SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: In vitro polymerase chain reaction (PCR)-based assay for detection of Human Papillomavirus (HPV) DNA.

Device Trade Name: Alinity m HR HPV (used on Alinity m System)

Device Procode: MAQ

Applicant's Name and Address: Abbott Molecular Inc.
1300 E. Touhy Ave
Des Plaines, IL 60018

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P230003

Date of FDA Notice of Approval: November 1, 2023

II. INDICATIONS FOR USE

Alinity m HR HPV is a qualitative in vitro test for the detection of Human Papillomavirus DNA in cervical specimens collected by a health care professional using an endocervical brush/spatula placed in ThinPrep PreservCyt Solution or an endocervical broom placed in SurePath Preservative Fluid. This test identifies high-risk (HR) HPV types 16, 18, 45, while reporting the concurrent detection of the other HR genotypes (31/33/52/58) and (35/39/51/56/59/66/68).

Alinity m HR HPV is indicated for use in routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (adjunctive screening) with cytology, and HPV primary screening of women to assess the risk for cervical pre-cancer and cancer. Patients should be followed-up in accordance with professional medical guidelines, results from prior screening, medical history, and other risk factors.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Alinity m HR HPV labeling.

V. DEVICE DESCRIPTION

The Alinity m HR HPV assay utilizes real-time PCR to amplify and detect DNA from 14 HR HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and human genomic DNA sequences that have been extracted from cervical specimens. Cervical specimens collected in ThinPrep PreservCyt Solution or SurePath Preservative Fluid can be used with Alinity m HR HPV assay.

The Alinity m HR HPV assay consists of two assay-specific components:

- Alinity m HR HPV AMP Kit (two trays, AMP TRAY 1 and 2)
- Alinity m HR HPV CTRL Kit

Additional necessary components include:

- Alinity m Sample Prep Kit 1
- Alinity m Tubes and Caps
- Alinity m System Solutions
- Alinity m System

The steps of the Alinity m HR HPV assay consist of sample preparation, PCR assembly, amplification/detection, and result calculation and reporting. All steps of the Alinity m HR HPV assay procedure are executed automatically by the Alinity m System. No intermediate processing or transfer steps are performed by the user.

Principles of Procedure

1. *Sample Preparation (Nucleic acid extraction and purification)*
   Nucleic acids from specimens are extracted using the Alinity m Sample Prep Kit 1 and Alinity m System Solutions. Nucleic acid extraction (lysis) disrupts the biological matrix to release the nucleic acid materials and allows for nucleic acids to adhere to the surface of magnetic microparticles. The magnetic microparticle technology facilitates nucleic acid capture, wash and elution. Nucleic acids bound to the surface of the magnetic microparticles are washed multiple times to remove any substances from the sample (i.e., lipids, proteins, therapeutic drugs) and from earlier sample preparation (i.e., ethanol, proteinase) that may potentially interfere with the later amplification and detection processes. Purified nucleic acids are released from the magnetic microparticle surface by mixing microparticles with an elution buffer. The resulting purified nucleic acids are then combined with the liquid unit-dose activator reagent (AMP TRAY 1), lyophilized unit-dose Alinity m HR HPV amplification/ detection reagents (AMP TRAY 2) and transferred into a reaction vessel.

2. *Nucleic acid amplification*

The lyophilized, unit-dose Alinity m HR HPV amplification/detection reagents are reconstituted following mixing with liquid unit-dose activator reagent, mixed with purified nucleic acids from the tested specimens. Alinity m Vapor Barrier Solution is then added to the reaction vessel which is then transferred to an amplification/detection unit for PCR amplification, and real-time fluorescence detection of HR HPV. Purified specimen nucleic acids are amplified by real-time polymerase chain reaction (PCR) using a mix composed of thermostable DNA polymerase, dNTPs, $MgCl_2$, and short oligonucleotide primers targeting the 14 HR-HPV targets and an endogenous human beta globin (BG) sequence. Amplification and detection of the BG sequence is a sample validity control for cell adequacy, sample extraction and amplification efficiency. The Alinity m HR HPV amplification/detection reagent also contains Uracil-DNA Glycosylase (UDG) as a control for contamination from amplicons containing uracil, which may be present in molecular laboratories.

3. *Nucleic acid detection*

Alinity m HR HPV assay primers allow for amplification of the 14 HR HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Within a single PCR well, the Alinity m HR HPV probes are labeled with different fluorophores that allow for genotype specific detection of HPV16, 18, and 45 while the remaining 11 HR HPV genotypes are detected as Other HR HPV A (HPV31/33/52/58 genotypes) or Other HR HPV B (HPV35/39/51/56/59/66/68). Amplification of BG is detected also reported separately using a uniquely labeled fluorescent probe. Real-time detection and discrimination of PCR products is accomplished by measuring the fluorescence for the HPV targets and BG, respectively.

4. *Assay Controls*

Assay controls are tested at or above an established minimum frequency to help ensure that instrument and reagent performance remain satisfactory. During each control event, a negative control and a positive control are processed through sample preparation and real-time PCR procedures that are identical to those used for specimens.

Instrumentation and Software

Alinity m System
The Alinity m System is a fully integrated and automated molecular diagnostics analyzer which utilizes real-time PCR technology in clinical laboratories. It is an integrated system for performing sample preparation and performing fluorescence-based real-time PCR to provide quantitative and qualitative detection of nucleic acid sequences. It provides sample-to-result uninterrupted processing workflow.

The Alinity m System enables continuous and random-access sample processing by using multiple sample processors and PCR thermal cycler/reader modules in parallel. Each individual sample occupies either one sample process lane or PCR Amplification and Detection (Amp-Detect) lane. Parallel lanes are provided to enable 300 tests in approximately eight hours.

Each Alinity m System utilizes four independent Assay Processing Units (APUs) to achieve the throughput and random-access requirements. Each APU consists of one extraction unit and one Amp-Detect unit, which automate the steps for nucleic acid purification/extraction and real-time PCR, respectively. This results in the ability to process up to twenty-four (24) different assay types simultaneously (i.e., up to 12 different assay types for purification/extraction and up to 12 different assay types for amplification and detection).

Alinity m Software
The Alinity m System software is the set of computer instructions that interprets system and assay information, calculates results, and provides the interface for controlling the system hardware. The Alinity m System software interprets the assay information provided in the specific Application Specification File, along with system information, to control the system hardware and identify the appropriate algorithms for data reduction.

Using application specifications, customers create orders for calibrators, controls, and specimens. Customers load racks of calibrators, controls, and specimens in the sample input to begin processing. Once the samples are processed, results are reviewed and released through the software user interface.

Alinity m HR HPV Application Specification File
The application specification file is a data file that contains a set of parameters in a software-industry-standard JSON (Java Script Object Notation) file format and is needed to run an Alinity m assay on the Alinity m System. The parameters determine how the software controls the instrument components to execute the selected assay. The Alinity m System software interprets the assay information provided in the specific Application Specification File, along with system information, to control the system hardware and identify the appropriate algorithms for data reduction.

<u>Interpretation of Alinity m HR HPV test results</u>
HPV16, 18, and 45 are detected using unique fluorophores and can be individually detected and reported in a specimen sample. The remaining 11 HR HPV genomes are amplified using unique oligonucleotide primers, but are detected and reported as two different groups, Other HR HPV A (HPV31/33/52/58) and Other HR HPV B (HPV35/39/51/56/59/66/68). Table 1 below summarizes reported result and interpretation by the Alinity m HR HPV assay on the Alinity m System.

Table 1: Summary of possible Alinity genotype results and specimen interpretation

Alinity m HR HPV Result	Interpretation
Negative	Negative
Negative	Negative
HPV16	HR HPV Positive (16 Positive)
HPV18	HR HPV Positive (18 Positive)
HPV45	HR HPV Positive (45 Positive)
Other HR HPV A	HR HPV Positive (A Positive)
Other HR HPV B	HR HPV Positive (B Positive)
HPV16; HPV18	HR HPV Positive (16;18 Positive)
HPV16; HPV45	HR HPV Positive (16;45 Positive)
HPV16; Other HR HPV A	HR HPV Positive (16;A Positive)
HPV16; Other HR HPV B	HR HPV Positive (16;B Positive)
HPV18; HPV 45	HR HPV Positive (18;45 Positive)
HPV18; Other HR HPV A	HR HPV Positive (18;A Positive)
HPV18; Other HR HPV B	HR HPV Positive (18;B Positive)
HPV45; Other HR HPV A	HR HPV Positive (45;A; Positive)
HPV45; Other HR HPV B	HR HPV Positive (45;B Positive)
Other HR HPV A; Other HR HPV B	HR HPV Positive (A;B Positive)
HPV16; HPV18; HPV45	HR HPV Positive (16;18;45 Positive)
HPV16; HPV18; Other HR HPV A	HR HPV Positive (16;18;A Positive)
HPV16; HPV18; Other HR HPV B	HR HPV Positive (16;18;B Positive)
HPV16; HPV45; Other HR HPV A	HR HPV Positive (16;45;A; Positive)
HPV16; HPV45; Other HR HPV B	HR HPV Positive (16;45;B Positive)
HPV16; Other HR HPV A; Other HR HPV B	HR HPV Positive (16;A;B Positive)
HPV18; HPV45; Other HR HPV A	HR HPV Positive (18;45;A Positive)
HPV18; HPV45; Other HR HPV B	HR HPV Positive (18;45;B Positive)
HPV18; Other HR HPV A; Other HR HPV B	HR HPV Positive (18;A;B Positive)
HPV45; Other HR HPV A; Other HR HPV B	HR HPV Positive (45;A;B Positive)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of cervical cancer precursors, including testing by cytology alone, co-testing with HPV alongside or as a follow-up to cytology, or HPV testing as a first line screening test for cervical cancer. There are also multiple FDA approved in vitro nucleic acid amplification tests for the qualitative measurement of HPV DNA in human specimens (i.e., Roche cobas HPV Test and cobas HPV assay, Aptima HPV Assay, Qiagen Hybrid Capture 2 High-Risk HPV DNA Test, BD Onclarity HPV Assay). Each alternative has its own advantages and disadvantages. A patient should fully

discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

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

VII. MARKETING HISTORY

The product is currently distributed/marketed in 34 countries. The product has not been withdrawn to date from the market in any country for reasons related to the safety or effectiveness of the device. The Alinity m HR HPV AMP Kit and Alinity m HR HPV CTRL Kit are identical in formulation and use similar application specification files to the US kits and are marketed outside the US as listed in Table 2.

Table 2. Current distribution of the Alinity m HR HPV assay

Australia	France	Portugal
Austria	Germany	Romania
Belgium	Italy	Slovenia
Brazil	Latvia	South Africa
Bulgaria	Malaysia	Spain
Chile	Mexico	Sweden
Colombia	Montenegro	Switzerland
Croatia	Netherlands	Taiwan
Czech Republic	New Zealand	Thailand
El Salvador	Norway	United Kingdom
Estonia	Poland	Vietnam
Finland		

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. False negative results may lead to delays in the timely diagnosis of cervical cancer, allowing an undetected condition to worsen and

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

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Clinical cutoff determination

The Alinity m HR HPV assay cutoffs were established using clinical specimens from subjects undergoing routine cervical cancer screening (Screening population) and subjects referred to colposcopy follow-up based on previous cervical screening that included HR HPV testing (Enriched population). The methods used for cutoff selection were chosen to achieve the maximum sensitivity for detecting ≥ CIN2 (Cervical Intraepithelial Neoplasia 2) disease while maintaining a clinically acceptable level of specificity. Based on these criteria, the clinical cutoff was set at a cycle number (CN) of 33 for HPV 16 and a CN of 32 for the remaining 13 HR HPV genotypes detected by the Alinity m HR HPV assay.

2. Analytical Sensitivity

a. Limit of Detection at the Clinical Cutoff

The limit of detection (LoD) at the clinical cutoff of the Alinity m HR HPV assay was determined by testing plasmids for 14 HR HPV genotype sequences (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and HPV positive cell lines (HPV16 SiHa and HPV18 HeLa) in pooled HR HPV negative clinical specimens collected in ThinPrep PreservCyt Solution (ThinPrep clinical matrix) and in pooled HR HPV negative clinical specimens collected in SurePath Preservative Fluid (SurePath clinical matrix). Each plasmid and cell line were diluted to concentrations at, below, and above the expected LoD level for each matrix. HPV 16, 18, 45, 58 (Other HR HPV A), and 39 (Other HR HPV B) plasmids and SiHa and HeLa cell lines were tested with three amplification reagent lots; the remaining HR HPV plasmids (HPV 31, 33, 35, 51, 52, 56, 59, 66, and 68) were tested with two amplification reagent lots. For each lot, a minimum of 20 replicates were tested across three days for each plasmid and cell line target concentration in each matrix.

The LoD was defined as the lowest target concentration having a ≥ 95% detection rate with all higher concentrations having a > 95% detection rate. Table 3 and Table 4 list result from the reagent lot producing the most conservative (highest) LoD at the clinical cutoff in the analysis for 14 HR HPV genotypes in ThinPrep and SurePath, respectively. These results are reported at a

concentration of cells/assay for the HPV positive cell lines and copies/assay for the 14 HR HPV plasmids. Displayed are the positivity rates and the 95% CI (confidence interval).

Table 3. Limit of Detection for HR HPVs in ThinPrep

HPV Target	Concentration	Positivity Rate%	95% CI
Cell line	**Cells/assay**		
SiHa (HPV16)	40	95.7	(79.0%, 99.2%)
HeLa (HPV18)	9.2	95.8	79.8%, 99.3%)
Plasmid	**Copies/assay**		
HPV16	480	100.0	86.2%, 100.0%)
HPV18	120	100.0	86.2%, 100.0%)
HPV31	300	95.8	79.8%, 99.3%)
HPV33	600	100.0	86.2%, 100.0%)
HPV35	300	95.8	79.8%, 99.3%)
HPV39	9600	100.0	86.2%, 100.0%)
HPV45	120	100.0	86.2%, 100.0%)
HPV51	600	95.5	78.2%, 99.2%)
HPV52	2500	100.0	86.2%, 100.0%)
HPV56	300	100.0	86.2%, 100.0%)
HPV58	1200	95.8	79.8%, 99.3%)
HPV59	150	100.0	83.9%, 100.0%)
HPV66	150	100.0	83.9%, 100.0%)
HPV68	300	100.0	86.2%, 100.0%)

Table 4. Limit of Detection for HR HPVs in SurePath

HPV Target	Concentration	Positivity Rate%	95% CI
Cell line	**Cells/assay**		
SiHa (HPV16)	80	100.0	(86.2%, 100.0%)
HeLa (HPV18)	4.8	95.7	(79.0%, 99.2%)
Plasmid	**Copies/assay**		
HPV16	120	95.8	79.8%, 99.3%)
HPV18	120	100.0	86.2%, 100.0%)
HPV31	300	100.0	86.2%, 100.0%)
HPV33	600	95.7	79.0%, 99.2%)
HPV35	600	100.0	86.2%, 100.0%)
HPV39	1200	100.0	86.2%, 100.0%)
HPV45	120	100.0	86.2%, 100.0%)
HPV51	600	95.7	79.0%, 99.2%)
HPV52	1250	100.0	86.2%, 100.0%)
HPV56	300	95.8	79.8%, 99.3%)

Table 4. Limit of Detection for HR HPVs in SurePath

HPV Target	Concentration	Positivity Rate%	95% CI
HPV58	300	100.0	83.9%, 100.0%)
HPV59	1200	100.0	85.7%, 100.0%)
HPV66	2400	100.0	85.1%, 100.0%)
HPV68	4800	100.0	83.9%, 100.0%)

3. Analytical Specificity

a. Cross-reactivity

The analytical specificity of the Alinity m HR HPV assay was evaluated with a panel of microorganisms that included low-risk HPV, bacteria, viruses, protozoan, and yeast as well as human cellular DNA (Table 5). Microorganisms were tested at 10^5 Units/mL (viruses and eukaryotes) or 10^6 Units/ml (bacteria), where the unit of measure is specific to each microorganism Human cellular DNA was tested at 10^6 Copies/ml. Each potential cross reactant was tested with HR HPV negative samples in both ThinPrep and SurePath matrices. No cross reactivity or interference in Alinity m HR HPV assay performance was observed in the presence of the tested potential cross reactants in either sample type.

Table 5. Microorganisms Tested

Virus	**Bacteria continued**
Adenovirus	*Klebsiella pneumoniae ss ozaenae*
Cytomegalovirus (CMV)	*Lactobacillus acidophilus*
Epstein Barr Virus (EBV)	*Mycoplasma genitalium*
Hepatitis B virus (HBV)	*Mycoplasma hominis*
Herpes simplex virus I	*Neisseria gonorrhoeae*
Herpes simplex virus II	*Neisseria meningitidis* Serogroup A
Human herpes virus 3	*Peptostreptococcus anaerobius*
Hepatitis C virus (HCV)	*Proteus mirabilis*
Human immunodeficiency virus (HIV-1)	*Pseudomonas aeruginosa*
Bacteria	*Staphylococcus aureus*
Bacteroides fragilis	*Staphylococcus epidermidis*
Bacteroides ureolyticus	*Streptococcus agalactiae*
Bifidobacterium adolescentis	*Streptococcus faecalisa*
Chlamydia trachomatis	*Streptococcus pneumoniae*
Clostridium perfringens	*Streptococcus pyogenes*
Corynebacterium genitalium	*Treponema pallidum*
Enterococcus faecalis	*Ureaplasma urealyticum*
Enterobacter cloacae	**Yeast**
Escherichia coli	*Candida albicans*
Fusobacterium necrophorum	**Other**
Gardnerella vaginalis	Human Cellular DNA
Haemophilus ducreyi	*Trichomonas vaginalis*

Low-risk (LR) HPV genomes							
HPV6	HPV26	HPV34	HPV43	HPV54	HPV61	HPV70	HPV85
HPV11	HPV30	HPV40	HPV44	HPV55B	HPV67	HPV73	
HPV13	HPV32	HPV42	HPV53	HPV57	HPV69	HPV82	

b. Interference

The effect of potentially interfering endogenous and exogenous substances that may be present in cervical specimens was assessed for the Alinity m HR HPV assay. Each substance was tested with HR HPV negative samples (above the corresponding cutoff) and HR HPV positive samples containing SiHa (HPV 16) and HeLa (HPV 18) cell lines at approximately 3X LoD in both ThinPrep and SurePath clinical matrices.

For both ThinPrep and SurePath, no interference was observed for any substance at the concentrations listed in Table 6. Assay interference was observed for Monistat-1 at concentrations higher than 0.75% in ThinPrep. Based on the reported CN values, detection of the 14 HR HPV genotypes for cervical samples stored in SurePath may be impacted by the presence of mucus at a concentration of 5% w/v.

Table 6. Endogenous and Exogenous Substances Evaluated

Endogenous Substance	Test Level
Whole Blood	10.00% v/v
Mucus	5.00% w/v[b]
PBMC (leukocytes)	10^6 Cells/mL
Exogenous Substance	**Test Level**
Clotrimazole Vaginal Cream	1.00% w/v
Terconazole Vaginal Cream 0.8%	1.00% w/v
Monistat-1	0.75% w/v[a]
KY Jelly Personal Lubricant	1.00% w/v
KY Warming Liquid	1.00% w/v
Zovirax (Acyclovir)	1.00% w/v
Summer's Eve Douche	1.00% w/v
Norforms Deodorant Suppositories	0.50% w/v
Metrogel-Vaginal	0.50% w/v
Vaginal Contraceptive Foam (VCF) Contraceptive Gel	0.50% w/v
Options Gyncol II Vaginal Contraceptive Gel	0.50% w/v
Hydrocortisone	0.50% w/v
Sigma Acetic Acid	0.50% w/v
Vagisil Dry Wash	0.50% w/v

[a] 1.00% w/v produced false negative results in ThinPrep clinical matrix.
[b] 5.00% w/v mucus may impact performance in SurePath clinical matrix

c. <u>Competitive Inhibition</u>

A study was performed to test whether high concentrations of HR HPV DNA could interfere with the genotyping capability of the Alinity m HR HPV assay to detect HPV types 16, 18, 45, Other HR HPV A (represented by HPV58), and Other HR HPV B (represented by HPV39) in ThinPrep and SurePath matrices. Each plasmid (at low concentration) was tested for detection in the presence of the other four competing, high concentration plasmids (at a concentration of 10^5 copies/ml). Testing was done in ThinPrep and SurePath matrices containing C33A cells.

No competitive inhibition was detected in ThinPrep matrix.

In SurePath, detection of Other HR HPV A genotypes (represented by HPV58 during testing) was inhibited by the presence of HPV18 at 10^5 copies/ml. Other HR HPV B genotypes (represented by HPV39 during testing) was inhibited by the presence of HPV16, 18, and 45 at a concentration of 10^5 copies/ml. During retesting, Group A and Group B were detected when the competing targeting analyte was present at a concentration of 10^4 copies/ml in SurePath.

4. Precision

Study 1

Within-laboratory precision of the Alinity m HR HPV assay was evaluated with a 22-member panel of samples in ThinPrep PreservCyt Solution and a 13-member panel of samples in SurePath Preservative Fluid. The ThinPrep panel included six pools made from clinical specimens collected in ThinPrep PreservCyt Solution and 16 contrived samples prepared with SiHa (HPV 16), HeLa (HPV 18), HPV 45, HPV 39, or HPV 58 plasmids in ThinPrep PreservCyt Solution containing HR HPV negative C33A cells. The SurePath panel included six pools made from clinical specimens collected in SurePath Preservative Fluid and seven contrived samples prepared with SiHa or HeLa in SurePath Preservative Fluid containing HR HPV negative C33A cells. For each sample type, one negative clinical pool and five moderate positive clinical pools representative of each genotype category (HPV 16, 18, 45, Other HR HPV A, and Other HR HPV B) were prepared. ThinPrep contrived panels consisted of high negative, low positive, and moderate positive target levels for each genotype category, in addition to a negative panel member. SurePath contrived panels consisted of high negative, low positive, and moderate positive target levels for SiHa and HeLa cell lines, in addition to a negative panel member. Each panel member was tested with two replicates, twice a day, for 12 days on three Alinity m Systems with three reagent lots.

A summary of the panel members and agreement rate relative to expected result (positive agreement for positive samples and negative agreement for negative samples), and analysis of CN variability are presented in Table 7 and Table 8 for the ThinPrep panel and Table 9 and Table 10 for the SurePath panel. For ThinPrep panel members, the total % CV (coefficient of variation) for target CN ranged from 1.4% to 6.5% across all genotypes at low and moderate positive levels (Table 8). For SurePath panel members, the total % CV for target CN ranged from 1.4% to 5.7% across all genotypes at low and moderate positive levels (Table 10).

Table 7. Summary of Within-laboratory Precision Study 1 Panel Members, Median CN, and Agreement Rates: ThinPrep

Panel Composition	Panel Description	No. Valid[a]	Median (CN)[b]	%Positive (n/N)[c]	% Negative, HPV amplified (n/N)	% Negative, HPV not amplified (n/N)
Pooled negative clinical sample	Negative	144	NA	0.0 (0/144)	0.0 (0/144)	100.0 (144/144)
HPV negative cell line	Negative	144	NA	0.0 (0/144)	0.0 (0/144)	100.0 (144/144)
HPV16 positive SiHa cell line	HPV16 high negative	144	32.86	56.9 (82/144)	24.3 (35/144)	18.8 (27/144)
HPV18 positive HeLa cell line	HPV18 high negative	144	36.00	10.4 (15/144)	2.8 (4/144)	86.8 (125/144)
HPV45 plasmid	HPV45 high negative	144	32.20	37.5 (54/144)	61.1 (88/144)	1.4 (2/144)

Table 7. Summary of Within-laboratory Precision Study 1 Panel Members, Median CN, and Agreement Rates: ThinPrep

Panel Composition	Panel Description	No. Valid[a]	Median (CN)[b]	%Positive (n/N)[c]	% Negative, HPV amplified (n/N)	% Negative, HPV not amplified (n/N)
Other HR HPV Plasmid A [d]	Other HR HPV A high negative	144	36.00	17.4 (25/144)	11.1 (16/144)	71.5 (103/144)
Other HR HPV Plasmid B [e]	Other HR HPV B high negative	144	36.00	33.3 (48/144)	9.0 (13/144)	57.6 (83/144)
Pooled clinical sample	HPV 16 moderate positive	144	27.67	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 18 moderate positive	144	28.01	98.6 (142/144)	0.0 (0/144)	1.4 (2/144)
	HPV 45 moderate positive	144	28.37	98.6 (142/144)	0.0 (0/144)	1.4 (2/144)
	Other HR HPV A moderate positive	144	27.72	99.3 (143/144)	0.0 (0/144)	0.7 (1/144)
	Other HR HPV B moderate positive	144	27.00	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
HPV 16 positive SiHa cell line	HPV 16 low positive	144	28.89	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 16 moderate positive	144	27.45	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
HPV 18 positive HeLa cell line	HPV 18 low positive	144	28.29	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 18 moderate positive	144	27.15	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
HPV 45 plasmid	HPV 45 low positive	144	30.50	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 45 moderate positive	144	29.95	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
Other HR HPV A Plasmid	Other HR HPV A low positive	144	30.18	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	Other HR HPV A moderate positive	144	29.96	99.3 (143/144)	0.7 (1/144)	0.0 (0/144)
Other HR HPV B Plasmid	Other HR HPV B low positive	144	30.73	97.2 (140/144)	0.0 (0/144)	2.8 (4/144)
	Other HR HPV B moderate positive	144	28.75	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)

[a] N is the number of valid replicates.

[b] The median CN value reported is calculated for all replicates measured in the negative and positive panel members, above and below the clinical cutoff. Negative replicates with no virus detected were assigned the last cycle of PCR (36.00). Due to 0% virus detection, median CN was not reported for negative panels (NA)

[c] The percent agreement is based on the number of valid replicates with a CN value below the clinical cutoff.

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 8. Variance Component Analysis Results for Within-Laboratory Precision Study 1: ThinPrep

					Within-Run		Between-Run		Between-Day		Between Instrument /Lot		Total[a]	
Panel	**Panel Description**	**N[b]**	**n[c]**	**Mean (CN)**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
Pooled Clinical Sample	HPV16 moderate positive	144	144	27.52	1.330	4.8	0.747	2.7	0.000	0.0	0.000	0.0	1.525	5.5
	HPV 18 moderate positive	144	142	27.67	1.425	5.1	0.344	1.2	0.362	1.3	0.213	0.8	1.525	5.5
	HPV 45 moderate positive	144	142	28.08	1.084	3.9	0.000	0.0	0.192	0.7	0.080	0.3	1.104	3.9
	Other HR HPV A moderate positive	144	143	27.17	1.510	5.6	0.852	3.1	0.000	0.0	0.310	1.1	1.762	6.5
	Other HR HPV B moderate positive	144	144	27.01	0.771	2.9	0.441	1.6	0.000	0.0	0.000	0.0	0.889	3.3
HPV16 positive SiHa cell line	HPV 16 low positive	144	144	28.89	0.378	1.3	0.087	0.3	0.175	0.6	0.000	0.0	0.425	1.5
	HPV 16 moderate positive	144	144	27.45	0.382	1.4	0.000	0.0	0.030	0.1	0.101	0.4	0.396	1.4
HPV18 positive HeLa cell line	HPV 18 low positive	144	144	28.30	0.752	2.7	0.000	0.0	0.205	0.7	0.204	0.7	0.806	2.8
	HPV 18 moderate positive	144	144	27.22	0.570	2.1	0.261	1.0	0.000	0.0	0.213	0.8	0.662	2.4
HPV45 plasmid	HPV 45 low positive	144	144	30.52	0.373	1.2	0.025	0.1	0.123	0.4	0.196	0.6	0.439	1.4
	HPV 45 moderate positive	144	144	29.96	0.373	1.2	0.000	0.0	0.172	0.6	0.090	0.3	0.421	1.4
Other HR HPV A plasmid [d]	Other HR HPV A low positive	144	144	30.23	0.386	1.3	0.000	0.0	0.133	0.4	0.000	0.0	0.409	1.4
	Other HR HPV A moderate positive	144	143	29.91	0.319	1.1	0.000	0.0	0.193	0.6	0.173	0.6	0.411	1.4
Other HR HPV B plasmid [e]	Other HR HPV B low positive	144	140	30.75	0.369	1.2	0.000	0.0	0.227	0.7	0.205	0.7	0.479	1.6
	Other HR HPV B moderate positive	144	144	28.83	0.327	1.1	0.000	0.0	0.146	0.5	0.167	0.6	0.395	1.4

Because only positive, detected test results with CN values below the cutoff were included, estimates of SD (and % CV may be underestimated.

[a] N is the number of valid replicates.

[b] n is the number of valid replicates with a CN value below the clinical cutoff

[c] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument/Lot Components

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 9. Summary of Within-laboratory Precision Study 1 Panel Members, Median CN, and Agreement Rates: SurePath

Panel Composition	Panel Description	No. Valid[a]	Median (CN)[b]	%Positive (n/N)[c]	% Negative, HPV amplified (n/N)	% Negative, HPV not amplified (n/N)
Pooled negative clinical sample	Negative	144	NA	0.0 (0/144)	0.0 (0/144)	100.0 (144/144)
HPV negative cell line	Negative	144	NA	0.0 (0/144)	0.0 (0/144)	100.0 (144/144)
HPV16 positive SiHa cell line	HPV16 high negative	144	36.00	25.0 (36/144)	0.7 (1/144)	74.3 (107/144)
HPV18 positive HeLa cell line	HPV18 high negative	144	36.00	14.6 (21/144)	0.0 (0/144	85.4 (123/144)
Pooled clinical sample	HPV 16 moderate positive	144	28.39	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 18 moderate positive	144	27.14	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 45 moderate positive	144	28.24	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	Other HR HPV A moderate positive [d]	144	27.39	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	Other HR HPV B moderate positive [e]	144	28.22	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
HPV 16 positive SiHa cell line	HPV 16 low positive	144	29.35	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
	HPV 16 moderate positive	144	27.91	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)
HPV 18 positive HeLa cell line	HPV 18 low positive	144	28.07	97.2 (140/144)	0.0 (0/144)	2.8 (4/144)
	HPV 18 moderate positive	144	26.77	100.0 (144/144)	0.0 (0/144)	0.0 (0/144)

[a] N is the number of valid replicates.

[b] The median CN value reported is calculated for all replicates measured in the negative and positive panel members, above and below the clinical cutoff. Negative replicates with no virus detected were assigned the last cycle of PCR (36.00). Due to 0% virus detection, median CN was not reported for negative panels (NA)

[c] The percent agreement is based on the number of valid replicates with a CN value below the clinical cutoff.

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 10. Variance Component Analysis Results for Within-Laboratory Precision Study 1: SurePath

					Within-Run		Between-Run		Between-Day		Between Instrument /Lot		Total[a]	
Panel	**Panel Description**	**N[b]**	**n[c]**	**Mean (CN)**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
Pooled Clinical Sample	HPV16 moderate positive	144	144	28.23	0.743	2.6	0.449	1.6	0.167	0.6	0.140	0.5	0.896	3.2
	HPV 18 moderate positive	144	144	27.21	1.271	4.7	0.000	0.0	0.347	1.3	0.000	0.0	1.318	4.8
	HPV 45 moderate positive	144	144	28.18	0.441	1.6	0.222	0.8	0.158	0.6	0.029	0.1	0.520	1.8
	Other HR HPV A moderate positive [d]	144	144	26.93	1.493	5.5	0.000	0.0	0.330	1.2	0.132	0.5	1.535	5.7
	Other HR HPV B moderate positive [e]	144	144	28.19	0.600	2.1	0.304	1.1	0.212	0.8	0.000	0.0	0.705	2.5
HPV16 positive SiHa cell line	HPV 16 low positive	144	144	29.38	0.370	1.3	0.092	0.3	0.171	0.6	0.081	0.3	0.425	1.4
	HPV 16 moderate positive	144	144	27.93	0.309	1.1	0.117	0.4	0.160	0.6	0.110	0.4	0.383	1.4
HPV18 positive HeLa cell line	HPV 18 low positive	144	140	28.26	0.834	3.0	0.000	0.0	0.311	1.1	0.000	0.0	0.890	3.1
	HPV 18 moderate positive	144	144	26.71	0.483	1.8	0.192	0.7	0.000	0.0	0.000	0.0	0.520	1.9

Because only positive, detected test results with CN values below the cutoff were included, estimates of SD (and % CV may be underestimated.

[a] N is the number of valid replicates.

[b] n is the number of valid replicates with a CN value below the clinical cutoff

[c] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument/Lot Components

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Study 2

An additional within-laboratory precision study was conducted with a six-member panel of contrived samples in SurePath Preservative Fluid. Contrived panel members were prepared with HPV 45, HPV 39, or HPV 58 plasmids in SurePath Preservative Fluid containing HR HPV negative C33A cells. Each HPV genotype was targeted to low positive and moderate positive target levels. Each panel member was tested with a minimum of two replicates twice each day for 12 days on each of three reagent lots on each of three instruments. A description of the panels, agreement rate relative to expected result (percent positive results), and analysis of CN variability are presented in Table 11 and 12 for the SurePath panel. The total % CV for CN ranged from 1.0% to 1.2% across all HPV genotypes targeted at low positive or higher (Table 12).

Table 11. Summary of Precision Study 2 Panel Members, Median CN, and Agreement Rates: SurePath

Panel Composition	Panel Description	No. Valid[a]	Median (CN)[b]	%Positive (n/N)[c]	% Negative, HPV amplified (n/N)	% Negative, HPV not amplified (n/N)
HPV45 Plasmid	HPV 45 low positive	643	29.06	99.8 (642/363)	0.2 (1/643)	0.0 (0/643)
	HPV 45 moderate positive	646	28.90	100.0 (646/646)	0.0 (0/646)	0.0 (0/646)
Other HR HPV A Plasmid [d]	Other HR HPV A low positive	647	30.76	97.4 (630/647)	0.3 (2/647)	2.3 (15/647)
	Other HR HPV A moderate positive	645	29.77	99.5 (642/645)	0.2 (1/645)	0.3 (2/645)
Other HR HPV A Plasmid [e]	Other HR HPV A low positive	594	31.40	86.4 (513/594)	5.4 (32/594)	8.2 (49/594)
	Other HR HPV A moderate positive	647	30.39	99.8 (646/647)	0.0 (0/647)	0.2 (1/647)

a N is the number of valid replicates.
b The median CN value reported is calculated for all replicates measured in the negative and positive panel members, above and below the clinical cutoff. Negative replicates with no virus detected were assigned the last cycle of PCR (36.00).
c The percent agreement is based on the number of valid replicates with a CN value below the clinical cutoff.
d HPV 58 was used for the Other HR HPV A panel.
e HPV 39 was used for the Other HR HPV B panel.

Table 12. Variance Component Analysis Results for Precision Study 2: SurePath

					Within Run		Between Run		Between Day		Between Lot		Between Instrument		Total[a]	
Panel	**Panel Description**	**N[b]**	**n[c]**	**Mean (CN)**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
HPV45 Plasmid	HPV 45 low positive	643	642	29.06	0.238	0.8	0.121	0.4	0.000	0.0	0.000	0.0	0.111	0.4	0.289	1.0
	HPV 45 moderate positive	646	646	28.90	0.247	0.9	0.067	0.2	0.061	0.2	0.044	0.2	0.170	0.6	0.316	1.1
Other HR HPV A Plasmid [d]	Other HR HPV A low positive	647	630	30.76	0.314	1.0	0.084	0.3	0.000	0.0	0.065	0.2	0.057	0.2	0.336	1.1
	Other HR HPV A moderate positive	645	642	29.78	0.332	1.1	0.000	0.0	0.074	0.2	0.026	0.1	0.107	0.4	0.358	1.2
Other HR HPV B Plasmid [e]	Other HR HPV A low positive	594	513	31.33	0.282	0.9	0.137	0.4	0.000	0.0	0.000	0.0	0.062	0.2	0.320	1.0
	Other HR HPV A moderate positive	647	646	30.39	0.306	1.0	0.046	0.2	0.075	0.2	0.098	0.3	0.093	0.3	0.346	1.1

Because only positive, detected test results with CN values below the cutoff were included, estimates of SD (and % CV may be underestimated.

[a] N is the number of valid replicates.

[b] n is the number of valid replicates with a CN value below the clinical cutoff

[c] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument/Lot Components

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

5. Lot-to-Lot Variability

The variability of Alinity m HR HPV reagent lots was assessed with HPV positive panels in ThinPrep and SurePath matrices containing HPV negative C33A cells. For both matrices, HPV positive panels were prepared with HPV 16, HPV 18, HPV 45, HPV 58, or HPV 39 plasmids at a low positive and moderate positive level. Each positive panel member was tested with three different reagent lots on one Alinity m System. A minimum of 20 replicates were tested per panel member per lot. For ThinPrep panel members, the total %CV for HPV CN ranged from 1.1% to 2.1% across all genotypes (Table 13). For SurePath panel members, the total % CV for HPV CN ranged from 1.0% to 2.0% across all genotypes (Table 14).

Table 13. Lot-to-Lot Precision Study: ThinPrep

						Within-Lot Component		Between-Lot Component		Total[a]	
Panel	**Target Level**	**N[b]**	**n[c]**	**Detection Rate**	**Mean (CN)**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
HPV 16 plasmid	Low positive	72	72	100.0%	29.94	0.314	1.0	0.097	0.3	0.329	1.1
	Moderate positive	72	72	100.0%	28.90	0.301	1.0	0.109	0.4	0.321	1.1
HPV 18 plasmid	Low positive	72	72	100.0%	28.87	0.347	1.2	0.190	0.7	0.395	1.4
	Moderate positive	72	72	100.0%	27.99	0.310	1.1	0.109	0.4	0.328	1.2
HPV 45 plasmid	Low positive	72	72	100.0%	30.08	0.315	1.0	0.108	0.4	0.333	1.1
	Moderate positive	72	72	100.0%	29.15	0.300	1.0	0.132	0.5	0.328	1.1
Other HR HPV A plasmid [d]	Low positive	60	60	100.0%	30.71	0.344	1.1	0.368	1.2	0.504	1.6
	Moderate positive	60	60	100.0%	29.11	0.274	0.9	0.220	0.8	0.351	1.2
Other HR HPV B plasmid [e]	Low positive	60	60	100.0%	30.20	0.278	0.9	0.282	0.9	0.396	1.3
	Moderate positive	60	60	100.0%	29.39	0.297	1.0	0.548	1.9	0.623	2.1

[a] Total includes Within-Lot and Between-Lot Components.

[b] N is the number of valid replicates.

[c] n is the number of positive tests, which contribute CN values to the variance component analysis.

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 14. Lot-to-Lot Precision Study: SurePath

						Within-Lot Component		Between-Lot Component		Total[a]	
Panel	**Target Level**	**N[b]**	**n[c]**	**Detection Rate**	**Mean (CN)**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
HPV 16 plasmid	Low positive	60	60	100.0%	30.50	0.413	1.4	0.437	1.4	0.601	2.0
	Moderate positive	60	60	100.0%	29.58	0.294	1.0	0.471	1.6	0.555	1.9
HPV 18 plasmid	Low positive	72	71	98.6%	30.06	0.426	1.4	0.000	0.0	0.426	1.4*
	Moderate positive	71	71	100.0%	29.39	0.355	1.2	0.246	0.8	0.432	1.5
HPV 45 plasmid	Low positive	60	60	100.0%	30.32	0.345	1.1	0.000	0.0	0.345	1.1
	Moderate positive	60	60	100.0%	29.47	0.281	1.0	0.109	0.4	0.302	1.0
Other HR HPV A plasmid [d]	Low positive	60	59	98.3%	30.84	0.351	1.1	0.285	0.9	0.452	1.5*
	Moderate positive	60	60	100.0%	30.00	0.265	0.9	0.248	0.8	0.363	1.2
Other HR HPV B plasmid [e]	Low positive	60	58	96.7%	31.06	0.366	1.2	0.167	0.5	0.402	1.3*
	Moderate positive	60	59	98.3%	30.44	0.323	1.1	0.161	0.5	0.361	1.2*

[a] Total includes Within-Lot and Between-Lot Components.

[b] N is the number of valid replicates.

[c] n is the number of positive tests, which contribute CN values to the variance component analysis.

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

*Calculated SD and CV (%) may be underestimated.

6. Reproducibility

Site-to-site reproducibility performance of the Alinity m HR HPV assay was evaluated with a 22-member panel of samples in ThinPrep PreservCyt Solution and a 13-member panel of samples in SurePath Preservative Fluid. The ThinPrep panel included six pools made from clinical specimens collected in ThinPrep PreservCyt Solution and 16 contrived samples prepared with SiHa (HPV 16), HeLa (HPV 18), HPV 45, HPV 39, or HPV 58 plasmids in ThinPrep PreservCyt Solution containing HR HPV negative C33A cells. The SurePath panel included six pools made from clinical specimens collected in SurePath Preservative Fluid and seven contrived samples prepared with SiHa or HeLa in SurePath Preservative Fluid containing HR HPV negative C33A cells. For each sample type, one negative clinical pool and five moderate positive clinical pools representative of each genotype category (HPV 16, 18, 45, Other HR HPV A, and Other HR HPV B) were prepared. ThinPrep contrived panels consist of high negative, low positive, and moderate positive target levels for each genotype category, in addition to a negative panel member. SurePath contrived panels consist of high negative, low positive, and moderate positive target levels for SiHa and HeLa cell lines, in addition to a negative panel member. Each panel member was tested with three lots of Alinity m HR HPV AMP Kit across three clinical sites, with one unique lot per site on five non-consecutive days. Each site

tested two runs per day and four replicates of each panel member per run on each of the five days. Each of the three clinical sites used different lots of Alinity m HR HPV CTRL Kits and Alinity m Sample Prep Kit 1. A summary of the reproducibility panel members and agreement rates, and analysis of cycle number (CN) variability are presented in Table 15 and Table 16 for the ThinPrep panel and Table 17 and Table 18 for the SurePath panel.

Table 15. Summary of Reproducibility Study Panel Members, Median CN, and Agreement Rates: ThinPrep

Panel Composition	Panel Description	No. Valid[a]	Median (CN)[b]	%Positive (n/N)[c]	% Negative, HPV amplified (n/N)	% Negative, HPV not amplified (n/N)
Pooled negative clinical sample	Negative	119	NA	0.0 (0/119)	0.0 (0/119)	100.0 (119/119)
HPV negative cell line	Negative	119	NA	0.0 (0/119)	0.0 (0/119)	100.0 (119/119)
HPV16 positive SiHa cell line	HPV16 high negative	118	33.03	50.0 (59/118)	18.6 (22/118)	31.4 (37/118)
HPV18 positive HeLa cell line	HPV18 high negative	117	36.00	10.3 (12/117)	1.7 (2/117)	88.0 (103/117)
HPV45 plasmid	HPV45 high negative	120	32.17	36.7 (44/120)	59.2 (71/120)	4.2 (5/120)
Other HR HPV Plasmid A [d]	Other HR HPV A high negative	119	36.00	18.5 (22/119)	22.7 (27/119)	58.8 (70/119)
Other HR HPV Plasmid B [e]	Other HR HPV B high negative	111	32.66	24.3 (27/111)	36.9 (41/111)	38.7 (43/111)
Pooled clinical sample	HPV 16 moderate positive	119	27.72	100.0 (119/119)	0.0 (0/119)	0.0 (0/119)
	HPV 18 moderate positive	119	28.28	98.3 (117/119)	0.0 (0/119)	1.7 (2/119)
	HPV 45 moderate positive	120	28.40	98.3 (118/120)	0.0 (0/120)	1.7 (2/120)
	Other HR HPV A moderate positive	119	28.02	98.3 (117/119)	0.0 (0/119)	1.7 (2/119)
	Other HR HPV B moderate positive	118	26.95	100.0 (118/118)	0.0 (0/118)	0.0 (0/118)
HPV 16 positive SiHa cell line	HPV 16 low positive	118	29.41	100.0 (118/118)	0.0 (0/118)	0.0 (0/118)
	HPV 16 moderate positive	117	28.06	100.0 (117/117)	0.0 (0/117)	0.0 (0/117)
HPV 18 positive HeLa cell line	HPV 18 low positive	120	28.16	96.7 (116/120)	0.8 (1/120)	2.5 (3/120)
	HPV 18 moderate positive	119	27.28	100.0 (119/119)	0.0 (0/119)	0.0 (0/119)
HPV 45 plasmid	HPV 45 low positive	120	30.45	99.2 (119/120)	0.8 (1/120)	0.0 (0/120)
	HPV 45 moderate positive	116	29.89	100.0 (116/116)	0.0 (0/116)	0.0 (0/116)
Other HR HPV A Plasmid	Other HR HPV A low positive	119	30.31	100.0 (119/119)	0.0 (0/119)	0.0 (0/119)
	Other HR HPV A moderate positive	118	29.75	100.0 (118/118)	0.0 (0/118)	0.0 (0/118)
Other HR HPV B Plasmid	Other HR HPV B low positive	120	30.47	97.5 (117/120)	0.0 (0/120)	2.5 (3/120)
	Other HR HPV B moderate positive	119	28.73	99.2 (118/119)	0.0 (0/119)	0.8 (1/119)

[a] N is the number of valid replicates.

[b] The median CN value reported is calculated for all replicates measured in the negative and positive panel members, above and below the clinical cutoff. Negative replicates with no virus detected were assigned the last cycle of PCR (36.00). Due to 0% virus detection, median CN was not reported for negative panels (NA)

[c] The percent agreement is based on the number of valid replicates with a CN value below the clinical cutoff.

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 16. Variance Component Analysis Results for Reproducibility Study: ThinPrep

					Within-Run		Between-Run		Between-Day		Between Instrument/ Lot		Total[a]	
Panel	**Panel Description**	**N[b]**	**n[c]**	**Mean (CN)**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
Pooled Clinical Sample	HPV16	119	119	27.47	1.391	5.1	0.000	0.0	0.000	0.0	0.441	1.6	1.459	5.3
	HPV 18 moderate positive	119	117	27.82	1.464	5.3	0.624	2.2	0.184	0.7	0.000	0.0	1.602	5.8
	HPV 45 moderate positive	120	118	28.12	1.355	4.8	0.000	0.0	0.319	1.1	0.189	0.7	1.405	5.0
	Other HR HPV A moderate positive	119	117	27.42	1.506	5.5	0.000	0.0	0.569	2.1	0.115	0.4	1.614	5.9
	Other HR HPV B moderate positive	118	118	26.94	0.550	2.0	0.285	1.1	0.147	0.5	0.035	0.1	0.638	2.4
HPV16 positive SiHa cell line	HPV 16 low positive	118	118	29.43	0.525	1.8	0.155	0.5	0.177	0.6	0.210	0.7	0.612	2.1
	HPV 16 moderate positive	117	117	28.18	0.525	1.9	0.134	0.5	0.387	1.4	0.148	0.5	0.682	2.4
HPV18 positive HeLa cell line	HPV 18 low positive	120	116	28.24	0.892	3.2	0.000	0.0	0.000	0.0	0.308	1.1	0.944	3.3
	HPV 18 moderate positive	119	119	27.25	0.667	2.4	0.000	0.0	0.000	0.0	0.000	0.0	0.667	2.4
HPV45 plasmid	HPV 45 low positive	120	119	30.51	0.435	1.4	0.221	0.7	0.000	0.0	0.054	0.2	0.491	1.6
	HPV 45 moderate positive	116	116	29.90	0.357	1.2	0.065	0.2	0.311	1.0	0.000	0.0	0.478	1.6
Other HR HPV A plasmid [d]	Other HR HPV A low positive	119	119	30.35	0.380	1.3	0.194	0.6	0.124	0.4	0.000	0.0	0.444	1.5
	Other HR HPV A moderate positive	118	118	29.85	0.383	1.3	0.200	0.7	0.324	1.1	0.039	0.1	0.542	1.8
Other HR HPV B plasmid [e]	Other HR HPV B low positive	120	117	30.46	0.391	1.3	0.122	0.4	0.184	0.6	0.102	0.3	0.461	1.5
	Other HR HPV B moderate positive	119	118	28.77	0.376	1.3	0.215	0.7	0.184	0.6	0.149	0.5	0.494	1.7

Because only positive, detected test results with CN values below the cutoff were included, estimates of SD (and % CV may be underestimated.

[a] N is the number of valid replicates.

[b] n is the number of valid replicates with a CN value below the clinical cutoff

[c] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument/Lot Components

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 17. Summary of Reproducibility Study Panel Members, Median CN, and Agreement Rates: SurePath

Panel Composition	Panel Description	No. Valid[a]	Median (CN)[b]	%Positive (n/N)[c]	% Negative, HPV amplified (n/N)	% Negative, HPV not amplified (n/N)
Pooled negative clinical sample	Negative	119	NA	0.0 (0/119)	0.0 (0/119)	100.0 (119/119)
HPV negative cell line	Negative	119	NA	0.0 (0/119)	0.0 (0/119)	100.0 (119/119)
HPV16 positive SiHa cell line	HPV16 high negative	119	36.00	20.2 (24/119)	0.8 (1/119)	79.0 (94/119)
HPV18 positive HeLa cell line	HPV18 high negative	118	36.00	25.4 (30/118)	0.0 (0/118)	74.6 (88/119)
Pooled clinical sample	HPV 16 moderate positive	119	28.52	100.0 (119/119)	0.0 (0/119)	0.0 (0/119)
	HPV 18 moderate positive	117	27.20	99.1 (116/117)	0.9 (1/117)	0.0 (0/117)
	HPV 45 moderate positive	119	28.11	100.0 (119/119)	0.0 (0/119)	0.0 (0/119)
	Other HR HPV A moderate positive [d]	118	27.46	99.2 (117/118)	0.0 (0/118)	0.8 (1/118)
	Other HR HPV B moderate positive [e]	118	28.26	99.2 (117/118)	0.0 (0/118)	0.8 (1/118)
HPV 16 positive SiHa cell line	HPV 16 low positive	120	29.57	100.0 (120/120)	0.0 (0/120)	0.0 (0/120)
	HPV 16 moderate positive	118	27.98	100.0 (118/118)	0.0 (0/118)	0.0 (0/118)
HPV 18 positive HeLa cell line	HPV 18 low positive	118	27.91	98.3 (116/118)	0.0 (0/118)	1.7 (2/118)
	HPV 18 moderate positive	119	26.54	100.0 (119/119)	0.0 (0/119)	0.0 (0/119)

[a] N is the number of valid replicates.

[b] The median CN value reported is calculated for all replicates measured in the negative and positive panel members, above and below the clinical cutoff.

[c] The percent agreement is based on the number of valid replicates with a CN value below the clinical cutoff.

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

Table 18. Variance Component Analysis Results for Reproducibility Study: SurePath

					Within-Run		Between-Run		Between-Day		Between Instrument /Lot		Total[a]	
Panel	**Panel Description**	**N[b]**	**n[c]**	**Mean (CN)**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**	**SD**	**% CV**
Pooled Clinical Sample	HPV16	119	119	28.44	0.889	3.1	0.000	0.0	0.054	0.2	0.189	0.7	0.911	3.2
	HPV 18 moderate positive	117	116	27.49	1.265	4.6	0.000	0.0	0.256	0.9	0.303	1.1	1.326	4.8
	HPV 45 moderate positive	119	119	28.05	0.785	2.8	0.265	0.9	0.000	0.0	0.181	0.6	0.848	3.0
	Other HR HPV A moderate positive [d]	118	117	27.28	1.110	4.1	0.287	1.1	0.000	0.0	0.045	0.2	1.148	4.2
	Other HR HPV B moderate positive [e]	118	117	28.14	1.102	3.9	0.000	0.0	0.371	1.3	0.542	1.9	1.283	4.6
HPV16 positive SiHa cell line	HPV 16 low positive	120	120	29.62	0.592	2.0	0.000	0.0	0.077	0.3	0.156	0.5	0.617	2.1
	HPV 16 moderate positive	118	118	28.02	0.439	1.6	0.025	0.1	0.121	0.4	0.051	0.2	0.458	1.6
HPV18 positive HeLa cell line	HPV 18 low positive	118	116	28.06	0.888	3.2	0.000	0.0	0.059	0.2	0.321	1.1	0.946	3.4
	HPV 18 moderate positive	119	119	26.57	0.636	2.4	0.000	0.0	0.000	0.0	0.066	0.2	0.640	2.4

Because only positive, detected test results with CN values below the cutoff were included, estimates of SD (and % CV may be underestimated.

[a] N is the number of valid replicates.

[b] n is the number of valid replicates with a CN value below the clinical cutoff

[c] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument/Lot Components

[d] HPV 58 was used for the Other HR HPV A panel.

[e] HPV 39 was used for the Other HR HPV B panel.

7. Alinity m System Carryover

Carryover studies were conducted to stress two areas of potential carryover on the Alinity m System: Sample Preparation and the AMP TRAY 1. Carryover rates were determined for each by testing alternating replicates of HR HPV high positive samples and HR HPV negative samples across multiple runs. The HR HPV high positive sample was prepared with HPV 16 at 6.9 x107 copies/ml.

The highest potential for carryover was determined to be at the Sample Preparation stage. Of 480 negative samples tested adjacent to high positive samples during sample preparation, 4 samples were detected, resulting in an overall carryover rate of 0.83% (4/480) and 95% confidence interval (CI) ranging from 0.32% to 2.12%.

8. Upstream Cytology Processor Carryover

The potential for sample carryover from upstream cytology processing systems when testing residual cytology samples with the Alinity m HR HPV assay was evaluated by processing alternating replicates of HPV high-positive samples and HPV negative samples on each of 3 systems: the ThinPrep 2000, ThinPrep 5000, and the BD PrepMate, followed by testing of the negative HPV samples on the Alinity m System. For each of the systems, the carryover rate was 0.0% (0 detected out of 120 valid HR HPV negative samples) with an upper bound of the two-sided 95% CI of 3.1%.

9. Reagent Stability

Expiration dating for the Alinity m HR HPV reagents has been established at 15 months for the Alinity m HR HPV AMP Kit stored at 2°C to 8°C and for the Alinity m HR HPV CTRL Kit stored at –25°C to –15°C. The shelf lives of the Alinity m HR HPV reagents were established in a real-time stability study.

10. Specimen Stability

Specimen stability studies demonstrated that when testing with Alinity m HR HPV, cervical specimens can be stored in ThinPrep at -20°C, 2-8 °C, and 15-30°C for up 6 months from the date of collection. Cervical specimens stored in SurePath can be stored at -20°C and 2-8°C for up to 3 months and at 15-30°C for up to 14 days from the date of collection. The observed changes in CN value between baseline and the different storage conditions did not change any reported results

B. Animal Studies

N/A

C. Additional Studies

N/A

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of HR HPV testing with Alinity m HR HPV for detection of HPV DNA in cervical specimens collected by a health care professional using an endocervical brush/spatula placed in ThinPrep PreservCyt Solution (ThinPrep) or an endocervical broom placed in SurePath Preservative Fluid (SurePath) 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

A prospective, multi-center clinical study was conducted and recruited 14,935 women ≥ 25 years across 96 collection sites throughout the US. The study included patients undergoing routine cervical cancer screening (Screening

population) and was supplemented with individuals referred for colposcopy follow-up based on previous cervical cancer screening that included HR HPV testing (Enriched population). A total of 14,702 (11,636 Screening and 3,066 Enriched) women were eligible to participate in the study. Eligible patients were treated between February 16, 2021, and June 16, 2022. Alinity m HR HPV testing was performed at four clinical testing sites within these dates.

A detailed description of the two populations (Screening and Enriched), the inclusion/exclusion criteria used to determine patient eligibility, and an account of the specimens collected and tested for either population is detailed below. Patients with valid HR HPV testing (Alinity m HR HPV and FDA approved tests) and final disease diagnosis results, used to assess the clinical performance of Alinity m HR HPV in either population, is further detailed in Subsection B. below entitled, "Accountability of PMA Cohort."

Screening Population

The collection sites served populations at low to high risks for HPV infection and included but were not limited to health clinics, OB/GYN practices, health integrated site networks/health systems, private practice and research centers, and universities and academic centers. All women in the Screening population had cervical specimens collected using an endocervical brush/spatula placed in ThinPrep PreservCyt Solution (ThinPrep). Approximately 80% of the women also had cervical specimens collected using a cervical broom-like collection device placed in SurePath Preservative Fluid (SurePath). When both cervical specimens were collected, the collection order was randomized to ensure that approximately half of the women had ThinPrep collected first, and the other half had SurePath collected first.

In the Screening population, specimens collected as the first (or only) specimen were used for cytology testing also. Cytology slides generated using ThinPrep cytology processors (ThinPrep 2000 (TP 2000), ThinPrep 5000 (TP 5000)), and SurePath cytology processors (SurePath PrepMate/PrepStain Systems) were diagnosed using the 2014 Bethesda System[1].

All specimens collected were tested for HPV infection by Alinity m HR HPV and an FDA approved HPV test performed according to manufacturer's instructions. Cytology results and up to four HPV results (from both the Alinity m HR HPV and the FDA approved HPV testing performed on both ThinPrep and SurePath specimens) were utilized to inform referral to colposcopy (see Follow-up Schedule). Women in the Screening population with ≥ ASC-US cytology, regardless of HPV test results, or with any cytology result and a positive HPV status (in at least one of four test results) were referred to colposcopy. Those with a NILM (Negative for Intraepithelial Lesion Malignancy) cytology and negative or undetermined HPV, or negative HPV and UNSAT (Unsatisfactory) or unavailable cytology, were not referred to colposcopy. All cytology and specimen testing with an FDA approved HPV test were performed at a reference laboratory and used for routine clinical management. A randomly selected subset of

specimens was sent for NGS at a reference laboratory to support Alinity m HR HPV genotyping performance.

Enriched population
Women referred for colposcopy follow-up based on previous cervical cancer screening that included HR HPV testing represented the Enriched population. All women in the Enriched population had both ThinPrep and SurePath specimens collected and were tested by both the Alinity m HR HPV assay and the FDA approved HPV test using non-cytology aliquots. All women in the Enriched population underwent colposcopy procedures (see Follow-up Schedule). All cytology and HPV testing by another FDA approved HPV test were performed at a reference laboratory and used for routine clinical management.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Alinity m HR HPV study was limited to patients who met the following inclusion criteria for the Screening and Enriched populations, respectively.

   Screening population inclusion criteria:
   Individuals were **eligible** if she met all the following criteria:
   - Is 25 years of age or older
   - Is attending a participating clinic for routine cervical cancer screening following screening guidelines
   - Has an intact cervix
   - Is willing and able to provide documented informed consent
   - Is willing and able to undergo colposcopy, biopsy, and endocervical curettage (ECC) within 12 weeks (≤ 84 days) from the baseline visit (if required)
   - Is willing and able to allow collection of two cervical cytology specimens

   Enriched population inclusion criteria:
   Individuals were **eligible** if she met all the following criteria:
   - Is willing and able to provide documented informed consent (or her legal representative is willing and able)
   - Is 25 years of age or older
   - Has had a colposcopy referral in which routine cervical cancer screening has included HR HPV testing (HPV primary screening, co-testing, or ASC-US cytology triage) performed within 12 weeks preceding the colposcopy visit
   - Has an intact cervix
   - Is willing and able to undergo colposcopy, biopsy, and endocervical curettage (ECC)
   - Is willing and able to allow collection of two cervical cytology specimens

Patients were not permitted to enroll in the Alinity m HR HPV study if they met any of the following exclusion criteria as it pertained to the Screening and Enriched populations:

Screening population exclusion criteria:

An individual was **ineligible** for the study if she met any of the following criteria:

- Is pregnant at the time of visit or plans to become pregnant within the following 12 weeks
- Has any known medical condition that, in the opinion of the investigator, would result in increased risk of bleeding at biopsy
- Has a known history of excisional or ablative therapy (e.g., LEEP [Loop Electrosurgical Excision Procedure], cone biopsy, cervical laser surgery, or cryotherapy) to the cervix in the last 12 months prior to the baseline visit
- Had a cervical cytology specimen collected within the last 4 months
- Is currently participating in any diagnostic trial for cervical cancer
- Had a complete or partial hysterectomy, either supra cervical or involving removal of the cervix
- Is currently participating or planning to participate in any clinical trial for HPV treatment (for the duration of this study)
- Previous participation in this study (in the Screening/Enriched population)

Enriched population exclusion criteria:

An individual was **ineligible** for the study if she met any of the following criteria:

- Is pregnant when presenting for colposcopy
- Has any known medical condition that, in the opinion of the investigator, would result in increased risk of bleeding at biopsy
- Has a known history of excisional or ablative therapy (e.g., LEEP, cone biopsy, cervical laser surgery, or cryotherapy) to the cervix in the last 12 months prior to the colposcopy visit
- Is currently participating in any diagnostic trial for cervical cancer
- Had a complete or partial hysterectomy, either supracervical or involving removal of the cervix
- Is currently participating or planning to participate in any clinical trial for HPV treatment (for the duration of this study)
- Is referred to colposcopy based on a cytology-only screening program
- HR HPV referral test is known to be the same FDA approved test used to assess clinical performance
- Previous participation in this study.

2. Follow-up Schedule

   Colposcopy procedures were conducted in the Screening and Enriched populations according to a standardized protocol: 1) an endocervical curettage was performed for all participants; 2) biopsies were obtained on all visible lesions, and 3) a single random biopsy of the visualized or partially visualized

squamocolumnar junction was obtained if no lesion was visible. In addition, during the colposcopy visit, loop electrosurgical excision procedure (LEEP) was performed when required by the standard of care. To avoid potential bias, study participants and colposcopists were blinded to HPV test results until colposcopy was completed. Cytology results were made available to colposcopists prior to colposcopy.

All tissue biopsies were examined by a Central Pathology Review Panel (CPRP) consisting of three expert pathologists. Discordant results were adjudicated according to a pre-defined standardized protocol. The CPRP was masked to patient information, including cytology, HPV results, and previous diagnoses. The slides prepared from the tissue biopsies were stained using conventional hematoxylin and eosin (H&E) staining, and with p16 IHC (immunohistochemistry) staining where applicable. For all tissue biopsies, the expert pathologists evaluated H&E slides to establish an H&E histologic diagnosis. When a tissue biopsy case met LAST (Lower Anogenital Squamous Terminology) Workshop guidelines, the expert pathologists evaluated both p16 and H&E slides for that tissue biopsy to establish a p16/H&E histologic diagnosis. The final CPRP histologic results for the biopsies meeting the LAST guidelines were defined by the p16/H&E histologic diagnosis. The final CPRP histologic results for the biopsies not meeting the LAST guidelines were defined by the H&E histologic diagnosis. After the slides from all collected tissues were reviewed for a woman, the disease status for the woman was determined based on the most severe histologic result across all tissues collected (≥ cervical intraepithelial neoplasia 3 [CIN3], CIN2, or ≤ CIN1). Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, as an in vitro diagnostic test, the Alinity m HR HPV assay is performed on cervical cells collected during routine pelvic exam (i.e., cervical cytology) using an endocervical brush/spatula or broom. The test, therefore, does not present any more safety hazard to an individual being tested than other tests where cervical cells are sampled in this manner (i.e., cervical cytology).

With regards to effectiveness, the clinical performance of the Alinity m HR HPV assay was evaluated against CPRP determined histologic diagnosis, with ≥CIN2 and ≥CIN3 as the disease endpoints in both the Screening and Enriched populations.

Clinical performance of the Alinity m HR HPV device in this study was evaluated by comparing the ratio of clinical sensitivity and the false positivity rate (FPR) between the Alinity test and a FDA approved test. These ratios were evaluated in both specimen matrices (ThinPrep and SurePath) and in both populations (Screening and Enriched) against the disease endpoints listed above.

B. Accountability of PMA Cohort

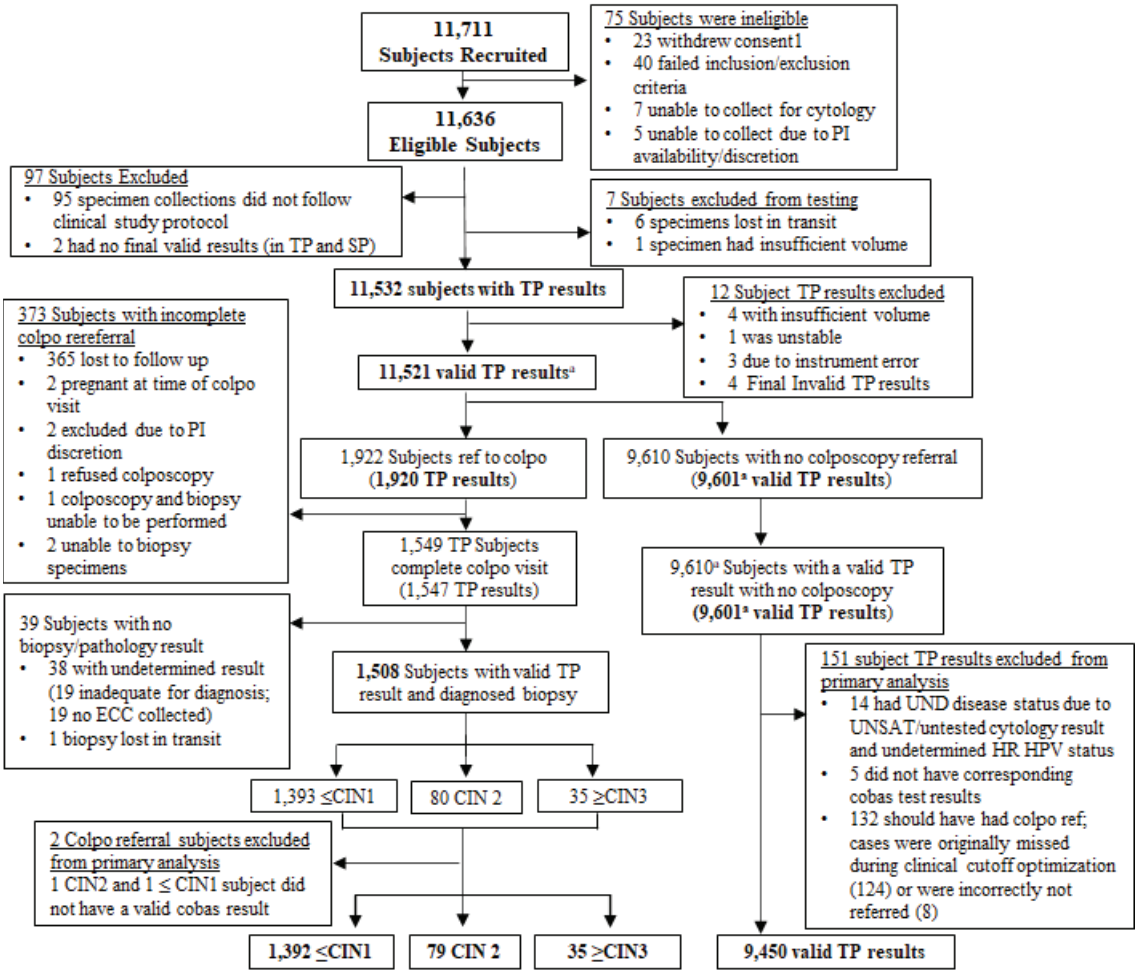
A total of 14,935 patients were recruited of which 14,702 (11,636 from the Screening population and 3,066 from the Enriched population) were eligible and enrolled in the PMA study. In the Screening population, 11,532 patients had valid HR HPV (Alinity and FDA approved) test and cytology results to determine colposcopy referral. In the Enriched population, 3,059 patients had patients had valid HR HPV (Alinity and FDA approved) test and cytology results.

Patient accountability, including the final number of subjects with a valid HR HPV test results (for Alinity and FDA approved tests) and CPRP diagnosis of the collected biopsy, for either matrix (ThinPrep and SurePath) and study population (Screening and Enriched), are presented in Figures 1 through 4 below. The final number of subjects used for the primary analysis (i.e., clinical sensitivity and FPR) are also indicated in the figures below.

Screening Population Accountability

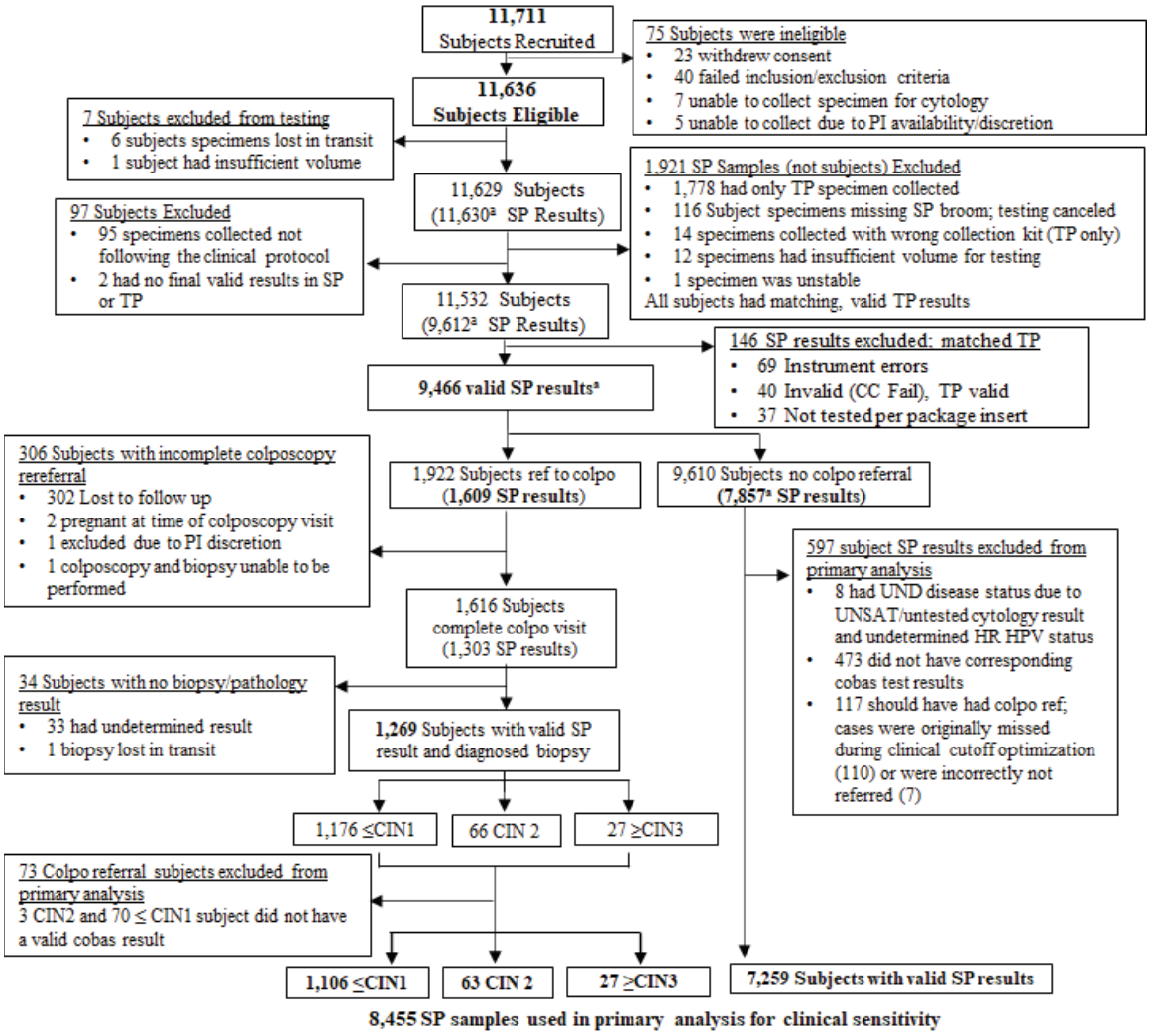
In the Screening population, 11,532 subjects had a valid HR HPV testing and cytology result to determine a colposcopy referral. A total of 11,521 valid ThinPrep results and 9,466 valid SurePath results were generated for these 11,532 women. Of 11,532 subjects, a total of 1,922 (16.7%) were referred to colposcopy based on cytology and/or HR-HPV status of their ThinPrep or SurePath specimen, while the remaining 9,610 subjects exited the study. Among the population who completed colposcopy and had successful biopsy diagnosis, 1,508 subjects had a valid ThinPrep result (35 ≥ CIN3, 80 CIN2, and 1,393 ≤CIN1) and, separately, 1,269 subjects had a valid SurePath result (27 ≥ CIN3, 66 CIN2, and 1,176 ≤CIN1). The Alinity clinical sensitivity and FPR (primary analysis) in the Screening population was determined using 10,956 patient ThinPrep and 8,455 patient SurePath results.

Figure 1. Subject and result accountability for ThinPrep Screening population samples



[a]1 subject in the Screening population had two cervixes; Four cervical swabs were collected (two stored in ThinPrep and two stored in SurePath). TP=ThinPrep and SP=SurePath, UND= Undetermined; UNSAT= Unsatisfactory

Figure 2. Subject and result accountability for SurePath Screening population samples

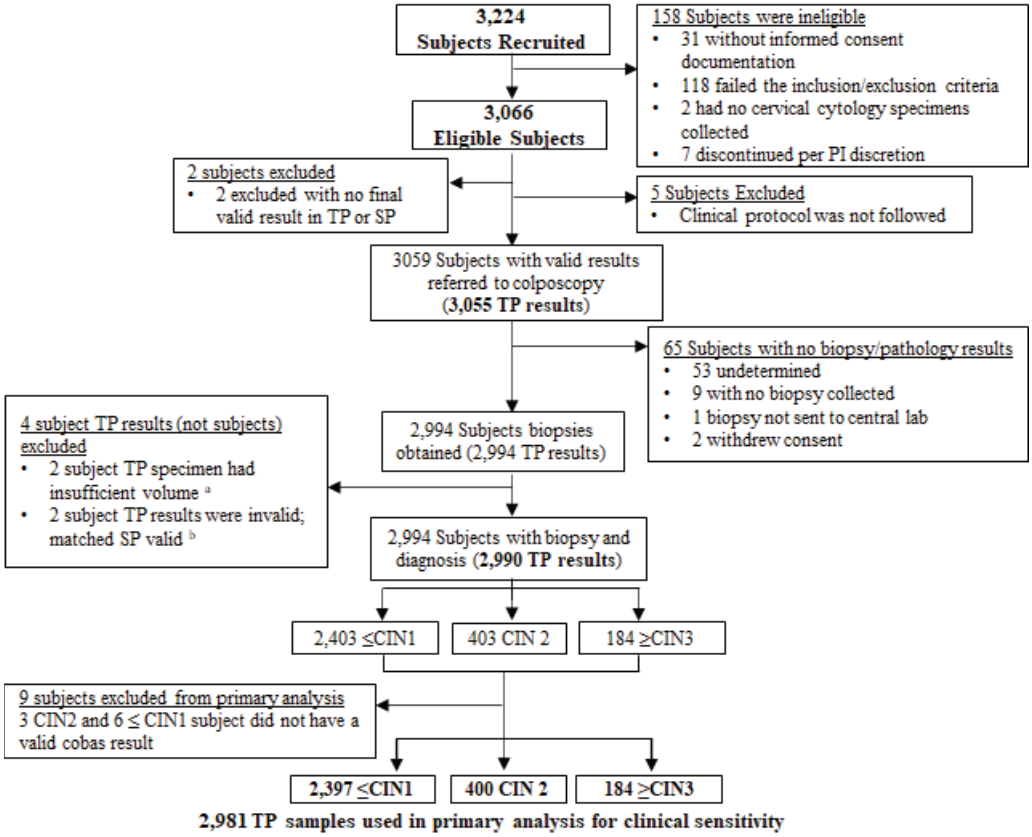


[a] 1 subject in the Screening population had two cervixes; Four cervical swabs were collected (two stored in ThinPrep and two stored in SurePath). TP=ThinPrep, SP=SurePath, UND= Undetermined; UNSAT= Unsatisfactory

Enriched Population Accountability

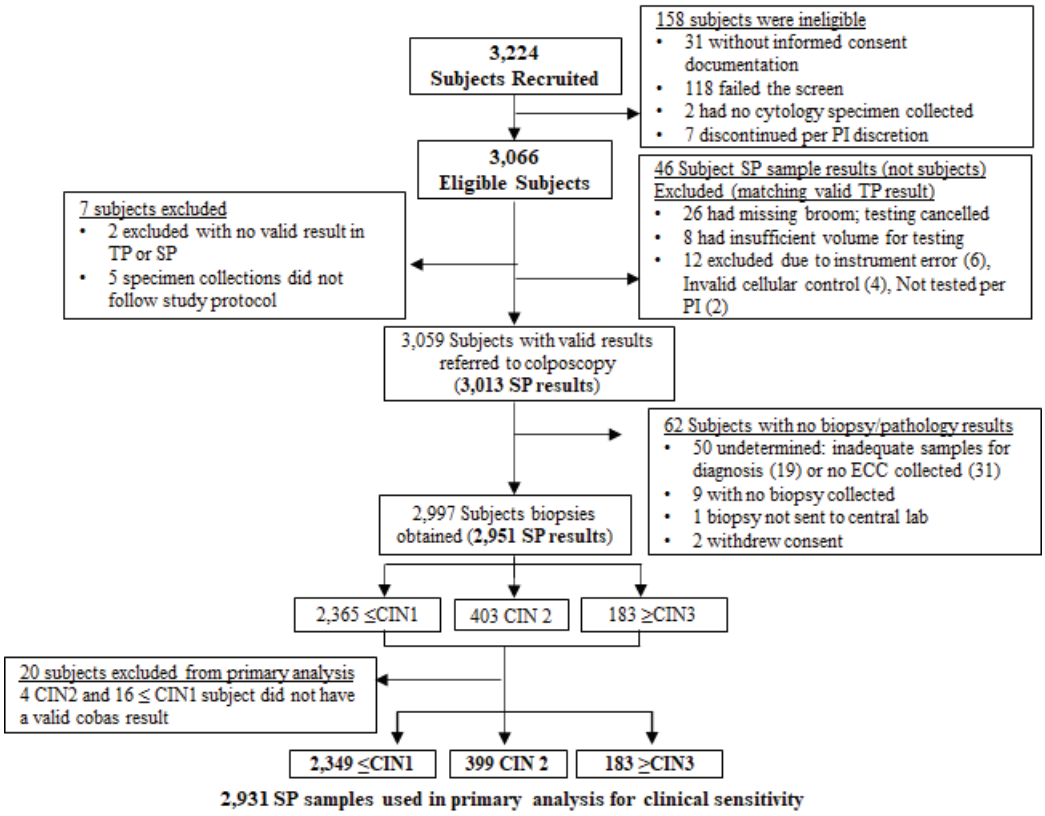
In the Enriched population, 3,059 subjects had a valid HR HPV testing (3,055 valid ThinPrep results and, separately, 3,013 SurePath results) and cytology result. Among the population who completed colposcopy and had successful biopsy diagnosis, 2,990 subjects had a valid ThinPrep result (184 ≥ CIN3, 403 CIN2, and 2,403 ≤CIN1) and, separately, 2,951 subjects had a valid SurePath result (183 ≥ CIN3, 403 CIN2, and 2,361 ≤CIN1). Alinity clinical sensitivity (primary analysis) in the Enriched population was determined in 2,981 patient ThinPrep and 2,931 patient SurePath results.

Figure 3. Subject and result accountability for ThinPrep Enriched population



TP = ThinPrep, SP= SurePath

Figure 4. Subject and result accountability for SurePath Enriched population



TP = ThinPrep, SP= SurePath

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical study performed in the US for a HPV molecular test.

In the Screening population, the median age of the women was 41 years, with 13.4% in age group 25-29 years, 30.9% in age group 30-39 years, and 55.7% in age group ≥ 40 years. In the Enriched population, the median age of the women was 37 years, with 18.9% in age group 25-29 years, 39.5% in age group 30-39 years, and 41.5% in age group ≥ 40 years.

The demographics of the study population (age, age group, HPV vaccination status, ethnicity, and race) for Screening and Enriched populations, is shown in Table 19 and Table 20.

Table 19. Demographic Characteristics Statistics	
Screening Population	
Age (years)	(N=11532)

Table 20. Demographic Characteristics Statistics	
Enriched Population	
Age (years)	(N=3059)

Table 19. Demographic Characteristics Statistics	
n	11532
Mean	43
Median	41
Minimum	25
Maximum	85
Age Group	**n (%)**
25-29	1548 (13.4)
30-39	3562 (30.9)
>=40	6422 (55.7)
Vaccination Status	**n (%)**
Has been vaccinated	1541 (13.4)
Never been vaccinated	9135 (79.2)
Unknown	856 (7.4)
Ethnicity	**n (%)**
Hispanic or Latino	1901 (16.5)
Not Hispanic or Latino	9190 (79.7)
Not Reported	441 (3.8)
Race	**n (%)**
White	8537 (74.0)
Black or African American	2369 (20.5)
Asian	233 (2.0)
American Indian or Alaska Native	35 (0.3)
Native Hawaiian or Other Pacific Islander	28 (0.2)
Other	72 (0.6)
Not Reported	258 (2.2)

Table 20. Demographic Characteristics Statistics	
n	3059
Mean	39
Median	37
Minimum	25
Maximum	81
Age Group	**n (%)**
25-29	579 (18.9)
30-39	1209 (39.5)
>=40	1271 (41.5)
Vaccination Status	**n (%)**
Has been vaccinated	606 (19.8)
Never been vaccinated	2238 (73.2)
Unknown	215 (7.0)
Ethnicity	**n (%)**
Hispanic or Latino	827 (27.0)
Not Hispanic or Latino	2161 (70.6)
Not Reported	71 (2.3)
Race	**n (%)**
White	2326 (76.0)
Black or African American	503 (16.4)
Asian	77 (2.5)
American Indian or Alaska Native	13 (0.4)
Native Hawaiian or Other Pacific Islander	6 (0.2)
Other	26 (0.8)
Not Reported	108 (3.5)

Table 21 shows the HPV positivity rate for the Alinity m HR HPV assay by specimen type and testing site in the Screening population. In the screening population the overall HPV positivity rate was 11.0% for ThinPrep samples and 11.5% for SurePath samples.

Table 21. HPV Positivity Rate for the Alinity m HR HPV Assay by Specimen Type, and Testing Site

Specimen Type	**Testing Site**	**Alinity m HR HPV Positivity Rate (n/N)**
		Screening
ThinPrep	1	10.6% (260/2442)
	2	10.8% (501/4643)

Table 21. HPV Positivity Rate for the Alinity m HR HPV Assay by Specimen Type, and Testing Site

Specimen Type	Testing Site	Alinity m HR HPV Positivity Rate (n/N)
		Screening
	3	11.7% (280/2397)
	4	11.1% (226/2039)
	Total	11.0% (1267/11521)
SurePath	1	11.4% (187/1639)
	2	11.1% (382/3449)
	3	11.6% (263/2261)
	4	12.2% (258/2117)
	Total	11.5% (1090/9466)

Table 22 shows HPV positivity rate for the Alinity m HR HPV assay by specimen type and age group in the Screening population. HPV positivity rate decreases with age when tested with either ThinPrep or SurePath.

Table 22. Summary of HPV Positivity Rate for the Alinity m HR HPV Assay by Specimen Type, and Age Group

Specimen Type	Age Group	Alinity m HR HPV Positivity Rate (n/N)
		Screening
ThinPrep	25-29	18.2% (281/1546)
	30-39	12.8% (454/3558)
	≥40	8.3% (532/6417)
	Total	11.0% (1267/11521)
SurePath	25-29	18.1% (236/1303)
	30-39	12.8% (373/2907)
	≥40	9.2% (481/5256)
	Total	11.5% (1090/9466)

The Alinity m HR HPV assay results for genotype/genotype groups stratified by specimen type and age group is outlined in Table 23 for the Screening population.

Table 23. The Alinity m HR HPV Assay Result by Specimen Type and Age Group for the Screening Population

Specimen Type	Age Group	HPV 16+ (n/N)	HPV 18+ (n/N)	HPV 45+ (n/N)	Other HR HPV A + (n/N)	Other HR HPV B + (n/N)	HPV Negative (n/N)
ThinPrep	25-29	1.2% (18/1546)	0.3% (5/1546)	1.4% (21/1546)	5.8% (89/1546)	11.7% (181/1546)	81.8% (1265/1546)
	30-39	1.3% (46/3558)	0.9% (31/3558)	1.2% (42/3558)	4.6% (163/3558)	6.3% (225/3558)	87.2% (3104/3558)
	≥40	1.1% (68/6417)	0.6% (40/6417)	0.7% (45/6417)	2.6% (167/6417)	4.1% (263/6417)	91.7% (5885/6417)
	Total	1.1% (132/11521)	0.7% (76/11521)	0.9% (108/11521)	3.6% (419/11521)	5.8% (669/11521)	89.0% (10254/11521)
SurePath	25-29	1.3% (17/1303)	0.2% (3/1303)	1.5% (20/1303)	5.4% (70/1303)	11.6% (151/1303)	81.9% (1067/1303)
	30-39	1.2% (36/2907)	1.0% (30/2907)	1.1% (33/2907)	4.7% (137/2907)	6.1% (178/2907)	87.2% (2534/2907)
	≥40	1.2% (61/5256)	0.6% (31/5256)	0.8% (43/5256)	2.9% (152/5256)	4.7% (247/5256)	90.8% (4775/5256)
	Total	1.2% (114/9466)	0.7% (64/9466)	1.0% (96/9466)	3.8% (359/9466)	6.1% (576/9466)	88.5% (8376/9466)

The Other HR HPV B positive result was the most frequent HR HPV detected in the overall population and within each age group and is followed by the Other HR HPV A positive result, based on the results in ThinPrep and SurePath specimen types. Among the individual genotypes reported, HPV16 was the most common positive result reported overall in both specimen types.

Alinity m HR HPV Assay Results by Cytology Result
Screening Population

Cytology results are reported for the intended use population only (Screening population). Specimens collected as the first (or only) specimen were also used for cytology testing. ThinPrep specimens were processed for cytology using the ThinPrep 2000 (TP 2000) or ThinPrep 5000 (TP 5000), and SurePath specimens were processed using the BD PrepMate/ PrepStain. ThinPrep specimens were randomized to ensure that approximately half were processed with TP 2000, and the remaining half with TP 5000. The slides generated from TP 2000, TP 5000 and PrepMate/PrepStain Systems were diagnosed using the 2014 Bethesda System[1].

A summary of Alinity m HR HPV results by cytology for the Screening population is shown in Table 24 and 25 for ThinPrep and SurePath, respectively. When cytology was UNSAT or not done and HPV status was undetermined (due to missing HPV result(s)), the disease status was considered undetermined. Women with NILM (normal) cytology and/or negative HPV status (all HPV results were negative) were also considered undetermined for disease status.

Table 24. The Alinity m HR HPV Assay Results by Cytology Result for Screening Population – ThinPrep

Alinity m HR HPV Result[a]	Cytology Result				
	>ASC-US	ASC-US	Normal[b]	UNSAT/ Unknown	Total
HPV 16	22	11	96	3	132
HPV 18	11	14	49	2	76
HPV 45	11	11	81	5	108
Other HR HPV A	48	56	305	10	419
Other HR HPV B	99	78	480	12	669
Negative	95	388	9500	271	10254

[a] Detection of more than 1 HR HPV genotype/genotype group is counted separately.

[b] Subjects with cytology result as NILM and "Other: Endometrial cells (in women aged ≥ 45 years)" are included in Normal Category.

Table 25. The Alinity m HR HPV Assay Results by Cytology Result for Screening Population – SurePath

Alinity m HR HPV Result[a]	Cytology Result				
	>ASC-US	ASC-US	Normal[b]	UNSAT/ Unknown	Total
HPV 16	21	8	84	1	114
HPV 18	7	12	45	0	64
HPV 45	9	10	73	4	96
Other HR HPV A	37	46	269	7	359
Other HR HPV B	79	68	423	6	576
Negative	82	306	7831	157	8376

[a] Detection of more than 1 HR HPV genotype/genotype group is counted separately.

[b] Subjects with cytology result as NILM and "Other: Endometrial cells (in women aged ≥ 45 years)" are included in Normal Category.

Enriched Population

For women in the Enriched population, specimens collected were tested by both the Alinity m HR HPV assay and another FDA approved HPV test using non-cytology aliquots. All women in the Enriched population underwent colposcopy

procedures. All cytology and HPV testing by the FDA approved HPV test were performed at a reference laboratory.

D. Safety and Effectiveness Results

1. Safety Results

   The Alinity m HR HPV assay involves cervical cells using an endocervical brush/spatula placed in ThinPrep PreservCyt Solution or using a cervical broom-like collection device placed in SurePath Preservative Fluid. The Alinity m HR HPV 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 or HPV testing).

   Adverse effects that occurred in the PMA clinical study:

   There were no adverse events reported attributed to the Alinity m HR HPV assay. All study related adverse events were reported. During the clinical study, only seven adverse events were reported that were related to the clinical study protocol. One event was related to the colposcopy procedure, where the patient had unanticipated hemorrhage requiring intervention but not hospitalization. An additional six adverse events were related to study participation [two vasovagal syncope, one vasovagal reaction, one vaginal bleeding, one endometriosis flare-up, one incidental expulsion of IUD (Intrauterine Device)]. None of these events impacted patient management, clinical safety, or clinical performance assessment of the Alinity m HR HPV assay. Seven additional events were determined not to be related to colposcopy [one subject experienced two adverse events was hospitalized with pneumonia and urinary tract infection, one was hospitalized for Systemic Inflammatory Response Syndrome; one subject died from a suspected drug overdose] or study participation [one subject had a seizure; one had a urinary tract infection; one had *Trichomonas vaginalis* infection]. Of these events, only the urinary tract infection and *Trichomonas vaginalis* infection needed to be treated.

2. Effectiveness Results

   Analysis of effectiveness was based on data in the following sections. The clinical performance data in this section is based on the ratio of clinical sensitivity and false positivity rate (FPR) detected between Alinity m HR HPV and the FDA approved device among histologically based disease cases. Alinity m HR HPV genotyping performance (reported as HPV16, 18, 45, Other HR HPV A and Other HR HPV B) is based on the percent agreements between the reported Alinity genotype result and the NGS DNA result.

   The results of the clinical study demonstrate that Alinity m HR HPV is acceptable for its intended use to detect Human Papillomavirus DNA in cervical specimens collected by a health care professional using an endocervical brush/spatula placed in ThinPrep or an endocervical broom placed into SurePath Preservative Fluid

and identify high-risk (HR) HPV types 16, 18, 45, while reporting the concurrent detection of the other HR genotypes (31/33/52/58) and (35/39/51/56/59/66/68).

Alinity m HR HPV may be used in routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (adjunctive screening) with cytology, and HPV primary screening of women to assess the risk for cervical pre-cancer and cancer.

Alinity m HR HPV Assay Performance for ≥CIN3 and ≥CIN2 Clinical Endpoints

The clinical performance was evaluated for the Screening and Enriched populations separately for ≥CIN3 and ≥CIN2 clinical endpoints. For the ≥ CIN3 endpoint, the disease positive women included those with either CIN3 or Cancer; the disease negative women (<CIN3) included those with histologic result categories of either negative, CIN1, or CIN2. For the ≥ CIN2 endpoint, the disease positive women included those with either CIN2, CIN3, or Cancer; the disease negative (<CIN2) women included those with histologic result categories of either negative or CIN1.

A positive test result is defined as HR HPV positive on the Alinity (reporting either HPV16, 18, HPV 45, Group A, or Group B) and/or the FDA approved HPV test (reported as HPV16, 18, or 12 Other). In the tables below the clinical sensitivity and FPR ratios between the Alinity and the FDA approved test are evaluated for the following HR HPV genotype results: HPV16/18 (combined), 12 Other HR HPV (include all those genotypes other than HPV16/18), and Negative (Neg).

<u>Alinity m HR HPV Assay performance in the Screening population</u>
In the Screening population, clinical sensitivity and the FPR were calculated for women who had valid cytology results, Alinity and FDA approved test results, and histology diagnosis (among the women sent to colposcopy). The performance of the Alinity m HR HPV assay was assessed based on the ratio of clinical sensitivity and the ratio of FPR between Alinity m HR HPV and the FDA approved HPV test. These ratios were used for evaluation because of the study design wherein only women with a positive HPV status and/or a cytology result of ≥ASC-US were referred to colposcopy and evaluated for both ≥ CIN3 and ≥ CIN2 clinical endpoints. Women who were HPV negative (by both tests and for all collected specimens tested) and did not have abnormal cytology results were not referred for colposcopy and did not undergo histological evaluation for possible disease (i.e., missed disease cases). Thus, it is not possible to calculate absolute sensitivity and specificity for the device. The two-sided 95% confidence intervals for the ratio of sensitivities and the ratio of false positive rates were also calculated.

The cross-tabulation of the Alinity and FDA approved tests against ≥CIN2 and ≥CIN3 disease endpoints, in both ThinPrep and SurePath matrices, are

present below for the Screening (Table 26 through 30) and Enriched (Table 31 through 35) populations

Table 26. HR HPV positive results reported by Alinity m and FDA approved test: ThinPrep Screening Population at ≥CIN2

		≥CIN2				<CIN2			
		FDA approved test				FDA approved test			
		HPV 16/18	12 Other	Negative	Total	HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	29	0	0	29	102	1	15	118
	12 Other	1	68	6	75	11	569	104	684
	Neg	1	2	7	10	11	87	9942	10040
	Total	31	70	13	114	124	657	10061	10842

Table 27. HR HPV positive results reported by Alinity m and FDA-approved test: ThinPrep Screening Population at ≥CIN3

		≥CIN3				<CIN3			
		FDA approved test				FDA approved test			
		HPV 16/18	12 Other	Negative	Total	HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	13	0	0	13	118	1	15	134
	12 Other	0	20	0	20	12	617	110	739
	Neg	0	0	2	2	12	89	9947	10048
	Total	13	20	2	35	142	707	10072	10921

Table 28. HR HPV positive results reported by Alinity m and FDA-approved test: SurePath Screening Population at ≥CIN2

		≥CIN2				<CIN2			
		FDA approved test				FDA approved test			
		HPV 16/18	12 Other	Negative	Total	HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	17	0	1	18	86	3	15	104
	12 Other	2	54	3	59	6	482	73	561
	Neg	1	3	9	13	8	114	7578	7700
	Total	20	57	13	90	100	599	7666	8365

Table 29. HR HPV positive results reported by Alinity m and FDA-approved test: SurePath Screening Population at ≥CIN3

		≥CIN3				<CIN3			
		FDA approved test				FDA approved test			
		HPV 16/18	12 Other	Negative	Total	HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	8	0	0	8	95	3	16	114
	12 Other	1	16	0	17	7	520	76	603
	Neg	0	0	2	2	9	117	7585	7711
	Total	9	16	2	27	111	640	7677	8428

Table 30. Ratios of Clinical Sensitivity and False Positivity Rate for ≥ CIN2 and ≥ CIN3 Clinical Endpoints: Screening Population

Specimen Type	Clinical endpoint	Clinical Sensitivity			Clinical endpoint	False Positivity Rate		
		Alinity m HR HPV %, (n/N) 95% CI)	FDA approved test %, (n/N) 95% CI)	Ratio (95%CI)		Alinity m HR HPV %, (n/N) 95% CI)	FDA approved test %, (n/N) 95% CI)	Ratio (95%CI)
ThinPrep	**≥CIN2**	91.2% (104/114) (84.6, 95.2)	88.6% (101/114) (81.5, 93.2)	1.03 (0.97, 1.09)	**<CIN2**	7.4% (802/10842) (6.9, 7.9)	7.2% (781/10842) (6.7, 7.7)	1.03 (0.99, 1.07)
	≥CIN3	94.3% (33/35) (81.4, 98.4)	94.3% (33/35) (81.4, 98.4)	1.0 N/A	**<CIN3**	8.0% (873/10921) (7.5, 8.5)	7.8% (849/10921) (7.3, 8.3)	1.03 (0.99, 1.06)
SurePath	**≥CIN2**	85.6% (77/90) (76.8; 91.4)	85.6% (77/90) (76.8; 91.4)	1.00 (0.93, 1.07)	**<CIN2**	7.9% (665/8365) (7.4, 8.5)	8.4% (699/8365) (7.8, 9.0)	0.95 (0.91, 0.99)
	≥CIN3	92.6% (25/27) (76.6, 97.9)	92.6% (25/27) (76.6, 97.9)	1.0 N/A	**<CIN3**	8.5% (717/8428) (7.9, 9.1)	8.9% (751/8428) (8.3, 9.5)	0.95 (0.91, 0.99)

N/A: A 95% CI was not calculated because Alinity and FDA-approved test have the same results for every specimen.

Alinity m HR HPV Assay performance in the Enriched population

Because all women in the Enriched population have histology results, clinical sensitivity and the FPR of Alinity and the FDA approved tests were calculated along with two-sided 95% CI. In addition, the ratio of clinical sensitivity and the ratio of FPR between Alinity and the FDA approved tests were calculated along with two-sided 95% CIs.

Table 31. HR HPV positive results reported by Alinity m and FDA-approved test: ThinPrep Enriched Population at ≥CIN2

		≥CIN2				<CIN2			
		FDA approved test				FDA approved test			
		HPV 16/18	12 Other	Negative	Total	HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	189	0	2	191	233	4	14	251
	12 Other	5	347	4	356	18	1251	122	1391
	Negative	0	9	28	37	5	99	651	755
	Total	194	356	34	584	256	1354	787	2397

Table 32. HR HPV positive results reported by Alinity m and FDA-approved test: ThinPrep Enriched Population at ≥CIN3

		≥CIN3					<CIN3			
		FDA approved test					FDA approved test			
		HPV 16/18	12 Other	Negative	Total		HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	87	0	1	88		335	4	15	354
	12 Other	0	86	1	87		23	1510	125	1658
	Negative	0	1	8	9		5	107	671	783
	Total	87	87	10	184		363	1621	811	2795

Table 33. HR HPV positive results reported by Alinity m and FDA-approved test: SurePath Enriched Population at ≥CIN2

		≥CIN2					<CIN2			
		FDA approved test					FDA approved test			
		HPV 16/18	12 Other	Negative	Total		HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	190	0	0	190		247	2	10	259
	12 Other	9	338	2	349		23	1248	94	1365
	Neg	0	18	25	43		6	126	593	725
	Total	199	356	27	582		276	1376	697	2349

Table 34. HR HPV positive results reported by Alinity m and FDA-approved test: SurePath Enriched Population at ≥CIN3

		≥CIN3					<CIN3			
		FDA approved test					FDA approved test			
		HPV 16/18	12 Other	Negative	Total		HPV 16/18	12 Other	Negative	Total
Alinity m HR HPV	HPV16/18	87	0	0	87		350	2	10	362
	12 Other	0	84	0	84		32	1500	96	1628
	Neg	0	4	8	12		6	140	610	756
	Total	87	88	8	183		388	1642	716	2746

Table 35. Ratios of Clinical Sensitivity and False Positivity Rate for ≥ CIN2 and ≥ CIN3 Clinical Endpoints: Enriched Population

Specimen Type	Clinical endpoint	Clinical Sensitivity			Clinical endpoint	False Positivity Rate		
		Alinity m HR HPV	FDA approved test	Ratio (95% CI)		Alinity m HR HPV	FDA approved test	Ratio (95% CI)
		%, (n/N) 95%CI)	%, (n/N) 95%CI)			%, (n/N) 95%CI)	%, (n/N) 95%CI)	
ThinPrep	≥CIN2	93.7% (547/584) (91.4, 95.4)	94.2% (550/584) (92.0, 95.8)	0.99 (0.98, 1.01)	<CIN2	68.5% (1642/2397) (66.6, 70.3)	67.17% (1610/2397) (65.26, 69.02)	1.02 (1.00, 1.04)
	≥CIN3	95.1% (175/184) (91.0, 97.4)	94.6% (174/184) (90.3, 97.0)	1.01 (0.99, 1.02)	<CIN3	71.99% (2012/2795) (70.29, 73.62)	70.98% (1984/2795) (69.27, 72.64)	1.01 (1.00, 1.03)
SurePath	≥CIN2	92.6% (539/582) (90.2, 94.5)	95.4% (555/582) (93.3, 96.8)	0.97 (0.96, 0.99)	<CIN2	69.14% (1624/2349) (67.24, 70.97)	70.33% (1652/2349) (68.45, 72.14)	0.98 (0.97, 1.00)
	≥CIN3	93.4% (171/183) (88.9, 96.2)	95.6% (175/183) (91.6, 97.8)	0.98 (0.95, 0.99)	<CIN3	72.47% (1990/2746) (70.77, 74.11)	73.93% (2030/2746) (72.25, 75.53)	0.98 (0.96, 1.00)

The ratio of clinical sensitivity between Alinity m HR HPV and the FDA approved HPV test for detecting disease (≥ CIN3) was 1.00 for both ThinPrep and SurePath specimens in the Screening population (the 95% CI could not be calculated as the same samples were positive by both tests). In the Enriched population the clinical sensitivity for ≥ CIN3 was 1.01 (95% CI: 0.99, 1.02) and 0.98 (95% CI 0.95, 0.99) for ThinPrep and SurePath specimens, respectively.

The FPR reported for both the Alinity m HR HPV and FDA approved test was high in the Enriched population as this was a biased colposcopy referral population with likely high viral loads related to disease. The FPR ratio for the <CIN3 endpoint was greater than 1.0 in ThinPrep specimens from both populations (1.03 in the Screening and 1.01 in the Enriched) as compared to SurePath (0.98 in Screening and Enriched).

The reported data above demonstrate that the clinical performance of Alinity m HR HPV test is comparable to currently FDA approved HPV tests.

Alinity m HR HPV genotype agreement with NGS

The Alinity m HR HPV assay detects HPV16, 18, and 45 as individual genotypes while the remaining 11 other HR HPV genotypes are detected as either Other HR HPV A (HPV31/33/52/58) or Other HR HPV B (HPV35/39/51/56/59/66/68). Alinity m HR HPV results were compared with NGS results. The agreement (PPA, NPA, and 95% CI) between Alinity m HR HPV and NGS genotyping results were estimated above (Detected) and below the clinical cutoff (Detected,

Below Clinical Cutoff) for each respective channel in the Screening population. The agreements between Alinity and NGS results for the individual Alinity genotype results (HPV16, 18, 45, Other HR HPV A, and Other HR HPV B) are summarized below for ThinPrep (Tables 36 through Table 40) and SurePath (Table 41 through Table 45).

Screening Population: ThinPrep

Table 36. Agreement Between Alinity m HR HPV and HPV DNA NGS for HPV16 Detection: ThinPrep

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	23	12	0	35	95.83% (23/24) (79.76, 99.26)	98.22% (716/729) (96.97, 98.95)	95.83% (23/24) (79.76, 99.26)	98.35% (717/729) (97.14, 99.06)
Negative (Detected)	0	1	0	1				
Negative (Not Detected)	1	716	5	722				
Total	24	729	5	758				

Table 37. Agreement Between Alinity m HR HPV and HPV DNA NGS for HPV18 Detection: ThinPrep

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	14	7	0	21	100.00% (14/14) (78.47, 100.0)	99.05% (732/739) (98.06, 99.54)	100.00% (14/14) (78.47, 100.0)	99.05% (732/739) (98.06, 99.54)
Negative (Detected)	0	0	0	0				
Negative (Not Detected)	0	732	5	737				
Total	14	739	5	758				

Table 38. Agreement Between Alinity m HR HPV and HPV DNA NGS for HPV45 Detection: ThinPrep

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	24	10	0	34	92.31% (24/26) (75.86, 97.86)	98.49% (716/727) (97.31, 99.15)	92.31% (24/26) (75.86, 97.86)	98.62% (717/727) (97.49, 99.25)
Negative (Detected)	0	1	0	1				
Negative (Not Detected)	2[a]	716	5	723				
Total	26	727	5	758				

[a] Of the 2 cases, the histology results included 1 negative and 1 undetermined due to inadequate histology specimen with no visible lesion by colposcopic review.

Table 39. Agreement Between Alinity m HR HPV and HPV DNA NGS for Other HR HPV A Detection: ThinPrep

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	88	22	0	110	87.38% (90/103) (79.60, 92.47)	96.62% (628/650) (94.93, 97.75)	85.44% (88/103) (77.35, 90.97)	96.62% (628/650) (94.93, 97.75)
Negative (Detected)	2	0	0	2				
Negative (Not Detected)	13[a]	628	5	646				
Total	103	650	5	758				

[a] Of the 13 cases, the histology results included 1 > CIN3, 1 CIN2, 2 CIN1, 8 negative and 1 undetermined due to loss to follow up. The > CIN3 case had NGS result of HPV 45/52, Alinity m HR HPV result of HPV 45, and comparator result of Other HR HPV. The CIN2 case had NGS result of HPV52/35/56, Alinity m HR HPV result of Other HR HPV B and comparator result of Other HR HPV.

Table 40. Agreement Between Alinity m HR HPV and HPV DNA NGS for Other HR HPV B Detection: ThinPrep

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	150	27	0	177	91.28% (157/172) (86.11, 94.64)	94.84% (551/581) (92.72, 96.36)	87.21% (150/172) (81.39, 91.40)	95.35% (554/581) (93.32, 96.79)
Negative (Detected)	7	3	0	10				
Negative (Not Detected)	15[a]	551	5	571				
Total	172	581	5	758				

[a] Of the 15 cases, the histology results included 1 CIN2, 1 CIN1, 7 negative, and 6 undetermined due to loss to follow up. The CIN2 case had NGS result of HPV 51 and negative comparator result.

Screening Population: SurePath

Table 41. Agreement Between Alinity m HR HPV and HPV DNA NGS for HPV16 Detection: SurePath

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	22	17	0	39	95.65% (22/23) (79.01, 99.23)	97.49% (698/716) (96.06, 98.40)	95.65% (22/23) (79.01, 99.23)	97.63% (699/716) (96.23, 98.51)
Negative (Detected)	0	1	0	1				
Negative (Not Detected)	1	698	5	704				
Total	23	716	5	744				

Table 42. Agreement Between Alinity m HR HPV and HPV DNA NGS for HPV18 Detection: SurePath

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	14	7	0	21	100.00% (14/14) (78.47, 100.0)	99.03% (718/725) (98.02, 99.53)	100.00% (14/14) (78.47, 100.0)	99.03% (718/725) (98.02, 99.53)
Negative (Detected)	0	0	0	0				
Negative (Not Detected)	0	718	5	723				
Total	14	725	5	744				

Table 43. Agreement Between Alinity m HR HPV and HPV DNA NGS for HPV45 Detection: SurePath

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	21	13	0	34	88.00% (22/25) (70.04, 95.83)	98.04% (700/714) (96.74, 98.83)	84.00% (21/25) (65.35, 93.60)	98.18% (701/714) (96.91, 98.93)
Negative (Detected)	1	1	0	2				
Negative (Not Detected)	3[a]	700	5	708				
Total	25	714	5	744				

[a] Of the 3 cases, the histology results included 1 negative, 2 undetermined due to loss to follow up or inadequate histology specimen with no visible lesion by colposcopic review.

Table 44. Agreement Between Alinity m HR HPV and HPV DNA NGS for Other HR HPV A Detection: SurePath

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	80	32	0	112	90.00% (81/90) (82.08, 94.65)	94.92% (616/649) (92.95, 96.36)	88.89% (80/90) (80.74, 93.85)	95.07% (617/649) (93.12, 96.49)
Negative (Detected)	1	1	0	2				
Negative (Not Detected)	9[a]	616	5	630				
Total	90	649	5	744				

[a] Of the 9 cases, the histology results included 1 > CIN3, 2 CIN2, 2 CIN1, 3 negative and 1 undetermined due to loss to follow up. The > CIN3 case had NGS result of HPV 45/52, Alinity m HR HPV result of

HPV 45 and comparator result of Other HR HPV. The 2 CIN2 cases had NGS result of HPV 52/59 and 52/35/56, Alinity m HR HPV result of Other HR HPV B and comparator result of Other HR HPV.

Table 45. Agreement Between Alinity m HR HPV and HPV DNA NGS for Other HR HPV B Detection: SurePath

	NGS Result				Detected		Detected (Below Clinical Cutoff)	
Alinity m HR HPV Result	**Positive**	**Negative**	**Invalid**	**Total**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**	**PPA% (n/N) (95% CI)**	**NPA% (n/N) (95% CI)**
Positive	137	36	0	173	90.97% (141/155) (85.41, 94.54)	91.95% (537/584) (89.46, 93.89)	88.39% (137/155) (82.39, 92.53)	93.84% (548/584) (91.58, 95.51)
Negative (Detected)	4	11	0	15				
Negative (Not Detected)	14[a]	537	5	556				
Total	155	584	5	744				

[a] Of the 14 cases, the histology results included 1 CIN2, 11 negative and 2 undetermined due to non-referral to colposcopy or loss to follow up. The CIN2 case had NGS result of HPV 51 and negative comparator result.

In the Screening population, the Alinity m HR HPV genotype agreements ranged from 85.44% to 100% in ThinPrep and 84.0% to 100% in SurePath when evaluated at the clinical cutoff and ranged from 87.38% to 100% in ThinPrep and 88% to 100% in SurePath when evaluated for detection (below the clinical cutoff). These results were comparable to the genotype agreements with NGS for other FDA approved HPV molecular tests.

3. Subgroup Analyses

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

Performance by Vaccination Status

The clinical sites enrolled both vaccinated and unvaccinated women. In the clinical study 13.4% (Screening population) and 19.8% (Enriched population) of the eligible women reported receiving the HPV vaccine. Alinity performance in vaccinated and unvaccinated patients was evaluated in both the Screening and Enriched populations using the ≥CIN2 disease endpoint. To accommodate the smaller size of this subgroup analysis, the groups were not stratified by age. The clinical sensitivity, false positivity rate, and ratio of both estimates for Alinity and the FDA approved test are presented in Table 46 and Table 47 by population

(Screening and Enriched), cohort (vaccinated or unvaccinated) and specimen type (ThinPrep or SurePath).

Table 46. Percent Estimates and Ratio of Clinical Sensitivity and False Positivity Rate for the ≥CIN2 Endpoint in Vaccinated vs. Unvaccinated Cohorts: Screening Population

Specimen Type	Cohort	Clinical Sensitivity				False Positivity Rate (<CIN2)		
		Alinity m HR HPV	FDA approved test	Ratio (95% CI)		Alinity m HR HPV	FDA approved Test	Ratio (95% CI)
		%, (n/N) 95%CI)	%, (n/N) 95%CI)			%, (n/N) 95%CI)	%, (n/N) 95%CI)	
ThinPrep	Vaccinated	95.5% (21/22) (78.2, 99.2)	90.9% (20/22) (72.2, 97.5)	1.05 (0.90,1.24)		10.0% (144/1441) (8.5, 11.6)	10.3% (148/1441) (8.8%, 11.9)	0.97 (0.90, 1.04)
	Unvaccinated	88.8% (71/80) (80.0, 94.0)	87.5% (70/80) (78.5, 93.1)	1.01 (0.96, 1.09)		6.6% (570/8616) (6.1, 7.2)	6.5% (558/8616) (6.0, 7.0)	1.02 (0.98, 1.07)
SurePath	Vaccinated	85.0% (17/20) (64.0, 94.8)	80.0% (16/20) (58.4, 91.9)	1.06 (0.82, 1.43)		10.4% (120/1159) (8.7, 12.2)	11.3% (131/1159) (9.6, 13.3)	0.92 (0.84, 1.00)
	Unvaccinated	83.1% (49/59) (71.5, 90.5)	84.7% (50/59) (73.5, 91.8)	0.98 (0.90, 1.04)		7.1% (466/6573) (6.5, 7.7)	7.4% (485/6573) (6.8, 8.0)	0.96 (0.91, 1.01)

Table 47. Percent Estimates and Ratio of Clinical Sensitivity and False Positivity Rate for the ≥CIN2 Endpoint in Vaccinated vs. Unvaccinated Cohorts: Enriched Population

Specimen Type	Cohort	Clinical Sensitivity			False Positivity Rate (<CIN2)		
		Alinity m HR HPV	FDA approved test	Ratio (95% CI)	Alinity m HR HPV	FDA approved Test	Ratio (95% CI)
		%, (n/N) 95%CI)	%, (n/N) 95%CI)		%, (n/N) 95%CI)	%, (n/N) 95%CI)	
ThinPrep	Vaccinated	93.0% (119/128) (87.2, 96.3)	94.5% (121/128) (89.1, 97.3)	0.98 (0.95,1.01)	71.0% (330/465) (66.7, 74.9)	70.5% (328/465) (66.2, 74.5)	1.01 (0.97, 1.04)
	Unvaccinated	93.5% (386/413) (90.7, 95.5)	93.7% (387/413) (90.9, 95.7)	1.00 (0.98, 1.02)	67.6% (1193/176) (65.4, 69.7)	66.5% (1173/1765) (64.2, 68.6)	1.02 (1.00, 1.04)
SurePath	Vaccinated	91.4% (117/128) (85.3, 95.1)	94.5% (121/228) (89.1, 97.3)	0.97 (0.93, 1.00)	68.9% (314/456) (64.5, 72.9)	73.2% (334/456) (69.0, 77.1)	0.94 (0.90, 0.98)
	Unvaccinated	93.2% (383/411) (90.3, 95.2)	95.4% (392/411) (92.9, 97.0)	0.98 (0.96, 0.99)	69.7% (1205/1728) (67.5, 71.9)	69.6% (1203/1728) (67.4, 71.7)	1.00 (0.98, 1.02)

In the Screening population the ratio of clinical sensitivity between Alinity and the FDA approved device against the ≥CIN2 disease endpoint was 1.05 (vaccinated) and 1.01 (unvaccinated) for the ThinPrep specimens and 1.06 (vaccinated) and 0.98 (unvaccinated) for the SurePath specimens. In the Enriched population the ratio of clinical sensitivity was 0.98 (vaccinated) and 1.00 (unvaccinated) for the ThinPrep specimens and 0.97 (vaccinated) and 0.98 (unvaccinated) for the SurePath specimens.

In the Screening population, the FPR ratio between Alinity and the FDA approved device was 0.97 (vaccinated) and 1.02 (unvaccinated) in ThinPrep and 0.92 (vaccinated) and 0.96 (unvaccinated). In the Enriched population the FPR ratio between Alinity and the FDA approved device was 1.01 (vaccinated) and 1.02 (unvaccinated) in ThinPrep and 0.94 (vaccinated) and 1.00 (unvaccinated). The data above demonstrated that the Alinity device performance in the vaccinated and unvaccinated cohorts is comparable to the FDA approved device for the size of the study used.

Comparison of the Alinity m HR HPV Assay Results for Pre-Quot and Post-Quot Clinical Samples

Additional testing was performed to compare the performance of the Alinity m HR HPV assay with ThinPrep and SurePath specimen aliquot for testing prior to (pre-quot) or after (post-quot) normal cytology processing. Post-quot specimens

selected using stratified random sampling were tested. Among the total samples tested, the number of pre- and post-quot pairs evaluated with known disease diagnosis were 371, 374, and 322 for TP 2000, TP 5000, and PrepMate/PrepStain, respectively. Cross-tabulation of the Alinity m HR HPV assay pre-quot and post-quot results are shown in Table 48, 49, and 50 after use with the indicated cytology processor. The percent agreements and 95% confidence intervals (CIs) between the pre-quot and post-quot Alinity m HR HPV assay results against the ≥CIN2 and <CIN2 endpoints are indicated for the HPV16, 18, 45, Other HR HPV A, and Other HR HPV B channels, as well as for a negative result reported by the Alinity m HR HPV assay, are reported below. Refer to Table 51 for TP 2000 processor, Table 52 for the TP 5000 processor, and Table 53 for PrepMate/PrepStain processor agreement results.

Table 48. Alinity m HR HPV Pre-Quot Versus Post-Quot Results: ThinPrep 2000 (TP 2000)

ThinPrep 2000	Alinity m Pre-Quot Result							
Alinity m Post-Quot Result	HPV16	HPV18	HPV45	Other HR HPV A	Other HR HPV B	HPV Negative (Detected)	HPV Negative (Not Detected)	Total
HPV16	14	0	0	0	0	0	0	14
HPV18	0	8	0	0	0	0	0	8
HPV45	0	0	14	0	0	0	0	14
Other HR HPV A	0	0	1	50	1	0	0	52
Other HR HPV B	0	0	0	1	61	1	4	67
HPV Negative (Detected)	0	1	0	0	2	1	1	5
HPV Negative (Not Detected)	2	0	1	1	2	0	188	194
Total	16	9	16	52	66	2	193	354[a]

[a]Total does not account for coinfected samples containing two HR HPVs in 17 samples (354+17 = 371)

Table 49. Alinity m HR HPV Pre-Quot Versus Post-Quot Results: ThinPrep 5000 (TP 5000)

ThinPrep 5000	Alinity m Pre-Quot Result							
Alinity m Post-Quot Result	HPV16	HPV18	HPV45	Other HR HPV A	Other HR HPV B	HPV Negative (Detected)	HPV Negative (Not Detected)	Total
HPV16	17	0	0	0	0	0	0	17
HPV18	0	10	0	0	1	0	0	11
HPV45	0	0	17	0	0	0	0	17
Other HR HPV A	0	0	0	41	0	0	0	41
Other HR HPV B	0	0	1	1	57	0	0	59
HPV Negative (Detected)	1	0	0	1	2	1	2	7
HPV Negative (Not Detected)	0	0	1	3	2	0	196	202
Total	18	10	19	46	62	1	198	354[a]

[a]Total does not account for coinfected samples containing two (16 samples) or three (2 samples) HR HPVs (354+16+2+2 = 374)

Table 50. Alinity m HR HPV Pre-Quot Versus Post-Quot Results: SurePath PrepMate/PrepStain

PrepMate/PrepStain	Alinity m Pre-Quot Result							
Alinity m Post-Quot Result	HPV16	HPV18	HPV45	Other HR HPV A	Other HR HPV B	HPV Negative (Detected)	HPV Negative (Not Detected)	Total
HPV16	8	0	0	0	0	0	0	8
HPV18	0	4	0	0	0	0	0	4
HPV45	0	0	10	0	0	0	0	10
Other HR HPV A	0	0	0	38	0	0	0	38
Other HR HPV B	1	0	0	2	45	0	0	48
HPV Negative (Detected)	0	1	0	2	1	1	1	6
HPV Negative (Not Detected)	0	1	0	0	3	1	193	198
Total	8	6	10	42	48	2	194	312[a]

[a]Total does not account for coinfected samples containing two (8 samples) or three (1 sample) HR HPVs (312+8+1+1 = 322)

Table 51. Agreement of Alinity m HR HPV Results in Pre-quot vs Post-quot: TP 2000

Disease Endpoint	**HPV16**	**HPV18**	**HPV45**	**Other HR HPV A**	**Other HR HPV B**	**Negative**
	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	NPA% (n/N) 95% CI)
≥CIN2	100.0% (3/3) (43.9,100.0)	100.0% (3/3) (43.9,100.0)	66.7% (2[a]/3) (20.8,93.9)	100.0% (11/11) (74.1,100.0)	100.0% (4/4) (51.0,100.0)	N/A
<CIN2	84.6% (11/13) (57.8,95.7)	85.7% (6/7) (48.7,97.4)	92.3% (12/13) (66.7,98.6)	95.5% (42/44) (84.9,98.7)	90.7% (68/75) (82.0,95.4)	97.4% (190/195) (94.1,98.9)
Total	87.5% (14/16) (64.0,96.5)	90.0% (9/10) (59.6,98.2)	87.5% (14/16) (64.0,96.5)	96.4% (53/55) (87.7,99.0)	91.1% (72/79) (82.8,95.6)	97.4% (190/195) (94.1,98.9)

[a] The CIN2 case was reported as HPV45, Other HR HPV A positive in the pre-quot and Other HR HPV A in post-quot. The subject would receive the same clinical treatment.

Table 52. Agreement of Alinity m HR HPV Results in Pre-quot vs Post-quot: TP 5000

Disease Endpoint	**HPV16**	**HPV18**	**HPV45**	**Other HR HPV A**	**Other HR HPV B**	**Negative**
	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	NPA% (n/N) 95% CI)
≥CIN2	100.0% (4/4) (51.0,100.0)	N/A	N/A	100.0% (8/8) (67.6,100.0)	100.0% (2/2) (34.2,100.0)	N/A

Table 52. Agreement of Alinity m HR HPV Results in Pre-quot vs Post-quot: TP 5000

Disease Endpoint	HPV16	HPV18	HPV45	Other HR HPV A	Other HR HPV B	Negative
	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	NPA% (n/N) 95% CI)
<CIN2	92.9% (13/14) (68.5,98.7)	90.9% (10/11) (62.3,98.4)	89.5% (17/19) (68.6,97.1)	85.4% (35/41) (71.6,93.1)	94.7% (72/76) (87.2,97.9)	100.0% (199/199) (98.1,100.0)
Total	94.4% (17/18) (74.2,99.0)	90.9% (10/11) (62.3,98.4)	89.5% (17/19) (68.6,97.1)	87.8% (43/49) (75.8,94.3)	94.9% (74/78) (87.5,98.0)	100.0% (199/199) (98.1,100.0)

Table 53. Agreement of Alinity m HR HPV Results in Pre-quot vs Post-quot: PrepMate/PrepStain

Disease Endpoint	HPV16	HPV18	HPV45	Other HR HPV A	Other HR HPV B	Negative
	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	PPA% (n/N) 95% CI)	NPA% (n/N) 95% CI)
≥CIN2	100.0% (1/1) (20.7,100.0)	100.0% (1/1) (20.7,100.0)	100.0% (1/1) (20.7,100.0)	88.9% (8[a]/9) (56.5,98.0)	100.0% (1/1) (20.7,100.0)	N/A
<CIN2	87.5% (7/8) (52.9,97.8)	66.7% (4/6) (30.0,90.3)	100.0% (9/9) (70.1,100.0)	89.2% (33/37) (75.3,95.7)	92.5% (49/53) (82.1,97.0)	100.0% (196/196) (98.1,100.0)
Total	88.9% (8/9) (56.5,98.0)	71.4% (5/7) (35.9,91.8)	100.0% (10/10) (72.2,100.0)	89.1% (41/46) (77.0,95.3)	92.6% (50/54) (82.4,97.1)	100.0% (196/196) (98.1,100.0)

[a] The CIN2 case was reported as HPV45, Other HR HPV A positive in the pre-quot and HPV45 in post-quot. The subject would receive the same clinical treatment.

The agreement of the Alinity m HR HPV results prior to (pre-quot) and after (post-quot) processing on the indicated cytology processors was reported as 100% for every channel at the ≥CIN2 disease endpoint with the exception of HPV45 on the TP 2000 (66.7%) and Other HR HPV A (88.9%) on the SurePath PrepMate/PrepStain processor. As indicated above in Table 50 and 52, the CIN2 cases with these discordant results were co-infected with both HPV45 and Other HR HPV A in the pre-quot, but only one of the genotypes was detected in post-quot as indicated. In both cases the subject would undergo the same clinical management (i.e., in the case of primary screening indication, reflexive cytology) as per the current medical guidelines for HPV screening.

Cervical Cancer Specimens

Cervical cancer specimens consist of cancer diagnosis of squamous cell carcinoma, moderately differentiated squamous cell carcinoma, neuroendocrine carcinoma, adenocarcinoma, endocervical adenocarcinoma, other undifferentiated carcinoma, and adenocarcinoma in situ. A total of 29 ThinPrep and 19 SurePath

cervical cancer specimens were sourced from outside vendors or obtained from the clinical study.

For cervical cancer specimens, the Alinity m detection rate is 89.7% for ThinPrep and 94.7% for SurePath, identical to the detection rates observed for the FDA approved HPV test (Table 53). In addition, the Alinity m and FDA approved test results matched for each individual specimen.

Table 54. High Risk HPV Detection Rate for Cervical Cancer Specimens

	Alinity m HR HPV Detection Rate		**FDA Approved Test Detection Rate**	
Specimen Type	**Estimate % (95% CI)**	**n/N**	**Estimate % (95% CI)**	**n/N**
ThinPrep	89.7 (73.6,96.4)	26/29	89.7 (73.6,96.4)	26/29
SurePath	94.7 (75.4,99.1)	18/19	94.7 (75.4,99.1)	18/19

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

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 clinical study included four investigators. None of the clinical investigators were full-time or part-time employees of the sponsor and none of the four investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: [None of the investigators]
- Significant payment of other sorts: [None of the investigators]
- Proprietary interest in the product tested held by the investigator: [None of the investigators]
- Significant equity interest held by investigator in sponsor of covered study: [None of the investigators]

The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not Applicable.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical study results, in combination with the non-clinical performance evaluations, support the effectiveness of the Alinity m HR HPV assay for the intended use to detect Human Papillomavirus DNA in cervical specimens collected by a health care professional using an endocervical brush/spatula placed in ThinPrep PreservCyt Solution or an endocervical broom placed in SurePath Preservative Fluid and identify high-risk (HR) HPV types 16, 18, 45, while reporting the concurrent detection of the other HR genotypes (31/33/52/58) and (35/39/51/56/59/66/68).

Alinity m HR HPV may be used in routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (adjunctive screening) with cytology, and HPV primary screening of women to assess the risk for cervical pre-cancer and cancer. The results of this test, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

B. Safety Conclusions

The risk of the device is based on data collected in the clinical study conducted to support PMA approval as described above. Based on the results of the clinical studies, the Alinity m HR HPV assay, when used according to the provided directions and in conjunction with all relevant clinical and laboratory findings, is safe to use and poses minimal risk to the patient due to false test results.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary benefits of the assay are the identification of individuals with potentially clinically significant HR HPV genotype infections that puts them at risk for the development of cervical pre-cancer or cancer. This assay, used for HPV primary screening or in conjunction with cytology (co-testing), can enable clinicians to determine the risk of cervical pre-cancer or cancer for individual patients and make management recommendations including the need for colposcopy or treatment. Early identification and treatment of pre-cancerous or cancerous lesions can improve morbidity and mortality associated with cervical cancer. The overall benefit of the candidate device is determined by the prevalence of HR HPV infections, risk of progression to cervical dysplasia or cervical

cancer, and the number of women who undergo cervical cancer screening using the candidate device and receive clinically appropriate follow-up and management of their screening results. Population health also benefits from the implementation of this device for cervical cancer screening widely in the intended use population.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Risks associated with the device, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the instrument. Risks of a false positive test include improper patient management and possible overtreatment (i.e., incorrect referral to colposcopy for further evaluation of possible pre-cancerous or cancerous cervical lesions). Colposcopies are invasive procedures that can be associated with substantial patient inconvenience, discomfort and pain. It is anticipated that some of the risks associated with colposcopy (e.g., pain, discomfort and bleeding or more rarely infection associated with cervical biopsies). These risks may be mitigated as biopsies would not be performed unless abnormal lesions are observed on examination, in which case the colposcopy may have been warranted. However, colposcopy is a generally safe and well-tolerated procedure with rare complications (i.e., infection, bleeding).

Risks of a false negative test include improper patient management, including missing the opportunity to detect pre-cancerous or early cancerous lesions and treat them before progression. Missed early detection could also be associated with missed opportunity for curative treatment response, thereby potentially resulting in increased morbidity and mortality.

Overall, the clinical performance of the device in the screening population supports a favorable benefit-risk profile for the device, demonstrated by comparable safety and effectiveness of this device to a previously marketed HPV assay. The relative clinical sensitivity and false positive rates were nearly identical between the candidate device and an FDA-approved comparator, both for overall HR HPV detection and by genotype (HPV 1618 and 12 Other HR HPV). In addition, in analytical studies, the candidate device demonstrates higher clinical sensitivity than a composite reference standard composed of two FDA-approved devices and Sequencing results for HR HPV detection in individuals with clinically significant disease (CIN3+). In addition, the clinical performance of this device was shown to be acceptable across different subpopulations, including age and HPV vaccination status. Important mitigation strategies include the marketing of this device as a prescription only device ordered by medical professionals in conjunction with other relevant clinical history and appropriate patient counseling & management. Therefore, it is anticipated that this device can be used safely and effectively to support cervical cancer screening.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above and the totality of the data provided above, the probable benefits outweigh the probable risks for the use of the Alinity m HR HPV test in routine cervical cancer screening as per professional medical guidelines, including triage of ASC-US cytology, co-testing (or adjunctive screen) with cytology, and HPV primary screening of women to assess the risk for cervical precancer and cancer.

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 Alinity m HR HPV assay when used according to the instructions for use as stated in the labeling, the warnings and precautions, and limitations sections of the labeling. The clinical studies and the statistical analysis of clinical data in this application has shown that the assay is safe and effective for use in routine cervical cancer screening for its approved indications when used according to the directions for use in the labeling.

XIV. CDRH DECISION

CDRH issued an approval order on November 1, 2023. The final clinical conditions of approval cited in the approval order are described below.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Nayar, R., & Wilbur, D. C. (Eds.). (2015). The Bethesda System for Reporting Cervical Cytology (Third ed.). Springer, Cham. doi:10.1007/978-3-319-11074-5.