22383	18.0 5340/29633
	Native Hawaiian or Other Pacific Islander	0.2 4/1960	0.3 60/22383	0.2 73/29633
	White	73.8 1446/1960	80.4 17988/22383	79.0 23400/29633
	Other	1.2 24/1960	0.8 180/22383	0.9 255/29633

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

Table 14 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 14: Summary of HPV Positivity of the BD Onclarity HPV Assay by Testing Sites and Study Population

BD Onclarity HPV Assay HR Positivity Rate			
Testing Site	**ASC-US (≥ 21 years)**	**NILM (≥ 30 years)**	**Primary Screening (≥ 25 years)**

1	39.5% (234/592)	9.3% (644/6921)	14.2% (1306/9167)
2	36.7% (126/343)	7.4% (369/4962)	12.0% (757/6300)
3	33.3% (259/778)	7.1% (372/5219)	12.7% (941/7434)
4	60.0% (144/240)	7.3% (376/5182)	11.3% (744/6612)
Total	39.1% (763/1953)	7.9% (1761/22284)	12.7% (3748/29513)

Table 15 shows HPV positivity rates by the BD Onclarity HPV Assay by age and study population. HPV positivity decreased with age in each study population.

Table 15: Summary of HPV Positivity Rates of the BD Onclarity HPV Assay by Age and Study Population

BD Onclarity HPV Assay 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% (1216/5432)
30 - 39	39.2% (204/521)	10.3% (889/8663)	13.8% (1310/9477)
≥ 40	22.9% (161/703)	6.4% (872/13621)	8.4% (1222/14604)
Total	39.1% (763/1953)	7.4% (1761/22284)	12.7% (3748/29513)

The BD Onclarity HPV Assay results stratified by age are outlined in Table 16 for the ASC-US population (≥ 21 years), in Table 17 for the NILM population (≥ 30 years), and in Table 18 for the primary screening population (≥ 25 years). In all populations, the 11 other HPV HR positive results were more frequent than HPV16, HPV18, and HPV45 positive results in general and within age groups. HPV positivity rates for each category decreases with age in all three populations.

Table 16: 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% (144/1953)	2.5% (48/1953)	2.4% (47/1953)	32.2% (629/1953)	60.9% (1190/1953)

Note: For this table, women with mixed infections were counted for each HPV type they were infected with (i.e., if a woman was infected with both HPV16 and 18, then she was included in both the HPV16+ and HPV18+ analysis).

Table 17: 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% (173/8663)	0.5% (45/8663)	0.8% (68/8663)	7.7% (671/8663)	89.7% (7774/8663)
≥ 40	1.2% (157/13621)	0.4% (53/13621)	0.4% (56/13621)	4.9% (671/13621)	93.6% (12749/13621)
Total	1.5% (330/22284)	0.4% (98/22284)	0.6% (124/22284)	6.0% (1342/22284)	92.1% (20523/22284)

Note: For this table, women with mixed infections were counted for each HPV type they were infected with (i.e., if a woman was infected with both HPV16 and 18, then she was included in both the HPV16+ and HPV18+ analysis).

Table 18: 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% (246/5432)	1.2% (63/5432)	18.9% (1025/5432)	77.6%(4216/5432)
30 - 39	2.9% (274/9477)	0.8% (78/9477)	11.2% (1063/9477)	86.2% (8167/9477)

≥ 40	1.5% (223/14604)	0.6% (84/14604)	6.9% (1010/14604)	91.6% (13382/14604)
Total	2.5% (743/29513)	0.8% (225/29513)	10.5% (3098/29513)	87.3% (25765/29513)

Note: For this table, women with mixed infections were counted for each HPV type they were infected with (i.e., if a woman was infected with both HPV16 and 18, then she was included in both the HPV16+ and HPV18+ analysis).

Safety and Effectiveness Results

1. Safety Results

As an *in vitro* diagnostic test, the BD Onclarity HPV Assay involves sampling cells from the cervix using an endocervical brush/spatula combination or broom. Collection of the sample, therefore, presents no more safety hazard to an individual being tested than other tests where cervical cells are sampled in this manner (such as cervical cytology).

Adverse effects that occurred in the PMA clinical study:

All serious adverse events (AE) reported during the study were captured in the subjects' chart and in the electronic database. The adverse events collected during this study were only those events related to the study-required colposcopy and biopsy procedure. Each AE was assigned a severity criterion (mild, moderate, marked) by the principal investigator or designee. Each AE was also evaluated for determination as a Serious Adverse Event by the principal investigator or designee. During the clinical study, there were 37 events reported, 28 of which were adverse events and 9 were serious adverse events.

Twenty-two subjects out of the 33,858 enrolled in the study (0.06%) reported a total of 28 adverse events. Of the 28 adverse events, 8 were assigned an unlikely relationship to the procedure, 8 were assigned a possible relationship to the procedure and 12 were assigned a probable relationship to the procedure. The adverse events with a possible relationship to the procedure were comprised of 1 bacterial vaginosis, 3 abdominal cramps or lower abdominal pain, 1 low grade fever, 2 vaginal bleeding and 1 urinary tract infection. The 12 adverse events with a probable relationship to the procedure were comprised of 3 cervical or vaginal bleeding, 3 uterine contractions or cramping, 2 vaginal or cervical pain, 1 abdominal bloating, 2 syncopal episodes and 1 fall with a laceration due to the syncopal episode. All the adverse events with a possible or probable relationship to the procedure resolved within 33 days of event onset.

Of the 9 serious adverse events, all were unlikely to have been a result of the BD HPV Assay or the investigational procedure. The serious adverse events were comprised of 6 cancers, 1 myomectomy, 1 reported death due to a prescription overdose, and 1 diverticulitis and sepsis resulting in death. Five of the 9 serious adverse events were resolved within 58 days of onset. Four serious adverse events remained unresolved at the study closure.

2. Effectiveness Results

The analysis of effectiveness was based on the data in the following sections for each claimed indication. The clinical performance data in this section are based on histology diagnoses using H&E+p16 assistance for slides meeting the LAST-adapted criteria and H&E alone for all other slides. For clinical performance estimates using H&E alone as the histologic endpoint for all slides, please see section XI: Summary of Supplemental Clinical Information. It should be noted

that no significant differences in performance were apparent when using either histologic endpoint for any of the three indications.

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

Study enrollment was completed in June 2015 with a total of 33,858 subjects. Of the total enrollment, 1,960 subjects ≥21 years of age had ASC-US cytology results. All subjects were referred to the colposcopy/biopsy visit, of which 1,619 returned. Satisfactory histological diagnoses were determined for 1,613 subjects. Six subjects (all <CIN2) had non-evaluable BD Onclarity HPV Assay results, leaving 1,607 evaluable subjects for estimating assay performance in support of the proposed ASC-US claim. Table 19 summarizes the BD Onclarity HPV Assay results stratified by CPR panel adjudicated histology diagnoses.

Table 19: BD Onclarity HPV Assay Results and CPR Panel diagnoses 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	1190
Invalid/Missing*	6	0	0	0	1	7
Total	1317	191	70	35	347**	1960

Note:
* Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results. Percent of Invalid/Missing results was 0.36% (7/1960).
** 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.

Of the 1,607 evaluable subjects, 105 subjects had ≥CIN2 (prevalence of 6.5%) and 35 had ≥CIN3 (prevalence of 2.2%).

The performance of the BD Onclarity HPV Assay in detecting high-grade cervical disease (≥CIN2 and ≥CIN3) is presented in Table 20. The sensitivity and 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 2.39, which indicates a positive BD Onclarity HPV Assay result is 2.39 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. The PLR and NLR using ≥CIN3 as an endpoint was 2.41 and 0.14, respectively.

Table 20: 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 (77.8, 91.1)	91.4 32/35 (77.6, 97.0)
Specificity (%) (95% CI)	64.1 963/1502 (61.7, 66.5)	62.0 975/1572 (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 (%)	6.5 105/1607	2.2 35/1607

Out of the 15 subjects with ≥CIN2 who were negative by the BD Onclarity, 9 were negative by both the FDA approved test and PCR/sequencing, 3 were negative by the FDA approved test and positive by PCR/sequencing for HR HPV, and 3 were positive by the FDA approved test and negative by PCR/sequencing. These latter three subjects were identified by sequencing as positive for low-risk HPV types 67 and/or 82.

Out of the 3 subjects with ≥CIN3 that were negative by the BD Onclarity, 1 was negative by both the FDA approved test and PCR/sequencing, 1 was negative by the FDA approved test and positive by PCR/sequencing for HR HPV, and 1 was positive by the FDA approved test and negative by PCR/sequencing. This latter subject was identified by sequencing as positive for low risk HPV type 67.

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 21. 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 21: Performance of the BD 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% (105/1601)				
Sensitivity (%)	85.7 (90/105)	(77.8, 91.1)	82.9 (87/105)	(74.5, 88.9)
Specificity (%)	64.1 (959/1496)	(61.6, 66.5)	61.4 (919/1496)	(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% (35/1601)				
Sensitivity (%)	91.4 (32/35)	(77.6, 97.0)	85.7 (30/35)	(70.6, 93.7)
Specificity (%)	62.0 (971/1566)	(59.6, 64.4)	59.5 (932/1566)	(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 in this analysis.

The performance of the BD Onclarity HPV Assay for detecting ≥CIN2 and ≥CIN3 evaluated by age group is presented in Table 22 below. The sensitivity for detecting ≥CIN2 was 93.6% (44/47) in the 21-29 age group, 83.3% (35/42) in the 30-39 age group, and 68.8% (11/16) in the 40 age group. The specificity was highest in the ≥40 age group, with an estimate of 78.1% (447/572).

The sensitivity for detecting ≥CIN3 was 92.9% (13/14) in the 21-29 age group, 92.9% (13/14) in the 30-39 age group, and 85.7% (6/7) in the ≥40 age group. Specificity was highest in the ≥40 age group, with an estimate of 77.6% (451/581).

Table 22: 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)
≥CIN2 prevalence (%)	8.2 (47/572)		9.5 (42/444)		2.7 (16/585)	
≥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)
≥CIN3 prevalence (%)	2.4 (14/572)		3.2 (14/444)		1.2 (7/585)	

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

Table 23 below summarizes the CPR adjudicated histology diagnoses reported by all possible BD Onclarity HPV Assay results for the ASC-US (≥21 years) population. The BD Onclarity HPV result is categorized hierarchically based on detected genotype (positive) 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 (i.e., women positive for HPV 16 and HPV 18 was categorized as HPV 16).

Table 23: Summary of BD Onclarity HPV Assay Results and Adjudicated Histology Diagnoses in the ASC-US (≥21 years) Population

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	1190
Total	1311	191	70	35	346[a]	1953

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

The likelihood ratios, along with 95% confidence intervals, for a given HPV type by the Onclarity HPV Assay test result and histologic determination are presented in Table 24.

Table 24: Likelihood Ratios by BD Onclarity HPV Assay Result in the ASC-US (≥21 years) Population

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)

For the ≥CIN2 endpoint, the likelihood ratio for an HPV HR positive result was 2.39 (95% CI 2.13, 2.63), indicating that an HPV positive result was 2.39 times more likely to be associated with a woman with ≥CIN2. Of the individual genotypes identified and reported by the BD Onclarity HPV Assay, a positive HPV 16 result had the highest positive likelihood ratio of 5.98 (95% CI 4.15, 8.42), indicating that a positive result is 5.98 times more likely to come from a subject with ≥CIN2 than without. The likelihood ratio of a combined HPV 16/18/45 test outcome was 4.12 (95% CI 3.07, 5.38). The likelihood ratio for an 11 other result was 1.75 (95% CI 1.38, 2.15). For an HPV HR negative result, the likelihood ratio was 0.22 (95% CI 0.14, 0.35), indicating that the negative result was 4.55 (1/0.22) times more likely to come from a subject without disease (i.e., <CIN2) than with disease.

For the ≥CIN3 endpoint, the likelihood ratio for an HPV HR positive result was 2.41 (95% CI 2.03, 2.64). Of the individual genotypes identified and reported by the BD Onclarity HPV Assay, a positive HPV 16 result had the highest positive likelihood ratio of 8.60 (95% CI 5.69, 12.08). The likelihood ratio of a combined HPV 16/18/45 test outcome was 5.35 (95% CI 3.72, 7.07). For an HPV HR negative result, the likelihood ratio was 0.14 (95% CI 0.05, 0.36), indicating that the negative result was 7.1 (1/0.14) times more likely to come from a subject without disease <CIN3, than with disease.

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

The risk of disease is the probability of having disease given an HPV test result. Table 25 summarizes the absolute risk of disease for each BD Onclarity HPV result. For the ≥CIN2 disease endpoint, the pre-test risk was 6.5% regardless of HPV test result (i.e., out of 1,607 evaluable subjects, 105 had ≥CIN2). A positive HPV HR test result increased this risk of disease to 14.3% (95% CI 13.0, 15.5). A positive HPV16 result yielded the highest risk of ≥CIN2, which was 29.5% (95% CI 22.5, 37.0). For women with a negative HPV HR result, the risk of ≥CIN2 was 1.5% (95% CI 1.0, 2.4), which was significantly lower than the pre-test risk.

For the ≥CIN3 disease endpoint, the pre-test risk was 2.2% (i.e., out of 1607 evaluable subjects, 35 had ≥CIN3). A positive HPV HR test result increased the risk of disease to 5.1% (95% CI 4.3, 5.6). A positive HPV16 result yielded the highest risk of ≥CIN3, which was 16.1% (95% CI 21.2,

21.2). For women with a negative HPV HR result, the risk of ≥CIN3 was 0.3% (95% CI 0.1, 0.8), which was significantly lower than the pre-test risk.

Table 25: Absolute Risk of Disease by BD Onclarity HPV Assay Result in the ASC-US (≥21 years) Population

BD Onclarity HPV Assay Test Results	***Absolute Risk of Disease (%) (95% CI)***	
	≥CIN2 *prevalence*: 6.5% (105/1607)	*≥CIN3* *prevalence: 2.2% (35/1607)*
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 risks of ≥CIN2 and ≥CIN3 were calculated between subjects with different HPV test results. These risks along with the 95% confidence intervals are outlined in Table 26. For the ≥CIN2 endpoint, all subjects with an HPV HR positive vs. negative result were significantly more likely to be associated with disease. The relative risk of a HPV HR positive vs. negative result was 9.33 (95% CI 5.49, 15.88), indicating that a woman with an HPV HR positive result was 9.33 more likely to have ≥CIN2 histology than a woman with an HPV negative result. When the HPV HR result is stratified by genotype, the relative risk of ≥CIN2 for a combined 16/18/45 result versus an HPV negative result is 14.57 (95% CI 8.30, 25.52). The relative risk for an HPV 11 other result vs. HPV negative is 7.10 (95% CI 4.05, 12.45).

Similar trends were observed when using ≥CIN3 as an endpoint. An overall HPV HR positive result was 16.59 times more likely to be associated with disease than an HPV negative result (i.e. relative risk of 16.59 with a lower bound of 5.42). A combined 16/18/45 positive result or HPV 11 other result was 34.68 (95% CI 11.09, 108.53) and 8.87 (95% CI 2.70, 29.14) times more likely to be associated with ≥CIN3 than a negative result, respectively.

Table 26: Relative Risk of Disease by BD Onclarity HPV Assay Result in the ASC-US (≥21 years) Population

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 risks associated with different HPV results were also calculated by age group and are outlined in Table 27 below. For all age groups, a positive HPV HR result and a combined HPV 16/18/45 positive result were both significantly more likely to be associated with disease (either ≥CIN2 or ≥CIN3) than an HPV negative result.

Table 27: Relative Risk of Disease by BD Onclarity HPV Assay Result in the ASC-US (≥21 years) Population

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)

PERFORMANCE CHARACTERISTICS IN THE ADJUNCT (NILM ≥30) POPULATION:

Subjects with NILM cytology results that were ≥30 years old were evaluated in support of the proposed Adjunct indication. Of the total enrollment, 22,383 subjects were 30 years or older and had NILM cytology results. All subjects with a positive HPV result from either the BD Onclarity or FDA-approved HPV test (1,991) and a subset of subjects with negative HPV results from both molecular test results (1,228) were invited to proceed to colposcopy, for a total of 3,219 subjects. Of these subjects, 2,591 subjects had evaluable histological diagnoses and BD Onclarity HPV results for estimating assay performance in support of the proposed Adjunct claim.

Verification bias adjustment was performed for the subsequent analyses to account for the study design in which not all subjects were referred to colposcopy. For these calculations, the likely number of disease cases that would have been found if all the subjects had undergone colposcopy/biopsy was calculated.

BD Onclarity HPV Assay results in the Adjunct population, compared to CPR adjudicated histology, are summarized in Table 28. From the subjects with NILM cytology and evaluable histology, 2,385 had negative histology, 130 had CIN1, 34 had CIN2, and 46 had ≥CIN3. Six specimens had invalid or missing BD Onclarity HPV Assay results.

Table 28: BD Onclarity HPV Assay Result and CPR Panel diagnosis in the NILM (≥30 years) Population

	Central Pathology Review Panel Diagnosis					
BD IUO HPV Assay Results	**NEG**	**CIN1**	**CIN2**	**>=CIN3**	**Unknown Disease Status**	**Total**
HPV 16	153	9	4	18	146	330
HPV 18	70	5	1	2	15	93
HPV 45	89	2	1	1	22	115
11 Other	886	77	21	22	217	1223
Negative	1184	36	7	3	19293	20523
Invalid/Missing[a]	5	1	0	0	93	99
Total	2387	130	34	46	19786[b]	22383

[a] Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results. Percent of Missing/Invalid Results was 0.44% (99/22383)

[b] 19,164 women were not assigned to the colposcopy visit. 609 women did not return or were no longer eligible for a colposcopy procedure. Six women had unsatisfactory histology results and 7 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 29. For the ≥CIN2 endpoint, the unadjusted (i.e. crude) estimates of sensitivity and specificity for detection of ≥CIN2 are 87.5% (95% CI 78.5, 93.1) and 48.6% (95% CI 46.6, 50.5), respectively. The positive likelihood ratio for the detection of ≥CIN2 was 1.70 (crude) and 5.86 (adjusted). The negative likelihood ratio for the detection of ≥CIN2 was

0.26 (crude) and 0.60 (adjusted). Verification bias adjusted sensitivity and specificity for ≥CIN2 are 44.4% (95% CI 27.2, 76.2) and 92.4% (95% CI 92.1, 92.8), respectively.

For the ≥CIN3 endpoint, unadjusted estimates of sensitivity and specificity for the detection of ≥CIN3 are 93.5% (95% CI 82.5, 97.8) and 48.2% (95% CI 46.3, 50.2), respectively. The positive likelihood ratio for the detection of ≥CIN3 was 1.81 (unadjusted) and 9.02 (adjusted). The negative likelihood ratio was 0.3 (adjusted). Verification bias adjusted sensitivity and specificity for the detection of ≥CIN3 are 69.3% (95% CI 42.0, 100.0) and 92.3% (95% CI 92.0, 92.7), respectively.

Table 29: Performance of the BD Onclarity HPV Assay in the NILM (≥30 years) Population

Performance	Central Pathology Review Panel Diagnosis			
	≥ CIN2		≥ CIN3	
	Unadjusted Estimate	Adjusted Estimate	Unadjusted Estimate	Adjusted Estimate
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 1220/2511 (46.6, 50.5)	92.4 (92.1, 92.8)	48.2 1227/2545 (46.3, 50.2)	92.3 (92.0, 92.7)
PPV % **(95% CI)**	5.1 70/1361 (4.6, 5.5)	5.1 (3.9, 6.3)	3.2 43/1361 (2.8, 3.4)	3.0 (2.1, 3.9)
NPV % **(95% CI)**	99.2 1220/1230 (98.6, 99.5)	99.5 (99.0, 99.9)	99.8 1227/1230 (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 80/2591	0.9 (0.5, 1.4)	1.8 46/2591	0.3 (0.2, 0.6)

The Performance of the BD Onclarity HPV Assay as well as the FDA approved test for detecting ≥CIN2 and ≥CIN3 is presented in Table 30.

Table 30: Performance of the BD Onclarity HPV Assay and an FDA Approved HPV Assay in the NILM (≥30 years) Population

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)

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%				
Specificity %	48.6	52.3	92.4	93.4
(95% CI)	1220/2508 (46.7, 50.6)	1312/2508 (50.4, 54.3)	(92.1, 92.8)	(93.1, 93.8)
PPV %	5.2	5.2	5.0	5.3
(95% CI)	70/1358 (4.6, 5.5)	66/1262 (4.6, 5.7)	(3.9, 6.1)	(4.1, 6.5)
NPV %	99.2	98.9	99.5	99.4
(95% CI)	1220/1230 (98.6, 99.5)	1312/1326 (98.4, 99.4)	(98.9, 99.9)	(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 %	93.5	87.0	69.5	63.3
(95% CI)	43/46 (82.5, 97.8)	40/46 (74.3, 93.9)	(42.8, 100.0)	(38.7, 94.9)
Specificity %	48.3	51.9	92.3	93.3
(95% CI)	1227/2542 (46.3, 50.2)	1320/2542 (50.0, 53.9)	(92.0, 92.7)	(93.0, 93.7)
PPV %	3.2	3.2	3.0	3.2
(95% CI)	43/1358 (2.8, 3.4)	40/1262 (2.7, 3.5)	(2.2, 4.0)	(2.3, 4.2)
NPV %	99.8	99.5	99.9	99.9
(95% CI)	1227/1230 (99.3, 99.9)	1320/1326 (99.1, 99.8)	(99.7, 100.0)	(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 31 presents all the possible BD Onclarity assay results in the NILM ≥30 years evaluable population together with the CPR panel diagnosis.

Table 31: BD HPV Assay Genotype Results and Adjudication Results in the NILM Population

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	0	0	0	0	1	1
HPV16 Pos, HPV18 Pos, HPV45 Neg, Other HPV	0	0	0	0	1	1

HPV16 Pos, HPV18 Pos, HPV45 Neg, Other HPV	1	2	0	0	0	3
HPV16 Pos, HPV18 Neg, HPV45 Pos, Other HPV	1	0	0	0	1	2
HPV16 Pos, HPV18 Neg, HPV45 Pos, Other HPV	3	0	0	0	0	3
HPV16 Pos, HPV18 Neg, HPV45 Neg, Other HPV	45	2	1	4	8	60
HPV16 Pos, HPV18 Neg, HPV45 Neg, Other HPV	103	5	3	14	135	260
HPV16 Neg, HPV18 Pos, HPV45 Pos, Other HPV	0	0	0	0	1	1
HPV16 Neg, HPV18 Pos, HPV45 Pos, Other HPV	2	0	0	0	0	2
HPV16 Neg, HPV18 Pos, HPV45 Neg, Other HPV	17	0	0	1	6	24
HPV16 Neg, HPV18 Pos, HPV45 Neg, Other HPV	51	5	1	1	8	66
HPV16 Neg, HPV18 Neg, HPV45 Pos, Other HPV	24	1	1	0	4	30
HPV16 Neg, HPV18 Neg, HPV45 Pos, Other HPV	65	1	0	1	18	85
HPV16 Neg, HPV18 Neg, HPV45 Neg, Other HPV	886	77	21	22	217	1223
HPV16 Neg, HPV18 Neg, HPV45 Neg, Other HPV	1184	36	7	3	19293	20523
Total	2382	129	34	46	19693*	22284

[a] Combined results of the 11 other HPV genotypes detected, but not differentiated, in the BD HPV assay.
*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 ratios along with 95% CIs for HPV 16, 18, 45 and 11 other positive and HPV HR negative for the NILM (≥ 30 years) population is presented in Table 32. Using the adjusted estimates for the ≥CIN2 and ≥CIN3 endpoints, an HPV HR positive result was 5.86 and 9.02 times, respectively, more likely to be associated with disease than without. An HPV16 positive result had the highest likelihood ratio for both the ≥CIN2 and ≥CIN3 endpoints (11.27 and 21.42, respectively). Similar likelihood ratio patterns were obtained using the crude estimates.

Table 32: Likelihood Ratio by the BD Onclarity HPV Assay Result in the NILM Population (≥30)

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 Assay results are presented in Table 33. The estimates were calculated with and without adjusting for verification bias. Using the adjusted estimates, for a NILM woman with a HPV HR positive result, the absolute risks of ≥CIN2 and ≥CIN3 are 5.1% (95% CI 3.9, 6.3) and 3.0% (95% CI 2.1, 3.9), respectively. An HPV16 result had the highest absolute risk of disease, which was 9.3% (95% CI 5.5, 13.7) for ≥CIN2, and 6.9% (95% CI 3.9, 9.9) for ≥CIN3. For a NILM woman who is HPV negative, the absolute risks for ≥CIN2 and ≥CIN3 are 0.5% (95% CI 0.1, 1.0) and 0.1% (95% CI 0.0, 0.3), respectively.

Table 33: 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 70/1361 (4.6, 5.5)	5.1 (3.9, 6.3)	3.2 43/1361 (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 43/1006 (3.4, 5.1)	4.3 (3.1, 5.5)	2.2 22/1006 (1.6, 2.8)	2.2 (1.4, 3.2)
HPV HR Negative	0.8 10/1230 (0.5, 1.4)	0.5 (0.1, 1.0)	0.2 3/1230 (0.1, 0.7)	0.1 (0.0, 0.3)

The relative risk of disease given one reported BD Onclarity HPV Result compared to another result is summarized in Table 34. Using the adjusted estimates, subjects with a positive HR HPV result were 9.31 (95% CI 4.5, 38.3) and 26.36 (95% CI 8.51, inf) times more likely to be associated with ≥CIN2 or ≥CIN3, respectively, than a NILM woman with an HPV negative result. Women who have a positive result for any combination of HPV 16/18/45 by the BD Onclarity HPV Assay were 12.56 (95% CI 5.62, 49.57) and 42.78 (95% CI 13.16, inf) times more likely to be associated with ≥CIN2 or ≥CIN3, respectively, than a NILM woman with an HPV negative result.

Table 34: Relative Risk of Disease by the BD Onclarity HPV Assay Result in the NILM Population (≥30)

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)

PERFORMANCE CHARACTERISTICS IN THE PRIMARY SCREENING POPULATION (≥25 YEARS)

The BD Onclarity HPV Assay primary screening strategy utilizes HPV genotype differentiation of 16/18 with reflex cytology. Women who test negative by the BD Onclarity HPV Assay should be followed up in accordance with the physicians' assessment of screening and medical history, other risk factors and professional guidelines (routine screening). Women who test positive for BD Onclarity HPV Assay genotypes 16/18 should be referred to colposcopy. Women who test BD Onclarity 12 Other HPV HR positive should be evaluated by cervical cytology to determine the need for referral to colposcopy. Subjects with ≥ASCUS cytology are referred to colposcopy. Subjects with NILM cytology are referred to follow up. A definition of primary screening strategy positive and negative results is presented below in Figure 1 and Table 40.

Figure 1: Primary Screening Algorithm

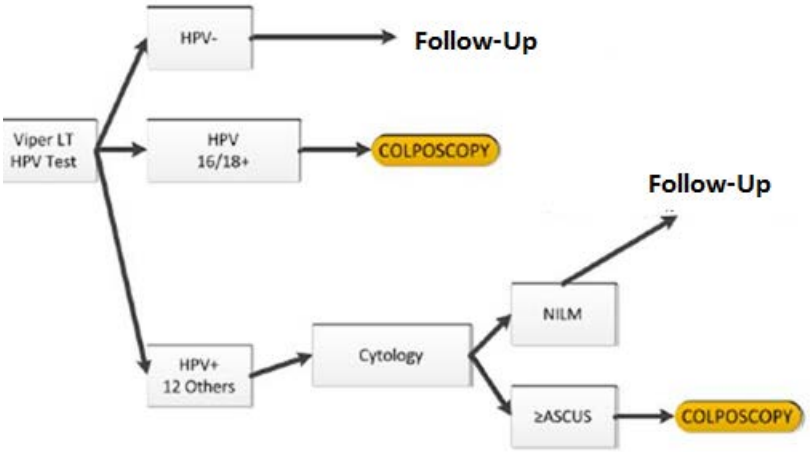


Table 40: Summary of Colposcopy Referral Population: Primary Screening Algorithm

BD Onclarity HPV Results	*>ASC-US*	*ASC-US*	*NILM*	
			≥30	*25-29*
HPV 16/18	+			
12 Other HPV HR Pos	+		-	
HPV HR Neg	-			

Note:"+" denotes women sent immediately to colposcopy.

Two clinical screening algorithms were used to compare against the primary screening algorithm. The first is consistent with the currently recommended cervical cancer screening paradigm (i.e., the "current practice algorithm"), which involves HPV triage of ASC-US cytology results in women less than 30 years of age and co-testing with HPV and cytology in women 30 and older. In this paradigm, women with cytology results >ASC-US, women who are ASC-US and HPV positive, and women with NILM cytology who are 30 or older and are positive for HPV 16 and/or HPV18 should proceed immediately to colposcopy. This screening paradigm is outlined in Table 41:

Table 41: Summary of Colposcopy Referral Population: Current Practice Screening Algorithm

BD Onclarity HPV Results	***>ASCUS***	***ASCUS***	***NILM***	
			≥30	*25-29*
HPV 16/18	+			-
12 Other HPV HR Pos	+		-	
HPV HR Neg	+	-		

"+" denotes women sent immediately to colposcopy.

The second algorithm is cytology screening alone, as this is currently an acceptable screening practice. This algorithm reflects longstanding clinical practice, is appropriate for all screening age groups and is independent of any HPV test result. This algorithm is used as a benchmark for evaluating the primary screening indications but is not intended to represent clinical optimal performance. It is a benchmark intended to represent clinically acceptable performance levels. This algorithm is consistent with the 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening. This algorithm is outlined in Figure 2 and Table 42:

Figure 2: Cytology Screening Algorithm

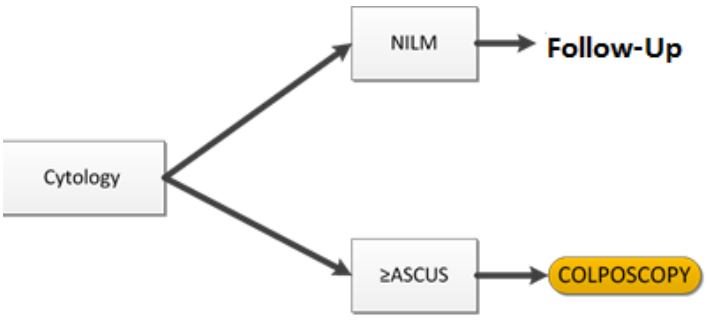


Table 42: Summary of Colposcopy Referral Population: Cytology Alone Screening Algorithm

BD Onclarity HPV Results	***>ASC-US***	***ASC-US***	***NILM***	
			≥30	*25-29*
HPV 16/18	+	+		
12 Other HPV HR Pos	+	+		
HPV HR Neg	+	+		

"+" denotes women sent immediately to colposcopy.

Definition of Positive and Negative Results and their Interpretations:

As described above, "positive" results for the screening algorithms are defined as women sent immediately to colposcopy. "Negative" results for the screening algorithms indicate that a woman will not be sent immediately to colposcopy. Any additional follow-up procedures are not directly assessed. Therefore, the BD Onclarity HPV Assay primary screening algorithm is being evaluated regarding its performance in directing immediate follow-up decisions. Longer-term follow-up decisions (i.e.,. subsequent screening visits) are not directly assessed.

Note that algorithm positive and negative results are distinct from the "disease positive" and "disease negative" results referred to in the clinical performance sections below, which are defined as women diagnosed with or without high grade CIN, respectively (results are presented for both ≥CIN2 and ≥CIN3). Therefore, when probability (i.e., risk) of disease is described in this document it refers to the probability that a woman has disease at the time of HPV testing.

Performance Evaluation in the Primary Screening Population:

A total of 29,633 women ≥ 25 years were enrolled in the study, of which 29,513 had evaluable cytology and BD Onclarity HPV results. A total of 5,534 women ≥25 years completed the colposcopy procedure with a valid CPR histology diagnosis 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 43.

Table 43: Number of Subjects in Primary Screening Population (≥25 years) with Adjudicated Histology Results

BD Onclarity HPV Result	Subjects	Cytology			Total
		>ASC-US	ASC-US	NILM	
HPV 16/18 Pos	Total	199	140	609	948
	Total With Adjudicated Histology	164	116	382	662
12 Other HPV HR Pos	Total	434	420	1946	2800
	Total With Adjudicated Histology	360	358	1596	2314
HPV HR Neg	Total	223	1060	24482	25765
	Total With Adjudicated Histology	180	881	1497	2558
Total	Total	856	1620	27037	29513
	Total With Adjudicated Histology	704	1355	3475	5534

Note: In women ≥25 years, there were 57 women with unsatisfactory cytology results who were excluded from the primary sceeening clinical performance analyses. These women were referred to colposcopy and their cervical disease statuses were <CIN2. Performance of the BD Onclarity HPV assay was calculated for women with satisfactory cytology results..

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 using the data from the women with histology diagnoses in different categories defined by HPV results, cytology results, and age.

Performance of the primary screening algorithm (HPV 16/18 Genotyping with reflex to Cytology) and the two comparator algorithms (Current Practice and Cytology alone) was evaluated in the primary screening population by estimating the sensitivity, specificity, Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR), Prevalence, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) in the identification of high-grade cervical disease. Results comparing the primary screening algorithm to the current practice and the cytology alone algorithms are outlined in Tables 44 and 45, respectively. For both the ≥CIN2 and ≥CIN3 endpoints, the primary screening algorithm had significantly higher sensitivity, specificity, PPV, NPV, and PLR and a significantly lower NLR as compared to the current practice and cytology alone screening algorithms. The colposcopy referral rate for the primary screening algorithm was significantly lower than the cytology alone algorithm (2.3% reduction) and similar to the current practice algorithm.

Table 44: Performance of the Primary Screening Algorithm Compared to the Current Practice Screening Algorithm in Women ≥25 years

Performance Metrics	≥CIN2; Prevalence (Adjusted) = 1.9%			≥CIN3; Prevalence (Adjusted) = 0.8%		
	Primary Screening Algorithm	ASCUS Triage and Co-Testing Algorithm	Difference	Primary Screening Algorithm	ASCUS Triage and 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	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

Table 45: Performance of the Primary Screening Algorithm Compared to the Cytology Alone Screening Algorithm in Women ≥25 years

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	53.72	47.42	6.30[a]	64.24	49.20	15.05 [a]

% (95% CI)	(44.18, 65.52)	(39.31, 57.77)	(2.39, 10.51)	(50.59, 79.65)	(38.31, 62.64)	(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	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 clinical performance for detection of ≥CIN3 for all three screening algorithms stratified by age group is summarized in Table 46:

Table 46: Performance of the BD Onclarity HPV Assay by Age Group in the Primary Screening, Cytology Alone and Current Practice Algorithms (≥CIN3)

Performance Metrics for ≥CIN3	**Primary Screening Algorithm**	**Cytology Screening Algorithm**	**ASCUS Triage and Co-Testing Algorithm**	**Primary Screening Algorithm**	**Cytology Screening Algorithm**	**ASCUS Triage and Co-Testing Algorithm**
Subgroup	**25-29 Years**			**30-39 Years**		
Sensitivity (%)	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 (%)	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 (%)	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 (%)	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	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	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	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 (%)	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 (%)	95.72 (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 (%)	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 (%)	99.90	99.84	99.92	99.97	99.93	99.97

Performance Metrics for ≥CIN3	Primary Screening Algorithm	Cytology Screening Algorithm	ASCUS Triage and Co-Testing Algorithm	Primary Screening Algorithm	Cytology Screening Algorithm	ASCUS Triage and Co-Testing Algorithm
	(99.81, 99.97)	(99.73, 99.95)	(99.83, 99.98)	(99.91, 100.00)	(99.85, 99.98)	(99.91, 100.00)
PLR	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	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	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)

Primary Screening (≥25) Population- Baseline Risks of High-Grade Cervical Disease

Follow-up data will be obtained during the longitudinal follow-up phase of the clinical study, which will allow estimation of cumulative disease risk up to 3 years. The baseline risk data is presented with this original PMA submission. The baseline risks of disease for several subject sub-populations with BD Onclarity HPV Assay HPV HR positive results were estimated using crude analysis since all HPV positive subjects were assigned to colposcopy by study design. For sub-populations consisting of BD HPV negative subjects, verification bias adjusted estimates were used due to the study design. Table 47 summarizes these baseline risks. Women who were HPV 16/18 positive and 12 other positive with ≥ASC-US cytology accounted for 3.21% and 2.89%, respectively, of the primary screening population and were referred for immediate colposcopy by the primary screening algorithm. The ≥CIN3 risks for these two populations were 12.25% (95% CI 10.05%, 14.54%) and 5.35% (95% CI 3.70%, 7.15%), respectively. Women who were NILM and 12 other HPV positive accounted for 6.59% of the primary screening population and had a ≥CIN3 risk of 1.94% (95% CI 1.27%, 2.65%). The majority (87.3%) of women were HR HPV negative and had a ≥CIN3 risk of 0.20% (95% CI 0.03%, 0.45%). Similar patterns were seen using ≥CIN2 as the endpoint.

Table 47: Baseline Risks of Disease in the Primary Screening Population (≥25 years)

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

The risks of ≥CIN2 and ≥CIN3 by age group for the primary screening algorithm are presented in Table 48. The risk of ≥CIN3 ranges from 4.26%-14.79% 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 48: Baseline Risks of Disease in the Primary Screening Population (≥25 years) 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)

The baseline risk of disease in the primary screening population was compared between women with a NILM cytology result, women with a negative BD Onclarity HPV result, and NILM women with a negative HPV result (i.e., a negative co-test) and is summarized in Table 49. Women with a negative BD Onclarity HPV result had a 0.21% 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 decreased the ≥CIN3 risk from 0.21% to 0.19%.

Table 49: Baseline risk comparisons between cytology negative, HPV negative and co-testing negative

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)

Primary Screening (≥25) Population- Benefit and Risk of Screening Strategies

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, current practice and cytology algorithms were evaluated and are summarized in Table 50. The primary screening algorithm detected more cases of ≥CIN2 (101 for primary screening vs. 89 for cytology alone and 94 for current practice) with fewer colposcopies (611 for primary screening vs. 839 for cytology alone and 623 for current practice). Additionally, fewer cases of ≥CIN2 were missed by the primary screening algorithm (87 vs. 98 for cytology alone and 93 for current practice). Moreover, fewer women with <CIN2 were sent to colposcopy with the primary screening algorithm (510 vs. 750 for cytology and 529 for current practice).

Table 50: Benefit and Risk of the Screening Algorithms Normalized to 10,000 Women

		Primary Screening Algorithm	Cytology Algorithm	Current Practice
Number of Tests and Procedures	**Cytology tests**	949	10000	10000
	BD Onclarity HPV tests	10000	0	8100
	Colposcopies	611	839	623
Benefits	**CIN2 detected**	46	47	45
	≥CIN3 detected	55	42	49
Risks	**CIN2 missed**	56	55	57
	≥CIN3 missed	31	43	36
	<CIN2 sent to colposcopy	510	750	529
Number of FP to 1 TP ≥CIN3		1:9.3	1:17.9	1:10.8

The benefit and risk per 100 colposcopies for the different screening algorithms was evaluated and is presented in Table 51. The primary screening algorithm detected a larger number of ≥CIN2 cases than either comparator algorithm (17 vs. 11 for cytology alone and 15 for current practice) with a lower number of <CIN2 women sent to colposcopy (84 for primary screening vs.

89 for cytology and 85 for current practice). While the primary screening algorithm missed fewer ≥CIN2 cases than the current practice algorithm (14 for primary screening vs. 15 for current practice), more ≥CIN2 cases were missed compared to the cytology alone algorithm (12). This is mainly due to more CIN2 cases being missed by primary screening than cytology alone (9 for primary screening vs. 7 for cytology alone). Both screening algorithms missed the same number of CIN3 cases (5). The rate of disease in women not referred to colposcopy was slightly lower by the primary screening algorithm (0.9%, 14/1,538) compared to the cytology algorithm (1.1%, 12/1,092) and the current practice algorithm (1.0%, 15/1,505). Additionally, a larger number of women were screened by the primary screening algorithm than by cytology alone in order to identify 100 colposcopy procedures (1,638 for primary screening vs. 1,192 for cytology).

Table 51: Benefit and Risk of the Screening Algorithms Normalized to 100 Colposcopies

Count	Primary Screening Algorithm	Cytology Algorithm	ASCUS Triage / Co-Testing Algorithm
Cytology tests	155	1192	1605
BD Onclarity HPV tests	1638	0	1300
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

AGREEMENT WITH A COMPOSITE COMPARATOR IN THE ASC-US ≥21 AND NILM ≥30 POPULATIONS

A subset of the enrolled subjects were analyzed by a composite comparator (CC), consisting of two components: 1. An FDA approved HPV test, and 2. PCR amplification, WAVE-dHPLC separation, and bi-directional sequencing for HR HPV types. This study evaluated the agreement between the BD Onclarity Assay and the CC in detecting the presence or absence of HR HPV nucleic acid. Positive CC results require positive results from both the approved HPV test and PCR/sequencing. Negative CC results require negative results from both the approved HPV test and PCR/sequencing. Disagreement between the FDA approved test and PCR/sequencing results are considered indeterminate. PCR/sequencing results were determined to be positive if the genotype detection was one of the 14 high-risk HPV types identified by the BD Onclarity HPV Assay. These analyses were conducted for the ASC-US (≥21 years) and Adjunct (NILM ≥30 years) intended use populations.

A subset of 1120 subjects with ASC-US cytology (≥21 years) was randomly selected for CC analysis. There were a total of 105 specimens with indeterminate results, resulting in 1015 specimens for CCM analysis.

A stratified random subset of 1,118 subjects with NILM (≥30 years) cytology results were selected for CC analysis. A total of 266 specimens were indeterminate within the CC, resulting in 852 concordant specimens by which agreement with the BD Onclarity HPV Assay was calculated.

Table 52 summarizes the agreement of the BD Onclarity HPV Assay with the CC for both populations. In the ASC-US population, positive percent agreement with the CCM was 97.4% (95% CI 95.5, 98.6). Negative percent agreement with the CCM was 98.5% (95% CI 97.1, 99.2). In the NILM ≥30 years population, the crude and adjusted positive percent agreement estimates of the BD Onclarity HPV Assay with the CC were 92.2% (95% CI 89.4, 94.3) and 92.0% (95% CI 89.8, 94.0), respectively. Negative percent agreement was 87.4% (95% CI 83.6, 90.4) and 99.4% (95% CI 99.3, 99.6) for the crude and adjusted estimates, respectively.

Table 52: Percent Agreement of the BD Onclarity HPV Assay vs. the Composite Comparator in the ASC-US (≥21 years) and NILM (≥30 years) Populations

Composite Comparator Results									
Population	**BD Onclarity HPV Assay**	**Positive**	**Negative**	**Indeterminate**	**Total**	**Unadjusted PPA (%) (95% CI)**	**Unadjusted NPA (%) (95% CI)**	**Adjusted PPA (%) (95% CI)**	**Adjusted NPA (%) (95% CI)**
ASC-US ≥21 Years	Positive	417	9	25	451	97.4 417/428 (95.5,98.6)	98.5 578/587 (97.1,99.2)	N/A	
	Negative	11	578	80	669				
	Total	428	587	105	1120				
NILM ≥30 Years	Positive	448	46	182	676	92.2 448/486 (89.4,94.3)	87.4 320/366 (83.6,90.4)	92.0 (89.8,94.0)	99.4 (99.3,99.6)
	Negative	38	320	84	442				
	Total	486	366	266	1118				

Positive and negative percent agreement of the BD Onclarity HPV Assay with PCR/bi-directional sequencing for specific genotypes was evaluated from randomly selected specimens. Negative results for the BD Onclarity HPV Assay are presented as "Negative", and stratified as "Negative, Virus Not Detected", and "Negative, Virus Detected". A "Negative" result is the total of any result that was above the clinical cutoff. "Negative, virus detected" indicates that there was genotype specific amplification detected that fell outside the clinical cutoff, whereas "negative, virus not detected" demonstrated no amplification. The PCR/bidirectional sequencing method used for comparison had no assigned cutoff and therefore identified the presence of HPV at low viral loads that may or may not be clinically relevant.

Table 53 summarizes the agreement study results in the ASC-US (≥21 years) population for the 16, 18 and 45 genotypes. HPV 16 had the highest positive percent agreement with sequencing results, which was 98.7% (95% CI 93.2, 99.8). Amplification of HPV 16 by the BD Onclarity HPV Assay was detected for the one subject negative by the Onclarity clinical cutoff but positive by sequencing, likely as a result of low viral load. Positive percent agreement for HPV 18 and HPV 45 was 88.0% (95% CI 70.0, 95.8) and 76.7 (95% CI 59.1, 88.2), respectively. Negative percent agreement for HPV 16, 18, and 45 was 98.9% (95% CI 98.1, 99.4), 99.8% (95% CI 99.3, 99.9), and 100.0% (95% CI 99.6, 100.0), respectively. PPA and NPA for the 11 other readout as well as the individual 11 other genotypes is provided in Table 54. PPA and NPA for the combined 11 other result was 89.0% (95% CI 85.6, 91.6) and 98.7% (95% CI 97.6, 99.3), respectively.

Table 53: Percent Agreement of the BD Onclarity HPV Assay with the Sequencing Comparator for HPV Types 16, 18 and 45 in the ASC-US (≥21 years) Population

BD HPV Assay		Sequencing Results					
		Positive	Negative	Invalid	Total	PPA % (95% CI)	NPA % (95% CI)
HPV 16	Positive	78	11	0	89	98.7 78/79 (93.2, 99.8)	98.9 1030/1041 (98.1, 99.4)
	Negative	1	1030	0	1031		
	Negative, Virus Not Detected	1	1028	0	1029		
	Negative, Virus Detected	0	2	0	2		
	Total	79	1041	0	1120		
HPV 18	Positive	22	2	0	24	88.0 22/25 (70.0, 95.8)	99.8 1093/1095 (99.3, 99.9)
	Negative	3	1093	0	1096		
	Negative, Virus Not Detected	1	1089	0	1090		
	Negative, Virus Detected	2	4	0	6		
	Total	25	1095	0	1120		
HPV 45	Positive	23	0	0	23	76.7 23/30 (59.1, 88.2)	100.0 1090/1090 (99.6, 100.0)
	Negative	7	1090	0	1097		
	Negative, Virus Not Detected	0	1087	0	1087		
	Negative, Virus Detected	7	3	0	10		
	Total	30	1090	0	1120		

Table 54: Percent Agreement of the BD Onclarity HPV Assay with the Sequencing Comparator for HPV 11 other in the ASC-US (≥21 years) Population

BD HPV Assay		Sequencing Results					
		Positive	Negative	Invalid	Total	PPA % (95% CI)	NPA % (95% CI)
HPV 31	Positive	44	1	0	45	88.0 44/50 (76.2, 94.4)	99.9 1068/1069 (99.5, 100.0)
	Negative	6	1068	0	1074		
	Negative, Virus not Detected	3	1062	0	1065		
	Negative, Virus Detected	3	6	0	9		
	Total	50	1069	0	1119		
HPV 33/58	Positive	40	2	0	42	78.4 40/51 (65.4, 87.5)	99.8 1066/1068 (99.3, 99.9)
	Negative	11	1066	0	1077		
	Negative, Virus not Detected	5	1063	0	1068		
	Negative, Virus Detected	6	3	0	9		
	Total	51	1068	0	1119		
HPV 52	Positive	83	6	0	89	94.3 83/88 (87.4, 97.5)	99.4 1025/1031 (98.7, 99.7)
	Negative	5	1025	0	1030		
	Negative, Virus not Detected	4	1019	0	1023		
	Negative, Virus Detected	1	6	0	7		
	Total	88	1031	0	1119		
HPV 51	Positive	60	3	0	63	85.7 60/70 (75.7, 92.1)	99.7 1046/1049 (99.2, 99.9)
	Negative	10	1046	0	1056		
	Negative, Virus not Detected	4	1038	0	1042		
	Negative, Virus Detected	6	8	0	14		
	Total	70	1049	0	1119		
HPV 39/68/35	Positive	118	2	0	120	78.1 118/151 (70.9, 84.0)	99.8 966/968 (99.2, 99.9)
	Negative	33	966	0	999		
	Negative, Virus not Detected	12	948	0	960		
	Negative, Virus Detected	21	18	0	39		
	Total	151	968	0	1119		
HPV 59/56/66	Positive	116	4	0	120	79.5 116/146 (72.2, 85.2)	99.6 969/973 (98.9, 99.8)
	Negative	30	969	0	999		
	Negative, Virus not Detected	12	952	0	964		
	Negative, Virus Detected	18	17	0	35		
	Total	146	973	0	1119		
11 Other	Positive	371	9	0	380		

BD HPV Assay		Sequencing Results					
		Positive	*Negative*	*Invalid*	*Total*	*PPA % (95% CI)*	*NPA % (95% CI)*
HPV[a]	*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	1120		

[a] Combined results of the 11 other HPV genotypes detected, but not differentiated, in the BD HPV assay.

Positive and negative percent agreement of the BD Onclarity HPV Assay for specific genotypes was calculated from the 1,118 Adjunct subjects with NILM cytology randomly selected for PCR/bidirectional sequencing. Agreement results for the individual BD Onclarity HPV Assay reported genotypes (16, 18 and 45) are summarized in Table 55. Crude and adjusted estimates for positive percent agreement for HPV 16 was 96.0% (95% CI 88.9, 98.6) and 86.5% (95% CI 59.4, 97.3), respectively. Crude and adjusted estimates for positive percent agreement for HPV 18 was 79.1% (95% CI 64.8, 88.6) and 61.9% (95% CI 30.4, 81.7), respectively. Crude and adjusted estimates for positive percent agreement for HPV 45 was 89.5% (95% CI 78.9, 95.1) and 72.2% (95% CI 39.3, 89.6), respectively. Negative percent agreement was ≥ 99.6 % for both crude and adjusted estimates. PPA and NPA for the 11 other readout as well as the individual 11 other genotypes is provided in Table 56. Crude and adjusted estimates for positive percent agreement for the combined 11 other result was 88.8% (95% CI 85.9, 91.1) and 61.6 (95% CI 50.4, 72.7), respectively. The NPA for the combined 11 other result was 93.1 (95% CI 90.6, 94.9) (crude) and 99.6 (95% CI 99.5, 99.7) (adjusted).

Table 55: Percent Agreement of the BD Onclarity HPV Assay with the Sequencing Comparator for HPV Types 16, 18 and 45 in the NILM (≥30 years) Population

BD HPV Assay		***Sequencing Results***				***Percent Agreement***			
						Unadjusted		*Adjusted*	
		Pos.	*Neg.*	*Invalid*	*Total*	***PPA*** % (95% CI)	***NPA*** % (95% CI)	***PPA*** % (95% CI)	***NPA*** % (95% CI)
HPV 16	Positive	72	17	0	89	96.0	98.4	86.5%	99.6%
	Negative	3	1026	0	1029	72/75	1026/1043		
	Negative, Virus Not Detected	1	1023	0	1024	(88.9, 98.6)	(97.4, 99.0)	(59.4, 97.3)	(99.5, 99.8)
	Negative, Virus Detected	2	3	0	5				
	Total	75	1043	0	1118				
HPV 18	Positive	34	5	0	39	79.1	99.5	61.9	99.9
	Negative	9	1070	0	1079	34/43	1070/1075		
	Negative, Virus Not Detected	3	1062	0	1065	(64.8, 88.6)	(98.9, 99.8)	(30.4, 81.7)	(99.9, 100.0)
	Negative, Virus Detected	6	8	0	14				
	Total	43	1075	0	1118				
HPV 45	Positive	51	2	0	53	89.5	99.8	72.2	100.0
	Negative	6	1059	0	1065	51/57	1059/1061		
	Negative, Virus Not Detected	2	1056	0	1058				

	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	1061	0	1118				

Table 56: Percent Agreement of the BD Onclarity HPV Assay with the Sequencing Comparator for HPV 11 Other in the NILM (≥30 years) Population

BD HPV Assay		***Sequencing Results***				***Percent Agreement***			
						Unadjusted		*Adjusted*	
		Pos.	*Neg.*	*Invalid*	*Total*	***PPA***	***NPA***	***PPA***	***NPA***
HPV 31	*Positive*	64	1	0	65	84.2 64/76 (74.4, 90.7)	99.9 1040/1041 (99.5, 100.0)	53.2 (30.0, 77.1)	100.0 (99.9, 100.0)
	Negative	12	1040	0	1052				
	Negative, Virus Not Detected	7	1030	0	1037				
	Negative, Virus Detected	5	10	0	15				
	Total	76	1041	0	1117				
HPV 33/58	*Positive*	68	11	0	79	81.9 68/83 (72.3, 88.7)	98.9 1023/1034 (98.1, 99.4)	56.1 (31.3, 77.7)	99.9 (99.8, 99.9)
	Negative	15	1023	0	1038				
	Negative, Virus Not Detected	13	1019	0	1032				
	Negative, Virus Detected	2	4	0	6				
	Total	83	1034	0	1117				
HPV 52	*Positive*	93	18	0	111	92.1 93/101 (85.1, 95.9)	98.2 999/1017 (97.2, 98.9)	79.5 (52.7, 92.2)	99.9 (99.8, 99.9)
	Negative	8	999	0	1007				
	Negative, Virus Not Detected	2	987	0	989				
	Negative, Virus Detected	6	12	0	18				
	Total	101	1017	0	1118				
HPV 51	*Positive*	32	3	0	35	69.6 32/46 (55.2, 80.9)	99.7 1069/1072 (99.2, 99.9)	58.0% (31.0, 76.0)	100.0 (99.9, 100.0)
	Negative	14	1069	0	1083				
	Negative, Virus Not Detected	5	1056	0	1061				
	Negative, Virus Detected	9	13	0	22				
	Total	46	1072	0	1118				
HPV 39/68/ 35	*Positive*	149	8	0	157	77.6 149/192 (71.2, 82.9)	99.1 918/926 (98.3, 99.6)	55.4 (38.5, 71.0)	99.9 (99.8, 100.0)
	Negative	43	918	0	961				
	Negative, Virus Not Detected	4	902	0	906				
	Negative, Virus Detected	39	16	0	55				
	Total	192	926	0	1118				
HPV 59/56/ 66	*Positive*	147	12	0	159	87.0 147/169 (81.1, 91.2)	98.7 936/948 (97.8, 99.3)	54.0 (35.6, 72.9)	99.9 (99.8, 99.9)
	Negative	22	936	0	958				
	Negative, Virus Not Detected	11	918	0	929				
	Negative, Virus Detected	11	18	0	29				
	Total	169	948	0	1117				
11 Other[a] hrHPV	*Positive*	507	38	0	545	88.8 507/571	93.1 509/547	61.6	99.6
	Negative	64	509	0	573				
	Negative, Virus Not Detected	23	478	0	501				

BD HPV Assay		Sequencing Results				Percent Agreement			
		Pos.	Neg.	Invalid	Total	Unadjusted		Adjusted	
						PPA	NPA	PPA	NPA
	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	1118				

[a] Combined results of the 11 other HPV genotypes detected, but not differentiated, in the BD HPV assay.

3. Additional Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

Vaccinated vs. Non-vaccinated Subjects:

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 in Tables 57 and 58 for women with ASC-US cytology (21-29 years old) and the primary screening population (25-29 years old), respectively. Performance was not stratified by vaccine status for the Adjunct population because of the very small number of vaccinated women over 30 years with disease.

Table 57: Performance of the BD Onclarity HPV Assay in the ASC-US (21-29 years) Population Stratified by Vaccine Status

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)
	≥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)

*Out of the three ≥CIN2 subjects who were negative by the BD Onclarity Assay, 2 were also negative by PCR sequencing and an FDA approved HPV test. One was negative by PCR sequencing and positive by an FDA approved test. This subject was found to be positive for the low risk HPV type 67.
**The one CIN3+ subject who was negative by the BD Onclarity Assay was negative for HR HPV by PCR/sequencing and positive by an FDA approved test. This subject was found to be positive for the low risk HPV type 67.

Table 58: Performance of the BD Onclarity HPV Assay in the Primary Screening Population (25-29) Stratified by Vaccine Status

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)	68.86 690/1002 (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)	67.68 712/1052 (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			1.70	1.39

Performance	Unadjusted Estimate		Adjusted Estimate	
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
(95% CI)			(0.92, 2.97)	(0.68, 2.25)

PreQuot vs. PostQuot:

An agreement study was performed to compare the performance of the BD Onclarity HPV Assay with a cervical specimen aliquoted for testing 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 collection vial was 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 the BD SurePath collection vial was transferred into a BD Onclarity HPV LBC Diluent tube (PostQuot). The results and comparative performance of the PreQuot to the PostQuot sample when tested with the BD Onclarity HPV Assay are shown in Tables 59 and 60:

Table 59: BD Onclarity HPV Assay PreQuot vs. PostQuot Results

BD HPV Assay PostQuot Result	BD 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	2431	35	3052
Total	73	132	85	19	186	2449	388	3082

Table 60: Agreement Results of the BD Onclarity HPV Assay in the 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%)
All subjects ≥25 yrs	91.0% (87.7%, 93.4%)	99.0% (98.6%, 99.3%)	98.1% (97.6%, 98.5%)

Levels of disagreement for the ASC-US (≥21 years) and NILM (≥30 years) populations were evaluated with regard to clinical significance. Regression analyses of the numeric Ct values and an analysis of closeness of the samples to the cutoff show that the levels of disagreement were clinically acceptable.

Cytology Blinding vs. Unblinding Study

In clinical practice and in the context of primary screening, cytologists and/or pathologists may be informed of the HPV status of the patient when interpreting cytology slides. In the clinical study, cytology slides were read by cytologists and, when applicable, pathologists without the

knowledge of any HPV result. In order to assess the performance of the BD HPV Assay as a primary screen for cervical disease, a subset of archived cytology slides from women 25 years or older who were enrolled in the clinical study were re-read with knowledge of the patient's HPV status. Sample selection for this study included cytology slides from women 25 years and older with a high risk HPV positive result, but were negative for HPV types 16 and 18. In addition, a random selection of cytology slides from subjects 25 years or older with high risk HPV negative results (irrespective of histology result), and HPV 16/18 positive results (<CIN2 or ≥CIN2 by H&E alone) were also re-read to mimic a routine real-world setting, where cytologists and/or pathologists read cytology slides from patients who are being screened with other cervical disease screening algorithms (i.e. ASCUS triage). The effects of unblinding of these slides, however, were not included in the analyses.

Cytology slides from 2,804 women 25 years or older with a valid cytology result who were 12 Other HPV positive were included in this study. Cytology slides from 251 subjects with HPV16/18 positive results and 100 slides from subjects with HPV negative results were re-read unblinded to HPV results as well but were not included in the analyses. Table 61 summarizes how cytology results changed in the blinded vs. unblinded scenarios:

Table 61: Comparison of Cytology Results that were Blinded vs. Unblinded to HPV Results

Unblinded:	***Blinded:***				
	>ASCUS	*ASCUS*	*NILM*	*UNSAT*	*Total*
>ASCUS	288	61	29	0	378 (13.5%)
ASCUS	86	147	131	1	365 (13.0%)
NILM	59	212	1783	0	2054 (73.3%)
UNSAT	1	0	3	3	7 (0.2%)
Total	434 (15.5%)	420 (15.0%)	1946 (69.4%)	4 (0.1%)	2804 (100.0%)

For cytology slides, knowledge of HPV status (12 Other HPV positive) changes the percent of ≥ASC-US cytology results by 0.87 times (743/854). Table 62 shows performance of the primary screening algorithm in both blinded and unblinded scenarios:

Table 62: Performance of the Primary Screening Algorithm when Cytology Results were Blinded vs. Unblinded to HPV Results

Performance	***CIN2+ Unblinded***	***CIN2+ Blinded***	***CIN3+ Unblinded***	***CIN3+ Blinded***
Sensitivity	52.78	53.84	66.19	64.24
Specificity	95.17	94.81	94.79	94.40
PPV	17.23	16.49	9.86	8.98
NPV	99.06	99.08	99.69	99.68
PLR	10.93	10.37	12.71	11.47
NLR	0.50	0.49	0.36	0.38
Colpo Rate	5.73	6.10	5.73	6.10

The benefit/risk analyses of the primary screening strategy in the sub-study (blinded vs. unblinded) normalized to 10,000 subjects (Table 63) or 100 colposcopies (Table 64) is shown below:

Table 63: Benefit/Risk Normalized to 10,000 Women

		Unblinded	***Blinded***
Normalized to 10,000 subjects	*Cytology tests*	947.8	948.7
	HR HPV tests	10000.0	10000.0
	HPV genotyping tests	1269.1	1269.9
	Colposcopies	573.0	610.6
	CIN2+ detected	98.7	100.6
	CIN3+ detected	56.4	54.8
	CIN2+ missed	88.3	86.7
	CIN3+ missed	28.8	30.5
	<CIN2 to colposcopy	474.4	509.9
	Number of FP to 1 TP≥CIN3	1:8.4	1:9.3

Table 64: Benefit/Risk Normalized to 100 Colposcopies

		Unblinded	***Blinded***
Normalized to 100 Colposcopies	*Cytology tests*	165.4	155.4
	HR HPV tests	1745.1	1637.8
	HPV genotyping tests	221.5	208.0
	Colposcopies	100.0	100.0
	CIN2+ detected	17.2	16.5
	CIN3+ detected	9.8	9.0
	CIN2+ missed	15.4	14.2
	CIN3+ missed	5.0	5.0
	<CIN2 to colposcopy	82.8	83.5

These results indicate that the performance of the BD Onclarity HPV Assay used in a primary screening algorithm is similar when the cytotechnologists/pathologists are unblinded to HPV results.

Brush vs. Broom Collection Devices:

Tables 65 and 66 below present clinical performance for the BD Onclarity HPV Assay for the ASC-US (≥21 years) and Adjunct (NILM ≥30 years) intended use populations by collection device:

Table 65: ASC-US (≥21 years) Performance by Collection Device

	Collection Device			
	Broom		*Brush/Spatula*	
	≥ CIN2	***≥ CIN3***	***≥ CIN2***	***≥ CIN3***
Sensitivity % (95% CI)	86.0 43/50 (73.8, 93.0)	94.1 16/17 (73.0, 99.0)	85.5 47/55 (73.8, 92.4)	88.9 16/18 (67.2, 96.9)
Specificity	64.0 492/769	62.1 498/802	64.3 471/733	61.9 477/770

% (95% CI)	(60.5, 67.3)	(58.7, 65.4)	(60.7, 67.6)	(58.5, 65.3)
PPV % (95% CI)	13.4 43/320 (11.5, 15.0)	5.0 16/320 (3.9, 5.6)	15.2 47/309 (13.1, 17.0)	5.2 16/309 (3.9, 5.9)
NP % (95% CI)	98.6 492/499 (97.4, 99.3)	99.8 498/499 (99.1, 100.0)	98.3 471/479 (97.0, 99.1)	99.6 477/479 (98.8, 99.9)
Disease Prevalence (%)	6.1 50/819	2.1 17/819	7.0 55/788	2.3 18/788

Table 66: Adjunct (NILM ≥30 years) Performance by Collection Device

	Collection Device: Broom			
	Crude Estimates		*Adjusted Estimates*	
	≥ CIN2	***≥ CIN3***	***≥ CIN2***	***≥ CIN3***
Sensitivity % (95% CI)	82.1 32/39 (67.3, 91.0)	87.5 21/24 (69.0, 95.7)	36.1 (18.4, 88.1)	51.9 (23.0, 100.0)
Specificity % (95% CI)	48.3 607/1256 (45.6, 51.1)	48.1 611/1271 (45.3, 50.8)	92.3 (91.8, 92.7)	92.2 (91.7, 92.7)
PPV % (95% CI)	4.7 32/681 (3.9, 5.3)	3.1 21/681 (2.4, 3.4)	4.4 (3.0, 6.1)	2.9 (1.8, 4.2)
NPV % (95% CI)	98.9 607/614 (97.9, 99.4)	99.5 611/614 (98.8, 99.8)	99.3 (98.5, 100.0)	99.8 (99.3, 100.0)
Disease Prevalence (%)	3.0 39/1295	1.9 24/1295	1.0 (0.4, 1.7)	0.5 (0.2, 0.9)
	Collection Device: Brush/Spatula			
	≥ CIN2	*≥ CIN3*	*≥ CIN2*	*≥ CIN3*
Sensitivity % (95% CI)	92.7 38/41 (80.6, 97.5)	100.0 22/22 (85.1, 100.0)	54.1 (29.5, 100.0)	100.0 (100.0, 100.0)
Specificity % (95% CI)	48.8 613/1255 (46.1, 51.6)	48.4 616/1274 (45.6, 51.1)	92.6 (92.1, 93.1)	92.5 (92.0, 92.9)
PPV % (95% CI)	5.6 38/680 (4.9, 6.0)	3.2 22/680 (3.2, 3.4)	5.7 (3.9, 7.8)	3.1 (1.9, 4.4)
NPV % (95% CI)	99.5 613/616 (98.7, 99.8)	100.0 616/616 (99.5, 100.0)	99.6 (99.0, 100.0)	100.0 (100.0, 100.0)
Disease Prevalence (%)	3.2 41/1296	1.7 22/1296	0.8 (0.4, 1.4)	0.2 (0.1, 0.3)

Cancer Panel

A separate study was conducted to provide additional supportive clinical evidence of the BD Onclarity HPV Assay's ability to detect HPV DNA in BD SurePath specimens from women that have been diagnosed with cervical cancer. Specimens were collected from patients using standard of care cytopathology and histopathology in the National Cancer Institute's (NCI) Improvement of Risk-Informed Cervical Screening (IRIS) study. A total of 486 BD SurePath specimens were tested from this blinded cohort, of which 27 had pathologically confirmed cancer.

Table 67 shows the performance of the BD Onclarity HPV Assay vs. Cytology on the IRIS study cancer samples. The BD Onclarity HPV Assay was positive for 13/14 (92.85%) of squamous cell cancers and 12/13 (92.30%) of adenocarcinomas. The comparator FDA-approved assay was positive for 14/14 (100%) of squamous cell cancers and 12/13 (92.30%) of adenocarcinomas. Of the two cases of cancer where the BD Onclarity HPV Assay was negative, one was also negative by the FDA-approved test (adenocarcinoma) and the other case was positive by the FDA-approved test (squamous cell cancer). The cancer case that was negative by both tests had AGC cytology.

Table 67: BD Onclarity HPV Results for Cancer Cases

BD Onclarity HPV Assay Result	***Cytology***			***Total***
	> ASC-US	*ASC-US*	*NILM*	
HPV 16/18 Positive	13	1	4	18
HPV 12 Other Positive	6	0	1	7
HR HPV Negative	2	0	0	2
Invalid	0	0	0	0
Total	21	1	5	27

Sensitivity for Primary Screening =88.9% (24/27).

Sensitivity for Cytology = 81.5% (22/27)

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 42 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

This section contains the clinical performance estimates for the BD Onclarity HPV Assay measured against a histologic endpoint using H&E staining alone for each of the three indications.

Performance Characteristics in the ASC-US Population (≥21 years)

Table 68: BD Onclarity HPV Assay Results and CPR Panel diagnoses in the ASC-US Population

BD Onclarity HPV Assay Results	***Central Pathology Review Panel Diagnosis***					***Unknown Histology***	***Total***
	NEG	*CIN1*	*CIN2*	*≥CIN3*	*Total*		
Positive	424	118	58	29	629	134	763
Negative	886	72	17	3	978	212	1190
*Non-evaluable**	6	0	0	0	6	1	7
Total	1316	190	75	32	1613	347**	1960

* Invalid/Missing results include mislabeled specimens, instrument errors and non-reportable results
** 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.

Table 69: Comparison of the Performance of the BD Onclarity HPV Assay and an FDA Approved HPV Test in the ASC-US Population (≥21 years)

Performance	***Central Pathology Review Panel Diagnosis***			
	BD Onclarity HPV Assay		*FDA Approved HPV Test*	
	≥CIN2	*≥CIN3*	*≥CIN2*	*≥CIN3*
Sensitivity % (95% CI)	81.3 87/107 (72.9, 87.6)	90.6 29/32 (75.8, 96.8)	79.4 (85/107) (70.8, 86.0)	87.5 28/32 (71.9, 95.0)
Specificity % (95% CI)	63.9 954/1494 (61.4, 66.3)	61.9 971/1569 (59.5, 64.3)	61.2 915/1494 (58.7, 63.7)	59.5 933/1569 (57.0, 61.9)
PPV % (95% CI)	13.9 87/627 (12.4, 15.2)	4.6 29/627 (3.9, 5.1)	12.8 85/664 (11.4, 14.0)	4.2 28/664 (3.5, 4.7)
NPV % (95% CI)	97.9 954/974 (97.0, 98.6)	99.7 971/974 (99.2, 99.9)	97.7 915/937 (96.7, 98.4)	99.6 933/937 (99.0, 99.8)
PLR (95% CI)	2.25 (1.98, 2.50)	2.38 (1.97, 2.62)	2.05 (1.80, 2.28)	2.16 (1.76, 2.41)
NLR (95% CI)	0.29 (0.19, 0.43)	0.15 (0.05, 0.39)	0.34 (0.23, 0.48)	0.21 (0.08, 0.47)
Prevalence	6.7 (107/1601)	2.0 (32/1601)	6.7 (107/1601)	2.0 (32/1601)

Table 70: Performance of the BD Onclarity HPV Assay by Age Group in the ASC-US (≥21years) Population (≥CIN2):

Performance Metrics	***21 - 29 Years***	***30 – 39 Years***	***≥40 Years***
Sensitivity (%) 95% CI	91.7 44/48 (80.4, 96.7)	82.9 34/41 (68.7, 91.5)	50.0 9/18 (29.0, 71.0)
Specificity (%) 95% CI	49.5 261/527 (45.3, 53.8)	63.0 254/403 (58.2, 67.6)	77.7 443/570 (74.1, 80.9)
PPV (%) 95% CI	14.2 44/310 (12.5, 15.6)	18.6 34/183 (15.5, 21.3)	6.6 9/136 (3.9, 9.5)
NPV (%) 95% CI	98.5 261/265 (96.5, 99.4)	97.3 254/261 (95.2, 98.6)	98.0 443/452 (97.2, 98.8)
PLR	1.82 (1.57, 2.03)	2.24 (1.80, 2.66)	2.24 (1.28, 3.32)
NLR	0.17 (0.07, 0.40)	0.27 (0.13, 0.50)	0.64 (0.37, 0.92)
Disease Prevalence (%)	8.3 48/575	9.2 41/444	3.1 18/588

Table 71: Performance of the BD Onclarity HPV Assay by Age Group in the ASC-US (≥21years) Population (≥CIN3):

Performance Metrics	***21 - 29 Years***	***30 – 39 Years***	***≥40 Years***
Sensitivity (%) 95% CI	91.7 11/12 (64.6, 98.5)	86.7 13/15 (62.1, 96.3)	100.0 5/5 (56.6, 100.0)
Specificity (%) 95% CI	46.9 264/563 (42.8, 51.0)	60.4 259/429 (55.7, 64.9)	77.5 452/583 (74.0, 80.7)
PPV (%) 95% CI	3.5 11/310 (2.5, 4.0)	7.1 13/183 (5.1, 8.3)	3.7 5/136 (3.6, 4.3)
NPV (%) 95% CI	99.6 264/265 (98.4, 99.9)	99.2 259/261 (97.8, 99.8)	100.0 452/452 (99.5, 100.0)
PLR	1.73 (1.21, 1.94)	2.19 (1.55, 2.60)	4.45 (4.32, 5.19)
NLR	0.18 (0.03, 0.76)	0.22 (0.06, 0.63)	0.0 (0.0, 0.56)
Disease Prevalence (%)	2.1 12/575	3.4 15/444	0.9 5/588

Table 72: Likelihood Ratios in the ASC-US (≥21years) Population for ≥CIN2 and ≥CIN3

BD Onclarity HPV Assay Test Results	***Likelihood Ratio (95% CI)***	
	≥ CIN2 vs. < CIN2	*≥ CIN3 vs. < CIN3*
HPV HR Positive	2.25 (1.98, 2.50)	2.38 (1.97, 2.62)
HPV 16 Positive	5.86 (4.07, 8.26)	8.81 (5.79, 12.36)
HPV 18 Positive	2.80 (1.21, 6.33)	1.41 (0.24, 7.32)
HPV 45 Positive	1.14 (0.37, 3.35)	0 (0, 4.26)
HPV 16 and/or HPV 18 and/or HPV 45 Positive	4.03 (3.01, 5.28)	5.21 (3.56, 6.97)
11 Other HPV HR Positive	1.59 (1.24, 1.99)	1.26 (0.74, 1.91)
HPV HR Negative	0.29 (0.19, 0.43)	0.15 (0.05, 0.39)

Table 73: Absolute Risk of Disease in the ASC-US (≥21years) Population

BD Onclarity HPV Assay Test Results	***Absolute Risk of Disease (%) (95% CI)***	
	≥CIN2	*≥CIN3*
HPV HR Positive	13.8 87/629 (12.4, 15.1)	4.6 29/629 (3.9, 5.1)
HPV 16 Positive	29.5 33/112 (22.5, 37.1)	15.2 17/112 (10.5, 20.1)
HPV 18 Positive	16.7 6/36 (7.9, 31.1)	2.8 1/36 (0.5, 12.9)
HPV 45 Positive	7.5 3/40 (2.6, 19.3)	0.0 0/40 (0.0, 8.0)
HPV 16 and/or HPV 18 and/or HPV 45 Positive	22.3 42/188 (17.7, 27.4)	9.6 18/188 (6.7, 12.4)
11 Other HPV HR Positive	10.2 45/441 (8.1, 12.4)	2.5 11/441 (1.5, 3.7)
HPV HR Negative	2.0 20/978 (1.4, 2.9)	0.3 3/978 (0.1, 0.8)

Performance Characteristics in the NILM (≥30 years) Population

Table 74: BD Onclarity HPV Assay Result and CPR Panel diagnosis in the NILM Population (≥30 years)

BD Onclarity HPV Assay Test Results	***Central Pathology Review Panel Diagnosis***				***Unknown Disease Status***	***Total***
	NEG	*CIN1*	*CIN2*	*≥ CIN3*		
HPV 16	154	8	6	16	146	330
HPV 18	71	5	0	2	15	93
HPV 45	89	2	1	1	22	115
HPV 11 Other	884	79	24	19	217	1223
Negative	1183	36	8	3	19293	20523
Invalid/Missing	5	1	0	0	93	99
Total	2386	131	39	41	19786	22383

Table 75: Performance of the BD Onclarity HPV Assay the NILM (≥30 years) population

Performance	*Central Pathology Review Panel Diagnosis*			
	≥ *CIN2*		≥ *CIN3*	
	Unadjusted Estimate	*Adjusted Estimate*	*Unadjusted Estimate*	*Adjusted Estimate*
Sensitivity (%) (95% CI)	86.3 69/80 (77.0%, 92.1%)	43.8 (27.5%, 74.6%)	92.7 38/41 (80.6%, 97.5%)	66.7 (39.0%, 100.0%)
Specificity (%) (95% CI)	48.5 1219/2511 (46.6%, 50.5%)	92.4 (92.1%, 92.8%)	48.1 1227/2550 (46.2%, 50.1%)	92.3 (91.9%, 92.6%)
PPV (%) (95% CI)	5.1 69/1361 (4.5%, 5.5%)	5.0 (3.8%, 6.2%)	2.8 38/1361 (2.4%, 3.0%)	2.7 (1.8%, 3.5%)
NPV (%) (95% CI)	99.1 1219/1230 (98.5%, 99.5%)	99.5 (99.0%, 99.9%)	99.8 1227/1230 (99.4%, 99.9%)	99.9 (99.7%, 100.0%)
PLR (95% CI)	1.68 (1.49, 1.81)	5.78 (3.58, 9.87)	1.79 (1.55, 1.91)	8.64 (5.04, 13.15)
NLR (95% CI)	0.28 (0.16, 0.47)	0.61 (0.28, 0.78)	0.15 (0.05, 0.40)	0.36 (0, 0.66)
Disease Prevalence (%)	3.1 80/2591	0.9 (0.5%, 1.4%)	1.6 41/2591	0.3 (0.2%, 0.5%)

Table 76: Likelihood Ratios and Risk Estimates in the NILM (≥30 years) population

BD Onclarity HPV Assay Test Results (%)	***Central Pathology Review Panel Diagnosis***			
	≥CIN2 vs. <CIN2		***≥CIN3 vs. <CIN3***	
	Crude	*Adjusted*	*Crude*	*Adjusted*
HPV HR Positive	1.68 (1.49, 1.81)	5.78 (3.58, 9.87)	1.79 (1.55, 1.91)	8.64 (5.04, 13.15)
HPV 16 Positive	4.26 (2.85, 6.12)	11.27 (5.91, 21.20)	5.92 (3.81, 8.54)	20.55 (9.93, 38.34)
HPV 18 Positive	0.83 (0.22, 2.91)	2.90 (0, 8.60)	1.64 (0.45, 5.53)	8.31 (0, 25.52)
HPV 45 Positive	0.69 (0.19, 2.43)	2.42 (0, 7.17)	0.68 (0.12, 3.53)	3.43 (0, 13.71)
HPV 16/18/45 Positive	2.48 (1.75, 3.37)	7.78 (4.22, 14.03)	3.52 (2.40, 4.75)	14.61 (7.53, 26.24)
11 Other HPV HR Positive	1.40 (1.11, 1.69)	4.92 (2.96, 8.48)	1.20 (0.83, 1.59)	6.08 (3.12, 10.89)
HPV HR Negative	0.28 (0.16, 0.47)	0.61 (0.28, 0.78)	0.15 (0.05, 0.40)	0.36 (0, 0.66)

Table 77: Absolute Risk of Disease by the BD Onclarity HPV Assay in the NILM (≥30 years) population

BD Onclarity HPV Assay Test Results	***Absolute Risk of Disease***			
	≥ *CIN2*		≥ *CIN3*	
	Unadjusted Estimate	*Adjusted Estimate*	*Unadjusted Estimate*	*Adjusted Estimate*
HPV HR Positive (%)	5.1 69/1361	5.0 	2.8 38/1361	2.7
(95% CI)	(4.5, 5.5)	(3.8, 6.2)	(2.4, 3.0)	(1.8, 3.5)
HPV 16 Positive (%)	12.0 22/184	9.3 	8.7 16/184	6.1
(95% CI)	(8.3, 16.3)	(5.5, 13.7)	(5.8, 12.1)	(3.3, 9.0)
HPV 18 Positive (%)	2.6	2.6	2.6	2.6

BD Onclarity HPV Assay Test Results	*Absolute Risk of Disease*			
	≥ CIN2		*≥ CIN3*	
	Unadjusted Estimate	*Adjusted Estimate*	*Unadjusted Estimate*	*Adjusted Estimate*
(95% CI)	2/78 (0.7, 8.5)	(0.0, 6.4)	2/78 (0.7, 8.2)	(0.0, 6.4)
HPV 45 Positive (%) *(95% CI)*	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 (%) *(95% CI)*	7.3 26/355 (5.3, 9.7)	6.6 (4.2, 9.5)	5.4 19/355 (3.7, 7.1)	4.4 (2.6, 6.4)
11 Other HPV HR Positive (%) *(95% CI)*	4.3 43/1006 (3.4, 5.1)	4.3 (3.0, 5.5)	1.9 19/1006 (1.3, 2.5)	1.9 (1.1, 2.8)
HPV HR Negative (%) *(95% CI)*	0.9 11/1230 (0.5, 1.5)	0.6 (0.1, 1.1)	0.2 3/1230 (0.1, 0.6)	0.1 (0.0, 0.3)

Performance Characteristics in the Primary Screening (≥25 years) Population

Table 78: Number of Subjects in the Primary Screening (≥25 years) Population 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	1946	2800
	Total With Adjudicated Histology	360	358	1596	2314
HPV HR Neg	*Total*	223	1060	24482	25765
	Total With Adjudicated Histology	180	881	1497	2558
Total	*Total*	856	1620	27037	29513
	Total With Adjudicated Histology	704	1355	3475	5534

Table 79: Performance Comparison of the Primary Screening and Current Practice Algorithms

Performance	*≥CIN2 Primary Screening*	*≥CIN2 Current Practice*	*≥CIN2 Difference*	*≥CIN3 Primary Screening*	*≥CIN3 Current Practice*	*≥CIN3 Difference*
Sensitivity (%) (95% CI)	50.88 (41.39, 62.81)	47.62 (38.71, 59.19)	3.25[a] (1.03, 5.93)	65.12 (51.10, 81.68)	60.90 (47.42, 77.15)	4.22[a] (0.78, 8.37)
Specificity (%) (95% CI)	94.78 (94.51, 95.05)	94.59 (94.32, 94.86)	0.19[a] (0.05, 0.32)	94.38 (94.11, 94.65)	94.22 (93.93, 94.50)	0.16[a] (0.02, 0.28)
PPV (%) (95% CI)	16.22 (14.28, 18.22)	14.87 (13.20, 16.81)	1.34[a] (0.61, 2.13)	8.70 (7.38, 10.21)	7.97 (6.66, 9.51)	0.73[a] (0.26, 1.22)
NPV (%) (95% CI)	98.98 (98.54, 99.37)	98.91 (98.47, 99.29)	0.07[a] (0.02, 0.12)	99.70 (99.46, 99.87)	99.66 (99.43, 99.84)	0.04[a] (0.01, 0.07)
PLR (95% CI)	9.75 (7.88, 12.20)	8.80 (7.11, 10.99)	0.95[a] (0.41, 1.59)	11.59 (9.04, 14.59)	10.53 (8.08, 13.38)	1.05[a] (0.39, 1.88)
NLR (95% CI)	0.52 (0.39, 0.62)	0.55 (0.43, 0.65)	-0.04[a] (-0.06, -0.01)	0.37 (0.19, 0.52)	0.42 (0.24, 0.56)	-0.05[a] (-0.09, -0.01)
Colpo Rate	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)
Prevalence (%) (95% CI)	1.95 (1.56, 2.37)	1.95 (1.56, 2.37)		0.82 (0.62, 1.05)	0.82 (0.62, 1.05)	

a: denotes statistical significance at the 0.05 level

Table 80: Performance Comparison of the Primary Screening and Cytology Alone Algorithms

Performance	*≥CIN2 Primary Screening*	*≥CIN2 Cytology Alone*	*≥CIN2 Difference*	*≥CIN3 Primary Screening*	*≥CIN3 Cytology Alone*	*≥CIN3 Difference*
Sensitivity (%) (95% CI)	50.88 (41.39, 62.81)	46.07 (37.00, 56.86)	4.81[a] (1.00, 8.67)	65.12 (51.10, 81.68)	53.03 (41.17, 67.91)	12.09[a] (6.44, 18.85)
Specificity (%) (95% CI)	94.78 (94.51, 95.05)	92.36 (92.03, 92.67)	2.42[a] (2.14, 2.71)	94.38 (94.11, 94.65)	91.98 (91.66, 92.29)	2.40[a] (2.11, 2.69)
PPV (%) (95% CI)	16.22 (14.28, 18.22)	10.69 (9.39, 12.13)	5.53[a] (4.30, 6.76)	8.70 (7.38, 10.21)	5.15 (4.25, 6.19)	3.54[a] (2.77, 4.35)
NPV (%) (95% CI)	98.98 (98.54, 99.37)	98.85 (98.40, 99.25)	0.13[a] (0.05, 0.21)	99.70 (99.46, 99.87)	99.58 (99.34, 99.77)	0.12[a] (0.07, 0.16)
PLR (95% CI)	9.75 (7.88, 12.20)	6.03 (4.81, 7.50)	3.72[a] (2.78, 5.02)	11.59 (9.04, 14.59)	6.61 (5.08, 8.47)	4.98[a] (3.62, 6.65)
NLR (95% CI)	0.52 (0.39, 0.62)	0.58 (0.47, 0.68)	-0.07[a] (-0.11, -0.02)	0.37 (0.19, 0.52)	0.51 (0.35, 0.64)	-0.14[a] (-0.21, -0.08)
Colpo Rate	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)
Prevalence (%) (95% CI)	1.95 (1.56, 2.37)	1.95 (1.56, 2.37)		0.82 (0.62, 1.05)	0.82 (0.62, 1.05)	

a: denotes statistical significance at the 0.05 level

Table 81: Baseline Risk of Disease for Categories in the Primary Screening Algorithm (≥ 25 years)

Subgroup	***Percentage with result***	***≥CIN2 Risk (95% CI)***	***≥CIN3 Risk (95% CI)***
hrHPV POS	12.70	10.24 (9.22, 11.37)	5.03 (4.30, 5.88)
HPV 16+	2.52	21.37 (17.95, 25.07)	13.02 (10.29, 16.03)
HPV 18+	0.69	10.84 (6.63, 15.72)	5.72 (2.52, 9.40)
HPV 16/18+	3.21	19.09 (16.10, 22.22)	11.44 (9.12, 13.79)
HPV 12 Other and ≥ASCUS	2.89	13.02 (10.77, 15.61)	5.65 (4.01, 7.47)
HPV 12 Other and NILM	6.59	4.70 (3.71, 5.74)	1.63 (1.05, 2.29)
hrHPV NEG	87.30	0.74 (0.33, 1.19)	0.20 (0.03, 0.45)

Table 82: Benefit and Risk of the Screening Algorithms per 10,000 Women

Metric	***Primary Screening***	***Cytology Alone***	***ASC-US Triage/Co-testing***
Number of cytology tests	948.7	10000.0	10000.0
Number of HR HPV tests	10000.0	0.0	8099.5
Number of HPV genotyping tests	1269.9	0.0	596.7
Number of colposcopies	610.6	839.0	623.1
Number of CIN2 detected	45.9	46.4	43.0
Number of CIN3+ detected	53.1	43.2	49.7
Number of CIN2 missed	67.2	66.7	70.1
Number of CIN3+ missed	28.4	38.3	31.9
Number of <CIN2 sent to colposcopy	511.6	749.3	530.4

Table 83: Benefit and Risk of the Screening Algorithms per 100 Colposcopies

Metric	*Primary Screening*	*Cytology Alone*	*ASC-US Triage/Co-testing*
Number of cytology tests	155.4	1192.0	1604.8
Number of HR HPV tests	1637.8	0.0	1299.8
Number of HPV genotyping tests	208.0	0.0	95.8
Number of colposcopies	100.0	100.0	100.0
Number of CIN2 detected	7.5	5.5	6.9
Number of CIN3+ detected	8.7	5.2	8.0
Number of CIN2 missed	11.0	7.9	11.2
Number of CIN3+ missed	4.7	4.6	5.1
Number of <CIN2 sent to colposcopy	83.8	89.3	85.1

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

Device did not go to panel.

A. Panel Meeting Recommendation

Not applicable

B. FDA's Post-Panel Action

Not applicable

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the BD Onclarity HPV Assay with cervical specimens collected by a physician using a cervical broom or brush/spatula and place in SurePath Preservative Fluid has been demonstrated for use in conjunction with cervical cytology in the following patient populations: women with ASC-US cytology aged 21 and older, women with NILM cytology aged 30 and older, and all women aged 25 and older. The results of this test, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory as well as data collected in a clinical study conducted to support PMA approval as described above. Based on the results of these studies, the BD Onclarity HPV Assay, when used according to the provided directions and together with the physician's interpretation of cytology

results, other risk factors, and professional guidelines, should be safe and pose minimal risk to the patient due to false test results.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The BD Onclarity HPV device has been shown to effectively assess a woman's risk for ≥CIN2 and ≥CIN3 by detecting high risk HPV nucleic acid.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support the claimed indications for use, and the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the BD Onclarity HPV Assay when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity, precision, reproducibility, and analytical specificity of the BD Onclarity HPV Assay when used according to instructions for use, warnings and precautions, and limitations sections of the labeling. The clinical studies and performance analysis of the clinical data in this application have shown that the assay is safe and effective for use in routine cervical cancer screening for its approved indications when used according to the directions for use in the labeling.

XIV. CDRH DECISION

CDRH issued an approval order on February 12, 2018. The final conditions of approval cited in the approval order are described below.

The post-approval study will provide additional longitudinal data regarding the use of cervical specimens collected in SurePath with the BD Onclarity HPV Assay to support the primary screening indication. This longitudinal study involves the follow-up of women aged 25 or older from the baseline study who underwent the colposcopy procedure but did not receive treatment. In addition, a random selection of NILM/HPV negative women who did not undergo colposcopy/biopsy will also be followed up in the longitudinal study. The study population encompasses women with abnormal cytology (i.e., ASC-US or greater), HPV positive women with normal cytology, a subset of women who were HPV negative with normal cytology, and those with unsatisfactory cytology results. Women will undergo annual cytology screening for three years, and those subjects with abnormal cytology will be invited to proceed to colposcopy. This study will provide additional data regarding the clinical performance of the BD Onclarity HPV

Assay, including absolute risks, predictive values, and likelihood ratios for women aged 25 years and older undergoing primary screening with the BD Onclarity HPV Assay.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Darragh, T et. al. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. 2012