IMMULITE

32

Third Generation PSA

DPC®

IMMULITE® Third Generation PSA

English

Intended Use: For in vitro diagnostic use with the IMMULITE Analyzer – for the quantitative measurement prostate-specific antigen (PSA) in human serum, 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. This assay is further indicated as an adjunctive test to aid in the management of prostate cancer patients.

Catalog Number: LKUP1 (100 tests), LKUP5 (500 tests)

Test Code: sPS **Color:** Red

Caution: In the United States, Federal law restricts this device to sale by or on the order of a physician.

> The concentration of PSA in a given specimen determined with different assays 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 assay used. Values obtained with different PSA assays cannot be used interchangeably. Before changing assays, the laboratory must confirm the baseline values for patients being serially monitored.

Summary and Explanation

Prostate specific antigen (PSA), first identified and characterized by Wang, et al in 1979, is a glycoprotein monomer with protease activity.[1,2] PSA has an isoelectric point of approximately 6.9 and a molecular weight of approximately 33-34 kilodaltons; it contains approximately 10% carbohydrate by weight.[1,2] The amino acid sequence of PSA was reported,[3] and the gene has been cloned.[4] PSA is biochemically and immunologically distinct from PAP and does not exhibit enzymatic phosphatase activity.[5]

PSA is localized in the cytoplasm of prostatic ductal epithelium and in secretions of the ductal lumina.[6] Because PSA is a secretory protein of the prostate, it can be recovered and purified both from prostatic tissue and from seminal plasma.[7] PSA has been found to be exclusively associated with prostate tissue;[17] and elevated serum PSA has been found in patients with prostate cancer, benign prostatic hypertrophy, and inflammatory conditions of other adjacent genitourinary tissues, but not in healthy men, men with nonprostatic carcinoma, healthy women or women with cancer.[5,8]

Serum PSA alone is not suitable as a screen for prostate cancer because elevated PSA concentrations are also observed in patients with benign prostatic hypertrophy (BPH)[6]; nor is it recommended as a guide in disease staging. The combination of PSA measurement and rectal examination with ultrasonography in the event of abnormal findings may provide a better method of detecting prostate cancer than rectal examination alone. Measurement of PSA offers several advantages over digital rectal examination or ultrasonography in detecting prostate cancer: the result is objective, quantitative, and obtained independent of the examiner's skill, and the procedure is more acceptable to patients than other procedures.[9]

Determinations of total immunoreactive PSA can be useful in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[10,11] Persistent elevation of PSA following treatment or an increase in the pretreatment PSA concentrations is indicative of recurrent or residual disease.[12–16] Hence, PSA is widely accepted as an aid in the management of prostate cancer patients.[12–16]

The American Cancer Society has recommended that both the PSA blood test and digital rectal examination be offered annually, beginning at age 50, to men who have at least a 10-year life expectancy, as well as younger men who are at high risk. Patients should be given information regarding potential risks and benefits of early detection and treatment. Men in high risks groups, such as those with two or more affected first-degree relatives may consider screening at a younger age, perhaps 45.[27]

Principle of the Procedure

Sequential Immunometric Assay.

Incubation Cycles: 2 × 30 minutes.

Specimen Collection

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting for up to 3 weeks using conventional PSA assays.[18] Studies have shown conflicting results on the existence of an effect of digital rectal examination on PSA level using conventional PSA assays.[19,20] Therefore, when possible, obtain PSA samples before digital rectal examination.

Centrifuging serum samples before a complete clot forms may result in the presence of fibrin. To prevent erroneous results due to the presence of fibrin, ensure that complete clot formation has taken place prior to centrifugation of samples. Some samples, particularly those from patients receiving anticoagulant therapy, may require increased clotting time.

Volume Required: 50 µL serum. (Sample cup must contain at least 100 µL more than the total volume required.)

Storage: 24 hours at 2–8°C.[21] Store at –18°C or colder if samples are to be assayed after extended storage.

Warnings and Precautions

For *in vitro* diagnostic use.

Reagents: Store at 2–8°C. Dispose of in accordance with applicable laws.

Follow universal precautions, and handle all components as if capable of transmitting infectious agents. Source materials derived from human blood were tested and found nonreactive for syphilis; for antibodies to HIV 1 and 2; for hepatitis B surface antigen; and for antibodies to hepatitis C.

Sodium azide, at concentrations less than 0.1 g/dL, has been added as a preservative. On disposal, flush with large volumes of water to prevent the buildup of potentially explosive metal azides in lead and copper plumbing.

Chemiluminescent Substrate: Avoid contamination and exposure to direct sunlight. (See insert.)

Water: Use distilled or deionized water.

Materials Supplied

Components are a matched set. The barcode labels are needed for the assay.

Third Generation PSA Test Units (LUP1)
Each barcode-labeled unit contains one bead coated with monoclonal murine anti-PSA antibody. Stable at 2–8°C until expiration date.
LKUP1: 100 units. **LKUP5:** 500 units.

Allow the Test Unit bags to come to room temperature before opening. Open by cutting along the top edge, leaving the ziplock ridge intact. Reseal the bags to protect from moisture.

Third Generation PSA Reagent Wedges (LUPA, LUPB)
With barcodes. **LUPA:** 6.5 mL protein buffer/serum matrix, with preservative. **LUPB:** 6.5 mL alkaline phosphatase (bovine calf intestine) conjugated to polyclonal goat anti-PSA antibody in buffer, with preservative. Store capped and refrigerated: stable at 2–8°C until expiration date. Recommended usage is within 30 days after opening when stored as indicated.
LKUP1: 1 set. **LKUP5:** 5 sets.

Third Generation PSA Adjustors (LUPL, LUPH)
Two vials (Low and High), 3 mL each, of PSA in a serum matrix, with preservative. Stable at 2–8°C for 30 days after opening, or for longer storage (aliquotted) at –20°C.
LKUP1: 1 set. **LKUP5:** 2 sets.

Kit Components Supplied Separately

PSA Sample Diluent (LPSZ)
25 mL PSA-free nonhuman serum/buffer matrix, with preservative, for the dilution of patient samples. Stable at 2–8°C for 30 days after opening, or for longer (aliquotted) at –20°C.

LSUBX: Chemiluminescent Substrate
LPWS2: Probe Wash Module
LKPM : Probe Cleaning Kit
LCHx-y: Sample Cup Holders (barcoded)
LSCP: Sample Cups (disposable)
LSCC: Sample Cup Caps (optional)

TMCO: Tri-level, multi-constituent control
LUPCM: Single-level Third Generation PSA Control Module

Also Required
Sample transfer pipets, distilled or deionized water, controls.

Assay Procedure

See the IMMULITE Operator's Manual for: preparation, setup, dilutions, adjustment, assay and quality control procedures.

Adjustment Interval: 4 weeks.

Quality Control Samples: Use controls or sample pools with at least two levels (low and high) of PSA.

Expected Values in Detection of Prostate Cancer

In two retrospective studies at two clinical sites for prostate cancer detection purposes, samples were collected from 1477 men, aged 50 or older. Of these, 64 (4%) were Asian; 242 (16%) were African American; 1150 (78%) were Caucasian; 7 (<1%) were other and 14 (<1%) provided no ethnic information. 1468 out of 1477 patients also underwent digital rectal examination (DRE). Of these, 88 were biopsied for elevated (> 4.0 ng/mL) PSA and/or suspicious DRE. The following table summarizes these clinical studies.

No. of Subjects (%)	No. of Biopsies (%)	No. of Prostate Cancers	% Positive Biopsies (95% CI)
All Subjects			
1468	88	35	39.8%
PSA > 4.0			
161	64	28	43.8%
11.0%	39.8%		(31.4%-56.7%)
DRE +			
106	31	15	48.4%
7.2%	29.2%		(31.0%-66.9%)
PSA > 4.0 DRE +			
35	16	10	62.5%
2.4%	45.7%		(35.4%-82.2%)
PSA <= 4.0 DRE +			
71	15	5	33.3%
4.8%	21.1%		(14.2%-61.6%)
PSA > 4.0 DRE –			
126	48	18	37.5%
8.6%	38.1%		(24.0%-52.6%)
PSA <= 4.0 DRE –			
1236	9	2	22.2%
84.2%	0.7%		(2.8%-60.6%)

The study demonstrated that PSA testing, when used in conjunction with DRE, was more effective in detecting prostate cancer than DRE alone. PSA determinations detected 51% (18/35) of cancers that DRE did not; PSA elevations greater than 4 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true: a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected 14% (5/35) of cancers that PSA determinations did not.

In the same studies, 1236 participants were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for these asymptomatic subjects in the clinical study who had both a negative PSA and DRE, and therefore, were not biopsied as well as for those subjects who were negative for cancer biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Distribution of PSA Levels	*n*	PSA Median	PSA 95th %ile
All subjects	1236	0.98	3.28
50–59 age group	612	0.81	2.73
60–69 age group	458	1.11	3.45
≥70 age group	168	1.35	3.65

In studies performed at four clinical sites, 2618 samples collected from 1965 patients were tested. Shown below is the distribution of IMMULITE PSA results from this study.

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Female Subjects					
253/253	100%	0%	0%	0%	0%
Healthy					
149/149	100%	0%	0%	0%	0%
Nonmalignant Diseases					
28/28	100%	0%	0%	0%	0%
Malignant Diseases					
76/76	100%	0%	0%	0%	0%
Healthy Male Subjects					
473/473	99.4%	0.6%	0%	0%	0%
Non-Malignant Diseases					
548/548	76.2%	19.3%	3.5%	0.9%	0%
BPH					
333/333	67.9%	25.8%	5.4%	0.9%	0%
Other Prostatic Diseases					
66/66	80.3%	18.2%	1.5%	0%	0%
Other Nonprostatic Diseases					
149/149	93.2%	5.4%	0%	1.3%	0%
Non-Prostatic Malignancies					
312/312	93.0%	6.1%	0.6%	0.3%	0%
Prostate Cancer (single specimens)					
274/274	42.3%	21.2%	13.1%	7.3%	16.1%
Prostate Cancer (serially monitored)					
105/758	54.8%	11.7%	10.7%	7.5%	15.3%

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Stage A					
17/174	64.9%	9.8%	9.2%	3.5%	12.6%
Stage B					
31/200	54.0%	14%	12%	8.5%	11.5%
Stage C					
19/102	56.9%	6.9%	7.8%	8.8%	19.6%
Stage D					
38/282	48.2%	13.1%	11.7%	8.9%	18.0%
Total:					
1965/2618	1962	275	138	83	160

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

Limitations

Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of malignant disease.[8]

Prediction of malignant prostatic disease recurrence should be based on a complete clinical evaluation of the patient, which may also include serial serum PSA determinations.

Samples should be obtained before biopsy, prostatectomy or prostatic massage.[18]

PSA expression may be altered due to hormonal therapy for prostate cancer. Consequently, a low PSA result following hormonal treatment may not adequately reflect the presence of residual or recurrent disease.[25]

This device is not intended to be used for early detection of prostate cancer.

Some individuals have antibodies to mouse protein which can cause interference in immunoassays that employ antibodies derived from mice. In particular, specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). These specimens may show erroneous results in such assays.[22-24] Therefore, results should be interpreted with caution for such patients.

Heterophilic antibodies in human serum can react with the immunoglobulins included in the assay components causing interference with *in vitro* immunoassays. [See Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem 1988:34:27-33.] Samples from patients routinely exposed to animals or animal serum products can demonstrate this type of interference potentially causing an anomalous result. These reagents have been formulated to minimize the risk of interference; however, potential interactions between rare sera and test components can occur. For diagnostic purposes, the results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.

Performance Data

See Tables and Graphs for data *representative* of the assay's performance. Results are expressed in ng/mL. (Unless otherwise noted, all were generated on serum samples collected in tubes without gel barriers or clot-promoting additives.)

Calibration Range: Up to 20 ng/mL

Analytical Sensitivity: 0.003 ng/mL

Functional Sensitivity: 0.01 ng/mL, as demonstrated by the studies summarized in the Precision section. (Functional sensitivity is defined as the lowest concentration that can be measured with an interassay CV of 20%.)

High-dose Hook Effect:
None up to 90,000 ng/mL.

Precision: Samples were assayed in duplicate over the course of 20 days, two runs per day, for a total of 40 runs and 80 replicates. Results are expressed in ng/mL.

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.012	0.0016	13%	0.0017	14%
2	0.026	0.002	7.7%	0.002	7.7%
3	0.50	0.017	3.4%	0.020	4.0%
4	1.0	0.03	3.0%	0.04	4.0%
5	3.8	0.14	3.7%	0.16	4.2%
6	7.6	0.35	4.6%	0.37	4.9%
7	18.1	0.68	4.2%	0.88	5.5%

In a second study,[26] six samples (prepared by adding known quantities of PSA-ACT to bovine serum albumin) were processed in duplicate over the course of 20 days, two runs per day, for a total of 40 runs and 80 replicates. Statistics from this published study are reproduced, with means expressed in ng/mL.

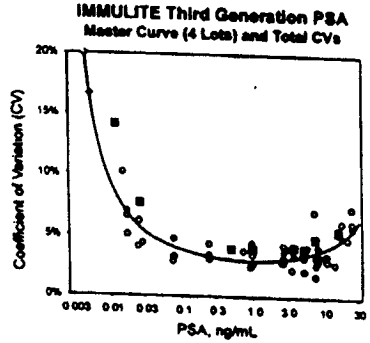
		Within-Run	Total
	Mean	CV	CV
1	0.0030	19.9%	20.9%
2	0.0043	14.4%	14.7%
3	0.029	4.1%	4.5%
4	0.144	4.9%	6.1%
5	0.290	5.4%	5.8%
6	3.066	3.4%	4.8%

In a third study, conducted at Mount Sinai Hospital in Toronto, Canada, nine samples (from post-prostatectomy patients) were assayed with the IMMULITE Third Generation PSA in 13 runs over 10 days. The results are tabulated, with means and SDs expressed in ng/mL.

	Mean	SD	CV
1	0.0038	0.0009	24%
2	0.0062	0.0022	35%
3	0.0100	0.0019	19%
4	0.0145	0.0017	12%
5	0.022	0.0030	14%
6	0.054	0.0053	10%
7	0.220	0.0108	4.9%
8	0.380	0.0133	3.5%
9	1.62	0.0609	3.8%

Precision Profile: The graph shows a within-run (intraassay) precision-dose profile for the IMMULITE Third Generation PSA, based on Master Curve data from four consecutive lots. Each point (open circle) represents the within-run CV, based on dose, for an individual sample, calculated from 10 or 20 replicates. The bowl-shaped contour line traces the approximate path of these points, as anchored by the zero calibrator. (The open diamonds at the upper left represent extrapolations, to 5 and 6 SDs, of the average imprecision at zero dose.)

For reference, the run-to-run (interassay or "total") CVs in the three precision studies tabulated above have been plotted on the same graph, as solid squares.



Linearity: Samples were assayed under various dilutions. Results are expressed in ng/mL.

	Dilution	Observed	Expected	%O/E
1	128 in 128	0.247	—	—
	64 in 128	0.135	0.124	109%
	32 in 128	0.069	0.062	111%
	16 in 128	0.032	0.031	103%
	8 in 128	0.016	0.015	107%
	4 in 128	0.008	0.008	100%
	2 in 128	0.004	0.004	100%
	1 in 128	< 0.003	0.002	—
2	16 in 16	0.498	—	—
	8 in 16	0.243	0.249	98%
	4 in 16	0.127	0.124	102%
	2 in 16	0.061	0.062	98%
	1 in 16	0.033	0.031	106%
3	64 in 64	0.734	—	—
	32 in 64	0.386	0.367	105%
	16 in 64	0.193	0.184	105%
	8 in 64	0.094	0.092	102%
	4 in 16	0.052	0.046	113%
	2 in 64	0.023	0.023	100%
	1 in 16	0.013	0.011	118%
4	16 in 16	1.84	—	—
	8 in 16	0.958	0.920	104%
	4 in 16	0.498	0.460	108%
	2 in 16	0.228	0.230	99%
	1 in 16	0.104	0.115	90%
5	128 in 128	2.23	—	—
	64 in 128	1.15	1.16	99%
	32 in 128	0.551	0.580	95%
	16 in 128	0.267	0.290	92%
	8 in 128	0.130	0.145	90%
	4 in 128	0.067	0.073	92%
	2 in 128	0.031	0.036	86%
	1 in 128	0.016	0.018	89%
6	16 in 16	5.44	—	—
	8 in 16	2.68	2.72	99%
	4 in 16	1.35	1.36	99%
	2 in 16	0.707	0.680	104%
	1 in 16	0.356	0.340	105%
7	16 in 16	18.2	—	—
	8 in 16	9.76	9.10	107%
	4 in 16	4.71	4.55	104%
	2 in 16	2.32	2.28	102%
	1 in 16	1.19	1.14	104%

Recovery: Samples spiked 1 to 19 with three PSA solutions (10.2, 46 and 91 ng/mL) were assayed.

	Solution	Observed	Expected	%O/E
1	—	0.01	—	—
	A	0.56	0.52	108%
	B	2.08	2.31	90%
	C	4.41	4.56	97%
2	—	6.82	—	—
	A	6.81	6.99	97%
	B	8.35	8.78	95%
	C	10.1	11.0	92%
3	—	11.0	—	—
	A	11.2	11.0	102%
	B	13.4	12.8	105%
	C	14.8	15.1	98%
4	—	13.0	—	—
	A	13.4	12.9	104%
	B	16.0	14.7	109%
	C	17.6	17.0	104%

Specificity: The antibody is highly specific for PSA.

Compound	Amount Added	% Cross-reactivity
AFP	10000 ng/mL	ND
CEA	100 ng/mL	ND
Ferritin	10000 ng/mL	ND
HCG	100000 mIU/mL	ND
Lactalbumin	10000000 ng/mL	ND
PAP	1000 ng/mL	ND
Prolactin	200 ng/mL	ND

ND: not detectable.

Bilirubin: No significant effect.

Hemolysis: No significant effect.

Method Comparison: All four of DPC's nonisotopic PSA assays were compared using Deming regression analysis. Samples used were within the working range of the assays. The table below presents the results of the Deming regressions, with columns as Y, and rows as X.

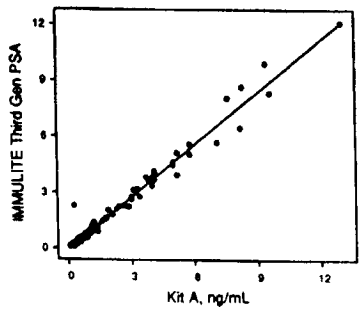
Results of Deming Regressions

		IMMULITE PSA	IMMULITE 2000 PSA	IMMULITE 3rd Generation PSA	IMMULITE 2000 3rd Generation PSA
IMMULITE PSA	*n*		477	474	473
	Slope (95% CI)		0.94 (0.93 to 0.95)	0.99 (0.98 to 1.00)	1.08 (1.07 to 1.10)
	Intercept (95% CI)		−0.11 (−0.15 to −0.07)	0.05 (0.02 to 0.09)	0.06 (0.02 to 0.11)
	Correlation Coefficient		0.992	0.993	0.991
IMMULITE 2000 PSA	*n*	477		474	473
	Slope (95% CI)	1.06 (1.05 to 1.08)		1.06 (1.05 to 1.08)	1.16 (1.14 to 1.17)
	Intercept (95% CI)	0.12 (0.08 to 0.16)		0.15 (0.11 to 0.20)	0.18 (0.14 to 0.23)
	Correlation Coefficient	0.992		0.988	0.990
IMMULITE 3rd Generation PSA	*n*	474	474		472
	Slope (95% CI)	1.01 (1.00 to 1.03)	0.94 (0.93 to 0.96)		1.10 (1.09 to 1.11)
	Intercept (95% CI)	−0.06 (−0.09 to −0.02)	−0.15 (−0.19 to −0.10)		−0.00 (−0.05 to 0.05)
	Correlation Coefficient	0.993	0.988		0.990
IMMULITE 2000 3rd Generation PSA	*n*	473	473	472	
	Slope (95% CI)	0.92 (0.91 to 0.94)	0.86 (0.85 to 0.87)	0.91 (0.90 to 0.92)	
	Intercept (95% CI)	−0.06 (−0.10 to −0.02)	−0.16 (−0.20 to −0.12)	0.00 (− 0.04 to 0.04)	
	Correlation Coefficient	0.991	0.990	0.990	

The assay was also compared to Kit A on 162 samples. (Concentration range: approximately 0.1 to 13 ng/mL.) By linear regression:

(IML 3rd Gen PSA) = 0.93 (Kit A) − 0.04 ng/mL
r = 0.989

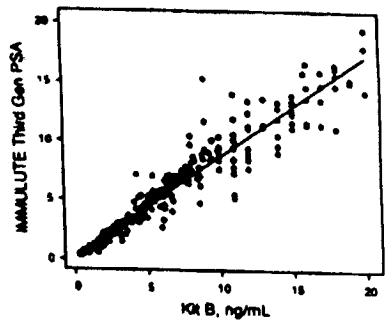
Means:
1.3 ng/mL (IML 3rd Gen PSA)
1.4 ng/mL (Kit A)



The assay was compared to Kit B on 285 samples. (Concentration range: approximately 0.3 to 20 ng/mL.) By linear regression:

(IML 3rd Gen PSA) = 0.85 (Kit B) + 0.16 ng/mL
r = 0.964

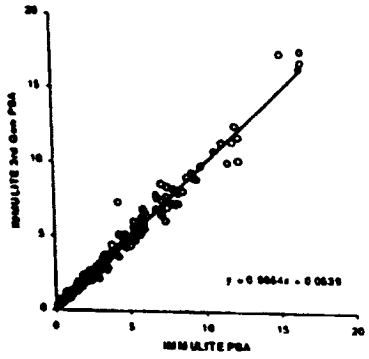
Means:
5.4 ng/mL (IMMULITE)
6.2 ng/mL (Kit B)



The assay was compared to DPC's IMMULITE PSA (LKPS) on 474 samples. (Concentration range: nondetectable to approximately 20 ng/mL.) By linear regression:

(IML 3rd Gen PSA) = 0.99 (IML PSA) + 0.05 ng/mL
r = 0.993

Means:
2.20 ng/mL (IML 3rd Gen PSA)
2.22 ng/mL (IML PSA)



References

1) Wang MC, et al. Purification of a human prostate specific antigen. Invest Urol 1979;17:159-63. 2) Kuriyama M, et al. Prostatic acid phosphatase and prostate- specific antigen in prostate cancer. In: International Advances in Surgical Oncology. New York: Alan R. Liss, Inc., 1982; 5:29-49. 3) Watt WK, Lee PJ, et al. Human prostate-specific antigen: structural and functional similarity with serine proteases. Proc Natl Acad Sci USA 1986;83:3166-70. 4) Lundwall A., Characterization of the gene for prostate specific antigen, a human glandular kallikrein. Biochem Biophys Res Commun 1989;161:1151-9. 5) Papsidero LD, et al. A prostate antigen in sera of prostatic cancer patients. Cancer Res 1980;40:2428-31. 6) Nadji M, et al. Prostatic-specific antigen: an immunohistologic marker for prostatic neoplasms. Cancer 1981;48:1229-32. 7) Wang MC, et al. Prostate antigen of human cancer patients. In: Methods in cancer research. Academic Press, Inc., 1982; 19:179-97. 8) Kuriyama M, et al. Quantitation of prostate-specific antigen in serum by a sensitive enyzme immunoassay. Cancer Res 1980;40:4658-62. 9) Catalona WJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. New Engl J Med 1991;324:1156-61. 10) Brawer MK, Lange PH. Prostate-specific antigen: its role in early detection, staging, and monitoring prostatic carcinoma. J Endocrinol 1989;3:227-36. 11) Killian CS, et al. Prognostic importance of prostate specific antigen for monitoring patients with stages B2 to D1 prostate cancer. Cancer Res 1985;45:886-91. 12) Stamey TA. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. In: Stamey TA, editor. Monographs in Urology. Princeton, NJ: Medical Directions Publishing, 1989; 10(4):50-64. 13) Ercole CJ, et al. Prostatic specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. J Urol 1987;138:1181-4. 14) Chan DW, et al. Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. Clin Chem 1987;33:1916-20. 15) Lange PH, et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol 1989;141:873-9. 16) 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. 17) Iwakiri J, Grandbois K, et al. An analysis of urinary prostate specific antigen before and after radical protatectomy: evidence for secretion of prostate specific antigen by the periurethral glands. J Urol 1993;149:783-6. 18) Stamey TA, Yang N, et al. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909-16. 19) Brawer MK, et al. The effect of digital rectal examination on serum levels of prostatic specific antigen. Arch Pathol Lab Med 1988;112:1110-2. 20) Hughes HR, et al. Serum prostatic specific antigen: in vitro stability and the effect of ultrasound rectal examination in vivo. Ann Clin Biochem 1987;24(Suppl):206-8. 21) Burtis CA, Ashwood ER, editors. Tietz textbook of clincal chemistry. 2nd ed. Philadelphia: W.B. Saunders, 1994. 22) Primus FJ, et al. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine antibody for diagnosis and therapy. Clin Chem 1988;34:261-4. 23) Hansen HJ, et al. Solving the problem of antibody interference in commercial "sandwich"-type immunoassay of carcinoembryonic antigen. Clin Chem 1989;35:146-51. 24) Schroff RJ, et al. Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy. Cancer Res 1985;45:879-85. 25) Morgan WR, 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. 26) Ferguson RA, Yu H, Kalyvas M, Zammit S, Diamandis EP. Ultrasensitive detection of prostate-specific antigen by a time-resolved immunofluorometric assay and the IMMULITE immunochemiluminescent third-generation assay. Clin Chem 1996;42:675-84. 27) Smith RA, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2000; 50(1):34-49.

Technical Assistance

In the United States, contact DPC's Technical Services department.
Tel: 800.372.1782 or 973.927.2828
Fax: 973.927.4101. Outside the United States, contact your National Distributor.

The Quality System of Diagnostic Products Corporation is registered to ISO 9001:1994.

Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, CA 90045-5597

2001-04-30 (ISO 8601)

May 1, 2001

PILKUP – 4

IMMULITE 2000

38.

PSA

DPC

IMMULITE 2000 PSA

English

Intended Use: For in vitro diagnostic use with the IMMULITE 2000 Analyzer – for the quantitative measurement of prostate-specific antigen (PSA) in human serum, 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. This assay is further indicated as an adjunctive test to aid in the management of prostate cancer patients.

Catalog Number: L2KPS2 (200 tests), L2KPS6 (600 tests)

Test Code: PSA **Color:** Brown

Caution: In the United States, Federal law restricts this device to sale by or on the order of a physician.

> The concentration of PSA in a given specimen determined with different assays 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 assay used. Values obtained with different PSA assays cannot be used interchangeably. Before changing assays, the laboratory must confirm the baseline values for patients being serially monitored.

Summary and Explanation

Prostate specific antigen (PSA) first identified and characterized by Wang et al in 1979 is a glycoprotein monomer with protease activity.[1,2] PSA has an isoelectric point of approximately 6.9 and a molecular weight of approximately 33-34 kilodaltons containing approximately 10% carbohydrate by weight.[1,2] Subsequently the amino acid sequence of PSA was reported[3], and the gene has been cloned.[4] PSA is biochemically and immunologically distinct from PAP and does not exhibit enzymatic phosphatase activity.[5]

PSA is localized in the cytoplasm of prostatic ductal epithelium and in secretions of the ductal lumina.[6] Because PSA is a secretory protein of the prostate, it can be recovered and purified both from prostatic tissue and from seminal plasma.[7] PSA has been found to be primarily associated with prostate tissue, and elevated serum PSA has been found in patients with prostate cancer, benign prostatic hypertrophy, and inflammatory conditions of other adjacent genitourinary tissues but not in healthy men, men with nonprostatic carcinoma, healthy women or women with cancer.[5,8]

Serum PSA alone is not suitable as a screen for prostate cancer because elevated PSA concentrations are also observed in patients with benign prostatic hypertrophy (BPH)[6]; nor is it recommended as a guide in disease staging. The combination of PSA measurement and rectal examination with ultrasonography in the event of abnormal findings may provide a better method of detecting prostate cancer than rectal examination alone. Measurement of PSA offers several advantages over digital rectal examination or ultrasonography in detecting prostate cancer: the result is objective, quantitative, and obtained independent of the examiner's skill, and the procedure is more acceptable to patients than other procedures.[9]

PSA determinations can be useful in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[10,11] Persistent elevation of PSA following treatment or an increase in the pretreatment PSA concentrations is indicative of recurrent or residual disease.[12–16] Hence PSA is widely accepted as an aid in the management of prostate cancer patients.[12–16] Concurrent measurement of PAP may contribute additional information.[17]

The American Cancer Society has recommended that both the PSA blood test and digital rectal examination be offered annually, beginning at age 50, to men who have at least a 10-year life expectancy, as well as younger men who are at high risk. Patients should be given information regarding potential risks and benefits of early detection and treatment. Men in high risks groups, such as those with two or more affected first-degree relatives may consider screening at a younger age, perhaps 45.[27]

Principle of the Procedure

Immunometric Assay.

Incubation Cycles: 1 × 30 minutes.

Specimen Collection

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting for up to 3 weeks.[18]

Studies have shown conflicting results on the existence of an effect of digital rectal examination on PSA level.[19,20] Therefore, when possible, obtain PSA samples before digital rectal examination.

Centrifuging serum samples before a complete clot forms may result in the presence of fibrin. To prevent erroneous results due to the presence of fibrin, ensure that complete clot formation has taken place prior to centrifugation of samples. Some samples, particularly those from patients receiving anticoagulant therapy, may require increased clotting time.

Volume Required: 10 µL serum.

Storage: Stable at 2–8°C for 24 hours[21], or at –20°C or colder if samples are to be assayed after extended storage.

Warnings and Precautions

For *in vitro* diagnostic use.

Reagents: Store at 2–8°C. Dispose of in accordance with applicable laws.

Follow universal precautions, and handle all components as if capable of transmitting infectious agents. Source materials derived from human blood were tested and found nonreactive for syphilis; for antibodies to HIV 1 and 2; for hepatitis B surface antigen; and for antibodies to hepatitis C.

Sodium azide, at concentrations less than 0.1 g/dL, has been added as a preservative. On disposal, flush with large volumes of water to prevent the buildup of potentially explosive metal azides in lead and copper plumbing.

Chemiluminescent Substrate: Avoid contamination and exposure to direct sunlight. (See insert.)

Water: Use distilled or deionized water.

Materials Supplied

Components are a matched set. The barcode labels are needed for the assay.

PSA Bead Pack (L2PS12)
With barcode. 200 beads, coated with polyclonal goat anti-PSA antibody, with desiccant. Stable at 2–8°C until expiration date.
L2KPS2: 1 pack. **L2KPS6:** 3 packs.

PSA Reagent Wedge (L2PSA2)
With barcode. 11.5 mL alkaline phosphatase (bovine calf intestine) conjugated to monoclonal murine anti-PSA antibody in buffer, with preservative. Store capped and refrigerated: Stable at 2–8°C until expiration date. Recommended usage is within 30 days after opening when stored as indicated.
L2KPS2: 1 wedge. **L2KPS6:** 3 wedges.

Before use, tear off the top of the label at the perforations, without damaging the barcode. Remove the foil seal from the top of wedge; snap the sliding cover down into the ramps on the reagent lid.

PSA Adjustors (LPSL LPSH)
Two vials (Low and High) 1.5 mL each of PSA in a chicken serum/buffer matrix, with preservative. Stable at 2–8°C for 30 days after opening, or for 6 months (aliquotted) at –20°C.
L2KPS2: 1 set. **L2KPS6:** 2 sets.

Before making an adjustment, place the appropriate Aliquot Labels (supplied with the kit) on test tubes so that the barcodes can be read by the on-board reader.

Kit Components Supplied Separately

Multi-Diluent 2 (L2M2Z, L2M2Z4)
For the on-board dilution of high samples. One vial with barcode containing concentrated (ready-to-use), nonhuman protein/buffer matrix, with preservative. Storage: 30 days (after opening) at 2–8°C or 6 months (aliquotted) at –20°C.
L2M2Z: 25 mL. **L2M2Z4:** 55 mL.

L2SUBM: Chemiluminescent Substrate
L2PWSM: Probe Wash
L2KPM: Probe Cleaning Kit
L2RXT: Reaction Tubes (disposable)

TMCO: Tri-level, multi-constituent control

Also Required
Distilled or deionized water; test tubes; controls.

Assay Procedure

See the IMMULITE 2000 Operator's Manual for: preparation, setup, dilutions, adjustment assay, and quality control procedures.

Adjustment Interval: 4 weeks.

Quality Control Samples: Use controls or sample pools with at least two levels (low and high) of PSA.

Expected Values in Detection of Prostate Cancer

In a retrospective study at one clinical site for prostate cancer detection purposes, samples were collected from 477 men, aged 50 or older. Of these, 20 (4%) were Asian; 8 (2%) were African American; 440 (92%) were Caucasian; 7 (<1%) were other and 2 (<1%) provided no ethnic information. All patients also underwent digital rectal examination (DRE). Of these, 52 were biopsied for elevated (> 4.0 ng/mL) PSA and/or suspicious DRE. The following table summarizes these clinical studies:

No. of Subjects (%)	No. of Biopsies (%)	No. of Prostate Cancers	% Positive Biopsies (95% CI)
All Subjects			
477	52	18	34.6%
PSA > 4.0			
70	38	15	39.5%
14.7%	54.3%		(24.0%-55.7%)
DRE +			
54	17	8	47.1%
11.3%	31.5%		(25.3%-72.2%)
PSA > 4.0 DRE +			
23	12	6	50.0%
4.8%	52.2%		(23.6%-76.4%)
PSA <= 4.0 DRE +			
31	5	2	40.0%
6.5%	16.1%		(7.6%-81.1%)
PSA > 4.0 DRE –			
47	26	9	34.6%
9.9%	55.3%		(18.0%-54.2%)
PSA <= 4.0 DRE –			
376	9	1	11.1%
78.8%	2.4%		(0.3%-48.3%)

The study demonstrated that PSA testing, when used in conjunction with DRE, was more effective in detecting prostate cancer than DRE alone. PSA determinations detected 50% (9/18) of cancers that DRE did not; PSA elevations greater than 4 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true: a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected 11% (2/18) of cancers that PSA determinations did not.

In the same study, 376 participants were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for these asymptomatic subjects in the clinical study who had both a negative PSA and DRE, and therefore, were not biopsied as well as for those subjects who were negative for cancer biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Distribution of PSA Levels	*n*	PSA Median	PSA 95th %ile
All subjects	376	0.78	2.98
50–59 age group	159	0.60	2.30
60–69 age group	143	0.91	2.84
≥70 age group	74	1.17	3.17

In studies performed at four clinical sites, 2618 samples collected from 1965 patients were tested. Shown below is the distribution of IMMULITE PSA results from this study.

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Female Subjects					
253/253	100%	0%	0%	0%	0%
Healthy					
149/149	100%	0%	0%	0%	0%
Nonmalignant Diseases					
28/28	100%	0%	0%	0%	0%
Malignant Diseases					
76/76	100%	0%	0%	0%	0%
Healthy Male Subjects					
473/473	99.4%	0.6%	0%	0%	0%
Non-Malignant Diseases					
548/548	76.2%	19.3%	3.5%	0.9%	0%
BPH					
333/333	67.9%	25.8%	5.4%	0.9%	0%
Other Prostatic Diseases					
66/66	80.3%	18.2%	1.5%	0%	0%
Other Nonprostatic Diseases					
149/149	93.2%	5.4%	0%	1.3%	0%
Non-Prostatic Malignancies					
312/312	93.0%	6.1%	0.6%	0.3%	0%
Prostate Cancer (single specimens)					
274/274	42.3%	21.2%	13.1%	7.3%	16.1%
Prostate Cancer (serially monitored)					
105/758	54.8%	11.7%	10.7%	7.5%	15.3%

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Stage A					
17/174	84.9%	9.8%	9.2%	3.5%	12.6%
Stage B					
31/200	54.0%	14%	12%	8.5%	11.5%
Stage C					
19/102	56.9%	6.9%	7.8%	8.8%	19.6%
Stage D					
38/282	48.2%	13.1%	11.7%	8.9%	18.0%
Total:					
1965/2618	1962	275	138	83	160

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

Limitations

Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of malignant disease, nor should serum PSA be used alone as a screening test for malignant disease.[8]

Prediction of malignant prostatic disease recurrence should be based on a complete clinical evaluation of the patient, which may also include serial serum PSA determinations.

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting up to 3 weeks.[18]

PSA expression may be altered due to hormonal therapy for prostate cancer. Consequently, a low PSA result following a prostatic cancer treatment which includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.[25]

Some individuals have antibodies to mouse protein which can cause interference in immunoassays that employ antibodies derived from mice. In particular, specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). These specimens may show erroneous results in such

assays.[22-24] Therefore, results should be interpreted with caution for such patients.

Heterophilic antibodies in human serum can react with the immunoglobulins included in the assay components causing interference with *in vitro* immunoassays. [See Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem 1988:34:27-33.] Samples from patients routinely exposed to animals or animal serum products can demonstrate this type of interference potentially causing an anomalous result. These reagents have been formulated to minimize the risk of interference; however, potential interactions between rare sera and test components can occur. For diagnostic purposes, the results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.

Performance Data

See Tables and Graphs for data *representative* of the assay's performance. Results are expressed in ng/mL. (Unless otherwise noted, all were generated on serum samples collected in tubes without gel barriers or clot-promoting additives.)

Working Range: 0.04 – 150 ng/mL

Analytical Sensitivity: 0.04 ng/mL

High-dose Hook Effect:
None up to 22,500 ng/mL.

Precision: Samples were processed in duplicate over the course of 20 days, two runs per day, for a total of 40 runs and 80 replicates. Results are expressed in ng/mL.

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	2.8	0.10	3.6%	0.14	5.0%
2	7.4	0.23	3.1%	0.36	4.9%
3	11.4	0.34	3.0%	0.60	5.3%
4	25	0.70	2.8%	1.1	4.4%
5	65	1.4	2.2%	2.5	3.9%
6	126	3.2	2.5%	4.7	3.7%

Linearity: Samples were assayed under various dilutions. Results are expressed in ng/mL.

	Dilution	Observed	Expected	%O/E
1	16 in 16[5]	1.03	—	—
	8 in 16	0.48	0.52	92%
	4 in 16	0.23	0.26	91%
	2 in 16	0.13	0.13	100%
	1 in 16	0.06	0.06	100%
2	16 in 16	7.8	—	—
	8 in 16	3.96	3.90	101%
	4 in 16	2.05	1.95	105%
	2 in 16	0.98	0.98	100%
	1 in 16	0.51	0.49	105%
3	16 in 16	27.2	—	—
	8 in 16	13.9	13.6	102%
	4 in 16	7.0	6.8	103%
	2 in 16	3.6	3.4	106%
	1 in 16	1.7	1.7	100%
4	16 in 16	99	—	—
	8 in 16	48	50	96%
	4 in 16	25	25	100%
	2 in 16	13	12	108%
	1 in 16	6.7	6.2	108%
5	16 in 16	126	—	—
	8 in 16	61	63	97%
	4 in 16	33	32	103%
	2 in 16	17	16	106%
	1 in 16	8.9	7.9	113%

Recovery: Samples spiked 1 to 19 with four PSA solutions (107, 208, 653 and 817 ng/mL) were assayed. Results are expressed in ng/mL.

	Spiking Solution	Observed	Expected	%O/E
1	—	0.46	—	—
	A	6.0	5.8	103%
	B	11.2	10.8	104%
	C	33	33	100%
	D	42	41	102%
2	—	6.4	—	—
	A	11.8	11.5	103%
	B	16	17	94%
	C	42	39	108%
	D	49	47	104%
3	—	26	—	—
	A	28	30	93%
	B	32	35	91%
	C	56	58	97%
	D	65	66	98%

Bilirubin: No significant effect.

Hemolysis: No significant effect.

Specificity: The assay is highly specific for prostate-specific antigen, with a particularly low crossreactivity to other naturally occurring compounds and chemotherapeutic agents that might be present in patient samples.

Compound	ng/mL Added	Percent Cross-reactivity
AFP	10000	ND
Amethopterin	100000	ND
CEA	100	ND
Cisplatin	100000	ND
Cyclophosphamide	1000000	ND
Diethylstilbestrol	10000000	ND
Doxazosin mesylate	1000000	ND
Doxorubicin Hydrochloride	100000	ND
Ferritin	10000	ND
Finasteride	10000000	ND
5-Fluorouracil	1000000	ND
Flutamide	100000	ND
HCG	10000	ND
Lactalbumin	1000000	ND
Leuprolide acetate	100000	ND
Megesterol	1000000	ND
Mitomycin C	100000	ND
PAP	1000	ND
Prolactin	500	ND
Vincristine	1000000	ND

ND: not detectable

Method Comparison: All four of DPC's nonisotopic PSA assays were compared using Deming regression analysis. Samples used were within the working range of the assays. The table below presents the results of the Deming regressions, with columns as Y, and rows as X.

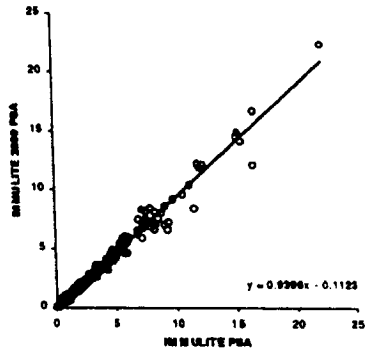
Results of Deming Regressions

		IMMULITE PSA	IMMULITE 2000 PSA	IMMULITE 3rd Generation PSA	IMMULITE 2000 3rd Generation PSA
IMMULITE PSA	*n*		477	474	473
	Slope (95% CI)		0.94 (0.93 to 0.95)	0.99 (0.98 to 1.00)	1.08 (1.07 to 1.10)
	Intercept (95% CI)		–0.11 (–0.15 to –0.07)	0.05 (0.02 to 0.09)	0.06 (0.02 to 0.11)
	Correlation Coefficient		0.992	0.993	0.991
IMMULITE 2000 PSA	*n*	477		474	473
	Slope (95% CI)	1.06 (1.05 to 1.08)		1.06 (1.05 to 1.08)	1.16 (1.14 to 1.17)
	Intercept (95% CI)	0.12 (0.08 to 0.16)		0.15 (0.11 to 0.20)	0.18 (0.14 to 0.23)
	Correlation Coefficient	0.992		0.988	0.990
IMMULITE 3rd Generation PSA	*n*	474	474		472
	Slope (95% CI)	1.01 (1.00 to 1.03)	0.94 (0.93 to 0.96)		1.10 (1.09 to 1.11)
	Intercept (95% CI)	–0.06 (–0.09 to –0.02)	–0.15 (–0.19 to –0.10)		–0.00 (–0.05 to 0.05)
	Correlation Coefficient	0.993	0.988		0.990
IMMULITE 2000 3rd Generation PSA	*n*	473	473	472	
	Slope (95% CI)	0.92 (0.91 to 0.94)	0.86 (0.85 to 0.87)	0.91 (0.90 to 0.92)	
	Intercept (95% CI)	–0.06 (–0.10 to –0.02)	–0.16 (–0.20 to –0.12)	0.00 (– 0.04 to 0.04)	
	Correlation Coefficient	0.991	0.990	0.990	

The following graph presents the comparison between IMMULITE 2000 PSA and IMMULITE PSA on 477 patient samples. (Concentration range: nondetectable to approximately 20 ng/mL.) By linear regression:

(IML 2000) = 0.94 (IML) – 0.11 ng/mL
r = 0.992

Means:
2.05 ng/mL (IMMULITE 2000)
2.30 ng/mL (IMMULITE)



References

1) Wang MC et al. Purification of a human prostate specific antigen. Invest Urol 1979;17:159-63. 2) Kuriyama M et al. Prostatic acid phosphatase and prostate- specific antigen in prostate cancer. In: International Advances in Surgical Oncology. New York: Alan R. Liss Inc. 1982; 5:29-49. 3) Watt WK, Lee PJ et al. Human prostate-specific antigen: structural and functional similarity with serine proteases. Proc Natl Acad Sci USA 1986;83:3166-70. 4) Lundwall A. Characterization of the gene for prostate specific antigen a human glandular kallikrein. Biochem Biophys Res Commun 1989;161:1151-9. 5) Papsidero LD et al. A prostate antigen in sera of prostatic cancer patients. Cancer Res 1980;40:2428-31. 6) Nadji M et al. Prostatic-specific antigen: an immunohistologic marker for prostatic neoplasms. Cancer 1981;48:1229-32. 7) Wang MC et al. Prostate antigen of human cancer patients. In: Methods in cancer research. Academic Press Inc. 1982; 19:179-97. 8) Kuriyama M et al. Quantitation of prostate-specific antigen in serum by a sensitive enyzme immunoassay. Cancer Res 1980;40:4658-62. 9) Catalona WJ et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. New Engl J Med 1991;324:1156-61. 10) Brawer MK, Lange PH. Prostate-specific antigen: its role in early detection staging and monitoring prostatic carcinoma. J Endocrinol 1989;3:227-36. 11) Killian CS et al. Prognostic importance of prostate specific antigen for monitoring patients with stages B2 to D1 prostate cancer. Cancer Res 1985;45:886-91. 12) Stamey TA. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. In: Stamey TA editor. Monographs in Urology. Princeton NY: Medical Directions Publishing Co. Inc. 1989; 10(4):50-64. 13) Ercole CJ et al. Prostatic specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. J Urol 1987;138:1181-4. 14) Chan DW et al. Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. Clin Chem 1987;33:1916-20. 15) Lange PH et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol 1989;141:873-9. 16) 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. 17) Kuriyama M et al. Multiple marker evaluation in human prostate cancer with the use of tissue-specific antigens. J Natl Cancer Inst 1982;68:99-105. 18) Stamey TA, Yang N et al. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909-16. 19) Brawer MK et al. The effect of digital rectal examination on serum levels of prostatic specific antigen. Arch Pathol Lab Med 1988;112:1110-2. 20) Hughes HR et al. Serum prostatic specific antigen: in vitro stability and the effect of ultrasound rectal examination in vivo. Ann Clin Biochem 1987;24:(Suppl)206-8. 21) Burtis CA, Ashwood ER, editors. Tietz textbook of clincal chemistry. 2nd ed. Philadelphia: W.B. Saunders 1994. 22) Primus FJ et al. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine antibody for diagnosis and therapy. Clin Chem 1988;34:261-4. 23) Hansen HJ et al. Solving the problem of antibody interference in commercial "sandwich"-type immunoassay of carcinoembryonic antigen. Clin Chem 1989;35:148-51. 24) Schroff RJ et al. Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy. Cancer Res 1985;45:879-85. 25) Morgan WR 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. 26) National Committee for Clinical Laboratory Standards. Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard. 4th ed. NCCLS Document H3-A4 Wayne PA: NCCLS 1998. 27) Smith RA, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2000; 50(1):34-49.

Technical Assistance

In the United States, contact DPC's Technical Services department.

Tel: 800.372.1782 or 973.927.2828
Fax: 973.927.4101. Outside the United States, contact your National Distributor.

The Quality System of Diagnostic Products Corporation is registered to ISO 9001:1994.

Diagnostic Products Corporation
5700 West 96th Street
Los Angeles CA 90045-5597

2001-05-01 (ISO 8601)

May 1, 2001

PIL2KPS – 4

43

IMMULITE 2000

44

Third Generation PSA

DPC

IMMULITE® 2000 Third Generation PSA

English

Intended Use: For in vitro diagnostic use with the IMMULITE 2000 Analyzer – for the quantitative measurement of prostate-specific antigen (PSA) in human serum, 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. This assay is further indicated as an adjunctive test to aid in the management of prostate cancer patients.

Catalog Number: L2KUP2 (200 tests) L2KUP6 (600 tests)

Test Code: **sPs** Color: **Red**

Caution: In the United States, Federal law restricts this device to sale by or on the order of a physician.

> The concentration of PSA in a given specimen determined with different assays 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 assay used. Values obtained with different PSA assays cannot be used interchangeably. Before changing assays, the laboratory must confirm the baseline values for patients being serially monitored.

Summary and Explanation

Prostate specific antigen (PSA), first identified and characterized by Wang, et al in 1979, is a glycoprotein monomer with protease activity.[1,2] PSA has an isoelectric point of approximately 6.9 and a molecular weight of approximately 33-34 kilodaltons; it contains approximately 10% carbohydrate by weight.[1,2] The amino acid sequence of PSA was reported,[3] and the gene has been cloned.[4] PSA is biochemically and immunologically distinct from PAP and does not exhibit enzymatic phosphatase activity.[5]

PSA is localized in the cytoplasm of prostatic ductal epithelium and in secretions of the ductal lumina.[6] Because PSA is a secretory protein of the prostate, it can be recovered and purified both from prostatic tissue and from seminal plasma.[7] PSA has been found to be exclusively associated with prostate tissue;[17] and elevated serum PSA has been found in patients with prostate cancer, benign prostatic hypertrophy, and inflammatory conditions of other adjacent genitourinary tissues, but not in healthy men, men with nonprostatic carcinoma, healthy women or women with cancer.[6,8]

Measurement of serum PSA is not suitable as a screen for prostate cancer because elevated PSA concentrations are also observed in patients with benign prostatic hypertrophy (BPH)[6]; nor is it recommended as a guide in disease staging. The combination of PSA measurement and rectal examination with ultrasonography in the event of abnormal findings may provide a better method of detecting prostate cancer than rectal examination alone. Measurement of PSA offers several advantages over digital rectal examination or ultrasonography in detecting prostate cancer: the result is objective, quantitative, and obtained independent of the examiner's skill, and the procedure is more acceptable to patients than other procedures.[9]

Determinations of total immunoreactive PSA can be useful in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[10,11] Persistent elevation of PSA following treatment or an increase in the pretreatment PSA concentrations is indicative of recurrent or residual disease.[12–16] Hence, PSA is widely accepted as an aid in the management of prostate cancer patients.[12–16]

The American Cancer Society has recommended that both the PSA blood test and digital rectal examination be offered annually, beginning at age 50, to men who have at least a 10-year life expectancy, as well as younger men who

are at high risk. Patients should be given information regarding potential risks and benefits of early detection and treatment. Men in high risks groups, such as those with two or more affected first-degree relatives may consider screening at a younger age, perhaps 45.[27]

Principle of the Procedure

Sequential Immunometric Assay.

Incubation Cycles: 2 × 30 minutes.

Specimen Collection

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting for up to 3 weeks using conventional PSA assays.[18] Studies have shown conflicting results on the existence of an effect of digital rectal examination on PSA level using conventional PSA assays.[19,20] Therefore, when possible, obtain PSA samples before digital rectal examination.

Centrifuging serum samples before a complete clot forms may result in the presence of fibrin. To prevent erroneous results due to the presence of fibrin, ensure that complete clot formation has taken place prior to centrifugation of samples. Some samples, particularly those from patients receiving anticoagulant therapy, may require increased clotting time.

Volume Required: 50 µL serum.

Storage: 24 hours at 2–8°C.[21] Store at –18°C or colder if samples are to be assayed after extended storage.

Warnings and Precautions

For *in vitro* diagnostic use.

Reagents: Store at 2–8°C. Dispose of in accordance with applicable laws.

Follow universal precautions, and handle all components as if capable of transmitting infectious agents. Source materials derived from human blood were tested and found nonreactive for syphilis; for antibodies to HIV 1 and 2; for hepatitis B surface antigen; and for antibodies to hepatitis C.

Sodium azide, at concentrations less than 0.1 g/dL, has been added as a preservative. On disposal, flush with large volumes of water to prevent the buildup of potentially explosive metal azides in lead and copper plumbing.

Chemiluminescent Substrate: Avoid contamination and exposure to direct sunlight. (See insert.)

Water: Use distilled or deionized water.

Materials Supplied

Components are a matched set. The barcode labels are needed for the assay.

Third Generation PSA Bead Pack (L2UP12)
With barcode. 200 beads, coated with monoclonal murine anti-PSA antibody. Stable at 2–8°C until expiration date. **L2KUP2:** 1 pack. **L2KUP6:** 3 packs.

Third Generation PSA Reagent Wedge (L2UPA2)
With barcode. 11.5 mL of a protein buffer/serum matrix, with preservative. 11.5 mL alkaline phosphatase (bovine calf intestine) conjugated to polyclonal goat anti-PSA antibody in buffer, with preservative. Stable at 2–8°C until expiration date.
L2KUP2: 1 wedge. **L2KUP6:** 3 wedges.

Before use, tear off the top of the label at the perforations, without damaging the barcode. Remove the foil seal from the top of wedge; snap the sliding cover down into the ramps on the reagent lid.

Third Generation PSA Adjustors (LUPL, LUPH)
Two vials (Low and High), 3 mL each, of PSA in a serum matrix, with preservative. Stable at 2–8°C for 30 days after opening, or for 6 months (aliquotted) at –20°C.
L2KUP2: 1 set. **L2KUP6:** 2 sets.

Before making an adjustment, place the appropriate Aliquot Labels (supplied with the kit) on test tubes so that the barcodes can be read by the on-board reader.

Kit Components Supplied Separately

Multi-Diluent 2 (L2M2Z, L2M2Z4)
For the on-board dilution of high samples. One vial with barcode containing concentrated (ready-to-use), nonhuman protein/buffer matrix, with preservative.
Storage: 30 days (after opening) at 2–8°C or 6 months (aliquotted) at –20°C.
L2M2Z: 25 mL. **L2M2Z4:** 55 mL

L2SUBM: Chemiluminescent Substrate
L2PWSM: Probe Wash
L2KPM: Probe Cleaning Kit
L2RXT: Reaction Tubes (disposable)

TMCO: Tri-level, multi-constituent control
LUPCM: Single-level Third Generation PSA Control Module

Also Required
Distilled or deionized water; test tubes; controls.

Assay Procedure

See the IMMULITE 2000 Operator's Manual for: preparation, setup, dilutions, adjustment, assay and quality control procedures.

Adjustment Interval: 4 weeks.

Quality Control Samples: Use controls or sample pools with at least two levels (low and high) of PSA.

Expected Values in Detection of Prostate Cancer

In a retrospective study at one clinical site for prostate cancer detection purposes, samples were collected from 477 men, aged 50 or older. Of these, 20 (4%) were Asian; 8 (2%) were African American; 440 (92%) were Caucasian; 7 (<1%) were other and 2 (<1%) provided no ethnic information. All patients also underwent digital rectal examination (DRE). Of these, 52 were biopsied for elevated (> 4.0 ng/mL) PSA and/or suspicious DRE. The following table summarizes these clinical studies:

No. of Subjects (%)	No. of Biopsies (%)	No. of Prostate Cancers	% Positive Biopsies (95% CI)
All Subjects			
477	52	18	34.6%
PSA > 4.0			
85	45	16	35.6%
17.8%	52.9%		(22.8%-51.2%)
DRE +			
54	17	8	47.1%
11.3%	31.5%		(25.3%-72.2%)
PSA > 4.0 DRE +			
25	13	7	53.8%
5.2%	52.0%		(26.0%-77.6%)
PSA <= 4.0 DRE +			
29	4	1	25.0%
6.1%	13.8%		(1.3%-75.1%)
PSA > 4.0 DRE –			
60	32	9	28.1%
12.6%	53.3%		(15.2%-46.2%)
PSA <= 4.0 DRE –			
363	3	1	33.3%
76.1%	0.8%		(0.8%-90.6%)

The study demonstrated that PSA testing, when used in conjunction with DRE, was more effective in detecting prostate cancer than DRE alone. PSA determinations detected 50% (9/18) of cancers that DRE did not; PSA elevations greater than 4 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true: a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected 6% (1/18) of cancers that PSA determinations did not.

In the same study, 363 participants were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for these asymptomatic subjects in the clinical study who had both a negative PSA and DRE, and therefore, were not biopsied as well as for those subjects who were negative for cancer biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Distribution of PSA Levels	*n*	PSA Median	PSA 95th %ile
All subjects	363	1.02	3.20
50–59 age group	157	0.88	2.83
60–69 age group	137	1.12	3.15
≥70 age group	69	1.48	3.58

In studies performed at four clinical sites, 2618 samples collected from 1965 patients were tested. Shown below is the distribution of IMMULITE PSA results from this study.

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Female Subjects					
253/253	100%	0%	0%	0%	0%
Healthy					
149/149	100%	0%	0%	0%	0%
Nonmalignant Diseases					
28/28	100%	0%	0%	0%	0%
Malignant Diseases					
76/76	100%	0%	0%	0%	0%
Healthy Male Subjects					
473/473	99.4%	0.6%	0%	0%	0%
Non-Malignant Diseases					
548/548	76.2%	19.3%	3.5%	0.9%	0%
BPH					
333/333	67.9%	25.8%	5.4%	0.9%	0%
Other Prostatic Diseases					
66/66	80.3%	18.2%	1.5%	0%	0%
Other Nonprostatic Diseases					
149/149	93.2%	5.4%	0%	1.3%	0%
Non-Prostatic Malignancies					
312/312	93.0%	6.1%	0.6%	0.3%	0%
Prostate Cancer (single specimens)					
274/274	42.3%	21.2%	13.1%	7.3%	16.1%
Prostate Cancer (serially monitored)					
105/758	54.8%	11.7%	10.7%	7.5%	15.3%

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Stage A					
17/174	64.9%	9.8%	9.2%	3.5%	12.6%
Stage B					
31/200	54.0%	14%	12%	8.5%	11.5%
Stage C					
19/102	56.9%	6.9%	7.8%	8.8%	19.6%
Stage D					
38/282	48.2%	13.1%	11.7%	8.9%	18.0%
Total:					
1965/2618	1962	275	138	83	160

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

Limitations

Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of malignant disease.[8]

Prediction of malignant prostatic disease recurrence should be based on a complete clinical evaluation of the patient, which may also include serial serum PSA determinations.

Samples should be obtained before biopsy, prostatectomy or prostatic massage.[18]

PSA expression may be altered due to hormonal therapy for prostate cancer. Consequently, a low PSA result following hormonal treatment may not adequately reflect the presence of residual or recurrent disease.[25]

This device is not intended to be used for early detection of prostate cancer.

Some individuals have antibodies to mouse protein which can cause interference in immunoassays that employ antibodies derived from mice. In particular, specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). These specimens may show erroneous results in such assays.[22-24] Therefore, results should be interpreted with caution for such patients.

Heterophilic antibodies in human serum can react with the immunoglobulins included in the assay components causing interference with *in vitro* immunoassays. [See Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem 1988:34:27-33.] Samples from patients routinely exposed to animals or animal serum products can demonstrate this type of interference potentially causing an anomalous result. These reagents have been formulated to minimize the risk of interference; however, potential interactions between rare sera and test components can occur. For diagnostic purposes, the results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.

Performance Data

See Tables and Graphs for data *representative* of the assay's performance. Results are expressed in ng/mL. (Unless otherwise noted, all were generated on serum samples collected in tubes without gel barriers or clot-promoting additives.)

Calibration Range: Up to 20 ng/mL

Analytical Sensitivity: 0.003 ng/mL

Functional Sensitivity: 0.01 ng/mL, as demonstrated by the studies summarized in the Precision section. (Functional sensitivity is defined as the lowest concentration that can be measured with an interassay CV of 20%.)

High-dose Hook Effect:
None up to 112,000 ng/mL.

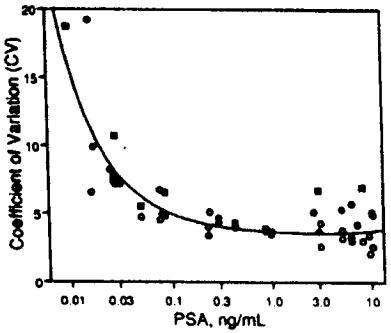
Precision: Samples were assayed in duplicate over the course of 20 days, two runs per day, for a total of 40 runs and 80 replicates. Results are expressed in ng/mL.

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.028	0.002	7.1%	0.003	10.7%
2	3.0	0.11	3.7%	0.20	6.7%
3	8.3	0.25	3.0%	0.57	6.9%

A second study included low-concentration pools, prepared from unspiked patient samples

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.0067	0.00136	20.3%	0.00141	21.0%
2	0.0098	0.00183	18.7%	0.00183	18.7%
3	0.027	0.0020	7.3%	0.0021	7.8%
4	0.050	0.0024	4.8%	0.0028	5.6%
5	0.086	0.0042	4.9%	0.0056	6.5%
6	0.294	0.0129	4.4%	0.0134	4.6%
7	0.430	0.0173	4.0%	0.0183	4.3%
8	0.861	0.0321	3.7%	0.0334	3.9%

Precision Profile: Based on within-run CVs from three Master Curve studies, 10 or 20 replicates per sample, in addition to the within-run CVs tabulated. The bowl-shaped contour line traces the approximate path of these points (open circles). For reference, the run-to-run ("total") CVs tabulated are plotted as solid squares.



Linearity: Samples were assayed under various dilutions. Results are expressed in ng/mL.

	Dilution	Observed	Expected	%O/E
1	8 in 8	0.109	—	—
	4 in 8	0.054	0.055	98%
	2 in 8	0.026	0.027	96%
	1 in 8	0.014	0.014	100%
2	8 in 8	1.5	—	—
	4 in 8	0.73	0.75	97%
	2 in 8	0.38	0.38	100%
	1 in 8	0.17	0.19	89%
3	8 in 8	6.5	—	—
	4 in 8	3.3	3.2	101%
	2 in 8	1.7	1.6	106%
	1 in 8	0.81	0.81	100%
4	8 in 8	12.3	—	—
	4 in 8	6.1	6.2	98%
	2 in 8	3.0	3.1	97%
	1 in 8	1.5	1.5	100%
5	8 in 8	17.7	—	—
	4 in 8	8.8	8.9	99%
	2 in 8	4.4	4.4	100%
	1 in 8	2.1	2.2	95%

Specificity: The antibody is highly specific for PSA.

Compound	Amount Added	% Cross-reactivity
AFP	10000 ng/mL	ND
CEA	100 ng/mL	ND
Ferritin	10000 ng/mL	ND
HCG	100000 mIU/mL	ND
PAP	1000 ng/mL	ND
Prolactin	200 ng/mL	ND

ND: not detectable.

Recovery: Samples spiked 1 to 19 with three PSA solutions (10.2, 46 and 91 ng/mL) were assayed. Results are expressed in ng/mL.

	Spiking Solution	Observed	Expected	%O/E
1	—	0.87	—	—
	A	1.8	1.8	100%
	B	2.8	2.8	100%
	C	4.7	5.0	94%
2	—	1.7	—	—
	A	2.5	2.6	96%
	B	3.6	3.6	100%
	C	5.2	5.8	90%
3	—	8.3	—	—
	A	9.0	8.8	102%
	B	9.6	9.9	97%
	C	11	12	92%
4	—	9.1	—	—
	A	8.9	9.6	93%
	B	11	11	100%
	C	12	13	92%
5	—	16	—	—
	A	17	17	100%
	B	18	17	106%
	C	19	19	100%
6	—	16	—	—
	A	17	17	100%
	B	17	17	106%
	C	18	19	95%

Bilirubin: No significant effect.

Hemolysis: No significant effect.

IMMULITE 2000 Third Generation PSA

Method Comparison: All four of DPC's nonisotopic PSA assays were compared using Deming regression analysis. Samples used were within the working range of the assays. The table below presents the results of the Deming regressions, with columns as Y, and rows as X.

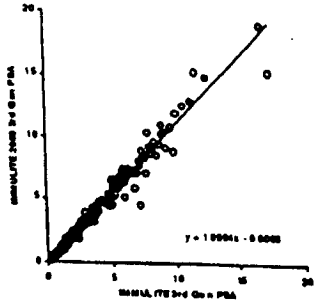
Results of Deming Regressions

		IMMULITE PSA	IMMULITE 2000 PSA	IMMULITE 3rd Generation PSA	IMMULITE 2000 3rd Generation PSA
IMMULITE PSA	*n*		477	474	473
	Slope (95% CI)		0.94 (0.93 to 0.95)	0.99 (0.98 to 1.00)	1.08 (1.07 to 1.10)
	Intercept (95% CI)		–0.11 (–0.15 to –0.07)	0.05 (0.02 to 0.09)	0.06 (0.02 to 0.11)
	Correlation Coefficient		0.992	0.993	0.991
IMMULITE 2000 PSA	*n*	477		474	473
	Slope (95% CI)	1.06 (1.05 to 1.08)		1.06 (1.05 to 1.08)	1.16 (1.14 to 1.17)
	Intercept (95% CI)	0.12 (0.08 to 0.16)		0.15 (0.11 to 0.20)	0.18 (0.14 to 0.23)
	Correlation Coefficient	0.992		0.988	0.990
IMMULITE 3rd Generation PSA	*n*	474	474		472
	Slope (95% CI)	1.01 (1.00 to 1.03)	0.94 (0.93 to 0.96)		1.10 (1.09 to 1.11)
	Intercept (95% CI)	–0.06 (–0.09 to –0.02)	–0.15 (–0.19 to –0.10)		–0.00 (–0.05 to 0.05)
	Correlation Coefficient	0.993	0.988		0.990
IMMULITE 2000 3rd Generation PSA	*n*	473	473	472	
	Slope (95% CI)	0.92 (0.91 to 0.94)	0.86 (0.85 to 0.87)	0.91 (0.90 to 0.92)	
	Intercept (95% CI)	–0.06 (–0.10 to –0.02)	–0.16 (–0.20 to –0.12)	0.00 (– 0.04 to 0.04)	
	Correlation Coefficient	0.991	0.990	0.990	

The following graph presents the comparison between IMMULITE 2000 Third Generation PSA and IMMULITE Third Generation PSA on 472 samples. (Concentration range: nondetectable to approximately 20 ng/mL. See graph.) By linear regression:

(IML 2000 3rd Gen. PSA) = 1.10 (IML 3rd Gen. PSA) – 0.00 ng/mL
r = 0.990

Means:
2.34 ng/mL (IML 2000)
2.18 ng/mL (IML)



References

1) Wang MC, et al. Purification of a human prostate specific antigen. Invest Urol 1979;17:159-63. 2) Kuriyama M, et al. Prostatic acid phosphatase and prostate- specific antigen in prostate cancer. In: International Advances in Surgical Oncology. New York: Alan R. Liss, Inc., 1982; 5:29-49. 3) Watt WK, Lee PJ, et al. Human prostate-specific antigen: structural and functional similarity with serine proteases. Proc Natl Acad Sci USA 1986;83:3166-70. 4) Lundwall A., Characterization of the gene for prostate specific antigen, a human glandular kallikrein. Biochem Biophys Res Commun 1989;161:1151-9. 5) Papsidero LD, et al. A prostate antigen in sera of prostatic cancer patients. Cancer Res 1980;40:2428-31. 6) Nadji M, et al. Prostatic-specific antigen: an immunohistologic marker for prostatic neoplasms. Cancer 1981;48:1229-32. 7) Wang MC, et al. Prostate antigen of human cancer patients. In: Methods in cancer research. Academic Press, Inc., 1982; 19:179-97. 8) Kuriyama M, et al. Quantitation of prostate-specific antigen in serum by a sensitive enyzme immunoassay. Cancer Res 1980;40:4858-62. 9) Catalona WJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. New Engl J Med 1991;324:1156-61. 10) Brawer MK, Lange PH. Prostate-specific antigen: its role in early detection, staging, and monitoring prostatic carcinoma. J Endocrinol 1989;3:227-36. 11) Killian CS, et al. Prognostic importance of prostate specific antigen for monitoring patients with stages B2 to D1 prostate cancer. Cancer Res 1985;45:886-91. 12) Stamey TA. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. In: Stamey TA, editor. Monographs in Urology. Princeton, NJ: Medical Directions Publishing, 1989; 10(4):50-64. 13) Ercole CJ, et al. Prostatic specific antigen and prostatic acid phoephatase in the monitoring and staging of patients with prostatic cancer. J Urol 1987;138:1181-4. 14) Chan DW, et al. Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. Clin Chem 1987;33:1916-20. 15) Lange PH, et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol 1989;141:873-9. 16) 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. 17) Iwakiri J, Grandbois K, et al. An analysis of urinary prostate specific antigen before and after radical prostatectomy: evidence for secretion of prostate specific antigen by the periurethral glands. J Urol 1993;149:783-6. 18) Stamey TA, Yang N, et al. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909-16. 19) Brawer MK, et al. The effect of digital rectal examination on serum levels of prostatic specific antigen. Arch Pathol Lab Med 1988;112:1110-2. 20) Hughes HR, et al. Serum prostatic specific antigen: in vitro stability and the effect of ultrasound rectal examination in vivo. Ann Clin Biochem 1987;24(Suppl):206-8. 21) Burtis CA, Ashwood ER, editors. Tietz textbook of clincal chemistry. 2nd ed. Philadelphia: W.B. Saunders, 1994. 22) Primus FJ, et al. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine antibody for diagnosis and therapy. Clin Chem 1988;34:261-4. 23) Hansen HJ, et al. Solving the problem of antibody interference in commercial "sandwich"-type immunoassay of carcinoembryonic antigen. Clin Chem 1989;35:146-51. 24) Schroff RJ, et al. Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy. Cancer Res 1985;45:879-85. 25) Morgan WR, 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. 26) Ferguson RA, Yu H, Kalyvas M, Zammit S, Diamandis EP. Ultrasensitive detection of prostate-specific antigen by a time-resolved immunofluorometric assay and the IMMULITE immunochemiluminescent third-generation assay. Clin Chem 1996;42:675-84. 27) Smith RA, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2000; 50(1):34-49.

Technical Assistance

In the United States, contact DPC's Technical Services department.
Tel: 800.372.1782 or 973.927.2828
Fax: 973.927.4101. Outside the United States, contact your National Distributor.

The Quality System of Diagnostic Products Corporation is registered to ISO 9001:1994.

Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, CA 90045-5597

2001-05-01 (ISO 8601)

May 1, 2001

PIL2KUP – 4

49

IMMULITE

50

PSA

DPC

English

Intended Use: For in vitro diagnostic use with the IMMULITE Analyzer - for the quantitative measurement of prostate-specific antigen (PSA) in human serum, 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. This assay is further indicated as an adjunctive test to aid in the management of prostate cancer patients.

Catalog Number: LKPS1 (100 tests), LKPS5 (500 tests)

Test Code: PSA **Color:** Brown

Caution: In the United States, Federal law restricts this device to sale by or on the order of a physician.

> The concentration of PSA in a given specimen determined with different assays 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 assay used. Values obtained with different PSA assays cannot be used interchangeably. Before changing assays, the laboratory must confirm the baseline values for patients being serially monitored.

Summary and Explanation

Prostate specific antigen (PSA) first identified and characterized by Wang et al in 1979 is a glycoprotein monomer with protease activity.[1,2] PSA has an isoelectric point of approximately 6.9 and a molecular weight of approximately 33-34 kilodaltons containing approximately 10% carbohydrate by weight.[1,2] Subsequently the amino acid sequence of PSA was reported[3], and the gene has been cloned.[4] PSA is biochemically and immunologically distinct from PAP and does not exhibit enzymatic phosphatase activity.[5]

PSA is localized in the cytoplasm of prostatic ductal epithelium and in secretions of the ductal lumina.[6] Because PSA is a secretory protein of the prostate, it can be recovered and purified both from prostatic tissue and from seminal plasma.[7] PSA has been found to be primarily associated with prostate tissue, and elevated serum PSA has been found in patients with prostate cancer, benign prostatic hypertrophy, and inflammatory conditions of other adjacent genitourinary tissues but not in healthy men, men with nonprostatic carcinoma, healthy women or women with cancer.[5,8]

Serum PSA alone is not suitable as a screen for prostate cancer because elevated PSA concentrations are also observed in patients with benign prostatic hypertrophy (BPH)[8]; nor is it recommended as a guide in disease staging. The combination of PSA measurement and rectal examination with ultrasonography in the event of abnormal findings may provide a better method of detecting prostate cancer than rectal examination alone. Measurement of PSA offers several advantages over digital rectal examination or ultrasonography in detecting prostate cancer: the result is objective, quantitative, and obtained independent of the examiner's skill, and the procedure is more acceptable to patients than other procedures.[9]

PSA determinations can be useful in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[10,11] Persistent elevation of PSA following treatment or an increase in the pretreatment PSA concentrations is indicative of recurrent or residual disease.[12–16] Hence PSA is widely accepted as an aid in the management of prostate cancer patients.[12–16] Concurrent measurement of PAP may contribute additional information.[17]

The American Cancer Society has recommended that both the PSA blood test and digital rectal examination be offered annually, beginning at age 50, to men who have at least a 10-year life expectancy, as well as younger men who are at high risk. Patients should be given information regarding potential risks and benefits of early detection and treatment. Men in high risks groups, such as those with two or more affected first-degree relatives may consider screening at a younger age, perhaps 45.[27]

Principle of the Procedure

Immunometric Assay.

Incubation Cycles: 1 × 30 minutes.

Specimen Collection

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting for up to 3 weeks.[18]

Studies have shown conflicting results on the existence of an effect of digital rectal examination on PSA level.[19,20] Therefore when possible obtain PSA samples before digital rectal examination.

Centrifuging serum samples before a complete clot forms may result in the presence of fibrin. To prevent erroneous results due to the presence of fibrin, ensure that complete clot formation has taken place prior to centrifugation of samples. Some samples, particularly those from patients receiving anticoagulant therapy, may require increased clotting time.

Volume Required: 10 µL serum. (Sample cup must contain at least 100 µL more than the total volume required.)

Storage: Stable at 2–8°C for 24 hours[21], or at –20°C or colder if samples are to be assayed after extended storage.

Warnings and Precautions

For *in vitro* diagnostic use.

Reagents: Store at 2–8°C. Dispose of in accordance with applicable laws.

Follow universal precautions, and handle all components as if capable of transmitting infectious agents. Source materials derived from human blood were tested and found nonreactive for syphilis; for antibodies to HIV 1 and 2; for hepatitis B surface antigen; and for antibodies to hepatitis C.

Sodium azide, at concentrations less than 0.1 g/dL, has been added as a preservative. On disposal, flush with large volumes of water to prevent the buildup of potentially explosive metal azides in lead and copper plumbing.

Chemiluminescent Substrate: Avoid contamination and exposure to direct sunlight. (See insert.)

Water: Use distilled or deionized water.

Materials Supplied

Components are a matched set. The barcode labels are needed for the assay.

PSA Test Units (LPS1)
Each barcode-labeled unit contains one bead coated with with polyclonal goat anti-PSA antibody. Stable at 2–8°C until expiration date.
LKPS1: 100 units. **LKPS5:** 500 units.

Allow the Test Unit bags to come to room temperature before opening. Open by cutting along the top edge, leaving the ziplock ridge intact. Reseal the bags to protect from moisture.

PSA Reagent Wedge (LPS2)
With barcode. 6.5 mL alkaline phosphatase (bovine calf intestine) conjugated to monoclonal murine anti-PSA antibody in buffer, with preservative. Store capped and refrigerated: Stable at 2–8°C until expiration date.
Recommended usage is within 30 days after opening when stored as indicated.
LKPS1: 1 wedge. **LKPS5:** 5 wedges.

PSA Adjustors (LPSL, LPSH)
Two vials (Low and High) 1.5 mL each of PSA in a chicken serum/buffer matrix, with preservative. Stable at 2–8°C for 30 days after opening, or for 6 months (aliquotted) at –20°C.
LKPS1: 1 set. **LKPS5:** 2 sets.

Kit Components Supplied Separately

PSA Sample Diluent (LPSZ)
For the manual dilution of patient samples. One vial 25 mL of a PSA-free chicken serum/buffer matrix, with preservative. Stable at 2–8°C for 30 days after opening or longer (aliquotted) at –20°C.

LSUBX: Chemiluminescent Substrate
LPWS2: Probe Wash Module
LKPM : Probe Cleaning Kit
LCHx-y: Sample Cup Holders (barcoded)

LSCP: Sample Cups (disposable)
LSCC: Sample Cup Caps (optional)

TMCO: Tri-level,human serum based multi-constituent control

Also Required
Sample transfer pipets, distilled or deionized water, controls.

Assay Procedure

See the IMMULITE Operator's Manual for: preparation, setup, dilutions, adjustment assay, and quality control procedures.

Adjustment Interval: 4 weeks.

Quality Control Samples: Use controls or sample pools with at least two levels (low and high) of PSA.

Expected Values in Detection of Prostate Cancer

In two retrospective studies and one prospective study performed at three clinical sites for prostate cancer detection purposes, samples were collected from 3810 men, aged 50 or older. Of these, 64 (2%) were Asian; 242 (6%) were African American; 3483 (91%) were Caucasian; 7 (<1%) were other and 14 (<1%) provided no ethnic information. 3438 out of 3810 patients also underwent digital rectal examination (DRE). Of these, 252 were biopsied for elevated (> 4.0 ng/mL) PSA and/or suspicious DRE. The following table summarizes these clinical studies.

No. of Subjects (%)	No. of Biopsies (%)	No. of Prostate Cancers	% Positive Biopsies (95% CI)
All Subjects			
3438	252	81	32.1%
PSA > 4.0			
417	225	74	32.9%
12.1%	54.0%		(26.8% – 39.1%)
DRE +			
157	50	24	48.0%
4.6%	31.8%		(33.6% – 62.6%)
PSA > 4.0 DRE +			
64	34	19	55.9%
1.9%	53.1%		(37.9% – 72.8%)
PSA <= 4.0 DRE +			
93	16	5	31.3%
2.7%	17.2%		(13.2% – 57.1%)
PSA > 4.0 DRE –			
353	191	55	28.8%
10.3%	54.1%		(22.5% – 35.5%)
PSA <= 4.0 DRE –			
2928	11	2	18.2%
85.2%	0.4%		(2.3% – 51.8%)

The study demonstrated that PSA testing, when used in conjunction with DRE, was more effective in detecting prostate cancer than DRE alone. PSA determinations detected 68% (55/81) of cancers that DRE did not; PSA elevations greater than 4 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true: a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected 6% (5/81) of cancers that PSA determinations did not.

In the same studies, 2928 participants were identified as asymptomatic subjects. The following table contains the distribution of PSA values by age decade for these asymptomatic subjects in the clinical study who had both a negative PSA and DRE, and therefore, were not biopsied as well as for those subjects who were negative for cancer biopsy. There is no certainty that all of these subjects were indeed free of prostate disease. Therefore, these data should be interpreted with caution since it is questionable whether these subjects represent a truly normal population. There are presently no data proving that the use of age-specific reference ranges are safe or effective.

Distribution of PSA Levels	*n*	PSA Median	PSA 95th %ile
All subjects	2928	1.00	3.30
50–59 age group	1338	0.93	3.00
60–69 age group	1144	1.20	3.40
≥70 age group	446	1.40	3.60

In studies performed at four clinical sites, 2618 samples collected from 1965 patients were tested. Shown below is the distribution of IMMULITE PSA results from this study.

Number of Subjects / Samples	0–4 ng/mL	4–10 ng/mL	10–20 ng/mL	20–40 ng/mL	>40 ng/mL
Female Subjects					
253/253	100%	0%	0%	0%	0%
Healthy					
149/149	100%	0%	0%	0%	0%
Nonmalignant Diseases					
28/28	100%	0%	0%	0%	0%
Malignant Diseases					
76/76	100%	0%	0%	0%	0%
Healthy Male Subjects					
473/473	99.4%	0.6%	0%	0%	0%
Non-Malignant Diseases					
548/548	76.2%	19.3%	3.5%	0.9%	0%
BPH					
333/333	67.9%	25.8%	5.4%	0.9%	0%
Other Prostatic Diseases					
66/66	80.3%	18.2%	1.5%	0%	0%
Other Nonprostatic Diseases					
149/149	93.2%	5.4%	0%	1.3%	0%
Non-Prostatic Malignancies					
312/312	93.0%	6.1%	0.6%	0.3%	0%
Prostate Cancer (single specimens)					
274/274	42.3%	21.2%	13.1%	7.3%	16.1%
Prostate Cancer (serially monitored)					
105/758	54.8%	11.7%	10.7%	7.5%	15.3%
Stage A					
17/174	64.9%	9.8%	9.2%	3.5%	12.6%
Stage B					
31/200	54.0%	14%	12%	8.5%	11.5%
Stage C					
19/102	56.9%	6.9%	7.8%	8.8%	19.6%
Stage D					
38/282	48.2%	13.1%	11.7%	8.9%	18.0%
Total:					
1965/2618	1962	275	138	83	160

Consider these limits as *guidelines* only. Each laboratory should establish its own reference ranges.

Limitations

Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of malignant disease, nor should serum PSA be used alone as a screening test for malignant disease.[8]

Prediction of malignant prostatic disease recurrence should be based on a complete clinical evaluation of the patient, which may also include serial serum PSA determinations.

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting up to 3 weeks.[18]

PSA expression may be altered due to hormonal therapy for prostate cancer. Consequently, a low PSA result following a prostatic cancer treatment which includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.[25]

Some individuals have antibodies to mouse protein which can cause interference in immunoassays that employ antibodies derived from mice. In particular, specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). These specimens may show erroneous results in such assays.[22-24] Therefore, results should be interpreted with caution for such patients.

Heterophilic antibodies in human serum can react with the immunoglobulins included in the assay components causing interference with *in vitro* immunoassays. [See Boscato LM, Stuart MC. Heterophilic antibodies: a problem for all immunoassays. Clin Chem 1988:34:27-33.] Samples from patients routinely exposed to animals or animal serum products can demonstrate this type of interference potentially causing an anomalous result. These reagents have been formulated to minimize the risk of interference; however, potential interactions between rare sera and test components can occur. For diagnostic purposes, the results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.

Performance Data

See Tables and Graphs for data *representative* of the assay's performance. Results are expressed in ng/mL. (Unless otherwise noted, all were generated on serum samples collected in tubes without gel barriers or clot-promoting additives.)

Working "Reportable" Range:
0.04 – 150 ng/mL

Analytical Sensitivity: 0.03 ng/mL

High-dose Hook Effect:
None up to 20,000 ng/mL.

Intraassay (Within-Run): Samples representing a broad spectrum of PSA values were assayed in 20 runs for each of 3 lots at each of four sites, using 10 replicates per run. The within-run means and CVs were averaged across these 240 runs. Results are expressed in ng/mL.

	Mean	SD	CV
1	0.21	0.0128	6.1%
2	0.46	0.0207	4.5%
3	1.4	0.057	4.1%
4	2.8	0.09	3.2%
5	4.7	0.15	3.2%
6	8.8	0.27	3.1%
7	44	1.55	3.5%
8	112	4.14	3.7%
9	157	5.97	3.8%

Interassay (Run-to-Run): The same data set was reanalyzed to determine run-to-run CVs for samples assayed *in singlicate*. The results were averaged across the four study sites and three lots. Results are expressed in ng/mL.

	Mean	SD	CV
1	0.21	0.0195	9.3%
2	0.46	0.0304	6.6%
3	1.4	0.087	6.2%
4	2.8	0.143	5.1%
5	4.7	0.24	5.1%
6	8.8	0.41	4.7%
7	44	2.73	6.2%
8	112	6.3	5.6%
9	157	10.3	6.6%

Linearity: Samples were assayed under various dilutions. Results are expressed in ng/mL.

	Dilution	Observed	Expected	%O/E
1	8 in 8^5	81.1	—	—
	4 in 8	47.3	40.5	117%
	2 in 8	23.2	20.3	114%
	1 in 8	12.5	10.1	124%
2	8 in 8	81.2	—	—
	4 in 8	45.5	40.6	112%
	2 in 8	21.7	20.3	107%
	1 in 8	11.0	10.2	108%
3	8 in 8	150	—	—
	4 in 8	76.3	75.0	102%
	2 in 8	40.5	37.5	108%
	1 in 8	18.4	18.8	98%

Recovery: Samples spiked 1 to 19 with three PSA solutions (50, 151 and 659 ng/mL) were assayed.

	Spiking Solution	Observed	Expected	%O/E
1	—	0.32	—	—
	A	2.6	2.8	93%
	B	6.8	7.9	86%
	C	32.6	33.3	98%
2	—	26.2	—	—
	A	27.1	27.4	99%
	B	30.2	33.5	90%
	C	51.1	57.9	88%
3	—	27.7	—	—
	A	29.4	28.8	102%
	B	33.6	33.9	99%
	C	60.3	59.3	102%

Specificity: The assay is highly specific for prostate-specific antigen.

Compound	ng/mL Added	Percent Cross-reactivity
AFP	10000	ND
Amethopterin	100000	ND
CEA	100	ND
Cisplatin	100000	ND
Cyclophosphamide	1000000	ND
Diethylstilbestrol	10000000	ND
Doxazosin mesylate	1000000	ND
Doxorubicin Hydrochloride	100000	ND
Ferritin	10000	ND
Finasteride	10000000	ND
5-Fluorouracil	1000000	ND
Flutamide	100000	ND
HCG	10000	ND
Lactalbumin	1000000	ND
Leuprolide acetate	100000	ND
Megesterol	1000000	ND
Mitomycin C	100000	ND
PAP	1000	ND
Prolactin	500	ND
Vincristine	1000000	ND

ND: not detectable

Bilirubin: No significant effect.

Hemolysis: No significant effect.

Method Comparison: All four of DPC's nonisotopic PSA assays were compared using Deming regression analysis. Samples used were within the working range of the assays. The table below presents the results of the Deming regressions, with columns as Y, and rows as X.

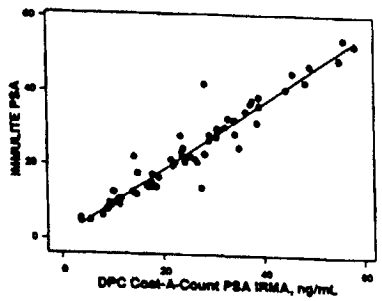
Results of Deming Regressions

		IMMULITE PSA	IMMULITE 2000 PSA	IMMULITE 3rd Generation PSA	IMMULITE 2000 3rd Generation PSA
IMMULITE PSA	*n*		477	474	473
	Slope (95% CI)		0.94 (0.93 to 0.95)	0.99 (0.98 to 1.00)	1.08 (1.07 to 1.10)
	Intercept (95% CI)		−0.11 (−0.15 to −0.07)	0.05 (0.02 to 0.09)	0.06 (0.02 to 0.11)
	Correlation Coefficient		0.992	0.993	0.991
IMMULITE 2000 PSA	*n*	477		474	473
	Slope (95% CI)	1.06 (1.05 to 1.08)		1.06 (1.05 to 1.08)	1.16 (1.14 to 1.17)
	Intercept (95% CI)	0.12 (0.08 to 0.16)		0.15 (0.11 to 0.20)	0.18 (0.14 to 0.23)
	Correlation Coefficient	0.992		0.988	0.990
IMMULITE 3rd Generation PSA	*n*	474	474		472
	Slope (95% CI)	1.01 (1.00 to 1.03)	0.94 (0.93 to 0.96)		1.10 (1.09 to 1.11)
	Intercept (95% CI)	−0.06 (−0.09 to −0.02)	−0.15 (−0.19 to −0.10)		−0.00 (−0.05 to 0.05)
	Correlation Coefficient	0.993	0.988		0.990
IMMULITE 2000 3rd Generation PSA	*n*	473	473	472	
	Slope (95% CI)	0.92 (0.91 to 0.94)	0.86 (0.85 to 0.87)	0.91 (0.90 to 0.92)	
	Intercept (95% CI)	−0.06 (−0.10 to −0.02)	−0.16 (−0.20 to −0.12)	0.00 (− 0.04 to 0.04)	
	Correlation Coefficient	0.991	0.990	0.990	

The assay was also compared to DPC's Coat-A-Count PSA IRMA on 69 patient samples. (Concentration range: approximately 5 to 55 ng/mL.) By linear regression:

(IML) = 0.92 (CAC IRMA) + 0.35 ng/mL
r = 0.964

Means:
23.5 ng/mL (IMMULITE)
25.1 ng/mL (CAC IRMA



In three additional studies, DPC's IMMULITE PSA was compared to three commercial kits, Kit A, Kit B and Kit C. The studies were performed at different sites on different sets of patient serum samples (see Expected Values). Samples with PSA concentrations exceeding the working range of an assay were reassayed under dilution by that assay. Results were subjected to linear regression analysis, with those below the detection limit of an assay being assigned that concentration for purposes of the analysis. In each of these pairwise comparisons, regression analysis was performed on three subsets of the data encompassing different concentration ranges: (a) all results, (b) results not exceeding the working range of either assay, and (c) results for data pairs involving an IMMULITE result of 20 ng/mL or less. Slope, intercept, correlation coefficient (r), and number of samples are tabulated below for each of these analyses, where

IMMULITE = *slope* × (Kit X) + *intercept*

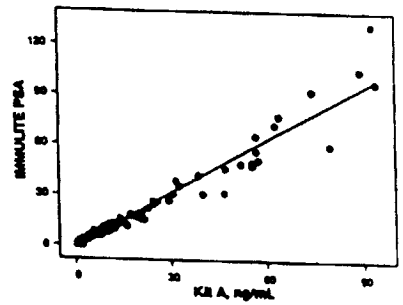
with the intercept expressed in ng/mL. Results are also displayed graphically for subsets (b) and (c). (See "Site 1", "Site 2" and "Site 3" graphs.)

Site 1: Kit A

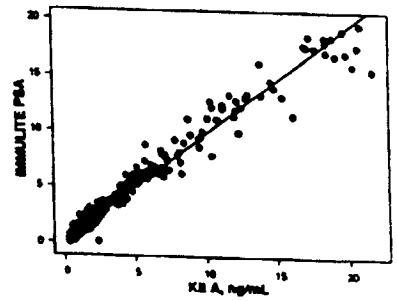
	Slope	Intercept	r	*n*
All Results (PSA Range: ND – 9567 ng/mL by IMMULITE)				
	1.01	0.21	0.994	710
Results Not Exceeding Either Working Range				
	1.06	−0.10	0.981	673
Results ≤20 ng/mL (by IMMULITE)				
	0.97	0.14	0.985	648

Site 1: IMMULITE PSA vs. Kit A

Results not exceeding either working range:



Results ≤20 ng/mL (by IMMULITE):

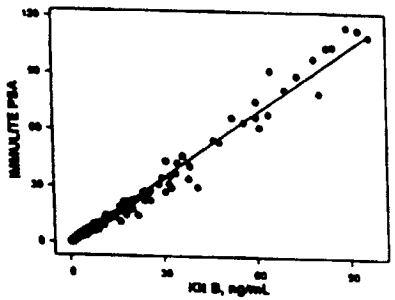


Site 2: Kit B

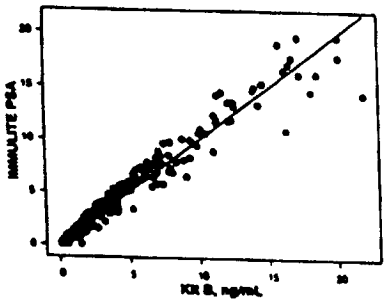
	Slope	Intercept	r	n
All Results (PSA Range: ND – 6725 ng/mL by IMMULITE)				
	1.14	–0.16	0.998	644
Results Not Exceeding Either Working Range				
	1.16	–0.27	0.992	621
Results ≤20 ng/mL (by IMMULITE)				
	0.98	0.16	0.981	573

Site 2: IMMULITE PSA vs. Kit B

Results Not Exceeding Either Working Range:



Results ≤20 ng/mL (by IMMULITE):

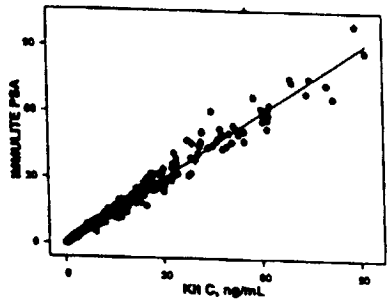


Site 3:

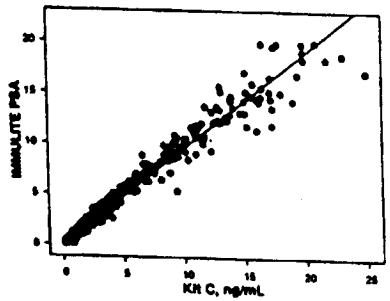
	Slope	Intercept	r	n
All Results (PSA Range: ND – 1061 ng/mL by IMMULITE)				
	0.96	0.14	0.988	1261
Results Not Exceeding Either Working Range				
	0.99	0.01	0.993	1239
Results ≤20 ng/mL (by IMMULITE)				
	0.95	0.07	0.987	1152

Site 3: IMMULITE PSA vs. Kit C

Results Not Exceeding Either Working Range:



Results ≤20 ng/mL (by IMMULITE):



References

1) Wang MC et al. Purification of a human prostate specific antigen. Invest Urol 1979;17:159-63. 2) Kuriyama M et al. Prostatic acid phosphatase and prostate- specific antigen in prostate cancer. In: International Advances in Surgical Oncology. New York: Alan R. Liss Inc. 1982; 5:29-49. 3) Watt WK, Lee PJ et al. Human prostate-specific antigen: structural and functional similarity with serine proteases. Proc Natl Acad Sci USA 1986;83:3166-70. 4) Lundwall A. Characterization of the gene for prostate specific antigen a human glandular kallikrein. Biochem Biophys Res Commun 1989;161:1151-9. 5) Papsidero LD et al. A prostate antigen in sera of prostatic cancer patients. Cancer Res 1980;40:2428-31. 6) Nadji M et al. Prostatic-specific antigen: an immunohistologic marker for prostatic neoplasms. Cancer 1981;48:1229-32. 7) Wang MC et al. Prostate antigen of human cancer patients. In: Methods in cancer research. Academic Press Inc. 1982; 19:179-97. 8) Kuriyama M et al. Quantitation of prostate-specific antigen in serum by a sensitive enyzme immunoassay. Cancer Res 1980;40:4658-62. 9) Catalona WJ et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. New Engl J Med 1991;324:1156-61. 10) Brawer MK, Lange PH. Prostate-specific antigen: its role in early detection staging and monitoring prostatic carcinoma. J Endocrinol 1989;3:227-36. 11) Killian CS et al. Prognostic importance of prostate specific antigen for monitoring patients with stages B2 to D1 prostate cancer. Cancer Res 1985;45:886-91. 12) Stamey TA. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. In: Stamey TA editor. Monographs in Urology. Princeton NY: Medical Directions Publishing Co. Inc. 1989; 10(4):50-64. 13) Ercole CJ et al. Prostatic specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. J Urol 1987;138:1181-4. 14) Chan DW et al. Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. Clin Chem 1987;33:1916-20. 15) Lange PH et al. The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol 1989;141:873-9. 16) 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. 17) Kuriyama M et al. Multiple marker evaluation in human prostate cancer with the use of tissue-specific antigens. J Natl Cancer Inst 1982;68:99-105. 18) Stamey TA, Yang N et al. Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987;317:909-16. 19) Brawer MK et al. The effect of digital rectal examination on serum levels of prostatic specific antigen. Arch Pathol Lab Med 1988;112:1110-2. 20) Hughes HR et al. Serum prostatic specific antigen: in vitro stability and the effect of ultrasound rectal examination in vivo. Ann Clin Biochem 1987;24:(Suppl)206-8. 21) Burtis CA, Ashwood ER, editors. Tietz textbook of clincal chemistry. 2nd ed. Philadelphia: W.B. Saunders 1994. 22) Primus FJ et al. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine antibody for diagnosis and therapy. Clin Chem 1988;34:261-4. 23) Hansen HJ et al. Solving the problem of antibody interference in commercial "sandwich"-type immunoassay of carcinoembryonic antigen. Clin Chem 1989;35:146-51. 24) Schroff RJ et al. Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy. Cancer Res 1985;45:879-85. 25) Morgan WR 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. 26) National Committee for Clinical Laboratory Standards. Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard. 4th ed. NCCLS Document H3-A4 Wayne PA: NCCLS 1998. 27) Smith RA, et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2000; 50(1):34-49.

Technical Assistance

In the United States, contact DPC's Technical Services department.
Tel: 800.372.1782 or 973.927.2828
Fax: 973.927.4101. Outside the United States, contact your National Distributor.

The Quality System of Diagnostic Products Corporation is registered to ISO 9001:1994.

DPC®
Diagnostic Products Corporation
5700 West 96th Street
Los Angeles CA 90045-5597

2001-04-30 (ISO 8601)

May 1, 2001

PILKPS – 4