

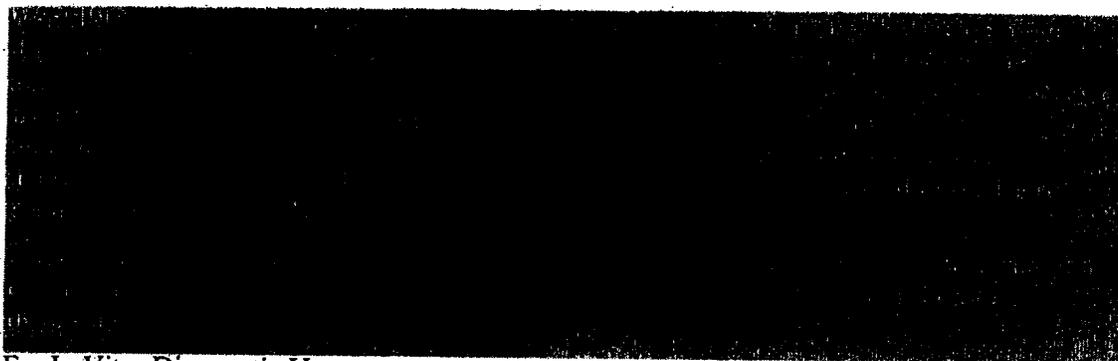
PSA2**+D****Contents**

Catalog Number	Contents	Number of Tests
110760	5 ReadyPack™ primary reagent packs containing ACS:Centaur PSA2 Lite Reagent and Solid Phase ACS:Centaur PSA2 Master Curve card	500
or		
110759	1 ReadyPack primary reagent pack containing ACS:Centaur PSA2 Lite Reagent and Solid Phase ACS:Centaur PSA2 Master Curve card	100

Intended Use

The Chiron Diagnostics ACS:Centaur PSA2 assay is an *in vitro* device for the quantitative measurement of prostate-specific antigen (PSA) in human serum using the Chiron Diagnostics ACS:Centaur™ Automated Chemiluminescence System. The assay is indicated for the following uses:

- As an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men aged 50 years or older. Prostatic biopsy is required for the diagnosis of cancer.
- As an aid in the management of patients with prostate cancer.



For In Vitro Diagnostic Use.

Materials Required But Not Provided

Catalog Number	Description	Contents
672183	Calibrator D	6 vials of low calibrator 6 vials of high calibrator
or		
672173	Calibrator D	2 vials of low calibrator 2 vials of high calibrator

Optional Reagents

Catalog Number	Description	Contents
110314	ACS:Centaur Multi-Diluent 2	2 ReadyPack primary reagent packs containing 10 mL/pack
672260	ACS:Systems Multi-Diluent 2	50 mL/vial
986000	Ligand Plus 1, 2, 3 quality control material	5 x 5 mL/level
976700	Tumor Marker Plus 1, 2 quality control material	3 x 2 mL/level
114925	Tumor Marker Plus 1, 2 barcode labels	60/level
570090	PSA2 Master Curve Material	6 x 1 mL

Summary and Explanation of the Test

The most common type of cancer in men in the U.S. and the second most common cancer in men worldwide is cancer of the prostate.^{1,2} It is the second leading cause of cancer deaths in American and European men^{1,3}, and the lifetime probability for U.S. men of developing prostatic cancer is approximately 1 in 5.⁴ Rates of prostate cancer increase with advancing age⁵; thus, as life-expectancy continues to rise, the number of new cases and deaths due to prostate cancer also continues to rise. Targets for decreasing prostate cancer mortality are to decrease incidence; improve therapy; and provide early detection, when treatment is more effective. Prior to the initiation of prostate specific antigen (PSA) screening, two thirds of cancers had spread beyond the prostate when first identified.⁶ Thus, the development of improved methods of early detection is critical to successful intervention. When PSA determinations were made in serial specimens from men who did and did not develop prostate cancer, the results showed a linear increase in PSA levels with increasing age. However, in men who developed prostate cancer, PSA levels started to rise exponentially approximately 7 years prior to a clinical diagnosis by digital rectal examination (DRE) of local/regional tumors and 9 years prior to a clinical diagnosis of advanced/metastatic tumors.⁷ PSA levels in these men rose to ≥ 4.0 ng/mL 2.6 to 11.2 years before the clinical diagnosis, and thus suggested that PSA screening should detect cancers at an earlier stage than DRE alone. Several recent studies have confirmed that the use of PSA testing, in combination with DRE, aids in the detection of prostate cancer before it spreads beyond the prostate gland.⁸⁻¹⁰ Studies have also shown that serum PSA levels are more predictive of prostate cancer than DRE.¹¹⁻¹³ Based on these studies, both the American Cancer Society and the American Urological Association have recommended the use of PSA in conjunction with DRE for detection of prostate cancer in men aged 50 or older.^{14,15} Prostate cancer screening programs have been developed in other parts of the world to aid in the early detection of organ-confined disease.¹⁶⁻¹⁸

PSA is a single-chain glycoprotein normally found in the cytoplasm of the epithelial cells lining the acini and ducts of the prostate gland.¹⁹ PSA is a neutral serine protease of 240 amino acids involved in the lysis of seminal coagulum.^{20,21}

PSA is detected in the serum of males with normal, benign hyperplastic, and malignant prostate tissue. PSA is not detected (or detected at very low levels) in the serum of males without prostate tissue (because of radical prostatectomy or cystoprostatectomy) or in the serum of most females.²² The fact that PSA is unique to prostate tissue makes it a suitable marker for monitoring men with cancer of the prostate. PSA is also useful for determining possible recurrence after therapy when used in conjunction with other diagnostic indices.^{23,24} PSA levels increase in men with cancer of the prostate, and after radical prostatectomy PSA levels routinely fall to the undetectable range.²⁵ If prostatic tissue remains after surgery or metastasis has occurred, PSA appears to be useful in detecting residual disease and early recurrence of tumor.^{25,26} Therefore, serial PSA levels can help determine the success of prostatectomy, and the need for further treatment, such as radiation, endocrine or chemotherapy, and in the monitoring of the effectiveness of therapy.^{23,24,27,28}

Assay Principle

The Chiron Diagnostics ACS:Centaur PSA2 assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is an affinity purified polyclonal sheep anti-PSA antibody labeled with acridinium ester. The second antibody, in the Solid Phase, is a monoclonal mouse anti-PSA antibody, which is covalently coupled to paramagnetic particles.

The system automatically performs the following steps:

- dispenses 100 μ L of sample into a cuvette
- dispenses 50 μ L of Lite Reagent and 250 μ L of Solid Phase and incubates for 7.5 minutes at 37°C

- separates, aspirates, and washes the cuvettes with reagent water²⁹
- dispenses 300 μ L each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction
- reports results according to the selected option, as described in the system operating instructions or in the online help system

A direct relationship exists between the amount of PSA present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Specimen Collection and Handling

Serum is the recommended sample type for this assay.

Plasma samples should not be used because their performance in this assay has not been determined.

The following recommendations for handling and storing blood samples are furnished by the National Committee for Clinical Laboratory Standards:³⁰

- Collect all blood samples observing universal precautions for venipuncture.
- Allow samples to clot adequately before centrifugation.
- Keep tubes stoppered and upright at all times.
- Do not use samples that have been stored at room temperature for longer than 8 hours.
- Tightly cap and refrigerate specimens at 2 to 8°C if the assay is not completed within 8 hours.
- Avoid multiple freeze/thaw cycles and mix thoroughly after thawing.
- Specimens that have undergone as many as three freeze-thaw cycles can be used in the assay.

Before placing samples on the system ensure that:

- Samples are free of fibrin or other particulate matter. Remove particulates by centrifugation at 1000 x g for 15 to 20 minutes.
- Samples are free of bubbles.

Samples for PSA determinations should be collected prior to performing invasive procedures such as prostatic biopsy or transurethral resection of the prostate (TURP), or the sample should not be collected for 3 to 4 weeks after such procedures.³¹ Studies on the effect of DRE, transrectal ultrasound (TRUS) or cystoscopy on PSA quantitation have shown variable results.²² When possible, the blood sample should be drawn before any prostatic manipulation. If this is not possible, subjects with borderline PSA results or results that are inconsistent with clinical evidence, may need to be redrawn and retested.²²

Reagents

Reagent Pack	Reagent	Volume	Ingredients	Storage	Stability
ACS:Centaur PSA2 ReadyPack primary reagent pack	Lite Reagent	5.0 mL/ reagent pack	purified polyclonal sheep anti-PSA antibody (~3.1 µg/pack) labeled with acridinium ester in buffered saline with sodium azide (0.1%) and preservatives	2*8°C	until the expiration date on the pack label or 28 consecutive days after loading the primary reagent pack
	Solid Phase	25.0 mL/ reagent pack	monoclonal mouse anti-PSA antibody (~316 µg/pack) covalently coupled to paramagnetic particles in buffered saline with sodium azide (0.1%) and preservatives	2*8°C	until the expiration date on the pack label or 28 consecutive days after loading the primary reagent pack
ACS:Centaur Multi-Diluent 2 ReadyPack ancillary reagent pack	Multi-Diluent 2	10.0 mL/ reagent pack	goat serum with sodium azide (0.1%) and preservatives	2*8°C	until the expiration date on the pack label or 28 consecutive days after accessing the ancillary reagent pack

WARNING: Sodium azide can react with copper and lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent the buildup of azides, if disposal into a drain is in compliance with federal, state, and local requirements.

CAUTION:

Lite Reagent and Solid Phase:

Very toxic if swallowed. Contact with acids liberates very toxic gas. After contact with skin, wash immediately with plenty of soap and water. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

POTENTIAL BIOHAZARD: Human and/or other biological source material. Handle as if potentially infectious.

This product may contain one or more of the following materials:

- human serum or plasma, or other human source material
- biological source material of non-human origin

While each human serum or plasma donor unit used in the manufacture of this product was tested and found non-reactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis C (HCV), and antibody to HIV-1/2 by FDA-approved methods, all products manufactured using human or non-human source material should be handled as potentially infectious. There are no approved tests for other human and/or non-human source material. Handle this product according to established good laboratory practices.³²⁻³⁴

Loading Reagents

Ensure that the system has sufficient primary and ancillary reagent packs. For detailed information about preparing the system, refer to the system operating instructions or to the online help system.

CAUTION: Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and resuspended. For detailed information about preparing the reagents for use, refer to Appendix C, *Handling Reagents*.

Load the primary reagent packs in the primary reagent area using the arrows as a placement guide. The system automatically mixes the primary reagent packs to maintain homogeneous suspension of the reagents. For detailed information about loading reagents, refer to the system operating instructions or to the online help system.

If automatic dilution of a sample is required, load ACS:Centaur Multi-Diluent 2 in the ancillary reagent entry.

CAUTION:

- Discard reagent packs 28 days after loading the reagent packs on the system. Do not use these reagents to calibrate the system or to assay samples.
- Do not use reagents beyond the expiration date.

Calibration

For detailed information about entering calibration values, refer to the system operating instructions or to the online help system.

Master Curve Calibration

The ACS:Centaur PSA2 assay requires a Master Curve calibration when using a new lot number of Lite Reagent and Solid Phase. For each new lot number of Lite Reagent and Solid Phase, use the barcode reader or keyboard to enter the Master Curve values on the system. The Master Curve card contains the Master Curve values. Six standards at levels in the range of 0, 0.3, 6.5, 33, 60, and 165 ng/mL (mass units) [0, 0.010, 0.216, 1.099, 1.998, and 5.495 nmol/L (SI units)] are used in the preparation of each new Master Curve.

Two-point Calibration Interval

The ACS:Centaur PSA2 assay requires a two-point calibration:

- every 28 days
 - when changing lot numbers of primary reagent packs
- when replacing system components
- when quality control results are repeatedly out of range

This assay requires the use of low (~0.4 ng/mL) (~0.013 nmol/L) and high (~100 ng/mL) (~3.330 nmol/L) levels of Calibrator D to adjust the system to the Master Curve calibration.

Calibrator D contains highly purified PSA in a matrix of goat serum, sodium azide, and preservatives. Values are determined from a full six-point Master Curve at the time of Calibrator D manufacture. Reference values initially were determined for Master Curve standards as described in *Standardization*.

Quality Control

For detailed information about entering quality control values, refer to the system operating instructions or to the online help system.

To monitor system performance and chart trends, as a minimum requirement, two levels of quality control material should be assayed on each day that samples are analyzed. Quality control samples should also be assayed when performing a two-point calibration. Treat all quality control samples the same as patient samples.

For quality control of the ACS:Centaur PSA2 assay, use Chiron Diagnostics Ligand Plus, Tumor Marker Plus, or an equivalent quality control material. Refer to the product inserts for the suggested Expected Values. If the quality control results do not fall within the suggested Expected Values or within the laboratory's established values, then do the following:

- review these instructions to ensure that the assay was performed according to the procedures recommended by Chiron Diagnostics
- verify that the materials are not expired

- verify that required maintenance was performed
- if necessary, rerun the quality control samples or contact Chiron Diagnostics for more assistance

Sample Volume

This assay requires 100 μL of sample for a single determination. This volume does not include the unusable volume in the sample container or the additional volume required when performing duplicates or other tests on the same sample.

Assay Procedure

For detailed procedural information, refer to the system operating instructions or to the online help system.

CAUTION: Do not load more than one size of sample container in each rack. The rack indicator must be positioned at the correct setting for the size of sample container.

1. Prepare the sample container for each sample, and place barcode labels on the sample containers, as required.
2. Load each sample container into a rack, ensuring that the barcode labels are clearly visible through the slot in the rack.
3. Place the racks in the entry queue.

Start the entry queue, if required.

Procedural Notes

Calculations

For detailed information about how the system calculates results, refer to the system operating instructions or to the online help system.

The system reports serum PSA results in ng/mL (mass units) or nmol/L (SI units), depending on the units defined when setting up the assay. The conversion formula is $1 \text{ ng/mL} = 0.0333 \text{ nmol/L}$.³⁵

Dilutions

- Serum samples with PSA levels greater than 135 ng/mL (4.496 nmol/L) must be diluted and retested to obtain accurate results.
- Patient samples can be automatically diluted by the system or prepared manually.
- For automatic dilutions, ensure that ACS:Centaur Multi-Diluent 2 is loaded and set the system parameters as follows:

Dilution point: $\leq 135 \text{ ng/mL}$ (4.496 nmol/L)

Dilution factor: 2, 5, 10, 20

For detailed information about automatic dilutions, refer to the system operating instructions or to the online help system.

- Manually dilute the patient samples when patient results exceed the linearity of the assay using automatic dilution, or when laboratory protocol requires manual dilution.
- Use ACS:Systems Multi-Diluent 2 to manually dilute patient samples, and then load the diluted sample in the sample rack, replacing the undiluted sample.
- Ensure that results are mathematically corrected for dilution. If a dilution factor is entered

when scheduling the test, the system automatically calculates the result.

High Dose Hook Effect

Patient samples with high PSA levels can cause a paradoxical decrease in the RLU's (high dose hook effect). In this assay, patient samples with PSA levels as high as 20,000 ng/mL (666 nmol/L) will assay greater than 135 ng/mL (4.496 nmol/L).

Disposal

Dispose of hazardous and biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with all federal, state, and local requirements.

Limitations



Prostate cancer patients under treatment with anti-androgens and LHRH agonists may exhibit markedly reduced levels of PSA. Also, men treated for benign prostatic hyperplasia with inhibitors of 5 α -reductase (finasteride) may demonstrate a significant reduction in PSA levels compared to values prior to treatment.³⁶ Care should be taken when interpreting values from these individuals.

The concentration of PSA in a given specimen determined with assays from different manufacturers can vary because of differences in assay methods, calibration, and reagent specificity.³⁷ PSA in serum and in seminal fluid exists primarily in complexed and free forms, respectively.³⁸ Quality control samples may be produced by introducing seminal fluid PSA into serum matrices. PSA levels in these controls, determined with different manufacturers' assays, will vary depending on the method of standardization, antibody specificity, and different reactivity with complexed and free forms of PSA. Therefore, it is important to use assay specific values to evaluate quality control results.

Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with in vitro immunoassays.³⁹ Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values can be observed. Additional information may be required for diagnosis.

<i>Serum specimens that are . . .</i>	<i>Have an Insignificant effect on the assay up to . . .</i>
hemolyzed	500 mg/dL of hemoglobin
lipemic	1000 mg/dL of triglycerides
icteric	20 mg/dL of bilirubin

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Expected Results

Detection of Prostate Cancer

A retrospective study was conducted at six clinical sites to evaluate the utility of the ACS:180 PSA2 assay, in conjunction with DRE, for the detection of prostate cancer. A total of 7039 men, aged 50 or older with no history of prostate cancer, comprised the screening population. All subjects had a blood sample drawn for PSA determination, followed by a digital rectal examination (DRE). A DRE was considered abnormal if the examiner recorded the result as being suspicious for the presence of cancer.

The mean age of the screening population was 62, with a range of 50 to 96 years. The ethnic origin of the subjects was as follows: 85% Caucasian (36% from the U.S., 49% from Chile), 13% African-American, 1% Asian, 1% Hispanic, 1% Other or Unknown.

Table 1 shows the number and percent of subjects in different age ranges who had abnormal results (based on results at the time of screening), the number and percent of the subjects with abnormal results who underwent biopsy, and the number and percent of those with biopsy results who had prostate cancer.

Table 1. Age of Subjects with Abnormal DRE and/or PSA Results > 4.0 ng/mL: Number and Percent with Biopsy and Cancer

Age	Total Number in Screening Population	Subjects with Abnormal Results (PSA Results > 4.0 ng/mL and/or Abnormal DRE)		
		No. and % with Abnormal Results	No. with Biopsy (% of Abnormals)	Number of Cancers (% of Biopsy)
50-60	3138	335 (11%)	152 (45%)	26 (17%)
60-70	2798	596 (21%)	334 (56%)	88 (26%)
≥ 70	1103	330 (30%)	166 (50%)	59 (36%)
Total	7039	1261 (18%)	652 (52%)	173 (27%)

The percent of subjects who had abnormal results increased with increasing age, and the percent of biopsies with cancer also increased with increasing age. These data are consistent with other reports in the literature.³ Table 2 shows the positive predictive values (PPV) for the ACS:180 PSA2 assay and for an abnormal DRE result when evaluated alone and in combination.

Table 2. Positive Predictive Values of ACS:180 PSA2 > 4.0 ng/mL and/or Abnormal DRE Results for Detection of Prostate Cancer. (Number of Subjects in Screening Population = 7039)

ACS:180 PSA2 and/or DRE Result	No. of Subjects in category	No. of Biopsies	No. of Cancers	Positive Predictive Values (% of Biopsies with Cancer and 95% CI*)
All Subjects with PSA2 > 4.0 ng/mL and/or Abnormal DRE	1040	506	147	29% (25, 33)
PSA2 > 4.0 ng/mL	613	380	127	33% (29, 38)
DRE abnormal	568	219	71	32% (26, 39)
PSA2 > 4.0 ng/mL, DRE abnormal	141	93	51	55% (44, 65)
PSA2 > 4.0 ng/mL, DRE normal	472	287	76	26% (21, 32)
PSA2 ≤ 4.0 ng/mL, DRE abnormal	427	126	20	16% (10, 23)

* CI = confidence interval.

The study demonstrated that ACS:180 PSA2 assay results > 4.0 ng/mL in conjunction with an abnormal DRE provided the greatest predictive value for the detection of prostate cancer. The predictive values for PSA results > 4.0 ng/mL were similar to those for abnormal DRE (33% and 32%, respectively). However, PSA2 detected a greater number of the total cancers (86%, 127/147) than did DRE (48%, 71/147). The PPV of a PSA2 result of > 4.0 ng/mL when the DRE was normal was 26%. This was greater than the PPV for an abnormal DRE result when the PSA2 result was ≤ 4.0 ng/mL (16%).

Serum PSA concentrations, regardless of the value, should not be interpreted as diagnostic for the presence or absence of prostate cancer. PSA testing should always be performed in conjunction with DRE, as the combination of an ACS:180 PSA2 value > 4.0 ng/mL and/or an abnormal DRE predicted the greatest number of cancers. Prostatic biopsy is required for a definitive diagnosis of prostate cancer.

Prognosis and Management

To confirm the distribution of ACS:180 PSA2 in patients as shown below, serum samples from 2371 patients were analyzed using the ACS:180 PSA2 reagents.⁴⁰

% Distribution of PSA by Diagnostic Category

<i>Patient Diagnosis</i>	<i>N</i>	<i>0.0-4.0 ng/mL (0.0-0.13 nmol/L)</i>	<i>4.1-10 ng/mL (0.137-0.333 nmol/L)</i>	<i>10.1-40 ng/mL (0.336-1.332 nmol/L)</i>	<i>> 40 ng/mL (> 1.332 nmol/L)</i>	<i>Median PSA (ng/mL)</i>	<i>Median PSA (nmol/L)</i>
Apparently Healthy							
Female	143	100	0.0	0.0	0.0	0.0	0.0
Male < 40	101	100	0.0	0.0	0.0	0.3	0.010
Male > 40	440	98.9	0.9	0.2	0.0	0.6	0.020
Total Males	541	99.7	0.2	0.1	0.0		
Prostate Cancer							
Stg A treated	48	58.3	39.6	2.1	0.0	3.3	0.110
untreated	65	47.7	33.9	16.9	1.5	4.4	0.147
Stg B treated	63	27.0	49.2	19.0	4.8	6.4	0.213
untreated	152	27.6	33.6	33.6	5.2	7.7	0.256
Stg C treated	91	16.5	38.4	41.8	3.3	9.2	0.306
untreated	115	8.7	13.9	38.3	39.1	25.9	0.862
Stg D treated	94	8.5	8.5	34.1	48.9	38.6	1.285
untreated	114	1.7	4.4	20.2	73.7	100.3	3.340
Total Prostate	742	20.6	25.2	28.6	25.6	12.1	0.403
Benign Diseases							
Prostate Hypertrophy (BPH)	485	71.7	21.9	6.0	0.4	2.0	0.067
Genitourinary (GU) ^a	104	67.3	25.0	7.7	0.0	3.2	0.107
Other Cancers							
Breast	61	100.0	0.0	0.0	0.0	0.0	0.0
Colorectal							
male ^b	51	82.4	3.9	9.8	3.9	0.6	0.020
female	35	100.0	0.0	0.0	0.0	0.0	0.0
Pulmonary							
male ^b	30	86.6	6.7	6.7	0.0	0.5	0.017
female	23	100.0	0.0	0.0	0.0	0.0	0.0
Misc. GU ^c							
male ^b	47	85.1	8.5	6.4	0.0	0.6	0.020
female	21	100.0	0.0	0.0	0.0	0.0	0.0
Other ^d							
male ^b	51	90.2	5.9	3.9	0.0	0.8	0.027
female	37	100.0	0.0	0.0	0.0	0.0	0.0

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Includes prostatitis, prostatodynia, urethritis, cystocele, hydrocele, urethral papilloma, and urinary infection.

5. Age > 64 years old for all values greater than 10 ng/mL (0.333 nmol/L).
6. Includes renal, bladder, testicular, vaginal, cervical, and endometrial.
7. Includes gastric, pancreatic, pituitary, nasopharyngeal, brain and skin cancers and leukemias, lymphomas and Hodgkin's disease.

These results were confirmed for the ACS:Centaur PSA2 assay by analyzing 287 samples in the range of 0.07 to 111.25 ng/mL (0.00 to 3.70 nmol/L). Refer to *Method Comparison*.

As with all diagnostic tests, each laboratory should determine the appropriateness of this range for the diagnostic evaluation of patient results.⁴¹

Performance Characteristics

Specificity

There are no known cross-reactants for PSA. Prostatic acid phosphatase at a concentration of 2000 ng/mL showed no interference when tested at three levels of PSA.

The potential interference of chemotherapeutic and anti-hormonal agents was tested by adding these agents to serum pools containing PSA at three different concentrations. The PSA level then was determined and was compared to a serum control that contained no agent.

Interference by Chemotherapeutic and Anti-hormonal Agents

Substance	Amount Added ($\mu\text{g/mL}$)	Mean % Recovery (Spike/control x 100)
Cyclophosphamide	330	98
Doxorubicin hydrochloride	10	100
Methotrexate	13	101
<i>Anti-androgen therapy</i>		
Megestrol acetate	79	101
Diethylstilbestrol	2.5	101
Leuprolide acetate	10	101
Flutamide	300	97

Sensitivity and Assay Range

The ACS:Centaur PSA2 assay measures PSA concentrations up to 135 ng/mL (4.496 nmol/L) with a minimum detectable concentration (analytical sensitivity) of less than 0.06 ng/mL (0.002 nmol/L). Analytical sensitivity is defined as the concentration of PSA that corresponds to the RLUs that are two standard deviations greater than the mean RLU of 20 replicate determinations of the PSA2 zero standard.

Method Comparison

For 287 samples in the range of 0.07 to 111.25 ng/mL (0.00 to 3.70 nmol/L), the relationship between the ACS:Centaur PSA2 assay and the ACS:180 PSA2 assay is described by the equation:

$$\text{ACS:Centaur PSA2} = 0.97 (\text{ACS:180 PSA2}) + 0.19 \text{ ng/mL}$$

Correlation coefficient (r) = 0.99

Dilution Recovery

Seven samples with concentrations of PSA in the range of 75.67 to 115.40 ng/mL (2.52 to 3.84 nmol/L) were diluted 1:2, 1:4, and 1:8 with Multi-Diluent 2 and assayed for recovery and parallelism. The recoveries ranged from 89.5% to 108.0% with a mean of 98.4%.

Sample	Dilution	Observed (ng/mL)	Expected (ng/mL)	Observed (nmol/L)	Expected (nmol/L)	Recovery %
1	—	109.40		3.64		
	1:2	57.74	54.70	1.92	1.82	105.6
	1:4	25.96	27.35	0.86	0.91	94.9
	1:8	12.57	13.67	0.42	0.46	91.9
	Mean					97.5
2	—	110.15		3.67		
	1:2	56.17	55.07	1.87	1.83	102.0
	1:4	26.23	27.54	0.87	0.92	95.2
	1:8	12.47	13.77	0.42	0.46	90.6
	Mean					95.9
3	—	99.83		3.32		
	1:2	50.08	49.91	1.67	1.66	100.3
	1:4	25.12	24.96	0.84	0.83	100.7
	1:8	12.34	12.48	0.41	0.42	98.9
	Mean					100.0
4	—	87.56		2.92		
	1:2	46.59	43.78	1.55	1.46	106.4
	1:4	22.56	21.89	0.75	0.73	103.1
	1:8	9.82	10.94	0.33	0.36	89.8
	Mean					99.8
5	—	87.92		2.93		
	1:2	45.02	43.96	1.50	1.46	102.4
	1:4	20.95	21.98	0.70	0.73	95.3
	1:8	9.96	10.99	0.33	0.37	90.6
	Mean					96.1
6	—	115.40		3.84		
	1:2	56.12	57.70	1.87	1.92	97.3
	1:4	27.85	28.85	0.93	0.96	96.5
	1:8	12.92	14.43	0.43	0.48	89.5
	Mean					94.5
7	—	75.67		2.52		
	1:2	40.86	37.84	1.36	1.26	108.0
	1:4	19.80	18.92	0.66	0.63	104.7
	1:8	9.62	9.46	0.32	0.32	101.7
	Mean					104.8
Mean					98.4	

Spiking Recovery

Known amounts of PSA were added to six serum samples with endogenous PSA levels ranging from 0.22 to 1.17 ng/mL (0.007 to 0.0390 nmol/L). The concentration of PSA added varied from 11.05 to 125.21 ng/mL (0.3680 to 4.1695 nmol/L). When compared to the expected value, the measured (recovered) levels of PSA averaged 98.3% with a range of 91.1% to 105.5%.

Sample	Amount Added (ng/mL)	Observed (ng/mL)	Amount Added (nmol/L)	Observed (nmol/L)	Recovery %
1	—	0.22	—	0.0073	
	11.05	11.40	0.3680	0.3796	101.2
	37.04	35.97	1.2334	1.1978	96.5
	66.93	64.86	2.2288	2.1598	96.6
	97.62	92.59	3.2507	3.0832	94.6
	125.21	120.02	4.1695	3.9967	95.7
Mean					96.9
2	—	1.17	—	0.0390	
	11.05	12.56	0.3680	0.4182	103.1
	37.04	37.42	1.2334	1.2461	97.9
	66.93	66.37	2.2288	2.2101	97.4
	97.62	95.59	3.2507	3.1831	96.7
	125.21	119.50	4.1695	3.9794	94.4
Mean					97.9
3	—	0.62	—	0.0206	
	11.05	12.01	0.3680	0.0400	103.1
	37.04	35.60	1.2334	1.1855	94.4
	66.93	64.28	2.2288	2.1405	95.1
	97.62	95.74	3.2507	3.1881	97.4
	125.21	114.66	4.1695	3.8182	91.1
Mean					96.2
4	—	0.39	—	0.0130	
	11.05	11.64	0.3680	0.3876	101.8
	37.04	36.63	1.2334	1.2198	97.8
	66.93	66.17	2.2288	2.2035	98.3
	97.62	96.53	3.2507	3.2144	98.5
	125.21	122.54	4.1695	4.0806	97.6
Mean					98.8
5	—	0.66	—	0.0220	
	11.05	12.32	0.3680	0.4103	105.5
	37.04	37.97	1.2334	1.2644	100.7
	66.93	68.43	2.2288	2.2787	101.3
	97.62	97.69	3.2507	3.2531	99.4
	125.21	122.13	4.1695	4.0669	97.0
Mean					100.8
6	—	0.78	—	0.0260	
	11.05	11.93	0.3680	0.3973	100.9
	37.04	37.00	1.2334	1.2321	97.8
	66.93	67.99	2.2288	2.2641	100.5
	97.62	98.21	3.2507	3.2704	99.8
	125.21	120.55	4.1695	4.0143	95.7
Mean					98.9
Mean					98.3

Precision

Five samples were assayed 6 times, in each of 12 runs, on 6 systems, (n = 72 for each sample), over a period of 3 days. The following results were obtained:

Mean (ng/mL)	Mean (nmol/L)	Within-run % CV	Run-to-run % CV	Total % CV
1.3	0.04	3.3	2.4	4.0
9.2	0.31	2.4	2.2	3.3
28.5	0.95	3.1	1.8	3.5
48.6	1.62	3.0	2.4	3.8
97.0	3.23	3.7	2.4	4.4

Standardization

The ACS:Centaur PSA2 assay was standardized using highly purified PSA. Value (concentration) assignment was based on adjustment to a reference immunoassay procedure.

Evaluating Results

The following is recommended when you observe poor reproducibility of PSA values at low levels or if you are not satisfied with assay performance:

- Ensure that the assay reagent and calibrator lot numbers and expiration dates match those entered in the system.
- Ensure that the calibrators, quality control materials, and assay reagents were prepared according to the recommended procedures.
- Ensure that the recommended sample collection and handling procedures were followed.

Ensure that the recommended system cleaning procedures were followed.

- Ensure that Type II reagent water was used when operating the system.²⁹
- Visually check the probe and tubing for obstructions, leaks, and deformities such as pinched or crimped tubing.
- Take further corrective action following established laboratory procedures.
- Calibrate the system using new assay reagents, calibrators, and quality control samples.
- Contact Chiron Diagnostics for technical assistance.

Technical Assistance

For technical assistance, customers in the United States may call Chiron Diagnostics at 800-CENTAUR (800-236-8287) or fax questions to the Technical Assistance Center at 508-660-4559. Customers outside the United States may contact an authorized Chiron Diagnostics representative.

For customer service or additional information, customers in the United States may call 800-255-3232. Customers outside the United States may contact an authorized Chiron Diagnostics distributor.

References

8. Wingo.PA, Tong T, Bolden S. Cancer Statistics, 1995. CA Cancer J Clin 1995; 45:8.
9. Jensen OM, Esteve J, Moller H, Renard H. Cancer in the European Community and its member states. Eur J Cancer 1990; 26:1167.
10. Denis, LJ, Murphy GP, Schroder FH. Report of the consensus workshop on screening and global strategy for prostate cancer. Cancer 1995; 75:1187.
11. Parker SL, Tong T, Bolden S, Wingo PA. Cancer Statistics, 1996. CA Cancer J Clin 1996; 46:5.
12. DeAntoni E. Eight years of "Prostate Cancer Awareness Week". Cancer 1997; 80:1845.
13. Catalona WJ, Smith DS, Ratliff TL, et. al. Measurement of Prostate-specific antigen in serum as a screening test for prostate cancer. New Eng J Med 1991; 324(17):1156.
14. Pearson JD and Carter HB. Natural history of changes in prostate specific antigen in early stage prostate cancer. J. Urol 1994; 152:1743.
15. Mettlin CJ, Murphy GP, Babaian RJ, et al. Observations on the early detection of prostate cancer from the American Cancer Society National Prostate Cancer Detection Project. Cancer 1997; 80:1814.
16. Smith DS, Humphrey PA, Catalona WJ. The early detection of prostate carcinoma with prostate specific antigen. Cancer 1997; 80:1852.
17. Smart CR. The results of prostate carcinoma screening in the U.S. as reflected in the Surveillance, Epidemiology, and End Results Program. Cancer 1997; 80:1835.
18. Crawford ED, DeAntoni EP, Etzioni R, et al. Serum prostate-specific antigen and digital rectal examination for early detection of prostate cancer in a national community-based program. Urology 1996; 47:863.
19. Slawin KM, Otori M, Dilliogluligil O, Scardino PT. Screening for prostate cancer: An analysis of the early experience. CA Cancer J Clin 1995; 45:134.
20. Bangma CH, Kranse R, Blijenberg BG, Schroder FH. The value of screening tests in the detection of prostate cancer. Part I: Results of a retrospective evaluation of 1726 men. Urology 1995; 46:773.
21. von Eschenbach A, Ho R, Murphy GP, Cunningham M, Lins N. American Cancer Society guidelines for the early detection of prostate cancer. Update, June 10, 1997. Cancer 1997; 80:1805.

22. American Urological Association - Early Detection of Prostate Cancer policy Statement. Board of Directors Minutes. 1992.
23. Auvinen A, Tammela T, Stenman, et al. Screening for prostate cancer using serum prostate-specific antigen: a randomised, population-based pilot study in Finland. *Br J Cancer* 1996; 74:568.
24. Schroder FH, Damhuis RAM, Kirkels WJ, De Koning, HJ, et al. European randomized study of screening for prostate cancer - the Rotterdam pilot studies. *Int. J Cancer* 1996; 65:145.
- Reissig A, Horninger W, Fink K, Klocker H, Bartsch G. Prostate carcinoma screening in the County of Tyrol, Austria. *Cancer* 1997; 80:1818.
25. Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate-specific antigen. *Invest Urol* 1979; 17:159.
26. Watt KWK, Lee PJ, M'Timkulu T. et al. Human prostate-specific antigen: structural and functional similarity with serine proteases. *Proc Nat Acad Sci.* 1986; 83:3166.
27. Lilja HA. A kallikren-like serine protease in prostatic fluid cleaves the predominant seminal vesicle protein. *J Clin Invest* 1985; 76:1899.
28. Bunting PS. A guide to the interpretation of serum prostate specific antigen levels. *Clin Biochem* 1995; 28:221.
29. Stamey TA, Yang N, Hay AR. et al. Prostate-specific antigen as a serum marker for adeno-carcinoma of the prostate. *New Eng J Med* 1987; 317(15):908.
30. Schellhammer PF, Schlossberg SM, El-Mahdi AM, et al. Prostate-specific antigen levels after definitive irradiation for carcinoma of the prostate. *J Urol* 1991; 145:1008.
31. Stamey TA, Kabalin JN, McNeal JE, et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J Urol* 1989; 141:1076.
32. Lange PH, Ercole CJ, Lightner DJ, et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol* 1989; 141:873.
33. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991; 145:907.
34. Killian CS, Yang N, Emrich LJ, et al. Prognostic importance of prostate specific antigen for monitoring patients with stages B2 to D1 prostate cancer. *Cancer Res* 1985;45: 886.
35. Reagent Water Technical Bulletin. Chiron Diagnostics Corporation, 107060.
36. National Committee for Clinical Laboratory Standards. Procedures for handling and processing of blood specimens; approved guideline. NCCLS Document H18-A. Villanova (PA): NCCLS; 1990 Dec. 34p.
37. Yuan JJ, Coplen DE, et al. Effects of rectal examination, prostatic massage, ultrasonography and needle biopsy on serum prostatic specific antigen levels. *J Urol* 1992; 147: 810.
38. Centers for Disease Control. 1988. Update: Universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus and other bloodborne pathogens in healthcare settings. *MMWR*, 37:377, 387, 388.
39. National Committee for Clinical Laboratory Standards. Protection of laboratory workers from instrument biohazards and infectious disease transmitted by blood, body fluids, and tissue; approved guideline. NCCLS Document M29-A. Villanova (PA): NCCLS; 1997 Dec. 90p.
- Federal Occupational Safety and Health Administration, Bloodborne Pathogens Standard, 29 CFR 1910.1030.
40. National Committee for Clinical Laboratory Standards. Primary reference preparations used to standardize calibration of immunochemical assays for serum prostate specific antigen(PSA); approved guideline. NCCLS Publication I/LA19-A; Villanova, PA, NCCLS: 1997.
41. Gormley GJ, Stoner E, Bruskewitz RC. et al. The effect of finasteride in men with benign prostatic hyperplasia. *New Eng J Med* 1992; 327(17):1185.
42. Graves HCB, Wehner N, and Stamey TA. Comparison of a polyclonal and monoclonal immunoassay for PSA: need for an international antigen standard. *J Urol* 1990; 144:1516.
43. Lilja H, Christensson A, Dahlén U, et al. Prostate-specific antigen in serum occurs predominantly in complex with alpha-1-antichymotrypsin. *Clin Chem* 1991; 37(9):1618.
44. Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. *Clin Chem* 1988;34:27-33.
45. Bluestein B, Zhou A, Tewari P, et al. Multi-site evaluation of an automated chemiluminescent immunoassay for prostate specific antigen (ACS PSA). *J Tumor Marker Oncology* 1992; 7(4):41.
46. National Committee for Clinical Laboratory Standards. How to define, determine, and utilize reference intervals in the clinical laboratory; approved guideline. NCCLS Document C28-A. Villanova (PA): NCCLS; 1995 June 59p.

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