510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K151502

B. Purpose for Submission:

New Device

C. Measurand:

ROMA (Risk of Ovarian Malignancy Algorithm) – Ovarian adnexal mass assessment score based on 2 serum analytes

D. Type of Test:

Software algorithm and two immunoassays

E. Applicant:

Fujirebio Diagnostics, Inc

F. Proprietary and Established Names:

ARCHITECT ROMA

G. Regulatory Information:

1. Regulation section:

   21 CFR §866.6050 – Ovarian adnexal mass assessment score test system

2. Classification:

   Class II

3. Product code:

   ONX; Ovarian adnexal mass assessment score test system

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended use(s):

   For *In Vitro* Diagnostic Use Only.

   The ARCHITECT Risk of Ovarian Malignancy Algorithm (ARCHITECT ROMA™) is a qualitative serum test that combines the results of the ARCHITECT HE4, ARCHITECT CA 125 II and menopausal status into a numerical score.

   ARCHITECT ROMA is intended to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ARCHITECT ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ARCHITECT ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.

PRECAUTION: ARCHITECT ROMA should not be used without an independent clinical/radiological evaluation and is **not** intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of ARCHITECT ROMA carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

2. Indication(s) for use:

   Same as Intended Use.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   ARCHITECT *i*2000SR system

I. Device Description:

The ARCHITECT ROMA is a qualitative serum test that combines the results of two analytes, HE4 (ARCHITEC HE4) and CA 125 (ARCHITECT CA 125II) and menopausal status into a numerical score between 0.0 and 10.0. The premenopausal or postmenopausal status must be based on ovarian function determined with information available from clinical evaluation and medical history.

The test system consists of the ARCHITECT HE4 assay, the ARCHITECT CA 125 II

assay and the ARCHITECT *i*2000SR. The ARCHITECT *i*2000SR is capable of calculating the ARCHITECT ROMA score. The immunoassays are performed according to the directions detailed in each product insert.

Both ARCHITECT HE4 and ARCHITECT CA 125 II are previously cleared devices, K093957 and K042731, respectively. The ARCHITECT HE4 assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of HE4 antigen in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer. ARCHITECT CA 125 II assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of CA 125 reactive determinants in human serum and plasma on the ARCHITECT *i* System and was previously cleared as an aid in monitoring response to therapy for patients with epithelial ovarian cancer.

Using an algorithm and the value of the two analytes, ARCHITECT ROMA scores (numerical score from 0.0–10.0) for both premenopausal and postmenopausal will be calculated and indicate a low likelihood or high likelihood for finding malignancy on surgery.

J. Substantial Equivalence Information:

1. Predicate device name:

   Fujirebio Diagnostics, Inc, ROMA™ (HE4 EIA + ARCHITECT CA 125 II)

2. Predicate 510(k) number:

   K103358

3. Comparison with predicate:

Similarities		
Item	Device ARCHITECT ROMA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
Intended Use/Indication for Use	For In Vitro Diagnostic Use Only. ARCHITECT Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of ARCHITECT HE4, ARCHITECT CA 125 II™ and menopausal status into a numerical score. ARCHITECT ROMA is intended	The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score. ROMA is intended to aid

Similarities		
Item	Device ARCHITECT ROMA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
	to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ARCHITECT ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ARCHITECT ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.	in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.
Warning (PRECAUTION)	Architect ROMA should not be used without an independent clinical /radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use carries the risk of unnecessary testing, surgery, and/or delayed diagnosis	Same
Sample matrix	Serum	Same
Type of test	Algorithm	Same
Measurand	Score based on two analytes and menopausal status	Same
Equation used for test	Different equation for premenopausal and postmenopausal	Same
Clinical Cut-off	<u>Premenopausal:</u> ARCHITECT ROMA score ≥ 1.31 High likelihood of finding malignancy	Same

Similarities		
Item	Device ARCHITECT ROMA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
	ARCHITECT ROMA score < 1.31 Low likelihood of finding malignancy <u>Postmenopausal:</u> ARCHITECT ROMA score ≥ 2.77 High likelihood of finding malignancy ARCHITECT ROMA score < 2.77 Low likelihood of finding malignancy	

Differences		
Item	Device ARCHITECT ROMA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
Analyte	ARCHITECT HE4 and ARCHITECT CA 125 II	Fujirebio manual HE4 EIA and ARCHITECT CA 125 II
Sample Volume	75 µL per reportable HE4 test result (singlicate) 75 µL per reportable CA 125 test result (singlicate)	50 µL per reportable HE4 test result (duplicate) 75 µL per reportable CA 125 test result (singlicate)
Instrument platform	ARCHITECT *i*2000SR Only	Manual ELISA for HE4 and ARCHITECT *i*2000SR for CA 125
Assay Format	Same immunoassay platform for the detection of HE4 and CA 125 in a single sample	Separate immunoassay platforms for the detection of HE4 and CA 125 in a single sample
Software	Provided on the ARCHITECT *i*2000SR for automated entry of assay values to obtain result	Provided as separate CD-ROM for manual entry of assay values to obtain result

K. Standard/Guidance Document Referenced:

CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Second Edition

CLSI guideline EP7-A2, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition

CLSI EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; approved Guideline – Third Edition

CLSI guideline C28-A3, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition

Guidance document entitled Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System

L. Test Principle:

The ARCHITECT HE4 assay is a two-step immunoassay for the quantitative determination of HE4 antigen in human serum using chemiluminescent microparticle immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex. In the first step, sample and anti-HE4 coated paramagnetic microparticles are combined. HE4 antigen present in the sample binds to the anti-HE4 coated microparticles. After washing, acridinium-labeled anti-HE4 conjugate is added. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of HE4 antigen in the sample and the RLUs detected by the ARCHITECT *i* System optics.

The ARCHITECT CA 125 II assay is a two-step sandwich technique immunoassay to determine the presence of OC 125 defined antigen in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex. In the first step of the assay, sample and antibody (mouse monoclonal anti-OC 125) coated paramagnetic microparticles are combined. CA 125 reactive determinants present in the sample bind to the antibody coated microparticles. After washing, a second acridinium-labeled antibody conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of CA 125 reactive determinants in the sample and the RLUs detected by the ARCHITECT™ i optical system.

The ARCHITECT *i*2000SR is capable of calculating the ARCHITECT ROMA score. Using the value of the two analytes, ARCHITECT ROMA scores (numerical score from 0.0–10.0) for both premenopausal and postmenopausal will be calculated and will indicate whether a woman is at low likelihood or high likelihood for finding malignancy on surgery. Both premenopausal and postmenopausal ARCHITECT ROMA results will be reported to the ordering physician who will decide which result to use based on patient's menopausal status.

M. Performance Characteristics:

1. <u>Analytical performance:</u>

   Both ARCHITECT HE4 and ARCHITECT CA 125 II are previously cleared devices. Analytical performance for ARCHITECT HE4 and ARCHITECT CA

125 II were validated in K093957 and K042731, respectively. There have been no modifications of assay methods for ARCHITECT HE4 and ARCHITECT CA 125 II since the original clearance for each assay. Thus, a limited study was done to evaluate the analytical performance of the ARCHITECT ROMA score.

a. Precision/Reproducibility:

Lot-to-Lot Precision Study: A panel of five serum samples was tested using a combination of three lots each of ARCHITECT HE4 and ARCHITECT CA 125 II reagents and calibrator kits for a total of four different reagent/calibrator combinations. Each kit was used according to the package insert. The panel consisted of human serum samples spiked with OC125 defined antigen and HE4 recombinant antigen. Samples were tested in two replicates per run, two runs per day for 10 days (n = 40 replicates per sample per lot).

Premenopausal and postmenopausal ARCHITECT ROMA scores were calculated using the ARCHITECT ROMA algorithm on-board the ARCHITECT analyzer utilizing the ARCHITECT System Software Version 9.00 or higher. The first ARCHITECT HE4 replicate and the first ARCHITECT CA 125 II replicate were used to compute the ARCHITECT ROMA score using both the premenopausal and postmenopausal algorithms. The second ARCHITECT HE4 replicate and the second ARCHITECT CA 125 II replicate were used to compute the ARCHITECT ROMA score using both the premenopausal and postmenopausal algorithms. This same process was used for calculating the four scores for the second run and subsequent panel runs on each day of testing. The following table displays the results for the lot-to-lot precision parameters. All data met the manufacturer's predetermined acceptance criteria.

Sample	Mean ROMA Value	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Premenopausal ARCHITECT ROMA score											
1	0.67	0.05	6.8%	0.02	2.3%	0.02	3.0%	0.03	4.0%	0.06	8.8%
2	1.44	0.09	6.2%	0.04	2.6%	0.02	1.7%	0.05	3.5%	0.11	7.8%
3	3.11	0.14	4.6%	0.06	1.9%	0.00	0.0%	0.10	3.3%	0.19	6.0%
4	1.11	0.07	6.1%	0.02	1.4%	0.02	1.4%	0.05	4.8%	0.09	8.0%
5	8.88	0.06	0.7%	0.03	0.3%	0.00	0.0%	0.08	0.9%	0.10	1.2%
Postmenopausal ARCHITECT ROMA score											
1	1.06	0.04	4.1%	0.02	1.4%	0.01	0.7%	0.02	2.1%	0.05	4.9%
2	2.59	0.08	2.9%	0.02	0.9%	0.02	0.8%	0.06	2.1%	0.10	3.8%
3	4.95	0.09	1.8%	0.03	0.6%	0.02	0.3%	0.13	2.7%	0.17	3.3%

Sample	Mean ROMA Value	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
4	2.63	0.07	2.8%	0.03	1.0%	0.00	0.0%	0.07	2.6%	0.10	4.0%
5	8.80	0.04	0.4%	0.02	0.2%	0.00	0.0%	0.09	1.0%	0.10	1.1%

Site-to-Site Precision Study: A panel of five serum samples was tested at three different sites. Samples were tested at each site in two replicates per run, two runs per day for 10 days (n = 40 replicates per sample per site). Premenopausal and postmenopausal ARCHITECT ROMA scores were calculated as for the lot-to-lot precision study. The following table displays the results for the site-to-site precision parameters. All data met the manufacturer's predetermined acceptance criteria.

Sample	Mean ROMA Value	Within-Run		Between-Run		Between-Day		Between-Site		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Premenopausal ARCHITECT ROMA score											
1	0.63	0.04	5.9%	0.02	3.5%	0.02	3.6%	0.04	6.5%	0.06	10.1%
2	1.37	0.09	6.8%	0.08	5.8%	0.00	0.0%	0.05	3.5%	0.13	9.6%
3	3.00	0.14	4.7%	0.08	2.6%	0.00	0.0%	0.07	2.5%	0.18	5.9%
4	1.05	0.06	5.9%	0.02	1.6%	0.03	2.5%	0.03	2.8%	0.07	7.2%
5	8.85	0.07	0.8%	0.00	0.0%	0.03	0.3%	0.01	0.1%	0.08	0.9%
Postmenopausal ARCHITECT ROMA score											
1	1.03	0.03	3.4%	0.02	2.4%	0.01	1.1%	0.04	3.9%	0.06	5.8%
2	2.53	0.08	3.2%	0.08	3.2%	0.00	0.0%	0.05	1.9%	0.12	4.9%
3	4.86	0.09	1.9%	0.05	1.0%	0.00	0.0%	0.09	1.8%	0.14	2.8%
4	2.57	0.07	2.8%	0.00	0.0%	0.02	1.0%	0.06	2.2%	0.09	3.7%
5	8.77	0.04	0.5%	0.01	0.1%	0.01	0.1%	0.04	0.4%	0.06	0.7%

Simulation precision: In order to demonstrate precision of all possible combinations of analytes, a simulation precision study for ARCHITECT ROMA score was conducted based on the precision profiles of HE4 and CA 125 with different combinations of values of these two analytes. The statistical analysis of simulation of ARCHITECT ROMA score precision showed acceptable precision covering the range of ARCHITECT ROMA score from 0.0–10.

b. Linearity/assay reportable range:

Linearity studies for the HE4 and CA 125 assay kits were presented in K093957 and K042731, respectively. No new linearity data were presented in

this submission.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability and stability studies for the HE4 and CA 125 assay kits were presented in K093957 and K042731, respectively. No new traceability and stability data were presented in this submission.

Each assay uses its own calibrator and controls.

ARCHITECT HE4 Calibrator and Controls: Ig-HE4 is a fusion protein consisting of a human Fc antibody fragment and Human Epididymis protein HE4. The Ig-HE4 antigen is used as a calibrator protein in the HE4 assay to determine HE4 concentrations in human serum samples. The protein is produced in a stably transfected Chinese Hamster Ovary (CHO) cell line. The cell line was adapted to serum free growth medium at Fujirebio Diagnostics, Inc. Recombinant antigen is used to prepare calibrators and controls for ARCHITECT HE4.

ARCHITECT CA 125 II Calibrator and Controls: The OC125 defined antigen is used in the ARCHITECT CA 125 II Calibrators and Controls. The concentrations are specific to each calibrator and control level. This material is obtained from Fujirebio Diagnostics, Inc. proprietary human ovarian carcinoma cell line, McDonalds. OC 125 defined antigen is produced by the McDonalds cell line. The stock solution for calibrators is prepared by adding OC 125 defined antigen to a diluent to achieve the desired concentrations. The stock solution is tested to determine its actual concentration. Each Calibrator and Control is then prepared based on the actual concentration of the stock solution.

Stability:

Specimen: ARCHITECT ROMA is intended for use with serum. The specimen stability and storage claims are limited to the ARCHITECT HE4 assay. Serum can be stored at 2–8°C for 4 days before being tested. Samples that will not be tested within that time period can be stored at −10°C or colder.

Calibration Curve: For ARCHITECT HE4 and ARCHITECT CA 125 II, the calibration curve is stable up to 30 days.

Reagent Closed-Vial: Users are instructed to refer to the individual stability information in the package insert of each assay. The claimed stability for ARCHITECT HE4 is up to 12 months at 2–8°C. The claimed shelf life for ARCHITECT CA 125 II is 12 months at 2–8°C.

Reagent Open-Vial: Users are instructed to refer to the stability information in the package insert for reagents used in the individual assay. The stability of the opened reagents used in ARCHITECT HE4 and ARCHITECT CA 125 II

kit are listed below:

Component	Stability	
	Opened Vial	Opened Vial/On-board
ARCHITECT CA 125 II Reagent Kit	2–8°C for 12 months	30 days at 2–8°C
ARCHITECT CA 125 II Calibrators	2–8°C for 12 months	
ARCHITECT HE4 Reagent Kit	2–8°C for 12 months	30 days at 2–8°C
ARCHITECT HE4 Calibrators	2–8°C for 12 months	

d. Detection limit:

The limits of detection and limits of quantitation reported in each assay's package insert are incorporated into the algorithm such that results outside of the measuring interval are not imported and do not yield an ARCHITECT ROMA score.

e. Analytical specificity:

Interference: Studies were conducted to evaluate the interference of ARCHITECT ROMA score by hemoglobin, bilirubin (conjugated and unconjugated), lipid (triglyceride), rheumatoid factor (RF), and human anti-mouse antibodies (HAMA). CLSI guideline, EP7-A2 was used to design the interference experiments. Three pooled serum samples with ARCHITECT ROMA score at low, medium, and high were used in the studies. These samples were then supplemented with each interfering substance. The control samples were prepared without corresponding interfering substance. The control samples and test samples were tested in replicates of five using ARCHITECT ROMA. The ARCHITECT ROMA score was calculated for each sample and its control sample using a mean of five replicates of ARCHITECT HE4 and the mean of five replicates of ARCHITECT CA 125 II. The effect of each interfering substance on the ARCHITECT ROMA score was assessed by comparing the measurement of each test sample to the control. The summary of the results are shown in the following table, and all data met the manufacturer's predetermined acceptance criteria.

Interferent	Substance Concentration	% Difference From Control					
		ROMA (low)		ROMA (med)		ROMA (high)	
		Pre[1]	Post[2]	Pre	Post	Pre	Post
Hemoglobin	1 mg/mL	−1	−1	2	0	5	1
Bilirubin (Conjugated)	20 mg/dL	−2	0	−5	−1	−6	−2
Bilirubin (Unconjugated)	20 mg/dL	1	1	−4	−2	−2	0
Protein	10 g/dL	−7	−3	−8	−6	−8	−3
Lipid	3 g/dL	−3	−4	−3	0	0	0
HAMA	1000 ng/mL	−2	8	−1	2	1	0
Rheumatoid Factor	500 IU/mL	−2	−2	−3	−1	0	0

[1]ROMA score used the equation for premenopausal status
[2]ROMA score used the equation for postmenopausal status

f. Assay cut-off:

See clinical cut-off

2. Comparison studies:

a. Method comparison with predicate device:

A total of 188 samples were used for the method comparison study covering the premenopausal ROMA range 0.1–10.0 and the postmenopausal ROMA range 0.3–9.8. The enrolled patients consist of 138 diseased patients (78 premenopausal women and 60 postmenopausal woman) and 50 apparently healthy women (25 premenopausal women and 25 postmenopausal women). The ARCHITECT CA 125 II assay is used in both the test device and the predicate, and was performed so that ROMA scores could be calculated, but the same ARCHITECT CA 125 II assay result was used to calculate the ROMA scores for both the HE4 EIA and the ARCHITECT HE4 platforms. This study, therefore, focused on the comparison of the two HE4 platforms. Data analysis was performed using Deming and Passing-Bablok regression analysis and all data met the manufacturer's predetermined acceptance criteria. The results are summarized in the following table:

Menopausal Status	Regression	Regression Equation	Slope (95% CI)	Intercept (95% CI)	r
Premenopausal	Deming	y = 0.98x − 0.01	0.94–1.03	−0.16–−0.03	0.98
	Passing-Bablok	y = 0.92x − 0.005	0.87–1.00	−0.04–0.03	0.98
Postmenopausal	Deming	y = 1.00x − 0.04	0.99–1.01	−0.07–−0.01	0.99
	Passing-Bablok	y = 1.00x − 0.02	0.99–1.00	−0.04–0.01	0.99

b. Matrix comparison:

Serum is the only claimed matrix.

3. Clinical studies:

a. Clinical Sensitivity/Clinical Specificity:

A clinical study was performed to evaluate the performance of ARCHITECT ROMA in pre- and postmenopausal women presenting to a generalist with an adnexal mass, for whom a decision to undergo surgery has been made. The study enrolled 512 patients at the 13 study sites. The patients were female patients over 18, presenting to a generalist at a general or specialty hospital with an ovarian cyst or an adnexal mass (defined as a simple, complex or a solid ovarian/pelvic mass) who were scheduled to undergo surgery. Blood samples were collected from all patients and tested with ARCHITECT HE4 and ARCHITECT CA 125 II at Fujirebio Diagnostics, Inc.

The Initial Cancer Risk Assessment (ICRA) and all clinical information relating to the surgical procedures, including imaging reports and final pathology reports, were collected. All patients underwent surgery and tissues were examined by local pathologists. An independent pathologist reviewed all imaging reports, case report forms and histopathology reports from each patient's institution pathologist, checking for discrepancies in the data. The performance of standalone use of ICRA, standalone use of ARCHITECT ROMA and adjunctive use of ICRA and ARCHITECT ROMA were evaluated by comparing to histopathology results for detecting the presence of ovarian malignancy.

Of the 512 patients, 53 patients were excluded from analysis. The most common reason for exclusion was no surgery was performed to remove an adnexal mass. In the final total of 459 (89.6%) evaluable patients, 250 (54.5%) were premenopausal and 209 (45.5%) were postmenopausal. All of the major racial groups were represented with 85% of White, 7% of Black, 3% Hispanic, 3% Asian, and 2% of other ethnicity.

The statistics for the 459 enrolled subjects with pathology classification are summarized in the following table:

Classification	All N = 459		Pre-menopausal N = 250		Post-menopausal N = 209	
	N	%	N	%	N	%
Histopathology Benign	374	81.5%	229	91.6%	145	69.4%
Borderline/LMP[1]	18	3.9%	7	2.8%	11	5.3%
EOC[2]	48	10.5%	9	3.6%	39	18.7%
Non-EOC	2	0.4%	0	0.0%	2	1.0%
Other Gynecological Cancer	9	2.0%	3	1.2%	6	2.9%

Classification	All N = 459		Pre-menopausal N = 250		Post-menopausal N = 209	
	N	%	N	%	N	%
Other Cancer	7	1.5%	1	0.4%	6	2.9%
Metastatic Cancer	1	0.2%	1	0.4%	0	0.0%

[1]Low malignant potential
[2]Epethelilian ovarian cancer

The ARCHITECT ROMA test used the following cut points to evaluate the performance of the test in pre- and postmenopausal women presenting to a generalist with an adnexal mass, for whom a decision to undergo surgery has been made:

Premenopausal:

ARCHITECT ROMA score ≥ 1.31: High likelihood of finding malignancy
ARCHITECT ROMA score < 1.31: Low likelihood of finding malignancy

Postmenopausal:
ARCHITECT ROMA score ≥ 2.77: High likelihood of finding malignancy
ARCHITECT ROMA score < 2.77: Low likelihood of finding malignancy

The information provided by the ARCHITECT ROMA test should be used only as an adjunctive test to complement, not replace, other diagnostic and clinical procedures. The ability of ARCHITECT ROMA to contribute to the ICRA was evaluated by comparing the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for standalone use of ARCHITECT ROMA, and adjunctive use of ICRA and ARCHITECT ROMA for the diagnosis of epithelian ovarian cancer (EOC) including tumors with low malignant potential (LMP) and all cancers including LMP. The results were cross-tabulated in a 2x2x2 table of the malignancy as determined by histopathology, test result (positive or negative) by ICRA, and test result (positive/high likelihood or negative/low likelihood) by ARCHITECT ROMA. The results are presented in the tables below.

Performance of ARCHITECT ROMA for Diagnosis of EOC including LMP (440 patients):

Combined pre- and postmenopausal subjects:

For diagnosis of EOC including LMP, the counts for combined pre- and postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are summarized in separate tables below.

Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	49	9	58
	Negative	2	6	8
	Total	51	15	66

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	20	32	52
	Negative	39	283	322
	Total	59	315	374

To examine whether the ARCHITECT ROMA test provides additional information when used in combination with ICRA, the ability of ARCHITECT ROMA to contribute to the ICRA was analyzed.

The following table presents the observed frequencies of malignancy tabulated according to ICRA and ARCHITECT ROMA test results from 440 patients.

	Frequency of Malignancy	95% CI
Prevalence of malignancy among patients with adnexal mass assessed: 15% (66/440)		
ICRA alone "Positive"	46.4% (51/110)	37.3%–55.6%
ICRA alone "Negative"	4.5% (15/330)	2.8%–7.4%
ARCHITECT ROMA alone "Positive"	52.7% (58/110)	43.5%–61.8%
ARCHITECT ROMA alone "Negative"	2.4% (8/330)	1.2%–4.7%
ICRA "Positive" and ARCHITECT ROMA "Positive"	71.0% (49/69)	59.4%–80.4%
ICRA "Positive" and ARCHITECT ROMA "Negative"	4.9% (2/41)	1.3%–16.1%
ICRA "Negative" and ARCHITECT ROMA "Positive"	22.0% (9/41)	12.0%–36.7%
ICRA "Negative" and ARCHITECT ROMA "Negative"	2.1% (6/289)	1.0%–4.5%

The same information about the frequencies of malignancy is presented by the likelihood ratios: Likelihood ratio (Result) = Pr(Result|Malignancy) / Pr(Result|No Malignancy). Likelihood ratio is a way of quantifying how much a given test result changes the pre-test probability of malignancy in a patient.

	Likelihood Ratio	95% CI
ICRA alone "Positive"	4.90	3.37–5.26
ICRA alone "Negative"	0.27	0.16–0.31
ARCHITECT ROMA alone "Positive"	6.32	4.35–6.79
ARCHITECT ROMA alone "Negative"	0.14	0.07–0.18
ICRA "Positive" and ARCHITECT ROMA "Positive"	13.88	8.25–15.94
ICRA "Positive" and ARCHITECT ROMA "Negative"	0.29	0.07–0.81
ICRA "Negative" and ARCHITECT ROMA "Positive"	1.59	0.76–2.11
ICRA "Negative" and ARCHITECT ROMA "Negative"	0.12	0.05–0.17

The likelihood ratio for identifying malignancy by adjunctive use of ARCHITECT ROMA and ICRA is 13.88, 2.8 times higher than the likelihood ratio by ICRA alone (4.90). The performance of adjunctive use of ARCHITECT ROMA and ICRA for diagnosis of EOC including LMP was further evaluated by calculating sensitivity, specificity, PPV, and NPV and compared to standalone use of ICRA. The table below shows the performance characteristics of the tests.

Performance of the Test for Diagnosis of EOC including LMP for both Pre- and Postmenopausal Subjects			
	ICRA	ARCHITECT ROMA	ICRA and ARCHITECT ROMA
Sensitivity (95% CI)	77.3% (51/66) (65.8%–85.7%)	87.9% (58/66) (77.9%–93.7%)	90.9% (60/66) (81.6%–95.7%)
Specificity (95% CI)	84.2% (315/374) (80.2%–87.6%)	86.1% (322/374) (82.2%–89.2%)	75.7% (283/374) (71.1%–79.7%)
PPV (95% CI)	46.4% (51/110) (37.3%–55.6%)	52.7% (58/110) (43.5%–61.8%)	39.7% (60/183) (32.3%–47.7%)
NPV (95% CI)	95.5% (315/330) (92.6%–97.2%)	97.6% (322/330) (95.3%–98.8%)	97.9% (252/258) (95.5%–99.0%)
Prevalence	15.0% (66/440)		

With adjunctive use of ICRA and ARCHITECT ROMA, sensitivity for malignancy increased from 77.3% to 90.9%. Specificity for malignancy decreased from 84.2% to 75.7%. PPV for the adjunctive use of ICRA and ARCHITECT ROMA decreased from 46.4% to 39.7% due to an increase in the number of false positive test added by addition of ARCHITECT ROMA to ICRA. However, NPV of adjunctive use of ICRA and ARCHITECT ROMA increased from 95.5% to 97.9%. This observed increase of 2.5% in NPV was statistically significant.

Pre-menopausal subjects:

To evaluate the ARCHITECT ROMA for diagnosis of EOC including LMP in premenopausal subjects, data and statistical analysis were performed and summarized below.

The counts for premenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in the following tables.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ARCHITECT ROMA	**Positive**	7	6	13
	Negative	0	3	3
	Total	7	9	16

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	6	25	31
	Negative	17	181	198
	Total	23	206	220

The performance of ICRA alone, ARCHITECT ROMA alone and adjunctive use of ARCHITECT ROMA and ICRA for diagnosed of EOC including LMP in premenopausal subjects are presented in the following table.

Performance of Test for Diagnosis of EOC Including LMP for Premenopausal Subjects			
	ICRA	ARCHITECT ROMA	ICRA and ARCHITECT ROMA
Sensitivity (95% CI)	43.8% (7/16) (23.1%–66.6%)	81.3% (13/16) (57.0%–93.1%)	81.3% (13/16) (57.0%–93.1%)
Specificity (95% CI)	90.0% (206/229) (85.4%–93.2%)	86.5% (198/229) (81.4%–90.3%)	79.0% (181/229) (73.3%–83.8%)
PPV (95% CI)	23.3% (7/30) (11.8%–40.8%)	29.5% (13/44) (18.2%–44.2%)	21.3% (13/61) (12.9%–33.1%)
NPV (95% CI)	95.8% (206/215) (92.2%–97.8%)	98.5% (198/201) (95.7%–99.5%)	98.4% (181/184) (95.3%–99.4%)
Prevalence	6.5% (16/245)		

The prevalence of EOC including LMP for premenopausal women was 6.5%. For premenopausal subjects, comparing to ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ARCHITECT ROMA increased from 43.8% to 81.3%, and specificity for malignancy decreased from 90.0% to 79.0%. PPV for the adjunctive use of ICRA and ARCHITECT ROMA decreased from 23.3% to 21.3% and NPV of adjunctive use of ICRA and ARCHITECT ROMA increased from 95.8% to 98.4%. The increase of 2.6% of NPV was statistically significant.

Post-menopausal subjects:

To evaluate the ARCHITECT ROMA for diagnosis of EOC including LMP in postmenopausal subject, data and statistical analysis were performed and summarized below.

The counts for postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	42	3	45
	Negative	2	3	5
	Total	44	6	50

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	14	7	21
	Negative	22	102	124
	Total	36	109	145

The performance of ICRA alone, ARCHITECT ROMA alone and adjunctive use of ARCHITECT ROMA and ICRA for diagnosis of EOC including LMP in postmenopausal subjects re presented in the following table.

Performance for the Test for Diagnosis of EOC including LMP for Postmenopausal Subjects			
	ICRA	ARCHITECT ROMA	ICRA and ARCHITECT ROMA
Sensitivity (95% CI)	88.0% (44/50) (76.2%–94.3%)	90.0% (45/50) (78.6%–95.6%)	94.0% (47/50) (83.8%–97.8%)
Specificity (95% CI)	75.2% (109/145) (67.6%–81.5%)	85.5% (124/145) (78.9%–90.3%)	70.3% (102/145) (62.5%–77.2%)
PPV (95% CI)	55.0% (44/80) (44.1%–65.4%)	68.2% (45/66) (56.2%–78.1%)	52.2% (47/90) (42.0%–62.2%)
NPV (95% CI)	94.8% (109/115) (89.1% – 97.6%)	96.1% (124/129) (91.2% – 98.3%)	97.1% (102/105) (91.9% – 99.0%)
Prevalence	25.6% (50/195)		

The prevalence of EOC including LMP for postmenopausal women was 25.6%. Comparing to use of ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ARCHITECT ROMA increased from 88.0% to 94% and specificity decreased from 75.2% to 70.3%. PPV for the adjunctive use of ICRA and ARCHITECT ROMA decreased from 55.0% to 52.2%

compared to ICRA alone, and NPV increased from 94.8% to 97.1%. The increase of 2.4% of NPV was statistically significant.

Performance of ARCHITECT ROMA for Diagnosis of All Cancers including LMP (459 patients):

Combined pre- and postmenopausal subjects:
To evaluate the ARCHITECT ROMA for diagnosis of All Cancers including LMP, data and statistical analysis were performed for total 459 subjects including both pre- and postmenopausal subjects.

The counts including both pre- and postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ARCHITECT ROMA	**Positive**	56	12	68
	Negative	6	11	17
	Total	62	23	85

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ARCHITECT ROMA	**Positive**	20	32	52
	Negative	39	283	322
	Total	59	315	374

The following table presents the observed frequencies of malignancy tabulated according to ICRA and ARCHITECT ROMA test results from the 459 patients.

	Frequency of Malignancy	95% CI
Prevalence of malignancy among patients with adnexal mass assessed: 18.5% (85/459)		
ICRA alone "Positive"	51.2% (62/121)	42.4%–60.0%
ICRA alone "Negative"	6.8% (23/338)	4.6%–10.0%
ARCHITECT ROMA alone "Positive"	56.7% (68/120)	47.7%–65.2%
ARCHITECT ROMA alone "Negative"	5.0% (17/339)	3.2%–7.9%
ICRA "Positive" and ARCHITECT ROMA "Positive"	73.7% (56/76)	62.8%–82.3%
ICRA "Positive" and ARCHITECT ROMA "Negative"	13.3% (6/45)	6.3%–26.2%
ICRA "Negative" and ARCHITECT ROMA "Positive"	27.3% (12/44)	16.3%–41.8%
ICRA "Negative" and ARCHITECT ROMA "Negative"	3.7% (11/294)	2.1%–6.6%

The same information about the frequencies of malignancy is presented by the observed likelihood ratio.

	Likelihood Ratio	95% CI
ICRA alone "Positive"	4.62	3.24–4.93
ICRA alone "Negative"	0.32	0.21–0.35
ARCHITECT ROMA alone "Positive"	5.75	4.01–6.15
ARCHITECT ROMA alone "Negative"	0.23	0.14–0.26
ICRA "Positive" and ARCHITECT ROMA "Positive"	12.32	7.39–14.07
ICRA "Positive" and ARCHITECT ROMA "Negative"	0.68	0.29–0.99
ICRA "Negative" and ARCHITECT ROMA "Positive"	1.65	0.85–2.07
ICRA "Negative" and ARCHITECT ROMA "Negative"	0.17	0.09–0.21

The likelihood ratio for identifying malignancy by adjunctive use of ARCHITECT ROMA and ICRA is 12.32, 2.7 times higher than the likelihood ratio by ICRA alone (4.62). The performance of adjunctive use of ARCHITECT ROMA and ICRA for diagnosis of All Cancers including LMP was further evaluated by calculating sensitivity, specificity, PPV, and NPV and compared to standalone use of ICRA. The table below shows the performance characteristics of the tests.

Performance of the Test for Diagnosis of All Cancers including LMP for both Pre- and Postmenopausal Subjects:			
	ICRA	ARCHITECT ROMA	ICRA and ARCHITECT ROMA
Sensitivity (95% CI)	72.9% (62/85) (62.7%–81.2%)	80.0% (68/85) (70.3%–87.1%)	87.1% (74/85) (78.3%–92.6%)
Specificity (95% CI)	93.2% (315/338) (90.0%–95.4%)	86.1% (322/374) (82.2%–89.2%)	75.7% (283/294) (71.1%–9.7%)
PPV (95% CI)	51.2% (62/121) (42.4%–60.0%)	56.7% (68/120) (47.7%–65.2%)	44.8% (74/165) (37.5%–52.5%)
NPV (95% CI)	93.2% (315/338) (90.0%–95.4%)	95.0% (322/339) (92.1%–96.8%)	96.3% (283/294) (93.4%–97.9%)
Prevalence	18.5% (85/459)		

Compared to use of ICRA alone, sensitivity of addition of ARCHITECT ROMA to ICRA from 72.9% to 87.1% and specificity decreased from 84.2% to 75.7%. PPV for the adjunctive use of ICRA and ARCHITECT ROMA decreased from 51.2% to 44.8% due to an increase in the number of false positive test added by addition of ARCHITECT ROMA to ICRA. NPV of adjunctive use of ICRA and ARCHITECT ROMA increased from 93.2% to 96.3%. The increase of 3.1% of NPV was statistically significant.

Premenopausal Subjects:

To evaluate the ARCHITECT ROMA for diagnosis of All Cancers including LMP in premenopausal subject, data and statistical analysis were performed and summarized below.

The counts for premenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ARCHITECT ROMA	**Positive**	7	8	15
	Negative	1	5	6
	Total	8	13	21

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	6	25	31
	Negative	17	181	198
	Total	23	206	229

The frequencies of malignancy and likelihood ratio were analyzed. The performance characteristics of ICRA alone, ARCHITECT ROMA alone and adjunctive use of ARCHITECT ROMA and ICRA for diagnosed of All Cancers including LMP in premenopausal subjects are presented in the following table.

Performance of the Test for Diagnosis of All Cancers including LMP in Premenopausal Subjects:			
	ICRA	ARCHITECT ROMA	ICRA and ARCHITECT ROMA
Sensitivity (95% CI)	38.1% (8/21) (20.7%–59.0%)	71.4% (15/21) (50.0%–86.0%)	76.2% (16/21) (54.9%–89.2%)
Specificity (95% CI)	90.0% (206/229) (85.4%–93.2%)	86.5% (198/229) (81.4%–90.3%)	79.0% (181/229) (73.3%–83.8%)
PPV (95% CI)	25.8% (8/31) (13.7%–43.1%)	32.6% (15/46) (20.9%–47.0%)	25.0% (16/64) (16.0%–36.8%)
NPV (95% CI)	94.1% (206/219) (90.1%–96.5%	97.1% (198/204) (93.7%–98.6%)	97.3% (181/186) (93.9%–98.8%)
Prevalence	8.4% (21/250)		

The prevalence of All Cancers including LMP for premenopausal women was 8.4%. Comparing to ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ARCHITECT ROMA increased from 38.1% to 76.2%, and specificity decreased from 90.0% to 79.0%. PPV for the adjunctive use of ICRA and ARCHITECT ROMA decreased from 25.8% to 25.0% and NPV of adjunctive use of ICRA and ARCHITECT ROMA increased from 94.1% to 97.3%. The increase of 3.2% of NPV was statistically significant.

Postmenopausal subjects:

To evaluate the ARCHITECT ROMA for diagnosis of All Cancers including LMP in postmenopausal subjects, data and statistical analysis were performed and summarized below.

The counts for postmenopausal subjects with malignancy by pathology and

with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	49	4	53
	Negative	5	6	11
	Total	54	10	64

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ARCHITECT ROMA	Positive	14	7	21
	Negative	22	102	124
	Total	36	109	145

The performance of ICRA alone, ARCHITECT ROMA alone and adjunctive use of ARCHITECT ROMA and ICRA for diagnosis of All Cancers including LMP in postmenopausal subjects presented in the following table.

Performance of the Test for Diagnosis of All Cancers including LMP for Postmenopausal Subjects:			
	ICRA	ARCHITECT ROMA	ICRA and ARCHITECT ROMA
Sensitivity (95% CI)	84.4% (54/64) (73.6%–91.2%)	82.8% (53/64) (71.8%–90.1%)	90.6% (58/64) (81.0%–95.6%)
Specificity (95% CI)	75.2% (109/145) (67.6%–81.5%)	85.5% (124/145) (78.9%–90.3%)	70.3% (102/145) (62.5%–77.2%)
PPV (95% CI)	60.0% (54/90) (49.7%–69.5%)	71.6% (53/74) (60.5%–80.6%)	57.4% (58/101) (47.7%–66.6%)
NPV (95% CI)	91.6% (109/119) (85.2%–95.3%)	91.9% (124/135) (86.0%–95.4%)	94.4% (102/108) (88.4%–97.4%)
Prevalence	30.6% (64/209)		

The prevalence of All Cancers including LMP for postmenopausal women was 30.6%. Comparing to use of ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ARCHITECT ROMA increased from 84.4% to 90.6%. and specificity for malignancy decreased from 75.2% to 70.3%. PPV for the adjunctive use of ICRA and ARCHITECT ROMA decreased from 60.0% to 57.4% and NPV of adjunctive use of ICRA and ARCHITECT ROMA increased from 91.6% to 94.4%. The increase of 2.8% of NPV was statistically significant.

Ability of Adjunctive Use of ARCHITECT ROMA and ICRA to Identify Additional Malignancies:

The Table below shows the counts of cancers identified by adjunctive use of ARCHITECT ROMA and ICRA compared to by ICRA alone.

Cancers	Premenopausal	Postmenopausal	Combined
EOC	4	0	4
EOC + LMP	6	3	9
All Cancers	6	1	7
All Cancers + LMP	8	4	12

According to sponsor, addition of ARCHITECT ROMA to ICRA detected 12 additional cancers missed by the ICRA with an acceptable rate of concomitant false positives.

Association between the ARCHITECT ROMA Score and Likelihood of Malignancy:

Summary statistics for the ARCHITECT ROMA scores, for subjects who had a primary ovarian malignancy (EOC + LMP) are given by cancer stage in the table below.

Number of Patients and Average ROMA Score for Patients with EOC + LMP						
		Unstaged	Stage I	Stage II	Stage III	Stage IV
Premenopausal	**N** **Mean**	3 3.28	5 4.12	1 9.20	7 7.97	0 N/A
Postmenopausal	**N** **Mean**	4 6.78	13 4.14	3 4.27	28 8.95	2 9.70

Summary statistics for the ARCHITECT ROMA scores, for subjects with all cancers + LMP are given by cancer stage in the table below.

Number of Patients and Average ROMA Score for Patients with all cancers + LMP						
		Unstaged	Stage I	Stage II	Stage III	Stage IV
Premenopausal	**N** **Mean**	3 3.28	8 9.20	1 9.20	9 7.35	1 0.44
Postmenopausal	**N** **Mean**	6 5.89	19 3.99	4 4.95	32 8.50	3 7.27

To demonstrate whether higher ARCHITECT ROMA is associated with an increased likelihood of cancer, additional analysis was conducted by splitting the patients at the cut-off point and finding the median ARCHITECT ROMA score within each split gives two balanced groups below the cutoff and additional groups above. The results are summarized below.

Premenopausal (cut-off 1.31)					
ARCHITECT ROMA Score		**0–0.47**	**0.47–1.31**	**1.31–1.79**	**1.79–10**
Benign	**Observed**	100	99	20	10
	Expected	95.3	92.5	20.2	21.1
Cancer	**Observed**	4	2	2	13
	Expected	8.7	8.5	1.8	1.9
Total		104	101	22	23
Cancer %		3.8% (4/104)	2.0% (2/101)	9.1% (2/22)	56.5% (13/23)
Postmenopausal (cut-off 2.77)					
ARCHITECT ROMA Score		**0–0.47**	**0.47–1.31**	**1.31–1.79**	**1.79–10**
Benign	**Observed**	65	59	18	3
	Expected	47.2	46.5	25.7	25.7
Cancer	**Observed**	3	8	19	34
	Expected	20.8	20.5	11.3	11.3
Total		68	67	37	37
Cancer %		4.4% (3/68)	11.9% (8/67)	51.4% (19/37)	91.9% (34/37)

4. Clinical cut-off**:**

   The following cut-offs are used to interpret the result. The ARCHITECT ROMA score is between 0.0 and 10.0.

   Premenopausal:
   ARCHITECT ROMA score ≥ 1.31: High likelihood of finding malignancy
   ARCHITECT ROMA score < 1.31: Low likelihood of finding malignancy

   Postmenopausal:
   ARCHITECT ROMA score ≥ 2.77: High likelihood of finding malignancy
   ARCHITECT ROMA score < 2.77: Low likelihood of finding malignancy

5. Expected values/Reference range:

   Expected values in healthy women: In order to determine the normal reference ranges of the ARCHITECT ROMA score in healthy women, 122 premenopausal samples and 120 postmenopausal samples were tested. Samples covered ages ranging from 18 to 87 and represented whites (95.0%), African American (3.3%) and Hispanic (0.1%) and Asian (0.1%) subjects. The results for the ARCHITECT ROMA score obtained from the pre- and postmenopausal populations are presented in the tables below:

	All Tested Subjects (N = 242)	Premenopausal Healthy Subjects (N = 122)	Postmenopausal Healthy Subjects (N = 120)
	ARCHITECT ROMA Score		
Mean (SD[1])	0.83 (0.56)	0.61 (0.48)	1.05 (0.55)
Median	0.83	0.43	0.91
Range (min, max)	0.11–3.56	0.11–2.88	0.36–3.56
Reference Interval (5^{th}, 95^{th} percentile)	0.24, 1.98	0.21, 1.65	0.46, 2.02
	ROMA Likelihood of finding malignancy (N, %)		
High Likelihood	11 (4.5%)	9 (7.4%)	2 (1.7%)
Low Likelihood	231 (95.5%)	113 (92.6%)	118 (93.3%)

[1]Standard deviation

Overall, 95% of the premenopausal healthy women had an ARCHITECT ROMA score equal to or below 1.65. 95% of the postmenopausal healthy women had a ARCHITECT ROMA score equal to or below 2.02. It is recommended that each laboratory establish its own reference value for the population of interest.

Expected values in Non-Ovarian Malignancy Condition:

To evaluate the performance of ARCHITECT ROMA in subjects with other benign and other malignant conditions, the ARCHITECT ROMA was evaluated in women with benign conditions (benign gynecological disease, congestive heart failure (CHF), hypertension, pregnant, and other benign disease) and in women with other malignant conditions (bladder cancer, breast cancer, endometrial cancer, gastrointestinal cancer, and lung cancer). 733 samples were analyzed. The tables below summarize the results analyzed for premenopausal and postmenopausal samples.

	Bladder Cancer (N=40)		Breast Cancer (N=40)		Endometrial Cancer (N=40)		GI Cancer (N=40)		Lung Cancer (N=40)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
N	2	38	12	28	8	32	5	35	2	38
ARCHITECT ROMA Score										
Mean (SD)	5.21 (6.68)	3.33 (2.26)	1.95 (2.59)	2.76 (2.01)	1.70 (2.63)	4.81 (3.29)	1.45 (1.51)	2.84 (2.01)	2.96 (3.46)	3.20 (1.81)
Median	5.21	2.67	1.20	1.94	0.67	5.10	0.81	2.33	2.96	3.13
Range (min-max)	0.49–9.93	0.60–9.82	0.25–9.79	0.32–6.90	0.30–8.05	0.73–9.95	0.70–4.14	0.64–9.08	0.51–5.40	0.61–7.82
5^{th}, 95^{th} percentile	0.96, 9.46	1.13, 7.62	0.43, 6.26	0.70, 6.86	0.31, 5.93	0.92, 9.66	0.71, 3.48	0.69, 7.37	0.75–5.16	0.78, 6.00
ROMA Likelihood of finding malignancy (N, %)										
High Likelihood	1 (50%)	18 (47%)	5 (42%)	11 (39%)	2 (25%)	19 (59%)	1 (20%)	21 (60%)	1 (50%)	21 (55%)
Low Likelihood	1 (50%)	20 (53%)	7 (58%)	17 (61%)	6 (75%)	13 (41%)	4 (80%)	14 (40%)	1 (50%)	17 (45%)

	Benign Gynecological Disease (N=374)		Other Benign Disease (N=39)		CHF (N=40)		Hypertension (N=40)		Pregnant (N=40)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
N	229	145	3	36	3	37	4	36	40	-
ARCHITECT ROMA Score										
Mean (SD)	0.72 (0.53)	1.77 (1.36)	0.26 (0.10)	3.15 (2.45)	0.79 (0.85)	2.61 (1.69)	0.82 (0.17)	2.21 (1.78)	0.58 (0.24)	-
Median	0.54	1.34	0.23	2.28	0.46	2.16	0.74	1.60	0.54	-
Range (min-max)	0.10–3.04	0.27–8.24	0.18–0.37	0.70–9.44	0.15–1.75	0.61–7.53	0.72–1.07	0.50–8.56	0.10–1.05	-
5^{th}, 95^{th} percentile	0.23, 1.70	0.58, 4.23	0.19–0.36	0.76, 8.50	0.18–1.62	0.63, 5.28	0.72, 1.02	0.70, 5.33	0.29, 1.01	-
ROMA Likelihood of finding malignancy (N, %)										
High Likelihood	31 (14%)	21 (14%)	0 (0.0%)	17 (47%)	1 (33%)	13 (35%)	0 (0%)	10 (28%)	0 (0%)	-
Low Likelihood	198 (86%)	124 (86%)	3 (100%)	19 (53%)	2 (67%)	24 (65%)	4 (100%)	26 (72%)	40 (100%)	-

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.