# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

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

Device Trade Name: cobas® HPV Test

Device Procode: MAQ

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

Date(s) of Panel Recommendation: March 12, 2014

Premarket Approval Application (PMA) Number: P100020/S008

Date of FDA Notice of Approval: April 24, 2014

Priority Review: Not Applicable

The original PMA P100020 was approved on April 19, 2011 and is indicated for:

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

The cobas® HPV Test is indicated:

1. 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.
2. To be used in patients 21 years and older with ASC-US cervical cytology results, to detect high-risk HPV genotypes 16 and 18. This information, together with the physician's assessment of screening history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy.
3. In women 30 years and older, the cobas® HPV Test can be used with cervical cytology to adjunctively screen to detect high risk HPV types. This information,

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

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

The SSED to support the indication is available on the CDRH website and is incorporated by reference here:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020

The current supplement was submitted to expand the indication for the cobas® HPV Test.

## II. INDICATIONS FOR USE

The new indication for use for the cobas® HPV Test submitted under P100020/S008:

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

## III. CONTRAINDICATIONS

None

## IV. WARNINGS AND PRECAUTIONS

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

## V. DEVICE DESCRIPTION

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

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

This is the first FDA-approved HPV test with an indication for use as a first line screening test for cervical cancer. There are several other alternatives for the detection of cervical cancer precursors (testing by cytology alone or testing for HPV alongside or as a follow-up to cytology). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with her physician to select the method that best meets expectations and lifestyle.

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

## VII. MARKETING HISTORY

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

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

## IX. SUMMARY OF PRECLINICAL STUDIES

The summary of preclinical studies for this device can be found in the SSED for the original PMA on the CDRH website at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100020

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant conducted a clinical study to establish a reasonable assurance of safety and effectiveness for the new indication for the cobas® HPV Test in the US. Data from this

clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

## A. Study Design

Patients were enrolled between May 2008 and August 2009. The database for this PMA supplement included 42,209 patients evaluated for the new indication. There were 61 investigational sites.

### 1. Clinical Inclusion and Exclusion Criteria

Inclusion Criteria:
a. Females age ≥25 years
b. Presenting for routine cervical cancer screening (see Glossary for definition)
c. Intact cervix
d. Willing and able to undergo colposcopy, biopsy, and endocervical curettage (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, i.e., 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 (e.g., 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.

### 3. Clinical Endpoints

A multicenter, prospective study (ATHENA Study) was conducted to evaluate the performance of the cobas® HPV Test for multiple intended use claims, one of which was as a primary screening test for cervical cancer (see Proposed New Indication for Use). The study consisted of a Baseline Phase, as well as a three year Follow-Up Phase.

**Baseline Phase**

In the Baseline Phase, subjects undergoing routine cervical cancer screening were invited to participate in the study. In total, 42,209 subjects ≥ 25 years old 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 on pre-aliquoted samples in secondary vials prior to cytology processing at five different laboratories; LBC testing was conducted at four of these five laboratories. Cytology samples were classified according to the criteria of the 2001 Bethesda System. A cervical sample 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 ~62% samples collected were stored and were within the window for sample stability at the time of testing. The remaining ~38% 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 cytology results was tested with an FDA-approved test according to the manufacturer's instructions.

The subjects ≥25 years old with ≥ASC-US cytology were invited to undergo colposcopy. In addition, all subjects ≥25 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 (CPR) panel consisting of three expert pathologists, and discordant results adjudicated according to a pre-defined protocol. For all analyses, the clinical performance of the cobas® HPV Test at Baseline was evaluated against CPR histology results. The analyses were performed for those subjects with histology ≥CIN2 and ≥CIN3 by CPR. Subjects with a 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 9,361 subjects who did not have histology ≥CIN2 by CPR were invited to participate in a three year longitudinal study. Of these, 7,642 subjects where eligible to participate and entered the Follow-Up Phase of the study. Subjects underwent annual visits for cervical sampling for cytology and HPV DNA testing (by the cobas® HPV Test). All

subjects with ≥ASC-US were invited to proceed to colposcopy. Colposcopy and biopsies were performed in a standardized manner as described above. All cervical biopsies were examined by the CPR panel. All subjects with ≥CIN2 by CPR exited the study and those with <CIN2 by CPR were invited to proceed to the next follow-up year visit. In order to maximize disease ascertainment, an exit colposcopy and endocervical curettage (ECC) was offered to all subjects in Year 3.

**B. Accountability of PMA Cohort**

At the time of database lock, of 42,209 patients ≥25 years enrolled in the PMA study, 97% (40, 944) of these patients were available for analysis at the completion of the Baseline Phase of the study. More details are provided below in terms of how women were selected for the Follow-up Phase of the study (only a subset of women were selected to participate in this phase of the study, which is analyzed separately as "Future Risk" starting on page 20 of the clinical performance data summaries).

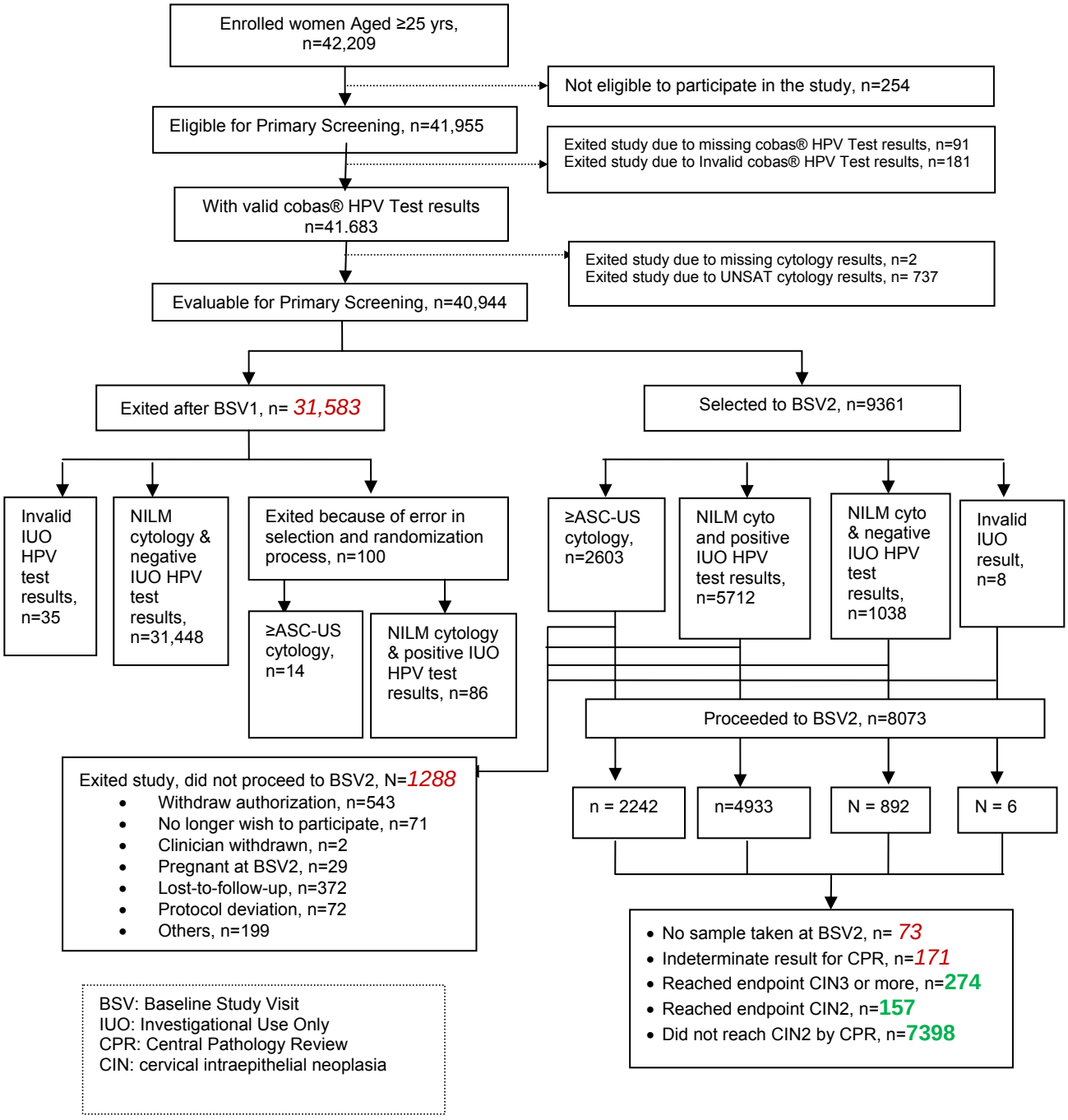
Of the 42,209 subjects ≥25 years of age, 41,955 were eligible to participate in the study. Subjects were not eligible if they (a) did not satisfy study inclusion/exclusion criteria (n=165), (b) enrolled in the study for a second time (n=82) or (c) withdrew authorization before undergoing study procedures at Study Visit 1(n=7). Among 41,955 subjects, 91 (0.22%) had missing cobas® HPV Test results. Valid results from cytology were available for 41,083 (97.9%) subjects. Valid cobas® HPV Test results were available for 40,944 of those eligible subjects (evaluable primary screening population). An analysis of missing values with regard to potential biases (analysis of covariate distributions) for the 91 subjects did not show that the subjects with missing HPV results were different from the subjects with available HPV results. The primary analysis includes 40, 944 subjects with valid cobas® HPV Test results and satisfactory cytology.

The Primary Screening algorithm was evaluated on these 40,944 subjects. A total of 31,583 subjects exited after Baseline Study Visit 1 (BSV1). A total of 9,361 subjects were selected or randomized for BSV2. These included 2,603 (27.8%) subjects with abnormal cytology results, 5,712 (61.1%) subjects with normal cytology results and positive IUO HPV Test results, 1,038 (11.1%) randomly selected subjects with normal cytology results and negative IUO HPV Test results, and 8 subjects with invalid IUO HPV Test results. The flow of primary screening subjects through the Baseline Phase of the study is shown in Figure 1.

A total of 8,073 (=2242 ≥ ASC-US + 4933 NILM and IUO HPV positive + 892 NILM and IUO HPV negative + 6 Invalid IUO HPV) subjects proceeded to BSV2. Of these, 157 (1.9%) subjects had a CIN2 biopsy result and 274 (3.4%) subjects had ≥CIN3 biopsy result based on CPR. No biopsy sample was available for 73 (0.9%) of these subjects. Totals shown in red are women with unverified disease status and totals shown in green are women with verified disease status in Figure 1 below.

**Figure 1. Flow of Subjects in the Baseline Phase**

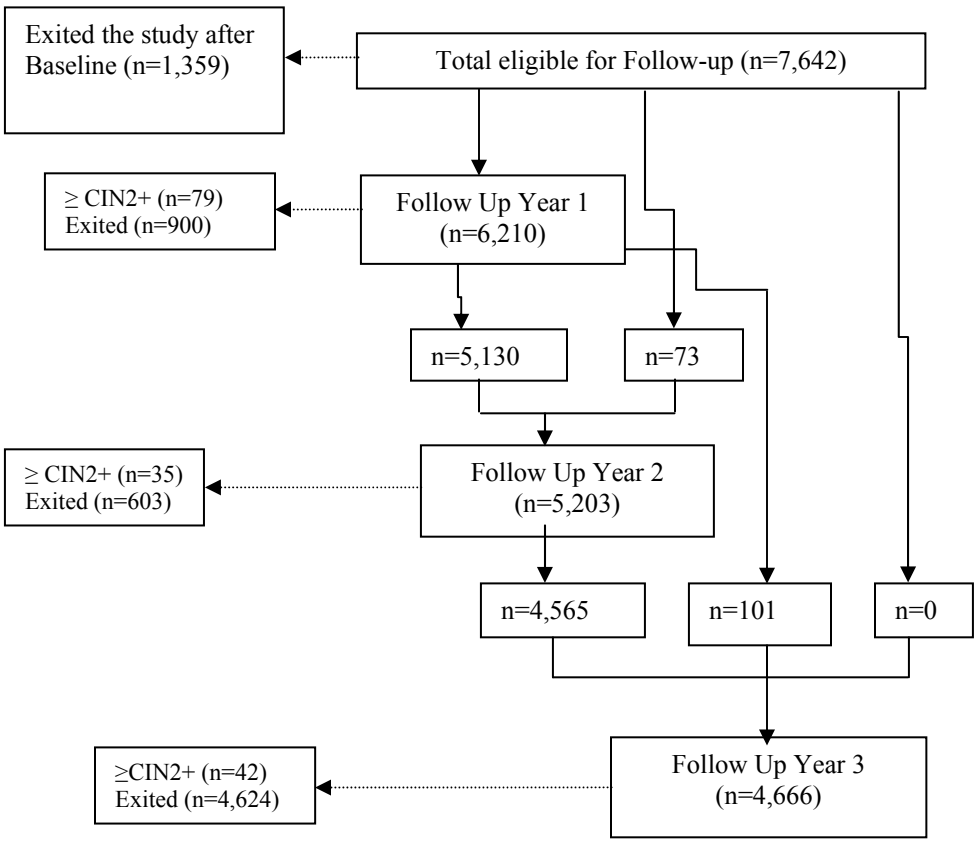
**Primary Screening (≥25 Years) Population**



A total of 1,288 out of 9,361 (13.8%) subjects did not return for the colposcopy visit at Baseline and therefore were not eligible for follow-up. A total of 431 subjects reached ≥CIN2 endpoint at Baseline and exited the study. Thus, 7,642 subjects were eligible for three year follow-up.

The flow of 7,642 eligible subjects through the follow up phase of the study is shown in Figure 2. A total of 1,359 subjects exited after the Baseline colposcopy. A total of 6,210 subjects returned to the follow-up Year 1. Out of these, 79 subjects exited due to a ≥CIN2 result by CPR panel and 900 others were lost to follow-up after the follow-up Year 1. The follow-up Year 2 visit was completed by 5,203 subjects, including 5,130 subjects from Year 1 and 73 subjects who were eligible for follow-up but missed Year 1. A total of 35 subjects reached ≥CIN2 endpoint in Year 2 and exited the study, in addition to 603 subjects who dropped out after their Year 2 visit. A total of 4,666 subjects completed the Year 3 study visit and 42 subjects reached ≥CIN2 endpoint. Thus, a total of 156 (=79+35+42) subjects reached ≥CIN2 endpoint during the three years of follow up.

**Figure 2: Flow of Subjects in the Follow-up Phase for the Primary Screening (≥25 Years) Population**



## C. Study Population Demographics and Baseline Parameters

The demographics of the study population shown in Table 1 are typical for a cervical cancer screening study performed in the US.

**Table 1. Summary of Demographic Characteristics for the Evaluable Primary Screening Population**

| Characteristics | Statistic | Evaluable Subjects n = 40,944 |
|---|---|---|
| **Age (Years)** | Mean | 41.8 |
| | SD | 11.3 |
| | Median | 41 |
| | (Min, Max) | (25, 93) |
| **Age Group (Years)** | | |
| 25-29 | n (%) | 6,654 (16.3) |
| 30-39 | n (%) | 12,260 (29.9) |
| 40-49 | n (%) | 11,695 (28.6) |
| ≥50 | n (%) | 10,335 (25.2) |
| **Race** | | |
| White | n (%) | 34,156 (83.4) |
| American Indian or Alaskan Native | n (%) | 226 ( 0.6) |
| Black or African American | n (%) | 5,602 (13.7) |
| Asian | n (%) | 639 ( 1.6) |
| Native Hawaiian or Other Pacific Islander | n (%) | 98 ( 0.2) |
| Any Combination [1] | n (%) | 220 ( 0.5) |
| Missing | n (%) | 3 (<0.1) |
| **Ethnicity** | | |
| Hispanic or Latino | n (%) | 7,370 (18.0) |
| Not Hispanic or Latino | n (%) | 33,572 (82.0) |
| Missing | n (%) | 2 (<0.1) |
| **Education** | | |
| Elementary | n (%) | 821 ( 2.0) |
| High School (or GED) | n (%) | 9,562 (23.4) |
| Vocational/Some College | n (%) | 10,684 (26.1) |
| College Degree | n (%) | 13,887 (33.9) |
| Some Graduate Work | n (%) | 1,114 ( 2.7) |
| Graduate Degree (Master's or Higher) | n (%) | 4,865 (11.9) |
| Missing | n (%) | 11 (<0.1) |

[1] Any Combination refers to subjects who selected more than one race.

## D. Safety and Effectiveness Results

1. Safety Results

As an *in vitro* diagnostic test, the cobas® HPV Test involves sampling cells from the cervix using an endocervical brush/spatula. The test, therefore, presents no more safety hazard to an individual being tested than other tests where cervical cells are sampled in this manner (such as cervical cytology).

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

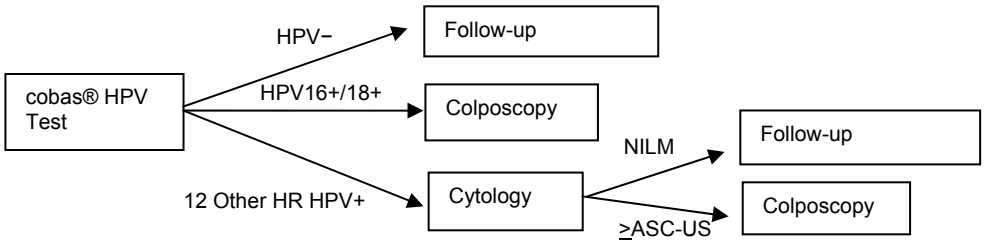
2. Effectiveness Results

The analysis of effectiveness was based on the following data.

**Primary Screening Algorithm (Candidate)**

The candidate algorithm (Primary Screening) is described by the proposed new indication for use (which again, would not replace the approved indications but would be an additional indication for the device). Women who test negative for high risk HPV types by the cobas® HPV Test should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the cobas® HPV Test should be referred to colposcopy. Women who test high risk HPV positive and 16/18 negative by the cobas® HPV Test (12 Other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

*Primary Screening algorithm (16/18 Genotyping with 12 Other HR HPV Positive to Cytology)*



**Definition of Positive and Negative Results***

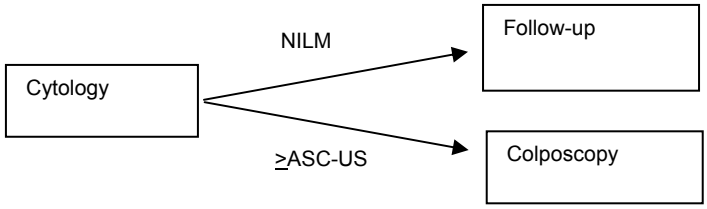
| | Cytology | | | |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| | | | ≥30 | 25-29 |
| HPV 16/18 Pos | | | | |
| 12 Other HR HPV Pos | | | | |
| HR HPV Neg | | | | |

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

**Cytology Algorithm (Comparator)**

The clinical comparator for the evaluation of this new indication is cervical cytology alone. FDA believes this is an appropriate comparator in that it reflects longstanding clinical practice, is appropriate for all screening age groups and is independent of any HPV test results. The sponsor is using the Cytology algorithm as a benchmark for safety and effectiveness when evaluating their new indication (Primary Screening algorithm, above). This benchmark is intended to represent clinically acceptable performance levels, but not necessarily clinically optimal performance. Positive results are defined as women sent immediately to colposcopy, depicted in green by the diagram below:

*Cytology algorithm (Cytology Alone)*




**Definition of Positive and Negative Results***

| | Cytology | | | |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| | | | ≥30 | 25-29 |
| HPV 16/18 Pos | | | | |
| 12 Other HR HPV Pos | | | | |
| HR HPV Neg | | | | |

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

Positive results for the Cytology algorithm are consistent with the 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests (herein referred to as the 2006 Guidelines[1]. Per the 2006 guidelines, women with ASC-US or greater cytology can be sent immediately to colposcopy. This comparator was selected prior to the 2012 update of the 2006 Guidelines[2] (2012 Guidelines), in which immediate colposcopy is no longer performed on women with ASC-US cytology and unknown HPV status. FDA still considers the 2006 cytology alone algorithm to be an appropriate comparator since it is more familiar to clinicians and has better sensitivity than the 2012 cytology alone algorithm.

**Additional Comparator**

The currently recommended cervical cancer screening paradigm involves HPV triage of ASC-US cytology results in women less than 30 years of age and co-testing with HPV and cytology in women 30 and older. In this paradigm, women with cytology results >ASC-US, women who are ASC-US and HPV positive, or women with NILM cytology who are 30 or older and are positive for HPV 16 and/or 18 should go immediately to colposcopy. This algorithm is being included because it represents a higher bar for cervical cancer screening performance as a currently preferred algorithm[3] (whereas cytology alone is considered acceptable). This screening paradigm is denoted as "ATRI NM≥30 GT" in this submission.

*Additional Comparator, ATRI NM≥30 GT: ASC-US Triage for Ages ≥25 and NILM HPV16/18+ genotyping for Ages ≥30.*

**Definition of Positive and Negative Results***

| | **Cytology** | | | |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| | | | ≥30 | 25-29 |
| HPV 16/18 Pos | | | | |
| 12 Other HR HPV Pos | | | | |
| HR HPV Neg | | | | |

*Green denotes positive and gray denotes negative results. Positive results are defined as women sent immediately to colposcopy.

**Definition of Positive and Negative Results and their Interpretation**

As described above, "positive" results for the candidate and comparator algorithms are defined as women sent immediately to colposcopy. "Negative" results for the candidate and comparator algorithms indicate that a woman will not be sent immediately to colposcopy. Any additional follow-up procedures are not directly assessed. Therefore, this device is being evaluated regarding its performance in directing immediate follow-up

decisions. Longer-term follow-up decisions (i.e. subsequent screening visits) are not directly assessed.

Note that algorithm positive and negative results are distinct from the "disease positive" and "disease negative" results referred to in the Clinical Study Results section below, which are defined as women diagnosed with or without high grade CIN, respectively (results are presented for both ≥CIN2 and ≥CIN3). Therefore, when probability of disease in the Baseline Phase of the clinical study is described in this document it refers to the probability that a woman has disease at the time of HPV testing (the exact time of disease onset can't reasonably be known).

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

Among the 47,208 women enrolled in the study, a total of 40,944 were evaluable for the analysis of the primary screening population. To be evaluable, the women must have been eligible for study enrollment at Baseline, have been 25 years or older with a valid cobas® HPV Test result, and a valid cytology result. The percent of Invalid cobas® HPV Test results was 0.43% (181/41,864) with 95% CI: 0.37% to 0.50%.

A total of 8,073 women (3,612 positive and 4,461 negative by the cobas® HPV Test) proceeded to colposcopy. Diagnosis of ≥CIN2 (by CPR) was observed in 431(5.5%) of 7,829 women with valid CPR results at colposcopy. A total of 7,642 women were eligible for the Follow-Up phase. A total of 6,168 women completed the Follow-Up Year 1 visit, 5,203 women completed the Follow-Up Year 2 visit, and 4,666 completed the Follow-Up Year 3 visit.

The number of patients with colposcopy results for each combination of cobas® HPV Test and cytology results are shown in Table 2. A correction for verification bias was applied due to the different rate of colposcopy in each category. Number of cases of disease was imputed for the women who did not have colposcopy data from the women who did go to colposcopy in each category based on their IUO HPV Test results, cytology results, and their age.

**Table 2. Number of Patients with Colposcopy Results by cobas® HPV Test and Cytology Results**

| cobas® HPV Test | Cytology | | | Total |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| HPV 16/18 Pos | 250<br>Colpo: 216 | 139<br>Colpo: 121 | 781<br>Colpo: 630 | 1,170 |
| 12 Other HR HPV Pos | 414<br>Colpo: 348 | 306<br>Colpo: 255 | 2,393<br>Colpo: 1,934 | 3113 |
| HR HPV Neg | 322<br>Colpo: 279 | 1,187<br>Colpo: 968 | 35,152<br>Colpo: 3,078 | 36,661 |
| Total | 986 | 1,632 | 38,326 | **40,944** |

**Performance Evaluation of the Primary Screening Algorithm in the Primary Screening (≥25 Years) Population**

Performance of the Primary Screening algorithm (HPV 16/18 Genotyping with reflex to Cytology) and the Cytology algorithm (Cytology alone) was evaluated and compared in the primary screening population by estimating the sensitivity, specificity, Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR), prevalence, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) in the identification of high-grade cervical disease; results are presented in Table 3 for ≥CIN2 and Table 4 for≥CIN3.

The performance of the Primary Screening algorithm was significantly better than the Cytology algorithm for both ≥CIN2 and ≥CIN3 endpoints in that the Primary Screening algorithm had significantly higher sensitivity, PPV and PLR, and also significantly lower (1-specificity), (1-NPV) and NLR compared with the Cytology algorithm. Also, the Primary Screening algorithm required 1.77% fewer colposcopies (Pos %) compared to the Cytology algorithm (Table 3 and 4).

**Table 3. Performance Comparison of the Primary Screening Algorithm and Cytology Algorithm (≥ CIN2)**

| | **Prevalence(%)=1.79 with 95% CI (1.37, 2.25)** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos (%)** | **PPV (%)** | **1-NPV (%)** | **Sensitivity (%)** | **1-Spec (%)** | **PLR** | **NLR** |
| Primary Screening | 4.62 | 17.62 | 1.03 | 45.41 | 3.87 | 11.73 | 0.57 |
| 95% CI | (4.42, 4.82) | (15.80, 19.54) | (0.60, 1.49) | (35.81, 59.65) | (3.68, 4.06) | (9.15, 15.43) | (0.42, 0.67) |
| | | | | | | | |
| Cytology | 6.39 | 9.89 | 1.24 | 35.31 | 5.87 | 6.02 | 0.69 |
| 95% CI | (6.16, 6.62) | (8.68, 11.20) | (0.81, 1.72) | (27.60, 46.74) | (5.64, 6.09) | (4.66, 8.01) | (0.57, 0.77) |
| | | | | | | | |
| Difference | -1.77 | 7.73 | -0.21 | 10.1 | -2.00 | 5.71 | -0.12 |
| 95% CI | (-2.01, -1.55) | (6.51, 8.93) | (-0.27,-0.15) | (6.57, 14.45) | (-2.22,-1.77) | (4.31, 7.66) | (-0.16,-0.08) |
| Stat Sign. | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 4. Performance Comparison of the Primary Screening Algorithm and the Cytology Algorithm (≥ CIN3)**

| | Prevalence(%)=0.97 with 95% CI (0.74, 1.28) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos (%)** | **PPV (%)** | **1-NPV (%)** | **Sensitivity (%)** | **1-Spec (%)** | **PLR** | **NLR** |
| Primary Screening | 4.62 | 12.25 | 0.42 | 58.26 | 4.09 | 14.24 | 0.44 |
| 95% CI | (4.42, 4.82) | (10.69, 13.91) | (0.20, 0.74) | (44.02, 74.37) | (3.89, 4.28) | (10.77, 18.29) | (0.27, 0.58) |
| | | | | | | | |
| Cytology | 6.39 | 6.47 | 0.59 | 42.63 | 6.04 | 7.06 | 0.61 |
| 95% CI | (6.16, 6.62) | (5.54, 7.50) | (0.36, 0.92) | (31.75, 55.41) | (5.81, 6.27) | (5.24, 9.26) | (0.47, 0.73) |
| | | | | | | | |
| Difference | -1.77 | 5.78 | -0.17 | 15.63 | -1.95 | 7.18 | -0.17 |
| 95% CI | (-2.01, -1.55) | (4.72, 6.94) | (-0.23, -0.12) | (10.28, 22.16) | (-2.18, -1.71) | (5.34, 9.40) | (-0.24, -0.12) |
| Stat Sign. | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

## Baseline Risks of High-Grade Cervical Disease for the Primary Screening Algorithm

Women with HPV16/18+ and 12 Other HR HPV+ with ≥ASC-US cytology accounted for 2.86% and 1.76%, respectively (Table 5), of the primary screening population ≥25 years and were referred for immediate colposcopy by the Primary Screening algorithm. The risks of ≥CIN2 were 19.8% (95% CI, 17.4-22.4) for HPV16/18+and 14.2% (95% CI, 11.4-17.1) for 12 Other HR HPV+ with ≥ASC-US cytology. These high risk estimates justify referral of these women for colposcopy. Women with12 Other HR HPV+ and NILM cytology accounted for 5.84% and had a risk of ≥CIN2 of 4.9%. The majority of women (89.6%) were HPV negative and had a risk of 0.77% for ≥CIN2.

**Table 5. The Risk of Disease in Each Category Related to the Primary Screening Algorithm (≥25 Years)**

| | **Percent of patients with results (%)** | **Risk of ≥ CIN3 (%) (95% CI)** | **Risk of ≥ CIN2 (%) (95% CI)** |
|---|---|---|---|
| HPV 16/18 + | **2.86** | **15.0** (13.0, 17.4) | **19.8** (17.4, 22.4) |
| 12 Other HR HPV + and ≥ASC-US cytology | **1.76** | **7.8** (5.6, 10.2) | **14.2** (11.4, 17.1) |
| 12 Other HR HPV + and NILM cytology | **5.84** | **2.8** (2.1, 3.5) | **4.9** (3.9, 5.9) |
| HR HPV - | **89.54** | **0.27** (0.05, 0.60) | **0.77** (0.33, 1.29) |

**Baseline Risks of High-Grade Cervical Disease by Age Group for the Primary Screening Algorithm**

The risks of high-grade cervical disease by age group for the Primary Screening algorithm are presented in Table 6. The risk of ≥CIN2 was above 10% in each age group for women with HPV16/18+ and women with 12 Other HR HPV + and ≥ASC-US cytology. The risk of ≥CIN3 was below 0.45% in each age group for women with a negative HPV test result.

**Table 6. The Risk of Disease in Each Category Related to the Primary Screening Algorithm by Age Groups**

| Age Group | Category | Percent of patients with results (%) | Risk of ≥ CIN3 (%) (95% CI) | Risk of ≥ CIN2 (%) (95% CI) |
|---|---|---|---|---|
| **25-29 Years** | HPV 16/18 + | **6.97** | **12.7** ( 9.65, 16.1 ) | **19.4** ( 15.7, 23.6 ) |
| | 12 Other HR HPV + and ≥ASC-US cytology | **3.61** | **5.83** ( 2.81, 9.57 ) | **15.0** ( 10.1, 19.7 ) |
| | 12 Other HR HPV + and NILM cytology | **10.55** | **3.56** ( 2.09, 5.20 ) | **5.56** ( 3.79, 7.52 ) |
| | HR HPV - | **78.87** | **0.08** ( 0.00, 0.17 ) | **0.30** ( 0.15, 0.49 ) |
| | | | | |
| **30-39 Years** | HPV 16/18 + | **3.18** | **20.2** ( 16.2, 24.5 ) | **24.9** ( 20.4, 29.6 ) |
| | 12 Other HR HPV + and ≥ASC-US cytology | **2.09** | **7.42** ( 4.07, 11.5 ) | **12.1** ( 8.10, 16.6 ) |
| | 12 Other HR HPV + and NILM cytology | **6.22** | **3.01** ( 1.87, 4.48 ) | **5.77** ( 4.08, 7.69 ) |
| | HR HPV - | **88.41** | **0.10** ( 0.05, 0.16 ) | **0.18** ( 0.09, 0.26 ) |
| | | | | |
| **40-49 Years** | HPV 16/18 + | **1.56** | **14.3** ( 8.85, 19.9 ) | **16.5** ( 10.6, 22.1 ) |
| | 12 Other HR HPV + and ≥ASC-US cytology | **1.22** | **10.5** ( 5.30, 16.8 ) | **18.2** ( 12.2, 26.0 ) |
| | 12 Other HR HPV + and NILM cytology | **4.33** | **2.77** ( 1.42, 4.69 ) | **4.94** ( 3.04, 7.34 ) |
| | HR HPV - | **92.89** | **0.39** ( 0.01, 1.13 ) | **0.80** ( 0.07, 1.84 ) |
| | | | | |
| **≥50 Years** | HPV 16/18 + | **1.18** | **8.20** ( 3.45, 14.2 ) | **9.84** ( 4.39, 15.7 ) |
| | 12 Other HR HPV + and ≥ASC-US cytology | **0.78** | **8.64** ( 2.35, 16.4 ) | **11.1** ( 3.90, 18.6 ) |
| | 12 Other HR HPV + and NILM cytology | **4.08** | **0.95** ( 0.00, 2.00 ) | **2.13** ( 0.68, 3.60 ) |
| | HR HPV - | **93.95** | **0.45** ( 0.01, 1.36 ) | **1.67** ( 0.44, 3.27 ) |

**Effect of Knowledge of HPV Status on Cytology (Un-blinded Results) for the Primary Screening Algorithm**

Cytologists were intentionally blinded to all other patient test results for the ATHENA Study to avoid biasing their assessment of the cytology slides based on the knowledge of

other test results (otherwise performance of cytology alone as a comparator algorithm could potentially be biased). However, cytology performance could be different in a real-life setting in the context of using the cobas® HPV Test as a primary screening test when cytologists know that essentially all the specimens they are screening are 12 Other HR HPV positive. To assess how different the performance of the Primary Screening algorithm could be in this real-life setting, a subset of cytology slides were re-read at the testing sites with knowledge of the HPV status available at the time of the repeat reading. Archived cytology slides from the Baseline Phase for all cases in women ≥25 years with a CPR diagnosis of ≥CIN2 (a total of 431 cases, 380 were cobas® HPV Test positive and 51 were cobas® HPV Test negative) were re-read at the original community laboratory where the initial reading was performed. A control group of approximately 1,140 HPV positive cases and 153 HPV negative case that were determined by CPR to be <CIN2 were also randomly selected from the archived slides (the control group was included to avoid cytologists' reading bias). The cytotechnologists were informed of the HPV status (HPV16 positive, HPV18 positive, 12 Other HR HPV positive or HPV negative) of the subject. For the Primary Screening algorithm, women with HPV negative results would be directed to follow-up and those with HPV16/18 positive results would go directly to colposcopy. The un-blinded cytology result would therefore not affect these two categories since cytology is not performed. Only women who are 12 Other HR HPV positive would be triaged with cytology to decide whether colposcopy is indicated. For 976 slides with 12 Other HR HPV positive results, 161 slides with ≥CIN2 and 815 slides with <CIN2 were read in blinded and un-blinded modalities. The results of this additional study were following:

For the cytology slides corresponding to ≥CIN2 colposcopy/biopsy results, knowledge of HPV status increased the percent of ≥ASC-US cytology results by 1.30 times (56.5%/43.5%); and for the cytology slides corresponding to <CIN2 colposcopy/biopsy results, knowledge of HPV status increased the percent of ≥ASC-US cytology results by 1.30 times (26.5%/20.4%). For the cytology slides corresponding to ≥CIN3 colposcopy/biopsy results, knowledge of HPV status increased the percent of ≥ASC-US cytology results by 1.35 times (56.2%/41.6%); and for the cytology slides corresponding to <CIN3 colposcopy/biopsy results, knowledge of HPV status increased the percent of ≥ASC-US cytology results by 1.29 times (29.0%/22.4%). Using these values, the crude estimates of performance for the Primary Screening algorithm were adjusted and then verification biased adjusted (VBA) estimates for ≥CIN3 (Table 7) were calculated.

For the Primary Screening algorithm, where women who are 12 Other HR HPV positive are reflexed to cytology, the sensitivity of the Primary Screening algorithm for ≥CIN3 increased by approximately 5% (Table 7) and specificity decreased by approximately 0.5% if the cytologists were un-blinded to HPV results. This resulted in approximately the same PPV, a small improvement in NPV and an 11% increase in the number of colposcopies (5.13%/4.62% =1.11).

**Table 7. Performance Comparison of Blinded and Un-blinded Cytology Using the Primary Screening Algorithm (≥CIN3)**

| Algorithm | Prevalence(%)=0.97 with 95% CI (0.74, 1.28) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Pos (%) | PPV (%) | 1-NPV (%) | Sensitivity (%) | 1-Spec (%) | PLR | NLR |
| **HPV Primary Screening Algorithm (Blinded to HPV status)** | 4.62 | 12.25 | 0.42 | 58.26 | 4.09 | 14.24 | 0.44 |
| **HPV Primary Screening Algorithm (Un-blinded to HPV status)** | 5.13 | 11.91 | 0.38 | 63.14 | 4.58 | 13.80 | 0.39 |
| **Difference** | -0.51 | 0.34 | 0.04 | -4.88 | -0.49 | 0.44 | 0.04 |

**Analysis of Unsatisfactory (UNSAT) Cytology on the Performance of the Primary Screening Algorithm**

In this clinical study 1.77% (737 out of 41,681) of women ≥25 years had UNSAT cytology results. The proportions of women with cobas® HPV Test negative, HPV 16/18 positive and 12 Other HR HPV positive results were similar for both women with satisfactory and UNSAT cytology results. These results do not contradict an assumption that the risk of ≥CIN3 for the women with UNSAT cytology is similar to the risk for women with satisfactory cytology. Taking this into account, for the 737 subjects with UNSAT cytology, the risk of having ≥CIN3 was estimated by their cobas® HPV Test status and age. The performances of the Primary Screening Algorithm in women with UNSAT cytology and without UNSAT cytology showed no differences (Table 8).

**Table 8. Performance of the Primary Screening Algorithm with and Without UNSAT Cytology (≥CIN3)**

| Primary Screening Algorithm | Pos (%) | PPV (%) | 1-NPV (%) | Sensitivity (%) | 1-Spec (%) | PLR | NLR |
|---|---|---|---|---|---|---|---|
| Without UNSAT | 4.62 | 12.25 | 0.42 | 58.26 | 4.09 | 14.24 | 0.44 |
| With UNSAT Cytology | 4.70 | 12.05 | 0.42 | 58.48 | 4.18 | 14.00 | 0.43 |

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

Benefit and risk per 10,000 screened women ≥25 years for the Primary Screening algorithm (Blinded to HPV status and Un-blinded to HPV status, based on cytology slides read with/without knowledge of HPV status) and Cytology algorithm were evaluated for detection of high-grade cervical disease (CIN2, ≥CIN3) (Table 9). The Primary Screening algorithm (Un-blinded to HPV status) detected a larger number of

disease cases when compared with the Cytology algorithm (88 vs. 63, respectively), with fewer colposcopies (514 vs. 639, respectively) and approximately the same number of screening tests (10,760 vs. 10,000). Additionally, fewer cases of high-grade cervical disease (CIN2, ≥CIN3) were missed by the Primary Screening algorithm (Un-blinded to HPV status) when compared to the Cytology algorithm (91 vs. 116). In addition, fewer false positive cases were identified with the Primary Screening algorithm vs. the Cytology algorithm (426 vs. 576).

**Table 9. Benefit and Risk of the Primary Screening, Cytology, and Additional Comparator Algorithms for the Primary Screening Population (≥25 Years) (per 10,000 Women)**

| Algorithm | Number of Tests and Procedures | | | Benefit | | Risk | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cytology | cobas® HPV Test | Colposcopy | True Positive | | False Negative | | False positive | Number of FP to 1 TP ≥CIN3 |
| | | | | ≥CIN3 | CIN2 | ≥CIN3 | CIN2 | | |
| Primary Screening Blinded to HPV Status | 760 | 10000 | 461 | 57 | 24 | 40 | 58 | 380 | 1:6.7 |
| Primary Screening Un-blinded to HPV Status | 760 | 10000 | 514 | 61 | 27 | 36 | 55 | 426 | 1:7.0 |
| Cytology | 10000 | 0 | 639 | 41 | 22 | 56 | 60 | 576 | 1:14.0 |
| ATRI NM≥30 GT | 10000 | 8458 | 468 | 52 | 22 | 45 | 60 | 394 | 1:7.6 |

**Benefits and Risk for the Primary Screening (≥25 Years) Population per 100 Colposcopy Procedures**

Benefit and risk per 100 colposcopy procedures in women ≥25 years for the Primary Screening algorithm and Cytology algorithm are presented in Table 10. The Primary Screening algorithm (Un-blinded to HPV status) detected a larger number of cases of disease (17 = 12+5) per 100 colposcopies performed than the Cytology algorithm and also had the lower false positive rate (83 vs. 90). Although the Primary Screening algorithm had the same number of false negatives (18= 7+11) as the Cytology algorithm (18=9+9) per 100 colposcopies performed, a larger number of women were screened by the Primary Screening algorithm than by the Cytology algorithm in order to identify women for 100 colposcopy procedures (24% more women, (1947/1,564)). In addition, the probability of disease among women not referred to colposcopy was 1.0% (18/1847) by the Primary Screening algorithm, which was lower compared with the Cytology algorithm, 1.2% (18/1464), and with the Additional Comparator (ATRI NM≥30 GT), 1.1% (23/2,037).

**Table 10. Benefit and Risk of the Primary Screening, Cytology and Additional Comparator Algorithms for the Primary Screening Population (≥25 Years) (per 100 Colposcopy Procedures)**

| Algorithm | Number of Test and Procedures | | | Benefit | | Risk | | |
|---|---|---|---|---|---|---|---|---|
| | Cytology | cobas® HPV Test | Colposcopy | True | | False | | False positive |
| | | | | ≥CIN3 | CIN2 | ≥CIN3 | CIN2 | |
| **Primary Screening (Blinded to HPV** | 165 | 2169 | 100 | 12 | 5 | 9 | 13 | 83 |
| **Primary Screening (Un-blinded to HPV status)** | 148 | 1947 | 100 | 12 | 5 | 7 | 11 | 83 |
| **Cytology** | 1564 | 0 | 100 | 7 | 3 | 9 | 9 | 90 |
| **ATRI NM≥30 GT** | 2137 | 180 | 100 | 11 | 5 | 10 | 13 | 84 |

**Baseline and 3-Year Cumulative Risks of High-Grade Cervical Disease for the Primary Screening Algorithm**

The risks (VBA estimates) of high-grade cervical disease (≥CIN2 and ≥CIN3) at Baseline (Current Risk) and the sum of Current Risk and Future Risk at Year 3 (cumulative risk at Year 3 Follow-Up) were calculated in the primary screening population (≥25 years) among women with different results from the cobas® HPV Test and cytology results.

The risks at the Baseline for women with HPV16 positive/HPV18 positive results were 19.83% and 15.04% for the ≥CIN2 and ≥CIN3 endpoints, respectively (Table 11). The cumulative risks from Baseline to follow up Year 3 for women with HPV16 positive/HPV18 positive results were 28.03% and 21.11% for the ≥CIN2 and ≥CIN3 endpoints, respectively.

The risks at the baseline for women with 12 Other HR HPV positive and ≥ASC-US cytology results were 14.17% and 7.78% for the ≥CIN2 and ≥CIN3 endpoints, respectively (Table 11). The cumulative risks from Baseline to follow up Year 3 for women with 12 Other HR HPV positive and ≥ASC-US cytology results were 20.56% and 11.11% for the ≥CIN2 and ≥CIN3 endpoints, respectively.

**Table 11. Risk of Disease in Women with HPV16 Positive/HPV18 Positive or with 12 Other HR HPV Positive and ≥ASC-US Cytology in the Primary Screening (≥25 Years) Population**

| | | Current Risk (%) (95% CI) | Current + Future Risk (%) at Year 3 (95% CI) |
|---|---|---|---|
| ≥CIN2 | HPV16+/18+ | 19.83 (17.39, 22.41) | 28.03 (24.91, 31.07) |
| | HPV16+ | 23.54 (20.56, 26.71) | 32.34 (28.73, 36.20) |
| | HPV18+ | 10.33 (6.73, 13.55) | 17.02 (12.02, 21.75) |
| | 12 Other HR HPV+ and ≥ASC-US | 14.17 (11.36, 17.06) | 20.56 (17.10, 23.94) |
| ≥CIN3 | HPV16+/18+ | 15.04 (12.98, 17.43) | 21.11 (18.47, 23.90) |
| | HPV16+ | 17.72 (15.19, 20.72) | 25.09 (21.89, 28.95) |
| | HPV18+ | 8.21 (5.10, 11.14) | 10.94 (7.06, 14.49) |
| | 12 Other HR HPV+ and ≥ASC-US | 7.78 ( 5.57, 10.15) | 11.11 ( 8.37, 13.92) |

Current Risk = Absolute Risk at baseline; Current + Future Risk at Year 3 = Cumulative Risk from baseline to follow up year 3; VBA = Verification Bias Adjusted.

The risks for women with positive results for 12 Other HR HPV genotypes and NILM cytology at the Baseline and sum of the current risk and future risk at years 1, 2, and 3 is presented in Table 12. The risks at the Baseline were 4.89% and 2.76% for the ≥CIN2 and ≥CIN3 endpoints, respectively. The cumulative risks from Baseline to follow up Year 3 for women with 12 Other HR HPV positive and NILM cytology results were 7.90% and 3.64% for the ≥CIN2 and ≥CIN3 endpoints, respectively.

**Table 12. Risk of Disease in Women with 12 Other HR HPV Positive and NILM Cytology in the Primary Screening (≥25 Years) Population**

| | ≥CIN2 (95% CI) | ≥CIN3 (95% CI) |
|---|---|---|
| Current Risk (%) | 4.89 ( 3.94, 5.87) | 2.76 ( 2.06, 3.45) |
| Current + Future Risk at Year 1 (%) | 6.14 ( 5.00, 7.24) | 3.13 ( 2.39, 3.88) |
| Current + Future Risk at Year 2 (%) | 6.60 ( 5.38, 7.69) | 3.34 ( 2.59, 4.15) |
| Current + Future Risk at Year 3 (%) | 7.90 ( 6.59, 9.25) | 3.64 ( 2.80, 4.52) |

The risks for women with HR HPV negative results at Baseline and sum of the current risk and future risk at years 1, 2, and 3 are presented in Table 13. The risks at Baseline were 0.77% and 0.27% for the ≥CIN2 and ≥CIN3 endpoints, respectively. The cumulative risks from Baseline to follow up Year 3 for women with HR HPV negative results were 0.94% and 0.34% for the ≥CIN2 and ≥CIN3 endpoints, respectively.

**Table 13. Risk of Disease in Women with HR HPV Negative Results in the Primary Screening (≥25 Years) Population**

| | ≥CIN2 (95% CI) | ≥CIN3 (95% CI) |
|---|---|---|
| Current Risk (%) | 0.77 ( 0.33, 1.29) | 0.27 ( 0.05, 0.60) |
| Current + Future Risk at Year 1 (%) | 0.81 ( 0.36, 1.31) | 0.28 ( 0.06, 0.61) |
| Current + Future Risk at Year 2 (%) | 0.87 ( 0.42, 1.38) | 0.31 ( 0.08, 0.64) |
| Current + Future Risk at Year 3 (%) | 0.94 ( 0.47, 1.45) | 0.34 ( 0.11, 0.66) |

**Comparing Risks of Disease for Women with NILM Cytology and Negative cobas® HPV Test Results**

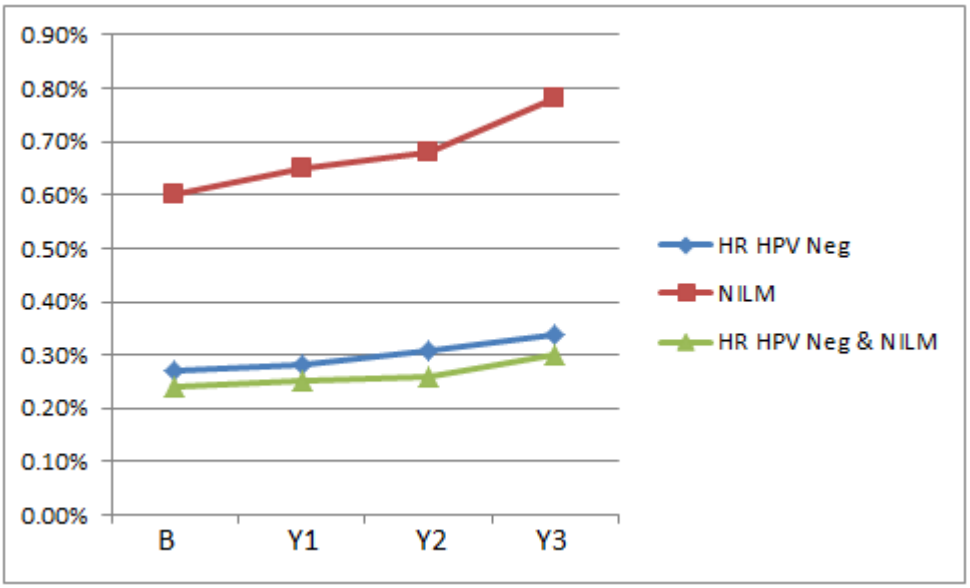
The risks of disease were compared in the primary screening population (≥25 years) between women with a NILM cytology result at baseline versus women with HR HPV negative results at baseline (Table 14 and Figure 3). For those with a HR HPV negative result at baseline, the 3-year cumulative risk of ≥CIN3 was 0.34% compared with 0.78% for those with NILM cytology, indicating that women with a HR HPV negative result have one half the risk of being diagnosed with ≥CIN3 over 3 years as compared to women with NILM cytology result. The addition of NILM cytology result to a HR HPV negative result (co-testing) decreased this risk of ≥CIN3 marginally (0.34 vs. 0.30).

**Table 14. Comparison of the Risk of Disease Between Women with a HR HPV Negative Result vs. a NILM Cytology Result at Baseline in the Primary Screening (≥25 Years) Population**

| Disease Endpoint | Baseline cobas® HPV Test /Cytology Result | Current Risk ,% (95% CI) | Current + Future Risk at Year 3, %, (95% CI) |
|---|---|---|---|
| ≥CIN2 | NILM | 1.24 (0.81, 1.72) | 1.67 (1.23, 2.15) |
| | HR HPV Neg | 0.77 (0.33, 1.29) | 0.94 (0.47, 1.45) |
| | NILM &HR HPV Neg | 0.73 (0.28, 1.26) | 0.85 (0.38, 1.37) |
| ≥CIN3 | NILM | 0.60 (0.36, 0.92) | 0.78 (0.53, 1.11) |
| | HR HPV Neg | 0.27 (0.05, 0.60) | 0.34 (0.11, 0.66) |
| | NILM &HR HPV Neg | 0.24 (0.02, 0.58) | 0.30 (0.06, 0.64) |

Current Risk = Absolute Risk at baseline; Current + Future Risk at Year 3 = Cumulative Risk from baseline to follow up year 3; All numbers are Verification Bias Adjusted.

**Figure 3: Risk of ≥CIN3 for Subjects with Various Negative Results (≥25 years)**




*Note: "B" is Baseline, "Y1" is Year 1, "Y2" is Year 2, and "Y3" is Year 3.*

**Primary Screening Algorithm vs. Additional Comparator (ATRI NM≥30 GT)**

Comparisons were also performed between the Primary Screening algorithm and the Additional Comparator (ATRI NM≥30 GT). Data from the clinical study for different combinations of cobas® HPV Test results, cytology results, and age for NILM patients are presented in Table 15 below.

**Table 15. Cytology, cobas® HPV Test Results and Age for NILM Women for the Evaluable Primary Screening (≥25 Years) Population at Baseline**

| | | Cytology | | | Total |
|---|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | | |
| | | | ≥30 Years | 25-29 Years | |
| **HPV 16/18 Pos** | 250 | 139 | 485 | 296 | 1,170 |
| **12 Other HR HPV Pos** | 414 | 306 | 1,691 | 702 | 3,113 |
| **HR HPV Neg** | 322 | 1,187 | 30,148 | 5,004 | 36,661 |
| **Total** | 986 | 1,632 | 32,324 | 6,002 | **40,944** |

The comparisons were performed also between the Primary Screening algorithm and the Additional Comparator (ATRI NM≥30 GT) for the evaluable primary screening (≥25 years) population. Comparisons of the verification bias adjusted (VBA) performances between algorithms are shown in Tables 16 and 17 for the ≥CIN2 and ≥CIN3 target conditions.

**Table 16: Performance Comparison of Primary Screening Algorithm and Additional Comparator (ATRI NM ≥30 GT) (≥ CIN2)**

| | Prevalence(%)=1.79 with 95% CI (1.37, 2.25) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos (%)** | **PPV (%)** | **1-NPV (%)** | **Sensitivity (%)** | **1-Spec (%)** | **PLR** | **NLR** |
| Primary Screening | 4.62 | 17.62 | 1.03 | 45.41 | 3.87 | 11.73 | 0.57 |
| 95% CI | (4.42, 4.82) | (15.80, 19.54) | (0.60, 1.49) | (35.81, 59.65) | (3.68, 4.06) | (9.15, 15.43) | (0.42, 0.67) |
| | | | | | | | |
| Add. Comp., ATRI NM ≥30 GT | 4.68 | 15.88 | 1.10 | 41.48 | 4.01 | 10.35 | 0.61 |
| 95% CI | (4.49, 4.88) | (14.21, 17.75) | (0.68, 1.55) | (32.69, 54.72) | (3.82, 4.20) | (8.08, 13.68) | (0.47, 0.70) |
| | | | | | | | |
| Difference | -0.06 | 1.74 | -0.07 | 3.93 | -0.14 | 1.38 | -0.04 |
| 95% CI | (-0.19, 0.06) | (0.84, 2.60) | (-0.12,-0.03) | (1.50, 6.51) | (-0.25,-0.02) | (0.64, 2.14) | (-0.07,-0.02) |
| Stat Sign. | No | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 17: Performance Comparison of Primary Screening Algorithm and Additional Comparator (ATRI NM ≥ 30 GT) (≥ CIN3)**

| | Prevalence(%)=0.97 with 95% CI (0.74, 1.28) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos (%)** | **PPV (%)** | **1-NPV (%)** | **Sensitivity (%)** | **1-Spec (%)** | **PLR** | **NLR** |
| Primary Screening | 4.62 | 12.25 | 0.42 | 58.26 | 4.09 | 14.24 | 0.44 |
| 95% CI | (4.42, 4.82) | (10.69, 13.91) | (0.20, 0.74) | (44.02, 74.37) | (3.89, 4.28) | (10.77, 18.29) | (0.27, 0.58) |
| | | | | | | | |
| Add. Comp., ATRI NM ≥ 30 GT | 4.68 | 11.04 | 0.48 | 53.22 | 4.20 | 12.66 | 0.49 |
| 95% CI | (4.49, 4.88) | (9.61, 12.55) | (0.26, 0.81) | (39.34, 68.35) | (4.00, 4.40) | (9.26, 16.46) | (0.33, 0.63) |
| | | | | | | | |
| Difference | -0.06 | 1.21 | -0.06 | 5.04 | -0.11 | 1.58 | -0.05 |
| 95% CI | (-0.19, 0.06) | (0.46, 1.96) | (-0.09,-0.01) | (1.49, 9.24) | (-0.23, 0.01) | (0.62, 2.71) | (-0.10,-0.01) |
| Stat Sign. | No | Yes | Yes | Yes | No | Yes | Yes |

The HPV Primary Screening algorithm is better than the Additional Comparator for the major performance characteristics (PPV, NPV, PLR and NLR) for both ≥CIN2 and ≥CIN3, and these improvements are statistically significant at the 95% confidence level:

- There was a statistically significant improvement in NPVs (98.97% vs. 98.90% for≥CIN2 and 99.58% vs. 99.52% for ≥CIN3) and
- There was a statistically significant improvement in PPVs (17.62% vs. 15.88% for ≥CIN2 and 12.25% vs. 11.04% for ≥CIN3).
- In this study, it was observed that the Primary Screening algorithm required 1.3% or 1.01 times fewer colposcopies ((4.62-4.68)/4.68=-1.3%, or (4.68/4.62=1.01)) compared to the Additional Comparator algorithm but the decrease in colposcopies was not statistically significant. Also, see Benefit Risk Analysis per 10,000 women and per 100 colposcopy procedures (section 10).

3. Subgroup Analyses

**Performance Evaluation by Age Group for the Primary Screening Algorithm in Women ≥ 25 Years**

The performance comparisons of the HPV Primary Screening algorithm and Cytology algorithm by age group for the ≥CIN3 endpoint are shown in Tables 18 to 22. The percent of women referred to colposcopy is significantly higher in the 25-29 age group for the HPV Primary Screening algorithm but significantly lower in all other age groups. Also of note, the prevalence of ≥CIN3 (1.53%) is higher in the 25-29 age group than in any other age group. Both the PPV and PLR of the HPV Primary Screening algorithm are significantly higher than the Cytology algorithm for all age groups. The point estimate of sensitivity, (1-NPV) and NLR all indicate superior performance of the HPV Primary Screening algorithm over the Cytology algorithm for all 4 age groups, but the difference is not statistically significant for the age groups 40-49 and 50 and older. The estimate of (1-specificity) is significantly lower for all age groups ≥30. Similar trends are seen when comparing the HPV Primary Screening algorithm and Cytology algorithm by age group for the ≥CIN2 endpoint, shown in Tables 23 to 26.

**Table 18. Performance Comparison of the Primary Screening Algorithm and the Cytology Algorithm in Age Group 25-29 (≥CIN3)**

| Algorithm | Prevalence ≥CIN3 =1.53 with 95% CI (1.22, 1.84) | | | | | | |
|---|---|---|---|---|---|---|---|
| | %Pos | PPV | 1-NPV | Sensitivity | 1-Spec | PLR | NLR |
| **Primary Screening** | 10.58 | 10.42 | 0.48 | 71.88 | 9.63 | 7.47 | 0.31 |
| **95% CI** | (9.84, 11.31) | (8.02, 13.06) | (0.30, 0.67) | (62.04, 81.44) | (8.92, 10.34) | (6.37, 8.66) | (0.20, 0.42) |
| **Cytology** | 9.80 | 6.77 | 0.96 | 43.29 | 9.28 | 4.67 | 0.63 |
| **95% CI** | (9.11, 10.51) | (4.81, 8.93) | (0.69, 1.23) | (33.50, 54.31) | (8.55, 10.03) | (3.57, 5.93) | (0.50, 0.73) |
| **Difference** | 0.78 | 3.65 | -0.48 | 28.59 | 0.35 | 2.80 | -0.32 |
| **95% CI** | (0.03, 1.47) | (1.87, 5.45) | (-0.69, -0.28) | (17.41, 38.77) | (-0.39, 1.01) | (1.55, 4.10) | (-0.43,-0.19) |
| **Statistical Significant?** | Yes | Yes | Yes | Yes | No | Yes | Yes |

**Table 19. Comparison of the Primary Screening Algorithm and the Cytology Algorithm in Age Group 25-29 (≥CIN3) (per 10,000 women)**

| | Number of Colposcopies | TP ≥CIN3 | FN ≥CIN3 | FP | Number of FP to 1 TP ≥CIN3 |
|---|---|---|---|---|---|
| **Primary Screening** | **1058** | **110** | **43** | **948** | **1:8.6** |
| **Cytology** | **980** | **66** | **87** | **914** | **1:13.8** |

**Table 20. Performance Comparison of the Primary Screening Algorithm and the Cytology Algorithm in Age Group 30-39 (≥CIN3)**

| Algorithm | Prevalence=1.09 with 95% CI (0.89, 1.28) | | | | | | |
|---|---|---|---|---|---|---|---|
| | %Pos | PPV | 1-NPV | Sensitivity | 1-Spec | PLR | NLR |
| Primary Screening | 5.37 | 15.14 | 0.29 | 74.86 | 4.60 | 16.26 | 0.26 |
| 95% CI | (4.98, 5.77) | (12.26, 17.98) | (0.20, 0.40) | (66.54, 81.75) | (4.23, 5.00) | (14.06, 18.52) | (0.19, 0.35) |
| Cytology | 6.92 | 8.36 | 0.54 | 53.33 | 6.42 | 8.31 | 0.50 |
| 95% CI | (6.48, 7.37) | (6.43, 10.39) | (0.41, 0.70) | (43.98, 62.11) | (5.99, 6.85) | (6.82, 9.91) | (0.40, 0.60) |
| Difference | -1.55 | 6.78 | -0.25 | 21.53 | -1.82 | 7.95 | -0.24 |
| 95% CI | (-1.98, -1.10) | (4.68, 8.74) | (-0.37, -0.14) | (11.99, 31.14) | (-2.23, -1.36) | (5.77, 10.13) | (-0.34, -0.13) |
| Statistical Significant? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 21. Performance Comparison of the Primary Screening Algorithm and the Cytology Algorithm in Age Group 40-49 (≥CIN3)**

| | Prevalence=0.83 with 95% CI (0.40, 1.53) | | | | | | |
|---|---|---|---|---|---|---|---|
| Algorithm | %Pos | PPV | 1-NPV | Sensitivity | 1-Spec | PLR | NLR |
| Primary Screening | 2.78 | 12.58 | 0.50 | 41.98 | 2.45 | 17.14 | 0.59 |
| 95% CI | (2.50, 3.09) | (8.54, 16.62) | (0.11, 1.22) | (20.51, 77.96) | (2.19, 2.75) | (8.41, 32.49) | (0.23, 0.81) |
| Cytology | 6.22 | 5.05 | 0.55 | 37.72 | 5.95 | 6.34 | 0.66 |
| 95% CI | (5.80, 6.67) | (3.36, 6.83) | (0.14, 1.29) | (18.61, 71.57) | (5.52, 6.41) | (3.09, 12.11) | (0.30, 0.87) |
| Difference | -3.44 | 7.53 | -0.05 | 4.26 | -3.50 | 10.80 | -0.07 |
| 95% CI | (-3.87, -3.01) | (4.73, 10.43) | (-0.13, 0.01) | (-3.52, 15.69) | (-3.94, -3.08) | (5.10, 21.88) | (-0.18, 0.02) |
| Statistical Significant? | Yes | Yes | No | No | Yes | Yes | No |

**Table 22. Performance Comparison of the Primary Screening Algorithm and the Cytology Algorithm in Age Group ≥50 years (≥CIN3)**

| | Prevalence=0.63 with 95% CI (0.18, 1.51) | | | | | | |
|---|---|---|---|---|---|---|---|
| Algorithm | %Pos | PPV | 1-NPV | Sensitivity | 1-Spec | PLR | NLR |
| Primary Screening | 1.96 | 8.72 | 0.47 | 27.26 | 1.80 | 15.11 | 0.74 |
| 95% CI | (1.71, 2.23) | (4.68, 13.08) | (0.04, 1.34) | (9.39, 83.22) | (1.56, 2.07) | (5.15, 47.43) | (0.17, 0.92) |
| Cytology | 3.77 | 4.50 | 0.48 | 27.04 | 3.63 | 7.46 | 0.76 |
| 95% CI | (3.42, 4.16) | (2.40, 6.85) | (0.05, 1.37) | (9.29, 80.44) | (3.28, 4.01) | (2.54, 22.81) | (0.20, 0.94) |
| Difference | -1.81 | 4.22 | -0.01 | 0.22 | -1.83 | 7.65 | -0.02 |
| 95% CI | (-2.18, -1.45) | (1.66, 7.17) | (-0.07, 0.04) | (-13.95, 15.21) | (-2.19, -1.47) | (2.05, 27.67) | (-0.17, 0.14) |
| Statistical Significant? | Yes | Yes | No | No | Yes | Yes | No |

The performance comparisons of the HPV Primary Screening Algorithm and Cytology algorithm by age group for the ≥CIN2 endpoint are shown below in Tables 22 to 25.

**Table 23. Comparison of Primary Screening vs. Cytology Algorithms in Age Group 25-29 (≥CIN2 endpoint)**

| | Prevalence=2.73 with 95% CI (2.31, 3.12) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **%Pos** | **PPV** | **1-NPV** | **Sensitivity** | **1-Spec** | **PLR** | **NLR** |
| Primary Screening | 10.58 | 17.88 | 0.93 | 69.36 | 8.93 | 7.77 | 0.34 |
| 95% CI | (9.84, 11.31) | (14.81, 21.09) | (0.66, 1.20) | (62.46, 77.01) | (8.22, 9.64) | (6.83, 8.84) | (0.25, 0.41) |
| Cytology | 9.80 | 13.40 | 1.57 | 48.16 | 8.72 | 5.52 | 0.57 |
| 95% CI | (9.11, 10.51) | (10.56, 16.45) | (1.21, 1.88) | (40.29, 56.71) | (8.00, 9.44) | (4.53, 6.68) | (0.47, 0.66) |
| Difference | 0.78 | 4.48 | -0.64 | 21.20 | 0.21 | 2.25 | -0.23 |
| 95% CI | (0.03, 1.47) | (2.19, 6.65) | (-0.88, -0.36) | (12.27, 28.94) | (-0.52, 0.86) | (1.11, 3.36) | (-0.32, -0.14) |
| Sta. Sign.? | Yes | Yes | Yes | Yes | No | Yes | Yes |

**Table 24: Comparison of Primary Screening vs. Cytology Algorithms in Age Group 30-39 (≥CIN2 endpoint)**

| | Prevalence=1.58 with 95% CI | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **%Pos** | **PPV** | **1-NPV** | **Sensitivity** | **1-Spec** | **PLR** | **NLR** |
| Primary Screening | 5.37 | 19.90 | 0.54 | 67.77 | 4.37 | 15.52 | 0.34 |
| 95% CI | (4.98, 5.77) | (16.78, 23.17) | (0.40, 0.69) | (60.21, 74.31) | (4.00, 4.74) | 13.52, 17.73) | (0.27, 0.42) |
| Cytology | 6.92 | 11.49 | 0.84 | 50.46 | 6.23 | 8.10 | 0.53 |
| 95% CI | (6.48, 7.37) | (9.12, 13.81) | (0.66, 1.03) | (42.38, 58.23) | (5.81, 6.66) | (6.73, 9.51) | (0.45, 0.61) |
| Difference | -1.55 | 8.41 | -0.30 | 17.31 | -1.86 | 7.42 | -0.19 |
| 95% CI | (-1.98, -1.10) | (6.16, 10.60) | (-0.43, -0.17) | (10.11, 24.61) | (-2.28, -1.40) | (5.51, 9.32) | (-0.27,-0.11) |
| Sta. Sign.? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 25: Comparison of Primary Screening vs. Cytology Algorithms in Age Group 40-49 (≥CIN2 endpoint)**

| | Prevalence=1.43 with 95% CI (0.73, 2.43) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **%Pos** | **PPV** | **1-NPV** | **Sensitivity** | **1-Spec** | **PLR** | **NLR** |
| Primary Screening | 2.78 | 17.21 | 0.98 | 33.33 | 2.33 | 14.28 | 0.68 |
| 95% CI | (2.50, 3.09) | (12.84, 21.75) | (0.27, 2.00) | (18.60, 64.64) | (2.08, 2.64) | (7.76, 28.29) | (0.36, 0.84) |
| Cytology | 6.22 | 7.42 | 1.04 | 32.17 | 5.84 | 5.51 | 0.72 |
| 95% CI | (5.80, 6.67) | (5.47, 9.38) | (0.30, 2.06) | (17.83, 62.79) | (5.41, 6.29) | (3.03, 10.89) | (0.39, 0.87) |
| Difference | -3.44 | 9.79 | -0.06 | 1.16 | -3.51 | 8.77 | -0.04 |
| 95% CI | (-3.87, -3.01) | (6.85, 13.12) | (-0.14, 0.03) | (-4.79, 7.65) | (-3.94, -3.08) | (4.41, 17.96) | (-0.10, 0.03) |
| Sta.Sign.? | Yes | Yes | No | No | Yes | Yes | No |

**Table 26: Comparison of Primary Screening vs. Cytology Algorithms in Age Group ≥50 years (≥CIN2 endpoint)**

| | Prevalence=1.85 with 95% CI (0.65, 3.36) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **%Pos** | **PPV** | **1-NPV** | **Sensitivity** | **1-Spec** | **PLR** | **NLR** |
| Primary Screening | 1.96 | 9.96 | 1.68 | 10.60 | 1.80 | 5.88 | 0.91 |
| 95% CI | (1.71, 2.23) | (5.87, 14.83) | (0.49, 3.20) | (5.03, 32.40) | (1.56, 2.07) | (2.69, 18.68) | (0.69, 0.97) |
| Cytology | 3.77 | 5.15 | 1.72 | 10.52 | 3.65 | 2.89 | 0.93 |
| 95% CI | (3.42, 4.16) | (2.93, 7.71) | (0.50, 3.27) | (4.93, 31.98) | (3.29, 4.02) | (1.30, 9.31) | (0.71, 0.99) |
| Difference | -1.81 | 4.81 | -0.04 | 0.08 | -1.85 | 2.99 | -0.02 |
| 95% CI | (-2.18, -1.45) | (2.24, 8.08) | (-0.09, 0.02) | (-3.29, 3.66) | (-2.23, -1.48) | (1.15, 10.38) | (-0.05, 0.02) |
| Sta.Sign.? | Yes | Yes | No | No | Yes | Yes | No |

The performance comparisons of the Primary Screening algorithm and the Additional Comparator ATRI NM ≥30 GT by age group for ≥CIN3 endpoint are shown in Tables 27 to 31.

**Table 27. Comparison of the Primary Screening Algorithm and ATRI NM ≥30 GT (≥CIN3) in the 25-29 Age Group**

| | Prevalence= 1.53 with 95% CI ( 1.22, 1.84) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos(%)** | **PPV(%)** | **1-NPV(%)** | **Sensitivity(%)** | **1-Spec(%)** | **PLR** | **NLR** |
| Primary Screening | 10.58 | 10.42 | 0.48 | 71.88 | 9.63 | 7.47 | 0.31 |
| 95% CI | ( 9.84, 11.31) | ( 8.02, 13.06) | ( 0.30, 0.67) | ( 62.04, 81.44) | ( 8.92, 10.34) | ( 6.37, 8.66) | ( 0.20, 0.42) |
| ATRI NM ≥30 GT | 7.21 | 9.20 | 0.94 | 43.29 | 6.65 | 6.51 | 0.61 |
| 95% CI | ( 6.61, 7.82) | ( 6.53, 12.21) | ( 0.68, 1.19) | ( 33.50, 54.31) | ( 6.04, 7.26) | ( 4.94, 8.32) | ( 0.49, 0.71) |
| Difference | 3.37 | 1.22 | -0.46 | 28.59 | 2.98 | 0.96 | -0.30 |
| 95% CI | ( 2.79, 3.94) | ( -0.93, 3.07) | ( -0.66, -0.25) | ( 17.41, 38.77) | ( 2.40, 3.53) | ( -0.76, 2.44) | ( -0.41, -0.17) |
| Stat. Sign. | Yes | No | Yes | Yes | Yes | No | Yes |

**Table 28. Comparison of the Primary Screening Algorithm and the ATRI NM≥30 GT (≥CIN3) in 25-29 Age Group (per 10,000 women)**

| | **Number of Colposcopies** | **TP ≥CIN3** | **FN ≥CIN3** | **FP** | **Number of FP to 1 TP ≥CIN3** |
|---|---|---|---|---|---|
| **Primary Screening** | **1058** | **110** | **43** | **948** | **1:8.6** |
| **ATRI NM≥30 GT** | **721** | **66** | **87** | **655** | **1:9.9** |

**Table 29. Comparison of the Primary Screening Algorithm and ATRI NM ≥30 GT (≥CIN3) in the 30-39 Age Group**

| | Prevalence= 1.09 with 95% CI ( 0.89, 1.28) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos(%)** | **PPV(%)** | **1-NPV(%)** | **Sensitivity(%)** | **1-Spec(%)** | **PLR** | **NLR** |
| Primary Screening | 5.37 | 15.14 | 0.29 | 74.86 | 4.60 | 16.26 | 0.26 |
| 95% CI | ( 4.98, 5.77) | ( 12.26, 17.98) | ( 0.20, 0.40) | ( 66.54, 81.75) | ( 4.23, 5.00) | ( 14.06, 18.52) | ( 0.19, 0.35) |
| ATRI NM ≥30 GT | 6.20 | 14.01 | 0.23 | 80.03 | 5.39 | 14.85 | 0.21 |
| 95% CI | ( 5.75, 6.60) | ( 11.42, 16.71) | ( 0.15, 0.33) | ( 72.39, 86.91) | ( 4.97, 5.78) | ( 13.14, 16.80) | ( 0.14, 0.29) |
| Difference | -0.83 | 1.13 | 0.06 | -5.17 | -0.79 | 1.41 | 0.05 |
| 95% CI | ( -0.99, -0.67) | ( 0.23, 1.91) | ( 0.02, 0.11) | ( -9.76, -1.65) | ( -0.94, -0.63) | ( 0.29, 2.38) | ( 0.02, 0.10) |
| Stat. Sign. | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 30. Comparison of the Primary Screening Algorithm and ATRI NM ≥30 GT (≥CIN3) in the 40-49 Age Group**

| | Prevalence= 0.83 with 95% CI ( 0.40, 1.53) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos(%)** | **PPV(%)** | **1-NPV(%)** | **Sensitivity(%)** | **1-Spec(%)** | **PLR** | **NLR** |
| Primary Screening | 2.78 | 12.58 | 0.50 | 41.98 | 2.45 | 17.14 | 0.59 |
| 95% CI | ( 2.50, 3.09) | ( 8.54, 16.62) | ( 0.11, 1.22) | ( 20.51, 77.96) | ( 2.19, 2.75) | ( 8.41, 32.49) | ( 0.23, 0.81) |
| ATRI NM ≥30 GT | 3.57 | 10.06 | 0.49 | 43.08 | 3.23 | 13.32 | 0.59 |
| 95% CI | ( 3.24, 3.90) | ( 6.86, 13.30) | ( 0.10, 1.21) | ( 20.86, 79.64) | ( 2.93, 3.56) | ( 6.49, 25.04) | ( 0.21, 0.82) |
| Difference | -0.79 | 2.52 | 0.01 | -1.10 | -0.78 | 3.82 | 0.00 |
| 95% CI | ( -0.96, -0.64) | ( 1.44, 3.67) | ( -0.01, 0.03) | ( -4.89, 0.00) | ( -0.96, -0.64) | ( 1.64, 7.89) | ( -0.01, 0.05) |
| Stat. Sign. | Yes | Yes | No | No | Yes | Yes | No |

**Table 31. Comparison of the Primary Screening Algorithm and ATRI NM ≥30 GT (≥CIN3) in the 50 and Above Age Group**

| | Prevalence= 0.63 with 95% CI ( 0.18, 1.51) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Algorithm** | **Pos(%)** | **PPV(%)** | **1-NPV(%)** | **Sensitivity(%)** | **1-Spec(%)** | **PLR** | **NLR** |
| Primary Screening | 1.96 | 8.72 | 0.47 | 27.26 | 1.80 | 15.11 | 0.74 |
| 95% CI | ( 1.71, 2.23) | ( 4.68, 13.08) | ( 0.04, 1.34) | ( 9.39, 83.22) | ( 1.56, 2.07) | ( 5.15, 47.43) | ( 0.17, 0.92) |
| ATRI NM ≥30 GT | 2.51 | 7.29 | 0.46 | 29.08 | 2.34 | 12.44 | 0.73 |
| 95% CI | ( 2.21, 2.79) | ( 3.98, 10.76) | ( 0.04, 1.33) | ( 10.09, 85.40) | ( 2.04, 2.62) | ( 4.28, 37.96) | ( 0.15, 0.92) |
| Difference | -0.55 | 1.43 | 0.01 | -1.82 | -0.54 | 2.67 | 0.01 |
| 95% CI | ( -0.69, -0.41) | ( -0.02, 2.69) | ( -0.01, 0.04) | (-12.19, 0.00) | ( -0.68, -0.39) | ( -0.02, 10.77) | ( -0.01, 0.12) |
| Stat. Sign. | Yes | No | No | No | Yes | No | No |

**Baseline Risks of High-Grade Cervical Disease for the Primary Screening Algorithm Based on Directed Biopsies Only**

Disease status of ≥CIN3 or ≥CIN2 was identified from directed and random biopsies by the CPR. Using only directed biopsies to determine disease status (assuming women with no directed biopsies had normal histology results because no visible lesions were present), the risks of ≥CIN3 and ≥CIN2 were estimated and presented in Table 32 below.

**Table 32: The Risk of Disease in Each Category Related to the Primary Screening Algorithm (≥25 Years) Based on Directed Biopsies Only**

| cobas® HPV Test results | Cytology | Risk of ≥ CIN3 (%) (95% CI) | Risk of ≥ CIN2 (%) (95% CI) |
|---|---|---|---|
| HPV16/18 pos | | 11.18 (9.45, 13.07) | 14.60 (12.47, 16.80) |
| 12 Other HR HPV pos | ≥HSIL, ASC-H | 27.10 (14.27, 40.86) | 33.58 (19.52, 48.39) |
| | LSIL, AGUS | 4.82 (2.58, 7.37) | 11.63 (8.08, 15.37) |
| | ASC-US | 4.27 (1.96, 7.00) | 7.07 (4.10, 10.28) |
| | NILM | 2.31 (1.65, 2.95) | 3.86 (3.02, 4.77) |
| HR HPV neg | | 0.15 (0.03, 0.37) | 0.42 (0.10, 0.81) |

**Expected Results**

A total of 47,208 women were enrolled in the study across 61 collection sites, and cervical samples were tested at five testing sites in the US. Among the 47,208 women enrolled in the study, a total of 40,944 were evaluable for the analysis of the primary screening population, evaluable women had valid results from cytology and the cobas® HPV Test.

The median age of evaluable women in the primary screening population was 41 years with ~16% of women in the age group 25-29 years and ~30% in the age group 30-39 years; the remaining ~54% women were ≥40 years. Approximately 83% of women were White and the majority (98%) had a high school or above education. Approximately 91% of women had cytology performed in the previous 5 years, and ~93% did not have a colposcopy in the previous 5 years. About 20% of women had an HPV test in the previous 5 years and among them ~18% were HPV positive.

Table 33 shows HPV prevalence by the cobas® HPV Test for the primary screening population by age. The overall HPV prevalence was 10.5% in the Primary Screening (≥25 years) population.

**Table 33. Summary of Four-Category cobas® HPV Test Result by Age Group for Evaluable Women (≥ 25 Years)**

| Age Group (Years) | cobas® HPV Test Result | | | | Total |
|---|---|---|---|---|---|
| | HPV16 Positive | HPV18 Positive | 12 Other HR HPV Positive | Negative | |
| **25-29** | 5.3% (355/6,654) | 1.6% (109/6,654) | 14.2% (942/6,654) | 78.9% (5,248/6,654) | 6654 |
| **30-39** | 2.3% (282/12,260) | 1% (120/12,260) | 8.3% (1019/12,260) | 88.4% (10839/12,260) | 12,260 |
| **40-49** | 1.1% (126/11,695) | 0.5% (56/11,695) | 5.5% (649/11,695) | 92.9% (10,864/11,695) | 11,695 |
| **50-59** | 0.8% (56/7,435) | 0.5% (37/7,435) | 5.1% (379/7,435) | 93.7% (6,963/7,435) | 7,435 |
| **60-69** | 0.8% (18/2,354) | 0.2% (5/2,354) | 4.3% (102/2,354) | 94.7% (2,229/2,354) | 2,354 |
| **≥ 70** | 0.7% (4/ 546) | 0.4% (2/ 546) | 4% (22/ 546) | 94.9% (518/ 546) | 546 |

*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 positive.*

### Disease Verification Status of Evaluable Subjects at Baseline

The number of women classified by disease status (≥ CIN2 and ≥ CIN3), cytology result, and cobas® HPV Test result are presented below in Table 34. These results are summarized for the evaluable primary screening population (≥ 25 years, n=40,944) at baseline. Women who exited the study after Baseline Study Visit 1 (BSV1) (31,583), women who were selected for BSV2 but did not go (1,288), and women who proceeded to BSV2 but had no sample taken or had indeterminate results for CPR (244) had unverified disease status. There were 7,829 women with verified disease status at Baseline (see also flow of subjects in the Baseline Phase).

**Table 34. Classification of Evaluable Subjects (≥ 25 Years) by cobas® HPV Test Result, Disease Status (≥ CIN2 and ≥ CIN3), and Disease Verification Status at Baseline**

| | | | | Verified Disease Status:≥ CIN2 | | Verified Disease Status:≥ CIN3 | | |
|---|---|---|---|---|---|---|---|---|
| **Cytology Result** | **cobas® HPV Test Result** | **Combined Results From Two IUO HPV Tests** | **Total No. Subjects** | **No. Diseased Subjects (≥ CIN2)** | **No. Non-Diseased Subjects (<CIN2)** | **No. Diseased Subjects (≥ CIN3)** | **No. Non-Diseased Subjects (<CIN3)** | **No. Subjects with Unknown Disease Status (Unverified)** |
| >ASC-US | HPV 16+/18+ | Positive | 249 | 88 | 127 | 69 | 146 | 34 |
| | | Negative | 1 | 0 | 1 | 0 | 1 | 0 |
| | | Invalid | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12 Other HR HPV+ | Positive | 409 | 60 | 285 | 31 | 314 | 64 |
| | | Negative | 5 | 1 | 2 | 1 | 2 | 2 |
| | | Invalid | 0 | 0 | 0 | 0 | 0 | 0 |
| | Negative | Positive | 75 | 8 | 58 | 5 | 61 | 9 |
| | | Negative | 247 | 7 | 206 | 5 | 208 | 34 |
| | | Invalid | 0 | 0 | 0 | 0 | 0 | 0 |
| Total: >ASC-US | | | 986 | 164 | 679 | 111 | 732 | 143 |
| ASC-US | HPV 16+/18+ | Positive | 139 | 26 | 95 | 17 | 104 | 18 |
| | | Negative | 0 | 0 | 0 | 0 | 0 | 0 |
| | | Invalid | 0 | 0 | 0 | 0 | 0 | 0 |
| | 12 Other HR HPV+ | Positive | 302 | 25 | 226 | 15 | 236 | 51 |
| | | Negative | 4 | 0 | 4 | 0 | 4 | 0 |
| | | Invalid | 0 | 0 | 0 | 0 | 0 | 0 |
| | Negative | Positive | 136 | 1 | 99 | 0 | 100 | 36 |
| | | Negative | 1050 | 6 | 861 | 3 | 864 | 183 |
| | | Invalid | 1 | 0 | 1 | 0 | 1 | 0 |
| Total: ASC-US | | | 1632 | 58 | 1286 | 35 | 1309 | 288 |
| Normal | HPV 16+/18+ | Positive | 764 | 83 | 545 | 64 | 564 | 136 |
| | | Negative | 14 | 0 | 1 | 0 | 1 | 13 |
| | | Invalid | 3 | 0 | 1 | 0 | 1 | 2 |
| | 12 Other HR HPV+ | Positive | 2319 | 97 | 1833 | 55 | 1875 | 389 |
| | | Negative | 69 | 0 | 3 | 0 | 3 | 66 |
| | | Invalid | 5 | 0 | 1 | 0 | 1 | 4 |
| | Negative | Positive | 2715 | 23 | 2198 | 7 | 2214 | 494 |
| | | Negative | 32403 | 6 | 848 | 2 | 852 | 31549 |
| | | Invalid | 34 | 0 | 3 | 0 | 3 | 31 |
| Total: Normal | | | 38326 | 209 | 5433 | 128 | 5514 | 32684 |

Table 35 below presents the verification bias adjusted estimates[1] for the same groups. Please note that this table cannot be derived directly from the table above since age was used as an additional factor for verification adjustment.

**Table 35. Classification of Evaluable Subjects (≥ 25 Years) by cobas® HPV Test Result, Disease Verification Status (≥ CIN2 and ≥ CIN3) at Baseline (Verification Bias Adjusted)**

| | | | Verified Bias Adjusted for (≥ CIN2) | | Verified Bias Adjusted for (≥ CIN3) | |
|---|---|---|---|---|---|---|
| **Cytology Result** | **cobas® HPV Test Result** | **Total No. Subjects** | **No. Diseased Subjects (≥ CIN2)** | **No. Non-Diseased Subjects (<CIN2)** | **No. Diseased Subjects (≥ CIN3)** | **No. Non-Diseased Subjects (<CIN3)** |
| >ASC-US | HPV 16+/18+ | 250 | 101.66 | 148.34 | 79.47 | 170.53 |
| | 12 Other HR HPV+ | 414 | 71.44 | 342.56 | 37.53 | 376.47 |
| | Negative | 322 | 17.31 | 304.69 | 11.52 | 310.48 |
| Total: >ASC-US | | 986 | 190.40 | 795.60 | 128.52 | 857.48 |
| ASC-US | HPV 16+/18+ | 139 | 29.53 | 109.47 | 19.26 | 119.74 |
| | 12 Other HR HPV+ | 306 | 30.12 | 275.88 | 17.94 | 288.06 |
| | Negative | 1187 | 8.88 | 1178.12 | 3.67 | 1183.33 |
| Total: ASC-US | | 1632 | 68.53 | 1563.47 | 40.86 | 1591.14 |
| Normal | HPV 16+/18+ | 781 | 100.20 | 680.80 | 77.31 | 703.69 |
| | 12 Other HR HPV+ | 2393 | 116.48 | 2276.52 | 66.01 | 2326.99 |
| | Negative | 35152 | 257.65 | 34894.35 | 84.64 | 35067.36 |
| Total: Normal | | 38326 | 474.34 | 37851.66 | 227.97 | 38098.03 |
| Total | | 40944 | 733.27 | 40210.73 | 397.35 | 40546.65 |

### Projected Number of Diseased and Non-diseased Subjects in each Outcome Category

Tables 36 and 37 below show the projected number of diseased and non-diseased subjects calculated to two significant digits. A total of 43 women with valid cytology but invalid IUO HPV test results are also included in the tables.

1 For the evaluation of clinical performance of test "T", ideally, all subjects in a clinical study should have the results of test T and verified disease status, D+ (Diseased) or D- (Non-Diseased). If the chance of disease verification depends on the test T result itself (with or without other covariates) and only subjects with verified disease status are used in the evaluation of test T, then the estimates of performance are likely to be biased. This type of bias is often referred to as verification bias. According to the design of this clinical study, the subjects with cobas® HPV Test negative results and NILM cytology had a lower chance to have verified disease status. If one uses only the results of subjects with verified disease status, then biased estimates of test T performance will be obtained; these estimates of performance are called "Crude". In order to correct the verification bias, one can impute the disease status in women with unverified disease status using the data collected on women with verified disease status for each category of test outputs in a given age range. This is accomplished using the multiple imputation method (multiplying by the appropriate inverse probability which depends on cobas® HPV Test result, cytology, two IUO HPV tests results and age). These unbiased estimates are called Verification Bias Adjusted (VBA) estimates. Crude estimates of the performance along with VBA estimates are provided.

**Table 36. Number of Subjects (VBA) in Primary Screening Population (≥ 25 Years) by Disease Status (≥CIN2), cobas® HPV Test and Cytology Results**

| cobas® HPV Test | Cytology Result | Projected No. of Diseased | Projected No. of Non-Diseased | Total |
|---|---|---|---|---|
| HPV 16+ | Normal | 84.60 | 463.40 | 548 |
| HPV 16+ | ASC-US | 28.53 | 68.47 | 97 |
| HPV 16+ | >ASC-US | 84.64 | 111.36 | 196 |
| HPV 18+ | Normal | 15.60 | 217.40 | 233 |
| HPV 18+ | ASC-US | 1.00 | 41.00 | 42 |
| HPV 18+ | >ASC-US | 17.03 | 36.97 | 54 |
| 12 Other HR HPV+ | Normal | 116.48 | 2276.52 | 2393 |
| 12 Other HR HPV+ | ASC-US | 30.12 | 275.88 | 306 |
| 12 Other HR HPV+ | >ASC-US | 71.44 | 342.56 | 414 |
| Negative | Normal | 257.65 | 34894.35 | 35152 |
| Negative | ASC-US | 8.89 | 1178.11 | 1187 |
| Negative | >ASC-US | 17.31 | 304.69 | 322 |
| Total | | 733.29 | 40210.71 | 40944 |

**Table 37. Number of Subjects (VBA) in Primary Screening Population (≥25 Years) by Disease Status (≥CIN3), cobas® HPV Test and Cytology Results**

| cobas® HPV Test | Cytology Result | Projected No. of Diseased | Projected No. of Non-Diseased | Total |
|---|---|---|---|---|
| HPV 16+ | Normal | 66.42 | 481.58 | 548 |
| HPV 16+ | ASC-US | 18.26 | 78.74 | 97 |
| HPV 16+ | >ASC-US | 64.68 | 131.32 | 196 |
| HPV 18+ | Normal | 10.89 | 222.11 | 233 |
| HPV 18+ | ASC-US | 1.00 | 41.00 | 42 |
| HPV 18+ | >ASC-US | 14.79 | 39.21 | 54 |
| 12 Other HR HPV+ | Normal | 66.01 | 2326.99 | 2393 |
| 12 Other HR HPV+ | ASC-US | 17.93 | 288.07 | 306 |
| 12 Other HR HPV+ | >ASC-US | 37.54 | 376.46 | 414 |
| Negative | Normal | 84.65 | 35067.35 | 35152 |
| Negative | ASC-US | 3.67 | 1183.33 | 1187 |
| Negative | >ASC-US | 11.53 | 310.47 | 322 |
| Total | | 397.37 | 40546.63 | 40944 |

The CPR results for the 43 women with valid cytology and invalid IUO HPV test results are presented in Table 38 by cobas® HPV Test and cytology results. A total of six of them underwent colposcopy and all of them had CPR results of <CIN2.

**Table 38. Disease (≥ CIN2) Distribution by cobas® HPV Test and Cytology Results for 43 Subjects with Invalid IUO HPV Test Result**

| cobas® HPV Test | Cytology Result | ≥ CIN2 | <CIN2 | Unverified | Total |
|---|---|---|---|---|---|
| HPV 16+ | Normal | 0 | 0 | 2 | 2 |
| HPV 18+ | Normal | 0 | 1 | 0 | 1 |
| 12 Other HR HPV+ | Normal | 0 | 1 | 4 | 5 |
| Negative | Normal | 0 | 3 | 31 | 34 |
| Negative | ASC-US | 0 | 1 | 0 | 1 |

**Crude vs. Verification Bias Adjusted Estimates for Primary Screening and Cytology Algorithms**

The summary of the Baseline crude and adjusted estimates of sensitivity, 1-specificity, PPV (absolute risk), 1-NPV, PLR, NLR, and % Pos for the Primary Screening algorithm is presented in Tables 39 and 40 for women ≥25 years and ≥30 years old. The estimates of these parameters for the Cytology algorithm are presented in Tables 41 and 42.
If the screening age is changed from ≥25 to ≥30 years old, the sensitivity (VBA) of the Primary Screening algorithm for ≥CIN3 endpoint decreases approximately by 5%, while the specificity increases by 1%. The PPV of the Primary Screening algorithm increases approximately by 1% and NPV remains the same. The colposcopy rate decreases by ~1% in ≥30 years screening population.
A similar trend is observed for the Cytology algorithm.

**Table 39. Performance of Primary Screening Algorithm in Detecting Disease in Screening Population (≥25 Years)**

| | | Crude | | VBA |
|---|---|---|---|---|
| Disease End point | Statistics | Estimate | 95% CI | Estimate (95% CI) |
| ≥CIN2 | Sensitivity (%) | 65.66 (283 / 431) | (61.06, 69.99) | 45.41 (35.81, 59.65) |
| | 1-Specificity (%) | 17.40 (1287 / 7398) | (16.55, 18.28) | 3.87 (3.68, 4.06) |
| | PPV (%) | 18.03 (283 / 1570) | (16.81, 19.31) | 17.62 (15.80, 19.54) |
| | 1-NPV (%) | 2.36 (148 / 6259) | (2.08, 2.69) | 1.03 (0.60, 1.49) |
| | PLR | 3.77 (283 / 431) / (1287 / 7398) | (3.47, 4.11) | 11.73 (9.15, 15.43) |
| | NLR | 0.42 (148 / 431) / (6111 / 7398) | (0.36, 0.47) | 0.57 (0.42, 0.67) |
| | Pos (%) | 3.83 (1570 / 40944) | (3.65, 4.02) | 4.62 (4.42, 4.82) |
| ≥CIN3 | Sensitivity (%) | 71.90 (197 / 274) | (66.30, 76.89) | 58.26 (44.02, 74.37) |
| | 1-Specificity (%) | 18.17 (1373 / 7555) | (17.32, 19.06) | 4.09 (3.89, 4.28) |
| | PPV (%) | 12.55 (197 / 1570) | (11.61, 13.55) | 12.25 (10.69, 13.91) |
| | 1-NPV (%) | 1.23 (77 / 6259) | (1.02, 1.48) | 0.42 (0.20, 0.74) |
| | PLR | 3.96 (197 / 274) / (1373 / 7555) | (3.62, 4.32) | 14.24 (10.77, 18.29) |
| | NLR | 0.34 (77 / 274) / (6182 / 7555) | (0.28, 0.42) | 0.44 (0.27, 0.58) |
| | Pos (%) | 3.83 (1570 / 40944) | (3.65, 4.02) | 4.62 (4.42, 4.82) |

**Table 40. Performance of the Primary Screening Algorithm in Detecting Disease in Screening Population (≥30 Years)**

| | | Crude | | VBA |
|---|---|---|---|---|
| Disease Endpoint | Statistics | Estimate | 95% CI | Estimate (95% CI) |
| ≥CIN2 | Sensitivity (%) | 63.57 (178 / 280) | (57.79, 68.99) | 37.53 (27.55, 53.96) |
| | 1-Specificity (%) | 14.30 (805 / 5629) | (13.41, 15.24) | 2.90 (2.72, 3.08) |
| | PPV (%) | 18.11 (178 / 983) | (16.54, 19.79) | 17.46 (15.28, 19.90) |
| | 1-NPV (%) | 2.07 (102 / 4926) | (1.78, 2.41) | 1.04 (0.54, 1.60) |
| | PLR | 4.45 (178 / 280) / (805 / 5629) | (3.98, 4.96) | 12.93 (9.40, 18.82) |
| | NLR | 0.43 (102 / 280) / (4824 / 5629) | (0.36, 0.50) | 0.64 (0.47, 0.75) |
| | Pos (%) | 2.87 (983 / 34290) | (2.70, 3.05) | 3.46 (3.28, 3.64) |
| ≥CIN3 | Sensitivity (%) | 71.96 (136 / 189) | (65.17, 77.88) | 53.56 (36.79, 76.01) |
| | 1-Specificity (%) | 14.81 (847 / 5720) | (13.91, 15.75) | 3.02 (2.85, 3.21) |
| | PPV (%) | 13.84 (136 / 983) | (12.59, 15.18) | 13.34 (11.29, 15.47) |
| | 1-NPV (%) | 1.08 (53 / 4926) | (0.86, 1.35) | 0.41 (0.16, 0.79) |
| | PLR | 4.86 (136 / 189) / (847 / 5720) | (4.36, 5.42) | 17.71 (12.45, 25.18) |
| | NLR | 0.33 (53 / 189) / (4873 / 5720) | (0.26, 0.41) | 0.48 (0.25, 0.65) |
| | Pos (%) | 2.87 (983 / 34290) | (2.70, 3.05) | 3.46 (3.28, 3.64) |

**Table 41. Performance of Cytology in Detecting Disease in Screening Population (≥25 Years)**

| | | Crude | | VBA |
|---|---|---|---|---|
| **Disease Endpoint** | **Statistics** | **Estimate** | **95% CI** | **Estimate (95% CI)** |
| ≥CIN2 | Sensitivity (%) | 51.51 (222 / 431) | (46.80, 56.19) | 35.31 (27.60, 46.74) |
| | 1-Specificity (%) | 26.56 (1965 / 7398) | (25.57, 27.58) | 5.87 (5.64, 6.09) |
| | PPV (%) | 10.15 (222 / 2187) | (9.28, 11.09) | 9.89 (8.68, 11.20) |
| | 1-NPV (%) | 3.70 (209 / 5642) | (3.37, 4.07) | 1.24 (0.81, 1.72) |
| | PLR | 1.94 (222 / 431) / (1965 / 7398) | (1.76, 2.14) | 6.02 (4.66, 8.01) |
| | NLR | 0.66 (209 / 431) / (5433 / 7398) | (0.60, 0.73) | 0.69 (0.57, 0.77) |
| | Pos (%) | 5.34 (2187 / 40944) | (5.13, 5.56) | 6.39 (6.16, 6.62) |
| ≥CIN3 | Sensitivity (%) | 53.28 (146 / 274) | (47.37, 59.11) | 42.63 (31.75, 55.41) |
| | 1-Specificity (%) | 27.02 (2041 / 7555) | (26.03, 28.03) | 6.04 (5.81, 6.27) |
| | PPV (%) | 6.68 (146 / 2187) | (5.98, 7.44) | 6.47 (5.54, 7.50) |
| | 1-NPV (%) | 2.27 (128 / 5642) | (2.00, 2.57) | 0.59 (0.36, 0.92) |
| | PLR | 1.97 (146 / 274) / (2041 / 7555) | (1.75, 2.22) | 7.06 (5.24, 9.26) |
| | NLR | 0.64 (128 / 274) / (5514 / 7555) | (0.56, 0.73) | 0.61 (0.47, 0.73) |
| | Pos (%) | 5.34 (2187 / 40944) | (5.13, 5.56) | 6.39 (6.16, 6.62) |

**Table 42. Performance of Cytology in Detecting Disease in Screening Population (≥30 Years)**

| | | Crude | | VBA |
|---|---|---|---|---|
| **Disease Endpoint** | **Statistics** | **Estimate** | **95% CI** | **Estimate (95% CI)** |
| ≥CIN2 | Sensitivity (%) | 53.21 (149 / 280) | (47.37, 58.98) | 31.09 (22.53, 45.05) |
| | 1-Specificity (%) | 26.56 (1495 / 5629) | (25.42, 27.73) | 5.32 (5.08, 5.57) |
| | PPV (%) | 9.06 (149 / 1644) | (8.14, 10.08) | 8.73 (7.40, 10.09) |
| | 1-NPV (%) | 3.07 (131 / 4265) | (2.72, 3.47) | 1.18 (0.66, 1.75) |
| | PLR | 2.00 (149 / 280) / (1495 / 5629) | (1.78, 2.25) | 5.85 (4.17, 8.58) |
| | NLR | 0.64 (131 / 280) / (4134 / 5629) | (0.56, 0.72) | 0.73 (0.58, 0.82) |
| | Pos (%) | 4.79 (1644 / 34290) | (4.57, 5.03) | 5.73 (5.49, 5.98) |
| ≥CIN3 | Sensitivity (%) | 57.67 (109 / 189) | (50.54, 64.49) | 42.40 (29.12, 60.23) |
| | 1-Specificity (%) | 26.84 (1535 / 5720) | (25.70, 28.00) | 5.41 (5.17, 5.66) |
| | PPV (%) | 6.63 (109 / 1644) | (5.87, 7.48) | 6.37 (5.22, 7.56) |
| | 1-NPV (%) | 1.88 (80 / 4265) | (1.59, 2.21) | 0.53 (0.25, 0.91) |
| | PLR | 2.15 (109 / 189) / (1535 / 5720) | (1.89, 2.45) | 7.83 (5.34, 11.30) |
| | NLR | 0.58 (80 / 189) / (4185 / 5720) | (0.49, 0.68) | 0.61 (0.42, 0.75) |
| | Pos (%) | 4.79 (1644 / 34290) | (4.57, 5.03) | 5.73 (5.49, 5.98) |

**Performance in Vaccinated Women**

In the clinical study, 1.19% (487 out of 40,944) women indicated that they had received an HPV vaccine. Information about whether they were really vaccinated and whether vaccination was performed according to the vaccine intended use was not available. A summary of cobas® HPV Test results for the detection of ≥CIN2 and ≥CIN3 in these subjects by cytology result are shown in Tables 43 and 44 respectively. Out of 487 total evaluable subjects ≥25 years of age, 12 were diagnosed with ≥CIN2 results by CPR, including 5 subjects with ≥CIN3 results.

**Table 43. Number of Subjects in the Primary Screening Vaccinated Population (≥25 Years) by Disease Status (≥CIN2), cobas® HPV Test Result and Cytology Result**

| cobas® HPV Test Result | Cytology Result | Diseased | Non-Diseased | Unverified | Total |
|---|---|---|---|---|---|
| HPV 16+ | Normal | 2 | 10 | 2 | 14 |
| | ASC-US | 0 | 3 | 1 | 4 |
| | >ASC-US | 1 | 2 | 2 | 5 |
| HPV 18+ | Normal | 0 | 4 | 1 | 5 |
| | ASC-US | 0 | 2 | 0 | 2 |
| | >ASC-US | 0 | 0 | 0 | 0 |
| Other 12 HR Positive | Normal | 5 | 60 | 15 | 80 |
| | ASC-US | 0 | 7 | 5 | 12 |
| | >ASC-US | 2 | 7 | 2 | 11 |
| Negative | Normal | 1 | 47 | 281 | 329 |
| | ASC-US | 1 | 12 | 5 | 18 |
| | >ASC-US | 0 | 6 | 1 | 7 |
| Total | | 12 | 160 | 315 | 487 |

**Table 44. Number of Subjects in the Primary Screening Vaccinated Population (≥25 Years) by Disease Status (≥CIN3), cobas® HPV Test Result and Cytology Result**

| cobas® HPV Test Result | Cytology Result | Diseased | Non-Diseased | Unverified | Total |
|---|---|---|---|---|---|
| HPV 16+ | Normal | 1 | 11 | 2 | 14 |
| | ASC-US | 0 | 3 | 1 | 4 |
| | >ASC-US | 1 | 2 | 2 | 5 |
| HPV 18+ | Normal | 0 | 4 | 1 | 5 |
| | ASC-US | 0 | 2 | 0 | 2 |
| | >ASC-US | 0 | 0 | 0 | 0 |
| Other 12 HR Positive | Normal | 2 | 63 | 15 | 80 |
| | ASC-US | 0 | 7 | 5 | 12 |
| | >ASC-US | 1 | 8 | 2 | 11 |
| Negative | Normal | 0 | 48 | 281 | 329 |
| | ASC-US | 0 | 13 | 5 | 18 |
| | >ASC-US | 0 | 6 | 1 | 7 |
| Total | | 5 | 167 | 315 | 487 |

A summary of the performance of the Primary Screening and Cytology algorithms in the vaccinated population for detecting ≥CIN2 and ≥CIN3 is given in Tables 45 to 48. Estimates of sensitivity and false positive rate (100-specificity) were higher in the vaccinated group compared to non-vaccinated women. Lower specificity resulted in smaller estimates of positive likelihood ratios in vaccinated compared to non-vaccinated women. Negative predictive values were similar in the two groups and positive predictive values were lower in the vaccinated group for both algorithms except for the Cytology algorithm in detecting ≥CIN2. Due to the limited number of diseased subjects in the vaccinated population and the relatively smaller size of the vaccinated population, these performance measures may not accurately reflect the future performance of the algorithms in a vaccinated population.

**Table 45. Performance Summary of Primary Screening and Cytology Algorithms in Detecting ≥CIN2 (Adjusted) in Vaccinated Women**

| Algorithms | Sensitivity | Specificity | 100-Specificity | PPV | NPV | PLR | NLR |
|---|---|---|---|---|---|---|---|
| Primary Screening | 46.7% | 90.3 % | 9.7 % | 13.2 % | 98.2 % | 4.79 | 0.59 |
| Cytology | 40.0% | 88.8 % | 11.2 % | 10.2 % | 97.9 % | 3.56 | 0.68 |

**Table 46. Performance Summary of Primary Screening and Cytology Algorithms in Detecting ≥CIN3 (Adjusted) in Vaccinated Women**

| Algorithms | Sensitivity | Specificity | 100-Specificity | PPV | NPV | PLR | NLR |
|---|---|---|---|---|---|---|---|
| Primary Screening | 66.7% | 89.8 % | 10.2 % | 7.5 % | 99.5 % | 6.54 | 0.37 |
| Cytology | 50.0% | 88.4 % | 11.6 % | 5.1 % | 99.3 % | 4.29 | 0.57 |

**Table 47. Performance Summary of Primary Screening and Cytology Algorithms in Detecting ≥CIN2 (Adjusted) in Non-Vaccinated Women**

| Algorithms | Sensitivity | Specificity | 100-Specificity | PPV | NPV | PLR | NLR |
|---|---|---|---|---|---|---|---|
| Primary Screening | 45.4% | 96.2 % | 3.8 % | 17.8 % | 99.0 % | 11.96 | 0.57 |
| Cytology | 35.3% | 94.2 % | 5.8 % | 9.9 % | 98.8 % | 6.08 | 0.69 |

**Table 48. Performance Summary of Primary Screening and Cytology Algorithms in Detecting ≥CIN3 (Adjusted) in Non-Vaccinated Women**

| Algorithms | Sensitivity | Specificity | 100-Specificity | PPV | NPV | PLR | NLR |
|---|---|---|---|---|---|---|---|
| Primary Screening | 57.9% | 96.0 % | 4.0 % | 12.4 % | 99.6 % | 14.42 | 0.44 |
| Cytology | 42.6% | 94.0 % | 6.0 % | 6.5 % | 99.4 % | 7.13 | 0.61 |

Table 49 displays cytology results classified by cobas® HPV Test results and combined AMP/LA HPV test results.

**Table 49. Cytology Result by cobas® HPV and Combined AMP/LA HPV Result**

| cobas® HPV Result | AMP/LA Result | Cytology | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | >ASC-US | ASC-US | Normal | UNSAT | Missing | |
| HPV16+/18+ | AMP/LA Positive | 249 | 139 | 764 | 19 | 0 | 1171 |
| | AMP/LA Negative | 1 | 0 | 14 | 0 | 0 | 15 |
| | AMP/LA Invalid Missing | 0 | 0 | 3 | 0 | 0 | 3 |
| Other 12 HR HPV+ | AMP/LA Positive | 409 | 302 | 2319 | 48 | 0 | 3078 |
| | AMP/LA Negative | 5 | 4 | 69 | 1 | 0 | 79 |
| | AMP/LA Invalid Missing | 0 | 0 | 5 | 3 | 0 | 8 |
| HPV - | AMP/LA Positive | 75 | 136 | 2715 | 50 | 0 | 2976 |
| | AMP/LA Negative | 247 | 1050 | 32403 | 600 | 0 | 34300 |
| | AMP/LA Invalid Missing | 0 | 1 | 34 | 16 | 2 | 53 |
| HPV Invalid | AMP/LA Positive | 2 | 2 | 15 | 7 | 0 | 26 |
| | AMP/LA Negative | 1 | 0 | 102 | 28 | 0 | 131 |
| | AMP/LA Invalid Missing | 0 | 0 | 8 | 12 | 4 | 24 |
| Missing | AMP/LA Positive | 0 | 1 | 0 | 0 | 0 | 1 |
| | AMP/LA Negative | 0 | 0 | 2 | 2 | 0 | 4 |
| | AMP/LA Invalid/Missing | 0 | 0 | 6 | 1 | 79 | 86 |
| Total | | 989 | 1635 | 38459 | 787 | 85 | 41955 |

## E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 61 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

### Women Subsequently Diagnosed with Cancer

An evaluation of the cobas® HPV Test was conducted in cytology samples of women subsequently diagnosed with cancer. Eight cases of invasive cervical cancer were identified in the ATHENA clinical study, in which the diagnosis of cancer was made by CPR. A summary of the results for these samples is shown below in Table 50.

**Table 50. Performance of the cobas® HPV Test for Eight Cancer Cases from ATHENA**

| | Cytology | | | Total |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| HPV 16/18 pos | 4 | | 1 | 5 |
| 12 Other HR HPV pos | 3 | | | 3 |
| HR HPV neg | | | | |
| Invalid | | | | |
| Total | 7 | | 1 | 8 |

Sensitivity for Primary Screening was 100% (8/8) and sensitivity for the Cytology was 87.5% (7/8).

In addition to those cases, 19 pre-aliquoted de-identified ThinPrep cervical samples from women who were subsequently diagnosed with invasive cervical cancer were obtained from an HPV Cytology Registry, independent of the ATHENA study. The diagnosis of invasive cervical cancer in the samples was confirmed by an expert pathology review panel. The women ranged in age from 27-84 years with a mean age of 52 years. One sample was found after cobas® HPV testing to be a poorly differentiated endometrioid cancer with uncertain origin, and a distinction between endometrial and endocervical primary cancer could not be made; this sample was included in the analysis (noted by * in Table 51 below).

**Table 51. Performance of the cobas® HPV Test for Non-ATHENA Archived Cancer Samples**

| | Cytology | | | Total |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| HPV 16/18 pos | 12 | 1 | | 13 |
| HPV Other pos | 2 | | 2 | 4 |
| HR HPV neg | | 1* | | 1 |
| Invalid | 1 | | | 1 |
| Total | 15 | 2 | 2 | 19 |

Sensitivity for Primary Screening was 83.3% (15/18) and percent of invalid was 5.3% (1/19).
Sensitivity for Cytology was 89.5% (17/19).

Combined data for all 27 (8+19) Cancer Samples is shown in Table 52.

**Table 52. Performance of the cobas® HPV Test for the Combined Cancer Sample Data**

| | Cytology | | | Total |
|---|---|---|---|---|
| | >ASC-US | ASC-US | NILM | |
| HPV 16/18 pos | 16 | 1 | 1 | 18 |
| HPV Other pos | 5 | | 2 | 7 |
| HR HPV neg | | 1 | | 1 |
| Invalid | 1 | | | 1 |
| Total | 22 | 2 | 3 | 27 |

The sensitivity of the Primary Screening algorithm was 88.5% (23/26) and the sensitivity of Cytology was 88.9% (24/27): the Primary Screening algorithm missed three cancers (two cases with 12 Other HR HPV positive, cytology=NILM and one case with HR HPV negative) and the Cytology algorithm missed three cancers (three cases with cytology=NILM).

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

### A. Panel Meeting Recommendation

At an advisory meeting held on March 12, 2014, the Microbiology Panel voted unanimously (thirteen to zero with none abstaining) that there is reasonable assurance the device is safe, unanimously (thirteen to zero with none abstaining) that there is reasonable assurance that the device is effective, and unanimously (thirteen to zero with none abstaining) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

Additional information on the panel meeting can be found on the CDRH Website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm388531.htm

### B. FDA's Post-Panel Action

The panel generally discussed whether the indicated age range (25 years of age and older) was appropriate for the proposed indication or if a more appropriate age range would be 30 years of age or older. Several panel members expressed concerns about the possibility of overtreatment in the 25 to 29 age year old group and the possible impact it may have on their future reproductive health, noting that the data on the impact of treatment on preterm labor remain inconclusive. Given that there is significant prevalence of CIN3 in this age range and that over-screening could be mitigated with proper screening intervals, the panel agreed that the benefits outweigh the risks.

The panel agreed that the triage testing proposed for the candidate algorithm (cytology and cobas® HPV Test 16/18 genotyping) are acceptable for determining

which high risk cobas® HPV Test positive patients need immediate referral to colposcopy.

Generally, the panel indicated that the benefit vs. risk in using the device for the proposed indication for use was acceptable, particularly in terms of the number of tests and colposcopies performed per 10,000 patients in relation to the proportion of disease diagnosed.

The panel discussed whether they anticipated any changes in clinical performance due to recent changes in recommended screening intervals or HPV vaccination. The panel did not anticipate, but could not definitively rule out changes in performance for the candidate algorithm, with the possible exception that HPV 16 and 18 would be less prevalent due to vaccination, which could affect the positive predictive value of screening tests. Several panelists indicated that any changes would likely also impact the comparator algorithm (cytology alone).

The Bethesda System for Classifying Cervical/Vaginal Diagnoses from cytology tests includes non-cancer related diagnostic categories such as the ability to detect microscopically certain organisms and abnormal endometrial cells. The device is not designed to screen for these additional diagnostic categories. Based on their clinical experience, the panel discussed the potential impact on patients if this additional diagnostic information is lost. The panel generally agreed that patients would not be adversely impacted by loss of these cytology categories since other better testing methods exist for these conditions that clinicians would utilize over cytology.

The panel also discussed what specific warnings and/or limitations could mitigate the risk that this test will be misused or used inappropriately for the proposed indication in patient management. Suggestions included that the warnings and/or limitations cover women who have undergone hysterectomy, non-indicated collection methods, and HPV negative cancers. One suggestion to add a warning against sending 12 other HR HPV positive women with NILM cytology to colposcopy was not included, since in certain scenarios this could occur in accordance with current guidelines[2].

FDA is following the Microbiology Panel recommendations and therefore has approved this PMA supplement with the new indication, recommended warnings (with noted exception) and limitations added to the device label.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The effectiveness of the cobas® HPV Test has been demonstrated for use in women 25 years and older as a first-line primary cervical cancer screening test to detect high risk HPV, including genotyping for 16 and 18. Women who test negative for high risk HPV types by the cobas® HPV Test should be followed up in accordance with the

physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the cobas® HPV Test should be referred to colposcopy. Women who test high risk HPV positive and 16/18 negative by the cobas® HPV Test (12 other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

## B. Safety Conclusions

The risks 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.

## C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. For 10,000 women, the candidate would be expected to involve 760 cytology, 10,000 cobas® HPV, and 461 colposcopy tests and procedures (514 colposcopies if un-blinded to HPV test results); the comparator would be expected to involve 10,000 cytology, 0 cobas® HPV, and 639 colposcopy tests and procedures. The candidate (un-blinded) detected a greater number of disease cases (61 vs. 41 for ≥CIN3 and 27 vs. 22 for CIN2) than the comparator.

Analysis with an additional comparator algorithm was considered and supported the device performance. Analytical performance studies also supported the device performance.

The proposed device indication was discussed on March 12, 2014 by the Microbiology Devices Panel of the Medical Devices Advisory Committee. The panel members voted 13 to 0 that the benefits of the cobas® HPV Test for the proposed indications for use outweigh the risks of the cobas® HPV Test for the proposed indications. In conclusion, given the available information described above, the data support that for the new indication, the probable benefits outweigh the probable risks.

## D. 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 have shown that the assay is safe and effective for its approved indications when used according to the directions for use in the labeling. The Microbiology Panel that convened on March 12, 2014 unanimously supported these overall conclusions.

## XIV. CDRH DECISION

CDRH issued an approval order on April 24, 2014. The final conditions of approval can be found in the approval order.

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

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES

[1] Wright T, Massad LS, Dunton C, et al. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. American Journal of Obstetrics and Gynecology. 2007; 197(4):346-55.

[2] Massad LS, Einstein MH, Huh WK, et al. 2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Obstet Gynecol. 2013 Apr;121(4):829-46.

[3] Saslow D, Solomon D, Lawson H, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. Am J Clin Pathol 2012;137:516-542.