



Technical Bulletin

Detailed information concerning methodology, specimen requirements, and reference ranges on new and specialized tests

TESTS FOR PROSTATIC DISEASE

• Test Name-Order Number, & CPT Code:	Total PSA - 773 CPT - 84153
	Complexed PSA - 4500 CPT - 84152
	Free PSA * - 4498 CPT - 84154
	*(includes total PSA, complexed PSA and a calculated % free PSA).
• Department:	ACM Medical Laboratory at Elmgrove
• Testing Schedule:	Monday through Saturday
• Specimen Requirement:	1 mL serum
• Reference Range:	tPSA 0-4.0 ng/mL, cPSA < 3.6 ng/mL, fPSA >25%
• Methodology:	Chemiluminescent Immunoassay
• Turn-Around-Time	24 hours

Clinical Significance

Total PSA:

Total prostate-specific antigen (tPSA or human kalikrein-3) is a serine protease produced by the epithelial cells of the prostate gland. Most of the PSA in serum in normal individuals is bound and inhibited by formation of complexes with serine protease inhibitors. PSA is detected in the serum of males with normal, benign hypertrophic and malignant disease.

Complexed PSA:

The major forms of PSA include **free PSA** (fPSA) and **complexed PSA** (cPSA), which make up the **total PSA** (tPSA). In normal men, 75 to 90% is **complexed PSA**, primarily with alpha-1-chymotrypsin (ACT) and small amounts of alpha-1-antitrypsin and inter-alpha-trypsin inhibitor. Alpha-2-macroglobulin also binds to PSA but is not measured in current assays.

In patients with adenocarcinoma of the prostate, a higher proportion of total PSA is bound, so the amount of **complexed PSA** tends to be higher than normal (>90%). **cPSA** has similar sensitivity and greater specificity compared to **total PSA** as reported in several studies by Brawer.^{1,2,5} The literature is still mixed on this issue but it appears to be leaning in favor of **complexed PSA** over **total PSA**.

Free PSA:

The amount of **free PSA** tends to be lower (<25%) in men with prostate cancer³. The probability of cancer increases as the amount of **free PSA** decreases. Thus, **free PSA** is used as an adjunct to **total PSA and DRE** in cases where the **total PSA** is in the range of 4-10 ng/mL.

Methods:

The tPSA and cPSA assays are equimolar assays, reacting equally with both free PSA and complexed PSA so changes in the amount of either material do not affect the assay differently. Complexed PSA assay is a two-site sandwich immunoassay using direct chemiluminometric technology. A direct relationship exists between the amount of cPSA in the sample and the amount of light produced by the assay system⁴. The assay is sensitive from 0.03 to 100 ng/mL.

Expected Values: **Total PSA** 0 - 4.0 ng/mL
Complexed PSA < 3.6 ng/mL
Free PSA > 25 %

Total PSA:	DRE Negative Individuals⁴		DRE Positive Individuals⁴	
	tPSA	Positive Biopsy	tPSA	Positive Biopsy
	<4.0 ng/mL	3.1%	<4.0 ng/mL	31.7%
	>4.0 ng/mL	15.2%	>4.0 ng/mL	48.8%

Complexed PSA: The expected values of **complexed PSA** obtained from 199 apparently healthy males gave a range of 0-3.5 ng/mL⁴.

The probability of a positive biopsy result for prostate cancer on an ultrasound guided sextant biopsy of more than six cores is given in the following tables. The risk is stratified by **complexed PSA** values.

DRE Negative Individuals⁴		DRE Positive Individuals⁴	
cPSA (ng/mL)	%Risk	cPSA (ng/mL)	%Risk
<3.6	27.2	<3.6	52.9
3.6-5.0	39.3	3.6-5.0	58.6
>5.0	51.3	>5.0	78.0

Free PSA:	tPSA	Probability of CA	Free PSA	Probability of CA³
	4-10 (ng/mL)	25%	0-10%	56%
			10-15%	28%
			15-20%	20%
			20-25%	16%
			>25%	8%

Clinical use of Free PSA: If <10% do biopsy, if 10-25% discuss risks and benefits and if > 25% do not biopsy as per NCCN guidelines.⁵

- Limitations:**
- 1) Heterophile antibodies in human serum of patients routinely exposed to animals can react with the reagent immunoglobulins, giving interference in these types of assays and may give anomalous values⁶.
 - 2) Cancer patients under treatment with anti-androgens and LRHH agonists and antagonists may exhibit markedly reduced levels of cPSA. Care should be used in interpreting values from these patients⁴.

Sample Stability: **Total PSA** and **complexed PSA** are stable refrigerated (4-8°C) for two days. Samples for longer storage must be frozen. **Free PSA** needs to be frozen as soon as separated from cells.

Patient Preparation: Digital rectal examination and ejaculation 48 hours prior to specimen collection may cause spurious elevations of results⁵.

References:

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1. Brawer et al Measurement of complexed PSA improves specificity for early detection of prostate cancer, Urol, 52: 372-378, 1998.
2. Brawer et al Complexed prostate specific antigen provides significant enhancement of specificity compared with total prostate specific antigen for detecting prostate cancer, J Urol 163: 1476-1480, 2000.
3. Catalona, WJ, et al, Use of the Percentage of Free Prostate-Specific Antigen to Enhance Differentiation of Prostate Cancer from Benign Prostatic Disease, NEJM, 279: 1542-1547, 1998.
4. Bayer package inserts, cPSA, Rev G, 2003-08, tPSA, Rev G, 2003-07.
5. NCCN, Prostate Cancer Early Detection, Clinical Practice Guidelines in Oncology, Version 1, 2004.
6. Boscato LM et al, Heterophile antibodies: a problem for all immunoassays, Clin Chem 34: 27-33, 1988.

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