p2PSA Specific Performance Characteristics

Imprecision

The Access p2PSA assay exhibits total imprecision of <20%CV at [-2]proPSA concentrations between the Limit of Quantitation (LOQ) of 3.23 pg/mL and 10 pg/mL, and ≤10%CV at [-2]proPSA concentrations >10 pg/mL. Reproducibility of the p2PSA assay was determined by assaying eight controls containing [-2]proPSA (six of which were serum-based). Data were collected over 20 days and analyzed based on CLSI EP5-A2 guidelines, and are summarized in Table 5.

Table 5. Imprecision of Access Hybritech p2PSA

Sample	Mean (pg/mL)	Within Run CV (%)	Total CV (%)
1	22.75	3.08	4.80
2	106.64	3.83	5.95
3	8.63	4.90	6.11
4	38.46	3.65	4.74
5	108.21	2.84	4.66
6	1179.71	3.09	4.46
7	2899.48	2.21	3.62
8	4748.60	2.36	2.94

Analytical Specificity / Interferences

Cross-reactivity with a mixture of PSA forms (PSA-ACT, fPSA, [-4]proPSA, [-5/-7] proPSA, and BPSA) at proportions typically seen in serum of prostate cancer patients[2] was determined to be 5% or less.

Serum samples containing up to 500 mg/dL (5 g/L) hemoglobin, 20 mg/dL (0.2 g/L) bilirubin, 1500 mg/dL (15 g/L) triglycerides, and a total protein concentration of 6.2 g/dL (62 g/L) do not interfere with the Access Hybritech p2PSA assay.

For patient samples containing elevated levels of total protein (>8 g/dL) the possibility exists for interference by total protein. Carefully evaluate the results of patients with elevated total protein levels.

Limit of Blank (Analytical Sensitivity)

Limit of Blank (LOB) for the p2PSA assay was determined to be 0.50 pg/mL (0.5 pg/mL) using a protocol based on CLSI EP17-A using 148 replicates of a zero analyte sample (S0 calibrator) measured in 12 runs.

References

1. Bryant RJ, Hamdy FC. Screening for prostate cancer: an update. Eur Urol 2008 Jan;53 (1):37-44.
2. Mikolajczyk SD, Rittenhouse HG. Pro PSA: a more cancer specific form of prostate specific antigen for the early detection of prostate cancer. Keio J Med 2003;52 (2):86-91.

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Access Hybritech p2PSA Assay

The novel p2PSA* immunoassay measures [-2]proPSA on the UniCel DxI and Access families of immunoassay systems. The p2PSA results are automatically combined with Access Hybritech PSA and Access Hybritech free PSA test results by a formula that resides in the system software to compute the Beckman Coulter Prostate Health Index *(phi)*.

The *phi* results are intended to be used as an aid in distinguishing prostate cancer from benign prostatic conditions in men 50 years of age and older with PSA results in the 2 to 10 ng/mL range and negative digital rectal examination (DRE) findings. The Access Hybritech p2PSA test results can only be combined with Access Hybritech PSA and Access Hybritech free PSA test results to calculate *phi*. The use of another manufacturer's PSA products is prohibited, as the interpretive criteria established for *phi* have not been validated using other PSA assays.

p2PSA Assay Details

Format	Two-site immunoenzymatic "sandwich" assay
Sample size:	50 µL
Sample type:	Serum
Time to first result:	Approximately 20 minutes
Open pack stability:	28 days
Dynamic range:	0.50 pg/mL to approximately 5,000 pg/mL
Total imprecision:	<20% CV at 3.2 to 10 pg/mL of [-2]proPSA; ≤10% CV at ≥10 pg/mL to approximately 5,000 pg/mL of [-2]proPSA
Calibration stability:	28 days

Background Information

Prostate cancer continues to be a leading cause of cancer mortality in men, accounting for approximately 85,000 deaths annually in Europe and the United States.[1]

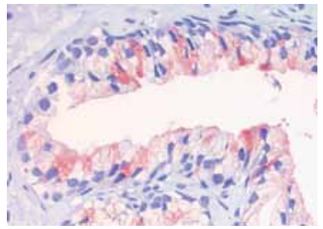
Prostate-specific antigen (PSA) was identified and purified by Wang and co-workers in 1979. PSA, a serine protease, is produced by epithelial cells of the prostate gland in both benign and malignant conditions. Abnormalities in the prostate gland architecture resulting from benign or malignant disease can lead to "leakage" of PSA into the bloodstream.

PSA is found in serum as either a free, non-complexed form (fPSA) or in a complex (cPSA) primarily with the serum protease inhibitor, alpha-1-antichymotrypsin (PSA-ACT). Typically, 70-90% of the PSA in serum is complexed PSA (cPSA), with the remainder being fPSA. Serum %fPSA (ratio of fPSA to PSA) demonstrates a significant improvement over total PSA in discriminating prostate cancer in patients with a negative DRE from benign prostatic conditions in patients with PSA levels in the 4 to 10 ng/mL range.

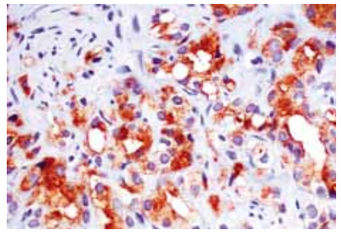
T-13157B

*Not available in the US

Precursor forms of PSA have been found in the serum and are known collectively as proPSA. The [-2]proPSA isoform of fPSA was identified as the most cancer-specific form found in tumor extracts, and shows higher immunohistochemical (IHC) staining in tissue from prostate cancer when compared to normal tissue using a monoclonal antibody developed by Beckman Coulter. The [-2]proPSA molecule is the most stable form of proPSA, i.e., least susceptible to degradation.



A) Normal prostate tissue



B) Gleason 7 (4+3) prostate cancer tissue

Figure A and B: IHC detection with MAb[-2]proPSA by Bostwick Laboratories, Glen Allen, Virginia, USA

The MAb[-2]proPSA antibody used in the IHC staining of [-2]proPSA is also used in the Access Hybritech p2PSA assay to quantitate [-2]proPSA in serum.

Results of a multi-center clinical trial found that Beckman Coulter *phi* significantly enhanced clinical specificity relative to PSA and %fPSA for prostate cancer detection. This improved specificity represents a substantial increase in the number of recommendations for delaying a prostate biopsy. This improved specificity may allow a substantial decrease in the number of prostate biopsies that are reported as negative for cancer.

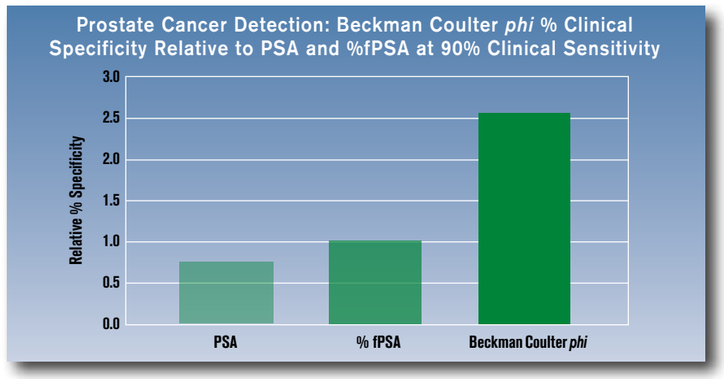


Figure C: Comparison of Specificities of change to %fPSA and phi *in the 2 to 10 ng/mL range*

The Beckman Coulter Prostate Health Index may be used to determine the relative risk of prostate cancer in individual men. Family and patient history should be used in combination with *phi* results to determine the best individualized patient management decisions.

Individual Patient Risk Assessment

Beckman Coulter *phi* demonstrates equivalent clinical performance with either the Hybritech or WHO calibration. Tables 1 and 2 demonstrate the clinical sensitivity and clinical specificity for detecting prostate cancer with biopsy based on *phi* cutoffs using PSA and fPSA calibrated to the Hybritech and WHO standards, respectively. PSA values were in the 2 to 10 ng/mL range using the Hybritech calibration and 1.6 to 7.8 ng/mL for the WHO calibration. Subjects ranged from 50 to 84 years old.

Table 1. Clinical Sensitivity and Specificity of Prostate Cancer Based on the Hybritech Calibration Cutoffs for Beckman Coulter *phi* for Men with Non-Suspicious DRE

Hybritech Calibration		
% Clinical Sensitivity	***phi* Cutoff**	**% Clinical Specificity**
95	21.13	18.2
90	23.82	30.4
88	25.00	33.6
85	26.34	38.8

Table 2. Clinical Sensitivity and Specificity of Prostate Cancer Based on the WHO Calibration Cutoffs for Beckman Coulter *phi* for Men with Non-Suspicious DRE

WHO Calibration		
% Clinical Sensitivity	***phi* Cutoff**	**% Clinical Specificity**
95	23.45	16.1
90	26.93	28.3
88	28.09	31.8
85	29.98	40.2

Tables 3 and 4 represent clinical study data analyzed to estimate an individual patient's probability of having detectable prostate cancer based on Beckman Coulter *phi* results. Note: Interpretive criteria using Hybritech calibration of PSA and free PSA (Table 3) change when using WHO calibration (Table 4) due to the 22% lower results obtained for PSA and free PSA with this calibration option.

Table 3. Risk of Prostate Cancer (Patients with PSA between 2 and 10 ng/mL)

Hybritech Calibration		
Beckman Coulter *phi* Range	**Probability of Cancer**	**95% Confidence Interval**
0-20.9	8.4%	1.9% - 16.1%
21.0-39.9	21.0%	17.3% - 24.6%
40+	44.0%	36.0% - 52.9%

Table 4. Risk of Prostate Cancer (Patients with PSA between 2 and 10 ng/mL)

WHO Calibration		
Beckman Coulter *phi* Range	**Probability of Cancer**	**95% Confidence Interval**
0-22.9	8.7%	2.0% - 17.0%
23.0-44.9	20.6%	17.1% - 24.1%
45+	43.8%	35.8% - 52.2%