

ADVIA Centaur Free PSA Assay: Performance and Clinical Utility

White Paper

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Abstract

Percent free PSA has increased specificity compared to total PSA for aiding in the diagnosis of prostate cancer among men with total PSA values in the gray zone. This increased specificity aids in reducing the number of unnecessary biopsies. Percent free PSA values are recognized as a useful adjunct to total PSA by the American Urological Association, European Association of Urology, National Comprehensive Cancer Network, European Group on Tumor Markers, and National Academy of Clinical Biochemistry guidelines for early prostate cancer detection. Even with the use of WHO standards, differences still exist between manufacturers' assays. Because of these differences, percent free PSA values must be determined using results from free PSA and total PSA companion assays run on the same platform. Using assays from different manufacturers and different platforms may complicate interpretation and the utility of percent free PSA values. The ADVIA Centaur® free PSA assay* demonstrated good performance and clinical utility when used with the ADVIA Centaur PSA assay as an aid in the diagnosis of prostate cancer among men with total PSA values between 4 and 10 ng/mL and nonsuspicious DRE.

Percent free PSA aids in prostate cancer diagnosis

Prostate-specific antigen (PSA) is a serine protease that exists in bound and free forms. Total PSA assays measure both bound and free PSA, while free PSA assays measure only free PSA. Percent free PSA is calculated as follows: $(\text{free PSA} / \text{total PSA}) \times 100$. The percent free PSA is associated with prostate cancer risk. Lower percent free PSA values are associated with a higher risk of prostate cancer on biopsy.¹⁻⁵ Higher percent free PSA values are associated with a lower risk of prostate cancer on biopsy. In one prospective study, 56% of men with percent free PSA of <10% had prostate cancer on biopsy, compared to 8% of men with percent free PSA of >25%.³

Among men with total PSA values of between 4 and 10 ng/mL (gray zone) and a nonsuspicious digital rectal exam (DRE), percent free PSA has been shown to increase the specificity of prostate cancer detection on biopsy. Percent free PSA determinations are widely used in this application and are acknowledged as increasing the specificity of prostate cancer detection in the European Association of Urology, American Urological Association, and the National Comprehensive Cancer Network guidelines for early detection of prostate cancer.¹⁻⁵ The guidelines from the National Academy of Clinical Biochemistry and European Group on Tumor Markers recommend the use of percent free PSA in men with total PSA values between 4 and 10 ng/mL and a negative DRE.^{2,4} The protocol recommended by the National Comprehensive Cancer Network includes suggested cutoffs;⁵ laboratories, however, should determine their own cutoff values.

*Not available for sale in the U.S.

Manufacturers' varying cutoffs require using companion assays

The introduction of the WHO reference standards for total PSA and free PSA have reduced the variation between manufacturers' assays, but variation still exists, and assays are not interchangeable.⁶⁻⁹ The differences in PSA assays are due to different antibodies and technologies used.⁶ Percent free PSA values should be determined from the results of total PSA and free PSA companion assays run on the same platform. Manufacturers' suggested cutoffs and regulatory approval are both based on percent free PSA values determined in this way. Calculating a percent free PSA using a free PSA result from one manufacturer's assay and a total PSA result from a different manufacturer's assay could provide an unexpected value. Moreover, percent free PSA cutoff values from different manufacturers have various levels of sensitivity and specificity and are not interchangeable.⁶⁻⁹ Each laboratory should establish its own percent free PSA cutoff values.

ADVIA Centaur free PSA assay demonstrated good performance characteristics

The ADVIA Centaur free PSA assay is a two-site sandwich immunoassay using direct chemiluminometric technology and two monoclonal mouse antibodies.¹⁰ The assay is intended to be used in conjunction with the ADVIA Centaur PSA assay to determine percent free PSA values in men aged 50 years or older with total PSA values between 4 and 10 ng/mL and a DRE that is nonsuspicious for cancer. Percent free PSA values aid in discriminating between prostate cancer and benign prostatic disease. The diagnosis of prostate cancer is based on prostate biopsy results.¹⁰

The ADVIA Centaur free PSA assay is traceable to the WHO 97/668 standard; a comparison over the range of the assay demonstrated a correlation coefficient of 1.00.¹⁰

$$\text{ADVIA Centaur free PSA} = 0.96 (\text{WHO 97/668}) + 0.11$$
$$r = 1.00$$

Excellent reproducibility

The ADVIA Centaur free PSA assay demonstrated excellent within-run, between-run, and total CVs of less than 8% (Table 1).¹⁰

Table 1. ADVIA Centaur free PSA assay within-run, between-run, and total CVs.

Mean (ng/mL) (µg/L)	Within-Run CV (%)	Between-Run CV (%)	Total CV (%)
0.42	3.2	1.6	4.3
0.96	2.0	1.7	3.7
2.33	2.6	1.2	3.5
13.71	2.8	0.8	4.0
19.44	5.3	5.2	7.9

For percent free PSA assays in general, percent free PSA values provide better discrimination between cancer and benign prostatic disease among men with total PSA values between 4 and 10 ng/mL and nonsuspicious DRE. However, manufacturers have different sensitivities at which percent free PSA values do not offer a significant clinical advantage over total PSA alone. For ADVIA Centaur percent free PSA sensitivity estimates above 88%, percent free PSA is equivalent to total PSA with respect to discrimination between cancer and benign prostatic disease.

Using the ADVIA Centaur assays and ROC analysis, two different studies compared percent free PSA and total PSA values for the detection of prostate cancer. Both studies showed similar results. In the one (internal) study, percent free PSA had an AUC of 0.66 and total PSA an AUC of 0.54 (Table 2 and Figure 1). In the other (external) study, percent free PSA had an AUC of 0.64 and total PSA an AUC of 0.51 (Table 3 and Figure 2).

Fewer unnecessary biopsies

The increased ability of percent free PSA to discriminate between cancer and benign prostatic disease is due to its increased specificity. Percent free PSA values determined from the ADVIA Centaur free PSA assay at a cutoff of 27% detected 90% of prostate cancers and avoided unnecessary biopsies in 15.5% of men without prostate cancer (Table 4).¹⁰

Table 2. AUC results of ROC analysis for ADVIA Centaur percent free PSA and total PSA for prostate cancer detection on biopsy (n = 543).

Assay	AUC	AUC 95% CI	SE
Percent free PSA	0.66	0.61 to 0.70	0.025
Total PSA	0.54	0.49 to 0.59	0.026

Table 3. AUC results of ROC analysis for ADVIA Centaur percent free PSA and total PSA values for prostate cancer detection on biopsy (n = 500).

Assay	AUC	AUC 95% CI	SE
Percent free PSA	0.64	0.59 to 0.68	0.025
Total PSA	0.51	0.46 to 0.56	0.026

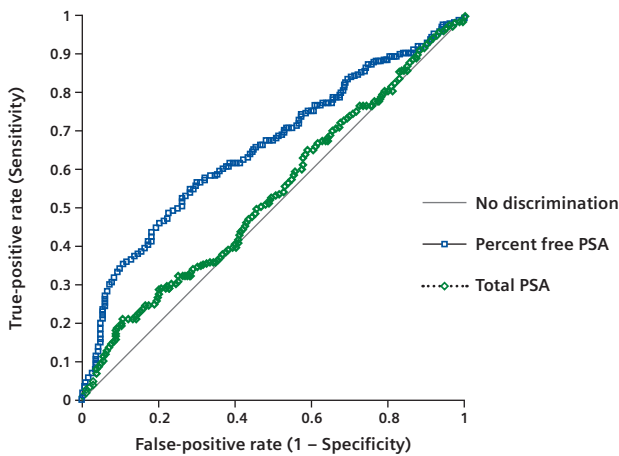


Figure 1. ROC analysis of the ADVIA Centaur percent free PSA and total PSA assays for prostate cancer detection on biopsy.

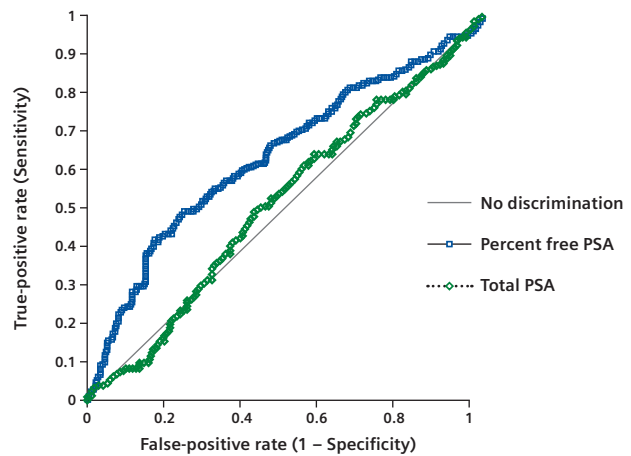


Figure 2. ROC comparison of the ADVIA Centaur percent free PSA and total PSA values for prostate cancer detection on biopsy.

Table 4. The ADVIA Centaur sensitivity and specificity for prostate cancer on biopsy by percent free PSA cutoff.¹⁰

Percent Free PSA Cutoff	Sensitivity		Specificity	
	Percentage of Prostate Cancers Detected ^a	95% CI ^b	Percentage of Biopsies Avoided in Men without Prostate Cancer ^c	95% CI ^b
23%	86.0% (172/200)	80.4%–90.5%	25.1% (86/343)	20.6%–30.0%
25%	88.0% (176/200)	82.7%–92.2%	19.5% (67/343)	15.5%–24.1%
27%	90.0% (180/200)	85.0%–93.8%	15.5% (53/343)	11.8%–19.7%
33%	95.5% (191/200)	91.6%–97.9%	7.6% (26/343)	5.0%–10.9%
51%	100% (200/200)	98.5%–100%	0.3% (1/343)	0.0%–1.6%

^aNumber of prostate cancers detected/total number of biopsy positive

^b95% CI: 95% confidence interval

^cNumber of biopsies avoided, without cancer/total number of biopsy negative

Comparisons to other percent free PSA ratios

The ADVIA Centaur percent free PSA ratio was compared to the Beckman Coulter ACCESS 2, Roche E 170, Siemens IMMULITE® 2000, and Perkin Elmer DELFIA free PSA ratios and demonstrated correlation coefficients (r) for percent free PSA ratios ranging from 0.899 to 0.994.

Comparison to the Beckman Coulter ACCESS 2 percent free PSA ratio

The percent free PSA ratios calculated from the ADVIA Centaur assay were comparable to the ratios determined from the ACCESS 2 free PSA assay and demonstrate a correlation coefficient of 0.976, n = 199 (Figure 3).¹¹

Comparison to the Siemens IMMULITE 2000 percent free PSA ratio

The ADVIA Centaur percent free PSA ratios were compared to the IMMULITE 2000 percent free PSA ratios and demonstrated a correlation coefficient of 0.994, n = 203 (Figure 4).¹¹

Comparison to the Roche E 170 percent free PSA ratio

The ADVIA Centaur percent free PSA ratios were compared to the E 170 percent free PSA ratios (external study) and demonstrated a correlation coefficient of 0.955, n = 99 (Figure 5).

Comparison to Perkin Elmer DELFIA percent free PSA ratio

The ADVIA Centaur percent free PSA ratios were compared to the DELFIA free PSA ratios (external study) and demonstrated a correlation coefficient of 0.899, n = 148 (Figure 6). The three outliers in the plot are all of percent free PSA values associated with a very low risk for prostate cancer.

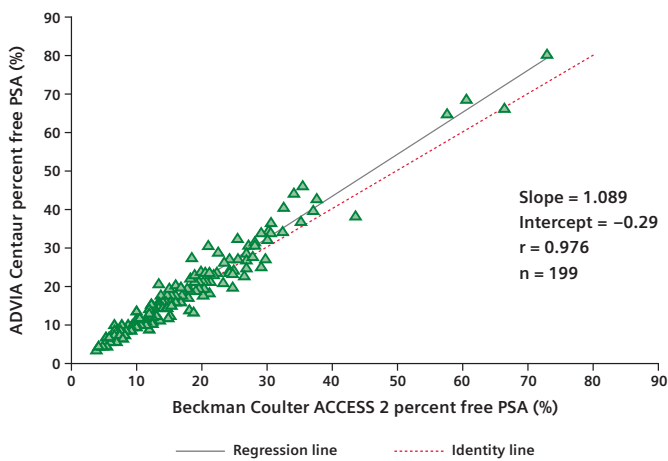


Figure 3. Comparison of the percent free PSA ratios determined by the ADVIA Centaur and ACCESS 2 assays.¹¹

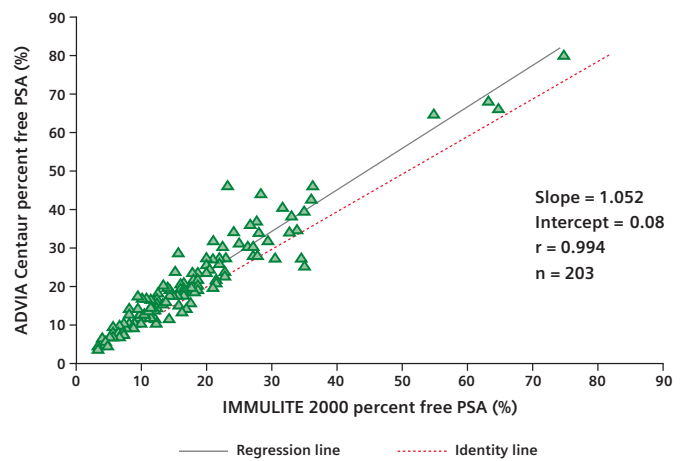


Figure 4. Comparison of the percent free PSA ratios determined by the ADVIA Centaur and IMMULITE 2000 assays.

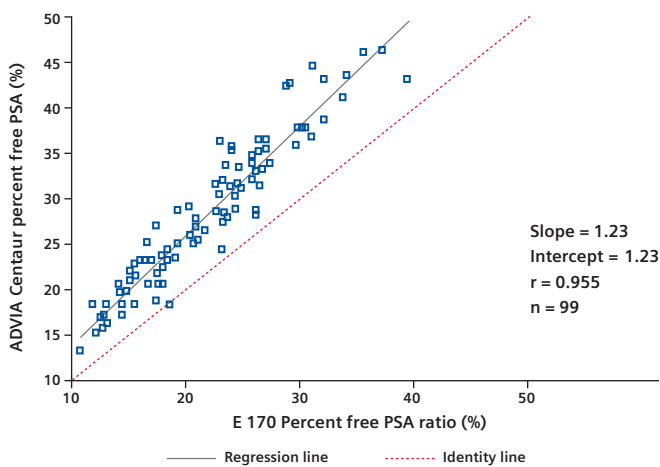


Figure 5. Comparison of the percent free PSA ratios determined by the ADVIA Centaur and E 170 assays.

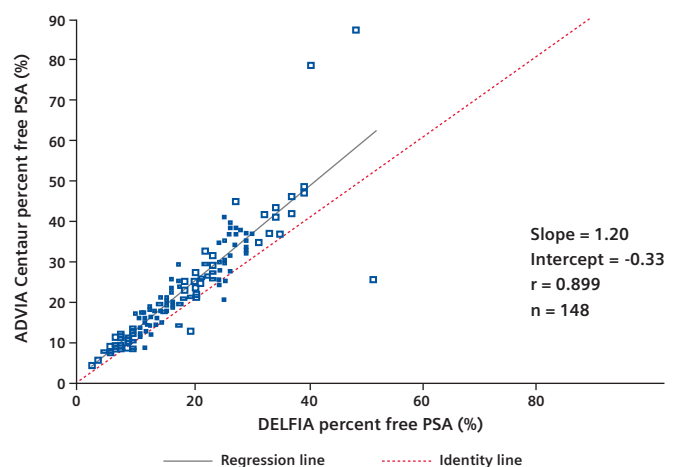


Figure 6. Comparison of the percent free PSA ratios determined by the ADVIA Centaur and DELFIA assays.

Percent free PSA ratios— ROC analysis comparisons

Percent free PSA ratios determined using the ADVIA Centaur free PSA and PSA assays demonstrated performance comparable to that of the IMMULITE 2000 and ACCESS 2 percent free PSA ratios for aiding in the diagnosis of prostate cancer.

ROC comparison to the IMMULITE 2000 percent free PSA ratio

Percent free PSA ratios were determined for 125 samples. On ROC analysis, the ADVIA Centaur percent free PSA ratios had AUC values comparable to those obtained with the IMMULITE 2000 percent free PSA values (0.67 [95% CI: 0.57–0.78] versus 0.7 [95% CI: 0.59–0.8]; $P = 0.1896$) (Figure 7).¹¹

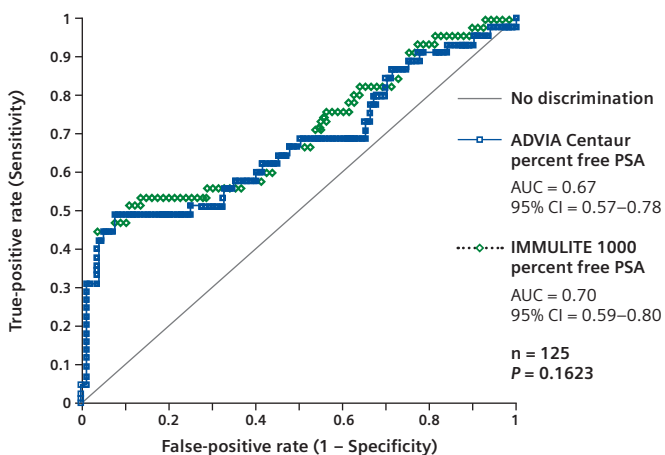


Figure 7. ROC analysis comparison of the ADVIA Centaur and IMMULITE 2000 percent free PSA ratios for detection of prostate cancer.¹¹

ROC comparison to the ACCESS 2 percent free PSA ratio

Percent free PSA ratios were determined for 130 samples. On ROC analysis, the ADVIA Centaur percent free PSA ratios had AUC values comparable to those obtained with the ACCESS 2 percent free PSA values (0.68 [95% CI: 0.57–0.78] versus 0.7 [95% CI: 0.59–0.8]; $P = 0.1896$) (Figure 8).¹¹

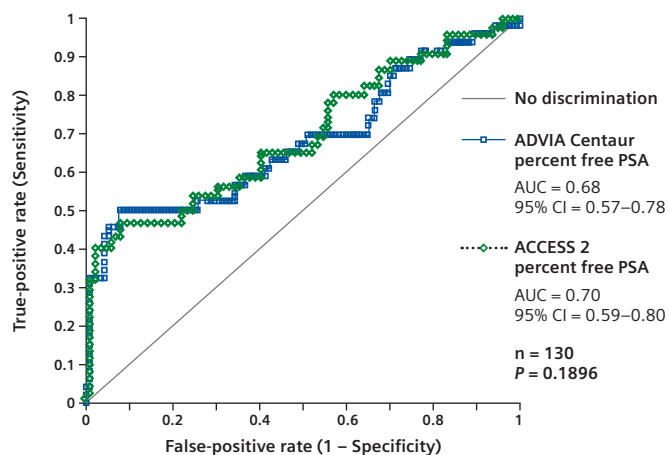


Figure 8. ROC analysis comparison of percent free PSA ratios calculated from the ADVIA Centaur and ACCESS 2 free PSA assays.¹¹

Conclusions

The ADVIA Centaur free PSA assay is intended to be used with the ADVIA Centaur PSA assay as an aid in the diagnosis of prostate cancer among men with total PSA values between 4 and 10 ng/mL and nonsuspicious DRE. The free PSA assay demonstrated excellent performance characteristics. ADVIA Centaur percent free PSA ratios were comparable to Siemens IMMULITE 2000 and Beckman Coulter ACCESS 2 percent free PSA ratios. Percent free PSA values and cutoffs of various manufacturers' assays are not interchangeable, and percent free PSA values should be determined using free PSA and total PSA assays measured on the same platform.

References:

1. American Urological Association. Prostate-specific antigen best practice statement: 2009 update. 2009. American Urological Association Education and Research, Inc.
2. European European Group on Tumor Markers. Tumour markers in prostate cancer—EGTM recommendations [Internet]. European Group on Tumor Markers. 2009 [Cited 2009 Nov 20]. Available from: http://www.egtm.eu/tumour_markers_in_prostate_cancer.htm.
3. Heidenreich A, Bolla M, Joniau S, van der Kwast TH, Matveev V, Mason MD, et al. Guidelines on prostate cancer [Internet]. Arnhem (Netherlands): European Association of Urology; c2009 [cited 2010 Aug 20]. Available from: http://www.uroweb.org/fileadmin/txeauguidelines/2009/Full/Prostate_Cancer.pdf.
4. National Academy of Clinical Biochemistry. Sturgeon CM, Diamandis EP, editors. Laboratory medicine practice guidelines. Use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers [Internet]. Washington DC: American Association for Clinical Chemistry; c2009 [cited 2010 Aug 20]. Available from: <http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/major/Documents/TumorMarkersMajor09.pdf>.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Prostate cancer early detection. V.2.2010. [Internet]. Fort Washington (PA): NCCN; 2009 [cited 2010 A 20]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
6. Slev PR, La'ulu SL, Roberts WL. Intermethod differences in results for total PSA, free PSA, and percentage of free PSA. *Am J Clin Pathol*. 2008 June;129(6):952-8.
7. Stephan C, Klaas M, Muller C, Schnorr D, Loening SA, Jung K. Interchangeability of measurements of total and free prostate-specific antigen in serum with 5 frequently used assay combinations: an update. *Clin Chem*. 2006 Jan;52(1):59-64.
8. Stephan C, Kramer J, Meyer HA et al. Different prostate-specific antigen assays give different results on the same blood sample: an obstacle to recommending uniform limits for prostate biopsies. *BJU Int*. 2007 June;99(6):1427-31.
9. Stephan C, Kopke T, Semjonow A et al. Discordant total and free prostate-specific antigen (PSA) assays: does calibration with WHO reference materials diminish the problem? *Clin Chem Lab Med*. 2009;47(11):1325-31.
10. Siemens Healthcare Diagnostics. Free PSA (fPSA). ADVIA Centaur and ADVIA Centaur XP systems. 2010. Tarrytown, New York, Siemens.
11. Kelley W, Ahnadi C, Gray J, Pomerleau JF, Montgomery-Chapman SE, Fan J, et al. A multicenter evaluation of the clinical performance of the ADVIA Centaur free PSA assay. Poster session presented at: American Association of Clinical Chemistry Annual Meeting; 2009 Jul 19-23; Chicago, IL.

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