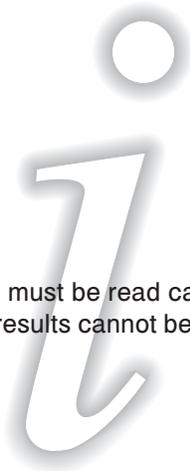


Total PSA

**IVD** **REF** 7K70

**B7K700**

77-4138/R2



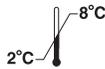
# Total PSA

This package insert must be read carefully prior to use. Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

**Note Changes Highlighted**

Revised June, 2007

## Key to symbols used

<b>REF</b>	List number		Expiration date
<b>IVD</b>	<i>In Vitro</i> Diagnostic Medical Device	<b>LOT</b>	Lot number
	Store at 2-8°C	<b>REAGENT LOT</b>	Reagent Lot
	Consult instructions for use	<b>SAMPLE CUPS</b>	Sample Cups
	Caution: consult accompanying documents	<b>SEPTUMS</b>	Septums
<b>SN</b>	Serial Number	<b>CONTROL NO.</b>	Control Number
	Manufacturer	<b>REACTION VESSELS</b>	Reaction Vessels
		<b>REPLACEMENT CAPS</b>	Replacement Caps

See **REAGENTS** section for a full explanation of symbols used in reagent component naming.

**WARNING:** The concentration of total PSA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the total PSA assay used. Values obtained with different assay methods, including Abbott PSA assays, cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining total PSA levels serially is changed, additional sequential testing should be carried out. Prior to changing assays, the laboratory MUST confirm baseline values for patients being serially monitored.

## NAME

ARCHITECT Total PSA (Prostate Specific Antigen)

## INTENDED USE

The ARCHITECT Total PSA assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of total PSA (both free PSA and PSA complexed to alpha-1-antichymotrypsin) in human serum:

1. As an aid in the detection of prostate cancer when used in conjunction with digital rectal exam (DRE) in men 50 years or older. Prostatic biopsy is required for diagnosis of cancer.
2. As an adjunctive test to aid in the management of prostate cancer patients.

## SUMMARY AND EXPLANATION OF TEST

Prostate specific antigen (PSA), a member of the human kallikrein gene family, is a serine protease with chymotrypsin-like activity. The mature form of PSA is a single chain glycoprotein of 237 amino acids containing 7-8% carbohydrate as a single N-linked oligosaccharide side chain. PSA has a molecular weight of approximately 30,000 daltons.<sup>1,8,33,34</sup>

The major site of PSA production is the glandular epithelium of the prostate. PSA has also been found in breast cancers, salivary gland neoplasms, periurethral and anal glands, cells of the male urethra, breast milk, blood and urine.<sup>1,2</sup> PSA produced in the prostate is secreted into the seminal fluid in high concentrations. A major function of PSA is the proteolytic cleavage of gel-forming proteins in the seminal fluid, resulting in the liquification of the seminal gel and increased sperm mobility.<sup>1</sup> Low levels of PSA are found in the blood as a result of leakage of PSA from the prostate gland. Increasing levels of serum PSA are associated with prostatic pathology, including prostatitis, benign prostatic hyperplasia (BPH), and cancer of the prostate.<sup>1,3-7</sup>

PSA occurs in three major forms in blood. The major immunodetectable form is PSA complexed with the serine protease inhibitor, alpha-1-antichymotrypsin (PSA-ACT). Uncomplexed, or free PSA, is the other immunodetectable form of PSA in serum. The majority of free PSA in serum appears to be an inactive form that cannot complex with protease inhibitors and may be either a PSA zymogen or an enzymatically-inactive, cleaved form of PSA. Equimolar-response PSA assays have an equivalent response to both free PSA and PSA-ACT.<sup>1</sup> The ARCHITECT Total PSA assay is an equimolar assay. A third form of PSA, a complex with alpha-2-macroglobulin, is not detectable with current immunoassays for PSA due to the engulfment and subsequent masking of PSA epitopes by the alpha-2-macroglobulin molecule.<sup>1,8,9</sup> Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths in men in the United States.<sup>10</sup> Early diagnosis of carcinoma of the prostate is hindered by the lack of symptoms in men with localized tumors. Therefore, early detection requires a simple, safe, and inexpensive test for the disease in asymptomatic men. The traditional method for detection of prostate cancer is the digital rectal examination (DRE). However, only 30 to 40% of cancers detected by DRE screening are expected to be confined to the prostate. The frequent finding of locally advanced prostate cancer in screened patients may be due to the inability of DRE to detect tumors of small volume that are most likely to be confined to the prostate.<sup>11</sup> Since patients with small tumors are believed to have the best prognosis, it can be concluded that DRE has limited sensitivity in detecting those tumors with the greatest potential for cure.<sup>12</sup>

In a 1990 publication by Cooner *et al.*, data was presented regarding the clinical use of other diagnostic modalities such as prostate ultrasonography and serum prostate specific antigen for early detection of prostate cancer. This study found that there was a significant increase in predictability for cancer when the DRE and PSA tests were abnormal.<sup>13</sup> Several other studies have shown that the

measurement of serum PSA concentrations offers several advantages in the early detection of prostate cancer. The procedure is more acceptable to patients, the result is objective and quantitative, and is independent of the examiners skill. In several recent studies of healthy men 50 years or older, serum PSA levels had the greatest ability to predict prostate cancer. These studies concluded that not only is serum PSA measurement a useful addition to rectal examination and ultrasonography in the detection of prostate cancer, but that it is also the most accurate of the three tests for this purpose.<sup>14,15</sup> In January 1992, the American Urological Association endorsed annual examination with DRE and PSA, for early detection of prostate cancer, beginning at age 50.<sup>16</sup> This was reaffirmed by the American Cancer Society in November 1992.<sup>17</sup> The combined use of DRE and PSA has been shown to result in an increased detection of early stage prostate cancer; however, the benefit of early detection on patient outcome has not been proven and is the subject of ongoing clinical trials.<sup>4-7,13-15,18,19</sup>

PSA testing can have significant value in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer. Persistent elevation of PSA following treatment, or an increase in a post-treatment PSA level is indicative of recurrent or residual disease. PSA testing is widely accepted as an adjunctive test in the management of prostate cancer patients.<sup>3-7</sup>

## BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT Total PSA assay is a two-step immunoassay to determine the presence of total PSA (both free PSA and PSA complexed to alpha-1-antichymotrypsin) in human serum, using Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample and anti-PSA coated paramagnetic microparticles are combined. PSA present in the sample binds to the anti-PSA coated microparticles. After washing, anti-PSA acridinium-labeled conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of total PSA in the sample and the RLUs detected by the ARCHITECT *i*\* optical system.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

\* *i* = immunoassay

## REAGENTS

### Reagent Kit, 100 Tests/500 Tests

**NOTE:** Reagent Kit Configurations vary based on order.

### ARCHITECT Total PSA Reagent Kit (7K70)

- **MICROPARTICLES** 1 or 4 Bottle(s) (6.6 mL for 100 test bottle/ 27.0 mL for 500 test bottle) Anti-PSA (mouse, monoclonal) coated Microparticles in TRIS buffer with protein (bovine) stabilizers. Preservative: Antimicrobial Agents.
- **CONJUGATE** 1 or 4 Bottle(s) (5.9 mL for 100 test bottle/26.3 mL for 500 test bottle) Anti-PSA (mouse, monoclonal) acridinium-labeled Conjugate in MES buffer with protein (bovine) stabilizers. Minimum concentration: 10 ng/mL. Preservative: Antimicrobial Agents.

### Assay Diluent

#### ARCHITECT *i* Multi-Assay Manual Diluent (7D82-50)

- **MULTI-ASSAY MANUAL DILUENT** 1 Bottle (100 mL) ARCHITECT *i* Multi-Assay Manual Diluent containing phosphate buffered saline solution. Preservative: Antimicrobial Agent.

### Other Reagents

#### ARCHITECT *i* Pre-Trigger Solution

- **PRE-TRIGGER SOLUTION** Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

#### ARCHITECT *i* Trigger Solution

- **TRIGGER SOLUTION** Trigger Solution containing 0.35N sodium hydroxide.

#### ARCHITECT *i* Wash Buffer

**NOTE:** Bottle and volume varies based on order.

- **WASH BUFFER** Wash Buffer containing phosphate buffered saline solution. Preservative: Antimicrobial Agent.

## WARNINGS AND PRECAUTIONS

- For *In Vitro* Diagnostic Use.



**CAUTION:** This product requires the handling of human specimens. It is recommended that all human sourced materials be considered potentially infectious and handled with appropriate biosafety practices.

### Safety Precautions

For product not classified as dangerous per European Directive 1999/45/EC as amended - Safety data sheet available for professional user on request.

- For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

### Handling Precautions

- Do not use reagent kits beyond the expiration date.
- **Do not mix reagents from different reagent kits.**
- Prior to loading the ARCHITECT Total PSA Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination, and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
- **To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.**
- Once a septum has been placed on an open reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts which have no effect on assay efficacy.
- For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

### Storage Instructions

-  The ARCHITECT Total PSA Reagent Kit must be stored at 2-8°C and may be used immediately after removal from 2-8°C storage.
- When stored and handled as directed, reagents are stable until the expiration date.
- The ARCHITECT Total PSA Reagent Kit may be stored on-board the ARCHITECT *i* System for a maximum of 30 days. After 30 days, the reagent kit must be discarded. For information on tracking on-board time, refer to the ARCHITECT System Operations Manual, Section 5.
- Reagents may be stored on or off the ARCHITECT *i* System. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** After reagents are removed from the system, you must initiate a scan to update the on-board stability timer.

## Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results may be invalid and may require retesting. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

### Elevated Sample Results

Protein build up on the sample pipetter probe may result in individual samples exhibiting elevated concentration due to carryover from a sample with very high PSA concentration. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

## INSTRUMENT PROCEDURE

- The ARCHITECT Total PSA assay file must be installed on the ARCHITECT *i* System from the ARCHITECT *i* Assay CD-ROM prior to performing the assay. For detailed information on assay file installation and on viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.
- For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.
- For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.
- The default result unit for the ARCHITECT Total PSA assay is ng/mL. An alternate result unit, µg/L, may be selected for reporting results by editing assay parameter "Result concentration units", to µg/L. The conversion factor used by the system is 1.0.

## SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

- Only human serum may be used in the ARCHITECT Total PSA assay. Follow the tube manufacturer's processing instructions for serum collection tubes.
- It is recommended to obtain specimens for PSA testing prior to procedures involving manipulation of the prostate.
- Follow these package insert instructions as well as the specimen collection tube manufacturer's instructions for specimen collection and preparation for analysis. Refer to the specimen collection tube manufacturer's instructions for centrifugation time and speed.
- Insufficient processing of sample, or disruption of the sample during transportation may cause depressed results.
- For optimal results, serum specimens should be free of fibrin, red blood cells, or other particulate matter. Centrifuge specimens containing fibrin, red blood cells, or particulate matter prior to use to ensure consistency in the results.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy may exhibit increased clotting time. If specimens are centrifuged before a complete clot forms, the presence of fibrin or particulate matter may cause erroneous results. Centrifuge specimens containing fibrin, red blood cells, or particulate matter. **Note that interfering levels of fibrin may be present in samples that do not have obvious or visible particulate matter.**
- If proper specimen collection and preparation cannot be verified, or if samples have been disrupted due to transportation or sample handling, an additional centrifugation step is recommended. Centrifugation conditions should be sufficient to remove particulate matter. Aliquots poured versus pipetted from specimen tube types that do not include serum separators are at higher risk of including particulates and generating depressed results.
- Failure to follow these instructions may result in depressed specimen results.

- Specimens may be stored for up to 24 hours at 2-8°C prior to being tested. If testing will be delayed more than 24 hours, specimens should be removed from the clot or serum separator and stored frozen at -20°C or colder.<sup>20,21</sup>
- **NOTE: Samples which may be tested for free PSA should be removed from the clot within 3 hours.**
- The ARCHITECT *i* System does not provide the capability to verify specimen type. It is the responsibility of the operator to verify the correct specimen type is used in the ARCHITECT Total PSA assay.
- Use caution when handling patient specimens to prevent cross contamination. Use of disposable pipettes or pipette tips is recommended.
- Do not use grossly hemolyzed specimens.
- **For optimal results, inspect all samples for bubbles. Remove bubbles with an applicator stick prior to analysis. Use a new applicator stick for each sample to prevent cross contamination.**
- Multiple freeze-thaw cycles of specimens should be avoided. Specimens must be mixed THOROUGHLY after thawing, by vortexing. Thawed samples containing red blood cells or particulate matter, **or which are hazy or cloudy in appearance** must be centrifuged prior to use to ensure consistency in the results.
- Specimens with obvious microbial contamination should not be used.
- When shipped, specimens must be packaged and labeled in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances. Specimens that will not be assayed within 24 hours should be stored/shipped frozen. Prior to shipment, it is recommended that specimens be removed from the clot or serum separator.
- ARCHITECT Total PSA Calibrators and Controls should be mixed by gentle inversion prior to use.

## PROCEDURE

### Materials Provided

- 7K70 ARCHITECT Total PSA Reagent Kit

### Materials Required but not Provided

- ARCHITECT *i* System
- ARCHITECT *i* Assay CD-ROM
- 7K70-01 ARCHITECT Total PSA Calibrators
- 7D82-50 ARCHITECT *i* **MULTI-ASSAY MANUAL DILUENT**
- ARCHITECT *i* **PRE-TRIGGER SOLUTION**
- ARCHITECT *i* **TRIGGER SOLUTION**
- ARCHITECT *i* **WASH BUFFER**
- ARCHITECT *i* **REACTION VESSELS**
- ARCHITECT *i* **SAMPLE CUPS**
- ARCHITECT *i* **SEPTUMS**
- ARCHITECT *i* **REPLACEMENT CAPS**
- Pipettes or pipette tips (optional) to deliver the volumes specified on the patient or control order screen.
- For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

### Materials Available but not Provided

- 7K70-10 ARCHITECT Total PSA Controls

## Assay Procedure

- Before loading the ARCHITECT Total PSA Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that have settled during shipment:
  - Invert the microparticle bottle 30 times.
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - Once the microparticles have been resuspended, remove and discard the cap. Wearing clean gloves, remove a septum from the bag. Squeeze the septum in half to confirm that the slits are open. Carefully snap the septum onto the top of the bottle.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
- Order tests.
- Load the ARCHITECT Total PSA Reagent Kit on the ARCHITECT *i* System. Verify that all necessary assay reagents are present. Ensure that septums are present on all reagent bottles.
- The minimum sample cup volume is calculated by the system and is printed on the Orderlist report. No more than 10 replicates may be sampled from the same sample cup. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.
  - Priority: 100 µL for the first Total PSA test plus 50 µL for each additional Total PSA test from the same sample cup
  - ≤ 3 hours onboard: 150 µL for the first Total PSA test plus 50 µL for each additional Total PSA test from the same sample cup
  - > 3 hours onboard: additional sample volume is required. Refer to the ARCHITECT System Operations Manual, Section 5 for information on sample evaporation and volumes.
- Press RUN. The ARCHITECT *i* System performs the following function:
  - Moves the sample to the aspiration point
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
  - To obtain the recommended volume requirements for the ARCHITECT Total PSA Calibrators and Controls, hold the bottles **vertically** and dispense 7 drops of each calibrator or 4 drops of each control into each respective sample cup.
- Load samples
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN. The ARCHITECT *i* System performs the following functions:
  - Moves the sample carrier to the aspiration point
  - Loads a reaction vessel (RV) into the process path
  - Aspirates and transfers sample into the RV
  - Advances the RV one position and transfers microparticles into the RV
  - Mixes, incubates and washes the reaction mixture
  - Adds conjugate to the RV
  - Mixes, incubates and washes the reaction mixture
  - Adds Pre-Trigger and Trigger Solutions
  - Measures chemiluminescent emission to determine the quantity of total PSA in the sample
  - Aspirates contents of RV to liquid waste and unloads RV to solid waste
  - Calculates the result
- For information on ordering patient specimens and controls, and general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- For optimal performance, it is important to follow the routine maintenance procedures defined in the ARCHITECT System Operations Manual, Section 9. If your laboratory requires more frequent maintenance, follow those procedures.

### Specimen Dilution Procedures

Specimens with a total PSA value exceeding 100 ng/mL are flagged with the code ">100.000" and may be diluted using either the Automated Dilution Protocol or the Manual Dilution Procedure.

- If using the Automated Dilution Protocol, the system performs a 1:10 dilution of the specimen and automatically calculates the concentration of the sample before dilution and reports the result.
- Dilutions other than 1:10 should be done manually.
  - For example, to perform a 1:20 dilution, add 50 µL of the patient specimen to 950 µL of ARCHITECT *i* Multi-Assay Manual Diluent (7D82-50).
  - The operator must enter the dilution factor in the Patient or Control order screen. All assays selected for that order will be diluted. The system will use this dilution factor to automatically calculate the concentration of the sample before dilution and report the result. The dilution should be performed so that the diluted result reads greater than 0.4 ng/mL.
- For detailed information on ordering dilutions, refer to the ARCHITECT System Operations Manual, Section 5.

### Calibration

- To perform an ARCHITECT Total PSA calibration, test calibrators 1 and 2 in duplicate. A single sample of all levels of total PSA controls must be tested to evaluate the assay calibration. Ensure that assay control values are within the concentration ranges specified in the control package insert. Calibrators should be priority loaded.
- Calibration range: 0 - 50 ng/mL.
- The assay protocol allows for the range to be extended to 100 ng/mL.
- Once an ARCHITECT Total PSA calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used.
  - Controls are out of range.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

### QUALITY CONTROL PROCEDURES

The recommended control requirement for the ARCHITECT Total PSA assay is a single sample of all control levels tested once every 24 hours each day of use. If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow your laboratory-specific procedures. Ensure that assay control values are within the concentration ranges specified in the package insert.

### Verification of Assay Claims

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B. The ARCHITECT Total PSA assay belongs to method group 1.

### RESULTS

The ARCHITECT Total PSA assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y weighted) to generate a calibration curve.

### Alternate Result Units

- The default result unit for the ARCHITECT Total PSA assay is ng/mL. When the alternate result unit, µg/L, is selected, the conversion factor used by the system is 1.0.
- Conversion Formula: (Concentration in ng/mL) x (1.0) = µg/L

### Flags

- Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

### LIMITATIONS OF THE PROCEDURE

- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies.<sup>22,23</sup> ARCHITECT Total PSA reagents contain a component that reduces the effect of HAMA reactive specimens. Additional clinical or diagnostic information may be required to determine patient status.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.<sup>24</sup> Patients routinely exposed to animals or animal serum products can be prone to this interference and anomalous values may be observed. Additional information may be required for diagnosis.
- The concentration of PSA in a given specimen, determined with assays from different manufacturers, can vary due to differences in assay methods, calibration, and reagent specificity.<sup>1,25,26</sup>
- Quality control samples may be produced by introducing seminal fluid PSA into a human serum matrix. PSA in serum and seminal fluid may exist in different forms. The concentration of PSA in these controls, determined with assays from different manufacturers, can vary due to differences in assay methods, calibration, reagent specificity, and the form of PSA that is present; therefore, it is important to use assay-specific values to evaluate control results.
- Hormonal therapy may affect PSA expression; therefore, a low PSA level after any treatment that includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.<sup>27</sup>
- In most instances, specimens obtained from patients immediately following digital rectal examination show no clinically significant increases in PSA levels.<sup>28</sup> However, prostatic massage, ultrasonography, and needle biopsy may cause clinically significant elevations.<sup>29</sup> PSA levels may also be increased following ejaculation.<sup>30</sup>
- Active free PSA in the serum at the time of blood sampling can continue to complex with serum protease inhibitors, especially alpha-2-macroglobulin, resulting in a rapid decrease in PSA levels of the active form of free PSA.<sup>31</sup>
- Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of prostate cancer. Elevated concentrations of PSA may be observed in the serum of patients with benign prostatic hyperplasia or other nonmalignant disorders as well as in prostate cancer. Furthermore, low PSA concentrations are not always indicative of the absence of cancer. The PSA value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures such as DRE. Some early cases of prostate cancer will not be detected by PSA testing; the same is true for DRE. Prostatic biopsy is required for the diagnosis of cancer.

### EXPECTED VALUES FOR DETECTION OF PROSTATE CANCER

[Values developed for the ARCHITECT *i*2000 analyzer.]

A prospective study was conducted at seven clinical sites to demonstrate the usefulness of PSA in the detection of prostate cancer when used in conjunction with DRE. All clinical data presented supporting the detection claim were generated using the ARCHITECT *i* System and ARCHITECT Total PSA assay reagents. A total of 531 men 50 years of age or older participated in the study. All subjects were biopsied based on an initial elevated PSA value and/or suspicious DRE result. A distribution of the ARCHITECT Total PSA results is presented in the following table:

### Distribution of Results from ARCHITECT Total PSA

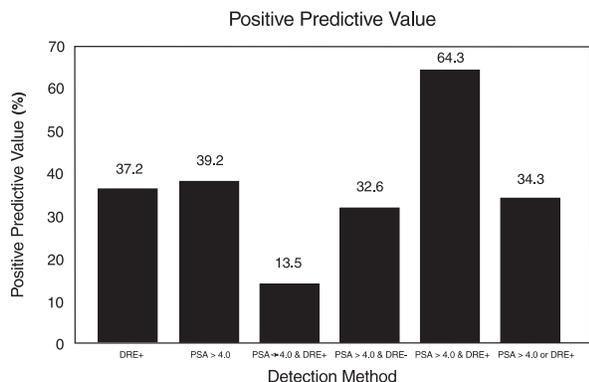
	PSA ≤ 4.0	PSA > 4.0	Total
DRE <sup>b</sup>	32 6.0%	319 60.1%	351 66.1%
DRE <sup>a</sup>	96 18.1%	84 15.8%	180 33.9%
Total	128 24.1%	403 75.9%	531 100.0%

Note: 499 patients tested positive by DRE and/or PSA.

<sup>a</sup> DRE+: Digital Rectal Examination (Suspicious for cancer)

<sup>b</sup> DRE-: Digital Rectal Examination (Not suspicious for cancer)

The positive predictive values for various combinations of DRE and PSA are presented graphically in the figure below and table below.



### Positive Predictive Values

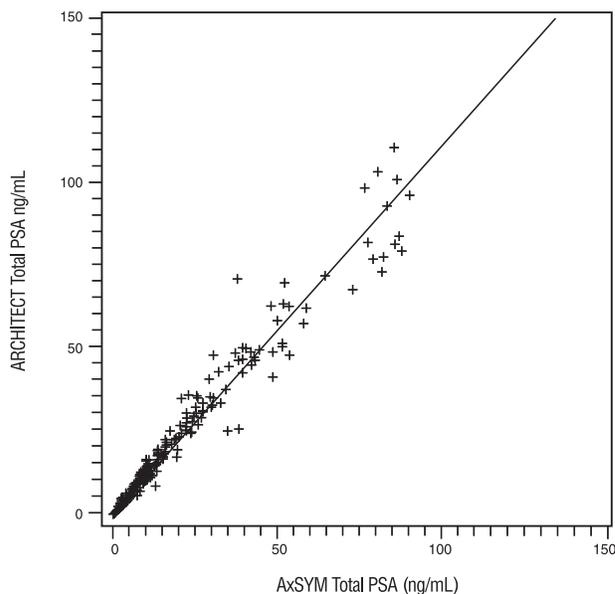
Detection Method	Positive Predictive Value (%)*	Number of Subjects with Cancer/ Number of Subjects Suspicious for Cancer
DRE+	37.2 (30.1-44.7)	67/180
PSA > 4.0	39.2 (34.4-44.2)	158/403
PSA ≤ 4.0 and DRE+	13.5 (7.4-22.0)	13/96
PSA > 4.0 and DRE-	32.6 (27.5-38.0)	104/319
PSA > 4.0 and DRE+	64.3 (53.1-74.4)	54/84
PSA > 4.0 or DRE+	34.3 (30.1-38.6)	171/499

\* 95% Confidence Interval (Lower Limit - Upper Limit)

Cancers were detected in 177 of the 531 subjects. The overall cancer detection rate was 96.6% (171/177) when at least one test was suspicious, 30.5% (54/177) when both tests were suspicious, 58.8% (104/177) for PSA alone, and 7.3% (13/177) for DRE alone.

### CORRELATION

To demonstrate that the ARCHITECT Total PSA assay results are comparable to the results from the AxSYM Total PSA assay, a least squares linear regression analysis was performed comparing the PSA values from both assays for 1,798 clinical specimens. The analysis yielded a correlation coefficient of 0.987, a slope of 1.06, and a Y-intercept of 0.344 for the specimens covering the range up to 100 ng/mL, as shown in the following figure:



These results demonstrate that the ARCHITECT Total PSA assay yields equivalent results compared to those obtained using the AxSYM Total PSA assay.

Serum PSA concentrations, regardless of the value, should not be interpreted as definitive evidence for the presence or absence of prostate cancer. In addition, PSA testing should be done in conjunction with DRE because PSA and DRE together detected the greatest number of cancers. Prostatic biopsy is required for the diagnosis of cancer.

### EXPECTED VALUES

[Values developed for the ARCHITECT i2000 analyzer.]

The distribution of ARCHITECT Total PSA values determined in 2,287 specimens is shown in the following table.

### Distribution of ARCHITECT Total PSA Values

		Number of Subjects	Percent (%)				
			0-4.0 (ng/mL)	>4.0-10 (ng/mL)	>10-30 (ng/mL)	>30-60 (ng/mL)	>60 (ng/mL)
Apparently Healthy Subjects	Females	296	100.0	0.0	0.0	0.0	0.0
	Males Ages 40 to 49	99	100.0	0.0	0.0	0.0	0.0
	Males Ages 50 to 59	120	97.5	2.5	0.0	0.0	0.0
	Males Ages 60 to 69	123	93.5	6.5	0.0	0.0	0.0
	Males Ages 70 to 79	124	91.9	7.3	0.8	0.0	0.0
	Non-malignant Disease						
BPH	352	42.6	42.3	12.8	1.1	1.1	
Cirrhosis	89	94.4	3.4	1.1	0.0	1.1	
Genitourinary	151	90.7	7.3	1.3	0.7	0.0	
Prostatitis	142	46.5	40.1	11.3	1.4	0.7	
Renal	140	90.0	5.7	2.9	1.4	0.0	
Malignant Disease	Prostate Stage A	94	46.8	30.9	17.0	1.1	4.3
	Prostate Stage B	166	30.1	44.0	23.5	0.6	1.8
	Prostate Stage C	141	26.2	22.7	29.1	12.8	9.2
	Prostate Stage D	95	15.8	12.6	32.6	10.5	28.4
	Genitourinary	155	92.9	3.9	1.9	0.6	0.6

In this study, 95.5% of the specimens from apparently healthy male subjects (n=466) had values of 4.0 ng/mL or less.

It is recommended that each laboratory establish its own expected reference range for the population of interest.

The malignant disease portion of the distribution table is derived primarily from carcinoma patients representing both active (clinical evidence of disease progression) and inactive (no clinical evidence of disease progression) disease states. When changing PSA assay methods in the course of monitoring a patient, additional sequential testing should be carried out to confirm baseline values.

## SPECIFIC PERFORMANCE CHARACTERISTICS

### Precision<sup>a</sup>

Architect Total PSA assay precision is  $\leq 8\%$ . Precision was determined as described in the National Committee for Clinical Laboratory Standards (NCCLS) Protocol EP5-A.<sup>32</sup> Six samples, consisting of three serum based panels and three total PSA controls, were assayed using three instruments in replicates of two at two separate times per day for twenty days (n=80 for each sample), using a single lot of reagents and a single calibration. Data from this study are summarized in the following table.\*

**Reproducibility of ARCHITECT Total PSA**

Sample	Instru- ment	Mean		Total		
		Total PSA (ng/mL)	Within Run SD	SD	%CV	
Low Control	1	0.498	0.0087	1.8	0.0109	2.2
	2	0.511	0.0203	4.0	0.0237	4.6
	3	0.504	0.0131	2.6	0.0194	3.9
Medium Control	1	4.030	0.1036	2.6	0.1107	2.7
	2	4.104	0.1517	3.7	0.1836	4.5
	3	4.101	0.1218	3.0	0.1714	4.2
High Control	1	24.565	0.7187	2.9	0.8121	3.3
	2	24.558	1.0663	4.3	1.1691	4.8
	3	24.210	0.7742	3.2	1.5808	6.5
Panel 1	1	4.130	0.1129	2.7	0.3230	7.8
	2	4.109	0.1479	3.6	0.1665	4.1
	3	4.139	0.1042	2.5	0.2099	5.1
Panel 2	1	49.191	1.6925	3.4	1.8405	3.7
	2	46.943	2.0034	4.3	2.6271	5.6
	3	47.770	1.5792	3.3	3.4934	7.3
Panel 3	1	66.952	2.0804	3.1	4.1157	6.1
	2	62.631	3.1461	5.0	3.2269	5.2
	3	61.632	1.5634	2.5	5.5307	9.0

\* Representative performance data are shown. Results obtained at individual laboratories may vary.

### MEASUREMENT RANGE

The measurement (reportable) range of the ARCHITECT Total PSA assay is 0.008 ng/mL to 100 ng/mL, as defined by the analytical sensitivity lower limit and the upper limit of the extended calibration range. For patient specimens with a Total PSA assay value exceeding 100 ng/mL refer to the sample dilution procedures section of this package insert.

### Recovery<sup>a</sup>

Known concentrations of serum PSA were added to ten normal human serum samples. Each sample was spiked at a low and a high level. The concentration of total PSA was determined using the ARCHITECT Total PSA assay and the resulting percent recovery was calculated. The mean recovery was 95.9% with values ranging from 89.8% to 99.6%.

### Sensitivity<sup>a</sup>

#### Functional

Functional sensitivity is defined as the lowest concentration that can be measured with an inter-assay coefficient of variation (CV) less than or equal to 20%. The calculated %CV for one reagent lot from all sites was plotted against the mean concentration of each panel. A parametric curve was fitted through the data, and the functional sensitivity was determined to be less than 0.05 ng/mL, which corresponded to less than 20% CV on the fitted curve.

### Analytical

The analytical sensitivity of the ARCHITECT Total PSA assay was calculated to be less than 0.008 ng/mL. This sensitivity is defined as the concentration at two standard deviations above the mean RLU for the ARCHITECT Total PSA MasterCheck Level 0 and represents the lowest measurable concentration of total PSA that can be distinguished from zero.

### Analytical Specificity<sup>a</sup>

The analytical specificity of the ARCHITECT Total PSA assay was determined by testing sera containing the following compounds. These compounds showed less than or equal to 10% interference in the ARCHITECT Total PSA assay at the levels indicated.

### INTERFERING SUBSTANCES

Test Compound	Concentration
Bilirubin	20 mg/dL
Hemoglobin	500 mg/dL
Total Protein	2.0 g/dL & 12.0 g/dL
Prostatic Acid Phosphatase	1000 ng/mL
Triglycerides	3000 mg/dL
Hytrin	10 µg/mL
Proscar	25 µg/mL
Flomax	1 µg/mL

### CHEMOTHERAPEUTIC AGENTS

Test Compound	Concentration
Cyclophosphamide	700 µg/mL
Diethylstilbestrol	2 µg/mL
Doxorubicin-HCl	16 µg/mL
Estramustine Phosphate	200 µg/mL
Flutamide	10 µg/mL
Goserelin Acetate	100 ng/mL
Lupron	100 µg/mL
Megestrol Acetate	90 µg/mL
Methotrexate	30 µg/mL

### Carryover<sup>a</sup>

No detectable carryover (less than 0.5 PPM) was observed when a sample containing 16,791 ng/mL of PSA was assayed. However, under circumstances where a PSA assay is performed following >230 tests of ARCHITECT B12, carryover of PSA due to protein build up on the sample pipettor probe may exceed 0.5 PPM.

To maintain optimum system performance and reduce the potential of carryover due to protein build up on the sample pipettor probe, it is important to follow the routine maintenance procedures defined in Section 9 of the ARCHITECT System Operations Manual, or, for troubleshooting information refer to the ARCHITECT System Operations Manual, Section 10.

### High Dose Hook<sup>a</sup>

High dose hook is a phenomenon whereby very high level specimens may read within the dynamic range of the assay. For the ARCHITECT Total PSA assay, no high dose hook effect was observed when samples containing up to approximately 48,000 ng/mL of PSA were assayed.

<sup>a</sup> [Values developed for the ARCHITECT i2000 analyzer.]

### Accuracy by Correlation

The ARCHITECT Total PSA assay reagents were compared on the ARCHITECT i2000/ i2000<sub>SR</sub> and the ARCHITECT i1000<sub>SR</sub> platforms. The results of specimen testing are shown below.

Statistical Method	Number of Observations	Intercept	Slope	Correlation Coefficient
Least Squares	151	-0.06	1.05	0.996
Passing-Bablok*	151	-0.03	1.04	0.996

\* A linear regression method with no special assumptions regarding the distribution of the samples and the measurement errors.<sup>35</sup>

In this evaluation, serum specimens tested ranged from 0.046 ng/mL to 81.710 ng/mL, by the i1000<sub>SR</sub> platform.

## BIBLIOGRAPHY

1. McCormack RT, Rittenhouse HG, Finlay JA, *et al.* Molecular Forms of Prostate-Specific Antigen and the Human Kallikrein Gene Family: A New Era. *Urology* 1995;45:729-44.
2. Graves HCB. Nonprostatic Sources of Prostate-Specific Antigen: A Steroid Hormone-Dependent Phenomenon? *Clin Chem* 1995;41:7-9.
3. Kuriyama M, Wang MC, Papsidero LD, *et al.* Quantitation of Prostate-Specific Antigen in Serum by a Sensitive Enzyme Immunoassay. *Cancer Res* 1980;40:4658-62.
4. Oesterling JE. Prostate Specific Antigen: A Critical Assessment of the Most Useful Tumor Marker for Adenocarcinoma of the Prostate. *J Urol* 1991;145:907-23.
5. Kantoff PW, Talcott JA. The Prostate Specific Antigen. Its Use as a Tumor Marker for Prostate Cancer *Hematol Oncol Clin N Amer* 1994;8:555-72.
6. Partin AW, Oesterling JE. The Clinical Usefulness of Prostate Specific Antigen: Update 1994. *J Urol* 1994;152:1358-68.
7. Bunting S. A Guide to the Interpretation of Serum Prostate Specific Antigen Levels. *Clin Biochem* 1995;28:221-41.
8. Christensson A, Laurell C-B, Lilja H. Enzymatic Activity of Prostate-Specific Antigen and its Reactions with Extracellular Serine Proteinase Inhibitors. *Eur J Biochem* 1990;194:755-63.
9. Stenman U-H, Leinonen J, Alfthan H, *et al.* A Complex Between Prostate-Specific Antigen and  $\alpha$ 1-Antichymotrypsin is the Major Form of Prostate-Specific Antigen in Serum of Patients with Prostatic Cancer: Assay of the Complex Improves Clinical Sensitivity for Cancer. *Cancer Res* 1991;51:222-6.
10. Parker SL, Tong T, Bolden S, *et al.* Cancer Statistics, 1997. *CA Cancer J Clin* 1997;47:5-27.
11. Gerber GS, Chodak GW. Routine Screening for Cancer of the Prostate (Review). *J Natl Ca Inst* 1991;83:329-35.
12. Lee F, Littrup PJ, Torp-Pedersen ST, *et al.* Prostate Cancer: Comparison of Transrectal US and Digital Rectal Examination for Screening. *Radiology* 1988;168:389-94.
13. Cooner WH, Mosely BR, Rutherford CL, *et al.* Prostate Cancer Detection in a Clinical Urological Practice by Ultrasonography, Digital Rectal Examination and Prostate Specific Antigen. *J Urol* 1990;143:1146-54.
14. Catalona WJ, Richie JP, Ahmann FR, *et al.* Comparison of Digital Rectal Examination and Serum Prostate Specific Antigen in the Early Detection of Prostate Cancer: Results of a Multicenter Clinical Trial of 6,630 Men. *J Urol* 1994;151:1283-90.
15. Crawford ED, DeAntoni EP, Etzioni R, *et al.* Serum Prostate-Specific Antigen and Digital Rectum Examination for Early Detection of Prostate Cancer in a National Community-Based Program. *Urology* 1996;47:863-9.
16. American Urological Association - Early Detection of Prostate Cancer Policy Statement. Board of Directors Minutes 1992.
17. Mettlin C, Jones G, Averette H, *et al.* Defining and Updating the American Cancer Society Guidelines for the Cancer-Related Checkup: Prostate and Endometrial Cancers. *CA-A Cancer Journal for Clinicians* 1993;43:42-6.
18. Walther PJ. Prostate Cancer Screening. Why the Controversy? *Surg Oncol Clin NA* 1995;4:315-34.
19. Jacobson JO. Can Screening for Early-Stage Prostate Cancer be Rationalized? *Hematol Oncol Clinics NA* 1996;10:549-64.
20. Woodrum D, French C, Shamel LB. Stability of Free Prostate-Specific Antigen in Serum Samples Under a Variety of Sample Collection and Sample Storage Conditions. *Urology (Suppl. 6A)* 1996;48:33-9.
21. Piironen T, Pettersson K, Suonpää M, *et al.* In Vitro Stability of Free Prostate-Specific Antigen (PSA) and Prostate-Specific Antigen (PSA) Complexed to  $\alpha$ 1-Antichymotrypsin in Blood Samples. *Urology (Suppl. 6A)* 1996;48:81-6.
22. Primus FJ, Kelley EA, Hansen HJ, *et al.* "Sandwich"-Type Immunoassay of Carcinoembryonic Antigen in Patients Receiving Murine Monoclonal Antibodies for Diagnosis and Therapy. *Clin Chem* 1988;34:261-4.
23. Schroff RW, Foon KA, Beatty SM, *et al.* Human Anti-Murine Immunoglobulin Responses in Patients Receiving Monoclonal Antibody Therapy. *Cancer Res* 1985;45:879-85.
24. Boscato LM, Stuart MC. Heterophilic Antibodies: A Problem for All Immunoassays. *Clin Chem* 1988;34(1):27-33.
25. Chan DW, Bruzek DJ, Oesterling JE, *et al.* Prostate-Specific Antigen as a Marker for Prostatic Cancer: A Monoclonal and a Polyclonal Immunoassay Compared. *Clin Chem* 1987;33:1916-20.
26. Hortin GL, Bahnson RR, Daft M, *et al.* Differences in Values Obtained with 2 Assays of Prostate Specific Antigen. *J Urol* 1988;139:762-5.
27. Morgan WR, Zincke H, Rainwater LM, *et al.* Prostate Specific Antigen Values after Radical Retropubic Prostatectomy for Adenocarcinoma of the Prostate: Impact of Adjuvant Treatment (Hormonal and Radiation). *J Urol* 1991;145:319-23.
28. Chybowski FM, Bergstralh EJ, Oesterling JE. The Effect of Digital Rectal Examination on the Serum Prostate Specific Antigen Levels. *J Urol* 1992;148:83-6.
29. Yuan JJ, Coplen DE, Petros JA, *et al.* Effects of Rectal Examination, Prostatic Massage, Ultrasonography and Needle Biopsy on Serum Prostate Specific Antigen Levels. *J Urol* 1992;147:810-4.
30. Tchetgen M-B, Song JT, Strawderman M, *et al.* Ejaculation Increases the Serum Prostate-Specific Antigen Concentration. *Urology* 1996;47:511-6.
31. Stenman U-H, Leinonen J, Zhang W-M. Problems in the Determination of Prostate Specific Antigen. *Eur J Clin Chem Biochem* 1996;34:735-40.
32. NCCLS. Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline. NCCLS document EP5-A (ISBN 1-56238-368-X). NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, USA, 1999.
33. Watt KWK, Lee P-J, M'Timkulu T, *et al.* Human Prostate-Specific Antigen: Structural and Functional Similarity with Serine Proteases. *Proc Natl Acad Sci USA* 1986;83:3166-70.
34. Belanger A, van Halbeek H, Graves HCB, *et al.* Molecular Mass and Carbohydrate Structure of Prostate Specific Antigen: Studies for Establishment of an International PSA Standard. *Prostate* 1995;27:187-97.
35. Passing H, Bablok W. A New Biometrical Procedure for Testing the Equality of Measurements from Two Different Analytical Methods. *J Clin Chem. Clin Biochem* 1983;21:709-20.

All trademarks are properties of their respective owners.

For additional product information, please contact your local customer service organization.



Abbott Ireland  
Diagnostics Division  
Finisklin Business Park  
Sligo  
Ireland  
+ 353-71-9171712

June 2007

© 2006, 2007 Abbott / ARCHITECT Total PSA