SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Total Prostate Specific Antigen (Total PSA)

Device Trade Name: Atellica IM total PSA II (tPSAII)

Device Procode: MTF – Total, prostate specific antigen (noncomplexed and complexed) for detection of prostate cancer

Applicant's Name and Address: Siemens Healthcare Diagnostics, Inc.
511 Benedict Avenue
Tarrytown, NY 10591

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240021

Date of FDA Notice of Approval: December 3, 2025

II. INDICATIONS FOR USE

The Atellica IM total PSA II (tPSAII) assay is for *in vitro* diagnostic use in the quantitative measurement of total prostate-specific antigen (PSA) in human serum and plasma (EDTA and lithium-heparin) using the Atellica IM Analyzer.

This assay is indicated as an aid in the detection of prostate cancer in conjunction with a digital rectal exam (DRE) in men aged 50 years and older. A prostate biopsy is required for the diagnosis of prostate cancer.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Atellica IM total PSA II (tPSAII) product insert.

V. DEVICE DESCRIPTION

The Atellica IM total PSA II (tPSAII) assay is a fully automated chemiluminescent sandwich immunoassay.

1. Device Component:

   Materials provided:

   The Atellica IM total PSA II (tPSAII) is available in a 1-pack (100 tests) kit and in a 5-pack (500 tests) kit. Both versions of the assay include:

   - tPSAII ReadyPack primary reagent pack consisting of:
     - Lite Reagent: 10.0 mL/reagent pack; Unlabeled monoclonal mouse anti-free-PSA (fPSA) antibody (~250 ng/mL); monoclonal mouse anti-PSA antibody (~180 ng/mL) labeled with acridinium ester; buffer; bovine serum albumin (BSA); preservative
     - Solid Phase: 20.0 mL/reagent pack; Monoclonal mouse anti-PSA antibody (~3.5 µg/mL) labeled with biotin and bound to streptavidin paramagnetic particles; buffer; BSA, bovine gamma globulin (BGG); sodium azide (< 0.1%); preservative
   - Atellica IM tPSAII master curve and test definition
   - tPSAII CAL low calibrator: 2.0 mL/vial; Purified PSA from human seminal fluid in buffer; BSA; sodium azide (< 0.1%)
   - tPSAII CAL high calibrator: 2.0 mL/vial; Purified PSA from human seminal fluid in buffer; BSA; sodium azide (< 0.1%)
   - Atellica IM tPSAII CAL calibrator assigned value sheet

   Materials needed but not provided:

   Atellica IM Analyzer – with additional system fluids to operate the system including Atellica IM Wash, Atellica IM Acid, Atellica IM Base, and Atellica IM Cleaner

   Optional materials may be used but not provided:

   Atellica IM Multi-Diluent 2
   Atellica IM tPSAII Mater Curve material

2. Assay Principles and Procedures:

   The assay uses three monoclonal mouse antibodies in the tPSAII ReadyPack primary reagent pack. The Lite Reagent contains a monoclonal anti-PSA antibody labeled with acridinium ester, and an unlabeled free-PSA-specific monoclonal mouse anti-PSA antibody. The Solid Phase contains a monoclonal mouse anti-PSA antibody labeled with biotin and bound to streptavidin paramagnetic latex particles. The sample is incubated with the Lite Reagent and Solid Phase simultaneously, and then the immune complex is washed. A direct relationship exists between the amount of analyte present in the patient sample and the amount of relative light units (RLUs) detected by the system.

The Atellica IM tPSAII assay utilizes two-point calibration (Low Calibrator, High Calibrator) which are provided with the reagent kit. The calibration procedure is detailed in the package of the Atellica IM tPSAII.

The Atellica IM analyzer automatically performs the following steps:

- Dispenses 30 µL of sample into a cuvette.
- Dispenses 200 µL of Solid Phase and 100 µL of Lite Reagent, then incubates the mixture for 8 minutes at 37°C.
- Performs a wash sequence using Atellica IM Wash.
- Dispenses 300 µL each of Atellica IM Acid and Atellica IM Base Reagent to initiate the chemiluminescent reaction.
- Reports results

3. Results Interpretation

The Atellica IM tPSAII assay measures prostate-specific antigen in serum or plasma, with a clinical cut-off of 4.0 ng/mL.
Elevated total PSA does not definitively indicate prostate cancer, as levels can rise due to benign prostatic hyperplasia, prostatitis, infections, or recent procedures. The assay aids detection of prostate cancer when combined with digital rectal examination (DRE) in men ≥50 years old.

4. Traceability

The Atellica IM Total PSA II is standardized to the WHO international standard 17/100.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternative practices and procedures that aid in the detection of prostate cancer, including physical examination using digital rectal examination (DRE) and diagnostic imaging by transrectal ultrasound (TRUS). Other devices for measuring total PSA, %free PSA, Prostate Health Index (*phi*), or multi-analytes (4Kscore Test) in venous blood sample (serum or plasma) are currently available to aid in the detection of prostate cancer in conjunction with DRE information in men aged 50 years and older. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his physician to select the method that best meets expectations and lifestyle. Confirmation of prostate cancer is determined by biopsy.

VII. MARKETING HISTORY

Atellica IM tPSAII assay has not been previously marketed in the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

For the detection of prostate cancer, total PSA measurements are used along with DRE and ultrasound guided biopsy. Subjects with falsely elevated PSA results could lead to an unnecessary biopsy. Subjects with falsely low total PSA results may not receive a necessary biopsy, therefore, could delay recognition of the presence of prostate cancer by the physician and could adversely delay the initiation of therapy. The PSA levels should be used in conjunction with symptoms, clinical evaluation, DRE, and other laboratory tests or imaging techniques.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Precision:

Precision studies for the Atellica IM tPSAII assay were performed according to Clinical and Laboratory Standards Institute (CLSI) EP05-A3: *Evaluation of Precision Performance of Quantitative Measurement Procedures; Approved Guideline—Third Edition*.

1. Within-Laboratory Precision:

Within-laboratory precision was evaluated by testing a panel of six native human serum samples including four unique donor samples and two pooled samples, and three controls. Each sample was tested in duplicate per run, two runs per day for 20 days, yielding a total of 80 measurements on one lot of reagents on one Atellica IM analyzer. The data for each sample were analyzed for the mean (ng/mL), standard deviation (SD) (ng/mL) and percent coefficient of variation (%CV) for repeatability (within-run), between-run, between-day, and within-laboratory precision. The results are summarized in Table 1.

Table 1: 20-Day Within-Laboratory Precision of the Atellica IM tPSAII

Sample	N	Mean (ng/mL)	Within-Run		Between-Run		Between-Day		Within-Lab	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum 1	80	0.024	0.001	5.0	0.000	0.0	0.001	3.8	0.002	6.4
Serum 2	80	0.214	0.005	2.1	0.003	1.2	0.002	0.7	0.005	2.5
Serum 3	80	3.718	0.062	1.7	0.054	1.4	0.020	0.5	0.085	2.3
Serum 4	80	10.196	0.174	1.7	0.208	2.0	0.000	0.0	0.271	2.7
Serum 5	80	19.768	0.327	1.7	0.227	1.1	0.233	1.2	0.461	2.3
Serum 6	80	38.232	0.563	1.5	0.679	1.8	0.606	1.6	1.070	2.8
Control 1	80	0.152	0.003	2.0	0.001	0.8	0.002	1.3	0.004	2.5
Control 2	80	4.463	0.061	1.4	0.092	2.1	0.040	0.9	0.112	2.6
Control 3	80	19.853	0.295	1.5	0.409	2.1	0.000	0.0	0.505	2.5

2. Lot-to-Lot Precision:

The lot-to-lot precision was evaluated by performing the same 20-day within-laboratory protocol described above on the two additional lots of Atellica IM tPSAII reagents on one Atellica IM analyzer. The combined data for each sample on all three lots (N=240) were analyzed. The results are summarized in Table 2.

Table 2: Lot-to-Lot Precision of the Atellica IM tPSAII

Sample	N	Mean (ng/mL)	Within-Run		Between-Run		Between-Day		Between-Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum 1	240	0.023	0.001	4.8	0.000	0.0	0.001	3.5	0.001	2.6	0.001	6.1
Serum 2	240	0.215	0.004	2.0	0.002	1.0	0.002	0.8	0.004	2.0	0.007	3.1
Serum 3	240	3.770	0.060	1.6	0.059	1.6	0.035	0.9	0.103	2.7	0.137	3.6
Serum 4	240	10.135	0.194	1.9	0.181	1.8	0.062	0.6	0.293	2.9	0.400	3.9
Serum 5	240	20.068	0.379	1.9	0.203	1.0	0.254	1.3	0.772	3.8	0.919	4.6
Serum 6	240	37.944	0.656	1.7	0.650	1.7	0.611	1.6	1.6417	4.3	1.980	5.2
Control 1	240	0.159	0.003	2.1	0.002	1.4	0.002	1.2	0.012	7.7	0.013	8.2
Control 2	240	4.445	0.065	1.5	0.080	1.8	0.056	1.3	0.136	3.1	0.180	4.0
Control 3	240	19.639	0.302	1.5	0.434	2.2	0.000	0.0	0.757	3.9	0.923	4.7

3. Site-to-Site Reproducibility

Reproducibility was evaluated according to CLSI EP05-A3 using a five-day study design. A panel of six native human serum samples and three controls were tested at three different sites using three different reagent lots and one Atellica IM instrument at each site. The samples were assayed in triplicates in two runs per day (with a minimum of two hours in between runs) for five days, yielding a total of 270 measurements for each sample. The reproducibility data for all lots and all sites combined is shown below.

Table 3: Site-to-Site Reproducibility of the Atellica IM tPSAII (n=270 per sample)

Sample	Mean (ng/mL)	Within-Run		Between-Run		Between-Day		Between-Lot		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum 1	0.102	0.002	1.7	0.002	1.6	0.001	0.5	0.001	1.1	0.002	1.4	0.003	2.9
Serum 2	2.061	0.030	1.5	0.021	1.0	0.014	0.7	0.038	1.8	0.026	1.3	0.061	2.9
Serum 3	4.201	0.062	1.5	0.028	0.7	0.019	0.4	0.058	1.4	0.063	1.5	0.111	2.6
Serum 4	10.304	0.153	1.5	0.145	1.4	0.000	0.0	0.119	1.2	0.119	1.2	0.270	2.6
Serum 5	20.248	0.296	1.5	0.265	1.3	0.085	0.4	0.130	0.6	0.582	2.9	0.721	3.6
Serum 6	42.673	0.753	1.8	0.454	1.1	0.279	0.7	0.000	0.0	1.167	2.7	1.487	3.5
Control 1	0.178	0.003	1.7	0.003	1.9	0.000	0.0	0.002	1.0	0.004	2.4	0.007	3.7
Control 2	5.066	0.080	1.6	0.111	2.2	0.000	0.0	0.053	1.0	0.113	2.2	0.185	3.7
Control 3	22.325	0.353	1.6	0.457	2.0	0.000	0.0	0.263	1.2	0.421	1.9	0.761	3.4

B. Detection Capability

The studies were conducted to determine Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) for the Atellica IM tPSA II according to CLSI EP17-A2: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*.

1. Limit of Blank (LoB)
   LoB was determined by testing five blank samples (human female serum sample pools) using three reagent lots. Each sample was tested in five replicates per run, two runs per day for three days on two Atellica IM instruments, yielding a total of 300 measurements per reagent lot. LoB was determined for each lot separately using a non-parametric approach, calculated as the 95th percentile of all values sorted from lowest to highest. The highest value across three lots was used to establish the LoB for this assay.

2. Limit of Detection (LoD)
   LoD was determined by testing five low PSA level of human serum samples using three reagent lots. Each sample was tested in five replicates per run, two runs per day for three days on one Atellica IM instrument, yielding a total of 150 measurements per reagent lot. The highest value across three lots was used to establish the LoD.

3. Limit of Quantitation (LoQ)
   LoQ was determined by testing a panel of 10 samples each prepared in three different matrices i.e., Serum, Lithium Heparin, and K2 EDTA. For each sample type, samples were tested in six replicates per run, two runs per day for five test days using three reagent lots on two Atellica IM instruments, yielding a total of 360 measurements per sample. LoQ for each reagent lot was determined as the analyte concentration corresponding to 15% within-laboratory %CV. The highest value was used to establish the LoD across three lots and across the claimed sample types.

The determined LoB/LoD/LoQ for the Atellica IM tPSAII is summarized in Table 4.

Table 4: Detection capability for the Atellica IM tPSAII

	Limit of Blank (LoB)	Limit of Detection (LoD)	Limit of Quantitation (LoQ)
Atellica IM tPSAII	0.004 ng/mL	0.006 ng/mL	0.009 ng/mL

C. Linearity:

Linearity of the Atellica IM tPSAII was established according to CLSI EP06-Ed2: *Evaluation of the Linearity of Quantitative Measurement Procedure*. A 17-level dilution series was prepared using a high total PSA sample (native human male serum pool) and a low sample (native human female serum) with PSA ranging from 0.007

ng/mL to 50.496 ng/mL. Samples were tested in six replicates each on one Atellica IM Analyzer with four reagent lots. The expected values were calculated based on dilution scheme and predicted value were calculated using weighted least squares regression analysis. The %Deviation from linearity were calculated for each level and the results are presented in Table 5.

Table 5: Linearity of the Atellica IM tPSAII

Range (ng/mL)	Linear Equation	Range of %Deviation from Linearity
0.007 – 50.496	Y= 0.9940*X	-3.0% – 6.2%

The data show that assay is linear from 0.007 – 50.496 ng/mL, which supports the analytical measuring interval (AMI) of 0.009 – 50.000 ng/mL.

1. High-Dose Hook Effect

   The study was conducted to evaluate the hook effect of the Atellica IM tPSAII. The high complexed PSA (PSA-ACT from Scripps) was spiked into a high native human male serum sample to achieve a target level of approximately 35,000 ng/mL. Five dilutions were prepared from this sample using multi-diluent 2, which is the recommended diluent for the patient samples above the analytical measuring range. All samples were tested in three replicates using three reagent lots on one Atellica IM Analyzer. Data was analyzed by plotting the actual mean instrument response (RLUs) versus the expected dose (ng/mL) of the samples. No hook effect was observed up to 25,000 ng/mL.

2. Assay Reportable Range:

   Analytical measuring interval for the Atellica IM tPSAII is 0.009 – 50.0 ng/mL.

D. Analytical Specificity/Interference

The effect of potential endogenous, exogenous substances and cross reactivity to the Atellica IM tPSAII was evaluated in interference studies in accordance with CLSI EP07-Ed2: *Interference Testing in Clinical Chemistry* and CLSI EP07-Ed3 *Interference Testing in Clinical Chemistry*.

1. Endogenous and Exogenous Interference:

   Three serum samples at ~0.1 ng/mL, 4.0 ng/mL and 10.0 ng/mL were spiked with the endogenous and exogenous interferants at the highest concentration. Control samples were prepared for each interfering substance by spiking appropriate diluents at equivalent volumes to the interferent into three serum samples. All samples were analyzed on one Atellica IM instrument using one reagent lot, with five replicates per sample for total protein (at 15 g/dL) and vincristine sulfate, and

three replicates per sample for all remaining interferents. The %Interference was calculated using the equation:

% Interference = [(Test Sample Mean - Control Sample Mean) / Control Sample Mean] × 100.

For endogenous substances, no significant interferences (%Interference within 10%), were observed up to the concentration listed in Table 6.

Table 6: Endogenous Interferences

Substance	Concentration
Bilirubin (Unconjugated)	60 mg/dL
Bilirubin (conjugated)	60 mg/dL
Hemoglobin	1000 mg/dL
Lipemia (Intralipid)	3300 mg/dL
Total Protein	15 g/dL
Cholesterol	500 mg/dL
Rheumatoid Factor (RF)	1890 IU/mL

For exogenous substances, no significant interferences (%Interference within 10%) were observed in the study up to the concentration listed in Table 7.

Table 7: Exogenous Interferences

Substance	Concentration	Substance	Concentration
Biotin	3500 ng/mL	HAMA*	2640 µg/L
Silwet L720	30 mg/mL	Goserelin acetate	7.2 µg/mL
Alfuzosin hydrochloride	12 µg/mL	Leuprolide acetate	10 mg/dL
Aminoglutethimide	72 µg/mL	Megestrol acetate	250 µg/mL
Casodex (bicalutamide)	60 µg/mL	Methotrexate	300 mg/dL
Cisplatin dichloride	0.25 mg/mL	Mitomycin C	100 µg/mL
Cyclophosphamide	800 µg/mL	Novantrone	0.5 mg/mL
Diethylstilbestrol	25 µg/mL	Oxaliplatin	0.25 mg/mL
Docetaxel	5.5 µg/mL	Paclitaxel	4 ng/mL
Doxazosin mesylate	4 µg/mL	Prazosin hydrochloride	85 ng/mL
Doxorubicin hydrochloride	7 mg/dL	Prednisone	1.65 µg/mL
Dutasteride	0.3 µg/mL	Sildenafil citrate	0.2 mg/mL
Estramustine phosphate	20 mg/dL	Terazosin HCl	1.45 mg/mL
Finasteride	25 µg/mL	Triptorelin	28 ng/mL
Flomax	1 µg/mL	Vincristine sulfate salt	1 mg/mL
5'-Fluorouracil	1.6 mg/mL	Vinblastine sulfate salt	12 µg/mL

*Human anti-mouse antibodies

2. Cross-Reactivity

The Serum samples were formulated by spiking male human serum sample with high PSA concentrations into female serum at the target concentrations. Test samples were spiked with the interferent at the highest concentration. A control

sample was prepared for each cross-reactant substance by spiking with the appropriate diluents at the same volume as the cross-reactant substance into three different serum samples at concentrations of 0.100 ng/mL, 4.000 ng/mL, and ~10.000 ng/mL. All samples were tested in three replicates for human kallikrein and prostatic aid phosphatase (PAP), and five replicates for other tested cross-reactants using one reagent lot on one Atellica IM Analyzer. None of the cross-reactants exceeded 2% interference to the Atellica IM tPSAII for the tested concentration as shown in Table 8:

Table 8: Cross-Reactivity of the Atellica IM tPSAII

Substance	Concentration
Alpha-fetoprotein (AFP)	10,000 ng/mL
Carcinoembryonic Antigen (CEA)	200 ng/mL
CA 19-9	1000 U/mL
Ferritin	10,000 ng/mL
Human Chorionic Gonadotropin (HCG)	10,000 mIU/mL
Human Kallikrein	100,000 ng/mL
Prolactin	500 ng/mL
Prostatic Acid Phosphatase (PAP)	1000mL

3. Anti-Nuclear Antibodies (ANA) interference

For ANA testing, serum samples from ANA positive individuals (confirmed positive [≥1.0 AI] status by BioRad ANA screening assay) were obtained from a commercially available vendor. Samples were screened for endogenous PSA and then spiked with additional PSA (native male serum with high PSA content) to target the Serum samples with concentrations of 0.100, 4.000, and 10.000 ng/mL. An equivalent amount of spiker was added to female serum containing a nominal amount of PSA. ANA positive samples (spiked w/ PSA and unspiked) and negative serum samples (spiked w/ PSA and unspiked) were analyzed in five replicates on one reagent lot on one Atellica IM analyzer. The difference in PSA concentration of the spiked vs unspiked ANA positive samples (test) was compared to the difference between the spiked and unspiked negative serum samples (control) and it was concluded that ANA did not affect the expected results indicating no interference.

E. Matrix Comparison

The equivalency of using K2 EDTA and lithium heparin plasma and serum for the Atellica IM tPSAII was assessed in accordance with CLSI EP35-Ed1, *Assessment of Equivalence or Suitability of Specimen Types for Medical Laboratory Measurement Procedures*.

The matched samples collected in serum separator tubes (SST) and plasma (K2-EDTA and lithium heparin) from 75 patients were tested in singlicate using one reagent lot.

Slope and Y-intercept results were calculated using Weighted Deming regression analysis. The results are presented in Table 9.

Table 9: Matrix Comparison of the Atellica IM tPSAII

N=75	Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	Correlation	%Bias at 4 ng/mL
K2-EDTA vs Serum	0.133–49.047	1.00 (0.96; 1.04)	-0.011 (-0.034; 0.013)	0.992	-0.3%
Li-Heparin vs Serum	0.133–49.047	1.01 (0.98;1.04)	-0.007 (-0.032;0.018)	0.996	0.8%

F. Equimolarity

The study was performed to demonstrate that the Atellica IM tPSAII can measure total PSA with both free form (free PSA) and the complexed form where PSA is complexed with alpha 1 antichymotrypsin (PSA-ACT) in an equimolar fashion. The complex PSA WHO standard (17/100) and free PSA WHO standard (17/102) was mixed in various ratios (0, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%) to create samples with targeted total PSA concentrations of 0.800, 4.000, 10.000, and 20.000 ng/mL in a 1% protease-free BSA solution. All samples were analyzed in three replicates using three reagent lots on one Atellica IM Analyzer. Results demonstrated that the total concentration of PSA remained constant while varying the amounts of complex PSA WHO standard and free PSA WHO standard across eleven different ratios.

G. Stability

1. Kit Stability

   a. Atellica IM tPSAII Reagent Pack

   The shelf-life of the Atellica IM tPSAII ReadyPack reagent pack was established by testing five native serum samples with total PSA concentration at 0.13 ng/mL, 1.0 ng/mL, 4.0 ng/mL, 10.0 ng/mL and 42.0 ng/mL with three different reagent lots stored at 2-8°C. The following reagent storage timepoints were tested: Day 0 (T0), 1 month, 3 months, 6 months, 7 months, 9 months, 10 months, 12 months, 13 months. At each timepoint, the samples were tested with three replicates per lot on two different Atellica IM analyzers. Stability results across three different lots demonstrated that the Atellica IM tPSA II reagent kit is stable for 12 months when stored at 2-8°C.

   The onboard stability (OBS) of the Atellica IM tPSAII ReadyPack reagent pack was established by testing five native patient samples with two different regent lots stated on the Atellica IM analyzer. At each timepoint, a fresh reagent pack was run alongside reagent packs that remained on the system for

the duration of the study. The onboard pack results were compared to the results of the fresh reagent pack. All samples were tested in five replicates on the "fresh" packs and three replicates with one replicate per pack on the "open" packs on days 0, 7, 9, 14, 15, 16, 21, 28, 35, 42, 43, and 44. Stability results across two different lots demonstrated reagent onboard stability for 42 days, pack calibration interval for 14 days, and lot calibration interval of 42 days.

b. tPSAII CAL (Calibrators)

The study was done to determine the stability the tPSAII CAL high and low calibrators at the following conditions:

- Shelf life (unopened): Testing was established along with the shelf-life stability of the reagent pack as shown in Section K.1.a above.
- Onboard the Atellica IM Analyzer at ambient temperature: testing was done at the baseline point, followed by subsequent testing at 2, 4, 6, 8, and 9 hours using two different lots.
- Opened vials stored in refrigerator at 2-8°C: testing was done at baseline point (Day 0), then tested at days 7, 14, 21, 28, 29, 30, and 32 in replicates of five across two different lots.

c. Multi-diluent 2 (MDIL-2)

The study was done to determine the shelf-life and onboard stability for Multi-diluent 2 (MDIL-2) which is used in auto-dilution for high patients sample out of the measuring range. Two patient samples with tPSA above the upper limit of measuring interval were tested for 1:5 and 1:500 dilution using MDIL-2 were used for the stability testing.

- For shelf life: the two lots of Atellica MDIL-2 stored at 2-8°C were evaluated and tested at timepoints up to 18 months.
- For onboard, the samples were tested using two lots of the MDIL2 packs which remained on the system for the duration of the study at timepoints up to 35 days. The onboard MDIL2 auto-dilution results were compared with day-zero MDIL2 auto-dilution results at each timepoint.

The claimed kit stability for the Atellica IM tPSAII is summarized in Table 10.

Table 10: Stability for the Atellica IM tPSAII

Kit Component	Storage	Stability Claim
tPSAII ReadyPack Reagent Pack	Unopened/Shelf-life	12 months at 2-8ºC
	On-board/In-Use	42 days
tPSAII CAL (calibrators)	Unopened/Shelf-life	12 months at 2-8ºC
	Open Vial	30 days at 2-8ºC
	On-board	8 hours
Multi-Diluent 2 (MDIL-2)	Unopened/Shelf-life	15 months at 2-8ºC
	On-board	28 days

2. Specimen Stability

Blood was collected from 10 male donors using four tube types (red top serum, SST, K2-EDTA, lithium heparin). The samples ranged from ~0.3 ng/mL to ~47.0 ng/mL. Donors 1-5 were tested as-is while Donors 6-10 were spiked with elevated PSA serum to cover the assay range, with spiking volume limited to <5% to avoid matrix effects. Six studies evaluated different storage conditions: Studies 1 and 2 assessed unprocessed samples at room temperature and processed samples on-clot at 2-8°C in primary tubes; Studies 3 and 4 examined separated samples in secondary containers at room temperature (20-25°C) and refrigerated (2-8°C); Studies 5 and 6 evaluated frozen storage at -80°C and freeze/thaw cycles (1-4 cycles). All samples were tested in triplicate using one reagent lot, with percent bias calculated relative to baseline T0 measurements to assess stability over time. The stability of specimens is summarized in Table 11.

Table 11: Stability for Specimens used for the Atellica IM tPSAII

Stability Conditions	Stability Claim
On clot	24 hours at 18-25ºC
Time to centrifugation	24 hours at 18-25ºC
In secondary tube	8 hours at 18-25ºC
	72 hours at 2-8ºC
	15 months at -80ºC
Freeze/Thaw	Up to 3 cycles

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Siemens performed the following studies under an approved IRB to establish a reasonable assurance of safety and effectiveness of the Atellica IM total PSA II (tPSAII) for use as an aid in the detection of prostate cancer in conjunction with DRE in men 50 years and older:

- Study 1. Reference Interval Study
- Study 2. Clinical Validation Study

A summary of each study is presented below.

STUDY 1. REFERENCE INTERVAL STUDY

A. Study Design

A study was conducted to establish the reference interval for the Atellica IM tPSA II using samples from apparently healthy men 50 years and older with no history or current prostate cancer or any other benign prostatic disease collected from, seven different sites across the U.S. The study was conducted according to CLSI EP28-A3C, *Defining,*

Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition.

1. Inclusion and Exclusion Criteria

   Enrollment in the reference interval study was limited to subjects who met the following inclusion criteria

   - Subject must be male and age 50 and older
   - Subject must understand and sign informed consent prior to any study procedure
   - Subject must be entered into this study only once

   Patients were not permitted to enroll in the reference interval study if they met any of the following exclusion criteria:

   - Subject assessed by the urologist in follow up to a referral by a primary care physician
   - Subject with history of prostate cancer prior to study blood draw
   - Subject who had undergone any form of treatment or procedure(s) for prostate disease known to impact PSA levels, including but not limited to prostate biopsy, prostate radiation, catheterization within 90 days prior to study blood draw
   - Subject who has taken medication for prostate disease within 90 days prior to study blood draw within the following classes of medication known to impact PSA levels: 5α-reductase inhibitors, anti-androgens, androgen therapy or hormone therapy (use of alpha blockers is allowed)
   - Subject who proceeds to biopsy within 60 days or less from the study blood draw
   - Subject had study specimens collected other than serum

2. Follow-up Schedule

   No follow-up schedule was required for the enrolled subjects. All subjects were prospectively enrolled at each site. Serum samples were collected from eligible subjects and tested using the Atellica IM tPSA II assay.

3. Endpoints

   The study is to define the reference interval of the Atellica IM Total PSA II values in apparently health population of men 50 years and older. The values of total PSA from the study dataset were analyzed for all subjects and for each age subgroups, i.e., 50-59, 60-69, and 70 and older.

B. Accountability of Study Subjects

A total of 1068 subjects were enrolled. Among them, 278 subjects were excluded based on eligibility criteria (185 subjects with presence of prostate disease, 45 with prostatitis, 43 under medications, 5 for suspicious DRE), 57 subjects were excluded as the samples were unavailable for testing, three (3) subjects were excluded due to inadequate study documentation, and three (3) subjects were excluded for protocol deviations. This resulted in 727 subjects to be included in the reference interval study analysis.

C. Study Population Demographics and Baseline Parameters

Table 12 below summarizes the demographics of the population used in the reference interval study.

Table 12: Demographics of Population (Reference Interval)

Demographics		N (%)
Race, Ethnicity	White	627 (86.2%)
	African American	81 (11.1%)
	Asian	14 (1.9%)
	Other	5 (0.7%)
Age	50-59	294 (40.4%)
	60-69	293 (40.3%)
	70-99	140 (19.3%)
Total		727 (100%)

D. Study Results:

1. All Subjects:

Reference interval of the Atellica IM tPSAII results by age decade among all apparently healthy population aged 50+ is summarized in the Table 13 and Table 14.

Table 13: Reference Interval of the Atellica IM tPSAII

	Age Decade			All
	50 – 59	**60 – 69**	**70 – 99**	
N	294	293	140	727
Mean (ng/mL)	1.4	1.9	2.2	1.7
Median (ng/mL)	0.9	1.2	1.6	1.1
2.5th percentile (ng/mL)	0.2	0.3	0.3	0.2
95th percentile (ng/mL)	3.9	4.8	6.6	4.7
97.5th percentile (ng/mL)	5.0	5.5	7.8	6.2

Table 14: Distribution of Total PSA Value of the Atellica IM tPSAII among Apparently Healthy Population Aged 50+

Age	N	Atellica IM tPSAII				
		<4.0 ng/mL	4.0-10.0 ng/mL	10.1-30.0 ng/mL	30.1-50.0 ng/mL	>50.0 ng/mL
		n (n/N%)				
50-59	294 (100)	280 (95.2)	13 (4.4)	1 (0.3)	0 (0.0)	0 (0.0)
60-69	293 (100)	271 (92.5)	20 (6.8)	0 (0.0)	1 (0.3)	1 (0.3)
70-99	140 (100)	122 (87.1)	17 (12.1)	1 (0.7)	0 (0.0)	0 (0.0)
Total	**727 (100)**	**673 (92.6)**	**50 (6.9)**	**2 (0.3)**	**1 (0.1)**	**1 (0.1)**

2. Subgroup Analysis – Race/Ethnicity

Reference interval of the Atellica IM tPSAII results by age decade among African American in all apparently healthy population aged 50+ is summarized in the Table 15 and Table 16.

Table 15: Reference Interval of the Atellica IM tPSA by Race/Ethnicity

	Age Decade			All
	50-59	60-69	70-99	
African American				
N	33	33	15	81
Mean (ng/mL)	1.6	3.0	2.6	2.4
Median (ng/mL)	0.8	1.2	2.1	1.2
2.5th percentile (ng/mL)	n/a	n/a	n/a	0.2
95th percentile (ng/mL)	6.6	16.9	7.6	6.9
97.5th percentile (ng/mL)	n/a	n/a	n/a	7.6
Non-African American				
N	261	260	125	646
Mean (ng/mL)	1.4	1.7	2.2	1.7
Median (ng/mL)	0.9	1.1	1.6	1.1
2.5th percentile (ng/mL)	0.2	0.3	0.2	0.2
95th percentile (ng/mL)	3.8	4.7	6.4	4.5
97.5th percentile (ng/mL)	4.5	5.4	7.9	5.5

Table 16: Distribution of Total PSA Value of the Atellica IM tPSAII by Race/Ethnicity in Apparently Healthy Population Aged 50+

Age	N	Atellica IM tPSAII				
		<4.0 ng/mL	4.0-10.0 ng/mL	10.1-30.0 ng/mL	30.1-50.0 ng/mL	>50.0 ng/mL
		n (n/N%)				
African American						
50-59	33 (100)	30 (90.9)	3 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
60-69	33 (100)	28 (84.8)	4 (12.1)	0 (0.0)	1 (3.0)	0 (0.0)
70-99	15 (100)	12 (80.0)	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	**81 (100)**	**70 (86.4)**	**10 (12.3)**	**0 (0.0)**	**1 (1.2)**	**0 (0.0)**
Non-African American						
50-59	261 (100)	250 (95.8)	10 (3.8)	1 (0.4)	0 (0.0)	0 (0.0)
60-69	260 (100)	243 (93.5)	16 (6.2)	0 (0.0)	0 (0.0)	1 (0.4)
70-99	125 (100)	110 (88.0)	14 (11.2)	1 (0.8)	0 (0.0)	0 (0.0)
Total	**646 (100)**	**603 (93.3)**	**40 (6.2)**	**2 (0.3)**	**0 (0.0)**	**1 (0.2)**

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. The device is indicated to be used in the population of men 50 years and older.

E. Financial Disclosure

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

STUDY 2. CLINICAL VALIDATION STUDY

A. Study Design

The clinical validation study was a prospective study conducted to evaluate the clinical performance of the Atellica IM Total PSA II assay in conjunction with Digital Rectal Examination (DRE) as an aid in detection of prostate cancer in men aged 50 years or older. The study included patients who met the inclusion/exclusion criteria described below from 25 clinical sites across the United States. All subjects had been referred to a urologist for evaluation of prostate cancer. In addition to the geographic distribution of clinical sites where specimens for diagnostic subjects were collected, subjects were also distributed across racial and ethnic groups, age

categories, and family history status. Each subject in the clinical validation study has quantitative result of tPSAII test (positive if tPSAII ≥4 ng/mL and negative if tPSAII <4ng/mL), DRE result (positive or negative) and prostate biopsy (positive or negative).

1. Inclusion and Exclusion Criteria

   Enrollment in the study was limited to patients who met the following inclusion criteria:

   - Subject must be male and age 50 and older
   - Subject must understand and sign informed consent prior to any study procedure
   - Subject must be entered into this study only once
   - Subject must have had a DRE either more than 5 days but within 20 days prior to study blood draw or will have a DRE within 30 days after study blood draw
   - Subjects must have auditable medical records available to verify required medical information
   - Subject must have a prostate biopsy within 60 days, after study blood draw, and the results must be known
   - If the biopsy results are positive for prostate cancer, clinical stage must be determined and Gleason score should be provided, if available

   Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

   - Subject with history of prostate cancer prior to study blood draw
   - Subject who has undergone any form of treatment or procedure(s) for prostate disease known to impact PSA levels, including but not limited to prostate biopsy, prostate radiation, catheterization within 90 days prior to study blood draw
   - Subject who has taken medication for prostate disease within 90 days prior to study blood draw within the following classes of medication known to impact PSA levels: 5α-reductase inhibitors, anti-androgens, androgen therapy or hormone therapy (use of alpha blockers is allowed)
   - Subject had study specimens collected other than serum

2. Follow-up Schedule

   No follow-up schedule was required for the enrolled subjects. All subjects were prospectively enrolled, based on the normal flow of patients scheduled to receive a prostate biopsy at each site.

3. Clinical Endpoints

The clinical performance of the Atellica IM Total PSA II test using the cutoff of 4.0 ng/mL in comparison to biopsy result was evaluated and measures of the clinical performances as sensitivity, specificity, positive and negative predictive values were calculated. The data should demonstrate that the Atellica IM Total PSA II test is statistically informative test: True Positive rate (sensitivity) > False Positive rate (1-specificity) or equivalently, PPV >prevalence and NPV >1-prevalence).

The Atellica IM Total PSA II is used in conjunction with DRE; therefore, it should be demonstrated that tPSAII provides an additional information beyond the DRE results. When used in conjunction with DRE, the added value of the Atellica IM Total PSA II to DRE results should be reflected by:

i) Statistically significant increase in the probability of positive biopsy for subjects with (DRE positive and tPSA II positive) results in comparison to the subjects with DRE positive results only.
ii) Statistically significant decrease in the probability of a positive biopsy results for the subjects with (DRE negative and tPSA II negative) results compared to the subjects with DRE negative results only.

B. Accountability of PMA Cohort

The clinical study enrolled 2,680 subjects from 256 geographically diverse urology clinics in the U.S. All subjects are aged 50 years or older who underwent local PSA testing in conjunction with DRE and were referred to a urologist for evaluation of prostate cancer. Of the 2,680 subjects collected, 496 subjects were analyzed as part of the derivation cohort, 586 were excluded for missing biopsy, 86 subjects were excluded due to protocol deviations, 43 subjects were excluded due to screen failure, 16 subjects were excluded due to enrollment under a prior version of study protocol, nine (9) subjects were excluded as the samples were unavailable for testing, and three (3) subjects were excluded due to inadequate study documentation. This resulted in 2,582 subjects to be included in the clinical performance evaluation of the Atellica IM tPSAII.

C. Study Population Demographics and Baseline Parameters

The distributions of demographic and clinical characteristics of the 2,582 subjects are described in Table 17.

Table 17: Distribution of Demographic and Clinical Information for Study Population

Demographic/Clinical Characteristics		Total N=2582
		n (%)
Race, Ethnicity	White	2196 (85.1%)
	African American	192 (7.4%)
	Asian	24 (0.9%)
	Other*	22 (0.8%)
	Unknown, Declined Answer	148 (5.7%)
Age Group	50 – 59	569 (22.0%)
	60 – 69	1191 (46.0%)
	70 – 91	822 (32.0%
DRE	Abnormal	671 (26.0%)
	Normal	1911 (74.0%)
Biopsy Result	Negative	1065 (41.2%)
	Gleason 6	442 (17.1%)
	Gleason 7 (3+4)	469 (18.2%)
	Gleason 7 (4+3)	254 (9.8%)
	Gleason 8	194 (7.5%)
	Gleason 9	138 (5.3%)
	Gleason 10	20 (0.8%)

* 22 subjects including Hispanic (N=6), Native American (N=6), Hawaiian (N=3), Armenian (N=1), and not specified (N=9).

Distributions of the Atellica IM Total PSA II results for subjects with different diagnostic categories are presented in Table 18.

Table 18: Expected Results of the Atellica IM tPSAII for Subjects with Different Diagnostic Categories

Diagnostic Category	N	<4 ng/mL (%)	4-10 ng/mL (%)	>10-30 ng/mL (%)	>30-50 ng/mL (%)	>50 ng/mL (%)	Median (ng/mL)
Prostate Cancer							
Gleason 6	442	18.2	70.4	10.0	0.9	0.2	5.806
Gleason 7+	1075	8.4	58.0	24.7	3.4	5.5	7.576
Total	1517	11.3	61.6	20.4	2.7	4.0	6.985
Benign Diseases							
BPH*	32	21.9	62.5	15.6	0.0	0.0	5.740
PIN	93	17.3	67.3	13.3	1.0	1.0	5.800

*Benign Prostatic Hyperplasia (BPH)
**Prostatic Intraepithelial neoplasia (PIN)

D. Safety and Effectiveness Results

1. Safety Results

Atellica IM Total PSA II involves testing whole blood samples. These specimens are routinely taken as part of the practice of medicine and, therefore, sample collection presents no additional safety hazard to the patient being tested.

The diagnosis of prostate cancer must be confirmed by biopsy. When using the Atellica IM Total PSA II, subjects with falsely elevated PSA results could lead to an unnecessary biopsy. Subjects with falsely low total PSA results may not receive a necessary biopsy, therefore, could delay recognition of the presence of prostate cancer by the physician and could adversely delay the initiation of therapy. The safety concern with respect to biopsy is often associated with infectious complications following the procedure. In this study, all enrolled subjects were men presenting to a practicing urologist with symptoms that would lead to an evaluation for prostate cancer and who are scheduled to receive a prostate needle biopsy. The Atellica IM Total PSA II result for these subjects did not alter the medical decision for these subjects, therefore, present no additional safety hazard to the subjects being tested.

2. Effectiveness Results

The analysis of effectiveness was based on the 2582 evaluable patients enrolled at 25 urology clinics in the U.S. The performance of Atellica IM Total PSA II as an aid in detection of prostate cancer is evaluated using the cut-off value of 4.0 ng/mL compared to the clinical diagnosis of each subject. The clinical diagnosis of prostate cancer for each subject was based on the pathological examination of the biopsy tissues yielding a Gleason Score 6 or greater. All other findings were grouped as non-cancer.

Poolability of data analysis:

Evaluable data were collected from 25 sites across the U.S. The Poolability of the data from different sites was evaluated using based on the prevalence of prostate cancer, age of subjects, tPSAII results, and DRE results.

i) The prevalence of prostate cancer in the study was 58.8% and the site-specific cancer prevalence ranged from 36.8% to 80.0%.
ii) The mean age of the study cohort was 65.9 years with the site-specific mean age ranged from 63.3 to 73.0 years.
iii) The median Atellica IM total PSAII Test value was 6.347 ng/mL, and the site-specific median of total PSA ranged from 4.312 to 8.246 ng/mL.
iv) The percent mean of abnormal DRE was 26% with the site-specific proportion of abnormal DRE ranged from 0% to 61.3%. One site with very low

enrollment had only eleven (11) eligible patients, all of whom were DRE normal.

Based on the above evaluation, the performance of the Atellica IM tPSAII test is evaluated using the pooled data across 25 sites.

Results

The clinical performance of the Atellica IM tPSAII when used in conjunction with DRE as an aid in the detection of prostate cancer in men 50 years or older was demonstrated based on the multi-center prospective study results using a total of 2582 patients. Each patient in the study had the Atellica IM tPSAII result, DRE result, and biopsy findings. The results of the Atellica IM tPSAII were based on the cut-off of 4.0 ng/mL as shown below:

tPSAII positive: Atellica IM tPSAII≥4 ng/mL
tPSAII negative: Atellica IM tPSAII<4 ng/mL

A patient with a Gleason score of ≥6 is defined as biopsy positive and a patient with a Gleason score of <6 is biopsy negative. The clinical performance of the Atellica IM tPSAII is analyzed according to the CLSI EP12-Ed3: *Evaluation of Qualitative, Binary Output Examination Performance* and summarized in Table 19, Table 20, and Table 21.

Table 19: Distribution of the Atellica IM tPSAII Values by Biopsy and DRE Result

	N	Atellica tPSAII (ng/mL)		
		Median	Minimum	Maximum
Biopsy positive: (Gleason score ≥6)				
DRE neg	1035	6.486	0.698	>50.000
DRE pos	482	7.807	0.847	>50.000
Total	1517	6.985	0.698	>50.000
Biopsy negative (Gleason score <6)				
DRE neg	876	5.820	0.211	>50.000
DRE pos	189	4.783	0.109	>50.000
Total	1065	5.698	0.109	>50.000

Table 20: Number of Subjects for DRE and Atellica IM tPSA II comparing to Prostate Cancer Detected by Biopsy

Biopsy Positive (N)				Biopsy Negative (N)			
tPSAII	DRE		Total	tPSAII	DRE		Total
	Pos	Neg			Pos	Neg	
Pos	431	914	1345	**Pos**	117	681	798
Neg	51	121	172	**Neg**	72	195	267
Total	482	1035	1517	**Total**	189	876	1065

The clinical performance measures including sensitivity, specificity, positive predicate value (PPV) and negative predicate value (NPV) of DRE alone, Atellica

tPSAII alone, and Atellica tPSA II assay in conjunction with DRE for detection of prostate cancer are summarized in Table 20. Clinical performance measures of the Atellica tPSAII assay in conjunction with DRE are calculated for:

i) Combination "OR" (DRE OR tPSAII): Combination OR is positive when either DRE positive or tPSAII positive and combination OR is negative when both DRE and tPSAII are negative.
ii) Combination AND (DRE AND tPSAII): Combination AND is positive when both DRE and tPSAII are positive and combination AND is negative when either DRE or tPSAII is negative.

Table 21: Clinical Performance of the Atellica IM tPSAII for All Subjects (N=2582, prevalence of 58.8%)

	Sensitivity (n/N) (95% CI) *	**Specificity (n/N) (95% CI) ***	**PPV (n/N) (95% CI) ****	**NPV (n/N) (95% CI) ****
DRE	31.8% (482/1517) (29.5; 34.2%)	82.3% (876/1065) (79.8; 84.4%)	71.8% (482/671) (68.8; 74.8%)	45.8% (876/1911) (44.7; 46.9%)
Atellica IM tPSA II	88.7% (1345/1517) (87.0; 90.2%)	25.1% (267/1065) (22.6; 27.8%)	62.8% (1345/2143) (61.9; 63.7%)	60.8% (267/439) (56.6; 64.9%)
DRE OR Atellica IM tPSA II	92.0% (1396/1517) (90.6; 93.3%)	18.3% (195/1065) (16.1; 20.7%)	61.6% (1396/2266) (59.6; 63.5%)	61.7% (195/316) (56.6; 66.6%)
DRE AND Atellica IM tPSA II	28.4% (431/1517) (26.2; 30.7%)	89.0% (948/1065) (87.0; 90.8%)	78.6% (431/548) (62.0; 81.7%)	46.6% (948/2034) (45.7; 47.6%)

* 95%CI for sensitivity and specificity are calculated using the Wilson score method

**95%CI for PPV and NPV were calculated using the 95%CI of the corresponding likelihood ratios (asymptotic method for a ratio of two independent binomial proportions) and the prevalence of 58.8% in the urology office setting in this study.

The results indicated the following:

- In the clinical performance study, the sensitivity of the tPSA II assay is **88.7%** (1345/1517) with 95% CI: **(87.0–90.2%)** and specificity is **25.1%** (267/1065) with 95% CI: **(22.5–27.8%)**. PPV for the tPSA II assay is **62.8%** with the lower bound of 95% CI of **60.7%** which is larger than prevalence of **58.8%**, indicating that PPV is statistically higher than the prevalence. NPV for the tPSA II assay is **60.8%** with the lower bound of 95% CI of **56.1%** which is larger than **41.2%** (one minus prevalence), indicating that NPV is statistically higher than the one minus prevalence. The data of the clinical performance study showed that the Atellica IM tPSAII assay is an informative test with regard to risks of prostate cancer.
- For combination OR of the Atellica tPSA II assay with DRE, the sensitivity increased by **60.2%** compared to the sensitivity of the DRE alone (from 31.8% to 92.0%) and this increase was statistically significant. The NPV for

the combination OR of the tPSA II assay with DRE was **61.7%** with 95%CI: (56.6; 66.6%) and NPV for DRE alone was 45.8% with 95%CI: (44.7; 46.9%). The increase in NPVs was **15.9%** with 95%CI: (9.3; 24.7%) (calculated by the bootstrap method) indicating that the increase in NPVs was statistically significant. There was also a decrease in the PPVs of the combination OR of the Atellica IM tPSAII assay with DRE compared to the PPV of the DRE alone by **10.2%** (from 71.8% to 61.6%).

- For combination AND of the Atellica tPSA II assay with DRE, the specificity increased by **6.7%** compared to the specificity of the DRE alone (from 82.3% to 89.0%) and this increase was statistically significant. The PPV for the combination AND of the tPSA II assay with DRE was **78.6%** with 95%CI: (62.0; 81.7%) and PPV for DRE alone was 71.8% with 95%CI: (68.8; 74.9%). The increase in the PPVs was **6.8%** with 95% CI: (1.7; 12.6%) (calculated by bootstrap method) indicating that the increase in the PPVs was statistically significant. There was no an observed decrease in NPV of combination AND of the Atellica IM tPSAII assay with DRE (NPV=46.6%) compared to the NPV of the DRE alone (NPV=45.8%).

In conclusion, the data of the clinical performance study support that Atellica IM tPSA II assay is an informative test and that the Atellica IM tPSAII testing used in conjunction with DRE was more effective in detecting prostate cancer than using DRE alone.

In addition, probability of positive biopsy for four combinations of tPSAII and DRE results is presented in Table 22.

Table 22: Probability of Positive Biopsy in All Subjects

	N of Positive Biopsy	**N of Negative Biopsy**	**Total**	**% of subjects with Positive Biopsy (95% CI)**
DRE pos	482	189	671	71.8% (68.8; 74.8%)
DRE neg	1035	876	1911	54.2% (53.1; 55.3%)
tPSAII≥4 ng/mL, DRE Pos	431	117	548	78.6% (62.0; 81.7%)
tPSAII≥4 ng/mL, DRE Neg	914	681	1595	57.3% (55.8; 58.8%)
tPSAII<4 ng/mL, DRE Pos	51	72	123	41.5% (33.3; 50.1%)
tPSAII<4 ng/mL, DRE Neg	121	195	316	38.3% (33.4; 43.4%)
All subjects	**1517**	**1065**	**2582**	Prevalence=58.8%

3. Subgroup Analyses

a. Increased prevalence and severity are known and well-documented for African American population in the United States. Clinical performance of the Atellica IM tPSAII in conjunction of DRE in detection of prostate cancer (Gleason score ≥6) stratified by race/ethnicity is analyzed as shown in the Table 23.

Table 23: Clinical Performance of the Atellica IM tPSAII Stratified by Race/Ethnicity

	Sensitivity* (n/N) (95% CI)	**Specificity* (n/N) (95% CI)**	**PPV** (n/N) (95% CI)**	**NPV** (n/N) (95% CI)**
African American (prevalence =64.1%)				
DRE	26.0% (32/123) (19.1; 34.4%)	87.0% (60/69) (77.0; 93.0%)	78.0% (32/41) (65.0; 87.6%)	39.7% (60/151) (36.2; 43.2%)
Atellica IM tPSAII	88.6% (109/123) (81.8; 93.1%)	23.2% (16/69) (14.2; 34.9%)	67.3% (109/162) (64.3; 70.9%)	53.3% (16/30) (37.4; 68.5%)
DRE OR Atellica IM tPSA II	90.2% (111/123) (83.7; 94.3%)	18.8% (13/69) (11.4; 29.6%)	66.5% (111/167) (63.8; 69.7%)	52.0% (13/25) (34.6; 68.8%)
DRE AND Atellica IM tPSA II	24.4% (30/123) (17.7; 32.7%)	91.3% (63/69) (82.3; 96.0%)	83.3% (30/36) (69.6; 91.9%)	40.4% (63/156) (37.3; 43.6%)
Non-African American (prevalence=58.3%)				
DRE	32.3% (450/1394) (29.9; 34.8%)	81.9% (816/996) (79.4; 84.2%)	71.4% (450/630) (68.2; 74.5%)	46.4% (816/1760) (45.2; 47.5%)
Atellica IM tPSAII	88.7% (1236/1394) (86.9; 90.2%)	25.2% (251/996) (22.6; 28.0%)	62.4% (1236/1981) (61.5; 63.4%)	61.4% (251/409) (57.0; 65.6%)
DRE OR Atellica IM tPSA II	92.2% (1285/1394) (90.7; 93.5%)	18.3% (182/996) (16.0; 20.8%)	61.2% (1285/2099) (60.4; 62.0%)	62.5% (182/291) (57.2; 67.6%)
DRE AND Atellica IM tPSA II	28.8% (401/1394) (26.5; 31.2%)	88.9% (885/996) (86.7; 90.7%)	78.3% (401/512) (74.9; 81.4%)	47.1% (885/1878) (46.1; 48.1%)

* 95%CI for sensitivity and specificity are calculated using the Wilson score method

**95%CI for PPV and NPV were calculated using the 95%CI of the corresponding likelihood ratios (asymptotic method for a ratio of two independent binomial proportions) and the prevalence of 64.1% for African American and 58.3% for non-African American in the urology office setting in this study cohort.

b. Distribution of the Atellica IM tPSAII value stratified by race/ethnicity and age groups

The distribution of the Atellica IM tPSA II in the study group (men aged 50+) presenting in urology clinical for evaluation of prostate cancer) was further analyzed in all patients (N=2582), African American (N=192) and non-African American (N =2390). The results are summarized in Tables 24 and 25 below.

Table 24: Distribution of the Atellica IM tPSAII Results by Age Decade Among Diagnostic Population Aged 50+

	Age Decade			All
	50-59	**60-69**	**70-99**	
All subjects				
N	569	1191	822	2582
Mean (ng/mL)	7.3	8.5	10.8	9.0
Median (ng/mL)	5.6	6.2	7.5	6.3
2.5th percentile (ng/mL)	1.3	7.7	2.0	1.6
95th percentile (ng/mL)	19.6	23.1	36.3	25.9
97.5th percentile (ng/mL)	31.9	44.2	50.0	49.3
African American				
N	51	91	50	192
Mean (ng/mL)	8.6	9.5	15.0	10.7
Median (ng/mL)	10.0	9.2	15.3	6.2
2.5th percentile (ng/mL)	5.4	6.2	8.4	1.9
95th percentile (ng/mL)	36.7	29.2	50.0	50.0
97.5th percentile (ng/mL)	47.2	50.0	50.0	50.0
Non-African American				
N	518	1100	772	2390
Mean (ng/mL)	7.1	8.4	10.5	8.8
Median (ng/mL)	5.6	6.2	7.5	6.4
2.5th percentile (ng/mL)	1.2	1.6	1.9	1.6
95th percentile (ng/mL)	18.0	22.6	34.3	24.8
97.5th percentile (ng/mL)	27.1	43.6	50.0	46.0

Table 25: Total Distribution of the Atellica IM tPSAII Categories by Age Decade Among Diagnostic Population Aged 50+

Age	**N**	**Atellica IM tPSAII**				
		<4.0 ng/mL	**4.0-10.0 ng/mL**	**10.1-30.0 ng/mL**	**30.1-50.0 ng/mL**	**>50.0 ng/mL**
		n (n/N%)				
All subjects						
50-59	569 (100)	137 (24.1)	362 (63.6)	56 (9.8)	9 (1.6)	5 (0.9)
60-69	1191 (100)	199 (16.7)	768 (64.5)	180 (15.1)	18 (1.5)	26 (2.2)
70-99	822 (100)	103 (12.5)	455 (55.4)	214 (26.0)	17 (2.1)	33 (4.0)
Total	**2582 (100)**	**439 (17.0)**	**1585 (61.4)**	**450 (17.4)**	**44 (1.7)**	**64 (2.5)**

Age	N	Atellica IM tPSAII				
		<4.0 ng/mL	4.0-10.0 ng/mL	10.1-30.0 ng/mL	30.1-50.0 ng/mL	>50.0 ng/mL
		n (n/N%)				
African American						
50-59	51 (100)	12 (23.5)	30 (58.8)	5 (9.8)	3 (5.9)	1 (2.0)
60-69	91 (100)	12 (13.2)	52 (57.1)	24 (26.4)	0 (0.0)	3 (3.3)
70-99	50 (100)	6 (12.0)	24 (48.0)	13 (26.0)	1 (2.0)	6 (12.0)
Total	**192 (100)**	**30 (15.6)**	**106 (55.2)**	**42 (21.9)**	**4 (2.1)**	**10 (5.2)**
Non-African American						
50-59	518 (100)	125 (24.1)	332 (64.1)	51 (9.8)	6 (01.2)	4 (0.8)
60-69	1100 (100)	187 (17.0)	716 (65.1)	156 (14.2)	18 (1.6)	23 (2.1)
70-99	772 (100)	97 (12.6)	431 (55.8)	201 (26.0)	16 (2.1)	27 (3.5)
Total	**2390 (100)**	**409 (17.1)**	**1479 (61.9)**	**408 (17.1)**	**40 (1.7)**	**54 (2.3)**

African Americans demonstrate consistently higher tPSAII levels compared to non-African Americans across all age groups, with a notably higher frequency of very elevated levels (>50.0 ng/mL) at 5.2% versus 2.3% overall, and this disparity becomes most pronounced in those aged 70-99 where 12.0% of African Americans versus only 3.5% of non-African Americans have levels exceeding 50.0 ng/mL.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. The device is indicated to be used in the population of men 50 years and older.

XI. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 3 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not Applicable.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory committee, for review and recommendation because the

information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The analytical performance studies support that the assay can quantitatively measure total PSA levels from 0.009 ng/mL to 50.0 ng/mL using whole blood samples. The clinical effectiveness of the Atellica IM tPSA II was demonstrated by testing 2582 subjects at 25 different sites within the U.S. In the detection of prostate cancer, digital rectal examination alone demonstrated a sensitivity of 31.8% (482/1517) with a 95% confidence interval (CI) of (29.5;34.2%) and specificity of 82.3% (876/1065) with a 95% CI of (79.8; 84.4%) when compared to biopsy, while tPSAII results showed a sensitivity of 88.7% (1345/1517) with a 95% CI of (87.0;90.2%) and specificity of 25.1% (267/1065) with a 95% CI of (22.6; 27.8%).

- The proportion of positive biopsy results among DRE positive subjects was compared to the proportion of positive biopsy results among subjects who were both DRE positive and tPSAII positive (above the tPSA II cutoff of 4.0 ng/mL); among subjects with tPSAII positive and DRE positive results, 78.6% (431/548) were biopsy positive. In comparison, 71.8% (482/671) of DRE positive subjects were biopsy positive. The 6.8% improvement provides significant evidence that tPSAII testing used in conjunction with DRE was more effective in detecting prostate cancer than using DRE alone.
- The proportion of positive biopsy subjects among DRE negative patients was compared to the proportion of positive biopsy among patients who were both DRE negative and tPSAII negative (below the tPSAII cutoff of 4.0 ng/mL): among subjects with tPSAII negative and DRE negative, 38.3% (121/316) were biopsy positive. In comparison, 54.2% (1,035/1,911) of DRE negative subjects were biopsy positive. The 15.9% improvement provides significant evidence that tPSAII testing used in conjunction with DRE was more effective in detecting prostate cancer than using DRE alone.

Therefore, the analytical and clinical performance studies support the effective use of the device for measuring total PSA in serum and plasma to aid in the detection of prostate cancer in men aged 50 years and older in conjunction with DRE. A prostate biopsy is required for the diagnosis of prostate cancer.

B. Safety Conclusions

The risks of the device are based on analytical performance testing as well as data collected in a clinical performance study conducted to support PMA approval as described above. As a routine diagnostic test, the FDA-approved total PSA assays which are currently used as standard-of care in clinical practice involve collection of whole blood for testing purposes. The Atellica IM tPSA II involves taking a blood

sample from the patients and is to be performed by trained healthcare professionals with CLIA moderate complexity testing certificate.

C. Benefit-Risk Determination

Assessment of Benefit:

The Atellica IM tPSA II is not a standalone diagnostic test or a standalone cancer screening test. It is indicated to be used as an aid in the detection of prostate cancer in combination with DRE. In this setting, the output of the device/test is likely to be used clinically to help inform the decision as to whether to perform a prostate biopsy. In some patients, this will result in a benefit which may include increased cure rates related to early diagnosis of prostate cancer with less morbidity due to unnecessary biopsies and thereby result in a better quality of life. For the individual patient, patient preferences are a major component of the decision-making process to measure total PSA and/or to do a prostate biopsy.

The above assessment is based in part on a sensitivity and specificity of Atellica IM tPSA II alone at a cut-off of 4.0 for detection of prostate cancer of 88.7 % with 95% CI: (87.0–90.2%) and 25.1% with 95% CI: (22.6-27.8%). Among subjects with DRE positive and tPSAII positive results, 78.6% (431/548) patients were biopsy positive. In comparison, 71.8% (482/671) of DRE positive subjects were biopsy positive. The 7% improvement provides significant evidence that tPSAII testing used in conjunction with DRE was more effective in detecting prostate cancer than using DRE alone. Among subjects with DRE negative and tPSAII negative results, 38.3% (121/316) were biopsy positive. In comparison, 54.2% (1,035/1,911) of DRE negative subjects were biopsy positive. The 15.9% improvement provides significant evidence that tPSAII testing used in conjunction with DRE was more effective in detecting prostate cancer than using DRE alone.

Assessment of Risk:

When the Atellica IM tPSA II is used according to the instructions provided, accurate assay results should be obtained. An error in the assay producing a falsely elevated PSA value could lead to an unnecessary biopsy. A falsely low PSA value could delay recognition of the presence of prostate cancer by the physician and could adversely delay the initiation of therapy.

As the use of the PSA test will result in a decision to perform a prostate biopsy in some patients, in addition to the relatively low direct risks of the biopsy procedure, there are risks of diagnosing ("over diagnosing") a prostate cancer that would never cause the patient any trouble (likely a Gleason 6 cancer) in addition to the risks of missing a significant cancer (likely a Gleason 7 or higher). A false negative PSA test may also occur and result in missing a cancer (which may or may not be potentially fatal). This is currently a controversial area, but these risks are widely understood in the medical community and are typically transmitted to patients with relevant

decisions to make. For the individual patient, patient preferences are a major component of the decision-making process to measure the PSA and/or to do a prostate biopsy. The result of this test is one of many factors that will be considered in the decision to do a biopsy.

Assessment of Benefit-Risk Balance:

For an individual patient, the Benefit-Risk balance is variable, with high uncertainty, and varies depending on many known as well as unknown factors. The current standard-of-care for the evaluation of men over the age of 50 years with respect to measuring total PSA and deciding whether to perform a prostate biopsy is based on the process of "shared decision-making." This is a highly individualized process between the patient and the physician and takes many factors into account, including personal risk factors such as age, ethnicity, family history, personal habits, expected longevity, tolerability of certain treatments and acceptability of the risks of those treatments, and beliefs about cancer, among others. The Benefit-Risk balance will differ widely among patients because a potential net benefit in reducing the risk of prostate cancer death for some men must be balanced against the risks of experiencing non–life-threatening harms. In addition, the willingness of different patients to accept different risks varies. It is also now recognized that the increased uptake of active surveillance by men with a low-risk prostate cancer might mitigate the harms of over-diagnosis. Accordingly, the results of the Atellica IM tPSAII are only one of many other factors that will be taken into consideration in shared decision-making. In this clinical setting, where there are many unknowns with respect to the likelihood of a diagnosis of prostate cancer, and the likely behavior of such a cancer should it be diagnosed, as an aid in diagnosis this test is judged to have an acceptable benefit-risk profile (i.e., on average in the intended use population, the potential benefits likely outweigh the risks).

1. Patient Perspective

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

In conclusion, given the available information above, the data supports that, for the Atellica IM tPSAII used as aid in the detection of prostate cancer in conjunction with a digital rectal exam (DRE) in men aged 50 years and older, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from analytical performance and clinical performance studies support the safety

and effectiveness of Atellica IM tPSAII as an aid in the detection of prostate cancer in men aged 50 years and older in conjunction with a DRE.

XV. CDRH DECISION

CDRH issued an approval order on December 3, 2025.

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

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

Not Applicable.