

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Human Papillomavirus RNA detection kit

Device Trade Name: APTIMA HPV Assay

Applicant's Name and Address:

Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, CA 92121-4362

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100042

Date of FDA Notice of Approval: October 28, 2011

Expedited: Not applicable

II. INDICATIONS FOR USE

APTIMA HPV Assay Indications For Use:

The APTIMA HPV Assay is an in vitro nucleic acid amplification test for the qualitative detection of E6/E7 viral messenger RNA (mRNA) from 14 high-risk types of human papillomavirus (HPV) in cervical specimens. The high-risk HPV types detected by the assay include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The APTIMA HPV Assay does not discriminate between the 14 high-risk types. Cervical specimens in ThinPrep Pap Test vials containing PreservCyt Solution and collected with broom-type or cytobrush/ spatula collection devices* may be tested with the APTIMA HPV Assay. The assay is used with the TIGRIS DTS System.

The use of the test is indicated:

1. To screen patients 21 years and older with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to determine the need for referral to colposcopy. The results of this test are not intended to prevent women from proceeding to colposcopy.
2. In women 30 years and older, the APTIMA HPV Assay can be used with cervical cytology to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

* Broom-type device (e.g., Wallach Pipette) or endocervical brush/spatula.

III. CONTRAINDICATIONS

None.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The APTIMA HPV Assay involves three main steps, which take place in a single tube: target capture; target amplification by Transcription-Mediated Amplification (TMA); and detection of the amplification products (amplicon) by the Hybridization Protection Assay (HPA). The assay incorporates an internal control to monitor nucleic acid capture, amplification, and detection, as well as operator or instrument error.

Specimens are transferred to a tube containing specimen transport media (STM) that lyses the cells, releases the mRNA, and protects it from degradation during storage. When the APTIMA HPV Assay is performed, the target mRNA is isolated from the specimen by use of capture oligomers that are linked to magnetic microparticles. The capture oligomers contain sequences complementary to specific regions of the HPV mRNA target molecules as well as a string of deoxyadenosine residues. During the hybridization step, the sequence-specific regions of the capture oligomers bind to specific regions of the HPV mRNA target molecule. The capture oligomer-target complex is then captured out of solution by decreasing the temperature of the reaction to room temperature. This temperature reduction allows hybridization to occur between the deoxyadenosine region on the capture oligomer and the poly-deoxythymidine molecules that are covalently attached to the magnetic particles. The microparticles, including the captured HPV mRNA target molecules bound to them, are pulled to the side of the reaction tube using magnets and the supernatant is aspirated. The particles are washed to remove residual specimen matrix that may contain amplification inhibitors.

After target capture is complete, the HPV mRNA is amplified using TMA, which is a transcription-based nucleic acid amplification method that utilizes two enzymes, MMLV reverse transcriptase and T7 RNA polymerase. The reverse transcriptase is used to generate a DNA copy of the target mRNA sequence containing a promoter sequence for T7 RNA polymerase. T7 RNA polymerase produces multiple copies of RNA amplicon from the DNA copy template.

Detection of the amplicon is achieved by HPA using single-stranded nucleic acid probes with chemiluminescent labels that are complementary to the amplicon. The labeled nucleic acid probes hybridize specifically to the amplicon. The Selection Reagent differentiates between hybridized and unhybridized probes by inactivating the label on

the unhybridized probes. During the detection step, light emitted from the labeled RNA-DNA hybrids is measured as photon signals called Relative Light Units (RLU) in a luminometer. Final assay results are interpreted based on the analyte signal-to-cutoff (S/CO).

Internal Control is added to each reaction via the Target Capture Reagent. The Internal Control monitors the target capture, amplification, and detection steps of the assay. Internal Control signal in each reaction is discriminated from the HPV signal by the differential kinetics of light emission from probes with different labels. Internal Control-specific amplicon is detected using a probe with a rapid emission of light (flasher). Amplicon specific to HPV is detected using probes with relatively slower kinetics of light emission (glower). The Dual Kinetic Assay (DKA) is the method used to differentiate between the signals from the flasher and glower labels.

Additional details can be found in the operator's manual for the device.

Test Interpretation

Assay test results are automatically determined by the assay software. A test result may be negative, positive, or invalid as determined by the Internal Control (IC) RLU and the signal-to-cutoff (S/CO) for the Analyte. A test result may also be invalid due to other parameters (abnormal kinetic curve shape) being outside the normal expected ranges. Invalid test results should be repeated.

APTIMA HPV Assay Result	Criteria
Negative	<i>Analyte S/CO < 0.50 Internal Control ≥ IC Cutoff Internal Control ≤ 2,000,000 RLU</i>
Positive	<i>Analyte S/CO ≥ 0.50 Internal Control ≤ 2,000,000 RLU Analyte ≤ 13,000,000 RLU</i>
Invalid	<i>Analyte S/CO < 0.50 and Internal Control < IC Cutoff Or Internal Control > 2,000,000 RLU Or Analyte > 13,000,000 RLU</i>

NOTE: Negative results are not intended to prevent women from proceeding to colposcopy.

NOTE: Negative results indicate HPV E6/E7 mRNA was not detected.

NOTE: Negative results may occur with HPV E6/E7 mRNA concentrations that are below the pre-set threshold.

NOTE: Positive results indicate the presence of HPV E6/E7 mRNA of any one or more of the high risk types.

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

Three alternatives for the detection of high-risk HPV are currently approved in the United States. All three alternative devices detect HPV DNA instead HPV mRNA. Each HPV detection method has its own advantages and disadvantages.

A patient should fully discuss these alternatives with her physician to select the screening method(s) that best meets expectations and her lifestyle.

VII. MARKETING HISTORY

The APTIMA HPV Assay is CE marked for use in the EU and is approved for use in multiple countries. A list of all countries where the APTIMA HPV Assay is marketed as of September 2011 is provided below. The APTIMA HPV Assay has not been withdrawn from these markets for any reason.

- Australia
- Austria
- Bahamas
- Belgium
- Bermuda
- Cambodia
- Chile
- Colombia
- Czech Republic
- Denmark
- Dominican Republic
- Finland
- France
- Germany
- Greece
- Honduras
- Hong Kong
- Hungary
- Indonesia
- Ireland
- Israel
- Italy
- Kenya
- Latvia
- Libya
- Luxembourg
- Madagascar
- Malaysia
- Mali
- Namibia
- Netherlands
- Pakistan
- Peru
- Philippines
- Poland
- Portugal
- Saudi Arabia
- Slovakia
- Slovenia
- South Africa
- Spain
- Sweden
- Tunisia
- UAE
- UK
- Vietnam

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. 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 and treatment. False negative results may lead to delays in the timely diagnosis of cervical cancer and treatment, 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 PRECLINICAL STUDIES

A. Laboratory Studies

Clinical Cutoff Determination for the APTIMA HPV Assay

The clinical cutoff for detecting high-grade cervical disease (\geq CIN2) for the APTIMA HPV Assay was established based on the evaluation of approximately 1000 women with ASC-US cytology results enrolled into the ASC-US Study. The method used for selection of the cutoff¹ was chosen to achieve the maximum sensitivity for detecting \geq CIN2 while maintaining a clinically acceptable level of specificity in the ASC-US population. Based on the method described above, the cutoff for the APTIMA HPV Assay was set at 0.50 S/CO.

Limit of Detection at the Clinical Cutoff

The Limit of Detection (LOD) at the clinical cutoff is the concentration of HPV RNA that gives a positive result (above the clinical cutoff) 95% of the time. The LoD of the APTIMA HPV Assay was determined by testing individual negative clinical PreservCyt liquid cytology specimens spiked with HPV in vitro transcripts or infected cells at various concentrations. Thirty replicates of each copy level were tested with each of three reagent lots for a total of 90 replicates. Testing was performed over 14 days, with 1 to 14 runs performed per day and 30 replicates of a given genotype tested in each run. The 95% detection limit was calculated from Probit regression analysis of the positivity results for each dilutional panel.

The Probit analysis results, in the table below, show that HPV 16, 18, 31, 33, 35, 39, 45, 58, 59, 66, and 68 had 95% detection limits less than 100 copies/reaction; and types 51, 52, and 56 had 95% detection limits between 100 and 300 copies/reaction. The four cell lines tested had 95% detection limits less than 1 cell/reaction. Each target analyte was diluted in STM prior to adding PreservCyt media at a 1:2.9 ratio for these LOD panel specimens. Therefore, the results of this study do not reflect any effects of sampling from a heterogenous non-lysed whole cell suspension prior to PreservCyt specimen transfer to STM.

Limit of Detection at Clinical Cutoff of the APTIMA HPV Assay

Target	Limit of Detection* (95% CI)
HPV 16	27.1 (21.7 - 36.1)
HPV 18	54.1 (42.9 - 73.2)
HPV 31	11.5 (9.2 - 15.6)

Target	Limit of Detection* (95% CI)
HPV 33	34.4 (26.9 - 47.4)
HPV 35	31.9 (23.6 - 47.3)
HPV 39	20.5 (16.2 - 28.0)
HPV 45	26.3 (21.1 - 34.9)
HPV 51	132.9 (116.7 - 159.6)
HPV 52	240.2 (191.4 - 320.3)
HPV 56	105.5 (88.0 - 133.2)
HPV 58	71.4 (55.9 - 97.3)
HPV 59	62.3 (47.7 - 89.7)
HPV 66	208.0 (168.4 - 270.0)
HPV 68	47.1 (35.9 - 67.9)
SiHa	0.288 (0.223 - 0.401)
HeLa	0.029 (0.024 - 0.036)
ME180	0.0012 (0.0009 - 0.0018)
MS751	0.018 (0.015 - 0.024)

* Copies per reaction for in vitro transcripts and cells per reaction for cell lines

Assay Precision

APTIMA HPV Assay precision was evaluated in two studies using the same 20-member panel. Study 1 was conducted at 3 external testing sites to determine assay reproducibility. Study 2 was conducted in-house to measure assay repeatability. The panel included 10 HPV-positive members with concentrations at or above the limit of detection of the assay (expected positivity: $\geq 95\%$), 4 HPV-positive members with concentrations below the limit of detection of the assay (expected positivity: $>0\%$ to $<25\%$), and 6 HPV-negative members. HPV-positive panel members were prepared by spiking in vitro RNA transcripts (IVT) into specimen transport medium (STM) or HPV-infected cultured cells (SiHa, HeLa, ME180 and MS751; ATCC, Manassas, Virginia) into PreservCyt Solution. HPV-negative panel members were prepared with STM or pooled residual PreservCyt Solution specimens.

In Study 1, 2 operators at each of the 3 testing sites (1 instrument per site) performed 1 APTIMA HPV Assay worklist per day over 3 days for each of 3 reagent lots. Each worklist contained 3 replicates of each of the reproducibility panel members. One hundred sixty-two (162) individual sample tubes were tested for each panel member (3 sites x 1 instrument x 2 operators x 3 lots x 3 worklists x 3 replicates). In Study 2, testing was conducted in-house over 20 days with a total of 162 reactions tested for each panel member (1 site x 3 instruments x 3 operators x 3 lots x 2 worklists x 3 replicates).

The panel members are described in the tables below, along with a summary of the agreement with expected results and analyte S/CO values at the 2.5th, 50th and 97.5th percentiles of the S/CO distribution.

APTIMA HPV Assay Reproducibility Study 1 and 2: Panel Description, Positive Agreement, and Percentile Distribution of Analyte S/CO Values for Panel Members with Expected Positive Results

Panel Description (copies or cells/reaction)	Study 1 (3 testing sites)				Study 2 (1 testing site)			
	% positive agreement (95% CI)	Analyte S/CO Percentile			% positive agreement (95% CI)	Analyte S/CO Percentile		
		2.5 th	50 th	97.5 th		2.5 th	50 th	97.5 th
HPV 16 & HPV 18 IVT (100 copies)	100 (161/161) (97.7, 100)	20.7	23.5	26.3	100 (162/162) (97.7, 100)	20.1	23.2	26.3
SiHa cells (3 cells) & HeLa cells (7.5 cells)	100 (162/162) (97.7, 100)	11.0	15.3	28.0	100 (162/162) (97.7, 100)	12.5	16.5	28.0
HPV 18 IVT (100 copies)	100 (162/162) (97.7, 100)	8.5	11.8	13.9	100 (160/160) (97.7, 100)	9.0	11.9	14.7
HPV 16 IVT (100 copies)	100 (162/162) (97.7, 100)	9.9	10.8	11.6	100 (162/162) (97.7, 100)	9.3	10.9	11.7
MS751 cells (1 cell)	99.4 (161/162) (96.6, 99.9)	6.1	13.9	16.0	96.9 (157/162) (93.0, 98.7)	0	14.5	16.6
ME180 cells (0.3 cells)	95.1 (154/162) (90.6, 97.5)	0	7.3	9.3	93.2 (151/162) (88.3, 96.2)	0	6.5	9.4
HPV 18 IVT (30 copies)	99.4 (161/162) (96.6, 99.9)	3.0	9.3	13.3	100 (162/162) (97.7, 100)	4.3	8.7	13.6
HPV 16 IVT (30 copies)	100 (162/162) (97.7, 100)	8.2	10.9	11.8	97.5 (158/162) (93.8, 99.0)	4.3	11.0	11.9
HeLa cells (2.5 cells)	100 (162/162) (97.7, 100)	6.6	12.9	15.8	95.6 (152/159) (91.2, 97.9)	0	12.9	16.5
SiHa cells (1 cell)*	77.2 (125/162) (70.1, 83.0)	0	10.5	12.1	79.0 (128/162) (72.1, 84.6)	0	10.5	11.8

IVT = in vitro transcript. IVT was spiked into STM and cells were spiked into PreservCyt Solution.

*Expected % positive agreement ~95%; observed lower possibly due to manufacturing variability of the panel member.

APTIMA HPV Assay Reproducibility Study 1 and 2: Panel Description, Negative Agreement, and Percentile Distribution of Analyte S/CO Values for Panel Members with Expected Negative Results

Panel Description (copies or cells/reaction)	Study 1 (3 testing sites)				Study 2 (1 testing site)			
	% negative agreement (95% CI)	Analyte S/CO Percentile			% negative agreement (95% CI)	Analyte S/CO Percentile		
		2.5 th	50 th	97.5 th		2.5 th	50 th	97.5 th
HPV 18 IVT (1 copy)*	78.8 (126/160) (71.8, 84.4)	0	0	4.6	83.3 (135/162) (76.8, 88.3)	0	0	5.2
HPV 16 IVT (1 copy)*	80.9 (131/162) (74.1, 86.2)	0	0	10.7	88.3 (143/162) (82.4, 92.4)	0	0	11.3
HeLa cells (0.05 cells)*	79.0 (128/162) (72.1, 84.6)	0	0	10.4	82.1 (133/162) (75.5, 87.2)	0	0	11.6
SiHa cells (0.03 cells)*	93.8 (152/162) (89.0, 96.6)	0	0	10.7	95.7 (155/162) (91.4, 97.9)	0	0	6.9
STM Lot 1	100 (162/162) (97.7, 100)	0	0	0.1	100 (162/162) (97.7, 100)	0	0	0
STM Lot 2	99.4 (160/161) (96.6, 99.9)	0	0	0.2	100 (162/162) (97.7, 100)	0	0	0
STM Lot 3	99.4 (161/162) (96.6, 99.9)	0	0	0.1	99.4 (161/162) (96.6, 99.9)	0	0	0
ThinPrep Pool 1	97.5 (158/162) (93.8, 99.0)	0	0	0.3	97.5 (158/162) (93.8, 99.0)	0	0	0.3
ThinPrep Pool 2	96.9 (157/162) (93.0, 98.7)	0	0	0.7	96.3 (156/162) (92.2, 98.3)	0	0	1.6
ThinPrep Pool 3	100 (162/162) (97.7, 100)	0	0	0.2	99.4 (161/162) (96.6, 99.9)	0	0	0

STM = specimen transport medium; IVT = in vitro transcript. IVT was spiked into STM and cells were spiked into PreservCyt Solution.

* Expected % negative agreement > 75% and < 100%.

The analyte S/CO variability for the panel members with expected positive results is shown in the tables below for Study 1 and Study 2. Positive agreement for the HPV-positive panel members with concentrations at or above the limit of detection of the assay ranged from 95.1% to 100% in Study 1 and from 93.2% to 100% in Study 2 for 9 of the 10 panel members. The remaining HPV-positive panel member yielded 77.2% agreement in Study 1 and 79.0% agreement in Study 2, which was lower than expected, but was consistent between the 2 studies. Negative agreement for the HPV-high negative panel members with concentrations below the limit of detection of the assay ranged from 78.8% to 93.8% in Study 1 and from 82.1% to 95.7% in Study 2. Agreement with expected results for the HPV-negative panel members ranged from 96.9% to 100% in Study 1 and from 96.3% to 100% in Study 2.

**APTIMA HPV Assay Reproducibility Study 1: Signal Variability for Panel Members
With Expected Positive Results**

Panel Description (copies or cells/reaction)	n	Mean S/CO	Between Sites		Between Operators		Between Lots		Between Worklists		Within Worklists		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
HPV 16 & HPV 18 IVT (100 copies)	161 [^]	23.4	0.1	0.4	0.1	0.4	0.9	4.0	0	0	1.6	7.0	1.9	8.1
SiHa cells (3 cells) & HeLa cells (7.5 cells)	162	17.9	0	0	1.4	8.1	0	0	0.6	3.1	5.1	28.6	5.3	29.9
HPV 18 IVT (100 copies)	162	11.8	0	0	0	0	0.8	6.4	0.1	0.9	1.2	10.1	1.4	12.0
HPV 16 IVT (100 copies)	162	10.8	0.2	1.5	0	0	0.1	1.1	0.3	2.6	0.3	3.1	0.5	4.5
MS751 cells (1 cell)	162	13.3	0.3	2.1	0	0	1.0	7.8	0.9	7.1	2.2	16.2	2.6	19.4
ME180 cells (0.3 cells)	162	6.5	0.2	3.2	0	0	0.6	8.6	0.4	5.5	2.4	36.2	2.5	37.7
HPV 18 IVT (30 copies)	162	9.0	0.7	7.3	0	0	0.7	7.2	0.8	8.3	2.3	25.3	2.6	28.5
HPV 16 IVT (30 copies)	162	10.8	0.1	0.8	0	0	0.1	1.3	0.4	3.8	0.9	8.4	1.0	9.3
HeLa cells (2.5 cells)	162	12.4	0	0	0.4	3.3	0.4	3.1	0	0	2.3	18.4	2.4	19.0
SiHa cells (1 cell)	162	7.5	0.3	3.7	1.0	13.0	0	0	0	0	4.8	63.6	4.9	65.0

SD = standard deviation; CV = coefficient of variation; IVT = in vitro transcript; S/CO = signal to cutoff ratio

[^]One sample had an invalid APTIMA HPV Assay result and was not included in the analyses.

Note: Variability from some factors may be numerically negative. This can occur if the variability due to those factors is very small. In these cases, SD and CV are shown as 0.

**APTIMA HPV Assay Reproducibility Study 2: Signal Variability for Panel Members
with Expected Positive Results**

Panel Description (copies or cells/reaction)	n	Mean S/CO	Between Instrumen ts		Between Operators		Between Lots		Between Worklists		Within Worklists		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
HPV 16 & HPV 18 IVT (100 copies)	162	23.2	0.4	1.5	0.6	2.3	0.8	3.4	0.8	3.4	1.5	6.3	2.0	8.4
SiHa cells (3 cells) & HeLa cells (7.5 cells)	162	18.6	0	0	1.7	9.3	0	0	3.5	18.6	3.7	20.0	5.4	28.9
HPV 18 IVT (100 copies)	160	11.9	0.1	0.6	0.2	1.6	0.8	7.0	0.4	3.6	1.3	11.3	1.7	13.8
HPV 16 IVT (100 copies)	162	10.8	0	0	0.1	1.3	0	0	0.2	2.2	0.7	6.1	0.7	6.6
MS751 cells (1 cell)	162	13.6	0	0	0.6	4.3	0	0	2.5	18.4	2.1	15.2	3.3	24.2
ME180 cells (0.3 cells)	162	5.8	0	0	0.6	10.8	0.5	9.4	2.2	36.9	1.7	29.7	2.9	49.5
HPV 18 IVT (30 copies)	162	8.8	0.4	4.4	0.5	6.0	0.7	7.9	1.0	11.5	1.9	21.4	2.4	26.6

HPV 16 IVT (30 copies)	162	10.5	0	0	0.1	1.3	0.2	2.0	1.6	14.9	1.2	11.2	2.0	18.8
HeLa cells (2.5 cells)	159	12.0	0.6	5.1	1.0	8.5	0	0	2.8	23.8	2.0	16.6	3.7	30.6
SiHa cells (1 cell)	162	7.4	0.9	12.5	0	0	0.7	9.3	1.8	24	4.2	56.8	4.7	63.8

SD = standard deviation; CV = coefficient of variation; IVT = in vitro transcript; S/CO = signal to cutoff ratio

^Five samples had invalid APTIMA HPV Assay results (2 for HPV 18 IVT (100 copies), 3 for HeLa cells (2.5 cells)) and were not included in the analyses.

Note: Variability from some factors may be numerically negative. This can occur if the variability due to those factors is very small. In these cases, SD and CV are shown as 0.

A third study was also conducted to determine assay reproducibility by testing a 6-member panel of pooled clinical PreservCyt specimens. Six unique pools of residual HPV-negative ThinPrep liquid cytology specimens were prepared as the matrix, two of which were tested as HPV-negative panel members. Four unique pools of HPV-positive ThinPrep liquid cytology specimens were used to prepare the low (n=2) and high (n=2) HPV-positive panel members. The low positive panel members had concentrations at the limit of detection of the assay (expected positivity: $\geq 95\%$ determined for each individual HPV-positive pool from testing serial dilutions of the pools). The high positive panel members had concentrations at 1-2 logs above the estimated limit of detection for each individual HPV positive pool (expected positivity: 100% positivity). Each panel member was transferred (1 mL) into an APTIMA Specimen Transfer tube containing STM on the day of testing. Testing was conducted in-house by 2 operators using 1 reagent lot, 3 instruments, over 6 days (3 days for each operator), testing 2 runs per day in which the panel was tested in duplicate.

The panel members are described below, along with a summary of the agreement with expected results and analyte S/CO values at the 2.5th, 50th, and 97.5th percentiles of the signal distribution.

APTIMA HPV Assay Reproducibility Study 3: Panel Description, Percent Agreement, and Percentile Distribution of Analyte S/CO Values

Panel Description	% agreement (95% CI)	Analyte S/CO Percentile		
		2.5 th	50 th	97.5 th
Low positive 1	98.6 (71/72) (92.5, 99.8)	1.5	10.1	19.3
Low positive 2	100 (72/72) (94.9, 100)	1.5	10.3	19.1
High positive 1	100 (72/72) (94.9, 100)	12.6	23.1	32.4
High positive 2	100 (72/72) (94.9, 100)	13.3	24.7	31.2
Negative 1	98.6 (71/72) (92.5, 99.8)	0	0	0.3
Negative 2	94.4 (68/72) (86.6, 97.8)	0	0	0.7

The analyte S/CO variability for the panel members with expected positive results is shown in the table below.

APTIMA HPV Assay Reproducibility Study 3: Signal Analysis for Panel Members with Expected Positive Results

Panel Description	n	Mean S/CO	Between Instruments		Between Operators		Between Lots		Between Worklists		Within Worklists		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Low positive 1	72	9.8	0	0	0	0	0	0	2.2	22.8	3.0	30.4	3.7	38.0
Low positive 2	72	10.5	0	0	2.2	21.0	0.9	9.0	3.7	35.3	2.7	26.1	5.2	49.5
High positive 1	72	22.7	1.3	5.6	0	0	0.1	0.5	3.0	13.3	3.7	16.4	5.0	21.9
High positive 2	72	23.9	0	0	0	0	0	0	2.9	12.3	3.0	12.4	4.2	17.4

SD = standard deviation; CV = coefficient of variation; S/CO = signal to cutoff ratio

Note: Variability from some factors may be numerically negative. This can occur if the variability due to those factors is very small. In these cases, SD and CV are shown as 0.

Cross-Reactivity

The analytical specificity of the APTIMA HPV Assay was evaluated with PreservCyt solution media diluted 1:2.9 into STM and spiked with cultured bacteria, yeast, or fungi; cultured virus; or low-risk HPV in vitro transcripts. The organisms and test concentrations are identified in the table below. The study criteria for assessing the effect of the presence of microorganism on the specificity of the assay were based on positivity. Cross-reactivity was observed with low-risk HPV genotypes 26, 67, 70, and 82, but not with any of the other organisms tested.

Analytical Specificity Panel: Organisms and Concentration with No Cross-Reactivity

Organism	Test Concentration with No Cross-Reactivity	Organism	Test Concentration with No Cross-Reactivity
Bacteria			
<i>Acinetobacter lwoffii</i>	1x10 ⁸ CFU/mL	<i>Listeria monocytogenes</i>	1x10 ⁸ CFU/mL
<i>Actinomyces israelii</i>	1x10 ⁸ CFU/mL	<i>Micrococcus luteus</i>	1x10 ⁸ CFU/mL
<i>Alcaligenes faecalis</i>	1x10 ⁸ CFU/mL	<i>Mobiluncus curtisii</i>	2x10 ⁷ CFU/mL
<i>Atopobium vaginae</i>	5x10 ⁷ CFU/mL	<i>Mycobacterium smegmatis</i>	1x10 ⁸ CFU/mL
<i>Bacillus cereus</i>	1x10 ⁸ CFU/mL	<i>Mycoplasma fermentans</i>	5x10 ⁷ CFU/mL
<i>Bacteroides fragilis</i>	1x10 ⁸ CFU/mL	<i>Mycoplasma genitalium</i>	1x10 ⁸ CFU/mL
<i>Bacteroides ureolyticus</i>	1x10 ⁸ CFU/mL	<i>Mycoplasma hominis</i>	5x10 ⁷ CFU/mL
<i>Bifidobacterium adolescentis</i>	1x10 ⁸ CFU/mL	<i>Neisseria gonorrhoeae</i>	1x10 ⁸ CFU/mL
<i>Bifidobacterium breve</i>	1x10 ⁸ CFU/mL	<i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i>	2.5x10 ⁷ CFU/mL 2.3x10 ⁵ TCID ₅₀ /mL
<i>Campylobacter fetus-fetus</i>	1x10 ⁸ CFU/mL	<i>Neisseria meningitidis</i>	1x10 ⁸ CFU/mL
<i>Chlamydia trachomatis</i>	3.2x10 ⁵ TCID ₅₀ /mL	<i>Peptoniphilus lacrimalis</i>	1x10 ⁸ CFU/mL

Organism	Test Concentration with No Cross-Reactivity	Organism	Test Concentration with No Cross-Reactivity
<i>Clostridium difficile</i>	6x10 ⁷ CFU/mL	<i>Peptostreptococcus anaerobius</i>	1x10 ⁸ CFU/mL
<i>Clostridium perfringens</i>	1x10 ⁸ CFU/mL	<i>Propionibacterium acnes</i>	1x10 ⁸ CFU/mL
<i>Corynebacterium genitalium</i>	1x10 ⁸ CFU/mL	<i>Proteus mirabilis</i>	1x10 ⁸ CFU/mL
<i>Corynebacterium xerosis</i>	1x10 ⁸ CFU/mL	<i>Proteus vulgaris</i>	1x10 ⁸ CFU/mL
<i>Enterobacter cloacae</i>	1x10 ⁸ CFU/mL	<i>Providencia stuartii</i>	1x10 ⁸ CFU/mL
<i>Enterococcus faecalis</i>	1x10 ⁸ CFU/mL	<i>Pseudomonas aeruginosa</i>	1x10 ⁸ CFU/mL
<i>Escherichia coli</i>	1x10 ⁸ CFU/mL	<i>Ruminococcus productus</i>	1x10 ⁸ CFU/mL
<i>Fingoldia magna</i>	1x10 ⁸ CFU/mL	<i>Serratia marcescens</i>	1x10 ⁸ CFU/mL
<i>Fusobacterium nucleatum</i>	1x10 ⁸ CFU/mL	<i>Staphylococcus aureus</i>	1x10 ⁸ CFU/mL
<i>Gardnerella vaginalis</i>	1x10 ⁸ CFU/mL	<i>Staphylococcus epidermidis</i>	1x10 ⁸ CFU/mL
<i>Haemophilus ducreyi</i>	1x10 ⁸ CFU/mL	<i>Staphylococcus saprophyticus</i>	1x10 ⁸ CFU/mL
<i>Klebsiella pneumoniae</i>	1x10 ⁸ CFU/mL	<i>Streptococcus agalactiae</i>	1x10 ⁸ CFU/mL
<i>Lactobacillus acidophilus</i>	1x10 ⁸ CFU/mL	<i>Streptococcus pyogenes</i>	1x10 ⁸ CFU/mL
<i>Lactobacillus crispatus</i>	1x10 ⁸ CFU/mL	<i>Streptococcus sanguinis</i>	1x10 ⁸ CFU/mL
<i>Lactobacillus delbrueckii ssp. bulgaricus</i>	1x10 ⁸ CFU/mL	<i>Ureaplasma urealyticum</i>	1x10 ⁸ CFU/mL
<i>Lactobacillus jensenii</i>	1x10 ⁸ CFU/mL		
Yeast/protozoa			
<i>Candida albicans</i>	1x10 ⁸ CFU/mL	<i>Trichomonas vaginalis</i>	1x10 ⁷ cells/mL
Viruses			
Adenovirus 2	1x10 ⁷ vp/mL	Herpes simplex virus 1	2.5x10 ⁵ TCID ₅₀ /mL
Cytomegalovirus	5.6x10 ² TCID ₅₀ /mL	Herpes simplex virus 2	5x10 ⁴ TCID ₅₀ /mL
Epstein-Barr virus	4.3x10 ⁶ vp/mL	SV40	1.2 x10 ⁴ TCID ₅₀ /mL
HIV-1	1.0x10 ⁶ copies/mL		
Non-targeted HPV genotypes			
HPV 6	2.5x10 ⁶ copies/mL	HPV 61	2.5x10 ⁶ copies/mL
HPV 11	2.5x10 ⁶ copies/mL	HPV 67	1 copy/mL
HPV 26	2.5 copies/mL	HPV 69	2.5x10 ⁶ copies/mL
HPV 30	2.5x10 ⁶ copies/mL	HPV 70	1 copy/mL
HPV 34	2.5x10 ⁶ copies/mL	HPV 71	2.5x10 ⁶ copies/mL
HPV 42	2.5x10 ⁶ copies/mL	HPV 73	2.5x10 ⁶ copies/mL
HPV 43	2.5x10 ⁶ copies/mL	HPV 81	2.5x10 ⁶ copies/mL
HPV 44	2.5x10 ⁶ copies/mL	HPV 82	2.5 copies/mL
HPV 53	2.5x10 ⁶ copies/mL	HPV 85	2.5x10 ⁶ copies/mL

HPV 54	2.5x10 ⁶ copies/mL		
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vp = viral particles

CFU = colony forming units

TCID₅₀ = tissue culture infective dose 50

Note: Bold indicates types where cross-reactivity (> 5% positivity) was observed when tested at concentrations greater than that noted in the table.

The analytical sensitivity of the APTIMA HPV Assay in the presence of microorganisms was evaluated with the same panel described directly above, which was also spiked with a low concentration of HPV infected SiHa cells (1 cell per reaction). The study criteria for assessing the effect of the presence of microorganism on the sensitivity of the assay were based on positivity. The sensitivity of the APTIMA HPV Assay was not affected by any of the organisms tested.

Interference

The substances described in the table below were individually spiked into PreservCyt solution at 1% and 10% v/v or w/v, diluted with STM and then tested in the APTIMA HPV Assay. All substances were tested in the presence and absence of HPV infected cultured cells (SiHa, 3 cells/reaction). Interference was observed with two of the seven lubricants that contained Polyquaternium 15, and one of the five anti-fungal medications that contained tioconazole. Interference was not observed with any of other substances tested.

Substances Tested for Possible Interference with the APTIMA HPV Assay

Product Category	Product Brand or Type	Highest Concentration* Tested that Did Not Interfere with Assay Performance
Lubricant	KY Sensual Mist	10% v/v
	KY Warming Jelly	10% w/v
	KY Warming Liquid	10% v/v
	CVS Brand Personal Lubricant	10% w/v
	Target Brand Warming Massage Lotion and Personal Lubricant	10% v/v
	Astroglide Personal Lubricant	0.3% w/v (0.075% w/v test sample)
	Target Brand Lubricating Liquid	0.1% v/v (0.025% v/v test sample)
Spermicide	Gynol II Vaginal Contraceptive Original Formula	10% w/v
	Gynol II Vaginal Contraceptive Extra Strength	10% w/v
	Delfen Vaginal Contraceptive Foam	10% w/v
	Encare Vaginal Contraceptive	10% w/v
	Conceptrol Vaginal Contraceptive	10% w/v
Anti-fungal/ Anti-Itch Medication	Vagisil Maximum Strength	10% w/v
	Monistat Soothing Care	10% w/v
	Monistat 3 Combination Pack	10% w/v

	Target Brand Tioconazole 1	0.3% w/v (0.075% w/v test sample)
	Target Brand Miconazole 3	10% w/v
Glacial Acetic Acid	EMD M/N AX0073-11	10% v/v
Whole Blood	whole blood	10% v/v

Reagent Stability

Expiration dating for this device has been established and approved at 18 months for the APTIMA HPV Assay when stored at 2 - 8°C, with the exception of the subset of reagents in the APTIMA HPV Room Temperature Box, which should be stored at 15 - 30°C.

Sample Handling and Collection

Cervical specimens should be collected in PreservCyt Solution, the ThinPrep Pap Test preservation system, using a broom-type device (e.g. Rovers Cervex Brush, Wallach Papette), or Endocervical Brush/Spatula.

Specimen stability studies demonstrated that for the APTIMA HPV Assay cervical specimens should be transported and stored at 2°C to 30°C, with no more than 30 days at temperatures above 8°C. PreservCyt specimens should be transferred to an APTIMA Specimen Transfer tube within 105 days of collection. PreservCyt Solution specimens transferred to an APTIMA Specimen Transfer tube may be stored at 2°C to 30°C for up to 60 days. If longer storage is needed, the PreservCyt Solution specimen or the PreservCyt Solution specimen diluted into the Specimen Transfer tube may be stored at -20°C for up to 24 months.

TIGRIS DTS System Carryover

A study was conducted to determine the rate of false positive results observed with the Aptima HPV Assay using the TIGRIS DTS System when samples containing high titer HPV were interspersed throughout specimen processing racks containing HPV-negative samples. High titer positive samples for this study were created by spiking HPV 16 in vitro transcript into a solution comprised of 1 part PreservCyt solution and 2.9 parts specimen transport media (STM) to a concentration of 2.5×10^6 copies/mL (1×10^6 copies/reaction). The sample to sample cross-contamination rate of the APTIMA HPV Assay on the TIGRIS DTS System was determined to be 0.3%.

ThinPrep Carryover Study

A study was conducted to determine the false positive rate observed with the APTIMA HPV Assay when PreservCyt liquid Pap specimens containing a high concentration of spiked HPV-positive cells, were alternately processed with HPV-negative specimens on the ThinPrep 2000 Processor. The study also evaluated the effectiveness of the cleaning procedure described in the APTIMA Specimen Transfer Kit package insert.

The observed false positive rate for specimens tested with the Aptima HPV Assay following processing on the TP2000 was 0.8% when the cleaning procedure described in the APTIMA Specimen Transfer Kit package insert was followed. When these instructions were not

followed, the false positive rate was higher (1.7%). Users should follow the cleaning instructions provided via the APTIMA Specimen Transfer kit for decontamination between specimens to minimize carryover risk.

B. Animal Studies

Not applicable

C. Additional Studies

Not applicable

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. Study Design

Patients were enrolled between March 2008 and December 2009. This was a prospective cohort, multi-center trial consisting of 2 sub-studies to support the two distinct indications for use of the assay, the ASC-US Study and the NILM (negative for intraepithelial lesions or malignancy) Study. The database for this PMA included 12,896 patients age 21 and older. There were 19 enrolling (collection) sites and 3 APTIMA HPV Assay testing sites. One of the collection sites was excluded from the final analysis due to protocol violations (see Section XI below).

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who attended a participating clinic and underwent a routine cytology test. In addition, the subject must have been able to comprehend and sign an IRB-approved Informed Consent Form and other applicable study enrollment documents. To be included in the ASC-US Study, the subject's referral cytology specimen must have had ASC-US results. To be included in the NILM Study, the subject must have been ≥ 30 years of age and the subject's referral cytology specimen must have had NILM cytology test results. Note that all women under age 21 that were enrolled in the ASC-US study have been removed from the dataset (n=99), including patient demographics and subject accountability. The approved indication does not cover this age range since HPV testing is not recommended in women under the age of 21².

Patients were not permitted to enroll in the either study if the subject, clinician, or medical record reported any of the following:

- History of cervical disease (cancer or precancerous condition) in the previous 12 months
- History of an abnormal cytology test result in the previous 12 months
- Under 18 years of age, without the documented consent of her parent or legal guardian
- Subject is known to be pregnant at enrollment
- History of illness that the investigator considers could interfere with or affect the conduct, results, and/or completion of the clinical trial

- History of illness that the investigator/physician considers to create an unacceptable risk to the subject if enrolled
- History of HPV vaccination prior to enrollment.

2. Follow-up Schedule

Patients were scheduled to return for follow-up examinations as described below.

APTIMA HPV Assay Clinical Trial Study Design

A prospective, multicenter US clinical study known as the CLEAR trial was conducted to determine the clinical performance of the APTIMA HPV Assay for detection of cervical intraepithelial neoplasia grade 2 or more severe cervical disease (\geq CIN2). Women were enrolled into either the ASC-US Study or the NILM Study based on cytology results from routine cervical cancer screening. The ASC-US Study population included women 21 years and older with ASC-US cytology results and the NILM Study population included women 30 years of age and older with NILM cytology results. The NILM Study was designed to support the adjunctive screening claim for women 30 years and older, since women in this age range with cytology results greater than ASC-US should proceed to colposcopy regardless of their HPV status.²

Women from 18 clinical sites, primarily obstetrics/gynecology clinics, which covered a wide geographic distribution and a diverse population, were analyzed. Eligible women were assigned to the ASC-US Study or NILM Study based on their referral ThinPrep PreservCyt liquid based cytology specimen. Residual referral specimens were tested with both the APTIMA HPV Assay and an FDA-approved HPV DNA test.

All women in the ASC-US Study were referred to colposcopy, regardless of their HPV test results. An endocervical curettage (ECC) biopsy and cervical punch biopsies (1 biopsy from each of the 4 quadrants) were obtained. If a lesion was visible, a punch biopsy was obtained (directed method; 1 biopsy per lesion) and quadrants without a visible lesion were biopsied at the squamocolumnar junction (random method).

In the NILM Study, women positive with the APTIMA HPV Assay and/or the FDA-approved HPV DNA test, as well as randomly selected women who were negative with both assays, were referred to colposcopy for the baseline evaluation. The randomly selected women who were negative for both assays were included to correct for verification bias with adjusted performance estimates generated using a multiple imputation method. An ECC biopsy was obtained from each woman who attended colposcopy. Punch biopsies were obtained from visible lesions only (directed method; 1 biopsy per lesion). Follow-up of women in the NILM Study who do not have \geq CIN2 is ongoing for 3 years with annual cytology visits. Women with ASC-US or more severe cytology results during the follow-up period are referred to colposcopy using the same biopsy procedure performed for the baseline evaluation.

For both studies, disease status was determined from a consensus histology review panel, which was based on agreement of at least 2 expert pathologists. The expert

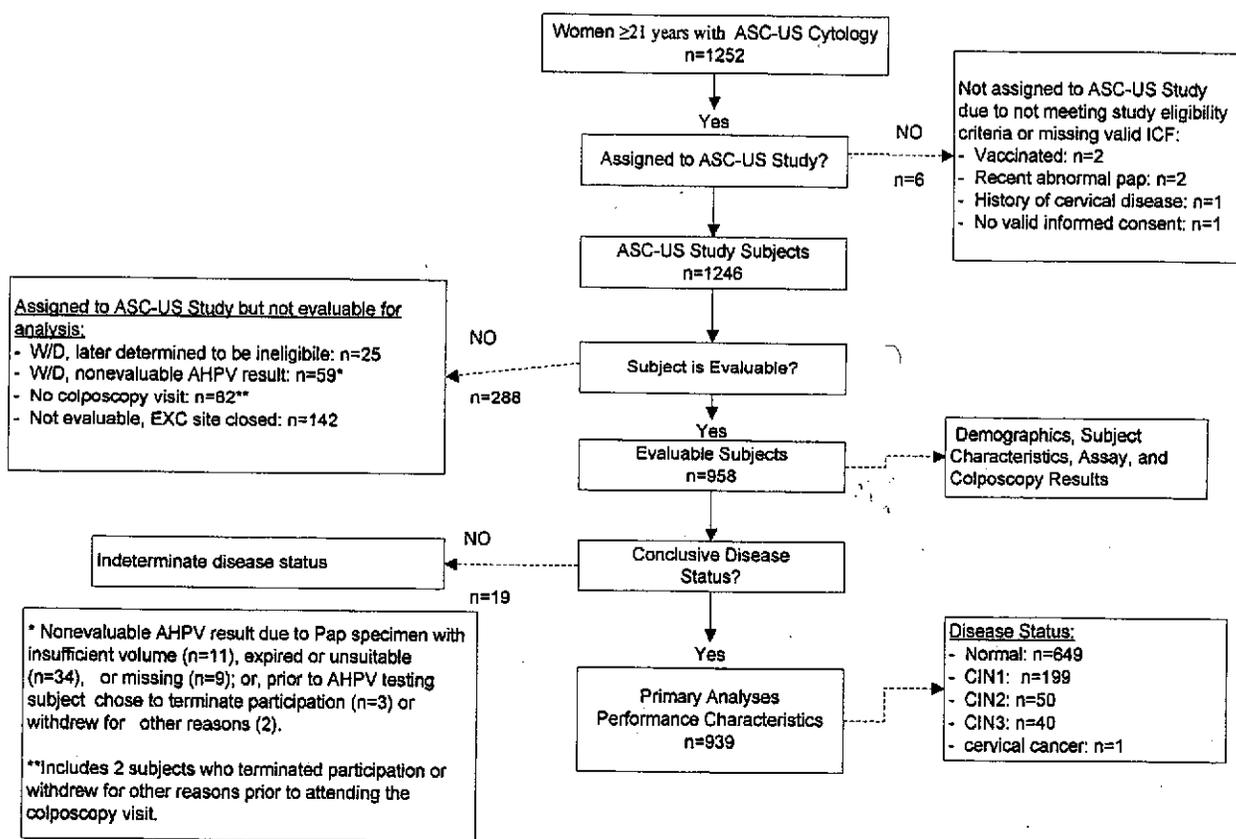
pathologists were masked to the woman's HPV and cytology status, as well as each other's histology diagnoses. Investigators, clinicians, and women were masked to the HPV test results until after completion of the colposcopy visit, to avoid bias. Clinical performance of the APTIMA HPV Assay was determined for detection of \geq CIN2 and cervical intraepithelial neoplasia grade 3 or more severe cervical disease (\geq CIN3). Clinical performance of the FDA-approved HPV DNA test was also determined for direct comparison to the APTIMA HPV Assay results.

B. Accountability of PMA Cohort

Accountability in ASC-US (\geq 21 years) Population

Subject enrollment began on March 19, 2008, and was completed on December 23, 2009. Colposcopy visits were completed on December 23, 2009. APTIMA HPV Assay testing was completed on January 29, 2010.

There were 958 evaluable women, 21 years or older, who met the selection criteria and were enrolled into the ASC-US Study. These evaluable women had a valid APTIMA HPV Assay result and attended the colposcopy visit. Nineteen (19) of the 958 women had indeterminate disease status. The remaining 939 subjects had conclusive disease status based on the evaluation of all biopsies performed (eg, directed punch, random, and ECC) and were included in the clinical performance analyses. The ASC-US study enrollment and sample accountability are described below.

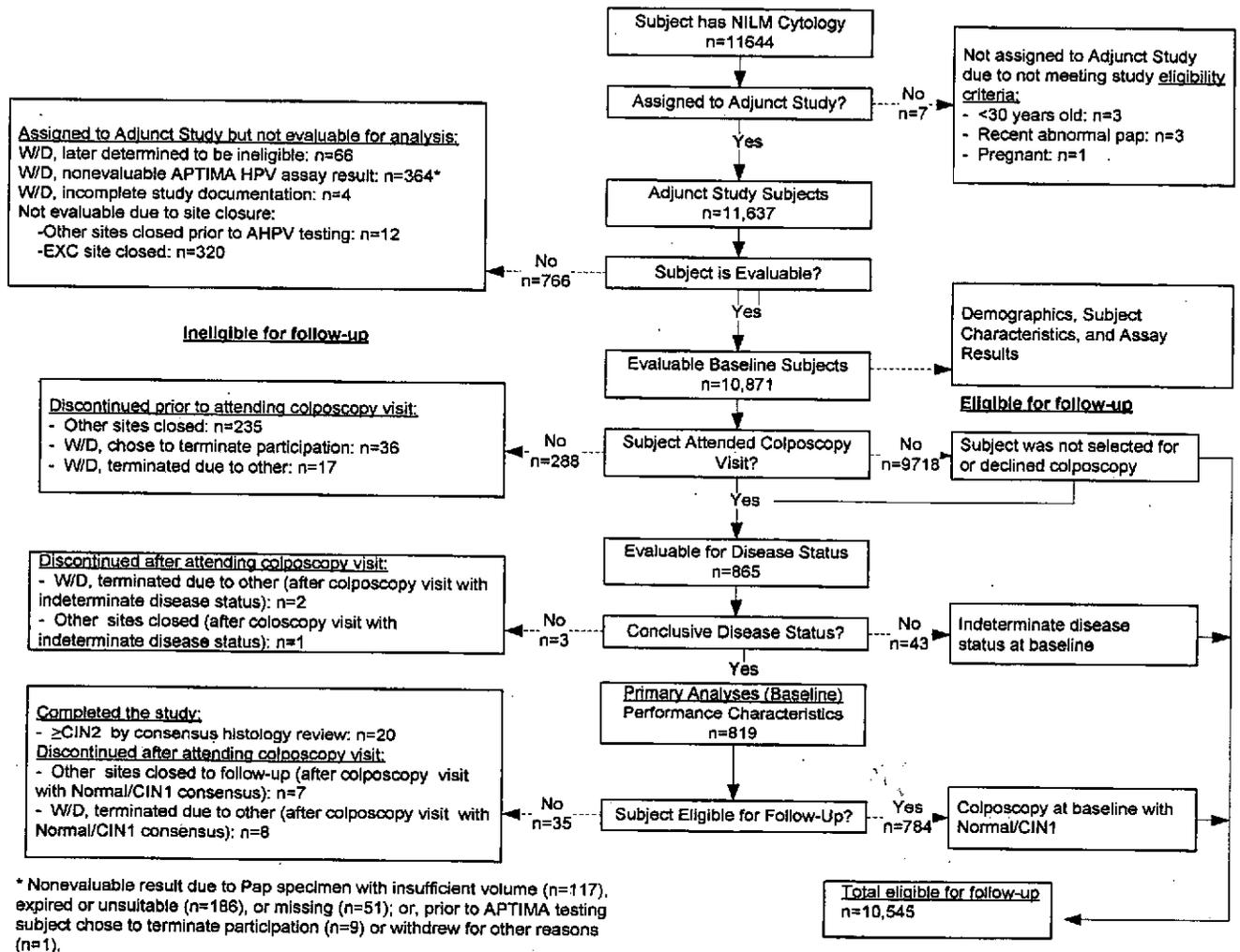


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Accountability in NILM (≥ 30 years) population

Subject enrollment began on March 31, 2008, and was completed on December 8, 2009. Baseline colposcopy visits were completed on February 2, 2010. APTIMA HPV Assay testing was completed on January 28, 2010. Follow-up is currently ongoing and is estimated to be completed by April 2013.

There were 10,871 evaluable women 30 years of age and older with NILM cytology results and APTIMA HPV Assay results. Of the 540 women with positive APTIMA HPV Assay results, 335 attended colposcopy. Of the 10,331 women with negative APTIMA HPV Assay results, 530 attended colposcopy (865 total). The NILM Study enrollment and sample accountability are described below.



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a prospective study performed in the US. See tables below for detailed demographic information on each study population.

ASC-US Subject Demographics (N=958)	
Age (years) at consent	
Mean	33.8
SD	10.3
Median	31.0
Min	21
Max	85
Race	
White	587
Black or African American	229
Asian	29
American Indian or Alaska Native	34
Native Hawaiian or Pacific Islander	1
Unknown / Refused	106
Ethnicity	
Hispanic or Latino	195
Not Hispanic or Latino	712
Unknown / Refused	51

NILM Subject Demographics (N=10871)	
Age (years) at consent	
Mean	44.1
SD	10.1
Median	43.0
Min	30
Max	89
Race	
White	6937
Black or African American	1390
Asian	658
American Indian or Alaska Native	152
Native Hawaiian or Pacific Islander	66
Unknown / Refused	1808
Ethnicity	
Hispanic or Latino	3421
Not Hispanic or Latino	6881
Unknown / Refused	569

D. Safety and Effectiveness Results

ASC-US \geq 21 Years Population: APTIMA HPV Assay Clinical Performance

In total, there were 1252 women 21 years of age and older with ASC-US cytology results enrolled in the ASC-US Study. Of these, 294 women were withdrawn and 19 had an undetermined disease diagnosis; all were excluded from analysis. The remaining 939 evaluable women were 21 years of age and older with ASC-US cytology results, APTIMA HPV Assay results, and conclusive disease status. Ninety-one (91) women had \geq CIN2 and forty-one (41) had \geq CIN3. Prevalence of \geq CIN2 and \geq CIN3 in evaluable women with ASC-US cytology results were 9.7% and 4.4%, respectively. The results of the APTIMA HPV Assay by the consensus histology review panel diagnoses are presented below.

ASC-US \geq 21 Years Population: Results of the APTIMA HPV Assay by Consensus Histology Review Panel Diagnosis

APTIMA HPV Assay Result*	HPV DNA Test	Consensus Histology Review Panel Diagnosis						Total
		Undetermined**	Normal	CIN1	CIN2	CIN3	Cancer	
Positive	Positive	6	170	113	41	32	1	363
Positive	Negative	0	7	0	1	2	0	10
Positive	No Result***	0	14	11	0	2	0	27
Negative	Positive	0	47	13	2	3	0	65
Negative	Negative	10	371	55	6	1	0	443
Negative	No Result***	3	40	7	0	0	0	50
Total		19	649	199	50	40	1****	958

*All samples had final valid results (upon initial testing or after resolution of initial invalids per procedure).

**19 subjects attended the colposcopy visit but a diagnosis could not be determined for the following reasons: < 5 biopsy specimens obtained all with histology results of Normal/CIN1 (n=15), no biopsies collected (n=3), and biopsy slides lost (n=1).

***77 women with APTIMA HPV Assay results did not have HPV DNA test results primarily due to insufficient volume of the cytology specimen.

****One subject had adenocarcinoma in situ (AIS).

Clinical performance estimates of the APTIMA HPV Assay including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of \geq CIN2 and \geq CIN3 based on evaluating all biopsies and including only directed biopsies are shown in the table below, as are the estimates for the FDA-approved HPV DNA test. Ninety-five percent two-sided confidence intervals for sensitivity and specificity were calculated using a score method³ and 95% two-sided confidence intervals for the PPV and NPV were calculated based on the confidence intervals of corresponding likelihood ratios (positive likelihood ratio for PPV and negative likelihood ratio for NPV).^{4,5}

ASC-US ≥ 21 Years Population: Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of ≥CIN2 and ≥CIN3

Performance	APTIMA HPV Assay N=939		HPV DNA Test N=865*			
	Estimate	(95% CI)	Estimate	(95% CI)		
≥CIN2	All Biopsies					
	Sensitivity (%)	86.8 (79/91)	(78.4, 92.3)	88.8 (79/89)	(80.5, 93.8)	
	Specificity (%)	62.9 (533/848)	(59.6, 66.0)	55.8 (433/776)	(52.3, 59.3)	
	PPV (%)	20.1 (79/394)	(18.1, 22.0)	18.7 (79/422)	(17.0, 20.4)	
	NPV (%)	97.8 (533/545)	(96.5, 98.8)	97.7 (433/443)	(96.2, 98.8)	
	Prevalence (%)	9.7 (91/939)		10.3 (89/865)		
	Directed Biopsies**					
	Sensitivity (%)	93.3 (56/60)	(84.1, 97.4)	93.2 (55/59)	(83.8, 97.3)	
	Specificity (%)	61.5 (539/876)	(58.3, 64.7)	54.5 (438/804)	(51.0, 57.9)	
	PPV (%)	14.2 (56/393)	(12.7, 15.6)	13.1 (55/421)	(11.7, 14.2)	
	NPV (%)	99.3 (539/543)	(98.3, 99.8)	99.1 (438/442)	(97.9, 99.7)	
	Prevalence (%)	6.4 (60/936)		6.8 (59/863)		
	≥CIN3	All Biopsies				
		Sensitivity (%)	90.2 (37/41)	(77.5, 96.1)	92.3 (36/39)	(79.7, 97.3)
Specificity (%)		60.2 (541/898)	(57.0, 63.4)	53.3 (440/826)	(49.9, 56.6)	
PPV (%)		9.4 (37/394)	(8.1, 10.4)	8.5 (36/422)	(7.4, 9.4)	
NPV (%)		99.3 (541/545)	(98.3, 99.8)	99.3 (440/443)	(98.3, 99.8)	
Prevalence (%)		4.4 (41/939)		4.5 (39/865)		
Directed Biopsies**						
Sensitivity (%)		93.1 (27/29)	(78.0, 98.1)	96.4 (27/28)	(82.3, 99.4)	
Specificity (%)		59.6 (541/908)	(56.4, 62.7)	52.8 (441/836)	(49.4, 56.1)	
PPV (%)		6.9 (27/394)	(5.8, 7.6)	6.4 (27/422)	(5.5, 7.0)	
NPV (%)		99.6 (541/543)	(98.8, 100)	99.8 (441/442)	(98.9, 100)	
Prevalence (%)		3.1 (29/937)		3.2 (28/864)		

*74 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

**Consensus histology result was derived using only results from directed biopsies. Women with no directed biopsies reflect a normal colposcopy and are included in these analyses as non-diseased (<CIN2 or <CIN3, as appropriate). A consensus was not always reached when only directed biopsies were included. There were 2 women excluded from both the \geq CIN2 and \geq CIN3 analysis based on evaluation of only directed biopsy slides: 1 woman had normal histology by one pathologist and undetermined by the second pathologist and the other woman had undetermined histology by both pathologists. One additional woman was excluded from the \geq CIN2 analysis based on evaluation of only directed biopsy slides because she was CIN1 by one pathologist and CIN2 by the second pathologist. She was included in the \geq CIN3 analysis as disease negative.

When evaluating all biopsies, clinical sensitivity estimates of the APTIMA HPV Assay and the FDA-approved HPV DNA test, where both assay results are available for the detection of \geq CIN2 and \geq CIN3, were similar (differences in sensitivity estimates were not statistically significant: sensitivity difference = -2.3% [95% CI: -9.5%, 4.8%]). Clinical specificity estimates of the APTIMA HPV Assay for the detection of \geq CIN2 and \geq CIN3 were higher than those of the FDA-approved HPV DNA test (differences in specificity estimates were statistically significant). For \geq CIN2, the specificity difference was 6.8% (95% CI: 4.9%, 9.0%). NPVs were similar but for the detection of \geq CIN2, the PPV for the APTIMA HPV Assay was slightly higher than PPV for the FDA-approved HPV DNA test (20.1% vs 18.7%).

Of the 91 \geq CIN2 cases, 60 (65.9%) were identified in directed biopsies and 31 (34.1%) were identified from random and/or ECC biopsies (i.e., not in directed biopsies). These findings are comparable to results from published studies, in which approximately 25% to 40% of \geq CIN2 cases were identified from random and/or ECC biopsy specimens only.^{6,7} Using only directed biopsies to determine disease status (assuming women with no directed biopsies had normal histology results because no visible lesions were present), prevalence of \geq CIN2 and \geq CIN3 in the study were 6.4% and 3.1%, respectively. The clinical sensitivity estimates for the detection of \geq CIN2 and \geq CIN3 were higher for both tests using directed biopsies only than estimates calculated using all biopsies. For both assays, clinical specificity using only directed biopsies was similar to the specificity obtained with all biopsies included. Accordingly, when using only directed biopsies, the APTIMA HPV Assay specificity was significantly higher than that of the FDA-approved HPV DNA test.

Clinical performance estimates of the APTIMA HPV Assay and the FDA-approved HPV DNA test are shown by age group in the tables below (\geq CIN2 and \geq CIN3, respectively, based on evaluating all biopsies).

ASC-US \geq 21 Years Population: Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of \geq CIN2 by Age Group

	Performance	APTIMA HPV Assay N=939		HPV DNA test N=865*	
		Estimate	(95% CI)	Estimate	(95% CI)
21 to 29 Years		N=415		N=389	
	Sensitivity (%)	90.2 (55/61)	(80.2, 95.4)	94.9 (56/59)	(86.1, 98.3)
	Specificity (%)	44.9 (159/354)	(39.8, 50.1)	35.5 (117/330)	(30.5, 40.8)
	PPV (%)	22.0 (55/250)	(19.6, 24.2)	20.8 (56/269)	(19.0, 22.5)
	NPV (%)	96.4 (159/165)	(93.0, 98.5)	97.5 (117/120)	(93.6, 99.4)
	Prevalence (%)	14.7 (61/415)		15.2 (59/389)	
30 to 39 Years		N=262		N=239	
	Sensitivity (%)	90.0 (18/20)	(69.9, 97.2)	80.0 (16/20)	(58.4, 91.9)
	Specificity (%)	68.2 (165/242)	(62.1, 73.7)	61.6 (135/219)	(55.1, 67.8)
	PPV (%)	18.9 (18/95)	(14.7, 22.7)	16.0 (16/100)	(11.8, 19.6)
	NPV (%)	98.8 (165/167)	(96.5, 99.8)	97.1 (135/139)	(94.1, 99.1)
	Prevalence (%)	7.6 (20/262)		8.4 (20/239)	
\geq 40 Years		N=262		N=237	
	Sensitivity (%)	60.0 (6/10)	(31.3, 83.2)	70.0 (7/10)	(39.7, 89.2)
	Specificity (%)	82.9 (209/252)	(77.8, 87.1)	79.7 (181/227)	(74.0, 84.4)
	PPV (%)	12.2 (6/49)	(5.8, 18.4)	13.2 (7/53)	(6.9, 18.7)
	NPV (%)	98.1 (209/213)	(96.6, 99.4)	98.4 (181/184)	(96.6, 99.6)
Prevalence (%)	3.8 (10/262)		4.2 (10/237)		

*74 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

ASC-US ≥ 21 Years Population: Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of ≥CIN3 by Age Group

	Performance	APTIMA HPV Assay N=939		HPV DNA test N=865*	
		Estimate	(95% CI)	Estimate	(95% CI)
21 to 29 Years		N=415		N=389	
	Sensitivity (%)	96.3 (26/27)	(81.7, 99.3)	100 (25/25)	(86.7, 100)
	Specificity (%)	42.3 (164/388)	(37.5, 47.2)	33.0 (120/364)	(28.3, 38.0)
	PPV (%)	10.4 (26/250)	(8.9, 11.4)	9.3 (25/269)	(8.2, 10.0)
	NPV (%)	99.4 (164/165)	(97.2, 100)	100 (120/120)	(97.5, 100)
	Prevalence (%)	6.5 (27/415)		6.4 (25/389)	
30 to 39 Years		N=262		N=239	
	Sensitivity (%)	88.9 (8/9)	(56.5, 98.0)	77.8 (7/9)	(45.3, 93.7)
	Specificity (%)	65.6 (166/253)	(59.6, 71.2)	59.6 (137/230)	(53.1, 65.7)
	PPV (%)	8.4 (8/95)	(5.2, 10.4)	7.0 (7/100)	(3.9, 9.1)
	NPV (%)	99.4 (166/167)	(97.6, 100)	98.6 (137/139)	(96.4, 99.8)
	Prevalence (%)	3.4 (9/262)		3.8 (9/239)	
≥ 40 Years		N=262		N=237	
	Sensitivity (%)	60.0 (3/5)	(23.1, 88.2)	80.0 (4/5)	(37.6, 96.4)
	Specificity (%)	82.1 (211/257)	(77.0, 86.3)	78.9 (183/232)	(73.2, 83.6)
	PPV (%)	6.1 (3/49)	(1.6, 10.2)	7.5 (4/53)	(2.9, 10.7)
	NPV (%)	99.1 (211/213)	(98.0, 99.9)	99.5 (183/184)	(98.2, 100)
	Prevalence (%)	1.9 (5/262)		2.1 (5/237)	

*74 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

The absolute risk of disease (\geq CIN2 and \geq CIN3, based on evaluating all biopsies) by APTIMA HPV Assay result and the relative risk of disease for positive versus negative APTIMA HPV Assay results are shown in the table below, as are the estimates for the FDA-approved HPV DNA test. The relative risk of \geq CIN2 was 9.1 (95% CI: 5.0, 16.5), indicating that a woman who was APTIMA HPV Assay positive was 9.1 times as likely to have \geq CIN2 than a woman who was APTIMA HPV Assay negative. The relative risk of \geq CIN3 was 12.8 (95% CI: 4.6, 35.6).

ASC-US \geq 21 Years Population: Absolute and Relative Risks of \geq CIN2 and \geq CIN3 for Results of the APTIMA HPV Assay and an FDA-approved HPV DNA Test

	Assay Result	APTIMA HPV Assay N=939		HPV DNA test N=865*	
		Absolute Risk (95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Relative Risk (95% CI)
\geq CIN2	Positive	20.1 (79/394) (18.1, 22.0)	9.1 (5.0, 16.5)	18.7 (79/422) (17.0, 20.4)	8.3 (4.4, 15.8)
	Negative	2.2 (12/545) (1.2, 3.5)		2.3 (10/443) (1.2, 3.8)	
	Prevalence (%)	9.7 (91/939)		10.3 (89/865)	
\geq CIN3	Positive	9.4 (37/394) (8.1, 10.4)	12.8 (4.6, 35.6)	8.5 (36/422) (7.4, 9.4)	12.6 (3.9, 40.6)
	Negative	0.7 (4/545) (0.2, 1.7)		0.7 (3/443) (0.2, 1.7)	
	Prevalence (%)	4.4 (41/939)		4.5 (39/865)	

*74 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

Absolute and relative risk estimates of disease (\geq CIN2 and \geq CIN3, based on evaluating all biopsies) for the APTIMA HPV Assay and the FDA-approved HPV DNA test are shown by age group in the table below.

ASC-US \geq 21 Years Population: Absolute and Relative Risks of \geq CIN2 and \geq CIN3 for Results of the APTIMA HPV Assay and an FDA-approved HPV DNA Test by Age Group

	Age	Assay Result	APTIMA HPV Assay N=939		HPV DNA test N=865*	
			Absolute Risk (95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Relative Risk (95% CI)
\geq CIN2	21 to 29 Years		N=415		N=389	
		Positive	22.0 (55/250) (19.6, 24.2)	6.1 (2.7, 13.7)	20.8 (56/269) (19.0, 22.5)	8.3 (2.7, 26.1)
		Negative	3.6 (6/165) (1.5, 7.0)		2.5 (3/120) (0.6, 6.4)	
		Prevalence (%)	14.7 (61/415)		15.2 (59/389)	
	30 to 39 Years		N=262		N=239	
		Positive	18.9 (18/95) (14.7, 22.7)	15.8 (3.8, 66.7)	16.0 (16/100) (11.8, 19.6)	5.6 (1.9, 16.1)
		Negative	1.2 (2/167) (0.2, 3.5)		2.9 (4/139) (0.9, 5.9)	
		Prevalence (%)	7.6 (20/262)		8.4 (20/239)	
	\geq 40 Years		N=262		N=237	
Positive		12.2 (6/49) (5.8, 18.4)	6.5 (1.9, 22.2)	13.2 (7/53) (6.9, 18.7)	8.1 (2.2, 30.2)	
Negative		1.9 (4/213) (0.6, 3.4)		1.6 (3/184) (0.4, 3.4)		
Prevalence (%)		3.8 (10/262)		4.2 (10/237)		
\geq CIN3	21 to 29 Years		N=415		N=389	
		Positive	10.4 (26/250) (8.9, 11.4)	17.2 (2.4, 125)	9.3 (25/269) (8.2, 10.0)	Not Calculable
		Negative	0.6 (1/165) (0.0, 2.8)		0.0 (0/120) (0.0, 2.5)	
		Prevalence (%)	6.5 (27/415)		6.4 (25/389)	
	30 to 39 Years		N=262		N=239	
		Positive	8.4 (8/95) (5.2, 10.4)	14.1 (1.8, 111)	7.0 (7/100) (3.9, 9.1)	4.9 (1.0, 22.9)
		Negative	0.6 (1/167) (0.0, 2.4)		1.4 (2/139) (0.2, 3.6)	
		Prevalence (%)	3.4 (9/262)		3.8 (9/239)	
	\geq 40 Years		N=262		N=237	
		Positive	6.1 (3/49) (1.6, 10.2)	6.5 (1.1, 38.0)	7.5 (4/53) (2.9, 10.7)	13.9 (1.6, 122)
		Negative	0.9 (2/213) (0.1, 2.0)		0.5 (1/184) (0.0, 1.8)	
		Prevalence (%)	1.9 (5/262)		2.1 (5/237)	

*74 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

NILM ≥ 30 Years Population (NILM Study): APTIMA HPV Assay Clinical Performance

In total, there were 11,644 women with NILM cytology results enrolled in the NILM Study. Of these, 773 women were withdrawn and excluded from analysis. The remaining 10,871 evaluable women were 30 years of age and older with NILM cytology results and APTIMA HPV Assay results. Of the 540 women with positive APTIMA HPV Assay results, 335 attended colposcopy. Of the 10,331 women with negative APTIMA HPV Assay results, 530 attended colposcopy. Twenty (20) women had ≥CIN2 and eleven (11) had ≥CIN3; 799 women had Normal/CIN1 histology; 46 women had undetermined disease status. The results of the APTIMA HPV Assay by the consensus histology review panel diagnosis are presented in the table below.

NILM ≥ 30 Years Population: Results of the APTIMA HPV Assay and Consensus Histology Review Panel Diagnosis

APTIMA HPV Assay Result*	HPV DNA Test	Consensus Histology Review Panel Diagnosis						Total
		Undetermined	Normal	CIN1	CIN2	CIN3	Cancer	
Positive	Positive	11	212	11	4	7	2	247
Positive	Negative	7	59	0	1	0	1	68
Positive	No Result**	3	16	1	0	0	0	20
Negative	Positive	10	170	8	2	1	0	191
Negative	Negative	15	313	9	1	0	0	338
Negative	No Result**	0	0	0	1	0	0	1
Total		46	770	29	9	8	3***	865

*All samples had final valid results (upon initial testing or after resolution of initial invalids per procedure).

**21 women with APTIMA HPV Assay results did not have HPV DNA test results primarily due to insufficient volume of the cytology specimen.

***Three women had adenocarcinoma in situ (AIS).

In total, 10,052 women had unverified (including undetermined) disease status. Because only randomly selected women with negative results for both the APTIMA HPV Assay and the FDA-approved HPV DNA test were referred to colposcopy, the proportion of women with unverified disease status was high in this group (96.6%). To adjust for this verification bias, a multiple imputation method was used to estimate the number of women with disease that would have been identified if all women had undergone colposcopy. Both verification-bias adjusted performance estimates and unadjusted performance estimates based on the 819 women with verified disease status are presented below.

NILM \geq 30 Years Population: Classification of Evaluable NILM Women by APTIMA HPV Assay and HPV DNA Test Results, Disease Status (\geq CIN2 and \geq CIN3), and Disease Verification Status

APTIMA HPV Assay Result*	HPV DNA Test	Total Women	Verified Disease Status: \geq CIN2		Verified Disease Status: \geq CIN3		Unverified Disease Status
			Diseased Women (\geq CIN2)	Non-Diseased Women ($<$ CIN2)	Diseased Women (\geq CIN3)	Non-Diseased Women ($<$ CIN3)	Women with Unknown Disease Status (% Unknown)
Positive	Positive	360	13	223	9	227	124 (34.4%)
Positive	Negative	150	2	59	1	60	89 (59.3%)
Positive	No Result**	30	0	17	0	17	13 (43.3%)
Negative	Positive	306	3	178	1	180	125 (40.8%)
Negative	Negative	9420	1	322	0	323	9097 (96.6%)
Negative	No Result**	605	1	0	0	1	604 (99.8%)
Total		10,871	20	799	11	808	10,052 (92.5%)

*All samples had final results (upon initial testing or after resolution of initial invalids per procedure).

**635 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

The adjusted prevalence of \geq CIN2 and \geq CIN3 in women with NILM cytology results were 0.9% and 0.4%, respectively. The adjusted absolute and relative risk estimates⁸ for detection of \geq CIN2 and \geq CIN3 are shown below.

NILM \geq 30 Years Population: Absolute and Relative Risks of \geq CIN2 and \geq CIN3 for Results of the APTIMA HPV Assay and an FDA-approved HPV DNA Test (Verification-Bias Adjusted Estimates)

Assay Result		APTIMA HPV Assay		HPV DNA test	
		Absolute Risk (95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Relative Risk (95% CI)
\geq CIN2	Positive	4.7 (2.9, 7.6)	8.1 (2.3, 28.1)	3.7 (2.3, 6.0)	7.3 (1.6, 33.4)
	Negative	0.6 (0.2, 1.9)		0.5 (0.1, 2.1)	
	Prevalence (%)		0.9		0.9
\geq CIN3	Positive	3.3 (1.4, 7.6)	34.5 (2.7, 443.3)	2.3 (1.3, 4.1)	21.0 (1.0, 423.4)
	Negative	0.1 (0.0, 1.6)		0.1 (0.0, 2.4)	
	Prevalence (%)		0.4		0.4

The adjusted relative risk of \geq CIN2 was 8.1 (95% CI: 2.3, 28.1), indicating that a woman who was APTIMA HPV Assay positive is 8.1 times as likely to have \geq CIN2 than a woman who is APTIMA HPV Assay negative. The adjusted relative risk of \geq CIN3 was 34.5 (95% CI: 2.7, 443.3). The unadjusted absolute and relative risk estimates for detection of \geq CIN2 and \geq CIN3 are shown overall and by age group in the tables below.

NILM \geq 30 Years Population: Absolute and Relative Risks of \geq CIN2 and \geq CIN3 for Results of the APTIMA HPV Assay and an FDA-approved HPV DNA Test (Unadjusted Estimates)

Assay Result		APTIMA HPV Assay N=819		HPV DNA test N=801*	
		Absolute Risk (95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Relative Risk (95% CI)
\geq CIN2	Positive	4.8 (15/314) (3.4, 5.8)	4.8 (1.8, 13.1)	3.8 (16/417) (2.9, 4.4)	4.9 (1.4, 16.7)
	Negative	1.0 (5/505) (0.4, 1.9)		0.8 (3/384) (0.2, 1.9)	
	Prevalence (%)	2.4 (20/819)		2.4 (19/801)	
\geq CIN3	Positive	3.2 (10/314) (2.2, 3.7)	16.1 (2.1, 125)	2.4 (10/417) (1.6, 2.7)	9.2 (1.2, 71.6)
	Negative	0.2 (1/505) (0.0, 0.9)		0.3 (1/384) (0.0, 1.1)	
	Prevalence (%)	1.3 (11/819)		1.4 (11/801)	

*18 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

NILM \geq 30 Years Population: Absolute and Relative Risks of \geq CIN2 and \geq CIN3 for Results of the APTIMA HPV Assay and an FDA-approved HPV DNA Test by Age Group (Unadjusted Estimates)

	Age	Assay Result	APTIMA HPV Assay N=819		HPV DNA test N=801*	
			Absolute Risk (95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Relative Risk (95% CI)
\geq CIN2	30 to 39 Years		N=384		N=377	
		Positive	4.8 (8/167) (2.1, 9.2)	10.4 (1.3, 82.3)	3.2 (7/216) (1.3, 6.6)	2.6 (0.5, 12.4)
		Negative	0.5 (1/217) (0.0, 2.5)		1.2 (2/161) (0.2, 4.4)	
		Prevalence (%)	2.3 (9/384)		2.4 (9/377)	

		N=435		N=424		
≥ 40 Years	Positive	4.8 (7/147) (1.9, 9.6)	3.4 (1.0, 11.5)	4.5 (9/201) (2.1, 8.3)	10.0 (1.3, 78.1)	
	Negative	1.4 (4/288) (0.4, 3.5)		0.4 (1/223) (0.0, 2.5)		
	Prevalence (%)	2.5 (11/435)		2.4 (10/424)		
≥CIN3	30 to 39 Years	N=384		N=377		
		Positive	3.0 (5/167) (1.0, 6.8)	6.5 (0.8, 55.1)	2.3 (5/216) (0.8, 5.3)	3.7 (0.4, 31.6)
		Negative	0.5 (1/217) (0.0, 2.5)		0.6 (1/161) (0.0, 3.4)	
	Prevalence (%)	1.6 (6/384)		1.6 (6/377)		
	≥ 40 Years	N=435		N=424		
		Positive	3.4 (5/147) (1.1, 7.8)	Not Calculable	2.5 (5/201) (0.8, 5.7)	Not Calculable
Negative		0.0 (0/288) (0.0, 1.3)	0.0 (0/223) (0.0, 1.6)			
Prevalence (%)	1.1 (5/435)		1.2 (5/424)			

*18 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

Adjusted clinical performance estimates of the APTIMA HPV Assay including sensitivity, specificity, PPV, and NPV for the detection of ≥CIN2 and ≥CIN3 are shown below, as are the estimates for the FDA-approved HPV DNA test.

NILM ≥ 30 Years Population: Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of ≥CIN2 and ≥CIN3 (Verification-Bias Adjusted Estimates)

	Performance	APTIMA HPV Assay		HPV DNA test	
		Estimate	(95% CI)	Estimate	(95% CI)
≥CIN2	Sensitivity (%)	31.0	(5.9, 56.1)	35.4	(3.8, 66.9)
	Specificity (%)	95.2	(94.8, 95.6)	93.7	(93.2, 94.2)
	PPV (%)	4.7	(2.9, 7.6)	3.7	(2.3, 6.0)
	NPV (%)	99.4	(98.1, 99.8)	99.5	(97.9, 99.9)
	Prevalence (%)	0.9		0.9	
≥CIN3	Sensitivity (%)	61.5	(14.0, 100)	56.4	(0.4, 100)
	Specificity (%)	95.2	(94.8, 95.6)	93.6	(93.1, 94.1)
	PPV (%)	3.3	(1.4, 7.6)	2.3	(1.3, 4.1)

NPV (%)	99.9	(98.4, 100)	99.9	(97.6, 100)
Prevalence (%)	0.4		0.4	

Unadjusted clinical performance estimates are shown in the table below. The APTIMA HPV Assay and the FDA-approved HPV DNA test had similar sensitivity, whereas specificity was significantly higher for the APTIMA HPV Assay (non-overlapping 95% CIs). Predictive value estimates of the APTIMA HPV Assay were clinically relevant and similar to the estimates for the FDA-approved HPV DNA test. NPVs were similar but for the detection of \geq CIN2, the PPV for the APTIMA HPV Assay was slightly higher than PPV for the FDA-approved HPV DNA test (4.7% vs 3.7%).

NILM \geq 30 Years Population: Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of \geq CIN2 and \geq CIN3 (Unadjusted Estimates)

	Performance	APTIMA HPV Assay N=819		HPV DNA test N=801*	
		Estimate	(95% CI)	Estimate	(95% CI)
\geq CIN2	Sensitivity (%)	75.0 (15/20)	(53.1, 88.8)	84.2 (16/19)	(62.4, 94.5)
	Specificity (%)	62.6 (500/799)	(59.2, 65.9)	48.7 (381/782)	(45.2, 52.2)
	PPV (%)	4.8 (15/314)	(3.4, 5.8)	3.8 (16/417)	(2.9, 4.4)
	NPV (%)	99.0 (500/505)	(98.1, 99.6)	99.2 (381/384)	(98.1, 99.8)
	Prevalence (%)	2.4 (20/819)		2.4 (19/801)	
\geq CIN3	Sensitivity (%)	90.9 (10/11)	(62.3, 98.4)	90.9 (10/11)	(62.3, 98.4)
	Specificity (%)	62.4 (504/808)	(59.0, 65.7)	48.5 (383/790)	(45.0, 52.0)
	PPV (%)	3.2 (10/314)	(2.2, 3.7)	2.4 (10/417)	(1.6, 2.7)
	NPV (%)	99.8 (504/505)	(99.1, 100)	99.7 (383/384)	(98.9, 100)
	Prevalence (%)	1.3 (11/819)		1.4 (11/801)	

*18 women with APTIMA HPV Assay results did not have HPV DNA Test results primarily due to insufficient volume of the cytology specimen.

While establishing clinical sensitivity and specificity requires completion of the 3-year follow-up, direct comparison of the APTIMA HPV Assay and the FDA-approved HPV DNA test demonstrates similar sensitivity and statistically significant improved specificity of the APTIMA HPV Assay over the FDA-approved HPV DNA test for detection of \geq CIN2 as shown by the ratios of true positive and false positive rates in the two tables below.

NILM \geq 30 Years Population: Ratio of True Positive Rates (APTIMA HPV Assay/ FDA-approved HPV DNA Test) for Women with \geq CIN2 (Unadjusted Estimates)

		HPV DNA Test		Total
		Positive	Negative	
APTIMA HPV Assay	Positive	13	2	15 (78.9%)
	Negative	3	1	4
	Total	16 (84.2%)	3	19
Ratio of True Positive Rates = 0.94 (15/16) (95% CI: 0.67, 1.20)				

NILM \geq 30 Years Population: Ratio of False Positive Rates (APTIMA HPV Assay/ FDA-approved HPV DNA Test) for Women with $<$ CIN2 (Unadjusted Estimates)

		HPV DNA Test		Total
		Positive	Negative	
APTIMA HPV Assay	Positive	223	59	282 (36.1%)
	Negative	178	322	500
	Total	401 (51.3%)	381	782
Ratio of False Positive Rates = 0.70 (282/401) (95% CI: 0.64, 0.77)				

3. Subgroup Analyses

The tables below present clinical performance for the APTIMA HPV Assay for the ASC-US population by testing site and collection device.

ASC-US ≥ 21 Years Population: Performance of the APTIMA HPV for Detection of ≥CIN2 by Testing Site

	Performance	APTIMA HPV Assay N=939	
		Estimate	(95% CI)
Testing Site 1		N=318	
	Sensitivity (%)	93.9 (31/33)	(80.4, 98.3)
	Specificity (%)	64.2 (183/285)	(58.5, 69.6)
	PPV (%)	23.3 (31/133)	(19.8, 26.7)
	NPV (%)	98.9 (183/185)	(96.7, 99.9)
	Prevalence (%)	10.4 (33/318)	
Testing Site 2		N=352	
	Sensitivity (%)	86.7 (26/30)	(70.3, 94.7)
	Specificity (%)	62.7 (202/322)	(57.3, 67.8)
	PPV (%)	17.8 (26/146)	(14.5, 20.7)
	NPV (%)	98.1 (202/206)	(95.8, 99.4)
	Prevalence (%)	8.5 (30/352)	
Testing Site 3		N=269	
	Sensitivity (%)	78.6 (22/28)	(60.5, 89.8)
	Specificity (%)	61.4 (148/241)	(55.1, 67.3)
	PPV (%)	19.1 (22/115)	(14.9, 23.0)
	NPV (%)	96.1 (148/154)	(93.0, 98.4)
	Prevalence (%)	10.4 (28/269)	

ASC-US ≥ 21 Years Population: Performance of the APTIMA HPV for Detection of ≥CIN2 by Collection Device

	Performance	APTIMA HPV Assay N=939	
		Estimate	(95% CI)
		N=386	
	Sensitivity (%)	83.3 (25/30)	(66.4, 92.7)

	Specificity (%)	61.8 (220/356)	(56.7, 66.7)
	PPV (%)	15.5 (25/161)	(12.5, 18.2)
	NPV (%)	97.8 (220/225)	(95.6, 99.2)
	Prevalence (%)	7.8 (30/386)	
Brush/ Spatula	N=530		
	Sensitivity (%)	87.7 (50/57)	(76.8, 93.9)
	Specificity (%)	62.6 (296/473)	(58.1, 66.8)
	PPV (%)	22.0 (50/227)	(19.3, 24.7)
	NPV (%)	97.7 (296/303)	(95.8, 99.0)
	Prevalence (%)	10.8 (57/530)	
Both Broom- like Device & Brush/ Spatula	N=23		
	Sensitivity (%)	100 (4/4)	(51.0, 100)
	Specificity (%)	89.5 (17/19)	(68.6, 97.1)
	PPV (%)	66.7 (4/6)	(36.2, 94.2)
	NPV (%)	100 (17/17)	(88.3, 100)
	Prevalence (%)	17.4 (4/23)	

APTIMA HPV Assay Agreement with a Composite Comparator

The analytical performance of the APTIMA HPV Assay was assessed against a composite comparator consisting of an FDA-approved HPV DNA test and a validated reverse transcription-polymerase chain reaction (RT-PCR) sequencing test specific for E6/E7 mRNA from the same 14 HR HPV types detected by the APTIMA HPV Assay. Sequencing was performed by an external commercial laboratory.

Cervical specimens collected from the ASC-US and NILM populations of the CLEAR trial were tested by the comparator assays and compared to the APTIMA HPV Assay results. In total, 434 samples were tested, with 217 from each of the ASC-US and NILM populations.

Women selected included approximately 150 randomly selected women with positive APTIMA HPV Assay results and <CIN2 disease, approximately 200 randomly selected women with negative APTIMA HPV Assay results and <CIN2 disease and all women identified with ≥CIN2 disease by consensus histology review at the time of sample selection (when about 80% of the trial enrollment was completed).

For the composite comparator analysis, samples were classified positive if the HPV DNA test and the E6/E7 RT-PCR sequencing test were both positive; negative if the HPV DNA test and the E6/E7 RT-PCR sequencing test were both negative; and indeterminate if the tests were discordant, or if one or both tests returned an invalid or indeterminate result.

Positive and negative percent agreements and associated 95% confidence intervals were calculated. Indeterminate results were not included in the agreement calculations. Results are presented for the ASC-US population (≥ 21 years) and the NILM population (≥ 30 years) in the tables below.

ASC-US ≥ 21 Years Population: APTIMA HPV Assay Agreement Results with a Composite Comparator (n=217)

		Composite Comparator			Total
		Positive	Negative	Indeterminate	
APTIMA HPV Assay	Positive	89	0	27	116
	Negative	2	86	13	101
	Total	91	86	40	217
Positive Percent Agreement: 97.8% (89/91) (95% CI: 92.3, 99.4)					
Negative Percent Agreement: 100.0% (86/86) (95% CI: 95.7, 100)					

NILM ≥ 30 Years Population: APTIMA HPV Assay Agreement Results with a Composite Comparator (n=217)

		Composite Comparator			Total
		Positive	Negative	Indeterminate	
APTIMA HPV Assay	Positive	55	15	46	116
	Negative	4	63	34	101
	Total	59	78	80	217
Positive Percent Agreement: 93.2% (55/59) (95% CI: 83.8, 97.3)					
Negative Percent Agreement: 80.8% (63/78) (95% CI: 70.7, 88.0)					

Expected Results: Prevalence of High-Risk HPV mRNA

The prevalence of high-risk HPV infection varies widely and is influenced by several factors, for which age is the greatest contributor. Many studies have investigated HPV prevalence as determined by the detection of HPV DNA, however few studies report

prevalence based on detection of HPV oncogenic mRNA. Women from a variety of clinical sites (n=18) representing a wide geographic distribution and a diverse population (10 states within the United States) were enrolled in a prospective clinical study known as the CLEAR trial. The prevalence of HPV mRNA-positive samples observed in the clinical trial was categorized overall, by age group, and by testing site. Results are shown below for the ASC-US and the negative for intraepithelial lesion or malignancy (NILM) populations.

	Positivity Rate % (x/n)	
	ASC-US Population (≥ 21 Years)	NILM Population (≥ 30 Years)
All	41.8 (400/958)	5.0 (540/10,871)
Age Group (years)		
21 to 29	60.3 (252/418)	N/A
30 to 39	36.8 (98/266)	6.9 (289/4199)
≥ 40	18.2 (50/274)	3.8 (251/6672)
Testing Site		
1	41.6 (134/322)	4.7 (172/3682)
2	41.4 (150/362)	5.2 (194/3702)
3	42.3 (116/274)	5.0 (174/3487)

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The database for this PMA included 12,896 patients age 21 and older. There were 19 enrolling (collection) sites and 3 APTIMA HPV Assay testing sites. One of the collection sites was excluded from the final analysis due to protocol violations (lack of data accountability, lack of proper source documentation, improper informed consenting and others). This excluded site will be called the EXC collection site in this section. Since 462 women were enrolled from the EXC collection site, this section provides a summary of the APTIMA HPV Assay performance including data from this site for transparency purposes.

ASC-US ≥ 21 Years Population (EXC Collection Site Included): APTIMA HPV Assay Clinical Performance

In the ASC-US Study, there were 939 evaluable women 21 years of age and older with ASC-US cytology results, APTIMA HPV Assay results, and conclusive disease status. At the EXC collection site there were an additional 134 evaluable women (142 women enrolled minus 5 who did not attend colposcopy and 3 that had insufficient volume for APTIMA HPV Assay). With the EXC collection site included there were 95 women with ≥CIN2 and 43 with ≥CIN3. Prevalences of ≥CIN2 and ≥CIN3 were 8.9% and 4.0%, respectively.

Including the EXC collection site, clinical performance estimates of the APTIMA HPV Assay including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of \geq CIN2 and \geq CIN3 based on evaluating all biopsies and including only directed biopsies are shown below, as are the estimates for the FDA-approved HPV DNA test.

ASC-US \geq 21 Years Population (EXC Collection Site Included): Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of \geq CIN2 and \geq CIN3

	Performance	APTIMA HPV Assay N=1073		HPV DNA Test N=991*	
		Estimate	(95% CI)	Estimate	(95% CI)
\geq CIN2	All Biopsies				
	Sensitivity (%)	86.3 (82/95)	(78.0, 91.8)	89.1 (82/92)	(81.1, 94.0)
	Specificity (%)	66.0 (645/978)	(62.9, 68.9)	59.4 (534/899)	(56.2, 62.6)
	PPV (%)	19.8 (82/415)	(17.8, 21.6)	18.3 (82/447)	(16.7, 19.9)
	NPV (%)	98.0 (645/658)	(96.9, 98.9)	98.2 (534/544)	(96.9, 99.0)
	Prevalence (%)	8.9 (95/1073)		9.3 (92/991)	
	Directed Biopsies**				
	Sensitivity (%)	93.3 (56/60)	(84.1, 97.4)	93.2 (55/59)	(83.8, 97.3)
	Specificity (%)	64.6 (652/1010)	(61.6, 67.4)	58.0 (539/930)	(54.8, 61.1)
	PPV (%)	13.5 (56/414)	(12.1, 14.8)	12.3 (55/446)	(11.0, 13.4)
	NPV (%)	99.4 (652/656)	(98.6, 99.8)	99.3 (539/543)	(98.3, 99.8)
	Prevalence (%)	5.6 (60/1070)		6.0 (59/989)	
\geq CIN3	All Biopsies				
	Sensitivity (%)	88.4 (38/43)	(75.5, 94.9)	92.5 (37/40)	(80.1, 97.4)
	Specificity (%)	63.4 (653/1030)	(60.4, 66.3)	56.9 (541/951)	(53.7, 60.0)
	PPV (%)	9.2 (38/415)	(7.8, 10.2)	8.3 (37/447)	(7.2, 9.1)
	NPV (%)	99.2 (653/658)	(98.4, 99.7)	99.4 (541/544)	(98.6, 99.9)
	Prevalence (%)	4.0 (43/1073)		4.0 (40/991)	
	Directed Biopsies**				
	Sensitivity (%)	93.1 (27/29)	(78.0, 98.1)	96.4 (27/28)	(82.3, 99.4)
	Specificity (%)	62.8 (654/1042)	(59.8, 65.6)	56.3 (542/962)	(53.2, 59.4)
	PPV (%)	6.5 (27/415)	(5.5, 7.2)	6.0 (27/447)	(5.2, 6.6)

NPV (%)	99.7 (654/656)	(99.0, 100)	99.8 (542/543)	(99.1, 100)
Prevalence (%)	2.7 (29/1071)		2.8 (28/990)	

**Consensus histology result was derived using only results from directed biopsies. Women with no directed biopsies reflect a normal colposcopy and are included in these analyses as non-diseased (<CIN2 or <CIN3, as appropriate). A consensus was not always reached when only directed biopsies were included.

NILM ≥ 30 Years Population (EXC Collection Site Included): APTIMA HPV Assay Clinical Performance

In the NILM Study, there were 10,871 evaluable women 30 years of age and older with NILM cytology results and APTIMA HPV Assay results. Of these, 865 attended colposcopy. At the EXC collection site there were an additional 309 evaluable women (320 enrolled minus 9 who had insufficient volume for the APTIMA HPV Assay and 2 who had no cytology sample for testing); 43 attended colposcopy. With the EXC collection site included, 20 women had ≥CIN2 and 11 had ≥CIN3; 841 women had Normal/CIN1 histology; 47 women had undetermined disease status.

Including the EXC collection site, the adjusted absolute and relative risk estimates for detection of ≥CIN2 and ≥CIN3 are shown below.

NILM ≥ 30 Years Population (EXC Collection Site Included): Absolute and Relative Risks of ≥CIN2 and ≥CIN3 for Results of the APTIMA HPV Assay and an FDA-approved HPV DNA Test (Verification-Bias Adjusted Estimates)

Assay Result		APTIMA HPV Assay		HPV DNA test	
		Absolute Risk (95% CI)	Relative Risk (95% CI)	Absolute Risk (95% CI)	Relative Risk (95% CI)
≥CIN2	Positive	4.6 (2.8, 7.5)	7.3 (1.9, 28.7)	3.8 (2.3, 6.1)	6.5 (1.5, 28.1)
	Negative	0.6 (0.2, 2.5)		0.6 (0.1, 2.4)	
	Prevalence (%)	1.0 (0.0, 2.2)		0.9 (0.0, 2.0)	
≥CIN3	Positive	3.3 (1.7, 6.2)	19.8 (0.6, 614.5)	2.5 (1.3, 4.7)	13.6 (0.4, 471.0)
	Negative	0.2 (0.0, 6.0)		0.2 (0.0, 6.6)	
	Prevalence (%)	1.1 (0.0, 7.8)		1.2 (0.0, 8.3)	

The adjusted clinical performance estimates of the APTIMA HPV Assay including sensitivity, specificity, PPV, and NPV for the detection of \geq CIN2 and \geq CIN3 are shown in the table below, as are the estimates for the FDA-approved HPV DNA test.

NILM \geq 30 Years Population (EXC Collection Site Included): Performance of the APTIMA HPV Assay and an FDA- approved HPV DNA Test for Detection of \geq CIN2 and \geq CIN3 (Verification-Bias Adjusted Estimates)

	Performance	APTIMA HPV Assay		HPV DNA test	
		Estimate	(95% CI)	Estimate	(95% CI)
\geq CIN2	Sensitivity (%)	29.4	(3.0, 57.7)	33.2	(3.1, 63.3)
	Specificity (%)	95.2	(94.8, 95.6)	93.5	(93.1, 94.0)
	PPV (%)	4.6	(2.8, 7.5)	3.8	(2.3, 6.1)
	NPV (%)	99.4	(97.5, 99.8)	99.4	(97.6, 99.9)
	Prevalence (%)	1.0 (0.0, 2.2)		0.9 (0.0, 2.0)	
\geq CIN3	Sensitivity (%)	52.2	(0, 100)	51.2	(0, 100)
	Specificity (%)	95.1	(94.5, 95.7)	93.4	(92.7, 94.2)
	PPV (%)	3.3	(1.7, 6.2)	2.5	(1.3, 4.7)
	NPV (%)	99.8	(94.0, 100)	99.8	(93.4, 100)
	Prevalence (%)	1.1 (0.0, 7.8)		1.2 (0.0, 8.3)	

Summary of Evaluation of the APTIMA HPV Assay in Canada

A study evaluating the performance of the APTIMA HPV Assay was conducted in Canadian women referred to colposcopy based on a newly diagnosed abnormal cytology or follow-up for a history of abnormal cytology.⁹ A total of 2416 women 21 years and older were enrolled from five tertiary care university sites representing five of the ten provinces in Canada. 1092 of these women were enrolled prior to inclusion of APTIMA testing. Of the remaining 1324 women, 15 had no histology results available and 32 had invalid APTIMA results.

Cervical specimens were collected immediately prior to colposcopy using the Cervex broom-type brush in PreservCyt solution. Cytology was performed first using the ThinPrep method in a central laboratory with results reported according to the 2001 Bethesda System. Residual cytology specimens were tested with both the APTIMA HPV Assay and an FDA-approved HPV DNA test. Participating obstetrics/gynecology specialists at the study sites performed colposcopy and, if warranted, cervical biopsy. An ECC biopsy was obtained if the transformation zone was not visible. Histology was read and reviewed independently at the respective study sites by pathologists who were masked to HPV results. If colposcopic examination did not warrant a biopsy to be taken then histology was considered normal.

In total, 1277 women had histology results and valid APTIMA HPV Assay and FDA-approved HPV DNA test results. Of these, 353 women aged 21 to 71 years had ASC-US cytology results and were evaluable for clinical performance. There were 159 women with normal histology, 101 with CIN1, 27 with CIN2, and 66 with CIN3+ histology. The APTIMA HPV Assay and the FDA-approved HPV DNA test positivity rates were 64.0% and 68.3%, respectively.

The tables below show the clinical performance estimates of the APTIMA HPV Assay including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) overall and by age group for the detection of \geq CIN2 and \geq CIN3, respectively, for both the APTIMA HPV Assay and the FDA-approved HPV DNA test in this non-screening population which has a higher prevalence of disease.

ASC-US \geq 21 Years Population (Canadian Study): Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of \geq CIN2 by Age Group

	Performance	APTIMA HPV Assay N=353		HPV DNA Test N=353	
		Estimate	(95% CI)	Estimate	(95% CI)
All	Sensitivity (%)	95.7 (89/93)	(89.5, 98.3)	92.5 (86/93)	(85.3, 96.3)
	Specificity (%)	47.3 (123/260)	(41.3, 53.4)	40.4 (105/260)	(34.6, 46.5)
	PPV (%)	39.4 (89/226)	(36.5, 42.5)	35.7 (86/241)	(33.0, 38.5)
	NPV (%)	96.9 (123/127)	(92.9, 99.0)	93.8 (105/112)	(88.5, 97.2)
	Prevalence (%)	26.4 (93/353)			
21 to 29 Years	N=192				
	Sensitivity (%)	95.9 (47/49)	(86.3, 98.9)	95.9 (47/49)	(86.3, 98.9)
	Specificity (%)	39.2 (56/143)	(31.5, 47.3)	29.4 (42/143)	(22.5, 37.3)
	PPV (%)	35.1 (47/134)	(31.6, 38.7)	31.8 (47/148)	(29.0, 34.6)
	NPV (%)	96.6 (56/58)	(89.6, 99.5)	95.5 (42/44)	(86.4, 99.3)
	Prevalence (%)	25.5 (49/192)			
30 to 39 Years	N=81				
	Sensitivity (%)	96.7 (29/30)	(83.3, 99.4)	93.3 (28/30)	(78.7, 98.2)
	Specificity (%)	47.1 (24/51)	(34.1, 60.5)	47.1 (24/51)	(34.1, 60.5)
	PPV (%)	51.8 (29/56)	(45.3, 59.5)	50.9 (28/55)	(43.6, 58.7)
	NPV (%)	96.0 (24/25)	(83.3, 99.9)	92.3 (24/26)	(78.7, 98.9)
	Prevalence (%)	37.0 (30/81)			
\geq 40 Years	N=80				
	Sensitivity (%)	92.9 (13/14)	(68.5, 98.7)	78.6 (11/14)	(52.4, 92.4)
	Specificity (%)	65.2 (43/66)	(53.1, 75.5)	59.1 (39/66)	(47.1, 70.1)
	PPV (%)	36.1 (13/36)	(27.3, 45.8)	29.0 (11/38)	(19.5, 37.7)
	NPV (%)	97.7 (43/44)	(90.7, 99.9)	92.9 (39/42)	(84.4, 98.2)
	Prevalence (%)	17.5 (14/80)			

ASC-US \geq 21 Years Population (Canadian Study): Performance of the APTIMA HPV Assay and an FDA-approved HPV DNA Test for Detection of \geq CIN3 by Age Group

	Performance	APTIMA HPV Assay N=353		HPV DNA Test N=353	
		Estimate	(95% CI)	Estimate	(95% CI)
All	Sensitivity (%)	95.5 (63/66)	(87.5, 98.4)	92.4 (61/66)	(83.5, 96.7)
	Specificity (%)	43.2 (124/287)	(37.6, 49.0)	37.3 (107/287)	(31.9, 43.0)
	PPV (%)	27.9 (63/226)	(25.5, 30.3)	25.3 (61/241)	(22.9, 27.5)
	NPV (%)	97.6 (124/127)	(94.0, 99.4)	95.5 (107/112)	(90.8, 98.4)
	Prevalence (%)	18.7 (66/353)			
21 to 29 Years	N=192				
	Sensitivity (%)	96.9 (31/32)	(84.3, 99.5)	96.9 (31/32)	(84.3, 99.5)
	Specificity (%)	35.6 (57/160)	(28.6, 43.3)	26.9 (43/160)	(20.6, 34.2)
	PPV (%)	23.1 (31/134)	(20.4, 25.7)	21.0 (31/148)	(18.6, 23.0)
	NPV (%)	98.3 (57/58)	(92.3, 99.9)	97.7 (43/44)	(89.8, 99.9)
	Prevalence (%)	16.7 (32/192)			
30 to 39 Years	N=81				
	Sensitivity (%)	95.5 (21/22)	(78.2, 99.2)	95.5 (21/22)	(78.2, 99.2)
	Specificity (%)	40.7 (24/59)	(29.1, 53.4)	42.4 (25/59)	(30.6, 55.1)
	PPV (%)	37.5 (21/56)	(31.8, 43.9)	38.2 (21/55)	(32.1, 44.9)
	NPV (%)	96.0 (24/25)	(83.2, 99.9)	96.2 (25/26)	(83.9, 99.9)
	Prevalence (%)	27.2 (22/81)			
\geq 40 Years	N=80				
	Sensitivity (%)	91.7 (11/12)	(64.6, 98.5)	75.0 (9/12)	(46.8, 91.1)
	Specificity (%)	63.2 (43/68)	(51.4, 73.7)	57.4 (39/68)	(45.5, 68.4)
	PPV (%)	30.6 (11/36)	(21.4, 39.1)	23.7 (9/38)	(14.4, 31.7)
	NPV (%)	97.7 (43/44)	(90.9, 99.9)	92.9 (39/42)	(84.6, 98.2)
Prevalence (%)	15.0 (12/80)				

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. Based on the results of the analytical and clinical studies, the APTIMA 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.

B. Effectiveness Conclusions

The effectiveness of the APTIMA HPV Assay has been demonstrated for use in conjunction with cervical cytology in the following patient populations. The test may be used in women 30 years and older to adjunctively screen to assess the presence or absence of high-risk human papillomavirus (HPV) types. Additionally, a reasonable determination of effectiveness of the APTIMA HPV Assay for use in screening women ≥ 21 years with ASC-US cervical cytology results has been demonstrated. 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.

C. Overall Conclusions

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

XIV. CDRH DECISION

CDRH issued an approval order on October 28, 2011. The final conditions of approval are described in the approval order.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820) on May 31, 2011.

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

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