SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Human Papillomavirus DNA detection kit

Device Trade Name: cobas HPV Test

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

Date of FDA Notice of Approval: April 19, 2011

Expedited: Not applicable

II. INDICATIONS FOR USE

The cobas HPV Test is indicated for use:

The cobas HPV Test is a qualitative *in vitro* test for the detection of Human Papillomavirus (HPV) in patient specimens. 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 HPV 16 and HPV 18 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 assess the presence or absence of high-risk HPV genotypes 16 and 18. This information, together with the physician's assessment of cytology 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 assess the presence or absence of high risk HPV types. This

information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

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

Cervical specimens that may be tested with the cobas HPV Test include the following liquid based collection media and collection device:

- ThinPrep Pap Test PreservCyt Solution
- Endocervical Brush/Spatula

III. CONTRAINDICATIONS

None.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the cobas HPV Test labeling.

V. DEVICE DESCRIPTION

The cobas HPV Test is a qualitative in vitro test for the detection of Human Papillomavirus (HPV) in patient specimens. 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). Specimens are limited to cervical cells collected with an endocervical brush/spatula in PreservCyt solution (Hologic Corp.). The cobas HPV Test is based on two major processes: (1) automated specimen preparation to simultaneously extract HPV and cellular DNA; (2) PCR amplification of target DNA sequences using both HPV and beta-globin specific complementary primer pairs and real-time detection of cleaved fluorescent-labeled HPV and beta-globin specific oligonucleotide detection probes. The concurrent extraction, amplification and detection of beta-globin in the cobas HPV Test monitors the entire test process.

The Master Mix reagent for the cobas HPV Test contains primer pairs and probes specific for the 14 high-risk HPV types and beta-globin DNA. The detection of amplified DNA (amplicon) is performed during thermal cycling using oligonucleotide probes labeled with four different fluorescent dyes which are read on 4 different channels. The amplified signal from twelve high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), is detected using the same fluorescent dye, while HPV16, HPV18 and beta-globin signals are each detected with their own dedicated fluorescent dye.

The Test is run on the cobas 4800 system. The cobas 4800 system is a multi-instrument platform that will perform qualitative in vitro nucleic acid amplification tests from human specimens. The cobas 4800 system integrates automated total nucleic acid isolation directly from secondary sample tubes, PCR setup, and real-time PCR.

The cobas 4800 system software includes a validated two stage data analysis algorithm to determine the cycle threshold value (Ct) — the cycle number where the signal of the accumulating PCR product starts to grow exponentially in each channel as well as to check for the integrity of the signal. "Positive," "Negative," or "Invalid" result are determined for each sample in each channel based on predefined parameters and Ct cut offs for each channel. The ultimate result reported for each specimen or control is determined as a combination of results from all four detection channels according to predefined data analysis algorithm.

The result reporting architecture includes two options: (1) HR HPV only, and (2) HR HPV plus genotyping of 16 and 18. For the HR HPV only option, any positive signal from Channel 1 and/or channel 2 and/or channel 3 is reported as "HR HPV positive" and channel 4 (beta-globin signal) must be valid. For HR HPV plus genotyping option, positivity is determined for each individual channel, thereby allowing the specific identification of HPV16 or HPV18 with the other HR HPV types detected collectively.

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

Interpretation of Results

Note: All assay and run validation is performed by the cobas 4800 software.
Note: A valid run may include both valid and invalid specimen results.
For a valid run, specimen results are interpreted as shown below:

Result Interpretation of the cobas HPV Test for Presence of HPV DNA

cobas HPV Test	Result Report and Interpretation
SubTest "HPV High Risk Panel":	
HR HPV POS	**High Risk HPV Positive** Specimen is positive for the DNA of any one of, or combination of, the following high risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.
HR HPV NEG	**High Risk HPV Negative*** HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold.
Invalid	**High Risk HPV Invalid** Results are invalid. Original specimen should be re-tested to obtain valid result.
Failed	**No Result for Specimen** Consult the **cobas** 4800 system Operator's Manual for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid result.
SubTest "HPV High Risk Panel Plus Genotyping"	
Other HR HPV POS, HPV16 POS, HPV18 POS	**Other High Risk HPV Positive, HPV16 Positive, HPV18 Positive.** Specimen is positive for HPV types 16 and 18 DNA and the DNA of any one of, or combination of, the following high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.
Other HR HPV POS, HPV16 POS, HPV18 NEG	**Other High Risk HPV Positive, HPV16 Positive, HPV18 Negative*.** Specimen is positive for HPV type 16 DNA and the DNA of any one of, or combination of, the following high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

cobas HPV Test	Result Report and Interpretation
	HPV type 18 DNA was undetectable or below the pre-set threshold.
Other HR HPV POS, HPV16 NEG, HPV18 POS	**Other High Risk HPV Positive, HPV16 Negative*, HPV18 Positive.** Specimen is positive for HPV type 18 DNA and the DNA of any one of, or combination of, the following high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. HPV type 16 DNA was undetectable or below the pre-set threshold.
Other HR HPV POS, HPV16 NEG, HPV18 NEG	**Other High Risk HPV Positive, HPV16 Negative*, HPV18 Negative*.** Specimen is positive for the DNA of any one of, or combination of, the following high risk HPV types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. HPV types 16 and 18 DNA were undetectable or below the pre-set threshold.
Other HR HPV NEG, HPV16 POS, HPV18 POS	**Other High Risk HPV Negative*, HPV16 Positive, HPV18 Positive.** HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold. Specimen is positive for HPV types 16 and 18 DNA.
Other HR HPV NEG, HPV16 NEG, HPV18 POS	**Other High Risk HPV Negative*, HPV16 Negative*, HPV18 Positive.** HPV types 16, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold. Specimen is positive for HPV type 18 DNA.
Other HR HPV NEG, HPV16 POS, HPV18 NEG	**Other High Risk HPV Negative*, HPV16 Positive, HPV18 Negative*.** HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold. Specimen is positive for HPV type 16 DNA.
Other HR HPV NEG, HPV16 NEG, HPV18 NEG	**Other High Risk HPV Negative*, HPV16 Negative*, HPV18 Negative*.** HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 DNA were undetectable or below the pre-set threshold.
Invalid	**Invalid.** The results are Invalid. Original specimen should be re-tested no more than two times to obtain valid results. If the results are still invalid a new specimen should be obtained.
Failed	**No Result for Specimen** Consult the **cobas** 4800 system Operator's Manual for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid results.

*A negative result does not preclude the presence of HPV infection because results depend on adequate specimen collection, absence of inhibitors and sufficient DNA to be detected.

Result Interpretation of the cobas HPV Test*

Results	Interpretation for Patients with ASC-US cytology who are ≥21 years old	Interpretation for Patients with NILM cytology who are ≥ 30 years old
Other HR HPV** NEG, HPV16 NEG, HPV18 NEG	Very low likelihood of underlying ≥ CIN2;	Lowest likelihood of underlying ≥ CIN2.
Other HR HPV** POS, HPV16 NEG, HPV18 NEG	Increased likelihood that underlying ≥ CIN2 will be detected at colposcopy.	Low likelihood of underlying ≥ CIN2.
HPV16 POS and/or HPV18 POS	Highest likelihood that underlying ≥ CIN2 will be detected at colposcopy[1,2].	Increased likelihood of underlying ≥CIN2.

**Other HR HPV DNA includes the following types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.
*According to the 2006 consensus guidelines[3], HPV testing should not be performed on women younger than 21 years of age. Also, women 21 years and older with greater than ASC-US cytology (including ASC-H, LSIL or above) should proceed to colposcopy regardless of their HPV test results.

NOTE: HPV negative results are not intended to prevent women from proceeding to colposcopy.
NOTE: In addition to the results tabulated above, invalid results for one or more combinations are also possible. If such a result is obtained, for example:
Other HR HPV NEG, HPV16 POS, HPV18 Invalid
The positive and negative results should be interpreted as shown in Table 1. In this example, HPV 18 results are invalid. The specimen should be re-tested to obtain valid results.
NOTE: Negative results indicate HPV DNA concentrations are undetectable or below the pre-set threshold.
NOTE: Positive test results indicates the presence of any one or more of the high risk types, but since patients are often co-infected with low-risk types it does not rule out the presence of low-risk types in patients with mixed infections.
NOTE: Results of this test should only be interpreted in conjunction with information available from clinical evaluation of the patient and patient history.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

Two alternatives for the detection of high-risk HPV DNA and one alternative for the detection of HPV 16 and 18 DNA are currently approved in the United States. At the time of this approval there are no alternative FDA approved devices that detect other HPV targets (such as HPV RNA or protein). Each DNA detection method has its own advantages and disadvantages.

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

VII. MARKETING HISTORY

This product is currently being marketed in Australia since the end of August, 2009. The product has also been available for sale in the European Union since December 2009. The product was licensed in Canada in 2010. It has not been withdrawn from these markets for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. As with any *in vitro* diagnostic test, the potential adverse effects are associated with incorrect test results or result interpretations. Failure of this device to perform as expected or failure to correctly interpret results may lead to incorrect HPV test results and subsequently, improper patient management decisions in cervical cancer screening and treatment. False negative results may lead to delays in the timely diagnosis of cervical cancer and treatment, allowing an undetected condition to worsen and potentially increasing morbidity and mortality. False positive results could lead many women to unnecessarily undergo more frequent screening and potentially invasive procedures such as colposcopy and biopsy.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Clinical Cutoff Determination of the cobas HPV Test

The clinical cutoff for detecting high-grade cervical disease (≥CIN2) for the cobas HPV test was selected based on approximately 29,000 subjects enrolled in Phase 1 of the ATHENA study. The method for selection of cutoff was based on Kondratovich[4] and was chosen to achieve a pre-defined level of sensitivity of 93% for ≥ CIN2 in the ASC-US population. Based on these criteria, the cutoff values of (40.0, 40.5, 40.0) in the 3 channels (12 Other HR HPV, HPV 16 and HPV 18, respectively) were selected for the cobas HPV test.

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 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 PreservCyt solution, and 2) HPV positive cell lines SiHa (HPV16) and HeLa (HPV18) in PreservCyt solution 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 level for each of 3 reagent lots. A total of 30 runs were performed in a period of 5 days using 4 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 results from the reagent lot producing the most conservative (highest) LOD in the analysis.

Limit of Detection Levels for HPV Types 31, 16, 18 and Cell Lines SiHa (HPV16) and HeLa (HPV18)

HPV Type	Concentration (copies or cells/mL)	Number of Positive/Tested	Mean CT	% Positives	95% Confidence Interval	
					Lower	Upper
31	600	60/60	36.6	100.0%	94.0%	100.0%
	300	**59/61**	**37.9**	**96.7%**	**88.7%**	**99.6%**
	150	49/60	38.7	81.7%	69.6%	90.5%
16	1500	60/60	36.5	100.0%	94.0%	100.0%
	600	**60/60**	**37.7**	**100.0%**	**94.0%**	**100.0%**
	300	55/61	39.1	90.2%	79.8%	96.3%
18	1,500	60/60	36.9	100.0%	94.0%	100.0%
	600	**60/60**	**38.0**	**100.0%**	**94.0%**	**100.0%**
	300	42/61	39.6	68.9%	55.7%	80.1%
SiHa (HPV16)	200	60/60	36.9	100.0%	94.6%	100.0%
	100	**60/60**	**38.0**	**100.0%**	**94.6%**	**100.0%**
	50	53/60	39.3	88.3%	77.4%	95.2%
HeLa (HPV18)	80	60/60	35.7	100.0%	94.0%	100.0%
	40	**60/60**	**36.8**	**100.0%**	**94.0%**	**100.0%**
	20	56/60	38.2	93.3%	83.8%	98.1%

3. Inclusivity Verification

To verify that the cobas HPV Test is capable of accurately detecting *all HPV high risk genotypes, the Limit of Detection (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 PreservCyt solution to concentrations below, above and at the expected LOD levels. Two lots of reagents 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 below contains results from the reagent lot producing the most conservative (higher) LOD in the analysis.

Summary of High Risk Genotype Limit Of Detection For cobas® HPV Genotype Inclusivity Study

HPV DNA *Type	LOD (copies/mL)	Number of Positive/Tested	Mean CT	Hit Rate	95% Confidence Interval	
					Lower	Upper
33	300	24/24	38.2	100.0%	85.7%	100.0%
35	600	23/24	38.4	95.8%	78.8%	99.8%
39	300	24/24	37.9	100.0%	85.7%	100.0%
45	150	23/24	38.0	95.8%	78.8%	99.8%
51	300	24/24	38.4	100.0%	85.7%	100.0%
52	2400	24/24	39.1	100.0%	85.7%	100.0%
56	1200	23/24	38.4	95.8%	78.8%	99.8%
58	600	24/24	38.6	100.0%	85.7%	100.0%
59	300	23/24	39.0	95.8%	78.8%	99.8%
66	1200	24/24	37.7	100.0%	85.7%	100.0%
68	1200	24/24	38.0	100.0%	85.7%	100.0%

*The LOD of the cobas HPV Test for HPV genotypes 16, 18 and 31 was determined as described above in this Package Insert.

4. Reproducibility

An 18-member panel composed of pools made from clinical samples collected into PreservCyt solution, and from samples derived from SiHa and HeLa cell lines was tested for Reproducibility Each panel member was tested for 18 days (6 days per kit lot), 2 replicates per run, at 3 testing sites. Two operators at each of 3 sites performed 2 runs per day for 3 days each on each of 3 reagent lots. A run was defined as 36 panel-member aliquots and 1 positive and 1 negative control.

Overall, 111 runs were performed to obtain 108 valid runs. The 3 invalid runs were due to instrument errors (percent of invalid runs was 2.7% (3/111) with 95% CI: 0.6%, 7.7%). A total of 3,888 tests were performed on the 18 panel members in the valid runs; 5 of those tests were invalid due to instrument errors.

All valid test results were included in the analyses that reported the percentage of correct results. There were no false positive results in 216 tests performed on the negative panel members (background negative cell and the pooled negative clinical sample; see Table below).

Results by Sample Type and Negative Panel Member for Lot and Site/Instrument

Sample Type	Panel Member	Ct SD	Ct CV %	Number Negative / Total Number Valid Results					
				Lot			Site/ Instrument		
				Lot ID	Negative/ Valid	%	Site ID	Negative/ Valid	%
Background cell line	Negative cell line	n/a	n/a	1	72/72	100.0	1	72/72	100.0
				2	72/72	100.0	2	72/72	100.0
				3	72/72	100.0	3	72/72	100.0
Pooled negative clinical sample	Negative	n/a	n/a	1	72/72	100.0	1	72/72	100.0
				2	72/72	100.0	2	72/72	100.0
				3	72/72	100.0	3	72/72	100.0

The percents of positive results for the positive panel members are presented below. With respect to sites, site 1 tended to have a lower percent positive for some weak-positive and moderate-positive panel members. This trend can be attributed to operator 1, who tended to have lower percent positive values in the weak positive and moderate positive panel members.

Analysis of variance of the Ct values from valid tests performed on positive panel members yielded overall CV (%) ranges of 1.1% to 2.5% for the SiHa cell lines, 1.5% to 2.5% for the HeLa cell lines, and 3.5% to 10.3% for the pooled clinical samples.

Results by Sample Type and Positive Panel Member for Lot and Site/Instrument

Sample Type	Panel Member	Ct SD	Ct CV %	Number Positive / Total Number Valid Results					
				Lot			Site/Instrument		
				Lot ID	Positive/ Valid	%	Site ID	Positive/ Valid	%
SiHa cell line	HPV16 - weak positive A (25 cells/mL)	0.45	1.1	1	41/72	56.9	1	22/72	30.6
				2	25/72	34.7	2	38/72	52.8
				3	23/72	31.9	3	29/72	40.3
SiHa cell line	HPV16 - weak positive B (60 cells/mL)	0.68	1.7	1	66/72	91.7	1	56/72	77.8
				2	64/72	88.9	2	71/72	98.6
				3	63/72	87.5	3	66/72	91.7
SiHa cell line	HPV16 - weak positive C (80 cells/mL)	0.68	1.8	1	68/72	94.4	1	61/72	84.7
				2	67/72	93.1	2	72/72	100.0
				3	69/72	95.8	3	71/72	98.6
SiHa cell line	HPV16 – positive (150 cells/mL)	0.94	2.5	1	71/72	98.6	1	71/72	98.6
				2	71/72	98.6	2	72/72	100.0
				3	72/72	100.0	3	71/72	98.6
HeLa cell line	HPV18 - weak positive A (8 cells/mL)	0.60	1.5	1	43/72	59.7	1	34/72	47.2
				2	35/72	48.6	2	46/72	63.9
				3	42/72	58.3	3	40/72	55.6
HeLa cell line	HPV18 - weak positive B (22 cells/mL)	0.90	2.4	1	67/72	93.1	1	59/72	81.9
				2	63/72	87.5	2	72/72	100.0
				3	67/72	93.1	3	66/72	91.7
HeLa cell line	HPV18 - weak positive C (27 cells/mL)	0.90	2.4	1	69/72	95.8	1	65/72	90.3
				2	67/72	93.1	2	71/72	98.6
				3	72/72	100.0	3	72/72	100.0
HeLa cell line	HPV18 – positive (50 cells/mL)	0.91	2.5	1	70/72	97.2	1	69/72	95.8
				2	71/72	98.6	2	72/72	100.0
				3	72/72	100.0	3	72/72	100.0
Pooled HPV 16 clinical sample	HPV16 - moderate positive	1.59	4.3	1	66/71	93.0	1	64/72	88.9
				2	66/71	93.0	2	68/70	97.1
				3	69/72	95.8	3	69/72	95.8
Pooled HPV	HPV16 - positive	1.21	3.5	1	72/72	100.0	1	72/72	100.0

Sample Type	Panel Member	Ct SD	Ct CV %	Number Positive / Total Number Valid Results					
				Lot			Site/Instrument		
				Lot ID	Positive/ Valid	%	Site ID	Positive/ Valid	%
16 clinical sample				2	71/71	100.0	2	72/72	100.0
				3	72/72	100.0	3	71/71	100.0
Pooled HPV 18 clinical sample	HPV18 - moderate positive	2.30	6.1	1	62/71	87.3	1	56/71	78.9
				2	63/72	87.5	2	71/72	98.6
				3	67/72	93.1	3	65/72	90.3
Pooled HPV 18 clinical sample	HPV18 - positive	3.51	10.3	1	72/72	100.0	1	71/71	100.0
				2	72/72	100.0	2	72/72	100.0
				3	71/71	100.0	3	72/72	100.0
Pooled HPV 31 clinical sample	HPV31 - moderate positive	2.95	8.0	1	67/72	93.1	1	61/72	84.7
				2	62/72	86.1	2	68/72	94.4
				3	63/72	87.5	3	63/72	87.5
Pooled HPV 31 clinical sample	HPV31 - positive	3.01	8.3	1	72/72	100.0	1	70/72	97.2
				2	68/72	94.4	2	72/72	100.0
				3	72/72	100.0	3	70/72	97.2
Pooled HPV 45 clinical sample	HPV45 - moderate positive	1.88	5.0	1	70/72	97.2	1	66/72	91.7
				2	66/72	91.7	2	70/72	97.2
				3	64/72	88.9	3	64/72	88.9
Pooled HPV 45 clinical sample	HPV45 - positive	1.80	5.0	1	72/72	100.0	1	72/72	100.0
				2	72/72	100.0	2	72/72	100.0
				3	72/72	100.0	3	72/72	100.0

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

Sample Type[1] / Conc.[2] (cells/mL)			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]													
			Within-Run		Between-Run		Between-Day		Between-Operator		Between-Lot		Between-Site/ Instrument		Total	
	n[3] / N	Mean CT	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
SiHa GT 16 weak positive A (25/mL)	89 / 216	39.80	0.38	0.96%	0.20	0.50%	0.08	0.21%	0.00	0.00%	0.09	0.23%	0.00	0.00%	0.45	1.13%
SiHa GT 16 weak positive B (60/mL)	193 / 216	39.14	0.53	1.36%	0.17	0.43%	0.19	0.48%	0.03	0.08%	0.25	0.64%	0.23	0.59%	0.68	1.74%
SiHa GT 16 weak positive C (80/mL)	204 / 216	38.73	0.58	1.50%	0.00	0.00%	0.18	0.47%	0.08	0.21%	0.21	0.55%	0.21	0.54%	0.68	1.76%
SiHa GT 16 positive (150/mL)	214 / 216	37.89	0.45	1.19%	0.22	0.57%	0.35	0.91%	0.35	0.91%	0.21	0.57%	0.58	1.53%	0.94	2.47%
HeLa GT 18 weak positive A (8/mL)	120 / 216	39.02	0.57	1.45%	0.00	0.00%	0.00	0.00%	0.00	0.00%	0.12	0.32%	0.16	0.41%	0.60	1.54%
HeLa GT 18 weak	197	38.10	0.72	1.89%	0.38	1.00%	0.11	0.29%	0.13	0.33%	0.17	0.44%	0.30	0.78%	0.90	2.36%

positive B (22/mL)	216															
HeLa GT 18 weak positive C (27/mL)	208/216	37.77	0.73	1.93%	0.13	0.35%	0.17	0.44%	0.31	0.83%	0.25	0.67%	0.26	0.69%	0.90	2.38%
HeLa GT 18 positive (50/mL)	213/216	36.76	0.64	1.74%	0.07	0.20%	0.29	0.79%	0.38	1.05%	0.32	0.87%	0.29	0.80%	0.91	2.48%
Clinical GT 16 weak positive	201/214	37.33	1.46	3.92%	0.44	1.18%	0.44	1.17%	0.00	0.00%	0.00	0.00%	0.00	0.00%	1.59	4.26%
Clinical GT 16 positive	215/215	34.95	1.05	3.02%	0.50	1.44%	0.00	0.00%	0.00	0.00%	0.18	0.51%	0.27	0.76%	1.21	3.46%
Clinical GT 18 weak positive	192/215	37.63	2.27	6.02%	0.00	0.00%	0.00	0.00%	0.00	0.00%	0.00	0.00%	0.39	1.05%	2.30	6.11%
Clinical GT 18 positive	215/215	34.17	3.16	9.25%	1.26	3.68%	0.00	0.00%	0.42	1.23%	0.00	0.00%	0.73	2.13%	3.51	10.26%
Clinical GT 31 weak positive	192/216	36.91	2.95	7.98	0.00	0.00%	0.00	0.00%	0.22	0.60%	0.00	0.00%	0.00	0.00%	2.95	8.00%
Clinical GT 31 positive	212/216	36.49	2.81	7.69%	0.00	0.00%	0.67	1.84%	0.00	0.00%	0.00	0.00%	0.86	2.35%	3.01	8.25%
Clinical GT 45 weak positive	200/216	37.37	1.88	5.03%	0.00	0.00%	0.00	0.00%	0.00	0.00%	0.00	0.00%	0.00	0.00%	1.88	5.03%
Clinical GT 45 positive	216/216	35.66	1.74	4.87%	0.21	0.58%	0.00	0.00%	0.00	0.00%	0.00	0.00%	0.41	1.14%	1.80	5.04%

[1] Moderate is abbreviated as mod.

[2] Analyte concentrations are given for the SiHa and HeLa cell lines.

[3] n is the number of positive tests, which contribute CT values to the analysis. N is the total number of valid tests for the panel member. Because only positive test results were included, estimates of SD (and %CV) may be underestimated.

5. Precision

In-house Precision was examined using a panel composed of HPV positive and negative cell lines diluted into PreservCyt solution and pooled HPV positive and negative cervical specimens collected in PreservCyt solution. 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 1-9 and 19-22 were prepared with HPV positive and negative cell lines (SiHa, HPV16; HeLa, HPV18; HCT-15, HPV negative) diluted at different levels into PreservCyt solution (panel level 1 was prepared with HPV negative cell line only). Panel members 10-18 were prepared with high risk HPV positive specimen in PreservCyt solution pools (HPV16, HPV18, HPV31 and HPV45) diluted at different levels into pooled HPV negative specimens in PreservCyt solution (panel level 10 was prepared with 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 in the table below. All panel levels at and above the limit of detection yielded the anticipated positivity rates.

Summary of the Precision Panel and Hit Rates For cobas HPV Precision Study

Panel Number	HPV Target	Description	Anticipated Positivity Rate	N Tested	N Pos	Positivity Rate	95% CI	
							Lower	Upper
1	N/A	HCT15 cell line (HPV negative)	0%	144	0	0.0%	0%	3%
2	HPV16	SiHa cell line	< 70%	143	80	55.9%	47%	64%
3	HPV16	SiHa cell line	90% — 95%	144	138	95.8%	91%	98%
4	HPV16	SiHa cell line	95% — 99%	144	144	100.0%	97%	100%
5	HPV16	SiHa cell line	> 99%	143	142	99.3%	96%	100%
6	HPV18	HeLa cell line	< 70%	144	96	66.7%	58%	74%
7	HPV18	HeLa cell line	90% — 95%	144	143	93.3%	96%	100%
8	HPV18	HeLa cell line	95% — 99%	144	142	98.6%	95%	100%
9	HPV18	HeLa cell line	> 99%	144	144	100.0%	97%	100%
10	N/A	Pooled HPV neg specimen	0%	141	1	0.7%	0%	4%
11	HPV16	High Risk HPV positive specimen	90% — 99%	144	140	97.2%	93%	99%
12	HPV16	High Risk HPV positive specimen	> 99%	143	143	100.0%	97%	100%
13	HPV18	High Risk HPV positive specimen	90% — 99%	144	140	97.2%	93%	99%
14	HPV18	High Risk HPV positive specimen	> 99%	144	144	100.0%	97%	100%
15	HPV31	High Risk HPV positive specimen	90% — 99%	143	142	99.3%	96%	100%
16	HPV31	High Risk HPV positive specimen	> 99%	144	144	100.0%	97%	100%
17	HPV45	High Risk HPV positive specimen	90% — 99%	144	133	92.4%	87%	96%
18	HPV45	High Risk HPV positive specimen	> 99%	144	144	100.0%	97%	100%
*19	HPV16 & HPV18	SiHa & HeLa cell lines	< 70%	143	88	61.5%	53%	70%
*20	HPV16 & HPV18	SiHa & HeLa cell lines	90% — 95%	144	144	100.0%	97%	100%
*21	HPV16 & HPV18	SiHa & HeLa cell lines	95% — 99%	144	144	100.0%	97%	100%
*22	HPV16 & HPV18	SiHa & HeLa cell lines	> 99%	144	144	100.0%	97%	100%
**19	HPV16 & HPV18	SiHa & HeLa cell lines	< 70%	143	103	72.0%	64%	79%
**20	HPV16 & HPV18	SiHa & HeLa cell lines	90% — 95%	144	143	93.3%	96%	100%
**21	HPV16 & HPV18	SiHa & HeLa cell lines	95% — 99%	144	142	98.6%	95%	100%
**22	HPV16 & HPV18	SiHa & HeLa cell lines	> 99%	144	144	100.0%	97%	100%

Analysis of variance of the Ct values from valid tests performed on positive panel members (see table below) 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.

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

#	Sample Type /Conc.[1] (cells/mL)			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]											
				Between-Lot		Between-Run/System		Between-Operator		Between-Day		Within-Run		Total	
		N[2] / N	Mean CT	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
1	SiHa HPV16 (25/mL)	80/143	39.8	0.000	0.000%	0.000	0.000%	0.065	0.20%	0.168	0.40%	0.410	1.00%	0.448	1.10%
2	SiHa HPV16 (60/mL)	138/144	38.8	0.172	0.40%	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.640	1.70%	0.663	1.70%
3	SiHa HPV16 (80/mL)	144/144	38.4	0.055	0.10%	0.000	0.00%	0.116	0.30%	0.142	0.40%	0.569	1.50%	0.601	1.60%
4	SiHa HPV16 (150/mL)	142/143	37.3	0.067	0.20%	0.092	0.20%	0.000	0.00%	0.284	0.80%	0.405	1.10%	0.508	1.40%
5	HeLa HPV18 (8/mL)	96/144	38.9	0.116	0.30%	0.073	0.20%	0.000	0.00%	0.000	0.00%	0.665	1.70%	0.680	1.70%
6	HeLa HPV18 (22/mL)	143/144	37.7	0.000	0.00%	0.000	0.00%	0.076	0.20%	0.074	0.20%	0.811	2.20%	0.818	2.20%
7	HeLa HPV18 (27/mL)	142/144	37.5	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.229	0.60%	0.675	1.80%	0.712	1.90%
8	HeLa HPV18 (50/mL)	144/144	36.5	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.157	0.40%	0.578	1.60%	0.599	1.60%
9	Clinical HPV16	140/144	37.2	0.000	0.00%	0.258	0.70%	0.000	0.00%	0.000	0.00%	1.650	4.40%	1.670	4.50%
10	Clinical HPV16	143/143	34.5	0.220	0.60%	0.135	0.40%	0.000	0.00%	0.441	1.30%	1.183	3.40%	1.288	3.70%
11	Clinical HPV18	140/144	36.7	0.378	1.00%	0.000	0.00%	0.000	0.00%	0.000	0.00%	3.081	8.40%	3.104	8.50%
12	Clinical HPV18	144/144	34.9	0.000	0.00%	0.692	2.00%	0.000	0.00%	1.291	3.70%	2.180	6.20%	2.626	7.50%
13	Clinical HPV31	142/143	37.1	0.000	0.00%	0.255	0.70%	0.323	0.90%	0.000	0.00%	2.351	6.30%	2.387	6.40%
14	Clinical HPV31	144/144	35.8	0.190	0.50%	0.000	0.00%	0.000	0.00%	0.746	2.10%	2.825	7.90%	2.928	8.20%
15	Clinical HPV45	133/144	37.3	0.000	0.00%	0.186	0.50%	0.101	0.30%	0.000	0.00%	1.915	5.10%	1.926	5.20%
16	Clinical HPV45	144/144	35.0	0.393	1.10%	0.246	0.70%	0.000	0.00%	0.000	0.00%	1.780	5.10%	1.839	5.30%
*17	SiHa HPV16 (25/mL) HeLa HPV18 (8/mL)	88/143	39.8	0.000	0.00%	0.000	0.00%	0.014	0.00%	0.000	0.00%	0.461	1.20%	0.461	1.20%

#	Sample Type /Conc.[1] (cells/mL)			Standard Deviation [SD] and Percent Coefficient of Variation [CV(%)]											
				Between-Lot		Between-Run/System		Between-Operator		Between-Day		Within-Run		Total	
		N[2]/N	Mean CT	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
*18	SiHa HPV16 (60/mL) HeLa HPV18 (22/mL)	144/144	38.4	0.106	0.30%	0.000	0.00%	0.034	0.10%	0.000	0.00%	0.591	1.50%	0.601	1.60%
*19	SiHa HPV16 (80/mL) HeLa HPV18 (27/mL)	144/144	38.3	0.134	0.30%	0.060	0.20%	0.000	0.00%	0.238	0.60%	0.405	1.10%	0.479	1.30%
*20	SiHa HPV16 (150/mL) HeLa HPV18 (50/mL)	144/144	37.2	0.088	0.20%	0.039	0.10%	0.000	0.00%	0.238	0.60%	0.405	1.10%	0.479	1.30%
**17	SiHa HPV16 (25/mL) HeLa HPV18 (8/mL)	103/143	38.8	0.000	0.00%	0.127	0.30%	0.065	0.20%	0.274	0.70%	0.579	1.50%	0.656	1.70%
**18	SiHa HPV16 (60/mL) HeLa HPV18 (22/mL)	143/144	37.6	0.182	0.50%	0.000	0.00%	0.000	0.00%	0.145	0.40%	0.710	1.90%	0.747	2.00%
**19	SiHa HPV16 (80/mL) HeLa HPV18 (27/mL)	142/144	37.3	0.000	0.00%	0.062	0.20%	0.000	0.00%	0.131	0.40%	0.626	1.70%	0.643	1.70%
**20	SiHa HPV16 (150/mL) HeLa HPV18 (50/mL)	144/144	36.4	0.000	0.00%	0.000	0.00%	0.000	0.00%	0.244	0.70%	0.481	1.30%	0.540	1.50%

[1] Analyte concentrations are given for the SiHa and HeLa cell lines.

[2] n is the number of positive tests, which contribute CT values to the analysis. N is the total number of valid tests for the panel member. Because only positive test results were included, estimates of SD (and %CV) may be underestimated.

*Results shown from detection channel 2 (HPV16)

** Results shown from detection channel 3 (HPV18)

N/A = Not applicable

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 in the table below were spiked at high concentrations ($\geq 1 \times 10^6$ *units/reaction with the exception of *Treponema pallidum* and Adenovirus-5, which were both tested at $\geq 1 \times 10^5$ *units/reaction) into HPV negative specimen in PreservCyt solution and into HPV negative specimen in PreservCyt solution 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 HPV 31, 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* which was quantified as Elementary Bodies (EBs). *Treponema pallidum* and 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). HBV and HIV-1 were quantified in International Units (IU) and SV40 was quantified in Infection Units (IU).

Microorganisms Tested for Analytical Specificity

Achromobacter xerosis	*Erysipelothrix rhusiopathiae*	*Mycoplasma hominis*	*Weissella paramesenteroides*
Acinetobacter calcaceticus	*Escherichia coli*	*Neisseria gonorrhea*	*Yersinia enterocolitica*
Acinetobacter lwoffi	*Ewingella americana*	*Neisseria meningitidis Serogroup A*	HPV 6
Acinetobacter sp. Genospecies 3	*Fusobacterium nucleatum*	*Pasteurella multocida*	HPV 11
Actinomyces israelii	*Gemella morbillorum*	*Pediococcus acidilactica*	HPV 26
Adenovirus 5	*Gardnerella vaginalis*	*Peptostreptococcus anaerobius*	HPV 30
Aerococcus viridans	*Haemophilus ducreyi*	*Propionibacterium acnes*	HPV 34
Alcaligenes faecalis	Hepatitis B virus (HBV)	*Proteus mirabilis*	HPV 40
Bacillus thuringiensis	Herpes simplex virus 1 (HSV-1)	*Proteus vularis*	HPV 42
Bacteroides fragilis	Herpes simplex virus 2 (HSV-2)	*Providencia stuartii*	HPV 53
Bacteroides ureolyticus	Human immunodeficiency virus (HIV-1)	*Pseudomonas aeruginosa*	HPV 54
Bifidobacterium longum	*Kingella kingae*	*Ruminococcus productus*	HPV 55B
Bifidobacterium adolescentis	*Klebsiella pneumoniae ss ozaenae*	*Salmonella minnesota*	HPV 61
Bifidobacterium brevi	*Lactobacillus acidophilus*	*Serratia marcescens*	HPV 62
Campylobacter jejuni	*Lactobacillus crisptus*	*Staphylococcus aureus*	HPV 64
Candida albicans	*Lactobacillus delbrueckii s. lactis*	*Staphylococcus epidermidis*	HPV 67
Chlamydia trachomatis	*Lactobacillus jensenii*	*Staphylococcus saprophyticus*	HPV 69
Chromobacter violaceum	*Lactobacillus vaginalis*	*Streptococcus agalactiae*	HPV 70
Citrobacter braakii	*Lactococcus lactis cremoris*	*Streptococcus anginosus*	HPV 71
Clostridium perfringens	*Legionella pneumophila*	*Streptococcus pyogenes*	HPV 72
Corynebacterium genitalium	*Micrococcus luteus*	*Streptococcus sanguis*	HPV 73
Cytomegalovirus (CMV)	*Mobiluncus curtsil s. curtsii*	Simian Virus 40 (SV40)	HPV 81
Eikenella corrodens	*Moraxella osloensis*	*Treponema Pallidum*	HPV 82
Enterobacter cloacae	*Morganella morganii*	*Trichomonas vaginalis*	HPV 83
Enterococcus faecalis	*Mycobacterium avium*	*Ureaplasma urealyticum*	HPV 84
Enterococcus faecium	*Mycobacterium smegmatis*	*Veillonela parvula*	HPV 85
Epstein Barr Virus (EBV)	*Mycoplasma genitalium*	*Vibrio parahaemolyticus*	HPV 89 (CP6108)

7. Interfering Substances

HPV positive and HPV negative cervical specimens as well as contrived specimens were used to assess the effects of endogenous and exogenous interfering substances that could potentially be present in cervical specimens. Testing materials used in these studies are described in the table below. The concentrations of endogenous and exogenous substances tested represent conditions that could occur during specimen collection. Whole blood, Peripheral Blood Mononuclear Cells (PBMC) and cervical mucus were tested as potential endogenous interfering substances found in cervical specimens. Levels of each potential interfering substance tested and performance observations are described

below. No interference was seen for PBMC or cervical mucus at all levels tested. Whole blood showed no interference when present in visually detectable amounts of up to 1.5%.

Interference Testing Sample Descriptions

Sample type	Description	Study
HPV-Positive Cervical Specimens	10 individual HPV positive cervical specimens in PreservCyt solution were aliquoted for testing with and without endogenous interfering substances	Endogenous Interference
HPV Negative Cervical Specimens	10 individual HPV negative cervical specimens in PreservCyt solution were aliquoted for testing with and without endogenous interfering substances	Endogenous Interference
Contrived HPV Positive Cervical Specimen	Cervical specimens in PreservCyt solution positive for one of the high risk HPV types other than HPV16 and/or HPV18 were diluted with HPV negative specimen to generate signal consistent with approximately 3 fold LOD. HPV types 16 and 18 plasmids were then added at concentrations of approximately 3 fold LOD.	Endogenous Interference
3 x LOD PreservCyt Specimen Pools	HPV types 31, 16, 18 plasmids were each diluted to 3 fold LOD into pools of negative cervical specimen in PreservCyt solution.	Exogenous Interference

Interference Testing Results with Endogenous Interferents

Interferent Tested	Concentrations Tested	Interference Observed
Whole Blood	1%, 1.5%, 2%, 3% v/v	Above 1.5%
PBMC	10^4, 10^5, 10^6 cells/mL	None
Cervical Mucus	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. Types of potential interferents tested and performance observations in 3 x LOD pools prepared from HPV negative cervical specimens in PreservCyt solution are described below.

Interference Testing Results with Exogenous Interferents

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

8. Reagent Stability

The cobas HPV Test consists of 5 kits. The following table lists each of these kits, along with their corresponding shelf life and storage temperature, as supported by the results of real-time stability studies:

Kits for the cobas HPV Test	Shelf Life (months)	Storage Temperature
cobas 4800 System Sample Preparation Kit	18	2-8°C
cobas 4800 System Liquid Cytology Preparation Kit	18	2-8°C
cobas 4800 System Wash Buffer Kit	18	15-25°C
cobas 4800 HPV Amplification/Detection Kit	18	2-8°C
cobas 4800 HPV Controls Kit	14	2-8°C

Each kit consists of different components required for sample preparation, performance monitoring (assay controls) and amplification/detection. The expiration date for each test kit is defined by the shortest dated component in that kit.

9. Sample Handling and Collection

Cervical specimens should be collected in PreservCyt Solution, the ThinPrep Pap Test preservation system, using an Endocervical Brush/Spatula.
Specimen stability studies demonstrated that for the cobas HPV Test cervical specimens can be stored at 2-30°C in PreservCyt Solution for up to 6 months prior to performing the cobas HPV Test. See PreservCyt solution labeling for storage requirements prior to cytology processing. PreservCyt specimens should not be frozen.

10. Cross-Contamination Study

Cross-contamination was examined using 3 cobas 4800 systems. HPV positive and negative samples were processed in a checkerboard configuration. HPV positive samples [PC(+)] were prepared by adding cultured CaSki cells [HPV16 positive, manufactured and quantified by Roche Culture Collection (RMSCC)] to PreservCyt Solution to generate a signal which covers 95% or more of the results found in specimens of diseased patients in the intended use population. PreservCyt Solution without spiked HPV cultures was used as negative samples [PC(-)].

Four runs were done with each cobas 4800 system for a total of 12 runs. The initial runs (run 1 for all systems) contained PreservCyt Solution only. These runs were done to verify that the system was free of contamination prior to the checkerboard runs. The subsequent two runs per system (runs 2 and 3 for all systems) contained both negative HPV samples and positive HPV samples in a checkerboard configuration. The last run (run 4 for all systems) contained negative HPV PreservCyt Solution only. This last negative run was used to determine the rate of run to run carry over. Of the six runs that examined the HPV high positive and negative checkerboard configuration, 2 out of 282 HPV negative samples showed positive results in channel 2, leading to a cross-contamination rate of 0.71%. There were no invalid runs or test results observed.

All negative runs, including prior to and after the checkerboard runs, yielded negative results, indicating no run-to-run contamination had occurred. There were no invalid runs or test results observed. The sample to sample cross-contamination rate was found to be 0.71% and no run to run carry over rate was observed on the cobas 4800 system.

B. Animal Studies

Not applicable

C. Additional Studies

Not applicable

X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study Design

Patients were enrolled between May 2008 and August 2009. The database for this PMA/PMA supplement included 47,208 patients. There were 61 investigational sites.

1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria:

a. Females age ≥21 years

b. Presenting for routine cervical cancer screening (see Glossary for definition)

c. Intact cervix

d. Willing and able to undergo colposcopy and biopsy and ECC ≤12 weeks (≤84 days) from Study Visit 1

e. Written informed consent
f. Willing and able to participate in the 3-year Follow-Up Phase

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, ie, either the principal investigator or someone to whom the principal investigator has appropriately delegated consenting authority)
b) Known pregnancy at Baseline Study Visit 1
c) Presenting for colposcopy at Study Visit 1
d) Any medical condition that, in the opinion of the investigator, would result in increased risk of bleeding at biopsy
e) Known history of ablative or excisional therapy (eg, LEEP, cryotherapy, cone biopsy) to the cervix in the 12 months before Baseline Study Visit 1
f) Hysterectomy (including supracervical)
g) Current or planned participation in any clinical trial for HPV treatment (for the 3-year duration of this study)

2. Follow-up Schedule:
Patients were scheduled to return for follow-up examinations as described under "follow-up phase" below.

Baseline phase
A multicenter, prospective study (ATHENA Study) was conducted to evaluate the performance of the cobas HPV Test as a triage test to stratify women with ASC-US cytology results for colposcopy, and also as an adjunctive test to cervical cytology to guide management decisions. The study consisted of a Baseline Phase, as well as a 3 year Follow-up Phase. In the Baseline Phase, Subjects ≥ 21 years old undergoing routine cervical cancer screening were invited to participate in the study. In total, 47,208 subjects were enrolled from May 2008 to August 2009 at 61 clinical sites in the Baseline Phase. Following written informed consent, demographic information and gynecologic histories were obtained. Two cervical samples were collected for HPV testing and ThinPrep liquid based cytology (LBC). HPV testing was performed at five different laboratories and LBC testing at four. Cytology samples were classified according to the criteria of the 2001 Bethesda System. The first cervical sample collected from each study participant was tested with the cobas HPV Test as well as an investigational use only (IUO) HR HPV test and an IUO HPV genotyping test. For testing with the cobas HPV Test, the first ~29,000 samples collected were stored and were within the window for sample stability at the time of testing. The remaining ~18,000 samples collected were tested prospectively, i.e., in "real time" by the testing sites at the time of cervical sample collection. The second sample collected from all subjects with ASC-US Pap test results was tested with an FDA-approved test according to the manufacturer's instructions.
Those subjects ≥ 21 years old with ASC-US cytology were invited to undergo colposcopy. In addition, all subjects ≥30 years old with NILM (negative for intraepithelial lesions or malignancy) cytology and a positive test result for HR HPV

DNA (positive by the IUO HR HPV test and/or the IUO HPV genotyping test), as well as a randomly selected subset of subjects (approximately 1:35) with NILM cytology/negative HR HPV DNA (by both the IUO HR HPV and the IUO HPV genotyping test), were invited to proceed to colposcopy. In order to avoid bias, both study participants and colposcopists were blinded to all HPV tests and cytology results until after the colposcopy was completed. Colposcopy was conducted according to a standardized protocol in which biopsies were obtained on all visible lesions; endocervical curettage was performed in all patients in whom the squamocolumnar junction was not visualized and a single random cervical biopsy was obtained if no lesions were visible. All biopsies were examined by a Central Pathology Review Panel (CPR) consisting of three expert pathologists, and discordant results adjudicated according to a pre-defined protocol. For all analyses, the clinical performance of cobas HPV Test was measured against CPR histology results. The analyses were performed for those subjects with histology ≥ CIN2 and ≥ CIN3 by CPR . Subjects with a CPR diagnosis of ≥ CIN2 by CPR exited the study. All subjects who had undergone colposcopy and biopsy, without a diagnosis of ≥ CIN2 by CPR were invited to proceed to the Follow-up Phase of the study.

Follow-up phase

All subjects who did not have histology ≥ CIN2 by CPR were invited to participate in a 3 year longitudinal study. Approximately 8,000 eligible subjects have entered the follow-up study. Subjects undergo annual visits for cervical sampling for cytology and HPV DNA testing (by the cobas HPV test). All subjects with ≥ ASC-US are invited to proceed to colposcopy. Colposcopy and biopsies are performed in a standardized manner as described above. All cervical biopsies are examined by the Central Pathology Review Panel. All subjects with ≥ CIN2 by CPR exit the study and those with < CIN2 by CPR are invited to proceed to the follow-up year visit. In order to maximize disease ascertainment, an exit colposcopy and endocervical curettage (ECC) will be offered to all subjects in Year 3.

Study design to demonstrate clinical sensitivity and specificity for screening patients with ASC-US cytology results to determine the need for referral for colposcopy

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

Study design to demonstrate clinical performance of the cobas HPV Test as an adjunct to cervical cytology in women ≥30 years old

All subjects ≥30 years old with NILM (negative for intraepithelial lesions or malignancy) cytology and a positive test result for HR HPV DNA (positive by the IUO HR HPV test and/or the IUO HPV genotyping test), as well as a randomly selected subset of subjects (approximately 1:35) with NILM cytology/negative HR HPV DNA (by both the IUO HR HPV and the IUO HPV genotyping test), were invited to proceed to colposcopy. The analyses were performed for histology results ≥ CIN2 and ≥ CIN3 by CPR. All subjects ≥

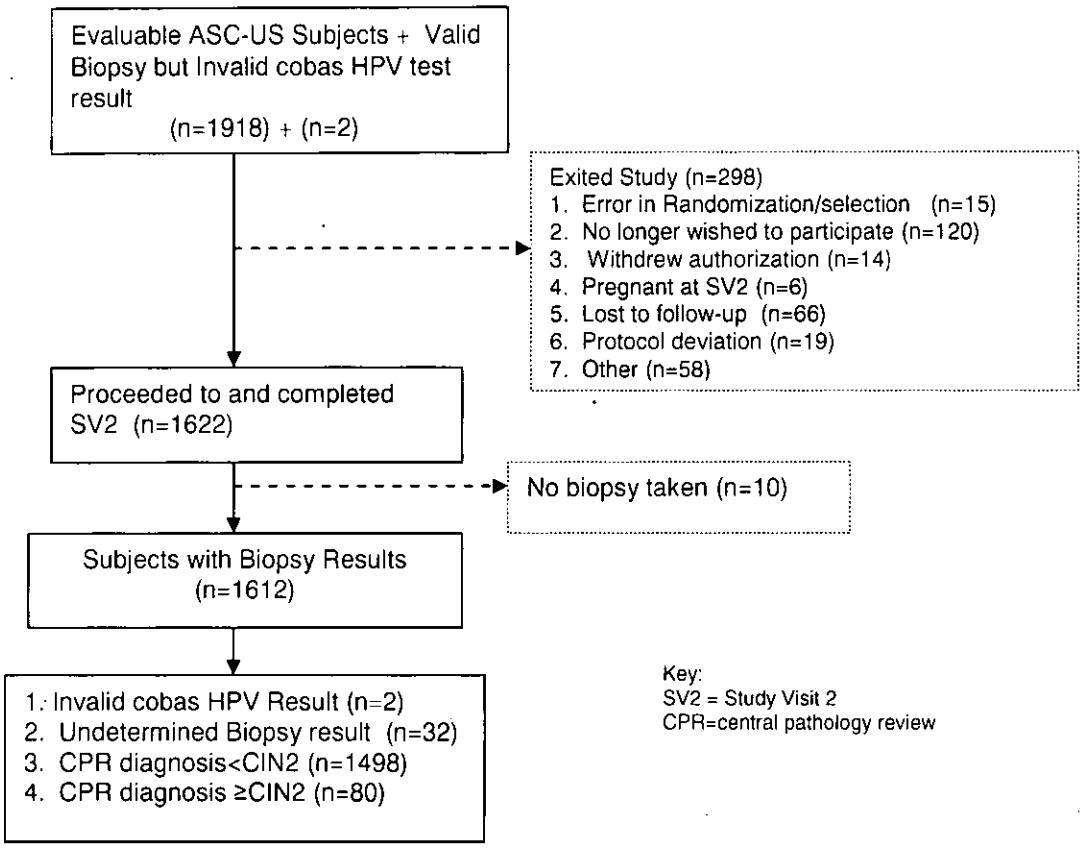
30 years who were invited to colposcopy and did not have histology ≥ CIN2 by CPR were eligible to participate in a 3 year longitudinal study for the cobas HPV Test. All subjects with follow-up cytology ≥ ASC-US are invited to proceed to colposcopy; colposcopy and biopsies are performed in a standardized manner as describe above. All cervical biopsies are examined by the CPR and all subjects with ≥ CIN2 exit the study. Exit colposcopy and ECC are offered to all subjects. The objectives of the follow-up phase of the study are to determine the 3-year risk (cumulative incidence rates, CIRs) of developing > CIN2 and > CIN3 in subjects ≥ 30 years with NILM cytology. Risk will be measured according to the baseline HPV status (as determined by the cobas HPV Test) for: positive and negative for HR HPV DNA and positive for genotype 16 and/or 18, as well as 12 other HR types. As with the baseline study, the histology of > CIN2 and >CIN3 will be determined by CPR.

B. Accountability of PMA Cohort

Accountability in ASC-US (≥ 21 years) Population

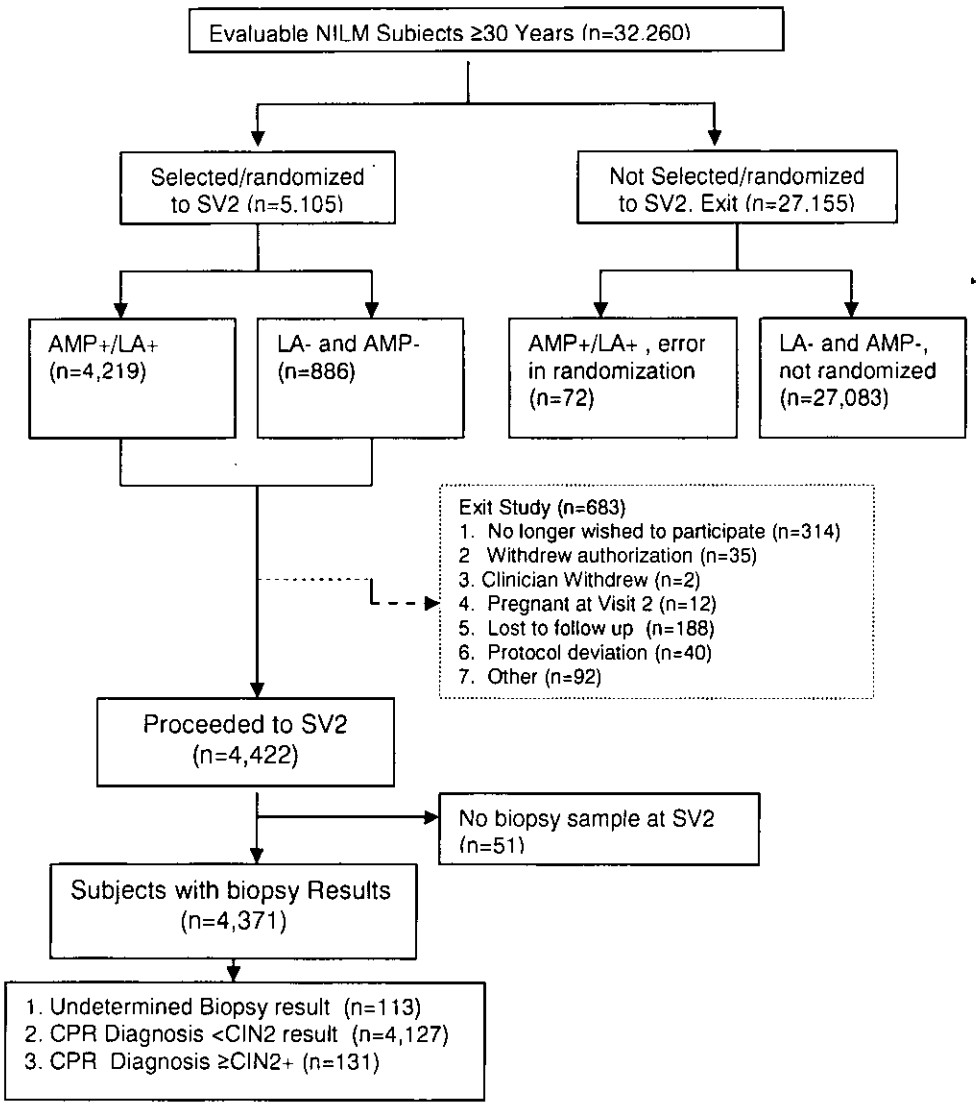
A total of 1,923 (4.1%) subjects out of 46,887 eligible subjects had an ASC-US cytology result. Of these, 1,918 (99.7%) subjects were evaluable and 5 subjects were not evaluable due to a missing/invalid IUO HR HPV test and/or IUO HPV genotyping test or cobas HPV Test results. Evaluable subjects were those who had ASC-US cytology results and had valid test results from the IUO HR HPV test, the IUO HPV genotyping test, and the cobas HPV Test. Of these, 1,620 (84.5%) proceeded to Study Visit 2. A total of 1,918 subjects were evaluable for the primary objectives of the study. Two additional subjects with valid biopsy results but invalid results for the cobas HPV test are also included as shown below.

No sample was taken at Study Visit 2 for 10 of 1,622 subjects who completed Study Visit 2, and 32 subjects that had undetermined biopsy results [i.e., inadequate tissue for diagnosis or sample(s) taken outside visit window]. A total of 1,612 subjects had valid biopsy results out of which a total of 1,578 evaluable ASC-US subjects had biopsy results. Detailed accountability of ASC-US(≥ 21 years) subjects is shown below:



Accountability in NILM (≥ 30 years) population

A total of 32,260 subjects was evaluable in the NILM (≥ 30 years) population. Evaluable subjects were defined as eligible subjects ≥ 30 years old with a NILM cytology result and who had valid results from the IUO HR HPV test, the IUO HPV genotyping test, and the cobas HPV Test. A total of 5,105 subjects were selected/randomized to Study Visit 2, but 683 of these subjects exited the study prior to Study Visit 2. Of the remaining subjects, 4,371 subjects had biopsy results and 4,258 subjects had *valid* biopsy results from central pathology review (CPR) panel. Detailed accountability of NILM (≥ 30 years) subjects is shown below:



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a prospective study performed in the US.

ASC-US Population Demographics

The demographics of the ASC-US population are described below. The median age of the ASC-US subjects was 36 years, with 32.6% subjects age 21-29 and 26.5% age 30-39; the remaining 40.9% subjects were ≥40 years. Approximately 80% of the ASC-US subjects were White, 17% were African American, and the remaining 3% were from other races. Most eligible subjects (97.4%) had high school or above education.

Summary of Demographic Characteristics for Evaluable ASC-US Subjects

Characteristics	Evaluable Subjects n = 1,918
Age (Years)	
Mean	37.2
Standard Deviation	11.5
Median	36
(Min, Max)	(21,80)
	n (%)
Age Group (Years)	
21-29	626 (32.6)
30-39	508 (26.5)
≥40	784 (40.9)
Race	
White	1,534 (80.0)
American Indian or Alaskan Native	10 (0.5)
Black or African American	322 (16.8)
Asian	32 (1.7)
Native Hawaiian or Other Pacific Islander	2 (0.1)
Any Combination*	18 (0.9)
Ethnicity	
Hispanic or Latino	368 (19.2)
Not Hispanic or Latino	1,550 (80.8)
Education	
Elementary	50 (2.6)
High School (or GED)	432 (22.5)
Vocational/Some College	522 (27.2)
College Degree	666 (34.7)
Some Graduate Work	54 (2.8)
Graduate Degree (Masters or Higher)	194 (10.1)

Note: This table summarizes all evaluable ASC-US subjects (evaluable for primary objective). To be considered evaluable, the subject must have been eligible, have had an ASC-US cytology result, and have had valid results from the IUO HR HPV Test, IUO HPV genotyping Test, and the cobas HPV Test.

* Any Combination refers to subjects who selected more than one race.

NILM Population Demographics

The demographics of the NILM population (≥30 years) are presented below. The median age was 44 years with ~35% subjects age 30-39 years and ~65% age ≥40 years. Approximately 84% of the NILM subjects were White, 13% were Black or African American, and the remaining 3% were from other races.

Summary of Demographic Characteristics for Evaluable NILM Subjects

Characteristics	Evaluable Subjects n = 32,260
Age (Years)	
Mean	44.9
Standard Deviation	10.1
Median	44
(Min, Max)	(30,93)
	n (%)
Age Group (Years)	
30-39	11,398 (35.3)
≥40	20,862 (64.7)
Race	
White	27,197 (84.3)
American Indian or Alaskan Native	173 (0.5)
Black or African American	4,199 (13.0)
Asian	466 (1.4)
Native Hawaiian or Other Pacific Islander	72 (0.2)
Any Combination*	150 (0.5)
Missing	3 (<0.1)
Ethnicity	
Hispanic or Latino	5,736 (17.8)
Not Hispanic or Latino	26,522 (82.2)
Missing	2 (<0.1)
Education	
Elementary	648 (2.0)
High School (or GED)	7,656 (23.7)
Vocational/Some College	8,290 (25.7)
College Degree	10,780 (33.4)
Some Graduate Work	847 (2.6)
Graduate Degree (Masters or Higher)	4,030 (12.5)
Missing	9 (<0.1)

Note: This table summarizes all evaluable NILM subjects. To be considered evaluable, the subject must have been eligible, must have been ≥30 years old, have had a NILM cytology result, and have had valid results from the IUO HR HPV Test, IUO HPV genotyping Test, and the cobas HPV Test.

* Any Combination refers to subjects who selected more than one race.

D. Safety and Effectiveness Results

1. Safety Results

   Not applicable, this was an IDE-exempt study

2. Effectiveness Results

The analysis of effectiveness was based on the following data.

Performance Characteristics in the ASC-US Population (≥ 21 Years)
A total of 1,612 subjects with ASC-US cytology completed Study Visit 2 procedures. The results of the cobas HPV Test reported as (HR HPV) Positive or (HR HPV) Negative together with the CPR diagnosis are presented below. In a total of 1,578 ASC-US subjects with valid CPR panel diagnoses, 80 subjects had a ≥ CIN2 result (prevalence of ~5.1%), and 46 subjects had a ≥ CIN3 result (prevalence of ~2.9%).

Results of the cobas HPV Test and Central Pathology Review Panel Diagnosis in the ASC-US Population (≥ 21 Years)

cobas HPV Test Result	Central Pathology Review Panel Diagnosis					Total
	Undetermined	Normal	CIN1	CIN2	≥CIN3	
Positive	13	351	91	29	43	527
Negative	19	989	67	5	3	1,083
Invalid	0	2	0	0	0	2
Total	32	1,340	158	34	46	1,612

Note: The 32 Undetermined CPR results were due to biopsy sample(s) collected out of study visit window or biopsy sample(s) found to be inadequate for diagnosis. These were excluded from the analysis, resulting in 1578 valid biopsy results.
Percent of Invalid cobas HPV Test results was 0.12% (2/1612) with 95% CI: 0.03% to 0.45%

Performance of the cobas HPV Test in detecting high-grade cervical disease (≥ CIN2 and ≥ CIN3) is presented in the table below. The sensitivity and the specificity of the test for detecting ≥ CIN2 histology were 90.0% ((72/80) with 95% CI: 81.5% to 94.8%) and 70.5% ((1,056/1,498) with 95% CI: 68.1% to 72.7%), respectively. The positive likelihood ratio (PLR) was estimated as 3.1, which implies a positive cobas HPV Test result is 3.1 times more likely in subjects with ≥ CIN2 than in subjects with < CIN2. The negative likelihood ratio (NLR) was estimated as 0.1, which implies that a negative cobas HPV Test result is 10 (1/0.1) times more likely in subjects with < CIN2 than in subjects with ≥ CIN2.
The sensitivity and specificity of the cobas HPV Test for detecting ≥ CIN3 histology were 93.5% ((43/46) with 95% CI: 82.5% to 97.8%) and 69.3% ((1,061/1,532) with 95% CI: 66.9% to 71.5%), respectively.

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

Performance	CPR Panel Diagnosis ≥ CIN2		CPR Panel Diagnosis ≥ CIN3	
	Point Estimate	95% CI	Point Estimate	95% CI
Sensitivity (%)	90.0 (72/80)	(81.5, 94.8)	93.5 (43/46)	(82.5, 97.8)
Specificity (%)	70.5 (1,056 /1,498)	(68.1, 72.7)	69.3 (1,061/1,532)	(66.9, 71.5)
PLR	3.1 (72/80) (442/1,498)	(2.7, 3.4)	3.0 (43/46)/(471/1,532)	(2.7, 3.4)
NLR	0.1 (8/80)/(1,056/1,498)	(0.1, 0.3)	0.1 (3 46)/(1,061/1,532)	(0.0, 0.3)
PPV (%)	14.0 (72/514)	(12.8, 15.3)	8.4 (43/514)	(7.6, 9.2)
NPV (%)	99.2 (1,056/1,064)	(98.6, 99.6)	99.7 (1,061/1,064)	(99.2, 99.9)
Prevalence (%)	5.1 (80/1,578)	(4.1, 6.3)	2.9 (46/1,578)	(2.2, 3.9)

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

The performance of the cobas HPV Test in detecting high-grade cervical disease (≥ CIN2 and ≥ CIN3) and the performance of the FDA approved HPV Test are presented in the table below. The sensitivity for detecting ≥ CIN2 histology was 90.0% ((72/80) with 95% CI: 81.5% to 94.8%) for the cobas HPV Test and 87.2% ((68/78) with 95% CI: 78.0% to 92.9%) for the FDA approved HPV Test. The specificity for detecting ≥ CIN2 histology was 70.5% (1,056/1,498) with 95% CI: 68.1% to 72.7%) for the cobas HPV Test and 71.1% ((1,056/1,495) with 95% CI: 68.8% to 73.4%) for the FDA approved HPV Test.

The sensitivity for detecting ≥ CIN3 histology was 93.5% ((43/46) with 95% CI: 82.5% to 97.8%) for the cobas HPV Test and 91.3% ((942/46) with 95% CI: 79.7% to 96.6%) for the FDA approved HPV Test. The specificity for detecting ≥ CIN3 histology was 69.3% ((1,053/1,517) with 95% CI: 66.9% to 71.5%) for the cobas HPV Test and 70.0% ((1,062/1,517) with 95% CI: 67.7% to 72.3%) for the FDA approved HPV Test.

Comparison of the Performance of the cobas HPV Test and an FDA approved HPV test in Detecting ≥ CIN2 and ≥ CIN3 in the ASC-US Population

	cobas HPV Test		FDA approved HPV Test	
	Point Estimate	**95% CI**	**Point Estimate**	**95% CI**
≥ CIN2				
Sensitivity (%)	90.0 (72/80)	(81.5, 94.8)	87.2 (68/78)[1]	(78.0, 92.9)
Specificity (%)	70.5 (1,056/1,498)	(68.1, 72.7)	71.1 (1,056/1,485)[2]	(68.8, 73.4)
PPV (%)	14.0 (72/514)	(12.8, 15.3)	13.7 (68/497)	(12.4, 15.1)
NPV (%)	99.2 (1,056/1,064)	(98.6, 99.6)	99.1 (1,056/1,066)	(98.3, 99.5)
Prevalence (%)	5.1 (80/1578)	(4.1, 6.3)	5.0 (78/1563)	(4.0, 6.2)
≥ CIN3				
Sensitivity (%)	93.5 (43/46)	(82.5, 97.8)	91.3 (42/46)	(79.7, 96.6)
Specificity (%)	69.3 (1,053/1,517)	(66.9, 71.5)	70.0 (1,062/1,517)	(67.7, 72.3)
PPV (%)	8.4 (43/514)	(7.6, 9.2)	8.5 (42/497)	(7.6, 9.4)
NPV (%)	99.7 (1,061/1,064)	(99.2, 99.9)	99.6 (1,062/1,066)	(99.0, 99.9)
Prevalence (%)	2.9 (43/1578)	(2.2, 3.9)	3.0 (46/1563)	(2.2, 3.9)

[1] Results for two subjects with a ≥ CIN2 diagnosis could not be determined by the FDA approved HPV Test due to insufficient volume resulting from repeated testing

[2] Results for thirteen subjects with a < CIN2 diagnosis could not be determined by the FDA approved HPV Test due to insufficient volume resulting from repeated testing.

Performance of the cobas HPV Test in detecting ≥ CIN2 and ≥ CIN3 evaluated by age group is presented in the table below. The sensitivity of the cobas HPV Test for detecting ≥ CIN2 histology was 93.3% ((42/45) with 95% CI: 82.1% to 97.7%) in the 21-29 year age group, 100% ((20/20) with 95% CI: 83.9% to 100%) in the 30-39 year age group, and 66.7% ((10/15) with 95% CI: 41.7% to 84.8%) in the ≥ 40 years age group. The specificity of the test was highest in ≥ 40 years, with an estimate of 85.0% (95% CI: 82.0% to 87.6%).

The sensitivity in detecting ≥ CIN3 was 100% ((24/24) with 95% CI: 74.1% to 100%) in the 21-29 year age group, 100% ((11/11) with 95% CI: 86.2% to 100%) in the 30-39 year age group, and 72.7% ((8/11) with 95% CI: 43.4% to 90.3%) in the ≥ 40 years age group. The specificity of the test was highest in ≥ 40 years, with an estimate of 84.8% ((535/631) with 95% CI: 81.8% to 87.4%).

Performance of the cobas HPV Test in Detecting ≥ CIN2 and ≥ CIN3 in the ASC-US Population by Age Group

Performance	21-29 Years	30-39 Years	≥ 40 Years
N	514	422	642
≥ CIN2			
Sensitivity (%)	93.3 (42/45)	100.0 (20/20)	66.7 (10/15)
95% CI (%)	(82.1, 97.7)	(83.9, 100.0)	(41.7, 84.8)
Specificity (%)	49.7 (233/469)	72.1 (290/402)	85.0 (533/627)
95% CI (%)	(45.2, 54.2)	(67.6, 76.3)	(82.0, 87.6)
PPV (%)	15.1 (42/278)	15.2 (20/132)	9.6 (10/104)
95% CI (%)	(13.6, 16.7)	(13.1, 17.5)	(6.6, 13.7)
NPV (%)	98.7 (233/236)	100.0 (290/290)	99.1 (533/538)
95% CI (%)	(96.3, 99.6)	(97.4, 100.0)	(98.1, 99.5)
≥ CIN2 prevalence	8.8% (45/514)	4.7% (20/422)	2.3% (15/642)
95% CI (%)	(6.6, 11.5)	(3.1, 7.2)	(1.4, 3.8)
≥ CIN3			
Sensitivity (%)	100.0 (24/24)	100.0 (11/11)	72.7 (8/11)
95% CI (%)	(86.2, 100.0)	(74.1, 100.0)	(43.4, 90.3)
Specificity (%)	48.2 (236/490)	70.6 (290/411)	84.8 (535/ 631)
95% CI (%)	(43.8, 52.6)	(66.0, 74.8)	(81.8, 87.4)
PPV (%)	8.6 (24/278)	8.3 (11/132)	7.7 (8/104)
95% CI (%)	(7.9, 9.5)	(7.0, 9.9)	(5.3, 11.1)
NPV (%)	100.0 (236/236)	100.0 (290/290)	99.4 (535/538)
95% CI (%)	(96.8, 100.0)	(97.5, 100.0)	(98.5, 99.8)
≥ CIN3 prevalence	4.7% (24/514)	2.6% (11/422)	1.7% (11/642)

Performance of the FDA approved HPV test in detecting ≥ CIN2 and ≥ CIN3 by age group is presented in the table below.

Performance of an FDA approved HPV test in Detecting ≥ CIN2 and ≥ CIN3 in the ASC-US Population by Age Group

Performance	21-29 Years	30-39 Years	≥ 40 Years
N	506	417	640
≥ CIN2			
Sensitivity (%)	88.4 (38 / 43)	100.0 (20 / 20)	66.7 (10 / 15)
95% CI (%)	(75.5, 94.9)	(83.9, 100.0)	(41.7, 84.8)
Specificity (%)	50.1 (232 / 463)	73.6 (292 / 397)	85.1 (532 / 625)
95% CI (%)	(45.6, 54.6)	(69.0, 77.6)	(82.1, 87.7)
PPV (%)	14.1 (38 / 269)	16.0 (20 / 125)	9.7 (10 / 103)
95% CI (%)	(12.5, 15.9)	(13.8, 18.5)	(6.7, 13.9)
NPV (%)	97.9 (232 / 237)	100.0 (292 / 292)	99.1 (532 / 537)
95% CI (%)	(95.3, 99.1)	(97.4, 100.0)	(98.1, 99.5)
≥ CIN2 prevalence	8.5 (43/506)	4.8 (20/417)	2.3 (15/640)
95% CI (%)	(6.4, 11.3)	(3.1, 7.3)	(1.4, 3.8)
≥ CIN3			
Sensitivity (%)	95.8 (23 / 24)	100.0 (11 / 11)	72.7 (8 / 11)
95% CI (%)	(79.8, 99.3)	(74.1, 100.0)	(43.4, 90.3)
Specificity (%)	49.0 (236 / 482)	71.9 (292 / 406)	84.9 (534 / 629)
95% CI (%)	(44.5, 53.4)	(67.4, 76.1)	(81.9, 87.5)
PPV (%)	8.6 (23 / 269)	8.8 (11 / 125)	7.8 (8 / 103)
95% CI (%)	(7.7, 9.5)	(7.3, 10.5)	(5.3, 11.2)
NPV (%)	99.6 (236 / 237)	100.0 (292 / 292)	99.4 (534 / 537)
95% CI (%)	(97.2, 99.9)	(97.5, 100.0)	(98.5, 99.8)
≥ CIN3 prevalence	4.7 (24/506)	2.6 (11/417)	1.7 (11/640)
95% CI (%)	(3.2, 7.0)	(1.5, 4.7)	(1.0, 3.1)

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 HPV 16 positive/18 positive, 12 Other HR, and HR HPV negative are presented below for the ASC-US (≥21 years) population.

For the ≥ CIN2 histology, the estimate of the LR of HPV16 positive/18 positive was 6.1, indicating that an HPV16 positive/18 positive result is 6.1 times more likely to come from a subject with disease (≥ CIN2) than from a subject without disease (< CIN2). The risk of a ≥ CIN2 outcome for an ASC-US subject with an HPV16 positive/18 positive result was 24.4%. The LRs of 12 Other HR HPV positive was 1.8. Both LRs were significantly greater than 1.

The estimate of the LR of a negative cobas HPV Test result was 0.1, indicating that a negative result was 10 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 outcome. The risk of disease (≥ CIN2) was 5.1% in the ASC-US population regardless of the HPV test result (prevalence =5.1%). The risk of disease was significantly increased for the test results of HPV16 positive/18 positive and 12 Other HR HPV positive and significantly decreased for an HR HPV negative result.

For ≥ CIN3 histology, both LRs of HPV16 positive/18 positive and 12 Other HR HPV positive were statistically significantly greater than 1, and the LR of an HPV negative result was statistically significantly less than 1. The risk of the disease (≥ CIN3) was 2.9% in the ASC-US population. The risk of ≥ CIN3 was significantly increased for the HPV16 positive/18 positive and 12 Other HR HPV positive, and significantly decreased for an HPV negative result.

Likelihood Ratios and Risk of Disease by cobas HPV Test Result in Detecting ≥CIN2 and ≥CIN3 in the ASC-US Population

Diagnosis by CPR	cobas HPV Test Result	Likelihood Ratio (95% CI)	Risk of Disease (%) Given the Test Result (95% CI)
≥CIN2	HPV 16 positive/18 positive	6.1 (4.7, 7.9)	24.4 (20.1, 29.7)
	12 Other HR HPV positive	1.8 (1.3, 2.4)	8.6 (6.6, 11.6)
	HPV Negative	0.1 (0.1, 0.2)	0.8 (0.3, 1.0)
	Prevalence	5.1%	
≥CIN3	HPV 16 positive/18 positive	6.3 (4.8, 8.3)	15.9 (12.5, 20.0)
	12 Other HR HPV positive	1.5 (1.0, 2.3)	4.4 (2.9, 6.5)
	HPV Negative	0.1 (0.0, 0.3)	0.3 (0.1, 0.9)
	Prevalence	2.9%	

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

The table below presents the CPR diagnosis by all possible cobas HPV Test result in ASCUS population.

Summary of cobas HPV Test Result and Central Pathology Review Panel Diagnosis in the ASC-US Population (>=21 years)

	Central Pathology Review Diagnosis					
cobas HPV Test Result	Undetermined	Negative	CIN1	CIN2	>=CIN3	Total
Other HR HPV NEG, HPV16 NEG, HPV18 NEG	19	989	67	5	3	1,083

	Central Pathology Review Diagnosis					
cobas HPV Test Result	Undetermined	Negative	CIN1	CIN2	>=CIN3	Total
Other HR HPV NEG, HPV16 NEG, HPV18 POS	1	21	3	0	1	26
Other HR HPV NEG, HPV16 POS, HPV18 NEG	0	40	8	13	12	73
Other HR HPV NEG, HPV16 POS, HPV18 POS	0	5	0	0	1	6
Other HR HPV POS, HPV16 NEG, HPV18 NEG	9	246	63	14	15	347
Other HR HPV POS, HPV16 NEG, HPV18 POS	2	12	8	0	1	23
Other HR HPV POS, HPV16 POS, HPV18 NEG	1	25	9	2	12	49
Other HR HPV POS, HPV16 POS, HPV18 POS	0	2	0	0	1	3
Invalid	0	2	0	0	0	0
Overall	32	1,342	158	34	46	1,612

Note1: Undetermined results include inadequate biopsy sample for diagnosis and sample collected outside the Study Visit window.

Note2: None of the subjects in the ASC-US population had a CPR diagnosis >CIN3

The table below presents the CPR diagnosis and the absolute risk of disease (≥ CIN2 and ≥ CIN3) by cobas HPV Test result. 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 subjects with results of HPV positive, HPV16 positive/18 positive, or 12 Other HR positive than in subjects with an HPV negative result.

Central Pathology Review Diagnosis and Absolute Risk of ≥ CIN2 and ≥ CIN3 for Different cobas HPV Test Results in the ASC-US Population (≥ 21 Years)

cobas HPV Test Result	Total	Central Pathology Review Diagnosis					Absolute Risk for ≥ CIN2 (%)	Absolute Risk for ≥ CIN3 (%)
		Undetermined	Normal	CIN1	CIN2	≥CIN3		
HPV positive	527	13	351	91	29	43	14.0 (72/514)	8.4 (43/514)
HPV16 positive and/or HPV18 positive	180	4	105	28	15	28	24.4 (43/176)	15.9 (28/176)
HPV16 positive	131	1	72	17	15	26	31.5 (41/130)	20.0 (26/130)
HPV18 positive	49	3	33	11	0	2	4.4 (2/46)	4.3 (2/46)
12 Other HR HPV positive	347	9	246	63	14	15	8.6 (29/338)	4.3 (15/338)
HPV negative	1,083	19	989	67	5	3	0.8 (8/1,064)	0.3 (3/1,064)

Note1: Undetermined results include inadequate biopsy sample for diagnosis and sample collected outside the Study Visit window.

Note 2: HPV16 positive and/ or HPV18 positive include all subjects with either or both of these genotypes occurring with or without 12 other HR positive results

Note 3: 12 Other HR HPV positive include all subjects with positive results for 12 Other HR HPV genotypes with negative results for HPV16 and HPV18.

The relative risks (RRs) of disease (≥ CIN2 and ≥ CIN3) were calculated between subjects with different cobas HPV Test results by RR and its associated 95% CIs as presented in the table below. The estimated RRs of ≥ CIN2 and of ≥ CIN3 for subjects with positive vs. negative cobas HPV Test results were 18.6 (95% CI: 9.0 to 38.4) and 29.7 (95% CI: 9.2 to 95.2), respectively, indicating that subjects with a positive result were 18.6 times more likely to have ≥ CIN2 histology and 29.7 times more likely to have ≥ CIN3 histology than were subjects with a negative test result.
Similarly, subjects who have HPV16 and/or HPV18 positive results from the cobas HPV Test were significantly more likely to have ≥ CIN2 than the subjects with (a) a positive result for 12 Other HR HPV types, or (b) a negative result. Subjects with a positive result for 12 Other HR HPV types were significantly more likely to have ≥ CIN2 than the subjects with a negative result. Similar results were observed for ≥ CIN3 histology.

Relative Risks of ≥ CIN2 and ≥ CIN3 for Different cobas HPV Test Results in the ASC-US Population (≥ 21 Years)

cobas HPV Test Result	CPR Diagnosis ≥ CIN2		CPR Diagnosis ≥ CIN3	
	Relative Risk	95% CI	Relative Risk	95% CI
HPV Positive vs. Negative	18.6	(9.0, 38.4)	29.7	(9.2, 95.2)
HPV16 positive/18 positive vs. Negative	32.5	(15.5, 69.7)	56.4	(17.3, 183.6)
HPV16 positive /18 positive vs. 12 Other HR HPV positive	2.8	(1.8, 4.4)	3.6	(2.0, 6.5)
12 Other HR HPV positive vs. Negative	11.4	(5.3, 24.7)	15.7	(4.6, 54.0)
Prevalence	5.1%		2.9%	

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

The relative risks of disease (≥ CIN2 and ≥ CIN3) were calculated between subjects with different cobas HPV Test results among different age groups and are presented below. The RRs of all comparisons were significantly greater than 1 for ≥ CIN2 histology, except for HPV 16 positive /18 positive vs. 12 Other HR HPV positive in ≥ 40 years.

Relative Risks of ≥ CIN2 and ≥ CIN3 by cobas HPV Test Result Stratified by Age in the ASC-US Population

cobas HPV Test Result	Age Group (Years)		
	21-29	30-39	≥40
Relative Risk for ≥ CIN2			
Positive vs. Negative	11.9 (3.7, 37.9)	87.9 (5.4, 1443.3)*	10.3 (3.6, 29.6)
HPV16 positive /18 positive vs. Negative	20.4 (6.3, 65.4)	163.6 (9.8, 2729.1)*	12.9 (3.3, 51.0)
HPV16 positive /18 positive vs. Other 12 HR HPV positive	3.3 (1.8, 6.1)	2.9 (1.3, 6.5)	1.4 (0.4, 4.8)
12 Other HR HPV positive vs. Negative	6.2 (1.8, 21.3)	56.1 (3.3, 959.0)*	9.5 (3.1, 29.3)
Prevalence	8.8%	4.7%	2.3%
Relative Risk for ≥ CIN3			
Positive vs. Negative	40.7 (2.5, 666.9)*	48.3 (2.9, 816.3)*	13.8 (3.7, 51.1)
HPV16 positive /18 positive vs. Negative	80.1 (4.9, 1315.5)*	89.2 (5.1, 1566.9)*	21.5 (4.6, 101.3)

cobas HPV Test Result	Age Group (Years)		
	21-29	30-39	≥40
HPV16 positive /18 positive vs. Other 12 HR HPV positive	5.6 (2.2, 14.6)	2.9 (0.9, 8.8)	1.9 (0.5, 7.4)
12 Other HR HPV positive vs. Negative	14.2 (0.8, 258.5)*	31.2 (1.7, 565.4)*	11.4 (2.8, 46.6)
Prevalence	4.7	2.6	1.7

* 0.5 was added to a cell with zero frequency in age group 21-29 years and 30-39 years and also for the HPV negative result.
Note 1: HPV16 positive and/ or HPV18 positive include all subjects with either or both of these genotypes occurring with or without 12 Other HR HPV positive results
Note 2: 12 Other HR HPV positive include all subjects with positive results for 12 other HR genotypes with negative results for HPV16 and HPV18 .

NILM (≥30 Years) Population

The risks of disease in the NILM (≥ 30 years) population were compared in subjects with a positive result to those with a negative result from the cobas HPV Test. In this population, all subjects with a positive result from the IUO HPV HR test or IUO HPV genotyping test were selected to proceed to Study Visit 2, whereas a random subset of subjects (1 of 35) with a negative result from both IUO HPV tests were randomized to Study Visit 2. To compare the risks of high-grade cervical disease (≥ CIN2 or ≥ CIN3) between subject groups with positive vs. negative cobas HPV Test results, an adjustment for verification bias was applied to account for the different rate of selection in these groups. This was accomplished by calculating the likely number of diseased cases that would have been found if all the subjects in a given subgroup had undergone colposcopy. In the study, there were 10 subjects with cobas HPV16/18 positive and (IUO HPV HR or IUO HPV genotyping) negative results and 52 subjects with cobas 12 Other HR HPV positive and (IUO HPV HR or IUO HPV genotyping) negative results. These subjects had not undergone colposcopy even they were positive by cobas HR HPV test. For these subjects, a worst case analysis for the performance of the cobas HR HPV test was considered (these subjects were considered as false positive). The table below presents the CPR diagnosis by all possible cobas HPV Test results in the NILM (≥ 30 years) population.

Summary of cobas HPV Test Result and Central Pathology Review Panel Diagnosis in the NILM Population (≥ 30 years)

	Central Pathology Review Diagnosis					
cobas HPV Test Result	Undetermined	Negative	CIN1	CIN2	≥ CIN3	Total
Other HR HPV NEG, HPV16 NEG, HPV18 NEG	63	2,391	101	14	8	2,577
Other HR HPV NEG, HPV16 NEG, HPV18 POS	2	78	7	2	6	95
Other HR HPV NEG, HPV16 POS, HPV18 NEG	6	147	13	3	24	193
Other HR HPV NEG, HPV16 POS, HPV18 POS	0	1	0	0	1	2
Other HR HPV POS, HPV16 NEG, HPV18 NEG	41	1,199	96	30	34	1,400
Other HR HPV POS, HPV16 NEG, HPV18 POS	0	27	4	0	1	32
Other HR HPV POS, HPV16 POS, HPV18 NEG	1	51	8	2	6	68
Other HR HPV POS, HPV16 POS, HPV18 POS	0	4	0	0	0	4
Overall	113	3,898	229	51	80	4,371

Note 1 Undetermined results include inadequate biopsy sample for diagnosis and sample collected outside the Study Visit window.

Note2: Of the 80 ≥ CIN3 subjects, 75 are CIN3 and 5 are ACIS.

The table below presents the CPR diagnosis and the crude estimate of absolute risk of disease (≥ CIN2 and ≥ CIN3) by cobas HPV Test result. HPV16 positive had the highest crude absolute risk for both ≥ CIN2 and ≥ CIN3. In general, the crude absolute risks for both ≥ CIN2 and ≥ CIN3 were higher in subjects with any results of HPV positive than in subjects with an HPV negative result.

Central Pathology Review Diagnosis and Different cobas HPV Test Results in the NILM Population (≥30 Years)

cobas HPV Test Result	Total	Central Pathology Review Diagnosis					Crude Absolute Risk for ≥ CIN2 (%)	Crude Absolute Risk for ≥ CIN3 (%)
		Undetermined	Normal	CIN1	CIN2	≥CIN3		
HPV positive	1794	50	1507	128	37	72	6.3 (109/1,744)	4.1 (72/1,744)
HPV16 positive and/or HPV18 positive	394	9	308	32	7	38	11.7 (45/385)	9.9 (38/385)
HPV16 positive	267	7	203	21	5	31	13.8 (36/260)	11.9 (31/260)
HPV18 positive	127	2	105	11	2	7	7.2 (9/125)	5.6 (7/125)
12 Other HR HPV positive	1400	41	1199	96	30	34	4.7 (64/1,359)	2.5 (34/1,359)
HPV negative	2577	63	2391	101	14	8	0.9 (22/2,514)	0.3 (8/2,514)

Note1: Undetermined results include inadequate biopsy sample for diagnosis and sample collected outside the Study Visit window.

Note 2: HPV16 positive and/ or HPV18 positive include all subjects with either or both of these genotypes occurring with or without 12 other HR positive results

Note 3: 12 Other HR HPV positive include all subjects with positive results for 12 Other HR HPV genotypes with negative results for HPV16 and HPV18.

The subjects in various subgroups are classified as shown in the table below. The combined results of the two IUO HPV Tests were considered positive if either of the two test results was positive. The combined results were considered negative if both tests results were negative.

Classification of Evaluable NILM Subjects (≥ 30 Years) by cobas HPV Test Result, Disease Status (≥ CIN2 and ≥ CIN3), and Disease Verification Status

cobas HPV Test Result	Combined Results From Two IUO HPV Test	Total No. Subjects	Verified Disease Status: ≥ CIN2		Verified Disease Status: ≥ CIN3		No. Subjects with Unknown Disease Status (Unverified)
			No. Diseased Subjects (≥ CIN2)	No. Non-Diseased Subjects (< CIN2)	No. Diseased Subjects (≥ CIN3)	No. Non-Diseased Subjects (< CIN3)	
HPV16 positive/18 positive	Positive	470	45	339	38	346	86
	Negative	11	0	1	0	1	10
12 Other HR HPV positive	Positive	1,634	64	1,292	34	1,322	278
	Negative	55	0	3	0	3	52
Negative	Positive	2,187	16	1,774	6	1,784	397
	Negative	27,903	6	718	2	722	27,179
Total		32,260	131	4,127	80	4,178	28,002

NILM (≥ 30 Years) Population – Performance Evaluation

For the NILM (≥30 years) population, estimates of sensitivity and specificity along with 95% CIs for HR HPV positive vs. HR HPV negative are presented in the tables below for unadjusted results and for verification bias adjusted results.

The unadjusted sensitivity and the specificity of the test for ≥ CIN2 histology were 83.2% ((109/131) with 95% CI: 75.9% to 88.6%) and 60.4% ((2492/4127) with 95% CI: 58.9% to 61.9%), respectively. The unadjusted sensitivity and specificity of the cobas HPV Test for detecting ≥ CIN3 histology were 90.0% ((72/80) with 95% CI: 81.5% to 94.8%) and 60.0% ((2506/4178) with 95% CI: 58.5% to 61.5%), respectively.

The verification bias adjusted sensitivity for ≥ CIN2 and ≥ CIN3 histology were 34.5% (with 95% CI: 22.1% to 61.4%) and 51.2% (with 95% CI: 29.3% to 94.4%), respectively, and the verification bias adjusted specificity for ≥ CIN2 and ≥ CIN3 histology were 93.6% (with 95% CI: 93.3%, to 93.9%) and 93.5% (with 95% CI: 93.2%, to 93.8%), respectively.

Performance of cobas HPV Test In the NILM (≥30 years) Population (Unadjusted Estimates)

CPR Diagnosis	Performance	Estimate	95% CI
≥CIN2	Sensitivity (%)	83.2 (109/131)	(75.9, 88.6)
	Specificity (%)	60.4 (2492/4127)	(58.9, 61.9)
	PPV (%)	6.3 (109/1744)	(5.8, 6.8)
	NPV (%)	99.1 (2492/2514)	(98.7, 99.4)
	Prevalence (%)	3.1(131/4258)	(2.6, 3.6)
≥CIN3	Sensitivity (%)	90.0 (72/80)	(81.5, 94.8)
	Specificity (%)	60.0 (2506/4178)	(58.5, 61.5)
	PPV (%)	4.1 (72/1744)	(3.8, 4.5)
	NPV (%)	99.7 (2506/2514)	(99.4, 99.8)
	Prevalence (%)	1.9(80/4258)	(1.5, 2.3)

Performance of cobas HPV Test In the NILM (≥30 years) Population
(Verification Bias Adjusted Estimates)

CPR Diagnosis	Performance	Estimate and 95% CI
≥CIN2	Sensitivity (%)	34.5 (22.1, 61.4)
	Specificity (%)	93.6 (93.3, 93.9)
	PPV (%)	6.1 (4.9, 7.2)
	NPV (%)	99.2 (98.5, 99.7)
	Prevalence (%)	1.2 (0.6, 1.8)
≥CIN3	Sensitivity (%)	51.2 (29.3, 94.4)
	Specificity (%)	93.5 (93.2, 93.8)
	PPV (%)	4.1 (3.1, 5.0)
	NPV (%)	99.7 (99.3, 100.0)
	Prevalence (%)	0.5 (0.3, 0.9)

NILM (≥ 30 Years) Population – Likelihood Ratios and Risk Estimates

Unadjusted estimates of likelihood ratios along with 95% CIs for HR HPV 16 positive /18 positive, 12 Other HR, and HR HPV negative for the NILM (≥30 years) population are presented below. The risks of ≥CIN2 and ≥CIN3 are 11.7% (45/385) and 9.9% (38/385), respectively for a NILM subject with HPV 16 positive /18 positive. The risks of ≥CIN2 and ≥CIN3 are 0.9% (22/2,514) and 0.3% (8/2,514) for a NILM subject with HPV negative, respectively.

Likelihood Ratios by cobas HPV Test Result in Detecting ≥CIN2 and ≥CIN3 in the NILM Population
(Unadjusted Estimates)

CPR Diagnosis	cobas HPV Test Result	Likelihood Ratio (95% CI)
≥CIN2	HPV 16 positive /18 positive	**4.2** (3.2, 5.4)
	12 Other HR HPV positive	**1.6** (1.3, 1.9)
	HPV Negative	**0.3** (0.2, 0.4)
≥CIN3	HPV 16 positive /18 positive	**5.7**(4.4, 7.3)
	12 Other HR HPV positive	**1.3** (1.0, 1.7)
	HPV Negative	**0.2** (0.1, 0.4)

Verification bias adjusted estimates of likelihood ratios along with 95% CIs for HR HPV 16 positive /18 positive, 12 Other HR, and HR HPV negative for the NILM (≥30 years) population are presented below.

Likelihood Ratios by cobas HPV Test Result in Detecting ≥ CIN2 and ≥ CIN3 in the NILM Population
(Verification-Bias Adjusted Estimates)

CPR Diagnosis	cobas HPV Test Result	Likelihood Ratio (95% CI)
≥CIN2	HPV 16 positive/18 positive	**10.7** (6.5, 19.6)
	12 Other HR HPV positive	**4.0** (2.4, 7.2)
	HPV Negative	**0.7** (0.4, 0.8)
≥CIN3	HPV 16 positive / 18 positive	**20.2** (10.7, 39.4)
	12 Other HR HPV positive	**4.6** (2.4, 9.4)
	HPV Negative	**0.5** (0.1, 0.8)

NILM (≥30 Years) Population – Absolute and Relative Risk Estimates

Estimates of absolute risks of ≥ CIN2 and ≥ CIN3 for cobas HPV Test results are presented below. The estimates are calculated with and without adjusting for verification bias. The risks of ≥ CIN2 and ≥ CIN3 are 11.4% (with 95% CI: 8.3% to 14.7%) and 9.8% (with 95% CI: 6.9% to 12.6%) for a NILM subject with HPV 16 positive /18 positive. The risks of ≥CIN2 and ≥CIN3 are 0.8% (with 95% CI: 0.3% to 1.5%) and 0.3% (with 95% CI: 0.0% to 0.7%), respectively for a NILM subject with HPV negative.

Absolute Risk of ≥ CIN2 and ≥ CIN3 for Different cobas HPV Test Results in the NILM Population (≥ 30 Years)

cobas HPV Test Result	≥CIN2	≥CIN3
Unadjusted Estimates		
HPV positive	6.3% (5.2, 7.5)	4.1% (3.3, 5.2)
HPV 16 positive/18 positive	11.7% (8.9, 15.3)	9.9% (7.3, 13.3)
Other 12 HR positive	4.7% (3.7, 6.0)	2.5% (1.8, 3.5)
HPV Negative	0.9% (0.6, 1.3)	0.3% (0.2, 0.6)
Verification Bias Adjusted Estimates		
HPV positive	6.1% (4.9, 7.2)	4.1% (3.1, 5)
HPV 16 positive/18 positive	11.4% (8.3, 14.7)	9.7% (6.9, 12.6)
Other 12 HR positive	4.6% (3.5, 5.7)	2.4% (1.6, 3.3)
HPV Negative	0.8% (0.3, 1.5)	0.3% (0, 0.7)

Note 1: HPV 16 positive /18 positive include all subjects with either or both of these genotypes occurring with or without 12 Other HR HPV positive results

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

Estimates of absolute risk of ≥CIN2 and ≥CIN3 for cobas HPV Test results stratified by age group are presented below. The risk of disease decreases with age for cobas HPV Test results of HPV 16 positive/18 positive and for 12 Other HR HPV positive results. The risk of disease with a cobas HPV Test negative result remains similar for the 30-39 years age group as well as for ≥40 years.

Absolute Risk Estimates in the NILM (≥30 Years) Population by cobas HPV Test Result and Age

Age Group	cobas HPV Test Result	≥CIN2	≥CIN3
30-39 Years	**Unadjusted Estimates**		
	HPV 16 positive/18 positive	16.1 (11.9, 21.5)	13.5 (9.6, 18.6)
	Other 12 HR positive	5.8 (4.2, 8.0)	3.1 (2.0, 4.8)
	HPV Negative	0.8 (0.4, 1.6)	0.3 (0.1, 0.9)
	Prevalence	4.4%	2.8%
	Verification Bias Adjusted Estimates		
	HPV 16 positive/18 positive	16.1(11.4, 20.8)	13.5 (9.1, 18.1)
	Other 12 HR positive	5.6 (3.8, 7.7)	3.0 (1.7, 4.5)
	HPV Negative	0.1 (0, 0.2)	0 .0(0, 0.1)
	Prevalence	0.8%	0.6%
≥40 Years	**Unadjusted Estimates**		
	HPV 16 positive/18 positive	5.6 (3.0, 10.2)	4.9 (2.5, 9.4)
	Other 12 HR positive	3.8 (2.6, 5.4)	2.0 (1.2, 3.3)
	HPV Negative	0.9 (0.6, 1.5)	0.3 (0.1, 0.8)

Age Group	cobas HPV Test Result	≥CIN2	≥CIN3
	Prevalence	2.1%	1.1%
	Verification Bias Adjusted Estimates		
	HPV 16 positive/18 positive	5.6 (2, 8.9)	4.7 (1.8, 8.1)
	Other 12 HR positive	3.7 (2.3, 5)	1.9 (1, 3.1)
	HPV Negative	1.2 (0.4, 2.2)	0.4 (0, 1)
	Prevalence	1.4%	0.5%

The relative risks of disease (≥ CIN2 and ≥ CIN3) were calculated between subjects with different cobas HPV Test results and are presented below. Subjects with positive cobas HPV Test results are 7.3 (95% CI = 3.99 to 22.11) times more likely to have ≥ CIN2 and 14.5 (95% CI = 5.81 to 230.4) times more likely to have ≥ CIN3, respectively, compared with subjects with a negative cobas HPV Test result. The risks of disease (both ≥ CIN2 and ≥ CIN3) were significantly higher in subjects with a positive compared with subjects with a negative HPV test result.

Also the risks of disease (≥ CIN2 and ≥ CIN3) were significantly higher in subjects who were HPV 16 and/or 18 positive than subjects with (a) a positive result for 12 Other HR HPV types, or (b) a negative result.

Similar results were also observed for risk of ≥ CIN3 by different cobas HPV Test results. The RRs of the ≥ CIN3 were higher than the RRs of the ≥ CIN2 for each comparison.

Relative Risks of ≥ CIN2 and ≥ CIN3 for Different the cobas HPV Test Results in the NILM Population (≥ 30 Years)

cobas HPV Test Result	CPR Diagnosis ≥ CIN2		CPR Diagnosis ≥ CIN3	
	Relative Risk	95% CI*	Relative Risk	95% CI*
HPV Positive vs. Negative	7.29	(3.99, 22.11)	14.53	(5.81, 230.4)
HPV16 positive /18 positive vs. Negative	13.71	(7.31, 41.92)	35.02	(12.96, 559.4)
HPV16 positive /18 positive vs. 12 Other HR HPV positive	2.51	(1.73, 3.61)	4.03	(2.57, 6.59)

*95% CI is 2.5 and 97.5 percentile of RR distribution based on 1000 bootstrap samples.
Note 1: HPV 16 positive and/ or HPV 18 positive include all subjects with either or both of these genotypes occurring with or without 12 Other HR HPV positive results
Note 2: 12 other HR HPV positive include all subjects with positive results for 12 Other HR HPV genotypes with negative results for HPV 16 and HPV 18 .

3. Additional Subgroup Analyses

Vaccinated vs. Non-Vaccinated Subjects

The clinical performance for HPV vaccinated and HPV non-vaccinated ASC-US subjects is presented below. The comparisons were done in the overall ASC-US subjects and in ASC-US subjects 21-29 years old. In the all ASC-US subjects comparison, the differences are largely due to the age disparity between the two populations, since 82 of the 84 vaccinated subjects are 21-24 years old. If the comparisons were limited to

subjects 21-24 years old, the observed differences between vaccinated and non-vaccinated subjects decrease.

The performance of cobas HPV Test in ASC-US (≥ 21 years) Population by Vaccination Status

Population	Vaccination Status	Vaccinated	Non-Vaccinated
ALL ASC-US Subjects	N	84	1834
	Percent of cobas HPV invalid Results (%)	N/A	N/A
	Percent of cobas HR HPV positive Results (%)	57.1 (46.5, 67.2)	30.8 (28.7, 32.9)
	Percent of cobas HPV 16/18 positive Results (%)	21.4 (14.0, 31.3)	10.2 (8.9, 11.7)
	Percent of ≥CIN2	10.3%	4.8%
		7/68	73/1510
		(5.1, 19.8)	(3.9, 6.0)
	Sensitivity for ≥CIN2	71.4%	91.8%
		5/7	67/73
		(35.9, 91.8)	(83.2, 96.2)
	Specificity for ≥CIN2	42.6%	71.7%
		26/61	1030/1437
		(31.0, 55.1)	(69.3, 73.9)
	Percent of ≥CIN3	7.4%	2.7%
		5/68	41/1510
		(3.2, 16.1)	(2.0, 3.7)
	Sensitivity for ≥CIN3	100.0%	92.7%
		5/5	38/41
		(56.6, 100.0)	(80.6, 97.5)
	Specificity for ≥CIN3	44.4%	70.3%
		28/63	1033/1469
		(32.8, 56.7)	(67.9, 72.6)
ASC-US (21-29 years)	N	82	544
	Percent of cobas HPV invalid Results (%)	N/A	N/A
	Percent of cobas HR HPV positive Results (%)	58.5 (47.7, 68.6)	52.8 (48.6, 56.9)
	Percent of cobas HPV 16/18 positive Results (%)	22.0 (14.4, 32.1)	21.0 (17.7, 24.6)
	Percent of ≥CIN2	10.4%	8.5%
		7/67	38/447
		(5.2, 20.0)	(6.3, 11.5)
	Sensitivity for ≥CIN2	71.4%	97.4%
		5/7	37/38
		(35.9, 91.8)	(86.5, 99.5)
	Specificity for ≥CIN2	41.7%	50.9%
		25/60	208/409
		(30.1, 54.3)	(46.0, 55.7)
	Percent of ≥CIN3	7.5%	4.3%
		5/67	19/447
		(3.2, 16.3)	(2.7, 6.5)
	Sensitivity for ≥CIN3	100.0%	100.0%
		5/5	19/19
		(56.6, 100.0)	(83.2, 100.0)
	Specificity for ≥CIN3	43.5%	48.8%
		27/62	209/428
		(31.9, 55.9)	(44.1, 53.6)

The clinical performance of the cobas HPV Test (sensitivity and specificity in detecting ≥CIN2 and ≥CIN3) for the ASC-US (≥21) population at each molecular testing is presented below.

The performance of cobas HPV Test in ASC-US (≥21 years) Population by Testing Site

Individual Site	1	2	3	4	5
N	504	280	204	306	628
Percent of cobas HPV invalid Results (%)	0.2 (0.0, 1.1)	N/A	0.5 (0.1, 2.7)	N/A	0.2 (0.0, 0.9)
Percent of cobas HR HPV positive Results (%)	32.7 (28.8, 37.0)	35.4 (30.0, 41.1)	36.3 (30.0, 43.1)	34.6 (29.5, 40.1)	26.8 (23.4, 30.3)
Percent of cobas HPV 16/18 positive Results (%)	9.9 (7.6, 12.8)	12.9 (9.4, 17.3)	12.7 (8.8, 18.0)	11.1 (8.1, 15.1)	9.4 (7.4, 11.9)
Percent of ≥CIN2[a]	4.8%	8.2%	5.5%	3.4%	4.6%
	19/396	19/231	9/164	9/268	24/519
	(3.1, 7.4)	(5.3, 12.5)	(2.9, 10.1)	(1.8, 6.3)	(3.1, 6.8)
Sensitivity for ≥CIN2	100.0%	94.7%	88.9%	88.9%	79.2%
	19/19	18/19	8/9	8/9	19/24
	(83.2, 100.0)	(75.4, 99.1)	(56.5, 98.0)	(56.5, 98.0)	(59.5, 90.8)
Specificity for ≥CIN2	69.2%	66.5%	67.7%	68.0%	75.4%
	261/377	141/212	105/155	176/259	373/495
	(64.4, 73.7)	(59.9, 72.5)	(60.0, 74.6)	(62.0, 73.3)	(71.4, 78.9)
Percent of ≥CIN3[a]	3.3%	5.2%	3.0%	2.6%	1.7%
	13/396	12/231	5/164	7/268	9/519
	(1.9, 5.5)	(3.0, 8.9)	(1.3, 6.9)	(1.3, 5.3)	(0.9, 3.3)
Sensitivity for ≥CIN3	100.0%	91.7%	100.0%	85.7%	88.9%
	13/13	11/12	5/5	6/7	8/9
	(77.2, 100.0)	(64.6, 98.5)	(56.6, 100.0)	(48.7, 97.4)	(56.5, 98.0)
Specificity for ≥CIN3	68.1%	64.4%	66.7%	67.4%	73.9%
	261/383	141/219	106/159	176/261	377/510
	(63.3, 72.6)	(57.8, 70.4)	(59.0, 73.5)	(61.5, 72.8)	(69.9, 77.5)

[a]: Results for Percent of ≥CIN2 and ≥CIN3 are calculated for the subjects with valid biopsy results

The clinical performance of the cobas HPV Test for the NILM (≥30 years) population at each molecular testing is presented below.

The performance of cobas HPV Test in NILM (≥30 years) by Testing Site

Individual Site	1	2	3	4	5
N	8977	6071	4402	5553	7399
Percent of cobas HPV invalid Results (%)	0.4 (0.3, 0.6)	0.3 (0.2, 0.5)	0.5 (0.3, 0.8)	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)
Percent of cobas HR HPV positive Results (%)	6.4 (5.9, 6.9)	6.5 (5.9, 7.2)	7.1 (6.4, 7.9)	7.0 (6.3, 7.7)	6.9 (6.3, 7.5)
Percent of cobas HPV 16/18 positive Results (%)	1.5 (1.2, 1.7)	1.3 (1.0, 1.6)	1.7 (1.4, 2.1)	1.6 (1.3, 2.0)	1.5 (1.2, 1.8)
Percent of ≥CIN2[a]	3.3%	3.9%	2.2%	3.4%	2.5%
	36/1100	31/794	13/597	26/767	25/1000

Individual Site	1	2	3	4	5
	(2.4, 4.5)	(2.8, 5.5)	(1.3, 3.7)	(2.3, 4.9)	(1.7, 3.7)
Percent of ≥CIN3 [a]	1.9%	1.9%	0.8%	2.5%	2.0%
	21/1100	15/794	5/597	19/767	20/1000
	(1.3, 2.9)	(1.1, 3.1)	(0.4, 1.9)	(1.6, 3.8)	(1.3, 3.1)
[a]: Results for Percent of ≥CIN2 and ≥CIN3 are calculated for the subjects with valid biopsy results					

Agreement with a Composite Comparator for the ASC-US ≥ 21 and, NILM ≥ 30

The analytical performance of the cobas HPV Test was evaluated by comparing results from the test with a composite comparator composed of HPV DNA sequencing and an FDA-approved HR HPV DNA test or directly with DNA sequencing. Sequencing was performed at a commercial lab. DNA was extracted from cervical specimens followed by a PCR amplification utilizing both ß-globin and PGMY primers. The ß-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[5]. PGMY-positive extracts were then amplified using HR HPV type-specific primers for subsequent sequencing reactions[6].

Representative cervical samples were selected from 2 subsets of subjects from the ATHENA Study: women ≥ 21 years who had ASC-US cytology results (n = 999) and women ≥ 30 years with NILM cytology results (n = 747).

The analytical accuracy of the cobas HPV Test was evaluated by estimating the positive percent agreement (PPA), negative percent agreement (NPA), overall percent agreement (OPA) and 95% confidence intervals (CIs) compared with the composite comparator or genotype-specific HPV DNA sequencing results as shown in the tables below. The indeterminate and invalid results are presented in the tables but not included in the calculation of percent agreement. The composite comparator result was indeterminate if results were discordant between HPV DNA sequencing result and the FDA-approved HR HPV DNA test result, or if the result from the FDA-approved test was indeterminate, or if HPV DNA sequencing result was invalid. The sequencing comparator result was invalid if ß-globin amplification produced null result during sequencing. All subjects tested for analytical accuracy had valid cobas HPV Test results.

Percent Agreement of the cobas HPV Test vs. the Composite Comparator

Population	cobas HPV Test Result	HPV Composite Comparator			Total	Agreement Estimate & 95% CI
		Positive	Negative	Indeterminate		
ASC-US ≥21 Years	Positive	268	28	29	325	PPA: 97.8% (268/274) 95% CI: (95.3%, 99.0%)
	Negative	6	618	50	674	NPA: 95.7% (618/646) 95% CI: (93.8%, 97.0%)
	Total	274	646	79	999	OPA: 96.3% (886/920) 95% CI: (94.9%, 97.3%)
NILM ≥30 Years	Positive	156	82	86	324	PPA: 96.3% (156/162) 95% CI: (92.2%, 98.3%)
	Negative	6	388	29	423	NPA: 82.6% (388/470) 95% CI: (78.9%, 85.7%)
	Total	162	470	115	747	OPA: 86.1% (544/632) 95% CI: (83.2%, 88.6%)

Note: subjects with indeterminate results were excluded from percent agreement calculation

Percent Agreement of the cobas HPV Test HPV16 Result vs. the HPV16 Sequencing Comparator

Population	cobas HPV Test: HPV16 Result	HPV 16 Sequencing Comparator			Total	Agreement Estimate & 95% CI
		Positive	Negative	Invalid		
ASC-US ≥21 Years	Positive	69	8	0	77	PPA: 97.2% (69/71) 95% CI: (90.3%, 99.2%)
	Negative	2	918	2	922	NPA: 99.1% (918/926) 95% CI: (98.3%, 99.6%)
	Total	71	926	2	999	OPA: 99.0% (987/997) 95% CI: (98.2%, 99.5%)
NILM ≥30 Years	Positive	39	17	0	56	PPA: 100.0% (39/39) 95% CI: (91.0%, 100.0%)
	Negative	0	689	2	691	NPA: 97.6% (689/706) 95% CI: (96.2%, 98.5%)
	Total	39	706	2	747	OPA: 97.7% (728/745) 95% CI: (96.4%, 98.6%)

Note: subjects with invalid results were excluded from percent agreement calculation

Percent Agreement of the cobas HPV Test HPV18 Result vs. the HPV18 Sequencing Comparator

Population	cobas HPV Test: HPV18 Result	HPV 18 Sequencing Comparator			Total	Agreement Estimate & 95% CI
		Positive	Negative	Invalid		
ASC-US ≥21 Years	Positive	38	0	0	38	PPA: 95.0% (38/40) 95% CI: (83.5%, 98.6%)
	Negative	2	957	2	961	NPA: 100.0% (957/957) 95% CI: (99.6%, 100.0%)
	Total	40	957	2	999	OPA: 99.8% (995/997) 95% CI: (99.3%, 99.9%)
NILM ≥30 Years	Positive	17	6	0	23	PPA: 94.4% (17/18) 95% CI: (74.2%, 99.0%)
	Negative	1	721	2	724	NPA: 99.2% (721/727) 95% CI: (98.2%, 99.6%)
	Total	18	727	2	747	OPA: 99.1% (738/745) 95% CI: (98.1%, 99.5%)

Note: subjects with invalid results were excluded from percent agreement calculation

Percent Agreement of cobas HPV Test 12 Other HR HPV Result vs. the 12 Other HR HPV Sequencing Comparator

Population	cobas HPV Test: 12 Other HR HPV Result	12 Other HR HPV Sequencing Comparator			Total	Agreement Estimate & 95% CI
		Positive	Negative	Invalid		
ASC-US ≥21 Years	Positive	226	32	1	259	PPA: 94.6% (226/239) 95% CI: (90.9%, 96.8%)
	Negative	13	726	1	740	NPA: 95.8% (726/758) 95% CI: (94.1%, 97.0%)
	Total	239	758	2	999	OPA: 95.5% (952/997) 95% CI: (94.0%, 96.6%)
NILM ≥30 Years	Positive	168	96	1	265	PPA: 88.4% (168/190) 95% CI: (83.1%, 92.2%)
	Negative	22	459	1	482	NPA: 82.7% (459/555) 95% CI: (79.3%, 85.6%)
	Total	190	555	2	747	OPA: 84.2% (627/745) 95% CI: (81.4%, 86.6%)

Note: subjects with invalid results were excluded from percent agreement calculation

Expected Results

A total of 47,208 subjects were enrolled in the study across 61 collection sites, and cervical samples were tested at 5 testing sites in the US. Of these, 46,887 (99.3%) subjects were eligible to participate in the study. Eligible subjects were women ≥ 21 years that had signed informed consent, satisfied study inclusion/exclusion criteria, had not enrolled in the study previously, and had not withdrawn authorization before undergoing any study procedures.

The median age of the eligible subjects was 39 years, with ~25% subjects in age group 21-29 years, ~27% in age group 30-39 years, and ~48% subjects in age group ≥ 40 years.

A total of 90.0% of subjects had NILM cytology, and 4.1% subjects had ASC-US cytology.

A total of 1,918 subjects (ASC-US population with age ≥ 21 years) were evaluable; evaluable subjects were those who had an ASC-US cytology result and had valid results from the IUO HR HPV Test, IUO HPV genotyping Test, and cobas HPV Test.

A total of 32,260 subjects (NILM population ≥ 30 years) were evaluable; evaluable subjects were eligible subjects ≥ 30 years who had a NILM cytology result and had valid results from the IUO HR HPV Test, IUO HPV genotyping Test, and cobas HPV Test.

The table below shows HPV prevalence by the cobas HPV Test by testing site and study population. The HPV prevalence was 31.9% in the ASC-US (≥ 21 years) population and 6.7% in the NILM (≥ 30 years) population.

Summary of HPV Prevalence by the cobas HPV Test by Testing Sites and Study Population

Testing Site	cobas HPV Test – HPV Prevalence	
	ASC-US Population (≥ 21 Years)	NILM Population (≥ 30 Years)
1	32.8% (165/503)	6.4% (572/8,925)
2	35.5% (99/279)	6.5% (395/6,041)
3	36.5% (74/203)	7.1% (309/4,370)
4	34.6% (106/306)	7.0% (387/5,539)
5	26.8% (168/627)	6.9% (507/7,385)
Overall	31.9% (612/1,918)	6.7% (2,170/32,260)

The table below shows HPV prevalence by cobas HPV Test result by age and study population. In the ASC-US population, HPV prevalence dropped from 53.5% in 21-29 years to 29.7% in 30-39 years and remained relatively constant at 15-20% after 40 years old. In the NILM population, HPV prevalence was 9.0% in 30-39 years and remained ~5% in ≥ 40 years.

Summary of HPV Prevalence by cobas HPV Test Result by Age and Study Population

Age Group (Years)	ASC-US Population (≥ 21 Years)	NILM Population (≥ 30 Years)
21-29	53.5% (335/626)	N/A
30-39	29.7% (151/508)	9.0% (1,029/11,398)
40-49	15.0% (76/508)	5.7% (627/10,944)
50-59	19.3% (40/207)	5.3% (378/7,106)
60-69	17.3% (9/52)	4.9% (111/2,287)
≥70	5.9% (1/17)	4.8% (25/525)

The cobas HPV Test results are presented below, stratified into four groups by age for the ASC-US and NILM populations. In both populations, the 12 Other HR HPV positive results were more frequent than HPV16 positive and HPV18 positive results in general and within age groups. HPV prevalence decreases with age in both populations.

Summary of cobas HPV Test Result (Four-groups) by Age Group for Evaluable ASC-US Subjects

Age Group (Years)	cobas HPV Test Result				Total
	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	Negative	
21-29	15.5% (97/626)	5.6% (35/626)	32.4% (203/626)	46.5% (291/626)	626
30-39	6.1% (31/508)	2.2% (11/508)	21.5% (109/508)	70.3% (357/508)	508
40-49	3.5% (18/508)	0.6% (3/508)	10.8% (55/508)	85.0% (432/508)	508
50-59	1.4% (3/207)	2.9% (6/207)	15.0% (31/207)	80.7% (167/207)	207
60-69	0.0% (0/52)	1.9% (1/52)	15.4% (8/52)	82.7% (43/52)	52
≥70	0.0% (0/17)	0.0% (0/17)	5.9% (1/17)	94.1% (16/17)	17

Note: HPV16 positive implies HPV16 positive, HPV18 positive or negative and 12 Other HR HPV positive or negative.
HPV18 positive implies HPV16 negative, HPV18 Positive and 12 Other HR HPV positive or negative.
12 Other HR HPV positive implies HPV16 negative, HPV18 negative and 12 Other HR HPV positive.

Summary of Four-Category cobas HPV Test Result by Age Group for Evaluable NILM Subjects

Age Group (Years)	cobas HPV Test Result				Total
	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	Negative	
30-39	1.6%(183/11,398)	0.7%(84/11,398)	6.7%(762/11,398)	91.0% (10,369/11,398)	11,398
40-49	0.7%(80/10,944)	0.4%(41/10,944)	4.6%(506/10,944)	94.3% (10,317/10,944)	10,944
50-59	0.6%(41/7,106)	0.4%(27/7,106)	4.4%(310/7,106)	94.7% (67,28/7,106)	7,106
60-69	0.7%(16/2,287)	0.2%(4/2,287)	4.0%(91/2,287)	95.1% (2,176/2,287)	2,287

Age Group (Years)	cobas HPV Test Result				Total
	HPV16 Positive	HPV18 Positive	12 Other HR HPV Positive	Negative	
≥70	0.8%(4/525)	0.2%(1/525)	3.8%(20/525)	95.2% (500/525)	525

Note: HPV16 positive implies HPV16 positive, HPV 18 positive or negative and 12 Other HR HPV positive or negative.
HPV18 positive implies HPV16 negative, HPV18 Positive and 12 Other HR HPV positive or negative.
12 Other HR HPV positive implies HPV16 negative, HPV18 negative and 12 other HR positive.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

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

B. Effectiveness Conclusions

The effectiveness of the cobas HPV Test has been demonstrated for use in conjunction with cervical cytology in the following patient populations. The test may be used in women 30 years and older to adjunctively screen to assess the presence or absence of high-risk human papillomavirus (HPV) types. Additionally, a reasonable determination of effectiveness of the cobas HPV Test for use in screening women ≥21 years with ASC-US cervical cytology results has been demonstrated. The results of this test, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data from the nonclinical studies demonstrated acceptable analytical sensitivity,

precision, and analytical specificity of the 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 statistical analysis of clinical data in this application has shown that the assay is safe and effective for its approved indications when used according to the directions for use in the labeling.

XIV. CDRH DECISION

CDRH issued an approval order on April 19, 2011. The final conditions of approval are described in the approval order.

The applicant's manufacturing facility(ies) was/were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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