SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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

Device Trade Name: Sangia Total PSA Test

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

Applicant's Name and Address: OPKO Diagnostics, LLC
4 Constitution Way, Suite F
Woburn, MA 01801

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170037

Date of FDA Notice of Approval: January 30, 2019

II. INDICATIONS FOR USE

The Sangia Total PSA Test is an immunoassay indicated to quantitatively measure total PSA in capillary whole blood from a fingerstick collected by a healthcare professional and is used in conjunction with a digital rectal exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years and older. The Sangia Total PSA Test is performed using the Claros 1 Analyzer in point-of-care settings. 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 Sangia Total PSA Test labeling.

V. DEVICE DESCRIPTION

An individual Sangia Total PSA Test consists of a Cassette Assembly and a Sample Collector. The Sangia Total PSA test is a microfluidic-based point-of-care (POC) immunoassay for quantitative measurement of total PSA from whole blood utilizing Silver Amplified NeoGold ImmunoAssay (Sangia) technology. The fingerstick sample is collected and fills into the Sample Collector. The Sample Collector connects to the Cassette Assembly that can be inserted to the Claros 1 Analyzer for the testing (see

Figure 1). Each sample run on a Sangia Total PSA Test cassette includes a separate positive and negative control check that must be passed for the Claros 1 Analyzer to report a total PSA sample result. The test is designed to give quantitative total PSA results in the POC setting utilizing a fingerstick whole blood sample in 10-12 minutes.

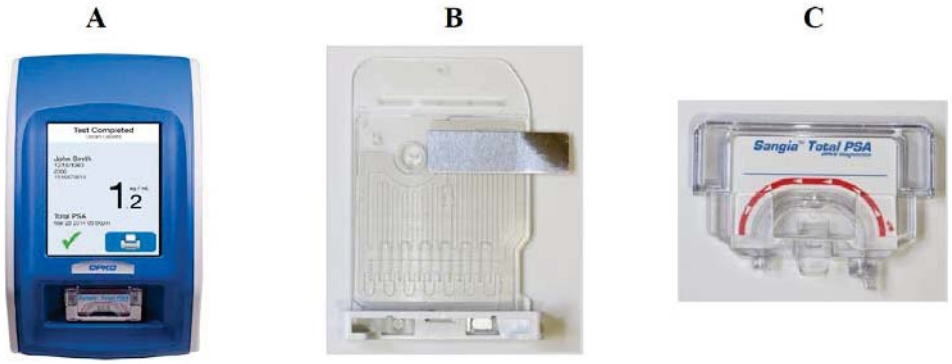

Figure 1. The Claros 1 Analyzer with test cassette inserted (A), the Sangia Total PSA Test consisting of a Cassette Assembly (B) and the Sample Collector (C).

The Claros 1 Analyzer is designed to be a standalone table-top unit. The Claros 1 Analyzer provides all the mechanical controls for the Test (thermal, vacuum and flow control, optics, and positioning) and a user interface through a touchscreen.

In addition, the Claros Total PSA External Control Levels 1 and 2 are required to monitor operation and performance of the Sangia Total PSA Test on the Claros 1 Analyzer. The Claros Total PSA External Controls are sold separately.

Each Sangia Total PSA Test box contains:

- (20) Sangia Total PSA Tests stored in individually sealed pouches
- (1) Lot Data Card with lot-specific calibration data
- (23) Soap Wipes, which contain water and sodium lauryl sulfate
- (1) Package Insert (Instructions for Use)

Each Sangia Total PSA Test includes:

- (1) Cassette Assembly, which contains trace amounts of monoclonal anti-PSA antibodies (bound to the surface of the measurement zone), aqueous solution of silver salt (45 µL), aqueous solution of reducing agent in acidic buffer (45 µL), aqueous wash buffers with surfactants (<5 µL), protein stabilizers and blockers, and preservatives.
- (1) Sample Collector, which contains NeoGold-labeled anti-PSA antibodies, anticoagulant, buffers, protein stabilizers, and surfactants in a lyophilized formulation.

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 in venous blood sample (serum or plasma) are currently available to aid in the detection of prostate cancer in conjunction with DRE 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

The Sangia Total PSA Test has not been previously marketed in the United States or any foreign country.

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 measuremens 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

Data from all nonclinical studies listed below met OPKO Diagnostics' pre-determined acceptance criteria.

A. Matrix Comparison

The Sangia Total PSA Test uses fingerstick capillary whole blood samples which have limitations on conducting certain analytical performance validation studies. The venous whole blood collected in a K_2EDTA (ethylenediaminetetraacetic acid) tube closely matches the fingerstick whole blood because the sample collector of the Sangia Total PSA Test contains EDTA. To demonstrate that K_2EDTA venous whole blood could be used in selected analytical studies in place of fingerstick whole blood, a matrix comparison study was performed. The study enrolled 131 subjects from four (4) clinical sites in the U.S. Samples were tested with total PSA concentrations covering the measuring range of the Sangia Total PSA Test. The matched specimens

of fingerstick whole blood and K_2EDTA venous whole blood from each subject were collected and assayed with the Sangia Total PSA Test.

Passing-Bablok regression analysis was performed to evaluate the correlation of the Sangia Total PSA Test results between the fingerstick whole blood samples and K_2EDTA venous whole blood samples. The results are shown in Table 1.

Table 1: Comparing Sangia Total PSA Test result from K_2EDTA venous blood (y) versus fingerstick whole blood (x)

N	Range (ng/mL)	Regression Equation	Slope (95% CI)	Intercept (95% CI)	Correlation
127	0.08–14.90	y = 1.091x – 0.045	1.091 (1.030,1.143)	-0.045 (-0.113, 0.020)	0.976

B. Precision and Reproducibility Studies:

Precision

Precision using fingerstick capillary whole blood was evaluated based on the following two (2) studies:

a. A single-site precision study was performed by enrolling eight (8) subjects with various total PSA concentration levels across the measuring range of the Sangia Total PSA Test. For each subject, a series of four (4) fingerstick collections and Sangia Total PSA tests were performed in the morning, followed by another series of four (4) fingerstick collections and tests in the afternoon. Two (2) Claros 1 Analyzers were used, but the samples from each subject were tested using the same Claros 1 Analyzer and by the same operator. Imprecision was then estimated for each subjects and the results are summarized in Table 2.

Table 2. Estimate of Repeatbility of Sangia Total PSA Test Using Fingerstick Samples

Subject	Mean (ng/mL)	N	SD	% CV
1	0.37	8	0.06	15.8%
2	0.41	8	0.05	11.2%
3	1.28	8	0.14	10.9%
4	1.54	8	0.11	6.9%
5	2.94	8	0.33	11.2%
6	5.13	8	0.71	13.9%
7	5.20	8	0.48	9.3%
8	12.87	6*	1.18	9.2%

*excluded two (2) measurements which were >15 ng/mL.

b. A multi-site study was performed to evaluate the imprecision of the Sangia Total PSA Test at multiple clinical sites with multiple operators performing the test on the

same patient in order to evaluate the variation between operators. A total of 72 subjects were enrolled at four (4) clinical sites in the U.S. Thirteen (13) operators (3 - 4 operators from each site) with required medical experience ranging from one to 10 years performed the test. At each site, each subject was tested with the Sangia Total PSA Test by three (3) operators, each operator collected the fingerstick sample from different fingers from the same subject. Of 72 subjects, eight (8) were excluded due to the Sangia Total PSA result outside the measuring range and three (3) were excluded for lacking valid Sangia Total PSA results. This resulted in 61 subjects with valid data for precision analysis.The mean, standard deviation (SD) and coefficient of variation (CV) were calculated for each patient. Table 3 summarizes the measurement of imprecision including variability from different operators using bins of total PSA concentration ranges, across the measuring interval.

Table 3. Measurement of Between-Operator Precision of Sangia Total PSA Test Using Fingerstick Samples

Group [Range of PSA concentration]	N	Mean (ng/mL)	SD	CV (%)
Very Low [0.08 – 0.6 ng/mL]	6	0.25	0.04	17.8%
Low [0.6 – 3.0 ng/mL]	11	1.91	0.22	11.6%
Medium [3.0 – 6.0 ng/mL]	18	4.74	0.70	14.8%
High [6.0 – 10.0 ng/mL]	18	8.04	0.84	10.5%
Very High [10.0 – 15.0 ng/mL]	8	11.88	1.66	13.9%
Total	**61**			

Precision using artificial samples (contrived materials) was performed as follows:

A 20-day precision study of the Sangia Total PSA Test was performed using six (6) samples with various PSA concentration levels according to CLSI EP05-A3, *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition*. The samples were contrived by spiking PSA-ACT in the matrix of the Claros External Controls. Each sample was tested in replicates of two (2) per run, two (2) runs per day for 20 days using a single lot of Sangia Total PSA Test on the same Claros 1 Analyzer. A total of 80 measurements (20 days x 2 runs x 2 replicates) were obtained per sample. The SD and %CV of the within-run, between-run, between-day, and total imprecision were calculated and results are summarized in the Table 4.

Table 4. 20-Day Precision Study of Sangia Total PSA Test using Artificial Samples

Sample	Mean (ng/mL)	N	Within-Run (Repeatbility)		Between-Run		Between-Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.16	80	0.02	9%	0.00	2%	0.01	6%	0.02	11%
2	0.29	80	0.03	10%	0.01	3%	0.01	2%	0.03	11%
3	0.94	80	0.09	9%	0.04	4%	0.04	4%	0.10	11%
4	3.06	80	0.29	9%	0.16	5%	0.00	0%	0.33	11%
5	4.43	80	0.45	10%	0.18	4%	0.20	4%	0.53	12%
6	13.81	80	0.90	7%	0.73	5%	0.73	5%	1.37	10%

Reproducibility

Reproducibility study was perfomed using venous K_2EDTA whole blood samples. A panel of eight (8) K_2EDTA venous whole blood samples was tested to evaluate the site-to-site reproducibility of the Sangia Total PSA Test. Each sample was tested in replicates of two (2) per run, two (2) runs per day for two (2) days using three (3) lots of Sangia Total PSA Test on six (6) Claros 1 Analyzers by six (6) operators at three (3) study sites (two (2) instruments and two (2) operators at each site) (N=144 per sample). The results are summarized in Table 5.

Table 5. Reproducibility of Sangia Total PSA Test Using Venous Whole Blood Samples

Mean (ng/mL)	N	Within-Run (Repeatability)		Between Run		Between Lot		Between Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
0.46	144	0.05	11%	0.01	2%	0.05	10%	0.02	5%	0.08	16%
0.57	144	0.06	10%	0.01	2%	0.06	10%	0.00	0%	0.09	15%
1.48	144	0.16	11%	0.03	2%	0.12	8%	0.00	0%	0.21	14%
2.53	144	0.28	11%	0.00	0%	0.26	10%	0.05	2%	0.38	15%
4.63	144	0.40	9%	0.00	0%	0.57	12%	0.00	0%	0.71	15%
6.71	144	0.65	10%	0.39	6%	0.79	12%	0.06	0%	1.10	16%
8.88	144	0.96	11%	0.27	3%	0.91	10%	0.24	3%	1.37	15%
12.38	144	1.38	11%	0.38	3%	1.00	8%	0.18	1%	1.78	14%

C. Linearity

Linearity of the assay was evaluated following CLSI guideline EP6-A, *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*. Two (2) dilution series were prepared: one positive K_2EDTA whole blood sample with total PSA concentration at 15.6 ng/mL was mixed with a PSA-negative K_2EDTA whole blood sample generating seven (7) consecutive dilutions; a second positive K_2EDTA whole blood sample with total PSA concentration at 7.90 ng/mL was mixed with a PSA-negative sample generating 10 dilutions. Each dilution was tested in replicates of five (5) using one lot of Sangia Total PSA Test. Data were analyzed per

CLSI EP6-A. The observed values were calculated as the average of five (5) replicates and the best fitted straight line of the observed values (y) to the expected results (x) or relative concentrations (RC) was estimated by the weighted linear regression analysis for each of the samples in the two dilution series and the combined data. Data for two (2) dilution series are presented in Table 6.

Table 6: Summary of Linearity Study

Level	Relative Concentration	Observed Value	Predicated Value*	Deviation	% Deviation
Dilution Series #1					
1	1	15.62	15.91	-0.29	-1.8%
2	0.857	14.36	13.63	0.73	5.3%
3	0.714	10.78	11.36	-0.58	-5.1%
4	0.571	8.86	9.09	-0.23	-2.5%
5	0.429	7.08	6.82	0.26	3.9%
6	0.286	4.12	4.54	-0.42	-9.4%
7	0.143	2.52	2.27	0.25	10.9%
Dilution Series #2					
1	1	7.90	7.55	0.35	4.6%
2	0.794	6.42	6.00	0.42	7.1%
3	0.680	5.20	5.14	0.06	1.2%
4	0.567	4.56	4.28	0.28	6.5%
5	0.454	3.50	3.43	0.07	2.1%
6	0.340	2.80	2.57	0.23	9.0%
7	0.227	1.70	1.71	-0.01	-0.8%
8	0.151	1.19	1.14	0.05	4.7%
9	0.080	0.61	0.60	0.01	1.3%
10	0.050	0.34	0.38	-0.04	-11.0%
11	0.025	0.16	0.19	-0.03	
12	0.013	0.08	0.10	-0.02	

The deviations from linearity for interval 0.08 – 15 ng/mL were <±15% for total PSA more than 0.25 ng/mL and <±0.04 ng/mL for total PSA less than 0.25 ng/mL.

D. Hook Effect

The high dose hook effect for the Sangia Total PSA Test was evaluated by spiking K_2EDTA whole blood with PSA-ACT stock to obtain doses far exceeding the upper end of the reporting range of the test. No hook effect was detected up to 1250 ng/mL.

E. Analytical Sensitivity/Detection Limit

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined using K_2EDTA venous whole blood samples in accordance with CLSI EP17-A2 guideline, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*.

The LoB was determined by assaying four (4) PSA-free samples in duplicates per sample over three (3) days on three (3) instruments using two (2) lots of reagents. LoB was calculated as the 95th percentile using the non-parametric method based on 72 measurements for each of the lots tested (a total of 144 measuements). The LoB was determined to be 0.017 ng/mL.

The LoD was determined using four (4) samples with low total PSA concentrations. Each sample was tested in triplicate over three (3) days on two (2) instruments with two (2) lots of Sangia Total PSA Test (a total of 144 measurements). The LoD value was calculated as the LoB + 1.645 x SD of the replicates for the low level samples. The LoD was determined to be 0.027 ng/mL.

The LoQ was determined as functional sensitivity using a set of seven (7) samples with low total PSA concentrations. Each sample was tested in replicates of three (3) over three (3) days using two (2) lots of Sangia Total PSA Test on four (4) instruments for a total of 72 data points per sample (a total of 504 measurements). The LoQ with K_2EDTA venous whole blood samples is defined as the value of the sample which fulfills the specification for total within-laboratory imprecision of %CV of 15% and was determined as 0.035 ng/mL.

The LoQ with fingerstick capillary whole blood samples was estimated based on the precision studies descriebed in Section IX.B, above. The LoQ with fingerstick capillary whole blood is defined as the value of the sample meeting the specification for total within-laboratory imprecision of %CV of 20% and was determined as 0.08 ng/mL. The claimed LoQ for the Sangia Total PSA Test is 0.08 ng/mL.

F. Equimolarity

PSA circulating in blood is present as a mixture of the free form (fPSA) and the complexed form (PSA-ACT), where PSA is complexed with alpha 1-antichymotrypsin. A study was performed to demonstrate that the Sangia Total PSA Test can measure both free and PSA-ACT complex in an equimolar fashion. PSA-free K_2EDTA whole blood samples were obtained from subjects having undergone radical prostatectomy (RP) and confirmed to have a Sangia Total PSA value < 0.05 ng/mL. The blood was then spiked with purified PSA in the form of fPSA and/or PSA-ACT in a series of pre-defined ratio. Equimolarity was demonstrated at three (3) levels of total PSA: 0.3, 3.0, and 14.0 ng/mL. Each sample was tested in replicates of 10, and the mean and percentage of recovery were calculated. The results are summarized in the Table 7.

Table 7. Summary of Results to Demonstrate Equimolarity

% of PSA-ACT	% of fPSA	Total PSA concentration					
		0.25 ng/mL		3.1 ng/mL		12.8 ng/mL	
		Mean (ng/mL)	Recovery (%)	Mean (ng/mL)	Recovery (%)	Mean (ng/mL)	Recovery (%)
0	100	0.27	107%	3.3	106%	12.3	96%
20	80	0.24	97%	3.1	101%	11.0	86%
50	50	0.23	91%	2.9	93%	11.8	91%
80	20	0.21	85%	3.1	101%	12.2	95%
100	0	0.25	100%	3.1	100%	12.8	100%

G. Interference/Analytical Specificity

Interference studies were performed according to the recommendations of CLSI protocol EP07-A3, *Interference Testing in Clinical Chemistry*.

The effect of the Sangia Total PSA Test in the presence of elevated level of endogenous substances was evaluated by testing three (3) K_2EDTA whole blood samples with total PSA concentrations of 0.3 ng/mL, 3 ng/mL, and 10 ng/mL spiked with varying levels of each interferent and analyzed using the same Sangia Total PSA Test lot. The % recovery for each sample spiked with the interfering substances was calculated by comparing its result to that of the corresponding control sample spiked with an equal volume of the solvent without the interfering substance. No significant interference was found for each endogenous substance at the concentrations listed in the Table 8.

Table 8. Effect of Endogenous Interferents on the Sangia Total PSA Test Results

Name of Interference Substance	Concentration
Hemoglobin	500 mg/dL
Bilirubin, unconjugated	20 mg/dL
Triglycerides	3.2 g/dL
Rheumatoid factor	150 IU/mL
Human IgG*	2.5 g/dL
Human serum albumin*	5.4 g/dL
Prostatic acid phosphatase*	21 ng/mL

*only tested at two PSA concentration levels: 0.3 and 3 ng/mL

The effect of presence of human anti-mouse antibody (HAMA) on the Sangia Total PSA Test was evaluated by testing three (3) K_2EDTA whole blood samples at total PSA concentrations of 0.3 ng/mL, 3 ng/mL, and 10 ng/mL. No significant interference was observed for HAMA up to 500 ng/mL.

The effect of the presence of exogenous substances on the performance of the Sangia Total PSA Test was evaluated by testing three (3) K_2EDTA whole blood samples with total PSA concentrations of 0.3 ng/mL, 3 ng/mL, and 10 ng/mL. The interfering substances include multivitamin, commonly used pharmaceuticals, antibiotics, anti-

fungal infection drugs, antidepressants, and drugs for benign prostatic hyperplasia (BPH), cardiovascular, diabetes, and gastroesophageal reflux disease. Percentage of recovery for each sample spiked with the interference substance was calculated by comparing its result to that of the corresponding control sample spiked with an equal volume of the solvent without the interference substance. No significant interference was found for each exogenous substance at the concentrations listed in the Table 9a.

Table 9a. Effect of Exogenous Interferents on the Sangia Total PSA Test Results

Name of Agent	Concentration	Name of Agent	Concentration
Acetylsalicylic Acid	1.9 mmol/L	Lisinopril	0.7 µmol/L
Cimetidine	79.2 µmol/L	Metformin HCL	310.0 µmol/L
Ciprofloxacin	30.2 µmol/L	Multivitamin	9.0 mL/L
Clomipramine HCl	2.7 µg/mL	Naproxen Sodium	2170.0 µmol/L
Doxazosin Mesylate	1.3 µmol/L	Prednisone	8.3 µmol/L
Doxycycline Hyclate	67.5 µmol/L	Sildenafil Citrate	2.8 µmol/L
Dutasteride	40 ng/mL	Tamsulosin	124.8 ng/mL
Ketoconazole	6.2 µg/mL	Warfarin HCl	32.5 µmol/L

The Table 9b lists the results of an interference study done by testing two (2) K_2EDTA whole blood samples with total PSA concentrations of 0.3 ng/mL and 3 ng/mL. No significant interference was found for each substance at the concentration listed in the Table 9b.

Table 9b. Effect of Sangia Total PSA Test results in Presenting Exogenous Substances

Name of Agent	Concentration	Name of Agent	Concentration
Acetaminophen	1324.0 µmol/L	Ibuprofen	2425.0 µmol/L
Alprazolam	6.5 µmol/L	Nitrofurantoin	16.8 µmol/L
Amlodipine Besylate	245.0 nmol/L	Omeprazole	17.4 µmol/L
Amoxicillin Trihydrate	206.0 µmol/L	Sildosin	184.8 ng/mL
Atorvastatin	600.0 µg/mL	Sulfamethoxazole	1.6 mmol/L
Fluoxetine HCl	11.2 µmol/L	Tadalfil	975.0 ng/mL
Furosemide	181.0 µmol/L	Trimethoprim	138.0 µmol/L
Hydroclorothiazide	20.2 µmol/L		

H. Reagent Stability Studies:

The reagent stability study was conducted using the samples prepared by spiking PSA-ACT in artificial matrix which is the same material used for making Clarios Total PSA External Controls. The real-time stability of the Sangia Total PSA Test reagents was evaluated using three (3) samples with PSA concentrations of 0.3 ng/mL (Level 1), 3.0 ng/mL (Level 2), and 10.0 ng/mL (Level 3). Sufficient aliquots of each of three (3) samples were stored frozen at -70 to -90°C. Three (3) lots of Sangia Total PSA Test were storted at 2-8ºC and stability was evaluated. The stability study was performed at the following time intervals: Day 0, Day 7, Day 15, Day 30 (1 month),

Day 60 (2 month), followed by testing monthly for up to 13 months. At each test point, the test was performed with 6-10 replicates for Level 1, 10 replicates for Level 2 sample, and 15–20 replicates for Level 3. The results support that the Sangia Total PSA Test is stable when stored at 2–8°C for three (3) months.

I. Method Comparison:

A method comparison study was conducted to demonstrate the accuracy of the Sangia Total PSA Test compared to an FDA-approved total PSA assay. The study was done at multiple sites according to CLSI guideline EP09-A3, *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Third Edition*. A total of 132 subjects were enrolled from four (4) clinical sites in U.S. Each subject provided a serum sample for testing with the FDA-approved total PSA device, Elecsys Total PSA Immunoassay (P990056), and a fingerstick capillary whole blood sample for testing with the Sangia Total PSA Test. Thirteen (13) operators performed the Sangia Total PSA Test at these four (4) sites. Of 132 subjects, eight (8) were excluded for the results outside the measuring range of Sangia Total PSA Test, and two (2) were excluded for error results without a valid repeat test. One was excluded due to inability collect a serum sample for the Elecsys Total PSA assay. This resulted in 122 samples with valid results within the measuring range of Sangia Total PSA Test to be included in the method comparison analysis. The correlation of the Sangia Total PSA Test (y) and Elecsys Total PSA assay (x) using Passing-Bablok regression analysis and the systematic differences between these two methods at the medical decision level (MDL) are shown in Table 10.

Table 10. Comparison of Sangia Total PSA Test versus Elecsys Total PSA Immunoassay (P990056)

N	Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	Correlation
122	0.1 – 13.1	0.995 (0.940, 1.073)	-0.011 (-0.091, 0.093)	0.951

Systematic Differences			
Total PSA Concentration	**Systematic Difference**	**% Systematic Difference**	**95% CI**
2.5 ng/mL	-0.023	-0.9%	(-4.9%, 5.8%)
4.0 ng/mL	-0.031	-0.8%	(-5.0%, 6.4%)
10.0 ng/mL	-0.061	-0.6%	(-5.4%, 6.8%)

X. SUMMARY OF PRIMARY CLINICAL STUDIES

OPKO Diagnostics performed the following studies under an approved IRB to establish a reasonable assurance of safety and effectiveness of the Sangia Total PSA for use as an aid in the detection of prostate cancer in conjunction with DRE in men 50 years and older:

- Study 1. Expected Value/Reference Interval Study
- Study 2. Clinical Study

A summary of each study is presented below.

STUDY 1. EXPECTED VALUE/REFERENCE INTERVAL STUDY

A. Study Design

To determine the expected value/reference interval for Sangia Total PSA Test for men across multiple age groups who do not have known prostate conditions or disease, a multi-center study was conducted at 13 geographically and demographically diverse facilities in the U.S. where sample collections (including blood draws) are typically performed. The study was conducted according to CLSI EP28-A3C, *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition*.

1. Clinical Inclusion and Exclusion Criteria

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

   - ≥50 years old
   - Apparently healthy men, regardless of race, who
     - are within 30 days prior to or following a physician visit or are having blood drawn within 30 days prior to or following a physician visit for non-urological or prostate related purposes, or
     - are having blood drawn according to a standing physician order/prescription such as for glucose monitoring, PT/INR (prothrombin time/international normalized ratio) monitoring, or other non-urological conditions, or
     - Do not have a near term physician visit or order/requisition for a blood draw and have the fingerstick collection only as long as they meet other inclusion criteria.
   - No known history of prostate disease
     - No history of treatment for BPH in three (3) months prior to study participation

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

   - < 50 years old
   - Known history of any prostate disease such as BPH, prostate cancer, prior negative prostate biopsy, or prostatitis
   - Currently taking prostate-related medications such as any 5-alpha-reductase inhibitor (5-ARI) therapy such as Avodart® (dutasteride), Jalyn® (which

includes dutasterida), Proscar® (finasteride), or any BPH related alpha-blocker medications, such as Flomax® (tamsulosin) or Rapaflo®

2. Follow-up Schedule

No follow-up schedule was required for the enrolled subjects. All subjects were prospectively enrolled at each site. Fingerstick whole blood samples were collected from eligible subjects and assayed near subjects using the Sangia Total PSA Test.

3. Clinical Endpoints

The study is to define and establish the exreference interval of the Sangia Total PSA Test values in appearently healthy population of men 50 years and older. The values of PSA from this cohort is used to define an empirical cumulative distribution. This distribution defines the order statistics for the cohort. Resampling techniques is employed to determine 95% confidence intervals around the 95th order statistic. In addition, the analysis is conducted for the subgroups ages 50-59, 60-69, and 70 and older.

B. Accountability of Study Cohort

The study was conducted at 13 medical facilities across the U.S. Twelve (12) facilities were patient service centers near physician offices where blood collections are routinely performed as a result of a physician order to draw and test blood. One facility was within a primary care physician office. A total of 487 subjects were enrolled and a total of 26 local healthcare professionals from 13 sites performed the Sangia Total PSA Test with 14 (median) / 20 (mean) tests ranging from 1 to 57 per operator. Of 487 subjects, two (2) were excluded later for not meeting the inclusion and exclusion criteria. Five (5) were excluded for protocol deviations. Seven (7) were excluded for not having informed consent forms. Forty-three (43) were excluded for error results without a valid repeat test. This resulted in 430 subjects to be included in the reference range study analysis of the Sangia Total PSA Test.

C. Study Population Demographics and Baseline Parameters

Table 11 summarizes the demographics of the population used in the expected value/reference interval study.

Table 11. Demographics of the Subjects in Reference Interval Study

	N=430
Age Categories, n (%)	
50 – 59 years	167 (38.8%)
60 – 69 years	142 (33.0%)
≥70 years	121 (28.1%)
Race, n (%)	
Caucasian	225 (52.3%)
African American	32 (7.4%)
Asian or Asian American	19 (4.4.%)
American Indian or Alaska Native	6 (1.4%)
Other*	110 (5.6%)
Not indicated	38 (8.8%)
* 81% of subjects identified as Hispanic or Latino Ethnicity	

D. Study Results:

The 430 normal healthy subjects were stratified into three (3) age groups: 50-59, 60-69, and >70 years old. Table 12 below summarizes the Sangia Total PSA Test values by each age group.

Table 12. The Sangia Total PSA Test Values for Normal Healthy Cohort by Age Group

	Age Group		
	50 – 59	**60 – 69**	**>70**
N	167	142	121
Mean (ng/mL)	1.4	2.0	2.4
Median (ng/mL)	0.9	1.5	1.5
% (n/N) of Subject with PSA < 4 ng/mL	97.0% (162/167)	88.0% (125/142)	83.5% (101/121)
95th percentile (ng/mL) (95% CI)	3.5 (2.4, 4.9)	5.3 (4.3, 7.8)	7.8 (5.4, 11.7)

Each laboratory should establish its own expected values/reference intervals.

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 poluation 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 13 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 STUDY

A. Study Design

To determine the performance of the Sangia Total PSA Test in conjunction with DRE as an aid in the detection of prostate cancer in men age 50 years or older, a multi-center clinical study was conducted at 11 geographically and demographically diverse facilities in the U.S. The study sites included a mix of 10 community urology practices located in urban areas in varying sizes and one academic research center where total PSA testing is routinely performed, and where POC total PSA testing is likely to be performed. The specific goals for this study are as follows:

- To determine the clinical validity and reliability of total PSA as measured by the device alone and in conjunction with DRE in detecting prostate cancer.
- To assess the clinical sensitivity and specificity of total PSA as measured by the device, which will be determined alone and in conjunction with DRE results.
- To assess the positive predictive power of total PSA as measured by the device alone and in conjunction with DRE result. In addition, the added value of PSA over DRE alone will be assessed.

1. Clinical Inclusion and Exclusion Criteria

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

- ≥ 50 years old
- All men, regardless of race, presenting to a practicing urologist with symptoms that would lead to an evaluation for prostate cancer and who are scheduled to receive a transrectal needle biopsy
- No prior evaluation (biopsy) or diagnosis of prostate cancer
- No history of treatment for BPH in three (3) months prior to study participation
- Medication not on the Exclusion list are allowable. Alpha blocker BPH medications (such as Tamsulosin / Flomax®, Rapaflo) are allowable

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

- < 50 years old

- Men with prior evaluation (biopsy) or diagnosis of prostate cancer
- Men who in the three (3) months prior to study participation received any invasive urologic procedure such as thermotherapy, microwave therapy, laser therapy, transurethral resection of the prostate (TURP), urethral catheterization, and lower genitourinary tract endoscopy (cystoscopy)
- Men who in the three (3) months prior to study participation received any 5-alpha-reductase inhibitor (5-ARI) therapy any 5-alpha-reductase inhibitor (5-ARI) therapy such as Avodart® (dutasteride), Jalyn® (which includes dutasteride), Proscar® (finasteride)
- Men who were subjected to DRE or prostate manipulation within four (4) days (96 hours) prior to blood sampling

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. A sample of fingerstick whole blood was collected from eligible subjects within 24 hours prior to the scheduled biopsy. The samples were assayed near the patient using the Sangia Total PSA Test.

3. Clinical Endpoints

The primary study end-point is based on sensitivity and specificity analysis. The success criteria are that the Sangia Total PSA is informative test based on a) if positive predictive value (PPV) is statistically larger than the prevalence, negative predictive value (NPV) is statistically larger than 1 minus prevalence; b) if sensitivity is statistically larger than false positive rate. When used in conjunction with DRE, the added value of the Sangia Total PSA Test to DRE results should be reflected by an increase in sensitivity by more than 20%.. The increase in sensitivity is determined as (Sensitivity DRE and Total PSA tests in parallel - Sensitivity DRE). The decrease in specificity should be reflected in the acceptable level of PPV for Sangia Total PSA test used in conjunction with DRE. The positive result of DRE and Total PSA tests in parallel is defined as DRE+ (abnormal) and/or Total PSA $\geq$ 4.0 ng/mL.

B. Accountability of PMA Cohort

The clinical study was conducted by enrolling a total of 490 subjects at 11 geographically diverse urology practices in the U.S. One site was later excluded from the study due to only one subject being enrolled and which resulted in an error. A total of 22 healthcare professionals performed the Sangia Total PSA Test at the remaining 10 sites with an average of 15 (median) / 23 (mean) tests ranging from 1 to 92 tests (including repeat testing) per operator. Of 490 subjects, six (6) were excluded for not meeting inclusion/exclusion criteria. Three (3) were excluded for not having any record of a DRE being performed prior to biopsy. Eight (8) were excluded for postponed or canceled biopsies. Three (3) were excluded for study

protocol deviation. One was excluded for not being able to collect a fingerstick blood sample. Thirty-five (35) were excluded for error results without a valid repeat test. This resulted in 434 subjects to be included in the effectiveness analysis of Sangia Total PSA Test.

C. Study Population Demographics and Baseline Parameters

The median age of all subjects was 65.1 years old. The site-specific median age of the subjects ranged between 62.0 and 67.8 years. The demographics and baseline characteristics of the patients are shown in Table 13.

Table 13. Demographic and Disease Characteristics of Subjects in the Clinical Study

	N=434
Demographics	
Median Age (min, max)	65.1 (50.0, 86.6)
Age Categories, n (%)	
50 – 59 years	117 (27%)
60 – 69 years	218 (50%)
≥70 years	99 (23%)
Race, n (%)	
Caucasian	369 (85.0%)
African American	33 (7.6%)
Hispanic	22 (5.1%)
Other	5 (1.15%)
Unknown	5 (1.15%)
Disease Characteristics	
Abnormal DRE	107 (25%)

Of all 434 subjects, 107 men (25%) were reported to have abnormal DRE, the rate of abnormal DRE in men varied from 0% to 31% by site.

D. Safety and Effectiveness Results

1. Safety Results

Sangia Total PSA Test involves testing capillary whole blood sample from fingerstick. These specimens are routinely taken as part of the practice of medicine for a typical POC device and, therefore, sample collection presents no additional safety hazard to the patient being tested.

The diagnosis of prostate cancer has to be confirmed by biopsy. When using the Sangia Total PSA Test, 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 Sangia Total PSA Test 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 434 evaluable patients enrolled at 10 urology clinics in the U.S. The performance of Sangia Total PSA Test 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 10 sites across the U.S. The poolability of the data was evaluated based on the prevalence of prostate cancer, age of subjects, Sangia Total PSA results, and DRE results.

The prevalence of prostate cancer in the study was 53.7% and the site-specific cancer prevalence ranged from 32% to 69%. Chi-square analysis of the homogeneity of the site-specific prevalence indicated there was no significant difference of the prevalence of prostate cancer across sites ($p=0.186$).

The mean age of the study cohort was 64.7 with the site-specific mean age ranged from 63.5 to 67.8. A one-way ANOVA indicated that there was no significant difference across the sites ($p=0.839$).

The median Sangia Total PSA Test value was 5.9 ng/mL and the site-specific median of Total PSA ranged from 4.4 - 7.4 ng/mL. Among patients diagnosed with prostate cancer, there was no significant difference in median total PSA across all clinical sites. Among the non-cancer patients, after adjusting for patient age, there was no significant difference across all clinical sites.

The site-specific DRE results were also evaluated. The mean of abnormal DRE was 25% with the site-specific proportion of abnormal DRE ranged from 0% to 31%. One site with very low enrollment had only two (2) eligible patients, both of whom were DRE normal.

Based on the above evaluation, the performance of the Sangia Total PSA Test is evaluated using the pooled data across 10 sites.

Results

A multi-center cohort study was performed by enrolling 434 subjects to demonstrate the effectiveness of the Sangia Total PSA Test when used in conjunction with DRE as an aid in the detection of prostate cancer in men 50 years or older. The distribution of the Sangia Total PSA Test values by biopsy results and DRE results is summarized in Table 14.

Table 14. The Distribution of the Sangia Total PSA Test by Biopsy and DRE Results

		Sangia Total PSA Test Value (ng/mL)		
	N	**Median**	**Minimum**	**Maximum**
Biopsy positive: (Prostate Cancer with Gleason score ≥6)				
[a]DRE -	159	5.95	1.60	>15.00
[b]DRE+	74	5.70	0.49	>15.00
Total	233	5.90	0.49	>15.00
Biopsy negative				
DRE -	168	5.10	0.76	13.70
DRE+	33	3.70	0.35	13.30
Total	201	5.00	0.35	13.70

[a] DRE-: Not suspicious for prostate cancer
[b] DRE+: Suspicious for prostate cancer

Table 15 summarizes the results for DRE and Sangia Total PSA Test for subjects with malignant or benign biopsy results.

Table 15. Results for DRE and Sangia Total PSA Test Comparing to Prostate Cancer Detected by Biopsy

	Biopsy Result		
	Malignancy	**Benign**	**Total**
DRE+	74	33	107
DRE-	159	168	327
Total	**233**	**201**	**434**
[a]PSA+	199	140	339
[b]PSA-	34	61	95
Total	**233**	**201**	**434**
PSA+ and DRE+	61	16	77
PSA+ and DRE-	138	124	262
PSA- and DRE+	13	17	30
PSA- and DRE-	21	44	65
Total (PSA+ or DRE+)	**233**	**201**	**434**

[a] PSA+: Sangia Total PSA Test value ≥ 4.0 ng/mL
[b] PSA-: Sangia Total PSA Test value <4.0 ng/mL

The performance parameters including sensitivity, specificity, PPV and NPV of DRE alone, Sangia Total PSA Test alone, and Sangia Total PSA Test in conjunction with DRE for detection of prostate cancer are summarized in Table 16.

Table 16. Summary of Diagnostic Parameters for Individual and Combined Tests

	Sensitivity (95% CI)	**Specificity (95% CI)**	**PPV* (95% CI)**	**NPV* (95% CI)**
DRE +	31.8% (74/233) (26.1–38.0%)	83.6% (168/201) (77.7–88.1%)	69.2% (74/107) (60.7–76.5%)	51.4% (168/237) (45.7–54.1%)
Sangia Total PSA Test (cut-off: 4 ng/mL)	85.4% (199/233) (80.3–89.4%)	30.3% (61/201) (24.4–37.0%)	58.7% (199/339) (56.2–61.4%)	64.2% (61/95) (55.2–72.5%)
DRE + or Sangia Total PSA Test	91.0% (212/233) (86.6–94.0%)	21.9% (44/201) (16.7–28.1%)	57.5% (212/369) (55.4–59.7%)	67.7% (44/65) (56.2–77.3%)

*PPV and NPV were calculated based on the prevalence of 54% in the urology office setting in this study cohort.

The results indicated the following:

- In this study cohort, the sensitivity of the Sangia Total PSA Test is 85.4% (199/233) with 95% CI: (80.3–89.4%) and specificity is 30.3% (61/201) with 95% CI: (24.4–37.0%). PPV for the Sangia Total PSA Test is 58.7% with the lower bound of 95% CI of 56.2% which is larger than prevalence of 53.7%, indicating that PPV is statistically higher than the prevalence. NPV for the Sangia Total PSA Test is 64.2% with the lower bound of 95% CI of 55.2% which is larger than 47.3 % (one minus prevalence), indicating that NPV is statistically higher than the one minus prevalence. These data of the clinical study showed that the Sangia Total PSA Test is an informative test with regard to risks of prostate cancer.
- When combinated with DRE, the sensitivity increased 59.2% compared to the sensitivity of DRE alone. The specificity of the Sangia Total PSA Test in conjunction with DRE decreased 61.7% compared to the DRE alone. NPV for the Sangia Total PSA test with DRE was 67.7% with the lower bound of 95% CI of 56.2% and NPV for the DRE alone was 51.4% with the upper bound of the 95% CI of 54.1% indicating that the NPV of the Sangia Total PSA test with DRE was higher than the NPV of the DRE alone by 16.3% and this increase was statistically significant. There was also a decrease in the PPV of the Sangia Total PSA with DRE compare to the PPV of the DRE alone by 11.7%.

3. Subgroup Analyses

By further categorizing the cancer as Gleason Score ≥6 or Gleason Score ≥7, the Sangia Total PSA Test as a standalone test is evaluated for identification of prostate cancers in all subjects. The summary of the results is shown in Table 17.

Table 17. Distribution of Prostate Cancers (Gleason Score ≥6 and Gleason Score ≥7) Based on Sangia Total PSA Test

Sangia Total PSA Test	N	N (%) of Men with Gleason Score ≥ 6 PCa	N (%) of Men with Gleason Score ≥ 7 PCa
<4.0 ng/mL	95	34 (36%)	17 (18%)
≥4.0 ng/mL	339	199 (59%)	120 (35%)
Total	**434**	**233 (54%)**	**137 (32%)**

Based on the Sangia Total PSA Test result alone, 36% (34/95) of the prostate cancer of the Gleason Score ≥6 and 18% (17/95) of all the Gleason Score ≥7 prostate cancer were not detected.

Table 18 showed the performance of detection of Gleason Score ≥6 or Gleason Score ≥7 prostate cancer with the combination of the DRE test with the Sangia Total PSA Test.

Table 18. Distribution of Prostate Cancers (Gleason Score ≥6 and Gleason Score ≥7) Based on the Combined DRE and Sangia Total PSA Test

Sangia Total PSA Test	N (%) of Men with Gleason Score ≥ 6 PCa			N (%) of Men with Gleason Score ≥ 7 PCa		
	N	DRE +	DRE -	N	DRE +	DRE -
<4.0 ng/mL	34	13 (38%)	21 (62%)	17	9 (53%)	8 (47%)
≥4.0 ng/mL	199	61 (31%)	138 (69%)	120	45 (38%)	75 (63%)
Total	**233**	74 (32%)	159 (68%)	**137**	54 (39%)	83 (61%)

The results showed that 21 prostate cancers of Gleason Score ≥6 and eight (8) prostate cancers of Gleason Score ≥7 were not detected by either DRE or the Sangia Total PSA test.

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 poluation 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 11 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.

XI. 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The preclinical studies support that the assay can quantitatively measure total PSA levels from 0.08 ng/mL to 15 ng/mL using capillary whole blood samples taken from the fingerstick. The test showed equivalent results within this measuring range compared to an FDA-approved device, Elecsys Total PSA Immunoassay (P990056), for measurement of total PSA that is used as the standard-of-care for the same intended use population.

The clinical effectiveness of the Sangia Total PSA Test was demonstrated by testing 434 subjects at 10 different sites within the U.S. The study results indicated that at a cut-off of 4.0 ng/mL, the clinical sensitivity of the Sangia Total PSA Test is 85.4% with a 95% confidence interval (CI) of 80.3–89.4% and the clinical specificity is 30.3% with a 95% CI of 24.4–37.0%. Based on a disease prevalence of 53.7% in the clinical study, the positive predicative value (PPV) for the Sangia Total PSA Test is 58.7% with the lower bound of the 95% CI of 56.2% and the negative predicative value (NPV) is 64.2% with the lower bound of the 95% CI of 55.2%. These data showed that the Sangia Total PSA Test is an informative test as an aid in the diagnosis of prostate cancer. When combined with DRE, the clinical sensitivity increased 59.2% compared to the clinical sensitivity of DRE alone, the clinical specificity of the Sangia Total PSA Test in conjunction with DRE decreased 61.7% compared to DRE alone. The NPV for the the Sangia Total PSA test in combination with DRE was 67.7%, which was greater than the NPV of the DRE alone by 16.3%. The PPV for the Sangia Total PSA in combination with DRE decreased 11.7% compared to DRE alone. These data indicate that the Sangia Total

PSA Test, when used in conjunction with DRE, contributes to the detection of prostate cancer in the intended use population.

Therefore, the studies support the effective use of the device for measuring total PSA using capillary whole blood sample from fingerstick at POC settings to aid in the detection of prostate cancer in men aged 50 years and older in conjunction with DRE.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory testing as well as data collected in a clinical 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 venous blood for testing purposes. The Sangia Total PSA Test involves taking a fingerstick blood sample from the patients and is to be performed by trained healthcare professionals in the POC site with CLIA moderate complexity testing certificate. The sample collection cassette of the device is single use and therefore presents no more safety hazard than other FDA-approved total PSA tests where blood is collected from subjects and no more safety hazard than other point-of-care devices.

C. Benefit-Risk Determination

Assessment of Benefit:

The Sangia Total PSA Test 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. The potential benefit relates to improved diagnosis of clinically significant prostate cancer. In some patients, this will result in a benefit which may include prolongation of the lifespan due to the detection and subsequent treatment of a potentially fatal cancer, and may also reduce cancer complications 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 Sangia Total PSA alone at a cut-off of 4.0 for detection of prostate cancer of 85.4% (199/233) with 95% CI: (80.3–89.4%) and 30.3% (61/201) with 95% CI: (24.4–37.0%). Data of the clinical study showed that the Sangia Total PSA Test is an informative test with regard to risks of prostate cancer. In combination with DRE, the sensitivity and specificity changed to 91.0% with 95% CI: (86.6–94.0%) and 21.9% with 95% CI: (16.7–28.1%), respectively. These sensitivity and specificity data are accompanied by PPV and NPV values (58.7% and 64.2%, respectively, for Sangia Total PSA alone; and 57.5% and 67.7% for Sangia Total PSA plus DRE).

The device represents a new POC technology that has an added benefit for patients and physicians. Test results can be conveniently obtained in the physician's office in 10–12 minutes after collecting a capillary blood sample from a fingerstick whereas standard-of-care total PSA tests require testing in a central laboratory with results available in days or weeks. This POC testing allows the patient and physician to have immediate face-to-face discussions on options and patient preferences for follow-up testing and/or active surveillance of suspected disease. In addition, any failed results can be immediately repeated, leading to a reduction in further delays due to reliance solely on central-lab testing.

Assessment of Risk:

When the Sangia Total PSA Test 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 ("overdiagnosing") 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 or not 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[1]. 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 Sangia Total PSA Test 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).

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 nonclinical and clinical studies support the utility of Sangia Total PSA Test as an aid in the detection of prostate cancer in men aged 50 years and older in conjunction with a DRE using capillary whole blood from a fingerstick collected by a healthcare professional in point-of-care settings.

XIII. CDRH DECISION

CDRH issued an approval order on January 30, 2019.

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

XIV. 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.

XV. REFERENCES

1. Hoffman, RM. 2018. Implications of the New USPSTF Prostate Cancer Screening Recommendation-Attaining Equipoise. JAMA Intern Med.178(7):889-891.