SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: cobas® HPV Test

Device Procode: MAQ

Applicant's Name and Address: Roche Molecular Systems, Inc. (RMS)
4300 Hacienda Drive
PO Box 9002
Pleasanton, CA 94588-0900

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100020/S017

Date of FDA Notice of Approval: July 7, 2016

Priority Review: Not Applicable

The original PMA P100020 was approved on April 19, 2011. A second submission for a Panel Track supplement PMA P100020/S008 was approved on April 24, 2014. Based on those two submissions, this device is indicated for:

The cobas® HPV Test is a qualitative *in vitro* test for the detection of Human Papillomavirus in cervical specimens collected by a clinician using an endocervical brush/spatula and placed in the ThinPrep® Pap Test™ PreservCyt® Solution. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types HPV16 and HPV18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).

The cobas® HPV Test is indicated:

(a) To screen patients 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results to determine the need for referral to colposcopy.

(b) To be used in patients 21 years and older with ASC-US cervical cytology results, to detect high-risk HPV genotypes 16 and 18. This information, together with the 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 cobas® HPV Test can be used with cervical cytology to adjunctively screen to detect high risk HPV types. This information, together with the physician's assessment of screening history, other risk factors, and professional guidelines, may be used to guide patient management.
(d) In women 30 years and older, the cobas® HPV Test can be used to detect HPV genotypes 16 and 18. This information, together with the physician's assessment of screening history, other risk factors, and professional guidelines, may be used to guide patient management.
(e) In women 25 years and older, the cobas® HPV Test can be used as a first-line primary cervical cancer screening test to detect high risk HPV, including genotyping for 16 and 18. Women who test negative for high risk HPV types by the cobas® HPV Test 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 cobas® HPV Test should be referred to colposcopy. Women who test high risk HPV positive and 16/18 negative by the cobas® HPV Test (12 other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

The SSEDs to support these indications are available on the CDRH website and are incorporated by reference here:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020
http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100020S008b.pdf

The current supplement was submitted to expand the intended use for the cobas® HPV Test for indications a-d, above.

II. INDICATIONS FOR USE

The additional intend use for the cobas® HPV Test submitted under P100020/S017:

The cobas® HPV Test is a qualitative *in vitro* test for the detection of Human Papillomavirus in cervical specimens collected by a clinician using a cervical broom and placed in SurePath™ Preservative Fluid. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types HPV16 and HPV18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).

The cobas® HPV Test is indicated:
(a) To screen patients 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results to determine the need for referral to colposcopy.
(b) To be used in patients 21 years and older with ASC-US cervical cytology results, to detect high-risk HPV genotypes 16 and 18. This information, together with the 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 cobas® HPV Test can be used with cervical cytology to adjunctively screen to detect high risk HPV types. This information, together with the physician's assessment of screening history, other risk factors, and professional guidelines, may be used to guide patient management.

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

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the cobas® HPV Test labeling. A warning pertaining to the expanded indications for use highlights that the new specimen type must be pretreated with the cobas® Sample Prep Buffer prior to being tested on the assay. Also, the SurePath specimen is not approved for use in primary HPV screening with the cobas® HPV Test.

V. DEVICE DESCRIPTION

Aside from the new specimen type intended for use with the cobas® HPV Test, the device is unchanged from the original approved device. The device description can be found in the SSED for the original PMA on the CDRH website at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020

For specimens stored in SurePath™ Preservative Fluid, there is a new/additional step. Specimens must first be pre-treated with the cobas® Sample Prep Buffer (a.k.a. pretreatment buffer). That manual process must be completed prior to the DNA extraction and amplification in order to reverse formalin-induced cross-linking.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Although there are several other alternatives for the detection of cervical cancer precursors, this is the first FDA-approved HPV test which can be used with a cervical specimen stored in SurePath™ Preservative Fluid. Specimens collected in other collection media have been approved for the detection of high-risk HPV DNA or RNA and for the further differentiation of HPV 16 and 18 subtypes. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets expectations and lifestyle.

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

VII. MARKETING HISTORY

The cobas® HPV Test is marketed in the following countries for cervical cancer screening: Australia, Brazil, China, Indonesia, Japan, Mexico, Russia, Serbia, Singapore, Taiwan, Venezuela, and countries within the European Union. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

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 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 of the cobas® HPV Test

The clinical cutoff was previously established. A description of how the cutoff was established is provided in the SSED for the original PMA on the CDRH website at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020

2. Limit of Detection at the Clinical Cutoff

The Limit of Detection (LoD) at the clinical cutoff of high risk HPV genotypes HPV16, HPV18, and HPV31 for specimens collected in SurePath™ Preservative Fluid was determined for the cobas® HPV Test. The LoDs were assessed using 1) plasmids of HPV31, HPV16, and HPV18 in the background of pooled HPV negative patient specimens collected in SurePath™ Preservative Fluid and 2) HPV positive cell lines SiHa (HPV16) and HeLa (HPV18) in SurePath™ Preservative Fluid containing an HPV negative cell line (HCT-15) background. Plasmid and cell lines were diluted to concentrations below, above, and at the expected LoD levels. A minimum of 60 replicates were tested for each plasmid or cell line for each of 3 reagent lots. A total of

49 runs were performed in a period of 12 days using 3 instrument systems. The LoD at the clinical cutoff is the level of HPV DNA in the sample that has positive test results (above the clinical cutoff) at least 95% of the time. The table below contains the results from the reagent lot producing the most conservative (highest) LoD in the analyses; those LoDs appear in bold.

Table 1. The Limit of Detection Levels for HPV Types 31, 16, and 18 and Cell Lines SiHa (HPV16) and HeLa (HPV18) in SurePath™ Preservative Fluid

HPV Type	Concentration (copies or cells/mL)	Number of Positive/Tested	Mean CT	% Positives	95% Confidence Interval	
					Lower	Upper
31	600	60/60	37.0	100.0%	94.0%	100%
	300	**60/60**	**38.0**	**100.0%**	**94.0%**	**100%**
	150	54/60	39.1	90.0%	79.5%	96.2%
16	600	60/60	37.9	100.0%	94.0%	100%
	300	**60/60**	**39.0**	**100.0%**	**94.0%**	**100%**
	150	51/60	40.1	85.0%	73.4%	92.9
18	1,500	60/60	36.5	100.0%	94.0%	100%
	600	**60/60**	**37.9**	**100.0%**	**94.0%**	**100%**
	300	55/59*	38.9	93.2%	83.5%	98.1
SiHa (HPV16)	400	60/60	36.7	100.0%	94.6%	100%
	200	**60/60**	**37.8**	**100.0%**	**94.6%**	**100%**
	100	55/60	39.3	91.7%	81.6%	97.2
HeLa (HPV18)	80	60/60	37.0	100.0%	94.0%	100%
	40	**59/60**	**38.3**	**98.3%**	**91.1%**	**100%**
	20	43/60	39.6	71.7%	58.6%	82.5

*One sample was not processed due to sample pipetting error

3. Inclusivity Verification

To verify that the cobas® HPV Test is capable of accurately detecting all HPV high risk genotypes in specimens collected in SurePath™ Preservative Fluid, the LoD at the clinical cutoff was determined for genotypes 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Quantified plasmid stocks of each HPV genotype were diluted into a background of pooled HPV negative patient specimens collected in SurePath™ Preservative Fluid to concentrations below, above and at the expected LoD levels. Two SurePath™ Preservative Fluid reagent lots were used to produce a minimum of 24 replicates for each positive level with each lot of reagents. For each HPV type, the reported LoD was defined as the lowest testing concentration having a >95% positive hit rate. Table 2 below contains results from the reagent lot producing the most conservative (higher) LoD in the analysis.

Table 2. Summary of High Risk Genotype Limit Of Detection For cobas® 4800 HPV Genotype Inclusivity Study in SurePath™ Preservative Fluid

HPV DNA* Type	LoD (copies/mL)	Number of Positive/Tested	Mean CT	Hit Rate	95% Confidence Interval	
					Lower	Upper
33	600	24/24	37.5	100.0%	85.7%	100%
	300	**24/24**	**38.6**	**100.0%**	**85.7%**	**100%**
	150	22/24	39.4	91.7%	73.0%	99.0%
35	1200	22/24	37.9	100.0%	85.7%	100%
	600	**23/24**	**39.2**	**95.8%**	**78.8%**	**99%.8**
	300	13/24	40.1	54.2%	32.8%	74.%4
39	300	48/48**	37.2	100.0%	92.6%	100%
	150	**24/24**	**38.1**	**100.0%**	**85.7%**	**100%**
	80	23/24	39.1	95.8%	78.8%	99.8%
45	600	48/48**	36.7	100.0%	92.6%	100%
	300	**24/24**	**37.3**	**100.0%**	**85.7%**	**100%**
	150	22/24	37.9	91.7%	73.0%	99.0%
51	1200	24/24	37.5	100.0%	85.7%	100%
	600	**23/24**	**38.9**	**95.8%**	**78.8%**	**99.9%**
	300	19/24	39.5	79.2%	57.8%	92.9%
52	7200	48/48**	38.5	100.0%	92.6%	100%
	4800	**24/24**	**38.9**	**100.0%**	**85.7%**	**100%**
	2400	11/24	40.0	45.8%	25.6%	67.2%
56	2400	24/24	38.2	100.0%	85.7%	100%
	1200	**23/24**	**39.3**	**95.8%**	**78.8%**	**99.8%**
	600	5/24	40.5	20.8%	7.1%	42.2%
58	1200	48/48**	37.0	100.0%	92.6%	100%
	600	**24/24**	**38.3**	**100.0%**	**85.7%**	**100%**
	300	20/24	39.6	83.3%	62.6%	95.3%
59	1200	24/24	37.4	100.0%	85.7%	100%
	600	**24/24**	**38.5**	**100.0%**	**85.7%**	**100%**
	300	22/24	39.6	91.7%	73.0%	99.0%
66	2400	24/24	37.0	100.0%	85.7%	100%
	1200	**24/24**	**38.6**	**100.0%**	**85.7%**	**100%**
	600	16/24	39.8	66.7%	44.7%	84.4%

68	600	48/48**	37.2	100.0%	92.6%	100%
	300	**24/24**	**38.4**	**100.0%**	**85.7%**	**100%**
	150	19/24	39.5	79.2%	57.8%	92.9%
*The LoD of the cobas® HPV Test for HPV genotypes 16, 18 and 31 was determined as described in the other LoD-related table.						

4. Reproducibility

A 13-member panel made from both HPV16/18 cells lines pools consisting of clinical samples collected into SurePath™ Preservative Fluid was tested for reproducibility. Each panel member was tested for 15 days (5 days per kit lot), 3 replicates per run, at 3 testing sites. Two operators at each of the 3 sites performed 1 run per day for 5 days each on each of the 3 lots. A run was defined as 39 panel-member aliquots and 1 positive and 1 negative control.

Overall, 92 runs were performed to obtain 90 valid runs. One invalid run was due to an invalid positive control and one run was aborted by an operator (percent of invalid runs was 2.2% (2/92) with a 95% CI: (0.3%, 7.6%)). A total of 3,510 replicates were performed on the 13 panel members in the valid runs; 4 results were missing because samples were not processed due to pipetting error.

All valid test results were included in the analyses that reported the percentage of correct results. There was one false positive result in 270 measurements (percent of false positive results was 0.4%) performed on the negative panel members (pooled negative clinical sample). The data are presented in table below.

Percents of positive results for the positive panel members are presented below. With respect to sites, site 3 exhibited lower percent of agreement for the HPV16/18 cell lines and this trend can be attributed to operator 5, who had lower percent positive values in HPV 16/18 cell line panel members.

Analysis of variance of the Ct values from valid results performed on positive panel members yielded total CV (%) ranges of 1.7% to 5.8% across all panel members. The CV (%) ranged from 0.0% to 2.5% for the cell line samples and 0.0% to 5.6% for the pooled clinical samples.

Table 3. Results by Sample Type and Negative Panel Member for Lot, Site/Instrument, Operator and Day - SurePath

Panel Member	Ct SD	Ct CV %	Number Positive / Total Number Valid Results					
			Lot			Site/Instrument		
			ID	Negative /Valid	%	ID	Negative /Valid	%
Negative Background Cell Line	n/a	n/a	1	90/90	100.0	1	90/90	100.0
			2	89/89	100.0	2	89/89	100.0
			3	90/90	100.0	3	90/90	100.0
Negative Pooled Clinical Samples	n/a	n/a	1	90/90	100.0	1	89/90	98.9
			2	89/90	98.9	2	90/90	100.0
			3	90/90	100.0	3	90/90	100.0

Table 4. Results by Sample Type and Positive Panel Member for Lot and Site/Instrument - SurePath

				Number Positive / Total Number Valid Results					
Panel Member		**Ct SD**	**Ct CV %**	**Lot**			**Site/Instrument**		
				ID	**Positive /Valid**	**%**	**ID**	**Positive /Valid**	**%**
HPV 16/18 High Negative (~0.5xLoD)	HPV 16 High Negative	1.02	2.5	1	62/90	68.9	1	61/90	67.8
				2	62/90	68.9	2	82/90	91.1
				3	67/90	74.4	3	48/90	53.3
	HPV 18 High Negative	1.17	3.0	1	60/90	66.7	1	59/90	65.6
				2	68/90	75.6	2	80/90	88.9
				3	57/90	63.3	3	46/90	51.1
HPV 16/18 Weak Positive (~1xLoD)	HPV 16 Weak Positive	0.89	2.3	1	86/90	95.6	1	88/90	97.8
				2	86/88	97.7	2	89/89	100.0
				3	87/90	96.7	3	82/89	92.1
	HPV 18 Weak Positive	1.22	3.2	1	75/90	83.3	1	85/90	94.4
				2	75/88	85.2	2	88/89	98.9
				3	87/90	96.7	3	64/89	71.9
HPV 16/18 Positive (~3xLoD)	HPV 16 Positive	0.64	1.7	1	88/90	97.8	1	89/89	100.0
				2	89/89	100.0	2	90/90	100.0
				3	90/90	100.0	3	88/90	97.8
	HPV 18 Positive	0.61	1.7	1	89/90	98.9	1	89/89	100.0
				2	89/89	100.0	2	90/90	100.0
				3	90/90	100.0	3	89/90	98.9
	Pooled HPV 16 Moderate Positive (~1xLoD)	1.69	4.6	1	87/90	96.7	1	90/90	100.0
				2	90/90	100.0	2	90/90	100.0
				3	90/90	100.0	3	87/90	96.7
	Pooled HPV 16 Positive (~3xLoD)	2.02	5.8	1	90/90	100.0	1	90/90	100.0
				2	90/90	100.0	2	90/90	100.0
				3	90/90	100.0	3	90/90	100.0
	Pooled HPV 18 Moderate Positive (~1xLoD)	1.72	4.7	1	87/90	96.7	1	89/90	98.9
				2	90/90	100.0	2	90/90	100.0
				3	89/90	98.9	3	87/90	96.7

				Number Positive / Total Number Valid Results					
Panel Member		Ct SD	Ct CV %	Lot			Site/Instrument		
				ID	Positive /Valid	%	ID	Positive /Valid	%
	Pooled HPV 18 Positive (~3xLoD)	1.48	4.3	1	90/90	100.0	1	90/90	100.0
				2	90/90	100.0	2	90/90	100.0
				3	90/90	100.0	3	90/90	100.0
	Pooled HPV A Moderate Positive (~1xLoD)	1.09	2.9	1	87/90	96.7	1	90/90	100.0
				2	90/90	100.0	2	89/90	98.9
				3	89/90	98.9	3	87/90	96.7
	Pooled HPV A Positive (~3xLoD)	1.77	4.9	1	88/90	97.8	1	90/90	100.0
				2	90/90	100.0	2	90/90	100.0
				3	90/90	100.0	3	88/90	97.8
	Pooled HPV B Moderate Positive (~1xLoD)	1.72	4.6	1	85/90	94.4	1	87/90	96.7
				2	89/90	98.9	2	88/90	97.8
				3	88/90	97.8	3	87/90	96.7
	Pooled HPV B Positive (~3xLoD)	1.86	5.2	1	89/90	98.9	1	90/90	100.0
				2	90/90	100.0	2	90/90	100.0
				3	90/90	100.0	3	89/90	98.9

Table 5. Overall Mean, Standard Deviations, and Coefficients of Variation (%) for Cycle Threshold, Estimated from Valid Samples of Positive Sample Type Panel Members (SurePath)

			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]					
Sample Type	**N**	**Mean CT**	**Between-Lot**	**Between-Site/ Instrument**	**Between-Operator**	**Between-Day**	**Within-Run**	**Total**
HPV 16/18 High Negative (~0.5xLoD)								
HPV 16 High Negative	270	40.2	0.00, (0.00%)	0.38, (0.95%)	0.13, (0.32%)	0.49, (1.21%)	0.80, (1.99%)	2.5
HPV 18 High Negative	270	39.5	0.11, (0.28%)	0.50, (1.28%)	0.09, (0.23%)	0.38, (0.97%)	0.98, (2.48%)	3.0
HPV 16/18 Weak Positive (~1xLoD)								
HPV 16 Weak Positive	268	39.0	0.08, (0.21%)	0.41, (1.06%)	0.08, (0.19%)	0.43, (1.09%)	0.65, (1.67%)	2.3
HPV 18 Weak Positive	268	38.6	0.00, (0.00%)	0.59, (1.53%)	0.16, (0.41%)	0.59, (1.53%)	0.88, (2.27%)	3.2
HPV 16/18 Positive (~3xLoD)								
HPV 16 Positive	269	37.1	0.00, (0.00%)	0.27, (0.72%)	0.07, (0.19%)	0.46, (1.24%)	0.36, (0.96%)	1.7
HPV 18 Positive	269	36.2	0.03, (0.09%)	0.28, (0.76%)	0.15, (0.42%)	0.38, (1.06%)	0.36, (0.99%)	1.7
Pooled HPV 16 Moderate Positive (~1xLoD)	270	37.0	0.00, (0.00%)	0.00, (0.00%)	0.30, (0.80%)	0.68, (1.84%)	1.52, (4.11%)	4.6
Pooled HPV 16 Positive (~3xLoD)	270	34.9	0.35, (1.01%)	0.33, (0.93%)	0.12, (0.34%)	0.28, (0.81%)	1.94, (5.56%)	5.8
Pooled HPV 18 Moderate Positive (~1xLoD)	270	36.9	0.28, (0.76%)	0.00, (0.00%)	0.25, (0.68%)	0.73, (1.98%)	1.51, (4.10%)	4.7
Pooled HPV 18 Positive (~3xLoD)	270	34.7	0.14, (0.40%)	0.00, (0.00%)	0.00, (0.00%)	0.38, (1.09%)	1.43, (4.11%)	4.3

			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]					
Sample Type	**N**	**Mean CT**	**Between-Lot**	**Between-Site/ Instrument**	**Between-Operator**	**Between-Day**	**Within-Run**	**Total**
Pooled HPV A Moderate Positive (~1xLoD)	270	37.6	0.09, (0.23%)	0.23, (0.62%)	0.28, (0.74%)	0.24, (0.65%)	0.99, (2.64%)	2.9
Pooled HPV A Positive (~3xLoD)	270	36.6	0.00, (0.00%)	0.14, (0.38%)	0.00, (0.00%)	0.36, (0.98%)	1.73, (4.74%)	4.9
Pooled HPV B Moderate Positive (~1xLoD)	270	37.3	0.00, (0.00%)	0.00, (0.00%)	0.36, (0.95%)	0.00, (0.00%)	1.68, (4.51%)	4.6
Pooled HPV B Positive (~3xLoD)	270	35.6	0.00, (0.00%)	0.12, (0.33%)	0.00, (0.00%)	0.23, (0.64%)	1.85, (5.18%)	5.2

5. Precision

In-house Precision was examined using a panel composed of HPV positive clinical specimens collected in SurePath™ Preservative Fluid and HPV positive cell lines (SiHa and HeLa) diluted into pooled negative cervical specimens collected in SurePath™ Preservative Fluid. The precision panel was designed to include members below (<70% positivity rate), at (90% to 99% positivity rate) and above (>99% positivity rate) the Limit of Detection of the cobas® HPV Test. Panel members 2-9 were prepared with HPV positive cell lines (SiHa, HPV16; HeLa, HPV18) diluted at different levels into SurePath™ Preservative Fluid. Panel members 10-12 were prepared with high risk HPV positive specimens in SurePath™ Preservative Fluid pools (HPV16, HPV18, and HR positive) diluted into pooled HPV negative specimens in SurePath™ Preservative Fluid. Panel member 1 consisted of HPV negative specimen pool only.

A description of the precision panel, anticipated performance in % positivity rate and the actual study performance in % positivity rate are shown below. All panel members at and above the LoD yielded the anticipated positivity rates. Analysis of variance of the Ct values from valid tests performed on positive panel members yielded overall CV (%) ranges of 1.1% to 1.7% for the SiHa cell lines, 1.5% to 2.2% for the HeLa cell lines, and 3.7% to 8.5% for the pooled clinical samples.

Table 6. Summary of the Precision Panel and Hit Rates For cobas® HPV Precision Study in SurePath™ Preservative Fluid

Panel Number	HPV Target	Description	Anticipated Positivity Rate	N Positive	N Tested	% Hit Rate	95% CI	
							Lower	Upper
1	N/A	Pooled HPV negative specimen	0%	0	216	0	0.0	1.7
2	HPV16	SiHa cell line	90% — 95%	216	216	100	98.3	100.0
3	HPV18	HeLa cell line	90% — 95%	216	216	100	98.3	100.0
4	HPV16	SiHa cell line	95% — 99%	216	216	100	98.3	100.0
5	HPV18	HeLa cell line	95% — 99%	216	216	100	98.3	100.0
6*	HPV16 & HPV18	SiHa & HeLa cell lines	90% — 95%	216	216	100	98.3	100.0
6**	HPV16 & HPV18	SiHa & HeLa cell lines	90% — 95%	216	216	100	98.3	100.0
7	HPV16	SiHa cell line	< 70%	53	216	25	19.0	30.8
8	HPV18	HeLa cell line	< 70%	135	216	63	55.7	69.0
9 *	HPV16 & HPV18	SiHa & HeLa cell lines	< 70%	78	216	36	29.7	42.9
9 **	HPV16 & HPV18	SiHa & HeLa cell lines	< 70%	122	216	57	49.6	63.2
10	High Risk Channel 1	High Risk HPV positive specimen	90% — 95%	216	216	100	98.3	100.0
11	HPV16	High Risk HPV positive specimen	90% — 95%	216	216	100	98.3	100.0
12	HPV18	High Risk HPV positive specimen	90% — 95%	208	216	96	92.8	98.4

*Results shown from detection channel 2 (HPV16)

** Results shown from detection channel 3 (HPV18)

N/A = Not applicable

Table 7. Overall Mean, Standard Deviations, and Coefficients of Variation (%) for Cycle Threshold, Estimated from Valid Samples of Positive Sample Type Precision Panel Members in SurePath™ Preservative Fluid

			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]											
	Sample Type / Conc. (cells/mL)	Mean CT	Between-Lot		Between-Run/System		Between-Operator		Between-Day		Within-Run		Total	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
2	SiHa HPV16 (200/mL)	37.9	0.188	0.50%	0.000	0.00%	0.072	0.20%	0.000	0.00%	0.000	0.00%	0.513	1.40%
3	HeLa HPV18 (40/mL)	37.6	0.161	0.40%	0.071	0.20%	0.000	0.00%	0.000	0.00%	0.015	0.00%	0.59	1.60%
4	SiHa HPV16 (600/mL)	36.4	0.132	0.40%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.09	0.20%	0.343	0.90%
5	HeLa HPV18 (120/mL)	36.0	0.091	0.30%	0.056	0.20%	0.044	0.10%	0.000	0.00%	0.071	0.20%	0.392	1.10%
6*	SiHa HPV16 (200/mL)	37.9	0.023	0.10%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.073	0.20%	0.436	1.10%
6**	HeLa HPV18 (40/mL)	37.7	0.081	0.20%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.134	0.40%	0.604	1.60%
7	SiHa HPV16 (20/mL)	41.2	0.000	0.00%	0.092	0.20%	0.116	0.30%	0.000	0.00%	0.000	0.00%	0.979	2.40%

			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]											
8	HeLa HPV18 (8/mL)	39.8	0.125	0.30%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.000	0.00%	1.042	2.60%
9*	SiHa HPV16 (20/mL)	40.9	0.146	0.40%	0.000	0.00%	0.155	0.40%	0.000	0.00%	0.084	0.20%	0.987	2.40%
9**	HeLa HPV18 (8/mL)	39.9	0.195	0.50%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.000	0.00%	1.095	2.70%
10	Clinical High Risk channel 1 (N/A)	37.2	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.000	0.00%	1.135	3.10%
11	Clinical HPV16 (N/A)	36.7	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.119	0.30%	0.000	0.00%	1.772	4.80%
12	Clinical HPV18 (N/A)	36.9	0.151	0.40%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.128	0.30%	1.848	5.00%

*Results shown from detection channel 2 (HPV16)
** Results shown from detection channel 3 (HPV18)

6. Analytical Specificity

A panel of bacteria, fungi and viruses, including those commonly found in the female urogenital tract, as well as several Human papillomavirus types classified as low or undetermined risk were tested with the cobas® HPV Test to assess analytical specificity. The organisms listed below were spiked at high concentrations ($\geq 1x10^6$*units/reaction with the exception of *Chlamydia trachomatis* and *all viruses*, which were all tested at $1x10^5$*units/reaction) into HPV negative clinical matrix in SurePath™ Preservative Fluid and into HPV negative clinical matrix in SurePath™ Preservative Fluid spiked with HPV31, HPV16 and HPV18 plasmid DNA at 3 times the Limit of Detection. Results indicated that none of these organisms interfered with detection of HPV31, HPV16, and HPV18 or produced false positive results in the HPV negative specimen.

All bacteria were quantified as Colony Forming Units (CFU) except *Chlamydia trachomatis* as Elementary Bodies (EBs). All HPV genotypes were quantified as DNA copies. Adenovirus was quantified as Plaque Forming Units (PFU). CMV, EBV, HSV-1 and HSV-2 were quantified as Viral Particles (VP).

Table 8. Microorganisms Tested for Analytical Specificity in SurePath™ Preservative Fluid

Adenovirus 5	Epstein Barr Virus (EBV)	*Pseudomonas fluorescens*	HPV 30
Bacteroides caccae	*Escherichia coli*	*Staphylococcus aureus*	HPV 34
Bifidobacterium adolescentis	*Fusobacterium varium*	*Staphylococcus epidermidis*	HPV 53
Candida albicans	Herpes simplex virus 1 (HSV-1)	*Streptococcus agalactiae*	HPV 67
Chlamydia trachomatis	Herpes simplex virus 2 (HSV-2)	*Streptococcus faecalis*	HPV 69
Clostridium beijerinckii	*Klebsiella pneumoniae ss ozaenae*	*Streptococcus pyogenea*	HPV 70
Corynebacterium glutamicum	*Lactobacillus acidophilus*	*Trichomonas vaginalis*	HPV 73
Cytomegalovirus (CMV)	*Neisseria gonorrhea*	HPV 6	HPV 82
Enterobacter aerogenes	*Peptostreptococcus anaerobius*	HPV 11	HPV 85
Enterococcus faecium	*Proteus mirabilis*	HPV 26	

7. Interfering Substances

Contrived specimens were used to assess the effects of endogenous and exogenous interfering substances that could potentially be present in cervical specimens. The concentrations of endogenous and exogenous substances tested represent conditions that could occur during specimen collection.

HPV negative clinical specimens were combined into pools which were then used to prepare HPV positive and HPV negative samples. HPV positive samples were prepared by spiking a portion of the negative pool with HPV plasmids (HPV31, HPV16 and HPV18) to a target level of approximately 3-fold the Limit of Detection. Twenty samples were tested with and without the addition of interfering endogenous substances. Whole blood was tested at concentrations of 0, 2, 4, 6, and 8% v/v. Peripheral blood mononuclear cells (PBMC) interference was assessed at concentrations 0, 10^4, 10^5, and 10^6 cells/mL. Cervical mucus was introduced into samples by immersing individual cervical cleaning swabs into corresponding HPV negative or positive test samples to test. No interference was seen in mucus or in clinically relevant levels for PBMC. Whole blood showed no interference when present in visually detectable amounts of up to 2% in SurePath samples.

Table 9. Interference Testing Results with Endogenous Interferents

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

A total of 18 over-the-counter (OTC) feminine hygiene and contraceptive products were tested as potential interfering substances. Each OTC product was added to the designated HPV positive or negative test sample. Both the positive and the negative test samples were tested in triplicate with and without the presence of the exogenous product within 24 hours of the sample preparation.

With the exception of Replens, none of the other OTC substances inhibited the test reaction. The observed interference appears to be unique to the SurePath Preservative Fluid sample since interference was not observed with the PreservCyt samples (P100020).

The types of interferents tested and performance observations are presented in the table below.

Table 10. Interference Testing Results with Exogenous Interferents

Product Name	Collection Medium	Active Ingredients	Interference Observed
Azo-Standard	SurePath™	Phenazopyridine Hydrochloride	None
Vaginal Contraceptive Foam	SurePath™	Nonoxynol-9	None
Clotrimazole 7	SurePath™	Clotrimazole	None
Gyne-Lotrimin 7	SurePath™	Clotrimazole	None
Gynecort	SurePath™	Hydrocortisone	None
Vagisil Satin	SurePath™	Hydrocortisone	None
Vagi-Gard (Douche)	SurePath™	Povidone-iodine	None
Miconazole	SurePath™	Miconazole nitrate	None
Monistat 3 Cream	SurePath™	Miconazole nitrate	None
Vagistat 1	SurePath™	Tiocanazole	None
VH essentials Medicated Cream	SurePath™	Benzocaine	None
Vagicaine Anti-Itch Cream	SurePath™	Benzocaine	None
Yeast Gard	SurePath™	Pulsatilla, Candida Parapsilosis, Candida albicans	None
Norforms	SurePath™	PEG-32,PEG-18, Peg-20 stearate	None
KY Jelly	SurePath™	Hydroxyethylcellulose, Chlorhexidine Gluconate	None
Vagisil Moisturizer	SurePath™	DMDM Hydantoin, Diazolidinyl urea	None
Replens	SurePath™	Polycarbophil	Yes*
Vagi-Gard (Lube Gel)	SurePath™	Glucano Delta Lactone, Chlorhexidine Gluconate	None

*Addition of 15 mg to the test sample produced false negative results.

8. Reagent Stability

Most of the reagent stability studies were previously established. A description of the studies is provided in in the SSED for the original PMA on the CDRH website at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020.

Additionally, specimens collected in SurePath require pretreatment with the cobas® Sample Prep Buffer prior to testing on the cobas® HPV test. The corresponding shelf

life and storage temperature, as supported by the results of stability studies is a shelf life of 24 months when stored at 15-30°C.

9. Sample Handling and Collection

Cervical specimens should be collected in SurePath Preservative Fluid, the SurePath container, using an endocervical broom.

Specimen stability studies demonstrated that for the cobas® HPV test, cervical specimens can be stored 2-8°C in SurePath for up to 6 months or at 15-30°C for up to 4 weeks after the date of collection provided that the SurePath™ Preservative Fluid matrix-induced crosslinks are reversed through treatment with the cobas® Sample Prep Buffer prior to HPV testing.

SurePath specimens treated with the cobas® Sample Prep Buffer can be stored at 2-30°C for up to 4 weeks prior to HPV testing on the cobas® 4800 System.

As noted in the labeling, samples not treated with the cobas® Sample Prep Buffer will likely provide false negative results.

10. Cross-Contamination Study

Cross-contamination was examined using one cobas® 4800 system. HPV positive and negative samples were process in a checkerboard configuration. HPV positive samples [(SP+)] were prepared by adding cultured CaSki cells [HPV16 positive, manufactured and quantified by Roche Culture Collection (RMSCC)] to SurePath™ Preservative Fluid to generate a signal which covers 95% or more of the results found in specimens of diseased patients in the intended use population. The HPV negative samples were prepared by spiking HCT-15 cells [manufactured and quantified by Roche Culture Collection (RMSCC)] at 50,000 cells/mL into SurePath™ Preservative Fluid.

Seven runs were performed on one cobas® 4800 system. The samples were processed to reverse formalin-induced cross-links through heating in the presence of a nucleophilic reagent. Prior to the checkerboard runs, a negative run containing SurePath™ Preservative Fluid only, was performed to verify that the system was free of contamination. The subsequent six runs contained both negative HPV samples and high positive HPV samples in a checkerboard configuration. Of the six runs that examined the HPV high positive and negative checkerboard configuration, 1 out of 143 HPV negative samples showed positive results in channel 2, leading to a cross-contamination rate of 0.7% with 95% CI: 0.1% to 3.9%. There were no invalid runs or test results observed. In the study, the percent of negative samples with Ct values (results were negative but HPV below the cutoff was detected) increased by 7.7% (95% CI: 3.9% to 13.4%).

A second study was conducted to assess the rate of sample-to-sample cross-contamination events during routine processing of SurePath™ Preservative Fluid

specimens on the BD PrepMate processor when using the cobas® HPV Test. Cross-contamination was examined by processing HPV negative and HPV high positive SurePath™ samples in alternating order on the BD PrepMate processor. The HPV negative samples were prepared by spiking HCT-15 cells [manufactured and quantified by Roche Culture Collection (RMSCC)] at 50,000 cells/mL into SurePath™ Preservative Fluid. HPV positive samples were prepared by adding cultured CaSki cells [HPV16 positive, manufactured and quantified by Roche Culture Collection (RMSCC)] to the HPV negative samples in SurePath™ Preservative Fluid to generate a signal which covers 95% or more of the results found in specimens of diseased patients in the intended use population. Prior to testing, 24 HPV negative samples were processed in 2 runs on the BD PrepMate processor. Immediately following these runs, a total of 72 HPV high positive and 72 HPV negative samples were process in an alternating pattern in 12 individual runs, each containing 12 vials of samples. After the runs were completed, 12 additional negative samples were processed in a single BD PrepMate processor. Processed samples were subsequently tested for HPV on a single cobas® 4800 system using the cobas® HPV Test. A cross-contamination rate of 1.4% (1 out of 71) with 95% CI: 0.2% to 7.6% was noted with SurePath™ specimens on the BD PrepMate.

B. Animal Studies

Not applicable

C. Additional Studies

Not applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant conducted a clinical study to establish a reasonable assurance of safety and effectiveness for the new intended use/indication for use for the cobas® HPV Test in the U.S. 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

Patients were enrolled between April 2012 and August 2015. The dataset for this PMA supplement included 952 patients evaluated for the new intended use/indication for use. There were two main collection sites (comprised of 21 clinics) and three testing sites.

A multi-center prospective study was conducted to evaluate the performance of the cobas® HPV test using specimens collected in SurePath Preservative Fluid™ as a triage test to stratify women with ASC-US cytology for colposcopy. Women ≥21 years presenting for routine cervical cancer screening had 2 cervical samples taken, the first in SurePath Preservative Fluid™ and the second in specimen transport medium (STM) as part of the standard of care. Women were enrolled at 2 main collection sites, comprised of 21 clinics, during April 2012 and August 2015 and tested at 3 testing sites. Cytology samples were classified according to the criteria of the 2001 Bethesda System. Those

women who had ASC-US cytology results on specimens collected in SurePath were invited to enroll in the study. A total of 952 subjects met the inclusion/exclusion criteria. After informed consent was obtained, demographic and gynecologic history information was recorded. Cobas® HPV testing was performed using pre-cytology aliquots (also referred to below as pre-aliquot, or pre-quot) and post-cytology aliquots (post-aliquot, or post-quot) of cervical specimens collected in SurePath Preservative Fluid™. The second sample in STM collected from all subjects with ASC-US Pap test results was tested with an FDA-approved test according to the manufacturer's instructions.

1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria:
a. Females age ≥21 years of age
b. ASC-US cervical cytology result from routine cervical cancer screening
c. Intact cervix
d. Willing and able to undergo colposcopy with biopsy, and/or endocervical curettage (ECC) ≤12 weeks (≤84 days) from cervical sample collection
e. Written informed consent provided by the subject.

Exclusion Criteria:
Subjects were excluded from enrollment if *any* of the following criteria were met:
a. Incomplete informed consent (lacking signature of study subject OR signature of appropriate consenting study personnel, i.e., either the principal investigator or someone to whom the principal investigator has appropriately delegated consenting authority)
b. Known pregnancy at colposcopy visit
c. Subject had been notified of the HPV test performed on her samples from the initial visit.
d. Cytology result of ASC, could not rule out high-grade lesion.
e. Any medical condition that, in the opinion of the investigator, would result in increased risk of bleeding at biopsy
f. Known history of ablative or excisional therapy (e.g., LEEP, cryotherapy, cone biopsy) to the cervix in the 12 months before enrollment; women who have had ablative or excisional treatment and who had not been returned to routine cervical cancer screening were excluded.
g. Hysterectomy (including supracervical)
h. Current or planned participation in any clinical trial for treatment of HPV infection

2. Clinical Endpoints

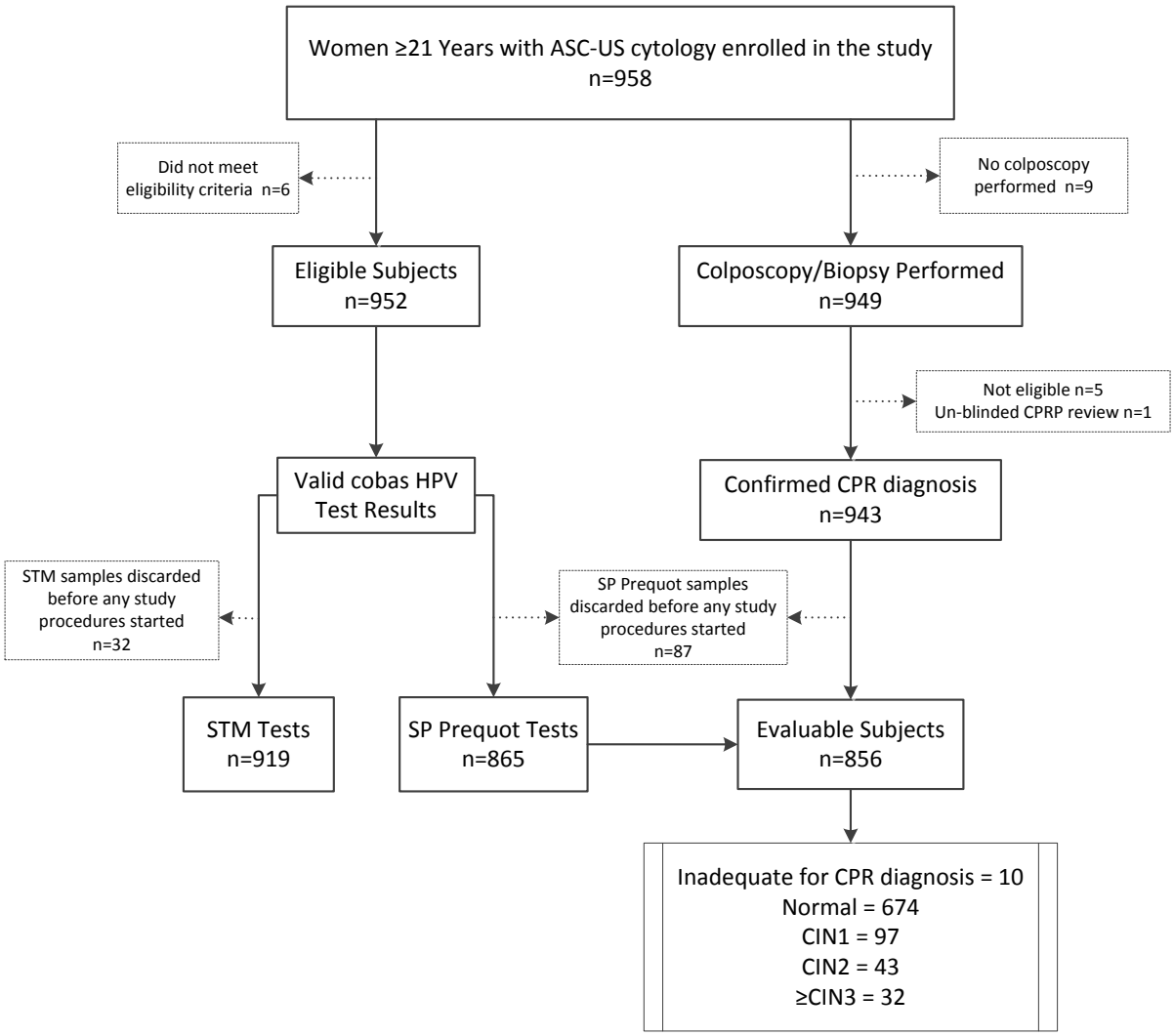
All women with ASC-US cytology results, who agreed to participate in the study, were referred to colposcopy within 12 weeks of the enrollment visit independent of their HPV status. To avoid bias, health care providers, study participants, and colposcopists remained blinded to all HPV results until after colposcopy. Colposcopy was conducted per protocol that required all visible cervical lesions to be biopsied; in those cases where no lesions were visible, a single random biopsy was taken at the squamocolumnar

junction. An endocervical curettage (ECC) was performed in all patients in whom the squamocolumnar junction was not visualized. All biopsies were examined by a Central Pathology Review Panel (CPRP) consisting of three expert pathologists, and discordant results were adjudicated according to a pre-defined protocol. For all analyses, the clinical performance of the cobas® HPV Test was measured against CPRP histology results, with ≥CIN2 and ≥CIN3 disease endpoints, respectively. The clinical performance below is presented for the pre-aliquot and post-aliquot specimens.

B. Accountability of PMA Cohort

A total of 952 subjects out of 958 subjects met the study eligibility criteria. Of 952 eligible women, 87 pre-quot samples were discarded before any testing with the cobas® HPV Test started; 865 had valid cobas® HPV Test result. The percent of invalid cobas® HPV Test results when test results are reported as positive and negative results was 0.0% (0/865) with 95% CI: 0.0% to 0.4%.

Of the 865 subjects with valid results, colposcopy was performed for 857 women; the histology review for 1 woman did not follow the protocol, therefore she was excluded from the study results analysis. The flow of ASC-US ≥21 subjects is shown in the figure below.



C. Study Population Demographics and Baseline Parameters

The demographics of the study population shown below are typical for a cervical cancer screening study performed in the U.S.

Table 11. Summary of Demographic Characteristics for the Evaluable Screening Population

Characteristics	Statistic	Evaluable Subjects n = 856
Age (Years)	Mean	35.4
	SD	11.5
	Median	32.0
	(Min, Max)	(21,75)

Characteristics	Statistic	Evaluable Subjects n = 856
Age Group (Years)		
21-24	n (%)	127 (14.8)
25-29	n (%)	227 (26.5)
30-39	n (%)	235 (27.5)
40-49	n (%)	142 (16.6)
≥50	n (%)	125 (14.6)
Race		
White	n (%)	614 (71.7)
American Indian or Alaskan Native	n (%)	9 (1.1)
Black or African American	n (%)	41 (4.8)
Asian	n (%)	90 (10.5)
Native Hawaiian or Other Pacific Islander	n (%)	9 (1.1)
Other	n (%)	65 (7.6)
Multiple Race	n (%)	27 (3.2)
Missing*	n (%)	1 (0.1)
Ethnicity		
Hispanic or Latino	n (%)	355 (41.5)
Not Hispanic or Latino	n (%)	499 (58.3)
Missing	n (%)	2 (0.2)
Education		
Elementary	n (%)	8 (.9)
High School (or GED)	n (%)	140 (16.4)
Vocational/Some College	n (%)	279 (32.6)
College Degree	n (%)	308 (36.0)
Some Graduate Work	n (%)	29 (3.4)
Graduate Degree (Master's or Higher)	n (%)	92 (10.7)
* Missing refers to “Not Reported” or “Unknown”		

D. Safety and Effectiveness Results

1. Safety Results

As an *in vitro* diagnostic test, the cobas® HPV Test involves sampling cells from the cervix using an endocervical 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).

False positive and false negative results are discussed in Section VIII. There were no adverse effects of the device reported during the clinical study.

2. Effectiveness Results

The analysis of effectiveness was based on the following data. Study results were determined for both a pre-aliquot and a post-aliquot sample.

Pre-Aliquot Data

Performance Characteristic in the ASC-US Population in Samples Collected in SurePath (≥ 21 Years)

The table below displays a summary of the CPRP diagnosis stratified by the cobas® HPV Test results (positive and negative) for 856 women. The histology results are undetermined, normal, cervical intraepithelial neoplasia (CIN) as CIN1, CIN2 or CIN3 or worse.

Table 12. Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis – SurePath

	Central Pathology Review Panel Diagnosis					
cobas® HPV Test Result	**Undetermined**	**Normal**	**CIN1**	**CIN2**	**≥CIN3**	**Total**
Positive	3	264	64	34	28	393
Negative	7	410	33	9	4	463
Total	10	674	97	43	32	856

Ten women had undetermined histology results which led to 846 women being included in the clinical performance estimates analysis; 576 non-vaccinated women and 270 vaccinated women were included in the analyses below.

Performance of the cobas® HPV Test in the ASC-US Population (≥ 21 Years) – Non-Vaccinated Subjects.

A total of 576 non-vaccinated subjects with ASC-US cytology completed the colposcopy procedures and had valid cobas® HPV results using the pre-aliquot specimen. The results

of the cobas® HPV Test reported as (HR HPV) Positive or (HR HPV) Negative together with the CPR diagnosis are presented below.

Table 13. Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis - SurePath - Non-Vacccinated Subjects

		CPRP Diagnosis – all biopsies				
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Positive	179	37	17	15	2	250
Negative	296	24	4[a]	2[b]	0	326
Total	475	61	21	17	2	576

[a] 3 CIN2 cases were FDA approved test negative and sequence negative; and 1 CIN2 case was FDA approved test positive and sequence negative.
[b] 1 CIN3 case was FDA approved test positive and sequence negative; and 1 CIN3 case was FDA approved test negative and sequence negative.

Percent of Invalid cobas® HPV Test results was 0.0% (0/576) with 95% CI: 0.0% to 0.7%.

Performance of the cobas® HPV Test in detecting cervical disease (≥ CIN2 and ≥ CIN3) is presented in the table below.

The sensitivity and the specificity of the test for detecting ≥ CIN2 histology were 85.0% ((34/40) with 95%: 70.9% to 92.9%) and 59.7% ((320/536) with 95%: 55.5% to 63.8%), respectively. The positive likelihood ratio (PLR) was estimated as 2.1, which implies a positive cobas® HPV Test results in 2.1 time more likely in subjects with ≥ CIN2 than in subjects with < CIN2. The negative likelihood ratio (NLR) was estimated as 0.25, which implies that a negative cobas® HPV Test results is 4 (1/0.25) times more likely in subjects with <CIN2 than in subjects with ≥ CIN2.

The sensitivity and the specificity of the test for detecting ≥ CIN3 histology were 89.5% ((17/19) with 95%: 68.6% to 97.1%) and 58.2% ((324/557) with 95%: 54.0% to 62.2%), respectively.

Table 14. Performance of the cobas® HPV Test in Detecting ≥ CIN2 and ≥ CIN3

Disease Endpoint		**cobas® HPV test**		**FDA approved test with STM**	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN2	**Sensitivity (%)**	85.0% (34/40)	(70.9, 92.9)	81.8 (36/44)	(68.0, 90.5)
	Specificity (%)	59.7% (320/536)	(55.5, 63.8)	58.9% (355/603)	(54.9, 62.7)
	PPV (%)	13.6% (34/250)	(11.4, 15.5)	12.7% (36/284)	(10.6, 14.4)
	NPV (%)	98.2% (320/326)	(96.5, 99.1)	97.8% (355/363)	(96.2, 98.9)

Disease Endpoint		cobas® HPV test		FDA approved test with STM	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
	PLR	2.1	(1.7, 2.5)	2.0	(1.6, 2.3)
	NLR	0.25	(0.12, 0.49)	0.31	(0.15, 0.55)
	Prevalence (%)	6.9% (40/576)		6.8% (44/647)	
≥CIN3	**Sensitivity (%)**	89.5% (17/19)	(68.6, 97.1)	90.5% (19/21)	(71.1, 97.4)
	Specificity (%)	58.2% (324/557)	(54.0, 62.2)	57.7% (361/626)	(53.8, 61.5)
	PPV (%)	6.8% (17/250)	(5.2, 7.8)	6.7% (19/284)	(5.3, 7.5)
	NPV (%)	99.4% (324/326)	(98.1, 99.9)	99.4% (361/363)	(98.3, 99.9)
	PLR	2.1	(1.6, 2.5)	2.1	(1.7, 2.4)
	NLR	0.18	(0.04, 0.56)	0.17	(0.03, 0.52)
	Prevalence (%)	3.3% (19/576)		3.2% (21/647)	

Note: PPV = Positive Predictive Value; NPV = Negative Predictive Value.
PLR = Positive Likelihood Ratio; NLR = Negative Likelihood Ratio.

In non-vaccinated population, for the women with negative results by the cobas® HPV Test, risk of ≥ CIN2 and ≥ CIN3 were 1.8% and 0.6%, respectively.

Performance of an FDA approved test in detecting cervical disease (≥ CIN2 and ≥ CIN3) is also presented in the table above. The sensitivity and the specificity of the test for detecting ≥ CIN2 histology were 81.8% (36/44) with 95%: (68.0% to 90.5%) and 58.9% (355/603) with 95%: (54.9% to 62.7%), respectively. The sensitivity and the specificity of the test for detecting ≥ CIN3 histology were 90.5% (19/21) with 95%: (71.1% to 97.4%) and 57.7% (361/626) with 95%: (53.8% to 61.5%), respectively.

Table below displays a summary of the CPRP diagnosis by redefining disease status based on the lesion directed biopsies; therefore, subjects without lesions would have had random biopsies and would be defined as non-diseased.

Table 15.Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis for the Direct Biopsy in Non-vaccinated ASC-US Population (≥ 21 Years) – SurePath

cobas® HPV Test Result	No Lesion	CPRP Diagnosis from lesion					
		Normal	CIN1	CIN2	CIN3	Cancer	Total
Positive	122	81	23	12	11	1	250
Negative	250	65	8	2[a]	1[b]	0	326
Total	372	146	31	14	12	1	576

[a] 2 CIN2 cases were FDA approved test negative and sequence negative.
[b] 1 CIN3 case was FDA approved test positive and sequence negative.

The table below presents the performance of the cobas® HPV Test and the performance of the FDA approved HPV Test in detecting ≥CIN2 and ≥CIN3 by redefining disease status in subjects who had random biopsies as non-diseased. Under this modified definition of disease the sensitivity of detecting ≥CIN2 was 88.9% (24/27) with 95% CI = 71.9% to 96.1% for the cobas® HPV Test and 90.3% (28/31) with 95% CI = 75.1% to 96.7% for the FDA approved HPV Test. The specificity for detecting ≥CIN2 was 58.8% (323/549) with 95% CI = 54.7% to 62.9% for the cobas® HPV Test and 58.4% (360/616) with 95% CI=54.5% to 62.3% for the FDA approved HPV Test.

Under this modified definition of disease the sensitivity of detecting ≥CIN3 was 92.3% (12/13) with 95% CI = 66.7% to 98.6% for the cobas® HPV Test for and 93.3% (14/15) with 95% CI = 70.2% to 98.8% for the FDA approved HPV Test. The specificity for detecting ≥CIN3 was 57.7% (325/563) with 95% CI = 53.6% to 61.7% for the cobas® HPV Test and 57.3% (362/632) (95% CI=53.4% to 61.1%) for the FDA approved HPV Test.

Table 16. Performance of the cobas® HPV Test Results Considering Non-vaccinated Subjects Without Lesions as Non-Diseased

Disease Endpoint		cobas® HPV test		FDA approved test with STM	
	Performance	Point Estimate	95% CI	Point Estimate	95% CI
≥CIN2	Sensitivity (%)	88.9% (24/27)	(71.9, 96.1)	90.3% (28/31)	(75.1, 96.7)
	Specificity (%)	58.8% (323/549)	(54.7, 62.9)	58.4% (360/616)	(54.5, 62.3)
	PPV (%)	9.6% (24/250)	(7.8, 10.9)	9.9% (28/284)	(8.2, 11.0)
	NPV (%)	99.1% (323/326)	(97.7, 99.7)	99.2% (316/363)	(97.9, 99.8)
	PLR	2.2	(1.7, 2.5)	2.2	(1.8, 2.5)
	NLR	0.19	(0.06, 0.48)	0.17	(0.05, 0.443)
	Prevalence (%)	4.7% (27/576)		4.8% (31/647)	

Disease Endpoint		cobas® HPV test		FDA approved test with STM	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN3	**Sensitivity (%)**	92.3% (12/13)	(66.7, 98.6)	93.3% (14/15)	(70.2, 98.8)
	Specificity (%)	57.7% (325/563)	(53.6, 61.7)	57.3% (362/632)	(53.4, 61.1)
	PPV (%)	4.8% (12/250)	(3.5, 5.4)	4.9% (14/284)	(3.7, 5.5)
	NPV (%)	99.7% (325/326)	(98.6, 99.9)	99.7% (362/363)	(98.7, 99.9)
	PLR	2.2	(1.6, 2.5)	2.2	(1.6, 2.5)
	NLR	0.13	(0.01, 0.60)	0.12	(0.01, 0.54)
	Prevalence (%)	2.3% (13/576)		2.3% (15/647)	

The performance of the cobas® HPV Test in detecting cervical disease (≥ CIN2 and ≥ CIN3) as determined by the type of biopsy taken is provided below. In instances where a lesion was detected, a lesion-directed biopsy was taken. In instance where no lesion was observed, a random biopsy was taken.

The sensitivity and the specificity of the cobas® HPV Test for detecting ≥ CIN2 histology for women with lesions were 88.9% (24/27) with 95%: (71.9% to 96.1%) and 41.2% (73/177) with 95%: (34.3% to 48.7%), respectively. The sensitivity and the specificity of the test for detecting ≥ CIN3 histology were 92.3% (12/13) with 95%: (66.7% to 98.6%) and 38.3% (75/191) with 95%: (32.6% to 46.3%), respectively.

Table 17. Performance of the cobas® HPV Test and an FDA Approved HPV Test by Subject Lesion Status in the Non-vaccinated ASC-US Population (≥ 21 Years) – SurePath

Disease Endpoint		*cobas® HPV test*		*FDA approved test in STM*	
	Performance	**Lesion-Directed Biopsy Point Estimate**	**No Lesion-Random Biopsy Point Estimate**	**Lesion-Directed Biopsy Point Estimate**	**No Lesion-Random Biopsy Point Estimate**
≥CIN2	**Sensitivity (%) 95% CI**	88.9% (24/27) (71.9, 96.1)	76.9% (10/13) (49.7, 91.8)	90.3% (28/31) (75.1, 96.7)	61.5% (8/13) (35.5, 82.3)
	Specificity (%) 95% CI	41.2% (73/177) (34.3, 48.7)	68.8% (247/359) (63.8, 73.4)	39.4% (82/208) (33.0, 46.2)	69.1% (273/395) (64.4, 73.5)
	Prevalence	13.2% (27/204)	3.5% (13/372)	13.0% (31/239)	3.2% (13/408)

Disease Endpoint		*cobas® HPV test*		*FDA approved test in STM*	
	Performance	**Lesion-Directed Biopsy Point Estimate**	**No Lesion-Random Biopsy Point Estimate**	**Lesion-Directed Biopsy Point Estimate**	**No Lesion-Random Biopsy Point Estimate**
≥CIN3	**Sensitivity (%) 95% CI**	92.3%(12/13) (66.7, 98.6)	83.3% (5/6) (43.7, 97.0)	93.3% (14/15) (70.2, 98.8)	83.3% (5/6) (43.7, 97.0)
	Specificity (%) 95% CI	38.3%(75/191) (32.6, 46.3)	68.0% (249/366) (63.1, 72.6)	37.5% (84/224) (31.4, 44.0)	68.9% (277/402) (64.2, 73.2)
	Prevalence	6.4% (13/204)	1.6% (6/372)	6.3% (15/239)	1.5% (6/408)
HPV positivity		62.7% (128/204)	32.8% (122/372)	64.4% (154/239)	31.9% (130/408)

Performance of the cobas® HPV Test in the ASC -US Population (≥ 21 Years) – Vaccinated Subjects.

A total of 270 vaccinated subjects with ASC-US cytology completed the colposcopy procedures and had valid cobas® HPV results using the pre-aliquot specimen. The results of the cobas® HPV Test reported as (HR HPV) Positive or (HR HPV) Negative together with the CPR diagnosis are presented below.

Table 18. Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis - SurePath

		CPRP Diagnosis				
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Positive	85	27	17	10	1	140
Negative	144	9	5[a]	2[b]	0	130
Total	199	36	22	12	1	270

[a] 2 CIN2 case was FDA approved test negative and sequence negative; and 2 CIN2 case was FDA approved test negative and sequence positive. 1 CIN2 case was FDA approved test positive and sequence positive.

[b] 1 CIN3 case was FDA approved test negative and sequence negative; and 1 CIN3 case was FDA approved test negative and sequence positive.

Percent of Invalid cobas® HPV Test results was 0.0% (0/270) with 95% CI: 0.0% to 1.4%.

Performance of the cobas® HPV Test in detecting cervical disease (≥ CIN2 and ≥ CIN3) is presented in the table below. The sensitivity and the specificity of the test for detecting ≥ CIN2 histology were 80.0% (28/35) with 95%: (64.1% to 90.0%) and 52.3% (123/235) with 95%: (46.0% to 58.6%), respectively. The positive likelihood ratio (PLR) was estimated as 1.7, which implies a positive cobas® HPV Test results in 1.7 time more likely in subjects with ≥ CIN2 than in subjects with < CIN2. The negative likelihood ratio (NLR) was estimated as 0.38, which implies that a negative cobas® HPV Test results is 2.6 (1/0.38) times more likely in subjects with <CIN2 than in subjects with ≥ CIN2.

The sensitivity and the specificity of the cobas® HPV Test for detecting ≥ CIN3 histology were 84.6% (11/13) with 95%: (57.8% to 95.7%) and 49.8% (128/257) with 95%: (43.7% to 55.9%), respectively.

Table 19. Performance of the cobas® HPV Test in Detecting ≥ CIN2 and ≥ CIN3 in Vaccinated ASC-US Population - SurePath

		cobas® HPV test		**FDA approved test with STM**	
Disease Endpoint	**Performance**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN2	**Sensitivity (%)**	80.0% (28/35)	(64.1, 90.0)	74.3% (26/35)	(57.9, 85.8)
	Specificity (%)	52.3% (123/235)	(46.0, 58.6)	49.8% (124/249)	(43.6, 56.0)
	PPV (%)	20.0% (28/140)	(16.2, 23.3)	17.2% (26/151)	(13.7, 20.4)
	NPV (%)	94.6% (123/130)	(90.6, 97.3)	93.2% (124/133)	(89.2, 96.2)
	PLR	1.7	(1.3, 2.0)	1.5	(1.1, 1.8)
	NLR	0.38	(0.19, 0.70)	0.52	(0.28, 0.86)
	Prevalence (%)	13.0% (35/270)		12.3% (35/284)	
≥CIN3	**Sensitivity (%)**	84.6% (11/13)	(57.8, 95.7)	76.9% (10/13)	(49.7, 91.8)
	Specificity (%)	49.8% (128/257)	(43.7, 55.9)	48.0% (130/271)	(42.1, 53.9)
	PPV (%)	7.9% (11/140)	(5.4, 9.4)	6.6% (10/151)	(4.3, 8.2)
	NPV (%)	98.5% (128/130)	(95.8, 99.7)	97.7% (130/133)	(95.1, 99.3)
	PLR	1.7	(1.1, 2.0)	1.5	(0.9, 1.9)
	NLR	0.31	(0.06, 0.86)	0.48	(0.15, 1.07)
	Prevalence (%)	4.8% (13/270)		4.6% (13/284)	

In the vaccinated population, for the women with negative results by the cobas® HPV Test, risk of ≥ CIN2 and ≥ CIN3 were 5.4% and 1.5%, respectively.

Performance of the FDA approved test in detecting cervical disease (≥ CIN2 and ≥ CIN3) is also presented in the table above. The sensitivity and the specificity of the test for detecting ≥ CIN2 histology were 74.3% ((26/35) with 95%: 57.9% to 85.8%) and 49.8% ((124/249) with 95%: 43.6% to 56.0%), respectively. The sensitivity and the specificity of the test for detecting ≥ CIN3 histology were 76.9% ((10/13) with 95%: 49.7% to 91.8%) and 48.0% ((130/271) with 95%: 42.1% to 53.9%), respectively.

The table below displays a summary of the CPRP diagnosis by redefining disease status based on the lesion directed biopsies; therefore, subjects without lesions would had have random biopsies and would be defined as non-diseased.

Table 20. Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis for the Direct Biopsy in Vaccinated ASC-US Population (≥ 21 Years) – SurePath

cobas® HPV Test Result	**No Lesion**	**CPRP Diagnosis from lesion**					
		Normal	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Positive	63	41	17	10	9	0	140
Negative	97	27	4	2[a]	0	0	130
Total	160	68	21	12	9	0	270

[a] 1 CIN2 case was FDA approved test negative and sequence negative; and 1 CIN2 case was FDA approved test negative and sequence positive.

The table below presents the performance of the cobas® HPV Test and the performance of the FDA approved HPV Test in STM in detecting ≥CIN2 and ≥CIN3 by redefining disease status in subjects who had random biopsies as non-diseased. Under this modified definition of disease the sensitivity of detecting ≥CIN2 was 90.5% (19/21) (95% CI = 71.1% to 97.4%) for the cobas® HPV Test and for the FDA approved HPV Test. The specificity for detecting ≥CIN2 was 51.4% (128/249) (95% CI = 45.2% to 57.6%) for the cobas® HPV Test and 49.8% (131/263) (95% CI=43.8% to 55.8%) for the FDA approved HPV Test.

Under this modified definition of disease the sensitivity of detecting ≥CIN3 was 100% (9/9) (95% CI = 70.1% to 100%) for the cobas® HPV Test and for the FDA approved HPV Test. The specificity for detecting ≥CIN3 was 49.8% (130/261) (95% CI = 43.8% to 55.8%) for the cobas® HPV Test and 48.4% (133/275) (95% CI=42.5% to 54.3%) for the FDA approved HPV Test.

Table 21. Performance of the cobas® HPV Test Results Considering Subjects Without Lesions as Non-Diseased in Vaccinated ASC-US Population (≥ 21 Years) - SurePath

Disease Endpoint		cobas® HPV test		FDA approved test with STM	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN2	**Sensitivity (%)**	90.5% (19/21)	(71.1, 97.4)	90.5% (19/21)	(71.1, 97.4)
	Specificity (%)	51.4% (128/249)	(45.2, 57.6)	49.8% (131/263)	(43.8, 55.8)
	PPV (%)	13.6% (19/140)	(10.7, 15.6)	12.6% (19/151)	(10.0, 14.4)
	NPV (%)	98.5% (128/130)	(95.4, 99.7)	98.5% (131/133)	(95.5, 99.7)
	PLR	1.9	(1.4, 2.2)	1.8	(1.4, 2.1)
	NLR	0.19	(0.04, 0.57)	0.19	(0.04, 0.59)
	Prevalence (%)	7.8% (21/270)		7.4% (21/284)	
≥CIN3	**Sensitivity (%)**	100% (9/9)	(70.1, 100)	100% (9/9)	(70.1, 100)
	Specificity (%)	49.8% (130/261)	(43.8, 55.8)	48.4% (133/275)	(42.5, 54.3)
	PPV (%)	6.4% (9/140)	(4.5, 7.2)	6.0% (9/151)	(4.2, 6.6)
	NPV (%)	100% (130/130)	(97.7, 100)	100% (133/133)	(97.8, 100)
	PLR	2.0	(1.4, 2.3)	1.9	(1.3, 2.2)
	NLR	0.00	(0.00, 0.67)	0.00	(0.00, 0.69)
	Prevalence (%)	3.3% (9/270)		3.2% (9/284)	

The performance of the cobas® HPV Test in detecting cervical disease (≥ CIN2 and ≥ CIN3) as determined by the type of biopsy taken is provided below. In instances where a lesion was detected, a lesion-directed biopsy was taken. In instance where no lesion was observed, a random biopsy was taken.

The sensitivity and the specificity of the cobas® HPV Test for detecting ≥ CIN2 histology for women with lesions were 90.5% (19/21) with 95%: (71.1% to 97.4%) and 34.8% (31/89) with 95%: (25.8% to 45.2%), respectively. The sensitivity and the specificity of the test for detecting ≥ CIN3 histology were 100% (9/9) with 95%: (70.1% to 100%) and 32.7% (33/101) with 95%: (24.3% to 42.3%), respectively.

Table 22. Performance of the cobas® HPV Test and an FDA Approved HPV test by Subject Lesion Status in the Vaccinated ASC-US Population (≥ 21 Years) – SurePath

Disease Endpoint		cobas® HPV test		FDA approved test with STM	
	Performance	Lesion-Directed Biopsy Point Estimate	No Lesion-Random Biopsy Point Estimate	Lesion-Directed Biopsy Point Estimate	No Lesion-Random Biopsy Point Estimate
≥CIN2	Sensitivity (%) 95% CI	90.5% (19/21) (71.1, 97.4)	64.3% (9/14) (38.8, 83.7)	90.5% (19/21) (71.1, 97.4)	50.0% (7/14) (26.8, 73.2)
	Specificity (%) 95% CI	34.8% (31/89) (25.8, 45.2)	63.0% (92/146) (54.9, 70.4)	30.3% (30/99) (22.1, 40.0)	62.7%(94/150) (54.7, 70.0)
	Prevalence	19.1% (21/110)	8.8% (14/160)	17.5% (21/120)	8.5% (14/164)
≥CIN3	Sensitivity (%) 95% CI	100% (9/9) (70.1, 100)	50.0% (2/4) (15.0, 85.0)	100% (9/9) (70.1, 100)	25.0% (1/4) (4.6, 69.9)
	Specificity (%) 95% CI	32.7% (33/101) (24.3, 42.3)	60.9% (95/156) (54.9, 70.4)	28.8% (32/111) (21.1, 37.9)	61.3% (98/160) (53.5, 68.5)
	Prevalence	8.2% (9/110)	2.5% (4/160)	7.5% (9/120)	2.4% (4/164)
HPV positivity		70.0% (77/110)	39.4% (63/160)	73.3% (88/120)	38.4% (63/164)

Performance of the cobas® HPV Test in Detecting ≥CIN2 and ≥CIN3 in the ASC-US Population (≥ 21 Years) by Age Group.

Performance of the cobas® HPV Test in detecting cervical disease (≥ CIN2 and ≥ CIN3) in the non-vaccinated subjects when evaluated by age group is presented in the table below. The sensitivity of the test for detecting ≥ CIN2 histology were 100% (7/7) with 95%: (64.6% to 100%) in the 21-29 year age group, 85.0% (17/20) with 95%: (64.0% to 94.8%) in the 30-39 year age group, and 76.9% (10/13) with 95%: (49.7% to 91.8%) in the ≥ 40 years age group. The specificity of the test was highest in ≥ 40 years, with an estimate of 69.8% (173/248) with 95%: (63.8% to 75.1%).

The sensitivity of the cobas® HPV Test for detecting ≥ CIN3 histology in the non-vaccinated subjects when evaluated by age group was 100% (4/4) with 95%: (51.0% to 100%) in the 21-29 year age group, 81.8% (9/11) with 95%: (52.3% to 94.9%) in the 30-39 year age group, and 100% (4/4) with 95%: (51.0% to 100%) in the ≥ 40 years age group.

Table 23. Performance of the cobas® HPV Test in Detecting ≥CIN2 and ≥CIN3 in the Non-Vaccinated ASC-US Population by Age Group - SurePath

Performance	21-29 Years	30-39 Years	≥ 40 Years
N	107	208	261
≥ CIN2			
Sensitivity (%)	100% (7/7)	85.0% (17/20)	76.9% (10/13)
95% CI (%)	(64.6, 100)	(64.0, 94.8)	(49.7, 91.8)
Specificity (%)	51.0% (51/100)	51.1% (96/188)	69.8% (173/248)
95% CI (%)	(41.3, 60.6)	(44.0, 58.1)	(63.8, 75.1)
PPV (%)	12.5% (7/56)	15.6% (17/109)	11.8% (10/85)
95% CI (%)	(8.2, 15.1)	(11.9, 18.5)	(7.6, 15.1)
NPV (%)	100% (51/51)	97.0% (96/99)	98.3% (173/176)
95% CI (%)	(95.0, 100)	(92.9, 99.0)	(96.3, 99.5)
≥ CIN2 prevalence	6.5% (7/107)	9.6% (20/208)	5.0% (13/261)
≥ CIN3			
Sensitivity (%)	100% (4/4)	81.8% (9/11)	100% (4/4)
95% CI (%)	(51.0, 100)	(52.3, 94.9)	(51.0, 100)
Specificity (%)	49.5% (51/103)	49.2% (97/197)	68.5% (176/257)
95% CI (%)	(40.1, 59.0)	(42.3, 56.2)	(62.6, 73.9)
PPV (%)	7.1% (4/56)	8.3% (9/109)	4.7% (4/85)
95% CI (%)	(3.6, 8.6)	(5.3, 10.2)	(2.3, 5.6)
NPV (%)	100% (51/51)	98.0% (97/99)	100% (176/176)
95% CI (%)	(96.0, 100)	(94.7, 99.6)	(98.9, 100)
≥ CIN3 prevalence	3.7% (4/107)	5.3% (11/208)	1.5% (4/261)

In non-vaccinated population, for the women of 21-29 years old with negative results by the cobas® HPV Test, risks of ≥ CIN2 and ≥ CIN3 were 0.0% ; for the women of 30-39 years old with negative results by cobas® HPV Test, risks of ≥ CIN2 and ≥ CIN3 were 3.0% and 2.0%, respectively; and for the women of ≥40 years old with negative results by cobas® HPV Test, risks of ≥ CIN2 and ≥ CIN3 were 1.7% and 0.0%, respectively.

Performance of the cobas® HPV Test in detecting disease (≥ CIN2 and ≥ CIN3) in the vaccinated subjects when evaluated by age group is presented in the table below. The sensitivity of the test for detecting ≥ CIN2 histology were 78.1% (25/32) with 95%: (61.2% to 89.0%) in the 21-29 year age group, and 100% (3/3) with 95%: (43.9% to 100%) in the 30-39 year age group.

The sensitivity the test for detecting ≥ CIN3 histology in the vaccinated subjects when evaluated by age was 81.8% (9/11) with 95%: (52.3% to 94.9%) in the 21-29 year age group and 100% (2/2) with 95%: (34.2% to 100%) in the 30-39 year age group.

Table 24. Performance of the cobas® HPV Test in Detecting ≥ CIN2 and ≥ CIN3 in Vaccinated ASC-US Population by Age Group - SurePath

Performance	21-29 Years	30-39 Years	≥ 40 Years
N	244	26	NA
≥ CIN2			
Sensitivity (%)	78.1% (25/32)	100% (3/3)	NA
95% CI (%)	(61.2, 89.0)	(43.9, 100)	
Specificity (%)	51.9% (110/212)	56.5% (13/23)	NA
95% CI (%)	(45.2, 58.5)	(36.8, 74.4)	
PPV (%)	19.7% (25/127)	23.1% (3/13)	NA
95% CI (%)	(15.7, 23.3)	(10.5, 34.3)	
NPV (%)	94.0% (110/117)	100% (13/13)	NA
95% CI (%)	(89.7, 96.9)	(86.8, 100)	
Prevalence (%)	13.1% (32/244)	11.5% (3/26)	NA
≥ CIN3			
Sensitivity (%)	81.8% (9/11)	100% (2/2)	NA
95% CI (%)	(52.3, 94.9)	(34.2, 100)	
Specificity (%)	49.4% (115/233)	54.2% (13/24)	NA
95% CI (%)	(43.0, 55.7)	(35.1, 72.1)	
PPV (%)	7.1% (9/127)	15.4% (2/13)	NA
95% CI (%)	(4.6, 8.6)	(3.5, 23.3)	
NPV (%)	98.3% (115/117)	100% (13/13)	NA
95% CI (%)	(95.5, 99.6)	(89.4, 100)	
Prevalence (%)	4.5% (11/244)	7.7% (2/26)	NA

In vaccinated population, for the women of 21-29 years old with negative results by the cobas® HPV Test, risks of ≥ CIN2 and ≥ CIN3 were 6.0% and 1.7%; for the women of 30-39 years old with negative results by cobas® HPV Test, risks of ≥ CIN2 and ≥ CIN3 were 0.0%.

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

Likelihood ratios (LRs) and the risks of disease (≥ CIN2 and ≥ CIN3) along with 95% CIs for cobas® HPV Test results (HR HPV16 positive/18 positive, other 12 HR, and HR HPV

negative are presented below for both the non-vaccinated and vaccinated subjects in the ASC-US (≥ 21 years) population.

For the ≥ CIN2 histology in the non-vaccinated population, the estimate of the LR of HPV16 positive/18 positive was 5.2 with the lower bound of CI of 3.2, indicating that an HPV16 positive/18 positive results 5.2 times more likely to come from a subject with disease (≥ CIN2) than from a subject without disease (<CIN2). The LR of Other 12 HR HPV positive was 1.4. The estimate of the LR of a negative cobas® HPV Test result was 0.3 with the upper bound of CI of 0.5, indicating that a negative result as 3.3 (1/0.3) times more likely to come from a subject without disease (<CIN2) than from a subject with disease (≥ CIN2).

The risk of disease (≥ CIN2) is the chance (probability) of having the disease given an HPV test result. In the non-vaccinated population, the pre-test risk of disease (≥ CIN2) regardless of the HPV result (prevalence) was 6.9%. The risk of ≥ CIN2 disease for women with HPV16 positive/18 positive results was 28.1% and it was significantly higher than the pre-test risk of 6.9%. For women with HPV negative results, the risk of ≥ CIN2 was 1.8% and it was significantly lower than the pre-test risk of 6.9%.

For ≥ CIN3 histology in the non-vaccinated population, the LR for HPV16 positive/18 positive was 7.0 with the lower bound of CI of 4.4 and the LR for a negative cobas® HPV Test result was 0.2 with the upper bound of 0.7. The pre-test risk of disease (≥ CIN3) was 3.3% in the non-vaccinated population. The risk of ≥ CIN3 for HPV16 positive/HPV18 positive 19.3% and it was significantly higher than the pre-test risk of 3.3%. For the women with HPV negative results, risk of ≥ CIN3 was 0.6%, and it was significantly lower than the pre-test risk of 3.3%.

Table 25. Likelihood Ratios and Risk of Disease by the cobas® HPV Test Result in Detecting ≥CIN2 and ≥CIN3 in the Non-Vaccinated ASC-US Population

Disease Endpoint	cobas® HPV Test Result	Likelihood Ratio (95% CI)	Risk of Disease (%) Given the Test Result (95% CI)
≥CIN2	HPV 16 Positive /18 Positive	5.2 (3.2, 8.5)	28.1 (16/57) (19.4, 38.7)
	Other 12 HR HPV Positive	1.4 (1.0, 2.0)	9.3 (18/193) (6.7, 12.9)
	Negative	0.3 (0.1, 0.5)	1.8 (6/326) (0.9, 3.8)
	Prevalence (%)	6.9% (5.6, 8.5)	
≥CIN3	HPV 16 Positive /18 Positive	7.0 (4.4, 11.2)	19.3 (11/57) (13.0, 27.7)
	Other 12 HR HPV Positive	0.9 (0.5, 1.8)	3.1 (6/193) (1.6, 5.9)
	Negative	0.2 (0.0, 0.7)	0.6 (2/326) (0.2, 2.2)
	Prevalence (%)	3.3% (2.4, 4.5)	

Likelihood ratios (LRs) and the risks of disease (≥ CIN2 and ≥ CIN3) with 95% CIs for cobas® HPV Test results (HR HPV16 positive/18 positive, 12 other HR, and HR HPV negative) are presented in the table below for the vaccinated ASC-US (≥21 years) population.

For ≥ CIN2 histology in the vaccinated population, the estimate of the LR of HPV16 positive/18 positive was 4.9 with the lower bound of CI of 2.1, indicating that an HPV16 positive/18 positive result is 4.9 times more likely to occur in a subject with disease (≥ CIN2) than in a subject without disease (< CIN2). The LR of Other 12 HR HPV positive was 1.3. The estimate of the LR of a negative cobas® HPV Test result was 0.4 with the upper bound of CI of 0.7, indicating that a negative result was 2.5 (1/0.4) times more likely to occur in a subject without disease (< CIN2) than in a subject with disease (≥ CIN2).

In the vaccinated population, the pre-test risk of disease (≥ CIN2) regardless of the HPV result (prevalence) was 13.0%. The risk of ≥ CIN2 disease for women with HPV16 positive/HPV18 positive results was 42.1% and it was significantly higher than the pre-test risk of 13.0%. For women with HPV negative results, the risk of ≥CIN2 was 5.4% and it was significantly lower than the pre-test risk of 13.0%.

For ≥ CIN3 histology in the vaccinated population, the LR for HPV16 positive/18 positive was 11.5 with the lower bound of CI of 5.1 and the LR for a negative cobas® HPV Test result was 0.3 with the upper bound of 0.9. The pre-test risk of disease (≥ CIN3) was 4.8% in the vaccinated population. The risk of ≥ CIN3 for HPV16 positive/HPV18 positive 36.8% and it was significantly higher than the pre-test risk of 4.8%. For the

women with HPV negative results, risk of ≥ CIN3 was 1.5%, and it was significantly lower than the pre-test risk of 4.8%.

Table 26. Likelihood Ratios and Risk of Disease by cobas® HPV Test Result in Detecting ≥ CIN2 and ≥CIN3 in Vaccinated ASC-US Population - SurePath

Target condition	cobas® HPV Test Result	Likelihood Ratio (95% CI)	Risk of Disease (%) Given the Test Result (95% CI)
≥ CIN2	HPV16 positive/18 positive	4.9 (2.1, 10.9)	42.1% (8/19) (23.9, 62.0)
	Other 12 HR HPV positive	1.3 (0.9, 1.8)	16.5% (20/121) (12.1, 20.9)
	HPV Negative	0.4 (0.2, 0.7)	5.4% (7/130) (2.7, 9.4)
	Prevalence (%)	13.0% (35/270)	
≥ CIN3	HPV16 positive/18 positive	11.5 (5.1, 23.5)	36.8% (7/19) (20.6, 54.3)
	Other 12 HR HPV positive	0.7 (0.3, 1.3)	3.3% (4/121) (1.4, 6.2)
	HPV Negative	0.31 (0.06, 0.86)	1.54% (2/130) (0.32, 4.19)
	Prevalence (%)	4.8% (13/270)	

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

The CPRP diagnosis by all possible cobas® HPV Tet result in non-vaccinated ASC-US population is presented in the table below.

Table 27. Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis in Non-Vaccinated ASC-US Population (≥21 years) - SurePath

	Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
NEG Other HR HPV, NEG HPV16, NEG HPV18	296	24	4	2	0	326
NEG Other HR HPV, NEG HPV16, POS HPV18	4	2	0	1	0	7
NEG Other HR HPV, POS HPV16, NEG HPV18	11	2	3	6	2	24

	Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
POS Other HR HPV, NEG HPV16, NEG HPV18	146	29	12	6	0	193
POS Other HR HPV, NEG HPV16, POS HPV18	7	0	0	1	0	8
POS Other HR HPV, POS HPV16, NEG HPV18	10	4	2	1	0	17
POS Other HR HPV, POS HPV16, POS HPV18	1	0	0	0	0	1
Total	475	61	21	17	2	576

The CPRP diagnosis and the absolute risk of disease (≥ CIN2 and ≥ CIN3) by cobas® HPV Test result are presented in table below for non-vaccinated ASC-US population. HPV16 positive/18 positive had the highest absolute risk for both ≥ CIN2 and ≥ CIN3. In general, the absolute risks for both ≥ CIN2 and ≥ CIN3 were higher in women with results of HPV positive, HPV16 positive/18 positive, or Other 12 HR positive than in women with an HPV negative result.

Table 28.Central Pathology Review Diagnosis and Absolute Risk of ≥CIN2 and ≥CIN3 for Different cobas® HPV Test Results in Non-Vaccinated ASC-US Population (≥21 Years) - SurePath

cobas® HPV Test Result	**Total**	**Central Pathology Review Diagnosis**					**Absolute Risk for ≥ CIN2 (%)**	**Absolute Risk for ≥ CIN3 (%)**
		Normal	**CIN1**	**CIN2**	**CIN3**	**Cancer**		
HPV16 positive	42	22	6	5	7	2	33.3% (14/42)	21.4% (9/42)
HPV18 positive	15	11	2	0	2	0	13.3% (2/15)	13.3% (2/15)
Other 12 HR HPV positive	193	146	29	12	6	0	9.3% (18/193)	3.1% (6/193)
HPV negative	326	296	24	4	2	0	1.8% (6/326)	0.6% (2/326)
HPV16 positive and/or HPV18 positive	57	33	8	5	9	2	28.1% (16/57)	19.3% (11/57)
HPV positive	250	179	37	17	15	2	13.6% (34/250)	6.8% (17/250)

Note 1: HPV16 positive and/or HPV18 positive include all women with either or both of these genotypes occurring with or without Other 12 HR positive results.

Note 2: Other 12 HR HPV positive include all women with positive results for Other 12 HR HPV genotypes with negative results for HPV16 and HPV18

The relative risks (RRs) of disease (≥ CIN2 and ≥ CIN3) were calculated for women with different cobas® HPV Test results by RR and its associated 95% CIs as presented in table below for non-vaccinated ASC-US population. The estimated RRs of ≥ CIN2 and of ≥ CIN3 for women with positive vs. negative cobas® HPV Test results were 7.4 (95% CI: 3.2 to 17.3) and 11.1 (95% CI: 2.6 to 47.5), respectively, indicating that women with a positive result were 7.4 times more likely to have ≥ CIN2 histology and 11.1 times more likely to have ≥ CIN3 histology than were women with a negative test result.

Similarly, women who have HPV16 and/or HPV18 positive results from the cobas® HPV Test were significantly more likely to have ≥ CIN2 than the women with (a) a positive result for Other 12 HR HPV types, or (b) a negative result. Women with a positive result for Other 12 HR HPV types were significantly more likely to have ≥ CIN2 than the women with a negative result. Similar results were observed for ≥ CIN3 histology.

Table 29. Relative Risks of ≥CIN2 and ≥CIN3 for Different cobas® HPV Test Results in Non-Vaccinated ASC-US Population (≥21 Years) - SurePath

cobas® HPV Test Result	**CPRP Diagnosis ≥ CIN2**		**CPRP Diagnosis ≥ CIN3**	
	Relative Risk	**95% CI**	**Relative Risk**	**95% CI**
HPV Positive vs. Negative	7.4	(3.2, 17.3)	11.1	(2.6, 47.5)
HPV16 positive/18 positive vs. Negative	15.3	(6.2, 37.3)	31.5	(7.2, 138.2)
HPV16 positive /18 positive vs. 12 Other HR HPV positive	3.0	(1.6, 5.5)	6.2	(2.4, 16.0)
12 Other HR HPV positive vs. Negative	5.1	(2.0, 12.5)	5.1	(1.0, 24.9)
Prevalence (%)	6.9%		3.3%	
Note 1: HPV16 positive and/or HPV18 positive include all women with either or both of these genotypes occurring with or without Other 12 HR positive results. Note 2: Other 12 HR HPV positive include all women with positive results for Other 12 HR HPV genotypes with negative results for HPV16 and HPV18				

The absolute risks of disease (≥ CIN2 and ≥ CIN3) by cobas® HPV Test result stratified by age group in non-vaccinated population are presented in table below. HPV16 positive/18 positive had the highest absolute risk for both ≥ CIN2 and ≥ CIN3 in each age group, followed by Other 12 HR positive.

Table 30. Absolute Risk of ≥ CIN2 and ≥ CIN3 by cobas HPV Test Result Stratified by Age in Non-Vaccinated ASC-US Population (≥ 21 Years) - SurePath

	Age Group (Years)		
cobas HPV Test Result	**21-29**	**30-39**	**≥ 40**
Absolute Risk for ≥ CIN2 (95% CI)			
HPV16 positive /18 positive	30.0% (3/10) (10.8, 60.3)	25.8% (8/31) (13.7, 43.2)	31.3% (5/16) (14.2, 55.6)
Other 12 HR HPV positive	8.7% (4/46) (3.4, 20.3)	11.5% (9/78) (6.2, 20.5)	7.2% (5/69) (3.1, 15.9)
Negative	0.0% (0/51) (0.0, 7.0)	3.0% (3/99) (1.0, 8.5)	1.7% (3/176) (0.6, 4.9)
Prevalence (%)	6.5% (7/107)	9.6% (20/208)	5.0% (13/261)
Absolute Risk for ≥ CIN3 (95% CI)			
HPV16 positive /18 positive	20.0% (2/10) (5.7, 51.0)	19.4% (6/31) (9.2, 36.3)	18.8% (3/16) (6.6, 43.0)
Other 12 HR HPV positive	4.3% (2/46) (1.2, 14.5)	3.8% (3/78) (1.3, 10.7)	1.4% (1/69) (0.3, 7.8)
Negative	0.0% (0/51) (0.0, 7.0)	2.0% (2/99) (0.6, 7.1)	0.0% (0/176) (0.0, 2.1)
Prevalence (%)	3.7% (4/107)	5.3% (11/208)	1.5% (4/261)

Note 1: HPV16 positive and/or HPV18 positive include all women with either or both of these genotypes occurring with or without Other 12 HR positive results.
Note 2: Other 12 HR HPV positive include all women with positive results for Other 12 HR HPV genotypes and with negative results for HPV16 and HPV18

The CPRP diagnosis by all possible cobas HPV Test result in vaccinated ASC-US population is presented in the table below.

Table 31. Summary of the cobas® HPV Test Results and Central Pathology Review Panel Diagnosis in Vaccinated Population

	Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
NEG Other HR HPV, NEG HPV16, NEG HPV18	296	24	4	2	0	326
NEG Other HR HPV, NEG HPV16, POS HPV18	4	2	0	1	0	7
NEG Other HR HPV, POS HPV16, NEG HPV18	11	2	3	6	2	24

	Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
POS Other HR HPV, NEG HPV16, NEG HPV18	146	29	12	6	0	193
POS Other HR HPV, NEG HPV16, POS HPV18	7	0	0	1	0	8
POS Other HR HPV, POS HPV16, NEG HPV18	10	4	2	1	0	17
POS Other HR HPV, POS HPV16, POS HPV18	1	0	0	0	0	1
Total	475	61	21	17	2	576

The CPRP diagnosis and the absolute risk of disease (≥ CIN2 and ≥ CIN3) by cobas® HPV Test result are presented in the table below for vaccinated ASC-US population. HPV16 positive/18 positive had the highest absolute risk for both ≥ CIN2 and ≥ CIN3. In general, the absolute risks for both ≥ CIN2 and ≥ CIN3 were higher in women with results of HPV positive, HPV16 positive/18 positive, or Other 12 HR positive than in women with an HPV negative result.

Table 32. Central Pathology Review Diagnosis and Absolute Risk of ≥CIN2 and ≥CIN3 for Different cobas® HPV Test Results in Vaccinated ASC-US Population (≥21 Years) - SurePath

cobas® HPV Test Result	**Total**	**Central Pathology Review Diagnosis**					**Absolute Risk for ≥ CIN2 (%)**	**Absolute Risk for ≥ CIN3 (%)**
		Normal	**CIN1**	**CIN2**	**CIN3**	**Cancer**		
HPV16 positive	13	6	0	1	6	0	53.8% (7/13)	46.2% (6/13)
HPV18 positive	6	5	0	0	0	1	16.7% (1/6)	16.7% (1/6)
Other 12 HR HPV positive	121	74	27	16	4	0	16.5% (20/121)	3.3% (4/121)
HPV negative	130	114	9	5	2	0	5.4% (7/130)	1.5% (2/130)
HPV16 positive and/or HPV18 positive	19	11	0	1	6	1	42.1% (8/19)	36.8% (7/19)
HPV positive	140	85	27	17	10	1	20.0% (28/140)	7.9% (11/140)

Note 1: HPV16 positive and/or HPV18 positive include all women with either or both of these genotypes occurring with or without 12 other HR positive results.
Note 2: Other 12 HR HPV positive include all women with positive results for Other 12 HR HPV genotypes and with negative results for HPV16 and HPV18

The relative risks (RRs) of disease (≥ CIN2 and ≥ CIN3) were calculated for vaccinated women with different cobas® HPV Test results and its associated 95% CIs. These results are presented in the table below. The estimated RRs of ≥ CIN2 and of ≥ CIN3 for women with positive vs. negative cobas® HPV Test results were 3.7 (95% CI: 1.7 to 8.2) and 5.1 (95% CI: 1.2 to 22.6), respectively, indicating that women with a positive result were 3.7 times more likely to have ≥ CIN2 histology and 5.1 times more likely to have ≥ CIN3 histology than were women with a negative test result.

Similarly, women who have HPV16 and/or HPV18 positive results from the cobas® HPV Test were significantly more likely to have ≥ CIN2 than the women with (a) a positive Other 12 HR HPV types were significantly more likely to have ≥ CIN2 than the women with a negative result. Similar results were observed for ≥ CIN3 histology.

Table 33. Relative Risks of ≥CIN2 and ≥CIN3 for Different cobas® HPV Test Results in Vaccinated ASC-US Population (≥21 Years) - SurePath

cobas® HPV Test Result	**CPRP Diagnosis ≥ CIN2**		**CPRP Diagnosis ≥ CIN3**	
	Relative Risk	**95% CI**	**Relative Risk**	**95% CI**
HPV Positive vs. Negative	3.7	(1.7, 8.2)	5.1	(1.2, 22.6)
HPV16 positive/18 positive vs. Negative	7.8	(3.2, 19.1)	23.9	(5.4, 106.9)
HPV16 positive /18 positive vs. Other 12 HR HPV positive	2.5	(1.3, 4.9)	11.1	(3.6, 34.5)
Other 12 HR HPV positive vs. Negative	3.1	(1.3, 7.0)	2.1	(0.4, 11.5)
Prevalence	13.0% (35/270)		4.8% (13/270)	
Note 1: HPV16 positive and/or HPV18 positive include all women with either or both of these genotypes occurring with or without Other 12 HR positive results. Note 2: Other 12 HR HPV positive include all women with positive results for Other 12 HR HPV genotypes and with negative results for HPV16 and HPV18				

The absolute risk of disease (≥ CIN2 and ≥ CIN3) by cobas® HPV Test result stratified by age group in vaccinated population are presented in table below. HPV16 positive/18 positive had the highest absolute risk for both ≥ CIN2 and ≥ CIN3 in each age group followed by Other 12 HR positive.

Table 34. Absolute Risk of ≥ CIN2 and ≥ CIN3 by cobas® HPV Test Result Stratified by Age in Vaccinated ASC-US Population (≥ 21 Years) - SurePath

	Age Group (Years)		
cobas® HPV Test Result	**21-29**	**30-39**	**≥ 40**
Absolute Risk for ≥CIN2			
HPV16 positive /18 positive	40.0% (6/15) (19.8, 64.3)	50.0% (2/4) (15.0, 85.0)	NA

	Age Group (Years)		
cobas® HPV Test Result	**21-29**	**30-39**	**≥ 40**
Other 12 HR HPV positive	17.0% (19/112) (11.1,25.0)	11.1% (1/9) (2.0,43.5)	NA
Negative	6.0% (7/117) (2.9,11.8)	0.0% (0/13) (0.0,22.8)	NA
Prevalence	13.1% (32/244) (9.4, 17.9)	11.5% (3/26) (4.0, 29.0)	NA
Absolute Risk for ≥CIN3			
HPV16 positive /18 positive	33.3% (5/15) (15.2, 58.3)	50.0% (2/4) (15.0, 85.0)	NA
Other 12 HR HPV positive	3.6% (4/112) (1.4, 8.8)	0.0% (0/9) (0.0, 29.9)	NA
Negative	1.7% (2/117) (0.5, 6.0)	0.0% (0/13) (0.0, 22.8)	NA
Prevalence	4.5% (11/244) (2.5, 7.9)	7.7% (2/26) (2.1, 24.1)	NA
Note 1: HPV16 positive and/or HPV18 positive include all women with either or both of these genotypes occurring with or without Other 12 HR positive results. Note 2: Other 12 HR HPV positive include all women with positive results for Other HR HPV genotypes and with negative results for HPV16 and HPV18			

Prevalence of Cervical Disease Stratified by Age and cobas® HPV Test Result

The following tables include information about the disease prevalence determined by CPRP diagnosis of histology in the non-vaccinated and vaccinated populations stratified by age. The factual information related to the vaccinated women, regarding the age they were vaccinated, and whether vaccination was performed according to the vaccine intended use was not available.

Table 35. Prevalence of ≥ CIN2 Stratified by Age in the Non-Vaccinated and Vaccinated ASC-US Population (≥ 21 Years) – SurePath

		Age Groups		
Disease Endpoint	Vaccine Status	21-24*	25-29	30-39
≥CIN2	Non-vaccinated	13.0% (3/23)	4.8% (4/84)	9.6% (20/208)
	Vaccinated	7.7% (8/104)	17.1% (24/140)	11.5% (3/26)

*The age group for 21-29 was divided into two age subgroups, 21-24 and 25-29, according to the 2012 Updated Consensus Guidelines (Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, Solomon D, Wentzensen N, Lawson HW. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Journal of Lower Genital Tract Disease. 2013; 17(5): S1-S27).

Table 36. Prevalence of ≥ CIN2 Stratified by Age and cobas® HPV Test Result in the Non-Vaccinated and Vaccinated ASC-US Population (≥ 21 Years) – SurePath

		Age Group		
	cobas HPV® Test Result	21-24*	25-29	30-39
Non-vaccinated	HPV 16/18 Pos	8.7% (2/23)	1.2% (1/84)	3.8% (8/208)
	Other HR HPV pos	4.3% (1/23)	3.6% (3/84)	4.3% (9/208)
	HR HPV neg	0.0% (0/23)	0.0% (0/84)	1.4% (3/208)
Vaccinated	HPV 16/18 Pos	1.9% (2/104)	2.9% (4/140)	7.7% (2/26)
	Other HR HPV pos	3.8% (4/104)	10.7% (15/140)	3.8% (1/26)
	HR HPV neg	1.9% (2/104)	3.6% (5/140)	0.0% (0/26)

*The age group for 21-29 was divided into two age groups, 21-24 and 25-29, according to the 2012 Updated Consensus Guidelines.

STUDY DESIGN TO DEMONSTRATE ANALYTICAL PERFORMANCE OF THE COBAS® HPV TEST IN ASC-US WOMEN ≥ 21 YEARS

To demonstrate analytical performance of cobas® HPV Test approximately 700 samples with ASC-US cytology results were compared to a composite comparator comprising HPV DNA and an FDA approved HR HPV DNA test from samples collected in STM. Cervical samples were obtained from all women ≥21 years with ASC-US cytology results who participated in the ASC-US study and who had valid cobas® HPV Test results in SurePath and STM samples available for evaluation.

Agreement with a Composite Comparator in Samples Collected in STM Compared to Samples Collected in SurePath for the ASC-US ≥21 Years Population

The analytical performance of the cobas® HPV Test was evaluated by comparing results from the cobas® HPV Test to a composite comparator comprising of HPV DNA sequencing and an FDA-approved HR HPV DNA test. Additionally, the test was also compared directly with DNA sequencing from samples collected in STM. Sequencing was performed at a commercial lab. DNA was extracted from cervical specimens followed by a PCR amplification utilizing both β-globin and PGMY primers. The β-globin amplification serves as a process control. The PGMY primers are a pool of consensus primers designed to amplify a portion of the polymorphic L1 region of the HPV genome. PGMY-positive extracts were then amplified using HR HPV type-specific primers for subsequent sequencing reactions.

All cervical samples were selected from the ASC-US study: women ≥21 years who had ASC-US cytology results, valid cobas® HPV Test results in SurePath and adequate STM sample volume (n = 678). Of these, 677 were from eligible subjects and had valid cobas® HPV Test results in the pre-aliquot; of these, 640 had valid sequencing results and 37 were invalid. Invalid samples were negative for both β-globin and PGMY primers. Table 79 displays the agreement between the cobas® HPV Test and the composite comparator (FDA-approved HPV test and HPV DNA Sequencing in STM). The agreements between the cobas® HPV test and the composite comparator were Positive Percent Agreement (PPA)=95.4% (206/216) with 95% CI = 91.7% to 97.5%, Negative Percent Agreement (NPA)=93.2% (288/309) with 95% CI = 89.8% to 95.5 % and Overall Percent Agreement (OPA)=94.1% (495/515) with 95% CI = 91.8% to 95.8 %. Seventeen percent (17%) of the composite comparator results were indeterminate (discordant between sequencing and the FDA-approved HPV test) and 5.5% (37/678) were invalid with sequencing.

Table 37. Agreement Between the cobas® HPV Test and the Composite Comparator (Sequencing/FDA-approved HPV test in STM) in ASC-US Population >=21 Years - SurePath

	Composite Comparator				
cobas® HPV Test in prequot	**Positive**	**Negative**	**Indeterminate**	**Invalid**	**Total**
Positive	206	21	57	16	301
Negative	10	288	58	21	377

	Composite Comparator				
cobas® HPV Test in prequot	**Positive**	**Negative**	**Indeterminate**	**Invalid**	**Total**
Total	216 (31.9%)	309 (45.6 %)	115 (17.0 %)	37 (5.5 %)	677
PPA: 95.4% (206/216), 95% CI: (91.7 %, 97.5 %)					
NPA: 93.2% (288/309), 95% CI: (89.8 %, 95.5 %)					
OPA: 94.1% (495/526), 95% CI: (91.8 %, 95.8 %)					

Tables below present the HPV genotype-specific percent agreement between the cobas® HPV Test and HPV DNA sequencing stratified by CPRP diagnosis (≥CIN2 and <CIN2) for the detection of HPV16, HPV18 and Other 12 HR HPV. The PPA, NPA and OPA between cobas® HPV Test and HPV DNA sequencing was ~ 94% for the detection of HPV16 and 100% for the detection of HPV18 among subjects with CPRP diagnosis ≥CIN2.

The PPA, NPA and OPA between cobas® HPV Test and HPV DNA sequencing for the detection of Other 12 HR HPV were ~ 83.0%, 79.2% and 81.5% respectively among subjects with CPRP diagnosis ≥CIN2. Of the 3 ≥CIN2 cases where cobas® HPV Test results were Other 12 HR HPV negative, 2 were HPV16 positive by the cobas® HPV Test whereas both HPV16 and 39 were positive by sequencing; one was HPV16 positive by cobas® HPV Test and both HPV16 and 59 positive by sequencing. Of the 4 ≥CIN2 cases with HPV negative by the cobas® HPV Test, 3 were ≥CIN2 and positive for HPV genotypes 33, 45, 56 and 66 by sequencing; 1 case was CIN3 and HPV 52 positive by sequencing.

Table 38.Percent Agreement Between the cobas® HPV Test HPV16 Results vs. HPV16 Sequencing in STM Comparator Stratified by CPRP Diagnosis of ≥ CIN2 or <CIN2 - SurePath

	Sequencing Results						
	≥ CIN2				**< CIN2**		
cobas® HPV Test Result in prequot	**HPV 16 Positive**	**HPV 16 Negative**	**Total**		**HPV 16 Positive**	**HPV 16 Negative**	**Total**
HPV 16 Detected	15	3	18		12	12	24
HPV 16 Not Detected, but either HPV 18 or Other 12 HR HPV Detected	1*	46	47		4	534	540
HR HPV Not Detected	0				2		
Total	16	49	65		18	546	564

	Sequencing Results					
	≥ CIN2			< CIN2		
cobas® HPV Test Result in prequot	**HPV 16 Positive**	**HPV 16 Negative**	**Total**	**HPV 16 Positive**	**HPV 16 Negative**	**Total**
PPA: 93.8% (15/16), 95% CI: (71.7 %, 98.9 %)				PPA: 66.7% (12/18), 95% CI: (43.7 %, 83.7 %)		
NPA: 93.9% (46/49), 95% CI: (83.5 %, 97.9 %)				NPA: 97.8% (534/546), 95% CI: (96.2 %, 98.7 %)		
OPA: 93.8% (61/65), 95% CI: (85.2 %, 97.6 %)				OPA: 96.8% (546/564), 95% CI: (95.0 %, 98.0 %)		

* Other 12 HR HPV positive by the cobas® HPV Test and HPV genotypes, 51, 56, and 68 were positive by sequencing.

Table 39. Percent Agreement between the cobas® HPV Test HPV18 Results vs. HPV18 Sequencing in STM Comparator Stratified by CPRP Diagnosis of ≥ CIN2 or <CIN2 - SurePath

	Sequencing Results					
	≥ CIN2			< CIN2		
cobas® HPV Test Result in prequot	**HPV 18 Positive**	**HPV 18 Negative**	**Total**	**HPV 18 Positive**	**HPV 18 Negative**	**Total**
HPV 18 Detected	3	0	3	12	3	15
HPV 18 Not Detected, but either HPV 16 or Other 12 HR HPV Detected	0	62	62	0	549	549
HR HPV Not Detected	0			0		
Total	3	62	65	12	552	564
PPA: 100.0% (3/3), 95% CI: (43.9 %, 100.0 %)				PPA: 100.0% (12/12), 95% CI: (75.8 %, 100.0 %)		
NPA: 100.0% (62/62), 95% CI: (94.2 %, 100.0 %)				NPA: 99.5% (549/552), 95% CI: (98.4 %, 99.8 %)		
OPA: 100.0% (65/65), 95% CI: (94.4 %, 100.0 %)				OPA: 99.5% (561/564), 95% CI: (98.4 %, 99.8 %)		

Table 40. Percent Agreement between the cobas® HPV Test Other 12 HR HPV Results vs. 12 Other HR HPV Sequencing in STM Comparator Stratified by CPRP Diagnosis of ≥ CIN2 or <CIN2 - SurePath

Sequencing Results							
	≥ CIN2				< CIN2		
cobas® HPV Test Result in prequot	**12 other HR HPV Positive**	**12 other HR HPV Negative**	**Total**		**12 other HR HPV Positive**	**12 other HR HPV Negative**	**Total**
Other 12 HPV Detected	34	5	39		156	57	213
Other 12 HPV Not Detected, but either HPV 16 or HPV 18 Detected	3[a]	19	26		0	314	351
HR HPV Not Detected	4[b]				37		
Total	41	24	65		193	371	564
PPA: 82.9% (34/41), 95% CI: (68.7 %, 91.5 %)					PPA: 80.8% (156/193), 95% CI: (74.7 %, 85.8 %)		
NPA: 79.2% (19/24), 95% CI: (59.5 %, 90.8 %)					NPA: 84.6% (314/371), 95% CI: (80.6 %, 87.9 %)		
OPA: 81.5% (53/65), 95% CI: (70.4 %, 89.1 %)					OPA: 83.3% (470/564), 95% CI: (80.0 %, 86.2 %)		

[a] 2 cases were HPV16 positive by the cobas® HPV Test and HPV16 and 39 positive by sequencing; 1 case was HPV16 positive by the cobas® HPV Test and HPV16 and 59 positive by sequencing.

[b] 3 cases were ≥CIN2 and HPV genotypes 33, 45, 56 and 66 by sequencing; 1 case was CIN3 and HPV 52 positive by sequencing

Performance of Characteristics in the ASC-US population (≥ 21 years) using the Post-quot specimen

Clinical performance was also assessed for the post-quot specimen type in the non-vaccinated and vaccinated population. The tables below provide sensitivity, specificity, PPV, NPV, PLR, prevalence, likelihood ratios and risk estimates for the post-quot specimen.

The analyses in this section included only subjects with valid test results from the cobas® HPV Test in the post-quot specimen and valid CPR diagnosis, with the one exception. One subject was excluded because the third CPR reviewer received unblinded histology slides to review.

Table 41. Summary of the Two-Category cobas® HPV Test Results in Post-Quot and Central Pathology Review Panel Diagnosis in Non-Vaccinated Population

	CPRP Diagnosis					
cobas® HPV Test Result in Pre-quot	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Positive	180	38	16	15	2	251
Negative	299	24	5	2	0	330
Total	479	62	21	17	2	581

Table 42. Performance of the cobas® HPV Test in Post-Quot and FDA Approved Test with STM in Detecting ≥CIN2 and ≥CIN3 for Non-Vaccinated Population

Disease Endpoint		**cobas® HPV Test**		***FDA approved test with STM***	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥ CIN2	**Sensitivity (%)**	82.5 (33/40)	(68.1, 91.3)	81.8 (36/44)	(68.0, 90.5)
	Specificity (%)	59.7 (323/541)	(55.5, 63.8)	58.9 (355/603)	(54.9, 62.7)
	PPV (%)	13.1 (33/251)	(11.3, 15.3)	12.7 (36/284)	(10.9, 14.7)
	NPV (%)	97.9 (323/330)	(95.9, 98.9)	97.8 (355/363)	(95.9, 98.8)
	PLR	2.0 (33/40)/ (218/541)	(1.7, 2.4)	2.0 (36/44)/ (248/603)	(1.7, 2.4)
	NLR	0.3 (7/40)/ (323/541)	(0.1, 0.6)	0.3 (8/44)/ (355/603)	(0.2, 0.6)
	Prevalence (%)	6.9 (40/581)	(5.1, 9.2)	6.8 (44/647)	(5.1, 9.0)
≥ CIN3	**Sensitivity (%)**	89.5 (17/19)	(68.6, 97.1)	90.5 (19/21)	(71.1, 97.3)
	Specificity (%)	58.4 (328/562)	(54.2, 62.4)	57.7 (361/626)	(53.8, 61.5)
	PPV (%)	6.8 (17/251)	(5.7, 8.0)	6.7 (19/284)	(5.7, 7.8)
	NPV (%)	99.4 (328/330)	(97.8, 99.8)	99.4 (361/363)	(98.0, 99.9)
	PLR	2.1 (17/19)/ (234/562)	(1.8, 2.6)	2.1 (19/21)/ (265/626)	(1.8, 2.5)
	NLR	0.2 (2/19)/ (328/562)	(0.0, 0.7)	0.2 (2/21)/ (361/626)	(0.0, 0.6)

Disease Endpoint		cobas® HPV Test		*FDA approved test with STM*	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
	Prevalence (%)	3.3 (19/581)	(2.1, 5.1)	3.2 (21/647)	(2.1, 4.9)

Table 43. Summary of the Two-Category cobas® HPV Test Results in Post-Quot and Central Pathology Review Panel Diagnosis in Non-Vaccinated Population from Lesion

		CPRP Diagnosis from Lesion					
cobas® HPV Test Result	**No Lesion**	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Positive	121	83	23	12	11	1	251
Negative	258	61	8	2	1	0	330
Total	379	144	31	14	12	1	581

Table 44. Performance of the cobas® HPV Test in Post-Quot and FDA Approved Test with STM after Redefining CPR Diagnosis from "Disease" (≥CIN2 and ≥CIN3) to 'Non-Disease' (<CIN2 and <CIN3) in Non-Vaccinated Population with Random Biopsy

Disease Endpoint		cobas® HPV Test		*FDA approved test with STM*	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN2	**Sensitivity (%)**	88.9 (24/27)	(71.9, 96.1)	90.3 (28/31)	(75.1, 96.7)
	Specificity (%)	59.0 (327/554)	(54.9, 63.0)	58.4 (360/616)	(54.5, 62.3)
	PPV (%)	9.6 (24/251)	(8.2, 11.1)	9.9 (28/284)	(8.6, 11.3)
	NPV (%)	99.1 (327/330)	(97.4, 99.7)	99.2 (360/363)	(97.6, 99.7)
	PLR	2.2 (24/27)/(227/554)	(1.8, 2.6)	2.2 (28/31)/(256/616)	(1.9, 2.5)
	NLR	0.2 (3/27)/(327/554)	(0.1, 0.5)	0.2 (3/31)/(360/616)	(0.1, 0.5)
	Prevalence (%)	4.6 (27/581)	(3.2, 6.7)	4.8 (31/647)	(3.4, 6.7)
≥CIN3	**Sensitivity (%)**	92.3 (12/13)	(66.7, 98.6)	93.3 (14/15)	(70.2, 98.8)
	Specificity (%)	57.9 (329/568)	(53.8, 61.9)	57.3 (362/632)	(53.4, 61.1)
	PPV (%)	4.8 (12/251)	(4.0, 5.7)	4.9 (14/284)	(4.2, 5.7)

Disease Endpoint		cobas® HPV Test		*FDA approved test with STM*	
≥CIN2	**Performance**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
	NPV (%)	99.7 (329/330)	(98.0, 100.0)	99.7 (362/363)	(98.2, 100.0)
	PLR	2.2 (12/13)/(239/568)	(1.8, 2.6)	2.2 (14/15)/(270/632)	(1.9, 2.6)
	NLR	0.1 (1/13)/(329/568)	(0.0, 0.9)	0.1 (1/15)/(362/632)	(0.0, 0.8)
	Prevalence (%)	2.2 (13/581)	(1.3, 3.8)	2.3 (15/647)	(1.4, 3.8)

Table 45. Performance of the cobas® HPV Test in the Post-Quot and FDA approved test with STM in Detecting ≥CIN2 and ≥CIN3 for Non-Vaccinated Population by Biopsy Type

Disease End point		cobas® HPV Test		*FDA approved test with STM*	
	Performance	**Lesion - Direct Biopsy Point Estimate**	**No Lesion - Random Biopsy Point Estimate**	**Lesion - Direct Biopsy Point Estimate**	**No Lesion-Random Biopsy Point Estimate**
≥CIN2	Sensitivity (%) 95%CI	88.9 (24/27) (71.9, 96.1)	69.2 (9/13) (42.4, 87.3)	90.3 (28/31) (75.1, 96.7)	61.5 (8/13) (35.5, 82.3)
	Specificity (%) 95%CI	39.4 (69/175) (32.5, 46.8)	69.4 (254/366) (64.5, 73.9)	39.4 (82/208) (33.0, 46.2)	69.1 (273/395) (64.4, 73.5)
	Prevalence (%) 95%CI	13.4 (27/202) (9.4, 18.7)	3.4 (13/379) (2.0, 5.8)	13.0 (31/239) (9.3, 17.8)	3.2 (13/408) (1.9, 5.4)
≥CIN3	Sensitivity (%) 95%CI	92.3 (12/13) (66.7, 98.6)	83.3 (5/6) (43.6, 97.0)	93.3 (14/15) (70.2, 98.8)	83.3 (5/6) (43.6, 97.0)
	Specificity (%) 95%CI	37.6 (71/189) (31.0, 44.7)	68.9 (257/373) (64.0, 73.4)	37.5 (84/224) (31.4, 44.0)	68.9 (277/402) (64.2, 73.2)
	Prevalence (%) 95%CI	6.4 (13/202) (3.8, 10.7)	1.6 (6/379) (0.7, 3.4)	6.3 (15/239) (3.8, 10.1)	1.5 (6/408) (0.7, 3.2)

Table 46. Summary of the Two-Category cobas® HPV Test Results in Post-Quot and Central Pathology Review Panel Diagnosis in Vaccinated Population

CPRP Diagnosis						
cobas® HPV Test Result in Post-quot	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Positive	84	27	17	10	1	139
Negative	114	9	5	2	0	130
Total	198	36	22	12	1	269

Table 47. Performance of the cobas® HPV in Post-Quot and FDA approved test with STM in Detecting ≥CIN2 and ≥CIN3 for Vaccinated population

Disease End point		**cobas® HPV Test**		**FDA approved test with STM**	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN2	**Sensitivity (%)**	80.0 (28/35)	(64.1, 90.0)	74.3 (26/35)	(57.9, 85.8)
	Specificity (%)	52.6 (123/234)	(46.2, 58.9)	49.8 (124/249)	(43.6, 56.0)
	PPV (%)	20.1 (28/139)	(16.9, 23.8)	17.2 (26/151)	(14.2, 20.8)
	NPV (%)	94.6 (123/130)	(90.0, 97.2)	93.2 (124/133)	(88.6, 96.1)
	PLR	1.7 (28/35)/(111/234)	(1.4, 2.1)	1.5 (26/35)/(125/249)	(1.2, 1.9)
	NLR	0.4 (7/35)/(123/234)	(0.2, 0.7)	0.5 (9/35)/(124/249)	(0.3, 0.9)
	Prevalence (%)	13.0 (35/269)	(9.5, 17.6)	12.3 (35/284)	(9.0, 16.7)
≥CIN3	**Sensitivity (%)**	84.6 (11/13)	(57.8, 95.7)	76.9 (10/13)	(49.7, 91.8)
	Specificity (%)	50.0 (128/256)	(43.9, 56.1)	48.0 (130/271)	(42.1, 53.9)
	PPV (%)	7.9 (11/139)	(6.2, 10.0)	6.6 (10/151)	(4.9, 8.9)
	NPV (%)	98.5 (128/130)	(94.7, 99.6)	97.7 (130/133)	(94.1, 99.2)
	PLR	1.7 (11/13)/(128/256)	(1.3, 2.2)	1.5 (10/13)/(141/271)	(1.1, 2.0)

Disease End point		cobas® HPV Test		FDA approved test with STM	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
	NLR	0.3 (2/13)/(128/256)	(0.1, 1.1)	0.5 (3/13)/(130/271)	(0.2, 1.3)
	Prevalence (%)	4.8 (13/269)	(2.8, 8.1)	4.6 (13/284)	(2.7, 7.7)

Table 48. Summary of the Two-Category cobas® HPV Test Results in Post-Quot and Central Pathology Review Panel Diagnosis in Vaccinated Population with Direct Biopsy

		CPRP Diagnosis from lesion					
cobas® HPV Test Result	**No Lesion**	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
HPV +	61	42	17	10	9	0	139
HPV -	99	25	4	2	0	0	130
Total	160	67	21	12	9	0	269

Table 49. Performance of the cobas® HPV Test in Post-Quot and FDA approved test with STM after Changing CPR Diagnosis from 'Disease' (≥CIN2and ≥CIN3) to 'Non-Disease' (<CIN2 and <CIN3) for Vaccinated Population with Random Biopsy

Disease Endpoint		cobas® HPV Test		FDA approved test with STM	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
≥CIN2	**Sensitivity (%)**	90.5 (19/21)	(71.1, 97.3)	90.5 (19/21)	(71.1, 97.3)
	Specificity (%)	51.6 (128/248)	(45.4, 57.8)	49.8 (131/263)	(43.8, 55.8)
	PPV (%)	13.7 (19/139)	(11.6, 16.1)	12.6 (19/151)	(10.7, 14.7)
	NPV (%)	98.5 (128/130)	(94.5, 99.6)	98.5 (131/133)	(94.6, 99.6)
	PLR	1.9 (19/21)/(120/248)	(1.5, 2.3)	1.8 (19/21)/(132/263)	(1.5, 2.2)
	NLR	0.2 (2/21)/(128/248)	(0.0, 0.7)	0.2 (2/21)/(131/263)	(0.1, 0.7)
	Prevalence (%)	7.8 (21/269)	(5.2, 11.6)	7.4 (21/284)	(4.9, 11.0)
≥CIN3	**Sensitivity (%)**	100.0 (9/9)	(70.1, 100.0)	100.0 (9/9)	(70.1, 100.0)
	Specificity (%)	50.0 (130/260)	(44.0, 56.0)	48.4 (133/275)	(42.5, 54.3)

Disease Endpoint		cobas® HPV Test		FDA approved test with STM	
	Performance	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
	PPV (%)	6.5 (9/139)	(5.4, 7.7)	6.0 (9/151)	(5.0, 7.1)
	NPV (%)	100.0 (130/130)	(94.6, 100.0)	100.0 (133/133)	(94.7, 100.0)
	PLR	2.0 (9/9)/(130/260)	(1.8, 2.3)	1.9 (9/9)/(142/275)	(1.7, 2.2)
	NLR	0.0 (0/9)/(130/260)	(0.0, 0.0)	0.0 (0/9)/(133/275)	(0.0, 0.0)
	Prevalence (%)	3.3 (9/269)	(1.8, 6.2)	3.2 (9/284)	(1.7, 5.9)

Table 50. Performance of the cobas® HPV Test in Post-Quot and FDA approved test with STM in Detecting ≥CIN2 and ≥CIN3 for Vaccinated Population by Biopsy Type

Disease Endpoint		cobas® HPV Test		FDA approved test with STM	
	Performance	Lesion – Direct Biopsy Point Estimate	No Lesion – Random Biopsy Point Estimate	Lesion – Direct Biopsy Point Estimate	No Lesion – Random Biopsy Point Estimate
≥CIN2	Sensitivity (%) 95%CI	90.5 (19/21) (71.1, 97.3)	64.3 (9/14) (38.8, 83.7)	90.5 (19/21) (71.1, 97.3)	50.0 (7/14) (26.8, 73.2)
	Specificity (%) 95% CI	33.0 (29/88) (24.0, 43.3)	64.4 (94/146) (56.3, 71.7)	30.3 (30/99) (22.1, 40.0)	62.7 (94/150) (54.7, 70.0)
	Prevalence (%) 95% CI	19.3 (21/109) (13.0, 27.7)	8.8 (14/160) (5.3, 14.2)	17.5 (21/120) (11.7, 25.3)	8.5 (14/164) (5.2, 13.8)
≥CIN3	Sensitivity (%) 95% CI	100.0 (9/9) (70.1, 100.0)	50.0 (2/4) (15.0, 85.0)	100.0 (9/9) (70.1, 100.0)	25.0 (1/4) (4.6, 69.9)
	Specificity (%) 95% CI	31.0 (31/100) (22.8, 40.6)	62.2 (97/156) (54.4, 69.4)	28.8 (32/111) (21.2, 37.9)	61.3 (98/160) (53.5, 68.5)
	Prevalence (%) 95% CI	8.3 (9/109) (4.4, 15.0)	2.5 (4/160) (1.0, 6.3)	7.5 (9/120) (4.0, 13.6)	2.4 (4/164) (1.0, 6.1)

Table 51. Performance of the cobas® HPV Test in Post-Quot in Detecting ≥CIN2 and ≥CIN3 Stratified by Age in Non-Vaccinated Population

	Age group (years)			
Disease Endpoint	**Performances**	**21-29**	**30-39**	**≥ 40**
≥ CIN2	**Sensitivity (%)**	100.0 (7/7)	81.0 (17/21)	75.0 (9/12)
	95% CI (%)	(64.6, 100.0)	(60.0, 92.3)	(46.8, 91.1)
	Specificity (%)	51.5 (52/101)	51.1 (96/188)	69.4 (175/252)
	95% CI (%)	(41.9, 61.0)	(44.0, 58.1)	(63.5, 74.8)
	PPV (%)	12.5 (7/56)	15.6 (17/109)	10.5 (9/86)
	95% CI (%)	(9.8, 15.9)	(12.5, 19.2)	(7.4, 14.5)

	Age group (years)			
Disease Endpoint	**Performances**	**21-29**	**30-39**	**≥ 40**
	NPV (%)	100.0 (52/52)	96.0 (96/100)	98.3 (175/178)
	95% CI (%)	(87.7, 99.9)	(90.8, 98.3)	(95.6, 99.4)
	Prevalence	6.5 (7/108)	10.0 (21/209)	4.5 (12/264)
≥ CIN3	**Sensitivity (%)**	100.0 (4/4)	81.8 (9/11)	100.0 (4/4)
	95% CI (%)	(51.0, 100.0)	(52.3, 94.9)	(51.0, 100.0)
	Specificity (%)	50.0 (52/104)	49.5 (98/198)	68.5 (178/260)
	95% CI (%)	(40.6, 59.4)	(42.6, 56.4)	(62.6, 73.8)
	PPV (%)	7.1 (4/56)	8.3 (9/109)	4.7 (4/86)
	95% CI (%)	(5.0, 10.1)	(6.2, 10.9)	(3.3, 6.6)
	NPV (%)	100.0 (52/52)	98.0 (98/100)	100.0 (178/178)
	95% CI (%)	(88.3, 99.9)	(93.3, 99.4)	(96.3, 100.0)
	Prevalence	3.7 (4/108)	5.3 (11/209)	1.5 (4/264)

Table 52. Performance of the cobas® HPV Test in Post-Quot in Detecting ≥CIN2 and ≥CIN3 Stratified by Age in Vaccinated Population

	Age Group (years)			
Disease Endpoint	**Performance**	**21-29**	**30-39**	**≥ 40**
≥ CIN2	**Sensitivity (%)**	78.1 (25/32)	100.0 (3/3)	0.0 (0/0)
	95% CI (%)	(61.2, 89.0)	(43.9, 100.0)	(0.0, 0.0)
	Specificity (%)	51.9 (110/212)	59.1 (13/22)	0.0 (0/0)
	95% CI (%)	(45.2, 58.5)	(38.7, 76.7)	(0.0, 0.0)
	PPV (%)	19.7 (25/127)	25.0 (3/12)	0.0 (0/0)
	95% CI (%)	(16.3, 23.6)	(14.7, 39.2)	(0.0, 0.0)
	NPV (%)	94.0 (110/117)	100.0 (13/13)	0.0 (0/0)
	95% CI (%)	(89.0, 96.8)	(66.1, 99.7)	(0.0, 0.0)
	≥CIN2 Prevalence	13.1 (32/244)	12.0 (3/25)	0.0 (0/0)
≥ CIN3	**Sensitivity (%)**	81.8 (9/11)	100.0 (2/2)	0.0 (0/0)
	95% CI (%)	(52.3, 94.9)	(34.2, 100.0)	(0.0, 0.0)
	Specificity (%)	49.4 (115/233)	56.5 (13/23)	0.0 (0/0)
	95% CI (%)	(43.0, 55.7)	(36.8, 74.4)	(0.0, 0.0)
	PPV (%)	7.1 (9/127)	16.7 (2/12)	0.0 (0/0)

	Age Group (years)			
Disease Endpoint	**Performance**	**21-29**	**30-39**	**≥ 40**
	95% CI (%)	(5.3, 9.4)	(8.4, 30.3)	(0.0, 0.0)
	NPV (%)	98.3 (115/117)	100.0 (13/13)	0.0 (0/0)
	95% CI (%)	(94.2, 99.5)	(68.0, 99.7)	(0.0, 0.0)
	≥CIN3 Prevalence	4.5 (11/244)	8.0 (2/25)	0.0 (0/0)

Table 53. Likelihood Ratios and Risk of Disease by cobas® HPV Test Results in Post-Quot in Detecting ≥ CIN2 and ≥ CIN3 in the Non-Vaccinated Population

Disease Endpoint	**cobas® HPV Test Results**	**Likelihood Ratio (95% CI)**	**Risk of Disease (%) Given Test Result (95% CI)**
≥ CIN2	HPV 16+/18+	5.3 (3.2, 8.8)	28.3 (15/53) (19.3, 39.5)
	Other 12 HR +	1.4 (0.9, 1.9)	9.1 (18/198) (6.5, 12.6)
	Negative	0.3 (0.1, 0.6)	2.1 (7/330) (1.1, 4.1)
	Prevalence (%)	6.9 (5.6, 8.5)	
≥ CIN3	HPV 16+/18+	7.7 (4.8, 12.5)	20.8 (11/53) (13.9, 29.8)
	Other 12 HR +	0.9 (0.5, 1.8)	3.0 (6/198) (1.6, 5.8)
	Negative	0.2 (0.0, 0.7)	0.6 (2/330) (0.2, 2.2)
	Prevalence (%)	3.3 (2.4, 4.5)	

Table 54. Likelihood Ratios and Risk of Disease by cobas® HPV Test Results in Post-Quot in Detecting ≥ CIN2 and ≥ CIN3 in the Vaccinated Population

Disease Endpoint	**cobas® HPV Test Results**	**Likelihood Ratio (95% CI)**	**Risk of Disease (%) Given Test Result (95% CI)**
≥ CIN2	HPV 16+/18+	5.3 (2.3, 12.6)	44.4 (8/18) (25.3, 65.4)
	Other 12 HR +	1.3 (1.0, 1.8)	16.5 (20/121) (12.5, 21.5)
	Negative	0.4 (0.2, 0.7)	5.4 (7/130) (2.8, 10.0)
	Prevalence (%)	13.0 (10.4, 16.1)	
≥ CIN3	HPV 16+/18+	12.5 (5.8, 27.0)	38.9 (7/18) (22.8, 57.8)
	Other 12 HR +	0.7 (0.3, 1.5)	3.3 (4/121) (1.5, 7.2)
	Negative	0.3 (0.1, 1.1)	1.5 (2/130) (0.4, 5.3)
	Prevalence (%)	4.8 (3.3, 7.0)	

Table 55. Summary of the cobas® HPV Test Results in Post-Quot and Central Pathology Review Panel Diagnosis in Non-Vaccinated Population

	Central Pathology Review Diagnosis					
cobas® HPV Test Result	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
Failed	2	0	0	0	0	2
NEG Other HR HPV, NEG HPV16, NEG HPV18	191	22	5	2	0	220
NEG Other HR HPV, NEG HPV16, POS HPV18	2	1	0	1	0	4
NEG Other HR HPV, POS HPV16, NEG HPV18	5	1	2	4	1	13
NEG Other HR HPV, POS HPV16, POS HPV18	1	0	0	0	0	1
Other HR HPV NEG, HPV16 NEG, HPV18 NEG	108	2	0	0	0	110
Other HR HPV NEG, HPV16 NEG, HPV18 POS	2	0	0	0	0	2
Other HR HPV NEG, HPV16 POS, HPV18 NEG	6	1	1	2	1	11
Other HR HPV POS, HPV16 NEG, HPV18 NEG	63	11	4	0	0	78
Other HR HPV POS, HPV16 NEG, HPV18 POS	3	0	0	0	0	3
Other HR HPV POS, HPV16 POS, HPV18 NEG	0	1	1	0	0	2
Other HR HPV POS, HPV16 POS, HPV18 POS	1	0	0	0	0	1
POS Other HR HPV, NEG HPV16, NEG HPV18	85	21	8	6	0	120
POS Other HR HPV, NEG HPV16, POS HPV18	4	0	0	1	0	5
POS Other HR HPV, POS HPV16, NEG HPV18	7	2	0	1	0	10
POS Other HR HPV, POS HPV16, POS HPV18	1	0	0	0	0	1
Total	481	62	21	17	2	583

Table 56. Central Pathology Review Diagnosis and Absolute Risk of ≥CIN2 and ≥CIN3 by cobas® HPV Test Result Status in Post-Quot in the Non-Vaccinated Population

		Central Pathology Review Diagnosis						
cobas® HPV Test Result	**Total**	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Absolute Risk for ≥CIN2 (%)**	**Absolute Risk for ≥CIN3 (%)**
HPV16 positive	39	21	5	4	7	2	33.3	23.1
HPV18 positive	14	11	1	0	2	0	14.3	14.3
Other 12 HR HPV positive	198	148	32	12	6	0	9.1	3.0
HPV negative	330	299	24	5	2	0	2.1	0.6
HPV16 positive and/or HPV18 positive	53	32	6	4	9	2	28.3	20.8
HPV positive	251	180	38	16	15	2	13.1	6.8

Table 57. Absolute Risk of ≥CIN2 and ≥CIN3 by cobas® HPV Test Result Status in Post-Quot Stratified by Age in the Non-Vaccinated Population

		Age Group (Years)		
Disease End Point	**cobas® HPV Test Result**	**21-29**	**30-39**	**≥ 40**
≥CIN2	HPV16 positive /18 positive	30.0 (3/10)	27.6 (8/29)	28.6 (4/14)
		(10.8,60.3)	(14.7,45.7)	(11.7,54.6)
	Other 12 HR HPV positive	8.7 (4/46)	11.3 (9/80)	6.9 (5/72)
		(3.4,20.3)	(6.0,20.0)	(3.0,15.2)
	Negative	0.0 (0/52)	4.0 (4/100)	1.7 (3/178)
		(0.0,6.9)	(1.6,9.8)	(0.6,4.8)
	Prevalence	6.5 (7/108)	10.0 (21/209)	4.5 (12/264)
		(3.2, 12.8)	(6.7, 14.9)	(2.6, 7.8)
≥CIN3	HPV16 positive /18 positive	20.0 (2/10)	20.7 (6/29)	21.4 (3/14)
		(5.7,51.0)	(9.8,38.4)	(7.6,47.6)
	Other 12 HR HPV positive	4.3 (2/46)	3.8 (3/80)	1.4 (1/72)
		(1.2,14.5)	(1.3,10.5)	(0.2,7.5)
	Negative	0.0 (0/52)	2.0 (2/100)	0.0 (0/178)
		(0.0,6.9)	(0.6,7.0)	(0.0,2.1)
	Prevalence	3.7 (4/108)	5.3 (11/209)	1.5 (4/264)
		(1.4, 9.1)	(3.0, 9.2)	(0.6, 3.8)

Table 58. Relative Risks of ≥ CIN2 and ≥ CIN3 by cobas® HPV Test Result Status (Post-Quot) in the Non-Vaccinated Population

	CPR Diagnosis ≥CIN2		**CPR Diagnosis ≥CIN3**	
cobas® HPV Test Result	**Relative Risk**	**95% CI**	**Relative Risk**	**95% CI**
HPV Positive vs. Negative	6.2	(2.8, 13.8)	11.2	(2.6, 47.9)
HPV16 positive/18 positive vs. Negative	13.3	(5.7, 31.2)	34.2	(7.8, 150.2)
HPV16 positive /18 positive vs. 12 Other HR HPV positive	3.1	(1.7, 5.8)	6.8	(2.7, 17.7)
12 Other HR HPV positive vs. Negative	4.3	(1.8, 10.1)	5.0	(1.0, 24.5)
Prevalence	6.9 (40/581)	(5.1, 9.2)	3.3 (19/581)	(2.1, 5.1)

Table 59. Summary of the cobas® HPV Test Results in Post-Quot and Central Pathology Review Panel Diagnosis in Vaccinated Population

	Central Pathology Review Diagnosis					
cobas® HPV Test Result in Post-quot	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
NEG Other HR HPV, NEG HPV16, NEG HPV18	100	9	5	2	0	116
NEG Other HR HPV, NEG HPV16, POS HPV18	1	0	0	0	1	2
NEG Other HR HPV, POS HPV16, NEG HPV18	2	0	0	2	0	4
Other HR HPV NEG, HPV16 NEG, HPV18 NEG	14	0	0	0	0	14
Other HR HPV POS, HPV16 NEG, HPV18 NEG	20	8	1	1	0	30
Other HR HPV POS, HPV16 POS, HPV18 NEG	1	0	0	0	0	1
POS Other HR HPV, NEG HPV16, NEG HPV18	54	19	15	3	0	91

	Central Pathology Review Diagnosis					
cobas® HPV Test Result in Post-quot	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Total**
POS Other HR HPV, NEG HPV16, POS HPV18	3	0	0	0	0	3
POS Other HR HPV, POS HPV16, NEG HPV18	3	0	1	4	0	8
Total	198	36	22	12	1	269

Table 60. Central Pathology Review Diagnosis and Absolute Risk of ≥CIN2 and ≥CIN3 by cobas® HPV Test Result Status in Post-Quot in the Vaccinated Population

cobas® HPV Test Result	**Total**	**Normal**	**CIN1**	**CIN2**	**CIN3**	**Cancer**	**Absolute Risk for ≥CIN2 (%)**	**Absolute Risk for ≥CIN3 (%)**
HPV16 positive	13	6	0	1	6	0	53.8	46.2
HPV18 positive	5	4	0	0	0	1	20.0	20.0
12 Other HR HPV positive	121	74	27	16	4	0	16.5	3.3
HPV negative	130	114	9	5	2	0	5.4	1.5
HPV16 positive and/or HPV18 positive	18	10	0	1	6	1	44.4	38.9
HPV positive	139	84	27	17	10	1	20.1	7.9

Table 61. Absolute Risk of ≥ CIN2 and ≥ CIN3 by cobas® HPV Test Result in Post-Quot Stratified by Age in the Vaccinated Population

		Age Group (Years)		
Disease End Point	**cobas® HPV Test Result**	**21-29**	**30-39**	**≥ 40**
≥ CIN2	HPV16 positive /18 positive	40.0 (6/15)	66.7 (2/3)	0.0 (0/0)
		(19.8,64.3)	(20.8,93.9)	(0.0, 0.0)
	Other 12 HR HPV positive	17.0 (19/112)	11.1 (1/9)	0.0 (0/0)
		(11.1,25.0)	(2.0,43.5)	(0.0, 0.0)
	Negative	6.0 (7/117)	0.0 (0/13)	0.0 (0/0)
		(2.9,11.8)	(0.0,22.8)	(0.0, 0.0)
	Prevalence	13.1 (32/244)	12.0 (3/25)	0.0 (0/0)
		(9.4, 17.9)	(4.2, 30.0)	(0.0, 0.0)

		Age Group (Years)		
Disease End Point	**cobas® HPV Test Result**	**21-29**	**30-39**	**≥ 40**
≥ CIN3	HPV16 positive /18 positive	33.3 (5/15)	66.7 (2/3)	0.0 (0/0)
		(15.2,58.3)	(20.8,93.9)	(0.0, 0.0)
	Other 12 HR HPV positive	3.6 (4/112)	0.0 (0/9)	0.0 (0/0)
		(1.4,8.8)	(0.0,29.9)	(0.0, 0.0)
	Negative	1.7 (2/117)	0.0 (0/13)	0.0 (0/0)
		(0.5,6.0)	(0.0,22.8)	(0.0, 0.0)
	Prevalence	4.5 (11/244)	8.0 (2/25)	0.0 (0/0)

Table 62. Relative Risks of ≥CIN2 and ≥CIN3 by cobas® HPV Test Result Status (Post-Quot) in the Vaccinated Population

	CPR Diagnosis ≥CIN2		**CPR Diagnosis ≥CIN3**	
cobas® HPV Test Result	**Relative Risk**	**95% CI**	**Relative Risk**	**95% CI**
HPV Positive vs. Negative	3.7	(1.7, 8.3)	5.1	(1.2, 22.8)
HPV16 positive/18 positive vs. Negative	8.3	(3.4, 20.0)	25.3	(5.7, 112.4)
HPV16 positive /18 positive vs. Other 12 HR HPV positive	2.7	(1.4, 5.2)	11.8	(3.8, 36.2)
Other 12 HR HPV positive vs. Negative	3.1	(1.3, 7.0)	2.1	(0.4, 11.5)
Prevalence	13.0 (35/269)	(9.5, 17.6)	4.8 (13/269)	(2.8, 8.1)

E. 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 two principal 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

Supplemental clinical data from Year 3 Visit of the ATHENA Study were provided to support the use of the SurePath specimen type for adjunct testing to cervical cytology in women ≥30 years old.

During Year 3 of the follow-up phase of the ATHENA study, a co-collection of samples in PreservCyt and SurePath collection media was performed if women consented to collection of an additional (second) specimen in SurePath. All study participants either underwent colposcopy if an abnormal cytology result was obtained or were offered an exit colposcopy and ECC to maximize disease ascertainment. Among the patients remaining in Year 3 of the study, 88% agreed to undergo the colposcopy/ECC. A total of 4,882 women completed the Year 3 follow-up. Of these, 4,023 women had valid test results for PreservCyt and SurePath cytology and cobas® HPV Test. Similarity between the performance estimates for specimens collected in PreservCyt and SurePath media was demonstrated in this study. A study to further demonstrate clinical performance of the cobas® HPV Test as an adjunct to cervical cytology in women ≥30 years of age is specified in the approval order as a condition of approval.

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. Effectiveness Conclusions

The effectiveness of the cobas® HPV Test with cervical specimens collected by a clinician using a cervical broom and placed in SurePath™ Preservative Fluid has been demonstrated for use in conjunction with cervical cytology in the following patient populations. Based on the totality of the analytical and clinical data in Sections IX and X, a reasonable determination of effectiveness of the cobas® HPV Test for use in screening women ≥21 years with ASC-US cervical cytology results has been demonstrated. Additionally, 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. 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 data collected in a clinical study conducted to support PMA supplement approval as described above. Based on the results of the

analytical and clinical studies, the cobas® HPV Test, 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 Conclusions

The benefits of the cobas® HPV Test for the proposed indications for use outweigh the risks of the cobas® HPV Test for the proposed indications.

The benefit-risk analysis of the clinical study data demonstrated that the cobas® HPV Test with SurePath specimens has a benefit-risk profile for non—vaccinated and vaccinated women similar to the benefit-risk profiles of other FDA approved HPV tests.

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

In conclusion, given the available information described above, the data support the new intended use/indication for use; 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 use of cervical specimens collected in SurePath™ Preservative Fluid with this device when used in accordance with the intended use/indications for use and the instructions for use.

The data from the nonclinical studies demonstrated acceptable analytical sensitivity, precision, and analytical specificity of the cobas® HPV Test when used according to the instructions for use, the warnings and precautions, and limitations sections of the labeling. The clinical studies and the pperformance analysis of clinical data in this application have 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 July 7, 2016. The final conditions of approval can be found in the approval order.

The applicant's manufacturing facility was 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, Warnings, Precautions, and Limitations in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

None