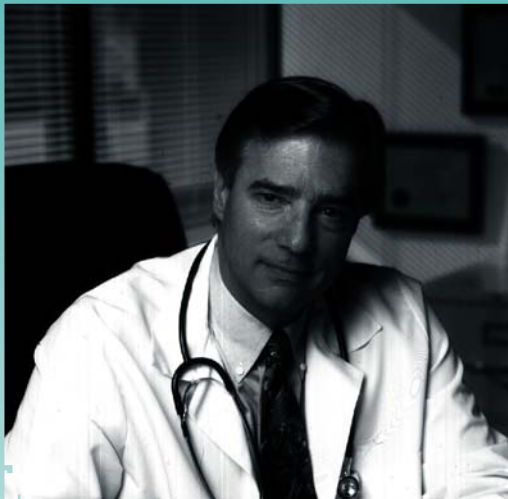


Hybritech®
free PSA

*A Diagnostic Tool to
Aid in Differentiating
Prostate Cancer from
Benign Conditions*





FOREWORD

This publication is intended to provide the physician with supplementary information regarding the use of free PSA testing as an aid in prostate cancer detection. Please call the Beckman Coulter PSA Hotline at 1-888-880-0518 to obtain additional copies of this brochure.

Beckman Coulter, Inc., 200 S. Kraemer Blvd., Brea, CA 92821

CAUTION: *Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to, by or on the order of a physician.*

WARNING

The free PSA Assay should be used only with the (total) PSA Assay to calculate the ratio of free PSA to total PSA (percent free PSA). Use of another manufacturer's total PSA assay may result in:

- (1) an inappropriate population of patients selected for free PSA testing; and
- (2) significantly different percent free PSA values, cutoffs and cancer probabilities than presented in the Clinical Studies section of this brochure.

Results contained in this brochure apply only to percent free PSA as measured by the free PSA and (total) PSA Assays.

The concentration of free PSA and total PSA in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must specify the manufacturer of the free and total PSA assays used. Values obtained with different manufacturers' assays cannot be used interchangeably.

Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted to, by or on the order of a physician.

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INTRODUCTION

Prostate cancer is the most common type of cancer found in men in the United States, with an incidence of approximately one case for every ten men. It is also the second leading cause of cancer deaths among American men.¹

Prostate-specific antigen (PSA) was identified and purified by Wang and coworkers in 1979.² PSA, a serine protease, is produced by the epithelial cells of the prostate, and is produced by both benign and malignant cells. Abnormalities in the prostate gland architecture resulting from trauma or disease can lead to “leakage” of PSA into the bloodstream.

A multicenter, prospective clinical trial conducted by Hybritech found that PSA was a safe and effective aid in the detection of prostate cancer.³ In this study of 6,630 men, PSA and DRE performed together detected approximately 81% more prostate cancer than DRE alone.

However, PSA is a tissue-specific rather than tumor-specific protein that has been shown to be elevated in both benign prostatic conditions and prostate cancer. Although measurement of PSA has been shown to be valuable in the early detection of prostate cancer, it is limited by its relative lack of specificity when the PSA concentration is in the range of 4 to 10 ng/mL. The false positive rate of the test in this range is reported to be 75%. It should be noted, however, that mammography, a widely-accepted cancer screening method, has a false positive rate of 80%. Serum total PSA is effective in the detection of prostate cancer, but any method that would increase specificity would be of great benefit to the medical community.

The American Urological Association and the American Cancer Society have recommended that men over the age of 50 have an annual prostate evaluation consisting of a digital rectal examination (DRE) and a serum PSA test. Men in high-risk groups and those with a family history of prostate cancer are urged to begin prostate examinations at a younger age (e.g., age 45).

PSA exists primarily as three forms in serum.⁴ One form of PSA is believed to be enveloped by a protease inhibitor, alpha-2 macroglobulin,⁵ and has been shown to lack immunoreactivity. A second form is complexed to another protease inhibitor, alpha-1 antichymotrypsin (ACT).^{5,6} The third form of PSA is not complexed to a protease inhibitor, and is termed free PSA.^{5,6} The latter two forms are immunologically detectable in commercially available PSA assays and are referred to collectively as total PSA.

Previous reports have shown that measurement of PSA forms enhances the specificity of total PSA for prostate cancer detection and is useful in the differentiation of prostate cancer from benign prostatic conditions.^{7,8} In patients with elevated PSA concentrations, men with prostate cancer tend to have lower percent free PSA (free PSA/total PSA) values than men with benign disease.⁹⁻¹² This difference in the distribution of percent free PSA values in men with and without cancer may be used to select cutoffs for biopsy decisions, maintaining 90% to 95% sensitivity, while sparing 20% to 30% of men with benign disease from biopsy.

Percent free PSA may also be used for risk assessment, to determine the probability of cancer for an individual patient. Lower percent free PSA values are associated with higher risk of cancer.⁹⁻¹²

In current clinical practice, prostate biopsy is recommended for men with a suspicious DRE result, regardless of the PSA level (Table 1). Patients with PSA greater than 10 ng/mL also undergo biopsy since the rate of cancer is high in this group (>50%). Biopsy is recommended for men with nonsuspicious DRE results and PSA between 4 and 10 ng/mL, and 25% of these men have cancer. But specificity could be improved in this population since 75% of the biopsies are negative. Therefore, this is the group selected for Hybritech's multicenter percent free PSA clinical trial.

This trial was designed to evaluate the ability of percent free PSA as measured by Hybritech's assays to distinguish prostate cancer from benign prostatic conditions in men aged 50 years or

Table 1. Current Clinical Practice (Biopsy/No Biopsy) and Proportion of Men with Cancer Based on PSA and DRE Findings.

PSA (ng/mL)				
	0 – 2	2 – 4	4 – 10	>10
DRE –	No Biopsy (1% Cancer)	No Biopsy (15% Cancer)	Biopsy (25% Cancer)	Biopsy (>50% Cancer)
DRE +	Biopsy (5% Cancer)	Biopsy (20% Cancer)	Biopsy (45% Cancer)	Biopsy (>75% Cancer)

*Gray Box: Percent free PSA Clinical Trial Population
(Comparison: Mammography for breast cancer detection = 20% cancer)*

older with a PSA between 4 and 10 ng/mL and a nonsuspicious DRE. This study found that use of percent free PSA would have eliminated 20% of the unnecessary biopsies in men without cancer, while still detecting 95% of the cancers.¹³

The results of this study are summarized in this brochure. This information is designed to instruct physicians on the use of free PSA and provide them with a valuable tool to enhance their cancer detection and patient management strategies.

In the previously mentioned Hybritech-sponsored clinical study of the (total) PSA assay for prostate cancer detection, 9% of the 6,630 men tested had a nonsuspicious DRE and a PSA between 4 and 10 ng/mL.³ Thus, in a prostate cancer detection program, DRE and PSA testing would identify this subgroup of all men undergoing evaluation for prostate cancer. Free PSA and percent free PSA (ratio of free PSA to total PSA x 100) would then be determined for these patients, and results would be used as an aid in patient management.

INTENDED USE

The free PSA Assays are *in vitro* devices for the quantitative measurement of free prostate specific antigen (free PSA) in human serum.

Hybritech's free PSA assays are intended to be used with (total) PSA to calculate the ratio of free PSA to total PSA expressed as a percentage (percent free PSA).

Percent free PSA as measured by Hybritech's assays is indicated for use as an aid in distinguishing prostate cancer from benign prostatic conditions, when used in conjunction with (total) PSA for prostate cancer detection in men aged 50 years or older who have total PSA values between 4 and 10 ng/mL and digital rectal examination findings that are not suspicious for cancer. Prostatic biopsy is required for diagnosis of cancer.

SPECIMEN COLLECTION AND PREPARATION

No special preparation of the patient is necessary. Specimens for free PSA testing should be drawn prior to such prostatic manipulations as digital rectal examination (DRE), prostatic massage, transrectal ultrasound (TRUS), and prostatic biopsy. DRE may cause a transient increase in both free and total PSA.¹⁴ A repeat total PSA measurement in the case of borderline elevation is recommended.¹⁵

Transrectal needle biopsy has also been shown to cause transient increases in free PSA and persisting total PSA elevations;^{14,15} thus, a six-week waiting period between needle biopsy and PSA sampling has been recommended.

Serum is required for the free PSA Assay. Plasma samples should **not** be used.

Only blood drawn by an acceptable medical technique into a collection tube with no anticoagulants should be used. Specimens should be collected in such a way as to avoid hemolysis.

The specimen should be allowed to clot and the serum separated by centrifugation. **Specimens should be processed (centrifuged) and refrigerated within three hours of blood draw.**

If the serum sample is to be assayed within 24 hours after collection, the specimen should be stored in a refrigerator at 2°C

to 8°C. Specimens held for longer times (up to five months) should be frozen at -20°C or colder.^{16,17} Specimens to be held for longer than five months should be frozen at -70°C.^{16,17} Repeated freeze-thaw cycles have no effect on free PSA, total PSA, or percent free PSA.¹⁶ However, prompt refreezing of the thawed samples is recommended.

Turbid serum samples or samples containing particulate matter should be centrifuged prior to assay.

CLINICAL STUDY RESULTS

A multicenter, prospective clinical trial was conducted to test the effectiveness of percent free PSA as an aid in distinguishing prostate cancer from benign prostatic conditions, when used in conjunction with (total) PSA for prostate cancer detection.

All subjects were between 50 and 75 years of age, with serum PSA values between 4 and 10 ng/mL and digital rectal examination (DRE) findings that were not suspicious for cancer. These men represent the “diagnostic gray zone,” in which total PSA has identified the men as high risk (25% cancer rate compared to a 4% cancer rate for the general population of men over 50 years of age), but where specificity could be improved. All men had undergone ultrasound-guided six-sector needle biopsies of the prostate, and thus had a histologically-confirmed diagnosis prior to determination of free PSA concentrations. The study was blinded; pathologists did not have access to percent free PSA values, and laboratorians did not have access to diagnoses. Exclusion criteria included acute prostatitis, urinary tract infection, prior transurethral resection of the prostate (TURP), or recent prostatic manipulation or medications that might alter serum PSA concentrations.

A total of 773 men participated in the study. Median age for both cancer and benign disease subjects was 64 years. The study population was 86% Caucasian, 9% African-American, 3% Hispanic, and 2% Asian.

Table 2 shows the expected values for free PSA (ng/mL), total

Table 2. Free PSA (ng/mL), Total PSA (ng/mL) and Percent free PSA (%): Expected Values, by Diagnosis

		Benign N = 394	Cancer N = 379	Total N = 773
free PSA	Median	1.0	0.7	0.9
	Mean ± SD	1.1 ± 0.6	0.8 ± 0.5	1.0 ± 0.6
	Range	0.2 – 4.9	0.2 – 3.6	0.2 – 4.9
Total PSA	Median	5.6	5.9	5.8
	Mean ± SD	6.0 ± 1.6	6.2 ± 1.7	6.1 ± 1.6
	Range	4.0 – 10.0	4.0 ± 10.0	4.0 ± 10.0
% free PSA	Median	17.9	12.2	15.3
	Mean ± SD	19.0 ± 7.8	13.4 ± 6.8	16.3 ± 7.9
	Range	4.3 – 52.2	2.3 – 42.1	2.3 ± 52.2

PSA (ng/mL), and percent free PSA [(free PSA / total PSA) x 100%] for this population of men.

In a prostate cancer detection program, DRE and PSA testing would identify men with nonsuspicious DRE results and PSA between 4 and 10 ng/mL. Free PSA and percent free PSA would then be determined on these patients, and results would be used as an aid in patient management.

The multicenter clinical trial results demonstrated that percent free PSA may be used in two ways:

- (1) individual patient risk assessment to aid in management decisions; or
- (2) a single cutoff (men with values less than or equal to a certain cutoff would be candidates for additional follow-up procedures such as biopsy).

Individual Patient Risk Assessment

Percent free PSA may be used to determine the relative risk of prostate cancer in individual men. Family and patient history can be used in combination with percent free PSA results to determine the best individualized patient management decisions.

Table 3. Probability of Prostate Cancer Based on PSA and Percent free PSA Results (for Men with Nonsuspicious DRE Results, Regardless of Patient Age)

PSA	Probability of Cancer	Percent free PSA	Probability of Cancer
0-2 ng/mL	1%	0-10%	56%
2-4 ng/mL	15%	10-15%	28%
4-10 ng/mL	25%	15-20%	20%
>10 ng/mL	>50%	20-25%	16%
		>25%	8%

Table 3 shows the probability of detecting prostate cancer with needle biopsy based on total PSA and percent free PSA results. PSA results in this table were obtained from a prior multicenter study evaluating the efficacy of total PSA for prostate cancer detection,^{3,18} and percent free PSA results were obtained from the current study.

It can be seen that rising PSA levels increase the risk of detectable cancer. Percent free PSA can further stratify risk for men with PSA values between 4 and 10 ng/mL and nonsuspicious digital rectal examination results. Lower percent free PSA values indicate higher risk. The risk of cancer ranged from 8% to 56% for this population. For purposes of comparison, the risk of prostate cancer is 4% for the general population of men over 50 years of age.³

Percent free PSA values should not be interpreted as definitive evidence for the presence or absence of prostate cancer. Prostatic biopsy is required for diagnosis of cancer. However, 20% of cancers are missed on the first biopsy. A patient who has undergone one biopsy with negative findings may be advised to undergo a second biopsy if the percent free PSA value indicates high risk.

The clinical trial results also demonstrated that older men were at higher risk than younger men. The probability of cancer by percent free PSA value and age is shown in Table 4 and Figure 1.

Table 4. Probability of Prostate Cancer (for Men with Nonsuspicious DRE Results and PSA between 4 and 10 ng/mL, by Patient Age)

Percent free PSA (% fPSA)	Patient Age	
	50 to 64 Years	65 to 75 Years
0.00 to 10.00%	56%	55%
10.01 to 15.00%	24%	35%
15.01 to 20.00%	17%	23%
20.01 to 25.00%	10%	20%
≥25.01%	5%	9%

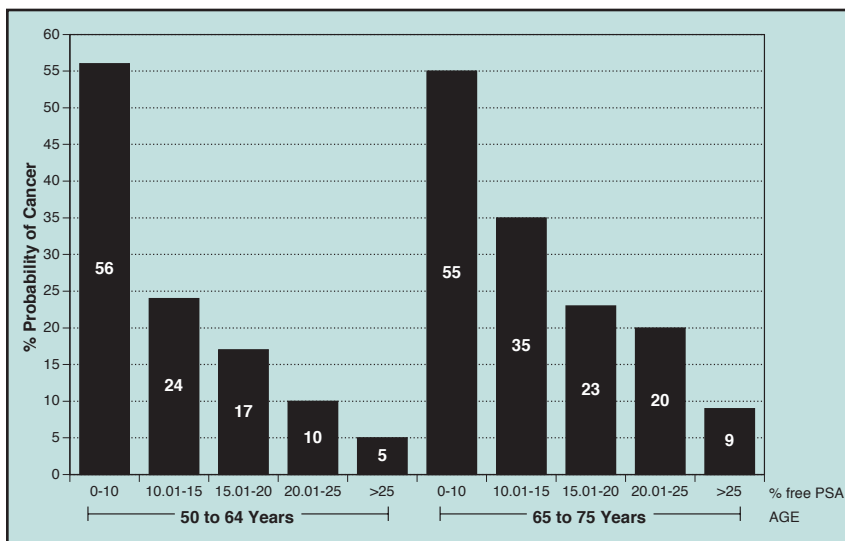


Figure 1. Probability of Cancer (by percent free PSA and patient age for patients with PSA between 4 and 10 ng/mL)

Single Cutoff

Rather than using risk assessment, a cutoff approach to patient management can also be used for interpreting patient results. Table 5 shows sensitivity (percentage of cancers detected) and specificity

Table 5. Sensitivity and Specificity for Various Percent free PSA (% FPSA) Cutoffs Recommended Cutoff: $\geq 25\%$ FPSA (Biopsy men with values *less than* or equal to this cutoff.)

% FPSA Cutoffs	Sensitivity (# of cancers detected/ # of total cancers)			Specificity (# of noncancers detected/ # of total noncancers)		
	%	(n/N)	95% CL*	%	(n/N)	95% CL*
$\leq 25\%$	95%	(358/379)	92-97%	20%	(80/394)	16-24%
$\leq 32\%$	98%	(373/379)	96-99%	6%	(25/394)	4-9%
$\leq 55\%$	100%	(379/379)		0%	(0/394)	

* 95% CL = 95% Confidence Intervals

(percentage of biopsies avoided in men without cancer) for various percent free PSA cutoffs. A cutoff of $\leq 25\%$ free PSA was selected based on data from the clinical trial. When men with values of 25% free PSA or less were biopsied, 95% of cancers were detected. The majority of men with PSA values between 4 and 10 ng/mL have benign disease. In this clinical trial, 20% of biopsied men with benign disease and a percent free PSA value greater than the 25% free PSA cutoff could have been spared from biopsy.

The cutoff of $\leq 25\%$ free PSA is based on results from this clinical trial. Additional follow-up may be recommended for men with percent free PSA values above this cutoff if the physician believes it is necessary based upon other factors in the patient's medical or family history.

Table 6 shows that the cancers occurring in men with a percent free PSA value above the 25% cutoff (i.e., those cancers which would be missed if men above the cutoff were not biopsied) are found primarily in older men with larger glands. Older men (those with less than a 10-year life expectancy) are often not affected by nor treated for prostate cancer. Thus, use of percent free PSA would result in a recommendation for biopsy in younger men, those most likely to gain from early detection.

Table 6. Characteristics of Cancer Subjects Above and Below Cutoff: Patient Age and Prostate Volume

Percent free PSA Cutoff	Median Patient Age	Median Prostate Volume
>25% free PSA	68 years	48 cc
≤25% free PSA	63 years	34 cc

The volume finding is clinically advantageous. Men with percent free PSA values near and above the cutoff tend to have large glands (benign prostatic hyperplasia), whereas men with cancer have lower percent free PSA values which tend to cluster progressively further away from the cutoff. Thus, when the recommendation is made not to biopsy men above the cutoff, this is the group with the lowest risk of cancer and the highest probability of benign disease (see Table 3 and discussion in the previous section, “Individual Patient Risk Assessment”).

Thus, the study found that the cancers above the cutoff, which would be missed, were more prevalent in older men. These cancers were also more likely to be less aggressive. Prostate cancer is generally slow growing. Therefore monitoring these cancer patients over time could allow for future follow-up if total PSA increases or percent free PSA decreases.

LIMITATIONS

- **General Information**

Serum PSA concentrations (free, total, or percent free PSA) should not be interpreted as absolute evidence for the presence or absence of prostate cancer. Elevated total PSA concentrations or decreased percent free PSA may be observed in the serum of patients with nonmalignant disorders, as well as those with prostate cancer. Furthermore, low total PSA concentrations or elevated percent free PSA are not necessarily

indicative of the absence of cancer. Serum free and total PSA values should be used in conjunction with information available from the clinical evaluation of the patient and other diagnostic procedures such as digital rectal examination (DRE). Some cases of early prostate cancer will not be detected by PSA testing; the same is true for DRE. Biopsy of the prostate is the standard method used to confirm the presence or absence of prostate cancer.

The five alpha-reductase inhibitor drugs may affect PSA levels in some patients. Other drugs used to treat BPH may also affect PSA levels. Care should be taken in interpreting results from patients taking these drugs.

- ***Appropriate Use of Free PSA Assay Results***

Study results were obtained using Hybritech's free PSA and total PSA assays. Recent studies have shown that percent free PSA cutoffs and clinical performance differ when various combinations of free and total PSA assays from different manufacturers are used.¹⁹⁻²² Mean percent free PSA values from identical serum samples may be two-fold higher using different assay combinations,²⁰ and 95% sensitivity cutoffs may vary from 22% to 34% using different assay combinations.²² Thus, the study results presented in this brochure apply only to the assays manufactured by Hybritech; results from other manufacturers may vary.

The efficacy of a total PSA assay for cancer detection should be proven prior to adding a second marker (percent free PSA) to enhance this indication. Each total PSA assay should establish its own reference range, positive predictive values, sensitivity and specificity. Numerous total PSA assays are available; however, they are not all equimolar and do not detect various PSA forms equally. These assays are also not calibrated to one another or to one set of standards. Therefore, the potential for incorrect percent free PSA values is high if a free PSA assay from one manufacturer is used with a total PSA assay from

another manufacturer. In addition, use of another manufacturer's total PSA assay which is not calibrated to the (total) PSA assay in the 4 to 10 ng/mL range could result in the wrong patient population being sent on for percent free PSA testing. The 4 to 10 ng/mL range for the assay could be 2.5 to 8 ng/mL for another manufacturer's total PSA assay. Also, patients with benign disease and high free PSA levels could be flagged by a nonequimolar assay to proceed to percent free PSA testing (nonequimolar assays over-report free PSA), whereas cancer patients may fall below the 4 ng/mL cutoff and remain untested and unbiopsied.

The use of free and total PSA assays to generate a percent free PSA value must be performed in a way that ensures accurate, reliable and easily interpretable results. To obtain this accuracy and reliability, the free and total PSA assays used to generate results must be from the same manufacturer. Physicians can ensure this by requesting that laboratories provide them with the name of the PSA assays used.

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