510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K242981

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

Atellica IM Thyroglobulin (Tg)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
MSW	Class II	21 CFR 866.6010 - Tumor-Associated Antigen Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New Device

B Measurand:

Thyroglobulin

C Type of Test:

Quantitative, Chemiluminescent Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Atellica IM Thyroglobulin (Tg) assay is for in vitro diagnostic use in the quantitative measurement of thyroglobulin in human serum and plasma (EDTA and lithium heparin) using the Atellica IM Analyzer.

Thyroglobulin measurements are used as an aid in monitoring differentiated thyroid cancer patients who have undergone thyroidectomy with or without radioiodine ablation.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The Instructions for Use of the device contains the following warning statement:

- The presence of autoantibodies against thyroglobulin (anti-Tg) can interfere with the determination of thyroglobulin (Tg) in patient samples. Samples that contain anti-Tg should not be tested for Tg.
- When monitoring patients over time, Tg values obtained with different methods cannot be used interchangeably due to differences in methods and reagent specificity.

D Special Instrument Requirements:

Atellica IM Analyzer (cleared under K151792)

IV Device/System Characteristics:

A Device Description:

The following materials are included in the Atellica IM Thyroglobulin (Tg):

- Tg ReadyPack primary reagent pack

  Solid Phase (15.0 mL/reagent pack): Streptavidin-coated paramagnetic microparticles preformed with biotinylated mouse monoclonal anti-human Tg antibody (~267 µg/mL), BSA, mouse IgG, buffer, stabilizers, and preservatives.

  Lite Reagent (7.5 mL/reagent pack): Mouse monoclonal anti-human Tg antibody labeled with acridinium ester (~1.13 µg/mL), bovine serum albumin (BSA), mouse IgG, buffer, stabilizers, and preservatives.

  Ancillary well reagent (6.0 mL/reagent pack): BSA, bovine gamma globulin, buffer, and preservatives.

- Tg CAL (2.0 mL/vial Lyophilized): After reconstitution, human thyroglobulin, BSA, buffer, stabilizers, and preservatives.

The following materials are needed but not supplied:

- Atellica IM Multi-Diluent 11 ReadyPack ancillary reagent pack (2 x 5.0 mL/pack): Tris buffer, goat serum, protein stabilizers and preservatives
- Atellica IM Multi-Diluent 11 (10.0 mL/vial): Tris buffer, goat serum, protein stabilizers and preservatives
- Atellica IM Tg Master Curve Material (Tg MCM).

B Principle of Operation:

This assay is an automated sandwich immunoassay using acridinium ester chemiluminescent technology, which uses constant amounts of two monoclonal antibodies. The first antibody, in the Lite Reagent, is a mouse monoclonal anti-human Tg antibody labeled with acridinium ester. The second antibody is a biotinylated mouse monoclonal anti-human Tg antibody that is bound to streptavidin-coated paramagnetic latex particles in the Solid Phase. A direct relationship exists between the amount of Tg present in the patient sample and the amount of relative light units (RLUs) detected by the system.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access Thyroglobulin

B Predicate 510(k) Number(s):

K241423

C Comparison with Predicate(s):

Device & Predicate Device(s):	K242981	K241423
Device Trade Name	Atellica IM Thyroglobulin (Tg)	Access Thyroglobulin
General Device Characteristic Similarities		
Intended Use/ Indications For Use	The Atellica IM Thyroglobulin (Tg) assay is for in vitro diagnostic use in the quantitative measurement of thyroglobulin in human serum and plasma (EDTA and lithium heparin) using the Atellica IM Analyzer.	Access Thyroglobulin assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of thyroglobulin levels in human serum and plasma using the Access Immunoassay Systems.

	Thyroglobulin measurements are used as an aid in monitoring differentiated thyroid cancer patients who have undergone thyroidectomy with or without radioiodine ablation.	This device is intended to aid in monitoring for the presence of persistent or recurrent/metastatic disease in patients who have differentiated thyroid cancer (DTC) and have had thyroid surgery (with or without ablative therapy), and who lack serum thyroglobulin antibodies.
Technology	Chemiluminescent	Same
Analyte	Thyroglobulin	Same
Sample Matrix	Serum and Plasma	Same
Measurement	Quantitative	Same
Operating Principle	Automated Sandwich immunoassay	Same
Antibodies	Mouse monoclonal antibodies	Same
Capture Antibody	Biotinylated mouse monoclonal anti-human Tg antibody	Same
Traceability	Traceable to the Community Bureau of Reference (BCR) Certified Reference Material (CRM) 457	Same
General Device Characteristic Differences		
Analytical Measuring Interval	0.05–150 ng/mL	0.1–500 ng/mL
Sample Volume	100 µL	40 µL
Detection Antibody	Mouse monoclonal anti-Tg labeled with acridinium ester	Mouse monoclonal anti-Tg-alkaline phosphatase
Calibration	2 levels	6 levels

VI Standards/Guidance Documents Referenced:

The following Clinical and Laboratory Standards Institute (CLSI) guidelines were used:

- CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition
- CLSI EP06 2nd Edition, Evaluation of Linearity of Quantitative, Measurement Procedures
- CLSI EP07 3rd Edition, Interference Testing in Clinical Chemistry
- CLSI EP09c 3rd Edition, Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP12-A2, User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition

- CLSI EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline
- CLSI EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition
- CLSI EP34 1st Edition, Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking
- CLSI EP37 1st Edition, Supplemental Tables for Interference Testing in Clinical Chemistry
- CLSI I/LA30-A, Immunoassay Interference by Endogenous Antibodies; Approved Guideline

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision testing was performed in accordance with CLSI guideline EP05-A3.

a) *Within-Laboratory Precision*

The studies were performed at a single site using one lot of the Atellica IM Thyroglobulin reagent on one Atellica IM Analyzer. Seven levels of human serum samples were run in a two replicates per run, two runs daily over the course of 20 days, resulting a total of 80 datapoints for each sample. The data were analyzed for repeatability (within-run), between-run, between-day, and within-laboratory precision. The mean (ng/mL), standard deviation (SD) (ng/mL) and percent coefficient of variation (%CV) are summarized in table below.

Sample	N	Mean (ng/mL)	Within-Run (Repeatability)		Between-Run		Between-Day		Within-Laboratory	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	80	0.08	0.01	6.4	0.00	3.8	0.00	5.1	0.01	9.0
2	80	0.15	0.00	2.0	0.00	1.3	0.00	2.0	0.01	3.3
3	80	1.79	0.03	1.8	0.01	0.3	0.03	1.5	0.04	2.3
4	80	6.12	0.08	1.3	0.03	0.5	0.12	1.9	0.15	2.4
5	80	25.14	0.58	2.3	0.00	0.0	0.55	2.2	0.79	3.2
6	80	78.93	0.98	1.2	0.77	1.0	1.71	2.2	2.12	2.7
7	80	136.36	2.59	1.9	1.48	1.1	2.59	1.9	3.95	2.9

b) *Lot-to-Lot Precision*

The lot-to-lot precision of the Atellica IM Thyroglobulin was performed using three reagent lots. Five levels of serum samples were run in three replicates per run, two runs

per day over the course of five days, resulting in a total of 90 datapoints for each sample. The data were analyzed for repeatability (within-run), between-day, between-reagent lot, and total precision. The mean (ng/mL), standard deviation (SD) (ng/mL) and percent coefficient of variation (%CV) are summarized in table below:

Sample	N	Mean (ng/mL)	Within-Run (Repeatability)		Between-Day		Between-Reagent Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	90	0.16	0.01	4.3	0.00	0.0	0.00	2.5	0.01	4.9
2	90	1.81	0.05	2.6	0.00	0.0	0.11	6.1	0.12	6.7
3	90	25.50	0.21	0.8	0.19	0.7	0.11	0.4	0.31	1.2
4	90	73.90	0.83	1.1	0.73	1.0	0.10	0.1	1.18	1.6
5	90	119.00	1.35	1.1	0.85	0.7	1.43	1.2	2.23	1.9

c) *Site-to-Site Reproducibility:*

The study was performed at one internal and two external sites. Five levels of human serum sample were run at three sites, using one lot of Atellica IM Thyroglobulin reagents, in three replicates per run, two runs per day over the course of a minimum five days (3 x 3 x 2 x 5, n=90 for each sample). The data was analyzed for repeatability (within-run), between-run, between-day, between-site, and reproducibility. The mean (ng/mL), standard deviation (SD) (ng/mL) and percent coefficient of variation (%CV) are summarized in the table below:

Sample	N	Mean (ng/mL)	Within-Run (Repeatability)		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	90	0.16	0.01	3.2	0.00	0.0	0.00	0.0	0.00	1.9	0.01	3.9
2	90	1.83	0.03	1.7	0.02	0.8	0.01	0.4	0.10	5.5	0.11	5.8
3	90	25.70	0.32	1.2	0.10	0.4	0.10	0.4	0.36	1.4	0.50	1.9
4	90	74.50	1.12	1.5	0.00	0.0	0.24	0.3	1.91	2.6	2.23	3.0
5	90	119.00	1.76	1.5	0.72	0.6	0.85	0.7	4.53	3.8	4.99	4.2

2. Linearity:

a) *Linearity studies:*

The linearity of the Atellica IM Thyroglobulin assay was performed in accordance with CLSI guideline EP06 2nd Edition. Two series were prepared. High samples were prepared by pooling human serum samples to achieve Thyroglobulin concentrations of 163.8 ng/mL (Sample-1) and 7.5 ng/mL (Sample-2). Low sample was created from human serum sample that was blended with stripped human serum to achieve a concentration below the low end of the AMI of the assay. The dilution series was prepared by mixing the high and low levels in known ratios. The dilution levels were run in replicates of six on one Atellica IM Analyzer using one Atellica IM Thyroglobulin reagent lot, one calibration for one day. The 'measured value' (mean Thyroglobulin ng/mL) was compared to its predicted value for deviation percentage using a weighted linear

regression analysis. This deviation was then compared to the allowable deviation from linearity (ADL). The results are summarized in the table below.

Sample	Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	R^2	% Deviation**
1	0.04 – 163.8	1.065 (1.040 – 1.090)	-0.005 (-0.042 – 0.033)	0.999	-6.1% – 4.5%
2	0.04 – 7.5	0.924 (0.907 – 0.941)	0.011 (0.001 – 0.021)	0.998	-3.6% – 8.1%
1 & 2*	0.04 – 163.8	0.946 (0.920 – 0.972)	0.007 (-0.010 – 0.025)	0.999	-5.3% – 15.0%

*Combined from Sample 1 and 2.
**Minimum and maximum deviation from linearity

The data support the linearity interval from 0.04−163.8 ng/mL with the deviations from linearity within acceptable % Deviation or Deviation of ≤ -0.008 ng/mL. The study results support the linearity of the claimed analytical measuring interval (AMI): 0.05–150 ng/mL.

b) *Extended Measuring Interval:*

Dilutional recovery testing was performed in accordance with CLSI guideline EP34 1st Edition.

i) Auto Dilution Recovery:

Auto dilution recovery studies were conducted using 5 – 9 pools of human serum samples with different Thyroglobulin concentrations. The samples above the assay range were diluted onboard the instrument with Atellica Multi-diluent 11 using the 'Instructions for Use' specified dilution factors of 10, 20, and 50. The samples were measured in five replicates per sample per instrument, using one Atellica IM Tg reagent lot, one calibration, one test day, one lot of sample diluent, two Atellica IM Analyzers. The mean recoveries were between 98% and 110%. The results show that the dilutions performed by the instrument are within specifications.

ii) Manual Dilution Recovery:

Manual dilution recovery studies were conducted using 5 – 9 pools of human serum samples with different Thyroglobulin concentrations. The samples above the assay range were diluted manually with Atellica Multi-diluent 11 using the 'Instructions for Use' specified dilution factors of 10, 20, and 50. Testing of dilution recovery was completed using one Atellica IM Tg reagent lot, one calibration, one test day, one lot of sample diluent, two operators, two manual dilutions per operator per dilution factor. Each operator ran samples on a separate instrument, for a total of two Atellica IM Analyzers. The mean recoveries were between 94% and 109%. The results show that the dilutions performed manually are within specifications.

c) *High Dose Hook Effect:*

Hook effect of the Atellica IM Thyroglobulin was determined by spiking purified Thyroglobulin solution in human serum. Twelve serial dilutions were prepared by diluting a high sample (≥40,000 Thyroglobulin ng/mL) with low sample. The study was completed by testing each sample level in six replicates, using one Atellica IM Tg reagent lot, one Atellica IM Analyzer, one calibration, and one high sample. The data shows that no hook effect was observed with the Atellica IM Tg assay in samples with concentrations as high as 82,972 ng/mL.

3. Analytical Specificity/Interference:

Interference study was performed according to CLSI guidelines EP07 (3rd Edition) and EP37 (1st Edition) to determine the effect of various endogenous and exogenous substances on the Atellica IM Thyroglobulin assay. Two human serum pools with a target concentration of approximately 0.2 ng/mL and 25 ng/mL were processed by paired-difference testing; samples with and without the interferent were measured, and the measurand concentration difference was determined. Test and control samples were each processed in five replicates, using a single Atellica IM Analyzer, one calibration, one test day. The percent bias was determined by comparing the result of sample with interferent or cross-reactant to a control sample without the interferent or cross-reactant. The percent difference was calculated [100 * (test recovery – control recovery) / control recovery] and an interference or cross-reactivity within ≤ 10% bias between the mean spiked sample value and the mean control value was considered non-significant.

a) *Endogenous Substance Interference:*

The following endogenous substances were tested using Atellica IM Thyroglobulin assay. No significant interference was found for each substance at the concentrations listed below.

Endogenous Substance	Concentration
Conjugated Bilirubin	60 mg/dL
Unconjugated Bilirubin	60 mg/dL
Hemoglobin	1,000 mg/dL
Immunoglobulin G	2 g/dL
Immunoglobulin M	0.3 g/dL
Lipemia using intralipid	1,900 mg/dL
Lipemia using triglycerides	1,500 mg/dL
Total Protein	120 mg/mL
Biotin	3,510 ng/mL

The interference of human anti-mouse antibodies (HAMA) on the Atellica IM Thyroglobulin assay was assessed in accordance with CLSI guideline I/LA30-A using one Atellica IM Analyzer and six HAMA positive samples. Each HAMA positive sample was run neat as the test condition and pretreated in a heterophilic blocking tube (HBT) as the control condition. Test and control samples were each processed in five replicates. The recovery of each serum sample containing HAMA compared to the serum sample

without HAMA was calculated. Of the five samples tested with HAMA concentrations ranging from 626 – 905 ng/mL, four were classified as non-interfering. The fifth sample, containing HAMA at a concentration of 775 ng/mL, showed interference that only became acceptable upon dilution to a HAMA concentration of 200 ng/mL. The Atellica IM Thyroglobulin 'instructions for use' contains the following statement of limitation: Patient samples may contain heterophilic antibodies that could react in immunoassays and cause falsely elevated or depressed results.

b) *Exogenous Substance Interference:*

The potential interference of 32 commonly used drugs (including those used for cancer treatment) and dietary supplements, was evaluated using Atellica IM Thyroglobulin assay. No significant interference was found for each substance at the concentrations listed below.

Exogenous Substance	Concentration	Exogenous Substance	Concentration
Acetaminophen	20 mg/dL	Itraconazole	3 mg/dL
Acetylsalicylic Acid	65 mg/dL	K3 EDTA	5.4 mg/mL
Amiodarone	8.92 µmol/L	Lenvatinib Mesylate	2.62 mg/dL
Ampicillin	33.0 mg/dL	Levodopa	0.75 mg/dL
Ascorbic Acid	2,590 mg/dL	Methyldopa	2.25 mg/dL
Cabozantinib-S-Malate	15.3 mg/dL	Metronidazole	12.3 mg/dL
Carbimazole	2.4 µg/mL	Octreotide Acetate	5.2 ng/mL
Cefoxitin	92.7 mg/dL	Perchlorate	200 µg/mL
Cyclosporine	0.075 mg/dL	Phenylbutazone	32.1 mg/dL
Doxycycline	4.5 mg/dL	Prednisolone	8.31 µmol/L
Fluocortolone	270 ng/mL	Propranolol	7.71 µmol/L
Fluorescein	6 µg/mL	Propylthiouracil	7.2 µg/mL
Hydrocortisone	984 ng/mL	Rifampicin	7.5 mg/dL
Ibuprofen	50 mg/dL	Silwet L720	0.03 mg/mL
Imatinib	13.4 µg/mL	Theophylline	6 mg/dL
Iodide	38 mg/dL	Thiamazole	300 ng/mL

c) *Cross-Reactivity:*

The potential cross-reactivity of the following substances was evaluated using Atellica IM Thyroglobulin assay. No significant interference was found for each substance at the concentrations listed below.

Cross-Reactive Substance	Concentration
AFP	881.2 ng/mL
Diiodothyronine	55 µg/mL
FSH	40 mIU/mL
Galectin-3	1 µg/mL
Rheumatoid Factor (RF)	550 IU/mL
T3	100 ng/mL

Cross-Reactive Substance	Concentration
T4	10 µg/mL
Thyroxine binding globulin	210 µg/mL
TSH	235 mIU/mL
VEGF	2,835 pg/mL

4. Assay Reportable Range:

The analytical measuring interval (AMI) for the Atellica IM Thyroglobulin (Tg) is 0.05–150 ng/mL.

Samples that exceed the high end of the measuring interval can be diluted 1:10, 1:20, and 1:50 with Atellica IM Multi-Diluent using automated dilution or manual dilution. The claimed extended measuring interval of the assay is 0.05–7500 ng/mL using a 1:50 dilution.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

a) *Traceability*:

The Atellica IM Thyroglobulin assay standardization is traceable to the Community Bureau of Reference (BCR) Certified Reference Material (CRM) 457.

b) *Kit Stability:*

The stability of the Atellica IM Thyroglobulin reagent kit was determined according to CLSI guideline EP25-A.

i) Reagent kit stability (shelf-life):

The shelf-life stability studies at 2–8°C were completed by testing 3 – 4 serum samples (at 0.20, 1.63, 20.97 and 111.9 ng/mL) in five replicates per sample using three Atellica IM Thyroglobulin reagent kit lots on one Atellica IM Analyzer at least at five timepoints. The testing was done at intervals past the 12-month timepoint (including 13 and 17 months). The current data support a Atellica IM Tg assay shelf-life claim of at least 12 months.

ii) Onboard stability:

The Atellica IM Thyroglobulin assay reagent onboard stability study was performed by testing fresh packs were tested at each timepoint, five packs remained on board through the study. Four serum samples (at 0.18, 1.63, 25.24 and 140.5 ng/mL) were tested in five replicates per sample using two Atellica IM Thyroglobulin reagent kit lots, a single Atellica IM Analyzer at five timepoints. The testing was done at intervals past 28-Day timepoint (including timepoints 38 and 40 days). The results support on-board stability claim for the Atellica IM Thyroglobulin reagents for 28 days.

c) *Sample Stability:*

i) Storage stability:

The sample stability of serum, Heparin plasma and K2-EDTA plasma was evaluated using samples stored at 20–30°C, 2–8°C, -20°C and at -70°C for each sample matrix. Six or more samples were prepared covering the AMI of the assay and tested using the Atellica IM Thyroglobulin on the Atellica IM Analyzer at Day 0 and at various testing timepoints during storage. At each testing point, measurements were performed in six replicates. For each sample type, a linear regression analysis of the % bias for each of the samples versus time was performed. For sample types with a regression slope p value of ≥ 0.05, the sample type was deemed stable for the duration of the study. For sample types with a regression slope p value of < 0.05, the stability duration was taken as the time at which the two-sided 90% confidence interval of the regression line intersects with the acceptance criterion. The data support the stability for serum sample type for up to four days at 20–30°C, seven days at 2–8°C; Heparin plasma and K2-EDTA plasma sample types for up to three days at 20–30°C and four days at 2–8°C; all sample types for up to 12 months at -20°C and for up to 24 months at -70°C.

ii) Freeze-Thaw stability:

Nine serum, Heparin plasma and K2-EDTA plasma samples across AMI were aliquoted. Nine of those aliquots from each sample type were tested at time point T0 (fresh measurement) and the other aliquots after claimed number of freeze/thaw cycles (each cycle consisted of freezing and storage at -20°C and thawing). The samples were tested in six replicates using the Atellica IM Thyroglobulin on the Atellica IM Analyzer. For each sample type, the allowable number of freeze thaw cycles was taken as the longest timepoint at which all calculated biases. The results support serum, Heparin plasma and K2-EDTA plasma Thyroglobulin concentrations stability up to four freeze and thaw cycles for samples stored at -20°C.

6. Detection Capability:

CLSI guideline EP17-A2 was followed to determine the Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) for the Atellica IM Thyroglobulin.

a) *LoB:*
Four blank samples were tested over three days, two runs per day, five replicates per run using two Atellica IM Thyroglobulin reagent lots on one Atellica IM Analyzer for a total of 30 replicates per low sample per reagent lot. One blank sample was a pool of human serum samples (otherwise unaltered). Three blank samples consisted of internally stripped human serum. The LoB for each reagent lot was calculated using the non-parametrically at the 95^{th} percentile of all measurements of the blank samples. The LoB was calculated separately for each reagent lot and the highest value was taken as the LoB value. LoB determined using the 95% non-parametric percentile of the replicates for each of the two reagent lots was 0.033 ng/mL and 0.039 ng/mL. The claimed LoB for the Atellica IM Thyroglobulin is 0.039 ng/mL.

b) *LoD:*

Seven serum samples containing low levels of Thyroglobulin were tested over five days, two runs per day, five replicates per run using two Atellica IM Thyroglobulin reagent lots on one Atellica IM Analyzer for a total of 50 replicates per low sample per reagent lot. The LoD was analyzed by using a precision profile approach. A nested, two factor (days and runs nested within days) ANOVA model consistent with the recommendations of CLSI guideline EP05-A3 was used to calculate the within-lab precision. For each lot, the Within-Lab Precision (SD) was plotted versus the sample mean (ng/mL). The LoD was determined as the lowest concentration of thyroglobulin that can be detected with a probability of 95%. The Atellica IM Thyroglobulin results on the Atellica IM Analyzer support an LoD is 0.044 ng/mL. The claimed LoD for the Atellica IM Thyroglobulin is 0.044 ng/mL.

c) *LoQ:*

The same samples and data which were used to evaluate LoD were used to evaluate LoQ. The LoQ data was analyzed using a nested, two factor (days and runs nested within days) ANOVA model in accordance with CLSI guideline EP05-A3. Within-lab precision estimates were calculated and the within-lab precision (%CV) was plotted versus the sample mean (ng/mL) per lot. The datasets were fitted as appropriate with power regressions. For each lot, the profile over the range tested was entirely below 20% CV limit. The LoQ corresponds to the lowest amount of thyroglobulin in a sample at which the within laboratory CV is ≤ 20%. The Atellica IM Tg results on the Atellica IM Analyzer supports an LoQ of 0.044 ng/mL. The claimed LoQ for the Atellica IM Thyroglobulin is 0.05 ng/mL.

7. Assay Cut-Off:

See Clinical Cut-Off below.

B Comparison Studies:

1. Method Comparison with Predicate Device:

CLSI guideline EP09c 3rd Edition was followed to compare the Atellica IM Thyroglobulin assay on Atellica IM Analyzer to the predicate device, the Access Thyroglobulin on the Access Immunoassay Systems. Patient samples falling within the AMI of the Atellica IM Thyroglobulin and the Access Thyroglobulin assay (0.1–150 ng/mL) were evaluated. A total of 483 serum samples were tested across 19 non-consecutive days with six Atellica IM Thyroglobulin reagents lots and six calibrator lots, on two Atellica IM Analyzers (candidate) and with four reagents lots and five calibrator lots, on one Access Immunoassay Systems (predicate). The comparison between paired measurements was analyzed using Passing-Bablok method by fitting the observed values from Atellica IM Thyroglobulin assay on Atellica IM Analyzer (dependent variable, y) into a linear regression model, with the observed values from the Access Thyroglobulin on the Access Immunoassay Systems (x, predicate). The results are summarized in the following table:

N	Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	R
483	0.1–150	1.09 (1.06; 1.12)	0.004 (-0.007; 0.016)	0.985

2. Matrix Comparison:

CLSI guideline EP09c 3rd Edition was followed to demonstrate that serum, Heparin plasma and K2-EDTA plasma matrices yield comparable values as serum with the Atellica IM Thyroglobulin. The study included 84 to 99 matched single samples with thyroglobulin concentration covering the analytical measuring interval of the assay. Samples were tested in two replicates using one Atellica IM Thyroglobulin reagent lot on one Atellica IM Analyzer. Using only the first replicate results, Passing-Bablok regression analyses were performed by comparing the results of samples from different plasma samples (y) to the results of corresponding serum samples (x). The results are summarized in the tables below.

Specimen type vs Comparison Specimen	N	Range (ng/mL)	Slope (95% CI)	Intercept ng/mL (95%	r
Serum[1] vs Serum[2]	84	0.06–141.3	1.01 (1.00, 1.02)	0.000 (-0.014, 0.025)	0.999
Plasma (Lithium heparin)	99	0.06–145.2	1.00 (0.99, 1.02)	-0.015 (-0.055, 0.006)	0.984
Plasma (Dipotassium EDTA) vs Serum[2]	99	0.05–138.0	0.99 (0.98, 1.00)	-0.007 (-0.041, 0.009)	0.987
Plasma[3] vs Serum[2]	84	0.05–145.2	0.99 (0.97, 1.00)	-0.006 (-0.022, 0.018)	0.993

[1] Serum, SST, gel barrier
[2] Serum, no gel barrier
[3] Plasma, PST, gel barrier

C Clinical Studies:

The effectiveness of the Atellica IM Thyroglobulin as an aid in monitoring differentiated thyroid cancer patients who have undergone thyroidectomy with or without radioiodine ablation, was determined through a prospective, multi-center study. The Atellica IM Thyroglobulin assay result was compared to evidence of structural disease (SD) with imaging on a subject visit level and analyzable study follow-up visits were conducted postoperatively at variable timepoints per subject.

Subject inclusion and exclusion criteria are as follows:

Inclusion criteria:

- Adult male or female, defined as subject 22 years of age or older.
- Patients diagnosed with DTC who have undergone:
  - Total thyroidectomy or completion thyroidectomy with or without RAI
  - Near-total thyroidectomy with or without RAI
- Patients are enrolled approximately 6-12 weeks or more after completing.

    - Total or completion thyroidectomy or
    - Near-total thyroidectomy or RAI therapy, whichever comes last. There is no upper limit after TT/NT/RAI treatment.
- Documented staging, risk stratification or diagnostic procedure used to diagnose and classify the risk of disease at enrollment (and at each follow up visit).

Exclusion criteria:

- Any female who is pregnant at time of enrollment or subject becomes pregnant after enrollment. Any samples collected prior to pregnancy will remain in the study.
- Cross-sectional imaging or functional imaging not completed within 30 days of the Tg sample collection.
- Subject received recombinant human TSH (rhTSH) stimulation within 72 hours of study blood draw.
- Beckman Access Thyroglobulin Antibody II results > 0.9 IU/mL.
- Grossly hemolyzed (red) or turbid samples or sample with visually detected microbial contamination.
- Samples not handled or stored as per sample handling instructions.
- Sample storage requirements are not met.

Four hundred seven (407) subjects were enrolled from three geographically distributed sites in the U.S. Seventy (70) subjects were excluded from analysis due to subject discontinuation, unavailable follow-up visits or other reasons. Only visits with an image taken within 30 days of the blood draw that met all inclusion criteria were considered evaluable. A total of 189 subjects, each with at least one evaluable visit, qualified for the study. As a result, 291 evaluable visits from these 189 subjects were analyzed. The distributions of demographic and clinical variables of the subjects are described in the table below:

Evaluable Subjects (N=189)			
Category	**Demographic or Clinical Variable**	**N**	**%**
Race	White	176	93.1%
	African American	4	2.1%
	Asian	3	1.6%
	American Indian or Alaska Native	0	0.0%
	Native Hawaiian or Other Pacific Islander	0	0.0%
	Other	4	2.1%
	Not Reported	2	1.1%
Ethnicity	Not Hispanic or Latino	175	92.6%
	Hispanic or Latino	10	5.3%
	Not Reported	3	1.6%
	Unknown	1	0.5%
Gender	Male	55	29.1%
	Female	134	70.9%
Age	Minimum	23 years	
	Mean Age	51.8 years	
	Maximum	81 years	

Evaluable Subjects (N=189)			
Category	**Demographic or Clinical Variable**	**N**	**%**
Initial Risk	Low Risk	71	37.6%
	Intermediate Risk	71	37.6%
	High Risk	47	24.9%
	Missing	0	0.0%

Study follow-up visits were scheduled at the same time as the standard-of-care (SOC) visits, as prescribed by the treating physician. All subject visits included in the primary analysis had imaging completed within 30 days of study blood draw. The clinical performance of the Atellica IM Thyroglobulin at a cut-off of 0.2 ng/mL was evaluated by comparing the test results with the clinical status, the presence of structural disease (SD). The Atellica IM Thyroglobulin assay result was considered "positive" (evidence of cancer recurrence after thyroidectomy) if the Thyroglobulin concentration was greater than or equal to 0.2ng/mL. Structural disease was established and classified as either positive or negative by any of the following:

- Evidence of disease on cross-sectional imaging (ultrasound, computer tomography (CT), or magnetic resonance imaging (MRI)).
- Evidence of disease by functional imaging (Positive Radioactive Iodine scan or FDG-PET scan).

Results:

The Atellica IM Tg assay results were compared to evidence of structural disease (SD) on a subject visit level to assess the diagnostic concordance between the Atellica IM Tg assay and imaging result. Sensitivity, specificity, and the two-sided 95% Wilson's Score Confidence Intervals (CI) of each parameter were calculated. Clinical sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were computed in accordance with CLSI guideline EP12-A2 as shown in tables below. A bootstrapping method was used to estimate the sensitivity, specificity, PPV, and NPV, which models the correlation between a subject's visits.

		Disease Status		**Total**
		SD+	**SD-**	
Atellica IM Tg Assay	≥ 0.2 ng/ml	54	110	164
	< 0.2 ng/ml	1	126	127
	Total	55	236	291

Clinical Performance Measures	**Estimate**	**95% CI**
Sensitivity	98.2%	(94.6%, 100.0%)
Specificity	53.4%	(47.8%, 58.0%)
PPV*	10.0%	(8.7%, 11.2%)
NPV*	99.8%	(99.5%, 100.0%)

*NPV and PPV were calculated for a prevalence of 4.99%

The pre-defined suppressed Tg concentrations according to the ATA Response Classification categories is shown in the table below:

Excellent Response	Tg < 0.2 ng/mL
Indeterminate Response	Tg ≥ 0.2 ng/mL AND Tg < 1.0 ng/mL
Biochemically Incomplete Response	Tg ≥ 1.0 ng/mL

The likelihood ratio (LR) of subjects, with and without RAI treatments, were calculated for excellent response, indeterminate response and biochemically incomplete response for subjects that had positive or negative imaging within 30 days of blood draw.

RAI-treated subjects.

RAI		Disease Status		Total	LR (95% CI)
		SD+	SD-		
Atellica IM Tg Assay	Tg < 0.2	1	84	85	0.15 (0.0, 2.03)
	Tg 0.2 <= Tg < 1.0	3	37	40	0.26 (0.0, 1.38)
	Tg >= 1.0	42	24	66	5.52 (5.14, 5.90)
Total		46	145	191	

Not RAI-Treated subjects

Non-RAI		Disease Status		Total	LR (95% CI)
		SD+	SD-		
Atellica IM Tg Assay	Tg < 0.2	0	42	42	0.72*
	Tg 0.2 <= Tg < 1.0	3	36	39	0.84 (0.0, 1.80)
	Tg >= 1.0	6	13	19	4.67 (3.98, 5.35)
Total		9	91	100	

*Indeterminate due to zero counts

The probability of SD+ for three ranges of the Atellica IM Tg assay described above is presented in the table below for RAI-treated and Not RAI-treated patients separately.

	Prevalence	Probability of SD+ (95% CI)		
		Tg <0.2ng/mL	Tg≥0.2 ng/mL and Tg <1.0ng/mL	Tg ≥ 1.0 ng/mL
RAI-Treated	24.1%	1.18% (2.10%, 6.37%)	7.50% (2.58%, 19.86%)	63.64% (51.58%, 74.19%)
Non-RAI Treated	9.0%	0.0% (0.0%, 8.38%)	7.69% (2.65%, 20.32%)	31.58% (15.36%, 53.99%)

The results from the clinical study demonstrated that at Tg concentrations ≥ 1.0 ng/mL (corresponding to ATA "Biochemical Incomplete Response"), the probability of structural disease (i.e., 63.6% for RAI-treated patients and 31.6% for Non-RAI-treated patients) was much higher than the probability of structural disease for Tg concentrations <0.2 ng/mL (corresponding to ATA "Excellent Response").

D Clinical Cut-Off:

The clinical cut-off for the Atellica IM Tg assay is 0.2 ng/mL based on ATA definition of excellent response. This was set based on 2015 ATA Guidelines (American Thyroid Association

Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, Thyroid, Volume 26, Number 1, 2016) which introduced an Excellent response (no clinical, biochemical, or structural evidence of disease defined by negative imaging and a suppressed Tg < 0.2 ng/mL in the absence of Tg antibodies), Indeterminate response (biochemical or structural findings that cannot be classified as either benign or malignant for patients without TSH stimulation at Tg ≥ 0.2 AND Tg < 1.0 ng/mL) and Biochemical incomplete response (abnormal Tg values in the absence of localizable disease are > 1.0 ng/mL).

E Expected Values/Reference Range:

A reference range of the Atellica IM Tg assay was established by testing serum samples from a total of 321 apparently healthy individuals including 157 males and 164 females. The reference interval was determined by calculating the 2.5th and 97.5th percentiles of the distribution of values. The results are summarized in the following table.

	Male	Female	Total
N	157	164	321
Age (years)	22 – 76	22 – 80	22 – 80
Min – Max (ng/mL)	1.3 – 99.1	0.08 – 194	0.08 – 194
Median (ng/mL)	16.4	15.2	15.9
2.5th percentile (ng/mL)	2.4	2.6	2.4
97.5th percentile (ng/mL)	70.1	78.3	74.9

Additionally, a total of 136 patient serum samples, which consisted male and female patients with Differentiated thyroid cancer (DTC) with no evidence of disease for 4 or more years following total/near total thyroidectomy with the following exclusion criteria: Subjects with aTg > LoQ, pregnant subjects, pediatric subjects < 22 years. The results showed that the thyroglobulin concentration were < 1.27 ng/mL; 95% of patients had thyroglobulin level 1.272 ng/mL.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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