510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K153607

B. Purpose for Submission:

New Device

C. Measurand:

Ovarian adnexal mass assessment score based on two analytes

D. Type of Test:

Software algorithm and two immunoassays

E. Applicant:

Roche Diagnostics, Inc

F. Proprietary and Established Names:

ROMA Calculation Tool Using Elecsys Assays (RCTUEA)

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):
   ROMA Calculation Tool Using Elecsys Assays (RCTUEA) is a qualitative test

for serum and plasma (K2-EDTA, K3-EDTA and Li-Heparin) that combines the results of the Elecsys HE4 assay, Elecsys CA 125 II assay and menopausal status into a numerical score.

RCTUEA 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. RCTUEA 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. RCTUEA 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.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.

PRECAUTION: RCTUEA 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 RCTUEA 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:

   Elecsys and cobas e immunoassay analyzers

I. Device Description:

RCTUEA is a qualitative serum and plasma test that combines the results of two analytes, HE4 (Elecsys HE4) and CA125 (Elecsys CA 125 II) and menopausal status into a numerical score between 0.00 and 10.00. 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 Elecsys HE4, Elecsys CA 125 II, the RCTUEA Calculator Tool, and the Elecsys or cobas e immunoassay analyzers. The Elecsys and cobas e immunoassay analyzers are not capable of calculating the ROMA score. The immunoassays are performed according to the directions detailed in each product insert.

Both Elecsys HE4 and Elecsys CA 125 II are previously 510(k) cleared Class II devices (K112624 and K143534, respectively). The Elecsys HE4 assay is an

electrochemiluminescent immunoassay for the quantitative determination of HE4 antigen in human serum and plasma (K2-EDTA, K3-EDTA, and Li-Heparin) on the Elecsys or cobas e immunoassay analyzers. 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. Elecsys CA 125 II assay is an electrochemiluminescent immunoassay for the quantitative determination of CA125 in human serum and plasma (di- and tri-potassium EDTA and Li-Heparin) on the Elecsys or cobas e immunoassay analyzers. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with ovarian cancer. Serial testing for patient CA125 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

RCTUEA scores (numerical score from 0.00–10.00) for both premenopausal and postmenopausal women are calculated using the RCTUEA Calculator Tool to indicate a low likelihood or high likelihood for finding malignancy on surgery using the value of the two immunoassays (Elecsys HE4 and Elecsys CA125II).

J. Substantial Equivalence Information:

1. Predicate device name:

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

2. Predicate 510(k) number:

   K103358

3. Comparison with predicate:

Similarities		
Item	Device RCTUEA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
Intended Use/Indication for Use	ROMA Calculation Tool Using Elecsys Assays (RCTUEA) is a qualitative test for serum and plasma (K2-EDTA, K3-EDTA and Li-Heparin) that combines the results of the Elecsys HE4 assay, Elecsys CA 125 II assay and menopausal status into a numerical score. RCTUEA is intended to aid in assessing whether a premenopausal or postmenopausal woman who presents with an	The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 IITM and menopausal status into a numerical score. ROMA is intended to aid in assessing whether a premenopausal or postmenopausal woman

Similarities		
Item	Device RCTUEA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
	ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. RCTUEA 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. RCTUEA 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. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.	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.
Precaution	PRECAUTION: RCTUEA 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 RCTUEA carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.	Same
Type of test	Algorithm	Same
Measurand	Score based on two analytes and menopausal status	Same
Software	Provided separately for manual entry of assay values to obtain RCTUEA score	Same

Differences		
Item	Device RCTUEA	Predicate ROMA (HE4 EIA + ARCHITECT CA 125 II) K103358
Clinical Cut-off	<u>Premenopausal</u> RCTUEA score ≥ 1.14: High likelihood of finding malignancy RCTUEA score < 1.14: Low likelihood of finding malignancy <u>Postmenopausal</u> RCTUEA score ≥ 2.99: High likelihood of finding malignancy RCTUEA score < 2.99: Low likelihood of finding malignancy	<u>Premenopausal</u> RCTUEA score ≥ 1.31: High likelihood of finding malignancy RCTUEA score < 1.31: Low likelihood of finding malignancy <u>Postmenopausal</u> RCTUEA score ≥ 2.77: High likelihood of finding malignancy RCTUEA score < 2.77: Low likelihood of finding malignancy
Analyte	Roche Elecsys HE4 and Elecsys CA125 II	Fujirebio manual HE4 EIA and ARCHITECT CA125 II
Sample matrix	Serum, K_2-EDTA plasma, K_3-EDTA plasma, Li-Heparin plasma	Serum
Instrument platform	Elecsys and cobas e immunoassay analyzers	Manual ELISA for HE4 and ARCHITECT i2000SR for CA125
Assay Format	Same immunoassay platform for the detection of HE4 and CA125 in a single sample	Separate immunoassay platforms for the detection of HE4 and CA125 in a single sample

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A3, "Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Third Edition (2014)"

CLSI EP09-A3, "Measurement Procedure Comparison and Bias Estimation Using Patient Samples; approved Guideline-Third Edition (2013)"

CLSI guideline C28-A3c, "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition (2010)"

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

L. Test Principle:

The Elecsys HE4 assay is a two-step sandwich immunoassay. First, sample is incubated with a biotinylated monoclonal HE4-specific antibody and a monoclonal HE4-specific antibody labeled with a ruthenium to form a sandwich complex. After addition of streptavidin-coated microparticles, the complex bounds to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed. A voltage is applied to the electrode to induce chemiluminescent emission which is measured by a photomultiplier. The results are determined via a calibration curve that is instrument-specifically generated by two-point calibration and a master curve provided via the reagent barcode.

The Elecsys CA 125 II assay is a two-step sandwich immunoassay. First, sample is incubated with a biotinylated monoclonal CA 125-specific antibody and a monoclonal CA 125-specific antibody labeled with a ruthenium to form a sandwich complex. After addition of streptavidin-coated microparticles, the complex bounds to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed. A voltage is applied to the electrode to induce chemiluminescent emission which is measured by a photomultiplier. The results are determined via a calibration curve that is instrument-specifically generated by two-point calibration and a master curve provided via the reagent barcode.

The RCTUEA Calculator Tool is used for calculating the ROMA score. Using the value of the two analytes, RCTUEA scores (numerical score from 0.00–10.00) 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 RCTUEA 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 Elecsys HE4 and Elecsys CA 125 II are previously 510(k)-cleared Class II devices. Analytical performance for Elecsys HE4 and Elecsys CA 125 II were validated in K112624 and K143534, respectively. There has been no modification of assay methods for Elecsys HE4 or Elecsys CA 125 II since the original clearance for each assay. Thus, a limited study was done to evaluate the analytical performance of the RCTUEA.

a. Precision/Reproducibility:

i. Total Imprecision:

A panel of six samples were tested using one lot each of Elecsys HE4 and Elecsys CA 125 II reagents and calibrator kits according to each assay's package insert. The panel consisted of four human serum samples and two human plasma samples spiked with recombinant HE4 and CA 125.

Total imprecision was calculated at one site by testing each sample in two runs with two replicates per run for 21 non-consecutive days (n = 84 replicates per sample). The overall study design was based on CLSI guideline EP05-A3.

The following table displays the results for the repeatability and with-in laboratory reproducibility. All data met the manufacturer's predetermined acceptance criteria.

Sample	Mean ROMA Value	Within-Run		Between-Runs		Between-Days		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Premenopausal RCTUEA Score									
1	0.71	0.03	3.7%	0.00	0.0%	0.04	5.3%	0.05	6.5%
2	1.00	0.03	3.4%	0.02	2.2%	0.03	3.2%	0.05	5.1%
3	1.09	0.03	3.1%	0.03	2.4%	0.04	3.7%	0.06	5.4%
4	3.30	0.10	3.1%	0.03	0.8%	0.07	2.2%	0.13	3.9%
5	7.74	0.06	0.8%	0.04	0.5%	0.07	0.9%	0.10	1.3%
6	8.72	0.04	0.4%	0.02	0.2%	0.04	0.5%	0.06	0.7%
Postmenopausal RCTUEA Score									
1	1.12	0.02	2.1%	0.00	0.0%	0.05	4.2%	0.05	4.7%
2	2.53	0.05	1.9%	0.02	0.9%	0.07	2.9%	0.09	3.6%
3	2.60	0.05	1.9%	0.02	0.8%	0.06	2.5%	0.08	3.2%
4	5.52	0.07	1.3%	0.02	0.3%	0.08	1.5%	0.11	2.0%
5	8.51	0.03	0.3%	0.02	0.2%	0.05	0.6%	0.06	0.7%
6	8.86	0.02	0.2%	0.01	0.1%	0.04	0.4%	0.05	0.5%

ii. Lot-to-Lot Study:

A panel of six samples were tested using three lots each of Elecsys HE4 and Elecsys CA 125 II reagents and calibrator kits according to each

assay's package insert. The panel consisted of four human serum samples and two human plasma samples spiked with recombinant HE4 and CA 125.

Imprecision was calculated at one site by testing each sample in two runs with two replicates per run for 21 non-consecutive days (n = 84 replicates per sample for each lot). The overall study was performed based on CLSI guideline EP5-A3.

The following table displays the results for the lot-to-lot reproducibility. 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 RCTUEA Score											
1	0.71	0.08	10.7%	0.00	0.%	0.04	5.9%	0	0.0%	0.09	12.2%
2	1.00	0.03	3.1%	0.03	2.9%	0.06	5.6%	0.02	1.9%	0.07	7.3%
3	1.09	0.05	4.8%	0.01	1.2%	0.07	6.2%	0.01	1.4%	0.09	8.1%
4	3.31	0.09	2.6%	0.05	1.4%	0.13	3.8%	0.05	1.6%	0.17	5.1%
5	7.74	0.06	0.8%	0.05	0.7%	0.11	1.5%	0.05	0.6%	0.15	1.9%
6	8.72	0.04	0.4%	0.04	0.5%	0.07	0.8%	0.03	0.3%	0.09	1.1%
Postmenopausal RCTUEA Score											
1	1.13	0.06	4.9%	0.01	1.0%	0.05	4.0%	0.02	1.6%	0.07	6.6%
2	2.54	0.04	1.7%	0.04	1.7%	0.08	3.2%	0.06	2.2%	0.12	4.6%
3	2.61	0.08	3.2%	0.01	0.5%	0.08	3.1%	0.03	1.2%	0.12	4.6%
4	5.53	0.06	1.1%	0.04	0.7%	0.10	1.8%	0.07	1.2%	0.14	2.5%
5	8.51	0.03	0.4%	0.04	0.4%	0.05	0.6%	0.04	0.4%	0.08	1.0%
6	8.86	0.02	0.3%	0.03	0.3%	0.04	0.5%	0.03	0.3%	0.06	0.7%

iii. Site-to-site study:

A panel of six serum were tested at three different sites using one lot each of Elecsys HE4 and Elecsys CA 125 II reagents and calibrator kits according to each assay's package insert.

Imprecision was calculated by testing each sample in two runs with two replicates per run for 10 non-consecutive days at each site (n = 40 replicates per sample at each site). The overall study was performed based on CLSI guideline EP05-A3.

The following table displays the results for the site-to-site reproducibility. 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 RCTUEA Score											
1	0.76	0.02	2.6%	0.01	1.9%	0.02	2.6%	0.02	2.5%	0.04	4.8%
2	1.09	0.03	2.7%	0.02	1.6%	0.03	2.4%	0.03	2.9%	0.05	4.9%
3	1.19	0.03	2.5%	0.02	1.6%	0.03	2.5%	0.03	2.8%	0.06	4.8%
4	3.55	0.07	1.9%	0.03	0.8%	0.08	2.2%	0.05	1.4%	0.12	3.3%
5	7.94	0.04	0.5%	0.03	0.3%	0.05	0.7%	0.02	0.3%	0.07	0.9%
6	8.86	0.03	0.3%	0.02	0.3%	0.02	0.3%	0.02	0.2%	0.05	0.5%
Postmenopausal RCTUEA Score											
1	1.18	0.02	1.3%	0.01	1.2%	0.02	2.0%	0.03	2.8%	0.05	3.9%
2	2.65	0.03	1.2%	0.02	0.8%	0.05	1.7%	0.07	2.6%	0.09	3.4%
3	2.72	0.03	1.1%	0.02	0.8%	0.04	1.6%	0.06	2.4%	0.09	3.2%
4	5.69	0.03	0.6%	0.03	0.4%	0.06	1.0%	0.06	1.0%	0.09	1.6%
5	8.62	0.02	0.2%	0.01	0.1%	0.03	0.3%	0.02	0.3%	0.04	0.5%
6	8.95	0.01	0.1%	0.01	0.2%	0.02	0.2%	0.02	0.2%	0.03	0.4%

iv. Simulation precision:

In order to demonstrate precision of all possible combinations of analytes, a simulation precision study for the RCTUEA 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 RCTUEA score precision showed acceptable precision covering the range of RCTUEA score from 0 to10.

b. Linearity/assay reportable range:

Linearity studies for HE4 and CA 125 assay kits were presented in K112624 and K143534, 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 K112624 and K143534, respectively. No new traceability and stability data were presented in this submission.

Calibrators:

Each assay uses its own calibrator and controls.

Elecsys CA125 II Calibrators

The Elecsys CA125 II CalCheck calibration verification solutions comprise three levels: low, mid, and high. The results are reported in U/mL and the method has been standardized against the Enzymun-Test CA 125 II method. This in turn has been standardized against the CA 125 II RIA from Fujirebio Diagnostics.

Elecsys HE4 Calibrators

The Elecsys HE4 CalCheck5 set contains five lyophilized levels of human HE4 from OvCar-3 culture in equine serum and has been standardized against the HE4 EIA method from Fujirebio Diagnostics, Inc.

Stability:

Sample Stability: RCTUEA is intended for use with serum and plasma (K_2-EDTA, K_3-EDTA, and Li-Heparin). The specimen stability and storage claims are limited to the Elecsys HE4 assay. Samples can be stored for five hours at 15–25°C, two days at 2–8°C, 12 weeks at −20°C with up to two freeze/thaw cycles.

Reagent Stability: Users are instructed to refer to the individual stability information in the package insert of each assay.

Elecsys HE4 is stable when stored at 2–8°C until the expiration date stated on the label outside of the kit box. The current shelf life of Elecsys HE4 is 12 months.

Elecsys CA125II is table when stored at 2–8°C until the expiration date stated on the label outside of the kit box. The current shelf life of Elecsys CA125II is 18 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 RCTUEA score.

e. Analytical specificity:

Interference: Studies were conducted to evaluate the interference of RCTUEA score by endogenous substances.

Four patient serum samples with RCTUEA scores across the measuring range (0.80–8.82) were tested in this study. These samples were supplemented with each interfering substance in increasing concentrations. The control samples were prepared without corresponding interfering substance. The control samples and test samples were tested in a single replicate and the RCTUEA score was calculated. The effect of each interfering substance on the RCTUEA score was assessed by comparing the measurement of each test sample to the control. All data met the manufacturer's predetermined acceptance criteria and no interferences were seen. The results are presented in the table below:

Interferent	Substance Concentration	% Difference From Control							
		Mean ROMA Score							
		Sample 1		Sample 2		Sample 3		Sample 4	
		Low		Medium		High 1		High 2	
		Pre[1]	Post[2]	Pre	Post	Pre	Post		
Bilirubin	52.5 mg/dL	5	1	-2	-2	-3	-1	-1	-1
Lipid	760 g/dL	3	2	-2	-1	-2	-1	-1	-1
Hemoglobin	10 g/L	-4	-8	0	-4	-2	-2	-1	-1
Serum Albumin	3 g/dL	9	5	6	2	-1	-1	-1	0
HAMA	400 µg/L	-8	-9	N/D	N/D	N/D	N/D	0	-1
Rheumatoid Factor	600 IU/mL	6	10	2	4	-2	0	0	-1

f. Assay cut-off:

See clinical cut-off

2. Comparison studies:

a. Method comparison with predicate device:

A total of 187 samples were used for the study. The enrolled patients consist of 137 diseased patients and 50 apparently healthy women. 105 of the samples were from premenopausal women, and 82 of the samples were from postmenopausal women. The premenopausal ROMA range for the samples was 0.16–10.0 and for the postmenopausal samples was 0.5–9.97. No samples were excluded from the data analyses. 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 = 0.99x−0.20	0.97–1.01	−2.47–−0.16	0.99
	Passing-Bablok	y = 0.90x−0.08	0.86–0.95	−0.13–−0.04	0.99
Postmenopausal	Deming	y = 1.00x−0.30	0.99–1.02	−0.37–−0.24	0.99
	Passing-Bablok	y = 0.97x + 0.01	0.95–0.99	−0.02–0.06	0.99

b. Matrix comparison:

A matrix comparison was performed to compare the performance of RUCTEA in serum and K_2-EDTA plasma. 89 samples matched samples were tested that covered the range of the assays (RCTUEA score 0–10). Deming regression analysis demonstrated that performance in the two matrices was equivalent. The data met the manufacturer's predetermined acceptance criteria and are presented in the tables below.

Menopausal Status	Regression	Regression Equation	Slope (95% CI)	Intercept (95% CI)	r
Premenopausal	Deming	y = 1.00x−0.08	0.99–1.02	−0.10–−0.06	0.99
Postmenopausal	Deming	y = 1.00x−0.09	0.99–1.01	−0.12–−0.06	0.99

Simulated Matrix Comparison Study:

A simulation study was performed to evaluate the worst-case conditions where both the Elecsys HE4 and Elecsys CA 125II results showed the maximal matrix effects. The maximal matrix effects were calculated using the data for the K2-EDTA plasma, K3-EDTA plasma, and Li-Heparin plasma matrix comparisons that were completed for Elecsys HE4 and Elecsys CA 125 II in K112624 and K143534, respectively. The results of the simulation study were acceptable.

3. Clinical studies:

a. Clinical Sensitivity/Clinical Specificity:

A clinical study was done to validate RCTUEA 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 Elecsys HE4 and Elecsys CA 125 II.

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 RCTUEA and adjunctive use of ICRA and RCTUEA were evaluated by comparing to histopathology results for detecting the presence of ovarian malignancy.

Of the 512 patients, 51 patients were excluded from analysis. The most common reason for exclusion was no surgery was performed to remove an adnexal mass. Five additional patients were excluded because there was not enough sample available for testing, and one patient was excluded because the Elecsys CA 125 II value was outside of the measuring range of the device. In the final total of 455 evaluable patients, 249 (55%) were premenopausal and 206 (45%) were postmenopausal. All of the major racial groups were represented with 85% White, 7% of Black, 3% Hispanic, 3% Asian, and 3% of other ethnicity. The age range of the patients was 18–89 with a median age of 49.

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

	All N = 455		Premenopausal N = 249		Postmenopausal N = 206	
	N	%	N	%	N	%
Histopathology Benign	371	81.5%	228	91.6%	143	69.4%
Borderline/Low Malignant Potential (LMP)	18	4.0%	7	2.8%	11	5.3%
Epithelian Ovarian Cancer (EOC)	47	10.3%	9	3.6%	38	18.4%
Non-EOC	2	0.4%	0	0.0%	2	1.0%
Other Gynecological Cancer	9	2.0%	3	1.2%	6	2.9%
Other Cancer	7	1.5%	1	0.4%	6	2.9%
Metastatic Cancer	1	0.2%	1	0.4%	0	0.0%

The RCTUEA 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. The cut-offs are the same for serum, K2-EDTA plasma, K3-EDTA plasma, and Li-Heparin plasma.

Premenopausal:

RCTUEA score $\geq$ 1.14: High likelihood of finding malignancy
RCTUEA score < 1.14: Low likelihood of finding malignancy

Postmenopausal:

RCTUEA score ≥ 2.99: High likelihood of finding malignancy
RCTUEA score < 2.99: Low likelihood of finding malignancy

The information provided by the RCTUEA test should be used by physician only as an adjunctive test to complement, not replace, other diagnostic and clinical procedures. The ability of RCTUEA 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 RCTUEA, and adjunctive use of ICRA and RCTUEA. The performance of RCTUEA evaluated for diagnosis of EOC including LMP are presented below.

Performance of RCTUEA for Diagnosis of EOC including LMP (436 patients):

Combined pre- and postmenopausal subjects:

For diagnosis of EOC including LMP, the counts for all 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**
RCTUEA	**Positive**	47	9	56
	Negative	3	6	9
	Total	50	15	65

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	24	52	76
	Negative	34	261	295
	Total	58	313	371

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

The following table presents the observed frequencies of malignancy tabulated according to ICRA and RCTUEA test results from 436 patients.

	Frequency of Malignancy	95% CI
Prevalence of malignancy among patients with adnexal mass assessed: 14.9% (65/436)		
ICRA alone “Positive”	46.3% (50/108)	36.7%–56.2%
ICRA alone “Negative”	4.6% (15/328)	2.6%–7.4%
RCTUEA alone “Positive”	42.4% (56/132)	33.9%–51.3%
RCTUEA alone “Negative”	3.0% (9/304)	1.4%–5.5%
ICRA “Positive” and RCTUEA “Positive”	66.2% (47/71)	54.0%–77.0%
ICRA “Positive” and RCTUEA “Negative”	8.1% (3/37)	1.7%–21.9%
ICRA “Negative” and RCTUEA “Positive”	14.8% (9/61)	7.0%–26.2%
ICRA “Negative” and RCTUEA “Negative”	2.3% (6/267)	0.8%–4.8%

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”	4.92	3.37–7.18
ICRA alone “Negative”	0.27	0.16–0.46
RCTUEA alone “Positive”	4.21	2.98–5.94
RCTUEA alone “Negative”	0.17	0.09–0.34
ICRA “Positive” and RCTUEA “Positive”	11.18	6.84–18.28
ICRA “Positive” and RCTUEA “Negative”	0.5	0.15–1.64
ICRA “Negative” and RCTUEA “Positive”	0.99	0.49–2.00
ICRA “Negative” and RCTUEA “Negative”	0.13	0.06–0.29

The likelihood ratio for identifying malignancy by adjunctive use of RCTUEA and ICRA is 11.18, 2.3 times higher than the likelihood ratio by ICRA alone (4.92).

The performance of adjunctive use of RCTUEA 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.

Performance of the Test for Diagnosis of EOC including LMP for both Pre- and Postmenopausal Subjects			
	ICRA	RCTUEA	ICRA and RCTUEA
Sensitivity (95% CI)	76.9% (50/65) (64.8%–86.5%)	86.2% (56/65) (75.3%–93.5%)	90.8% (59/65) (81%–96.5%)
Specificity (95% CI)	84.4% (313/371) (80.3%–87.9%)	79.5% (295/371) (75%–83.5%)	70.4% (261/371) (65.4%–75%)
PPV (95% CI)	46.3% (50/108) (36.7%–56.2%)	42.4% (56/132) (33.9%–51.3%)	34.9% (59/169) (27.8%–42.6%)
NPV (95% CI)	95.4% (313/328) (92.6%–97.4%)	97% (295/304) (94.5%–98.6%)	97.8% (261/267) (95.2%–99.2%)
Prevalence	14.9% (65/436)		

With adjunctive use of ICRA and RCTUEA for diagnosis of EOC including LMP, sensitivity for malignancy increased from 76.9% to 90.8%. Specificity for malignancy decreased from 84.4% to 70.4%. PPV for the adjunctive use of ICRA and RCTUEA decreased from 46.3% to 34.9% due to an increase in the number of false positive tests added by the addition of RCTUEA to ICRA. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 95.4% to 97.8%. The increase of NPV was 2.3% and was statistically significant.

Premenopausal subjects:

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

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	8	43	51
	Negative	15	162	177
	Total	23	205	228

The performance of adjunctive use of RCTUEA 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.

Performance of the Test for Diagnosis of EOC including LMP for Premenopausal Subjects			
	ICRA	RCTUEA	ICRA and RCTUEA
Sensitivity (95% CI)	43.8% (7/16) (19.8%–70.1%)	81.3% (13/16) (54.4%–96%)	81.3% (13/16) (54.4%–96.0%)
Specificity (95% CI)	89.9% (205/228) (85.2%–93.5%)	77.6% (177/228) (71.7%–82.9%)	71.1% (162/228) (64.7%–76.8%)
PPV (95% CI)	23.3% (7/30) (9.9%–42.3%)	20.3% (13/64) (11.3%–32.2%)	16.5% (13/79) (9.1%–26.5%)
NPV (95% CI)	95.8% (205/214) (92.2%–98.1%)	98.3% (177/180) (95.02%–99.7%)	98.2% (162/165) (94.8%–99.6%)
Prevalence	6.6% (16/244)		

With adjunctive use of ICRA and RCTUEA for diagnosis of EOC including LMP, sensitivity for malignancy increased from 43.8% to 81.3%. Specificity for malignancy decreased from 89.9% to 71.1%. PPV for the adjunctive use of ICRA and RCTUEA decreased from 23.5% to 16.5% due to an increase in the number of false positive tests added by the addition of RCTUEA to ICRA. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 95.8% to 98.2%. The increase of NPV was 2.4% and was statistically significant.

Postmenopausal subjects:

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	40	3	43
	Negative	3	3	6
	Total	43	6	49

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	16	9	25
	Negative	19	99	118
	Total	35	108	143

The performance of adjunctive use of RCTUEA 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.

Performance of the Test for Diagnosis of EOC including LMP for Postmenopausal Subjects			
	ICRA	RCTUEA	ICRA and RCTUEA
Sensitivity (95% CI)	87.8% (43/49) (75.2%–95.4%)	87.8% (43/49) (75.2%–95.4%)	93.9% (46/49) (83.1%–98.7%)
Specificity (95% CI)	75.5% (108/143) (67.6%–82.3%)	82.5% (118/143) (75.3%–88.4%)	69.2% (99/143) (61%–76.7%)
PPV (95% CI)	55.1% (43/78) (43.4%–66.4%)	63.2% (43/68) (50.7%–74.6%)	51.1% (46/90) (40.3%–61.8%)
NPV (95% CI)	94.7% (108/114) (88.9%–98%)	95.2% (118/124) (89.8%–98.2%)	97.1% (99/102) (91.6%–99.4%)
Prevalence	25.5% (49/192)		

With adjunctive use of ICRA and RCTUEA for diagnosis of EOC including LMP, sensitivity for malignancy increased from 87.8% to 93.9%. Specificity for malignancy decreased from 75.5% to 69.2%. PPV for the adjunctive use of ICRA and RCTUEA decreased from 55.1% to 51.1% due to an increase in the number of false positive tests added by the addition of RCTUEA to ICRA. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 94.7% to 97.1%. The increase of NPV was 2.3% and was statistically significant.

Performance of RCTUEA for Diagnosis of All Cancers including LMP (455 patients):

Combined pre- and postmenopausal subjects:

For diagnosis of all cancers including LMP, the counts for all 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**
RCTUEA	**Positive**	54	13	67
	Negative	7	10	17
	Total	61	23	84

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	24	52	76
	Negative	34	261	295
	Total	58	313	371

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

The following table presents the observed frequencies of malignancy tabulated according to ICRA and RCTUEA test results from 455 patients.

	Frequency of Malignancy	95% CI
Prevalence of malignancy among patients with adnexal mass assessed: 18.5% (84/455)		
ICRA alone “Positive”	51.3% (61/119)	41.9%–60.5%
ICRA alone “Negative”	6.8% (23/336)	4.4%–10.1%
RCTUEA alone “Positive”	46.9% (67/143)	38.5%–55.4%
RCTUEA alone “Negative”	5.4% (17/312)	3.2%–8.6%
ICRA “Positive” and RCTUEA “Positive”	69.2% (54/78)	57.8%–79.2%
ICRA “Positive” and RCTUEA “Negative”	17.1% (7/41)	7.2%–32.1%
ICRA “Negative” and RCTUEA “Positive”	20.0% (13/65)	11.1%–31.8%
ICRA “Negative” and RCTUEA “Negative”	3.7% (10/271)	1.8%–6.7%

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”	4.65	3.24–6.65
ICRA alone “Negative”	0.32	0.21–0.50
RCTUEA alone “Positive”	3.89	2.80–5.41
RCTUEA alone “Negative”	0.25	0.16–0.41
ICRA “Positive” and RCTUEA “Positive”	9.94	6.14–16.07
ICRA “Positive” and RCTUEA “Negative”	0.91	0.40–2.05
ICRA “Negative” and RCTUEA “Positive”	1.10	0.60–2.03
ICRA “Negative” and RCTUEA “Negative”	0.17	0.09–0.32

The likelihood ratio for identifying malignancy by adjunctive use of RCTUEA and ICRA is 9.94, 2.1 times higher than the likelihood ratio by ICRA alone (4.65).

The performance of adjunctive use of RCTUEA 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.

Performance of the Test for Diagnosis of All Cancers including LMP for both Pre- and Postmenopausal Subjects			
	ICRA	RCTUEA	ICRA and RCTUEA
Sensitivity (95% CI)	72.6% (61/84) (61.8%–81.8%)	79.8% (67/84) (69.6%–87.7%)	88.1% (74/84) (79.2%–94.1%)
Specificity (95% CI)	84.4% (313/371) (80.3%–87.9%)	79.5% (295/371) (75%–83.5%)	70.4% (261/371) (65.4%–75.0%)
PPV (95% CI)	51.3% (61/119) (41.9%–60.5%)	46.9% (67/143) (38.5%–55.4%)	40.2% (74/184) (33.1%–47.7%)
NPV (95% CI)	93.2% (313/336) (89.9%–95.6%)	94.6% (295/312) (91.4%–96.8%)	96.3% (261/271) (93.3%–98.2%)
Prevalence	18.5% (84/455)		

With adjunctive use of ICRA and RCTUEA for diagnosis of all cancers including LMP, sensitivity for malignancy increased from 72.6% to 88.1%. Specificity for malignancy decreased from 84.4% to 70.4%. PPV for the adjunctive use of ICRA and RCTUEA decreased from 51.3% to 40.2% due to an increase in the number of false positive tests added by the addition of RCTUEA to ICRA. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 93.2% to 96.3%. The increase of NPV was 3.2% and was statistically significant.

Premenopausal subjects:

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

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	8	43	51
	Negative	15	162	177
	Total	23	205	228

The performance of adjunctive use of RCTUEA 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.

Performance of the Test for Diagnosis of All Cancers including LMP for Premenopausal Subjects			
	ICRA	RCTUEA	ICRA and RCTUEA
Sensitivity (95% CI)	38.1% (8/21) (18.1%–61.6%)	71.4% (15/21) (47.8%–88.7%)	76.2% (16/21) (52.8%–91.8%)
Specificity (95% CI)	89.9% (205/228) (85.2%–93.5%)	77.6% (177/228) (71.7%–82.9%)	71.1% (162/228) (64.7%–76.8%)
PPV (95% CI)	25.8% (8/31) (11.9%–44.6%)	22.7% (15/66) (13.3%–34.7%)	19.5% (16/82) (11.6%–29.7%)
NPV (95% CI)	94.0% (205/218) (90%–96.8%)	96.7% (177/183) (93%–98.8%)	97.0% (162/167) (93.2%–99%)
Prevalence	8.4% (21/249)		

With adjunctive use of ICRA and RCTUEA for diagnosis of all cancers including LMP, sensitivity for malignancy increased from 38.1% to 76.2%. Specificity for malignancy decreased from 89.9% to 71.1%. PPV for the adjunctive use of ICRA and RCTUEA decreased from 25.8% to 19.5% due to an increase in the number of false positive tests added by the addition of RCTUEA to ICRA. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 94.0% to 97.0%. The increase of NPV was 3.0% and was statistically significant.

Postmenopausal subjects:

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	47	5	52
	Negative	6	5	11
	Total	53	10	63

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
RCTUEA	**Positive**	16	9	25
	Negative	19	99	118
	Total	35	108	143

The performance of adjunctive use of RCTUEA 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.

Performance of the Test for Diagnosis of All Cancers including LMP for Postmenopausal Subjects			
	ICRA	RCTUEA	ICRA and RCTUEA
Sensitivity (95% CI)	84.1% (53/63) (72.7%–92.1%)	82.5% (52/63) (70.9%–90.9%)	92.1% (58/63) (82.4%–97.4%)
Specificity (95% CI)	75.5% (108/143) (67.6%–82.3%)	82.5% (118/143) (75.3%–88.4%)	69.2% (99/143) (61%–76.7%)
PPV (95% CI)	60.2% (53/88) (49.2%–70.5%)	67.5% (52/77) (55.9%–77.8%)	56.9% (58/102) (46.7%–66.6%)
NPV (95% CI)	91.5% (108/118) (85%–95.9%)	91.5% (118/129) (85.3%–95.7%)	95.2% (99/104) (89.1%–98.4%)
Prevalence	30.6% (63/206)		

With adjunctive use of ICRA and RCTUEA for diagnosis of EOC including LMP, sensitivity for malignancy increased from 84.1% to 92.1%. Specificity for malignancy decreased from 75.5% to 69.2%. PPV for the adjunctive use of ICRA and RCTUEA decreased from 60.2% to 56.9% due to an increase in the number of false positive tests added by the addition of RCTUEA to ICRA. However, NPV of the adjunctive use of ICRA and RCTUEA increased from 91.5% to 95.2%. The increase of NPV was 3.7% and was statistically

significant.

Association between the RCTUEA Score and Likelihood of Malignancy:

Summary statistics for the RCTUEA 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 RCTUEA Score for Patients with EOC + LMP						
		Unstaged	Stage I	Stage II	Stage III	Stage IV
Premenopausal	N Mean	3 3.33	5 4.39	1 9.22	7 7.94	0 N/A
Postmenopausal	N Mean	4 6.99	13 4.36	3 4.80	27 8.89	2 9.67

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

Number of Patients and Average RCTUEA Score for Patients with All Cancers + LMP						
		Unstaged	Stage I	Stage II	Stage III	Stage IV
Premenopausal	N Mean	3 3.33	8 3.16	1 9.22	9 7.35	1 0.70
Postmenopausal	N Mean	6 6.07	19 4.26	4 5.43	31 8.45	3 7.63

To demonstrate whether a higher RCTUEA score 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 RCTUEA score within each split giving two balanced groups below the cutoff and additional groups above. The results are summarized below.

Premenopausal (cut-off 1.14)					
RCTUEA Score		0–0.61	0.61–1.14	1.14–1.84	1.84–10
Benign	Observed	90	87	33	18
	Expected	84.2	83.3	30.2	30.2
Cancer	Observed	2	4	0	15
	Expected	7.8	7.7	2.8	2.8
Total		92	91	33	33
Cancer %		2.2% (2/90)	4.4% (4/91)	0.0% (0/33)	45.5% (15/33)
Postmenopausal (cut-off 2.99)					
RCTUEA Score		0–1.50	1.50–2.99	2.99–6.57	6.57–10
Benign	Observed	62	57	21	3
	Expected	45.1	45.1	26.4	26.4

Cancer	Observed	3	8	17	35
	Expected	19.9	19.9	11.6	11.6
Total		65	65	38	38
Cancer %		4.6% (3/65)	12.3% (8/65)	44.7% (17/38)	92.1% (35/38)

4. Clinical cut-off**:**

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

Premenopausal:

RCTUEA score ≥ 1.14: High likelihood of finding malignancy
RCTUEA score < 1.14: Low likelihood of finding malignancy

Postmenopausal:

RCTUEA score ≥ 2.99: High likelihood of finding malignancy
RCTUEA score < 2.99: Low likelihood of finding malignancy

5. Expected values/Reference range:

Expected values in Healthy Subjects:

In order to determine the normal and reference ranges of RCTUEA score in healthy women, 120 premenopausal samples and 120 postmenopausal samples (total = 240 samples) were tested. Samples covered age ranging from 18 to 87 and represented whites (96%), African American (2%), Hispanic (1%) and Asian (1%) subjects. The results for RCTUEA score obtained from the pre- and post-menopausal populations are presented below:

	All Tested Subjects (N = 240)	Premenopausal Healthy Subjects (N = 120)	Postmenopausal Healthy Subjects (N = 120)
	RCTUEA Score		
Mean (SD[1])	1.01 (0.71)	0.71 (0.57)	1.32 (0.70)
Median	0.84	0.54	1.16
Range (min, max)	0.21–5.58	0.21–3.70	0.38–5.58
Reference Interval (5^{th}, 95^{th} percentile)	0.33, 2.39	0.26, 1.70	0.61, 2.58
	RCTUEA Likelihood of Finding Malignancy (N, %)		
High Likelihood	17 (7.1%)	14 (11.7%)	3 (2.5%)
Low Likelihood	223 (92.9%)	106 (88.3%)	117 (97.5%)

Overall, 95% of the premenopausal healthy female subjects had a RCTUEA score equal to or below 1.70. Ninety-five percent of the postmenopausal healthy female subjects had a RCTUEA score equal to or below 2.58. These values were chosen

based on the 95th percentile of the population tested. It is recommended that each laboratory establish its own reference value for the population of interest.

Expected values in Non-Ovarian Malignancy Conditions:

To evaluate the performance of RCTUEA in subjects with other benign and other malignant conditions, RCTUEA 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). 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	37	12	28	12	28	9	31	3	37
RCTUEA										
Mean (SD)	5.40 (6.41)	3.11 (2.23)	2.17 (2.54)	3.12 (2.15)	1.95 (1.58)	3.37 (2.78)	1.35 (0.70)	2.31 (2.04)	0.61 (0.35)	3.41 (0.94)
Median	5.4	2.45	1.24	2.03	1.49	2.18	1.18	1.54	0.41	3.59
Range (min–max)	0.86–9.93	0.65–9.66	0.44–9.61	0.47–6.64	0.67–5.69	0.69–887	0.54–2.97	0.68–9.14	0.4–1.01	0.95–4.8
5^{th}, 95^{th} percentile	1.31, 9.48	0.81, 7.99	0.57, 6.35	0.66, 6.50	0.69, 5.15	0.74, 8.45	0.69, 2.46	0.81, 6.49	0.40, 0.95	1.82, 4.62
RCTUEA Likelihood of finding malignancy (N, %)										
High Likelihood	1 (50%)	13 (35%)	8 (67%)	12 (43%)	8 (67%)	10 (36%)	5 (56%)	6 (19%)	0 (0.0%)	29 (78%)
Low Likelihood	1 (50%)	24 (65%)	4 (33%)	16 (57%)	4 (33%)	18 (64%)	4 (44%)	25 (81%)	3 (100%)	8 (22%)

	Benign Gynecological Disease (N = 366)		Other Benign Disease (N = 40)		CHF (N = 40)		Hypertension (N = 40)		Pregnant (N = 40)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
N	233	147	2	38	0	40	4	36	40	0
RCTUEA Score										
Mean (SD)	0.96 (0.82)	2.15 (1.52)	0.58 (0.23)	2.92 (2.53)	–	2.48 (1.53)	0.54 (0.10)	2.35 (1.77)	0.54 (0.19)	–
Median	0.72	1.67	0.58	1.76	–	2.12	0.55	1.97	0.52	–
Range (min–max)	0.13–6.87	0.36–8.40	0.42–0.74	0.48–9.44	–	0.69–7.31	0.43–0.63	0.67–8.58	0.19–0.97	–
5^{th}, 95^{th} percentile	0.32, 2.29	0.68, 5.02	0.44, 0.72	0.85, 8.55	–	0.90, 5.69	0.44, 0.63	0.75, 5.42	0.26, 0.89	–
RCTUEA Likelihood of finding malignancy (N, %)										
High Likelihood	56 (24%)	29 (20%)	0 (0.0%)	11 (29%)	–	12 (30%)	0 (0.0%)	9 (25%)	0 (0.0%)	–
Low Likelihood	177 (76%)	118 (80%)	2 (100%)	27 (71%)	–	28 (70%)	4 (100%)	27 (75%)	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