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Advances in Prostate Cancer Diagnosis: Triggers for Prostate Biopsy

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Abstract

In the early years of screening for prostate cancer with serum PSA, absolute cutoffs were typically utilized such as greater than 4.0 ng/mL or even 2.5 ng/mL. A biopsy of the prostate would commonly be recommended in a man with greater than 10-year life expectancy who had a confirmed elevation above such a threshold or in the presence of an abnormal digital rectal examination. The unmet need, however, is to be more selective in recommending a prostate biopsy, due to the risk of complications and the high rate of false-positive PSAs. More recently, various clinical nomograms can be used to refine selection. In addition, clinicians can now utilize various advanced serum biomarkers that have enhanced specificity—especially for the patient with a rising PSA with prior negative biopsy. In this chapter, we will focus on the biomarkers PCA3, Prostate Health Index, and 4 K score to illustrate key concepts in biomarker development and clinical utility.

Keywords: prostate cancer, prostate biopsy, PCA3, urine, Prostate Health Index, serum, 4 K score, serum

1. Introduction—a narrative on contemporary management of prostate cancer risk with ordinary clinical tools

The male disease process “prostate cancer” is a heterogeneous entity at multiple subtopics including epidemiology, screening, diagnosis, treatment options, side effects, and cancer control results. It is common to introduce a peer-reviewed article or text chapter focused on any aspect of prostate cancer with the observation that the disease is common but a much smaller subset result in a disease-specific mortality—almost to the point of

useless repetition. The heterogeneity of prostate cancer extends well beyond population statistics, and in this chapter, we will focus on one aspect of heterogeneity—diagnosis. The key paradigm in contemporary practice is a male screened for prostate cancer with serum prostate specific antigen (PSA) and digital rectal examination (DRE). The alternate/related paradigm is the male with lower urinary tract or other pelvic symptoms who is evaluated for prostate cancer with serum PSA/DRE as a differential diagnosis. Performing a biopsy and subsequent treatment has certainly altered key statistics in prostate cancer compared to pure clinical detection. The incidence has increased as well as treatment numbers. Recently, Welch et al. demonstrated with SEER/Medicare data that the incidence of metastatic disease at diagnosis significantly declined with the introduction of PSA, compared with the relatively flat effect of mammography screening to breast cancer staging [1].

The problem faced from this paradigm is that the results of a prostate biopsy are frustrating for a growing list of reasons:

1. Too many negative or indeterminate biopsies.
2. Too many negative or indeterminate biopsies that are found to be falsely negative with future evaluations.
3. Too many positive biopsies for low grade disease—leads to overtreatment.
4. Too many positive biopsies for low grade disease that with future radical prostatectomy or repeat biopsies are found to have missed higher grade disease.
5. Cost, discomfort, and an occasional septic infection as the side effects of this effort to make the *correct* diagnosis for a patient.

The concepts can be illustrated in the following case vignettes:

- A patient with Gleason Score 3+3 on biopsy has a radical prostatectomy, and the final pathology showed Gleason 4+4.
- A patient with three negative biopsies has a continuous rising PSA—should he have a 4th biopsy or accept the cause as benign?
- A patient with a negative biopsy and stable PSA—should he continue screening? What age to stop?
- An elderly patient with Gleason 7 prostate cancer is unsure of overall longevity—does he need curative therapy or just watchful waiting based on symptoms?

Physicians managing patients at risk for prostate cancer can certainly use clinical features to frame many questions. In the asymptomatic patient who might have clinically localized disease, a life expectancy of less than 10 years would be treated differently than a life expectancy greater than 10 years. Family history of prostate cancer (father, brothers, uncles) and African American race are well-known adverse risk features for prostate cancer. The PSA has its statistical problems with specificity (related to false positives), but does have sensitivity (related to true positives) related to its value—higher PSAs have more risk of cancer, but hard

to determine a clear line to draw where you call the test clearly normal versus abnormal. Translating these narrated elements into summary numerical estimates (noncited as widely available):

- For the common case with elevated PSA between 2.5 and 6.0, and leading to a prostate biopsy, the overall cancer detection rate can be 30%, $\pm 10\%$ depending upon region. Of all positive biopsies, 10–25% may have high grade elements. This means that the majority of prostate biopsies are free of cancer, and an even higher number are free of clinically significant cancer.
- For men with a previous negative biopsy, a repeat biopsy for continued rise is often positive in 10–20%. Subsequent repeat biopsies lower the rate further but not to something approaching zero.
- For men placed on active surveillance for low grade cancer, approximately 30% will be upgraded at some point with repeat testing.

Moving forward, the unmet needs in prostate cancer evaluation are to increase the detection of clinically significant disease when it is present, and to effectively rule out significant disease when it is not present, such that subsequent monitoring can be reduced or eliminated. *To emphasize—both of these needs are critical and equal: the need to diagnose cancer that is present and potentially lethal, and the need to eliminate diagnostic attempts when cancer is absent or nonlethal.*

2. Prostate biopsy triggers—mild improvement from mathematics and clinical trials

In a state-of-the-art lecture at the 2015 American Urological Association Annual Meeting, Stacy Loeb (New York, USA) made the key analogy that the first 10 or more years of use of PSA was analogous to a pregnancy test—in search of when to call the test positive or negative. The initial cut-point was 4.0, and many labs still flag a result in red at >4.0 , and subsequent proposals were for >2.5 . Clinical experience clearly showed the fallacy of this version of laboratory medicine—a man's risk of prostate cancer does not go from zero at PSA 3.9 to 100% at PSA of 4.1. The point was well illustrated by a follow-up report from the Prostate Cancer Prevention Trial that showed the biopsy results of men with different PSA cut-points who were all biopsied and on a placebo medication—sample size of 2950 participants and 449 cancers [2]. **Table 1** shows a sample of their report. Note that the pregnancy illustration was carried forward in this trial, as men with a PSA > 4.0 were biopsied “for cause” and the data represent the men followed for the 7-year duration of the trial who were considered clinically “normal range”. Prior to this publication, there was very limited data available on the results of a prostate biopsy in men with a normal DRE and PSA < 4.0 .

With this data, you can certainly counsel a man on the concept of a relative range of prostate cancer risk rather than oversimplify it to a positive/negative result. This same dataset was refined further into an online calculator tool where you can input multiple clinical variables

and receive an estimate on overall cancer detection and high grade (Gleason 7 or higher) cancer. The web link is: <http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>.

Here are two example cases:

- 1. Race Caucasian, age 59, PSA 2.1, no family history, abnormal DRE, no prior biopsy. Result: 3% high-grade cancer, 14%, low-grade cancer, and 83% negative biopsy.
- 2. Race African American, age 59, PSA 9.8, positive family history for prostate cancer, DRE abnormal, no prior biopsy. Result: 35% high-grade cancer, 20% low-grade cancer, 45% negative biopsy.

PSA level	Percentage positive biopsy	Percentage of positive biopsies with high grade
≤0.5	6.6	12.5
0.6–1.0	10.1	10.0
1.1–2.0	17.0	11.8
2.1–3.0	23.9	19.1
3.1–4.0	26.9	25.0

Table 1. Data from the Prostate Cancer Prevention Trial [2]. This cohort of men were biopsied as part of the trial design and were on a placebo. Men with a PSA > 4.0 would have been biopsied earlier “for cause”.

The results also remind you that regardless of the biopsy result, there may be a 2–4% chance of an infection requiring hospitalization. Thus, the absolute risks of cancer and side effects can be discussed and a personalized choice made. We should not forget why we are considering these efforts. The third update to the Bill-Axelson trial of radical prostatectomy versus watchful waiting reminds us that the treatment arm had a 12.7% absolute difference in overall mortality, with a relative risk of 0.71 in favor of surgery and number needed to treat to avoid a death of 1:8 [3]. Additional benefits were observed in palliation, metastatic progression, and androgen deprivation utilization.

3. Biomarkers in prostate cancer—highlights of evaluation and early improvement of specificity

As established thus far, PSA is the gold standard for prostate cancer detection. Many experts have voiced the opinion that this might change in the next generation [4]. First, we should review key biomarker nomenclature recognized by the FDA—whether a biomarker is serum, urine, or tissue base. **Table 2** shows four key distinctions and a biomarker such as PSA has elements of all four.

Data on biomarkers is a separate and vast topic and we will not review it. But the key headings would be whether a study is in preclinical exploratory trials, assay development, assay validation, retrospective use/repositories, prospective screening, or randomized controlled.

Biomarkers can be described based on their validity with a number of statistical expression and eventually need to be described based upon clinical utility, i.e., strength of ability to alter key clinical decisions and add value to health care.

Biomarker type	When	Indications
Prognostic	Prior to treatment	Risk of a specific outcome
Predictive	Prior to treatment	Identify which patients benefit from a treatment
Response indicator	During or after treatment	Response to treatment (pharmacology, physiology)
Efficacy-response (surrogate)	After treatment	Early/accurate prediction of a clinical endpoint

Table 2. FDA biomarker classification based on context of use.

As stated, there are many statistical advantages to PSA screening compared to using prostatic acid phosphatase (PAP) [5], or clinical exam [6]. However, there is significant room to improve accuracy and especially specificity. Early efforts to make progress were numerous such as adding the percent-free PSA to PSA ratio [7], age adjustment [8], PSA velocity of ≥ 0.75 ng/mL/year [9], and PSA density of 0.15 [10]. These methods all made incremental practice, but perhaps the most significant is in making decisions about a repeat biopsy versus a primary biopsy. Another useful contribution to PSA screening interval questions came from Lilja et al., who showed that a single PSA before age 50 could be predictive of lifetime prostate cancer incidence [11].

4. A focus on novel diagnostic biomarkers: prostate Health Index and 4 K score

Similar themes in advancing future prostate cancer screening have come from focusing on “isomers” or molecular variants of the PSA molecule. Another variant of PSA is called Pro-PSA and can be more prevalent in the free-fraction within cancer versus noncancer [12]. In a validation study of Pro-PSA versus percent-free PSA, the area under the curve (AUC) was 0.68 for %ProPSA and 0.567 for %free PSA. At sensitivity of 75%, the %ProPSA would eliminate 59% of negative biopsies versus 33% with %fPSA [13]. Catalona et al. [14] also did a serum bank study on biopsied patients with elevated PSA and found the %proPSA can eliminate 19–33% of biopsies while holding 90% sensitivity.

The next iteration came from the discovery of an isoform p2PSA, and the concept of combining the information with free PSA and total PSA into an equation: $([-2]pPSA/fPSA)/\sqrt{(tPSA)}$. This is now the Prostate Health Index and licensed by Beckman Coulter laboratories. Jansen et al. [15] reported a multisite study showing that prostate cancer patients had higher PHI levels and %p2PSA. A U.S. validation study of 829 patients holding sensitivity at 95% had specificity of 16% for PHI and 8.5% for %fPSA [16]. Relevant to our case vignettes in the introductory narrative, the higher PHI values were also correlating with a higher risk of Gleason score ≥ 7 .

A PHI score is currently reported in four “brackets” of results: 0–24.9, 25.0–34.9, 35.0–54.9, and >55. The PHI, as stated will include a total PSA, the free PSA, and the Pro-PSA. The PHI result is then translated into a percentage risk of prostate cancer. The source reference [16] includes the high grade numbers, but an actual test result for some reason does not. **Table 3** shows a commercial report range. The study listed ranges for Gleason ≥ 7 were PHI 0–24.9 = 26.1%, PHI 25.0–34.9 of 28.2%, PHI 35.0–54.9 of 30.1%, and PHI >55.0 of 42.1%. Thus, the trends are strongest comparing the lowest versus highest PHI brackets.

Biomarker	Sample result	Reference interval			
Total PSA	7.8	Normal < 2.0 At risk $\geq$ 2.0			
Free PSA	1.16	See below			
Pro2PSA	20.78	See PHI			
%free PSA	15	% Free PSA prostate cancer probability by age			
		%Free PSA	<60	60–70	>70
		<7	85%	95%	96%
		7–15	25%	50%	60%
		16–25	11%	27%	35%
		>25	2%	6%	10%
		PHI	Cancer probability		
		0–24.9	11.0%		
		25.0–34.9	18.1%		
PHI	49.9	35.0–54.9	32.7%		
		>55.0	52.1%		

Table 3. PHI result reporting as of 2015.

A European cohort was published by Lazzeri et al. [17] and showed an AUC of 0.67 for PHI as well as %proPSA—both superior to total PSA and %free PSA. At a PHI cutoff of 27.6, biopsies could have been avoided in 15.5%. The Gleason ≥ 7 trend was also observed in their statistical analyses.

Another research direction developing in parallel has been human glandular kallikrein 2—hK2. It is also part of the serine protease family along with PSA. Nam et al. [18], for example, looked at hK2 and hK2 to %free PSA ratios could find trends elevated in PCa. Vickers et al. then expanded the concept as a panel of Kallikrein markers: total PSA, free PSA, intact PSA, and hK2. This coined the phrase 4 K score [19]. The process developed a nomogram that includes the four markers, age, DRE, and determines a probability of cancer. The model adds to a clinical base model and increases prediction for high grade prostate cancer. The AUC for the full model was 0.832 and high-grade cancer was 0.870, and a decision curve analysis is

presented to propose a threshold value of 20% as a biopsy trigger that would spare a significant number of biopsies and only miss 3% high-grade cancers. Parekh et al. [20] then published a U.S. prospective trial that used the PCPT risk calculator above as a control. Again, the full model had an AUC of 0.821 and higher AUC for Gleason ≥ 7 , as well as decision curve benefit. As an illustration, a 4 K score cutoff of 9% led to 43% of biopsies avoided and 2.4% risk of delay in Gleason ≥ 7 diagnosis.

For the clinician, the question then becomes which test to use? PHI had a slight advantage in being earlier in regulatory approval. Nordstrom et al. presented a comparison study of PHI versus 4 K [21]. The PHI and 4 K both had improved prediction for overall and high grade prostate cancer. The AUC for 4 K was 0.69 and for PHI was 0.704, and for high-grade prostate cancer was 0.718 and 0.711, respectively. Comparable metrics were observed with a 4 K cutoff of 10% and PHI of 39.

	PHI	4K	PCA3
Components	Serum $([-2]pPSA/fPSA)/\sqrt{(tPSA)}$	Serum tPSA, fPSA, intact PSA, hk2, age Clinical model (add DRE results)	Urine; (mRNA PCA3/mRNA PSA) $\times$ 1000
Patient population	>50 y/o, PSA 4–10 ng/mL, normal DRE	Any patient referred for TRUS Bx	>50 y/o; prior negative Bx
FDA approval	2012	n/a	2012
Outcome measure	PCa	High risk PCa (GS ≥ 7)	PCa
Cutoff	0–29 = low risk; 8.7% risk PCa 21–39.9 = mod risk; 20.6% risk PCa 40 = high risk; 43.8% risk PCa	$\geq 9\%$, eliminates 43% of unnecessary Bx, w/2.4% risk of delayed dx of HG PCa	>35 sensitivity = 58%, and specificity = 72% for PCa
Disadvantages		Not currently covered by private insurances/Medicaid/Medicare	Requires prostate message
Comparisons	Comparable diagnostic accuracy to both 4 K and PCA3, and both their recommended indications	No comparison to PCA3; comparable accuracy and utility to 4 K	No comparison to 4 K; comparable diagnostic accuracy to PCA3 for initial & repeat Bx
Cost	\$71–80	\$395	\$385

Table 4. Comparison of serum biomarkers PHI, 4K, and urine biomarker PCA3.

Another biomarker with a little more clinical experience and validation data is the PCA3 score –different in being a urinary marker rather than serum as for PHI and 4 K. The assay uses a

ratio of messenger RNA for the PCA3 molecule with a PSA ratio built in. The AUCs for PCA3 are generally in the 0.68–75 range [22]. In the validation study for repeat biopsy patients, Marks et al. showed an AUC of 0.68 for PCA3 versus 0.52 for PSA [23]. The cutoffs recommended are in the 25–35 range. In the Marks study, a PCA3 cutoff of 35 showed 58% sensitivity and 72% specificity. A particular advantage of PCA3 has been that it is not affected by prostate volume and performed well across multiple PSA levels [24].

Back to comparative studies, Ferro et al. compared PCA3 to PHI in a prospective observational study [25]. The diagnostic accuracy was similar at 90% sensitivity: PHI specificity of 40% and PCA3 of 40% with 31.6 and 22 cutoffs, respectively. In a decision curve analysis, PHI had slightly higher benefit at probability of 25%. The Scattoni study [26] looked at these markers in initial and repeat biopsy populations and found a slight benefit to PHI but not significant. A comparison of AUC for initial biopsy showed PSA of 0.54, %fPSA of 0.67, PCA3 of 0.57, and PHI of 0.69. In repeat biopsy, it showed PSA of 0.60, %fPSA of 0.52, PCA3 of 0.63, and PHI of 0.72.

In **Table 4**, we consolidate these statistics into a final comparison with existing data.

The cost comparison certainly favors PHI, although the PCA3 test has more clinical experience and strong metrics in repeat biopsy decisions. It remains to be determined whether the 4 K cost is justified; however, when this test is up and running and through regulation, it may give a more objective reporting of specific high grade prostate cancer risk that clinicians may prefer.

5. Moving forward—similar themes in imaging, biopsy techniques, and tissue biomarkers

In this chapter, we have outlined the PSA problem with emphasis on triggers for a biopsy. A separate but related topic is the technique of biopsy. The gold standard for all of these biomarker studies has been the 10–12 core transrectal ultrasound-guided biopsy. Emerging data, however, demonstrate that a transperineal template biopsy may sample the apex and anterior zones better. Other areas of research are looking at improvements in multiparametric MRI staging, and commercial software platforms that fuse the images such that an ultrasound biopsy now has a more accurate target to sample rather than random sampling by anatomic region. The endpoints are the same—ability to improve Gleason score ≥ 7 and the ability to trust that a negative test is actually negative. For diagnosed patients, commercial genetic profiling products can then look at specific grades of prostate cancer and offer additional prognostic information such as risk of upgrading/upstaging at surgery, mortality rates untreated, biochemical relapse after surgery, or metastatic relapse after surgery [27]. These topics can be separate chapters, but the themes are consistent—solving heterogeneity in prostate cancer diagnosis such that the downstream monitoring and treatment decisions are optimized.

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References

- [1] Welch HG, Gorski DH, Albertsen PC. Trends in metastatic breast and prostate cancer —lesson in cancer dynamics. *N Engl J Med* 2016; 374: 596.
- [2] Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *N Engl J Med* 2004; 350: 2239–2246.
- [3] Bill-Axelsson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014; 370: 10.
- [4] Loeb S. Time to replace prostate-specific antigen (PSA) with the Prostate Health Index (PHI)? Yet more evidence that the PHI consistently performs PSA across diverse populations. *BJU Int* 2015; 115: 500.
- [5] Seamonds B, Yang N, Anderson K, et al. Evaluation of prostate-specific antigen and prostatic acid phosphatase as prostate cancer markers. *Urology* 1986; 28: 472–479.
- [6] Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991; 324: 1156–1161.
- [7] Catalona WJ, Smith DS, Eolfert RL, et al. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. *JAMA* 1995; 274: 1214–1220.
- [8] Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993; 270: 860–864.
- [9] Smith DS, Catalona WJ. Rate of change in serum prostate specific antigen levels as a method for prostate cancer detection. *J Urol* 1994; 152: 1163–1167.
- [10] Benson MC, Whang IS, Pantuck A, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *J Urol* 1992; 147: 815–816.

- [11] Lilja H, Cronin AM, Dahlin A, et al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. *Cancer* 2011; 117: 1210–1219.
- [12] Mikolajczyk SD, Millar LS, Wang TJ, et al. A precursor form of prostate-specific antigen is more highly elevated in prostate cancer compared with benign transition zone prostate tissue. *Cancer Res* 2000; 60: 756–759.
- [13] Sokioll LJ, Chan DW, Mikolajczyk SD, et al. Proenzyme psa for the early detection of prostate cancer in the 2.5-4.0 ng/ml total psa range: preliminary analysis. *Urology* 2003; 61: 274–276.
- [14] Catalona WJ, Bartsch G, Rittenhouse HG, et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 nl/ml. *J Urol* 2003; 170: 2181–2185.
- [15] Jansen FH, van Schaik RH, Kurstjens J, et al. Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. *Eur Urol* 2010; 57: 921–927.
- [16] Le BV, Griffin CR, Loeb S, et al. [-2]Proenzyme prostate specific antigen is more accurate than total and free prostate specific antigen in differentiating prostate cancer from benign disease in a prospective prostate cancer screening study. *J Urol* 2010; 183: 1355–1359.
- [17] Lazzeri M, Haese A, de la Taille A, et al. Serum isoform [-2] proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2–10 ng/ml: a multicentric European study. *Eur Urol* 2013; 63: 986–994.
- [18] Nam RK, Diamandis EP, Toi A, et al. Serum human glandular kallikrein-2 protease levels predict the presence of prostate cancer among men with elevated prostate-specific antigen. *J Clin Oncol* 2000; 18: 1036–1042.
- [19] Vickers AJ, Cronin AM, Aus G, et al. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening on Goteborg, Sweden. *BMC Med* 2008; 6: 19.
- [20] Parekh DJ, Punnen S, Sjoberg D, et al. A multi-institutional prospective trial in the USA confirms that the 4 K score accurately identifies men with high grade prostate cancer. *Eur Urol* 2015; 68: 464–470.
- [21] Nordstrom T, Vickers A, Assel M, et al. Comparison between the four-kallikrein panel and the prostate health index for predicting prostate cancer. *Eur Urol* 2015; 68: 139–146.
- [22] Groskopf J, Aubin SM, Deras IL, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem* 2006; 52: 1089–1095.

- [23] Marks LS, Fradet Y, Deras IL, et al. PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. *Urology* 2007; 69: 532–535.
- [24] Deras IL, Aubin SM, Blase A, et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. *J Urol* 2008; 179: 1587–1592.
- [25] Ferro M, Bruzzese D, Perdoni S, et al. Prostate health index (PHI) and prostate cancer antigen3 (PCA3) significantly improve prostate cancer detection at initial biopsy in a total PSA range of 2–10 ng/ml. *Plos One* 2013; 8.
- [26] Scattoni V, Lazzeri M, Lughezzani G, et al. Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy. *J Urol* 2013; 190: 496–501.
- [27] Davis JW. Novel commercially available genomic tests for prostate cancer: a roadmap to understanding their clinical impact. *BJU Int* 2014; 112: 531–532.