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Biomarkers in prostate cancer: what's new?

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Abstract

Purpose of review—This review is intended to provide an overview of the current state of biomarkers for prostate cancer (PCa), with a focus on biomarkers approved by the US Food and Drug Administration (FDA) as well as biomarkers available from Clinical Laboratory Improvement Amendment (CLIA)-certified clinical laboratories within the last 1–2 years.

Recent findings—During the past 2 years, two biomarkers have been approved by the US FDA. These include proPSA as part of the Prostate Health Index (phi) by Beckman Coulter, Inc and PCA3 as Progensa by Gen Probe, Inc. With the advances in genomic and proteomic technologies, several new CLIA-based laboratory-developed tests have become available. Examples are Oncotype DX from Genomics Health, Inc, and Prolaris from Myriad Genetics, Inc. In most cases, these new tests are based on a combination of multiple genomic or proteomic biomarkers.

Summary—Several new tests, as discussed in this review, have become available during the last 2 years. Although the intended use of most of these tests is to distinguish PCa from benign prostatic conditions with better sensitivity and specificity than prostate-specific antigen, studies have shown that some of them may also be useful in the differentiation of aggressive from nonaggressive forms of PCa.

Keywords

aggressiveness; biomarkers; genomics; prostate cancer; proteomics

INTRODUCTION

Prostate cancer (PCa) is the most common noncutaneous solid tumor in men in the United States. However, the mortality of PCa ranks number 5 [1,2]. In 2013, the estimated new cases will exceed 230 000, with approximately 29 000 deaths (~12%). About 60% of all PCa

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Conflicts of interest

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diagnosis occurs in men at age 66 or older and 97% occurs in men at 50 or older, with early diagnosis between the ages 35 and 40 being rare. African-American men have a 60% increased rate of being diagnosed with PCa compared with Caucasian or Hispanic/Latino men. Asian men have a 50% lower incidence of PCa than Caucasian men [2,3]. According to longitudinal statistics, men have a one in six chance of being diagnosed with PCa and a one in 35 chance of dying from PCa. Men surviving PCa are the largest population of male cancer survivors and comprise approximately 40% of all cancer survivors [4]. In the large, national registry of biopsy-proven PCa cases, nearly 45% have received a radical prostatectomy, which makes it the most common curative treatment in men less than 75 years old [5].

With the introduction of prostate-specific antigen (PSA) testing, the number of PCa diagnoses has increased, but the rate of dying from PCa has decreased [6–10]. Although a routine test, PSA screening has garnered a lot of criticism over the years due to the possibility of over detection, which leads to over treatment [11–14]. In particular, the controversial recommendation against PCa screening by the United States Preventive Services Task Force has generated a lot of debate about PSA-based screening [15▪▪]. Despite significant efforts to find an improved biomarker to replace PSA, as of today, PSA still remains the first-line biomarker option for the detection of PCa. The great majority of biomarkers published during the last few years are still in the investigation or validation phase. The fact remains that the clinical validation and translation of discovered biomarkers into clinical diagnostics, with approval/clearance by the US Food and Drug Administration (FDA), often takes 5–10 years.

The current focus of PCa biomarker research is to find markers for aggressive disease. However, there is no consensus on the definition of aggressiveness. The most widely used definition for high-risk localized PCa is the National Comprehensive Cancer Network (NCCN) guideline defined as biopsy Gleason sum greater than or equal to 8, PSA greater than 20 ng/ml or clinical stage greater than or equal to T3a [16]. However, most clinicians will consider PCa as aggressive with a Gleason sum greater than or equal to 7 (3 +4 or 4 +3). Jonathan Epstein (Johns Hopkins University) defines men with very low risk PCa as having the following criteria: Stage T1c, PSA density less than 0.15 ng/ml/cm^3, Gleason score of less than or equal to 6 with no Gleason pattern of 4 or 5, and with two or fewer cores with cancer (not more than 50% cancer in any one core) out of a 12-core biopsy [17]. The goal for biomarker research is to find a biomarker or a combination of biomarkers that can predict PCa aggressiveness, either before or after biopsy.

The present review provides an update on newly FDA-approved tests, as well as Clinical Laboratory Improvement Amendments (CLIA)-based clinical laboratory developed tests (LDTs), that became available in 2012 and 2013. These tests take advantage of some of the recent advances in genomics and proteomics. The challenge with these biomarkers is to provide improved clinical sensitivity and specificity. In some instances, the new biomarkers can be associated with the relative aggressiveness of clinical PCa. It should be noted that the landscape of PCa biomarkers is evolving rapidly so that some of the current emerging biomarkers may not be relevant in the future, whereas new ones may become available for clinical use over time.

REGULATORY (FOOD AND DRUG ADMINISTRATION) APPROVED TESTS

The importance of using an FDA-approved test is the assurance that both analytical and clinical performances of the test have been reviewed and approved by the regulatory agency. These are important criteria for an acceptable cancer diagnostic test. The analytical requirements for a robust biomarker assay include precision, trueness, specificity, interference, and carryover. The clinical considerations include diagnostic accuracy, area under the curve (AUC) by receiver-operating characteristic analysis, and positive (PPV) and negative predictive values (NPV). Clinicians need to establish the test's clinical utility and determine the clinical acceptance for (and by) their patients [18▪]. The other potential benefit of an FDA-approved test is that the patient's health insurance is more likely to reimburse for the cost of the test.

proPSA AND PROSTATE HEALTH INDEX

proPSA, which contains a seven amino acid pro leader peptide, is a molecular form of free PSA (fPSA), and is more likely to be associated with PCa. Truncated forms of proPSA also exist in serum, which contain five, four, or two more amino acids than PSA. The [2] proPSA (p2PSA) form has been identified as the most prevalent form in tumor extracts, which suggests a role for these molecular forms of PSA for the early detection of PCa, and for possibly identifying aggressive PCa [19,20,21▪▪,22▪,23,24].

Prostate health index (phi) developed by Beckman Coulter, Inc in partnership with the NCI Early Detection Research Network was approved by the FDA in 2012. This new test is actually a mathematical formula of three biomarkers –(p2PSA/fPSA) × $PSA^{½}$. By use of this calculation, the clinician will be able to see each individual result as well as make a potentially better informed recommendation to the patient. The intended use of phi is to distinguish PCa from benign prostatic conditions in men aged 50 years and older with a total serum PSA between 4 and 10 ng/ml, and in whom the digital rectal examination is not suspicious for cancer [25]. Two recent studies published by Lazzeri *et al.* [21▪▪,22▪] demonstrated that the use of p2PSA and phi significantly improved the predictive accuracy for detection of PCa. In the first study of about 650 men from five European centers, patients had PSA levels between 2 and 10 ng/ml. The researchers demonstrated that p2PSA and phi improved the detection of PCa with a Gleason score of greater than or equal to 7 disease compared with PSA and fPSA. In the other study by Lazzeri *et al.*, in a small cohort of about 150 men with a positive family history of PCa, phi significantly outperformed tPSA and %fPSA (AUCs 0.73, 0.55, and 0.60, respectively) for the detection of aggressive PCa.

PROSTATE CANCER ANTIGEN 3 AND PROGENSA

Prostate cancer antigen 3 (*PCA3* or *DD3*) is a prostate-specific gene. The Progensa PCA3 assay is an in-vitro nucleic acid amplification test. The assay measures the concentration of prostate cancer gene 3 (*PCA3*) and PSA RNA molecules and calculates the ratio of PCA3 RNA molecules to PSA RNA molecules (PCA3 score) in postdigital rectal examination (DRE) urine specimens. Gen-Probe, Inc obtained FDA approval in 2012 with the intended use for men who have a suspicion of PCa based on PSA level and/or DRE and/or one or more negative biopsy results. A PCA3 score less than 25 is associated with a decreased

likelihood of PCa [26▪▪,27,28]. In a recent study by Crawford *et al.* [26▪▪], lowering the PCA3 score cutoff to 10 from 35 reduced the number of false positives by 34.5%, whereas the false-negative rate increased by only 5.6%. In a review written by Vlaeminick-Guillem *et al.* [27], they summarized 11 clinical studies conducted at six multicenters and five individual centers that encompassed a total of 2737 men. Seven of the studies used the currently available FDA-approved test kit (Progensa). AUC values ranged from 0.66 to 0.75. Sensitivity ranged from 53 to 69%, with specificity ranging from 71 to 83%. For patients who had a previous negative biopsy, sensitivity averaged 52.6% and specificity averaged 71.6%, which gives a PPV of about 40% and a NPV of about 80%. The overall accuracy is about 66%. Overall, PCA3 appears promising, and the specimen for PCA3 analysis is easily obtained after DRE.

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS-BASED LABORATORY-DEVELOPED TESTS

These tests have not been approved by the FDA but are offered under a laboratory's CLIA certificate. The LDT is required to demonstrate certain analytical performances. However, the validation is much more limited as compared with the requirements for regulatory approval. The major concern is the variability of such validation studies from laboratory to laboratory. Some of the LDTs described here have undergone extensive validations while others have very limited data available. Caution should be exercised in judging the acceptance of some of these tests.

ONCOTYPE DX

As a LDT, Genomic Health Inc offers the Oncotype DX Prostate Cancer Assay. The Oncotype DX was developed to test small (1 mm) fixed paraffin-embedded tissue samples that were obtained by needle biopsy. The assay measures the expression of 12 cancer-related genes which represent four different biological pathways [androgen pathway (AZGP1, KLK2, SRD5A2, and RAM13C); cellular organization (FLNC, GSN, TPM2, and GSTM2); proliferation pathway (TPX2); and stromal response (BGN, COL1A1 and SFRP4)] and five reference genes (used to normalize and control preanalytical and analytical variability), which are algorithmically combined to calculate the Genomic Prostate Score [29▪▪]. Together with NCCN risk criteria, GPS improves risk discrimination of PCa into very low, low and modified intermediate risk in order to help clinicians select appropriate candidates for active surveillance.

PROLARIS SCORE

As a LDT, Myriad Genetics, Inc offers a molecular test that directly measures tumor cell growth characteristics to stratify disease risk of progression. By testing formalin-fixed paraffin-embedded tissue obtained by biopsy or prostatectomy, Myriad tests 46 different gene expressions, which include 31 cell cycle progression (*CCP*) genes and 15 housekeeper genes that were selected because of correlation with proliferation of PCa [30,31,32▪]. They found that low expression is associated with a low risk of disease progression, whereas high

expression is more indicative of higher risk of disease progression, suggesting either close monitoring or additional therapy for the latter group of patients.

PROSTARIX

Prostarix is an LDT performed by the CLIA lab at Metabolon, Inc and offered through Boswick Laboratories. The test is to aid clinicians in the decision for initial or repeat prostate biopsy in men with negative DRE and modestly elevated PSA levels. Prostarix DRE urine test is based on a proprietary metabolic signature of four metabolites determined by liquid chromatography–mass spectrometry (LC-MS) on the pellet obtained from a centrifuged urine specimen. Similar to the PCA3 test, the urine needs to be collected immediately after a vigorous DRE [33▪▪,34–36]. McDunn *et al.* [33▪▪] analyzed over 500 prostate tissue samples (331 prostate tumors and 178 cancer free). Through the use of gas chromatography–mass spectrometry and LC-MS-MS, the study was able to find significantly different metabolite profiles between tissue that contained PCa and tissue that was cancer free. The profile improved prediction of organ confinement (AUC from 0.53 to 0.62) and 5-year recurrence (AUC 0.53–0.64).

TMPRSS2:ERG AND Mi-PROSTATE SCORE

The recurrent TMPRSS2-ERG fusion is a common rearrangement in diagnosed PCa cases [37–39]. The TMPRSS2-ERG (or T2-ERG) fusion has a low sensitivity of 37% but a high specificity of 93%, which gives a PPV of 94% after a DRE. Even though the specificity is high, most PCa tumors have multiple foci, which make T2-ERG more heterogeneous. One way to overcome this heterogeneity is to combine T2-ERG with other markers [40▪▪,41,42]. There have been several studies that investigated the association of T2-ERG with aggressiveness of PCa. In one study, among 1180 men who were treated by a radical prostatectomy, T2-ERG was found in 49% of the cases [42]. There was a significant correlation with high stage tumor (P <0.01), but there was little correlation with Gleason score (P =0.58), lethality (P =0.99), and biochemical reoccurrence (P =0.60). In earlier studies, there were demonstrated correlations with higher Gleason score (P =0.01) and lethality (P <0.01) in a smaller group of men (n=111) who were diagnosed with low-grade PCa. In yet another study, T2-ERG was highly expressed in patients with T3-T4, Gleason more than or equal to 7 disease (P =0.003 and P <0.01, respectively).

The Mi-Prostate Score (University of Michigan Health System) combines the urine tests for PCA3 from Progensa, T2:ERG, and serum PSA levels to produce a risk assessment of PCa that potentially indicates the likelihood of aggressive cancer. This test has been validated on approximately 2000 urine specimens [40▪▪,41,42].

ConfirmMDx

ConfirmMDx, offered by MDxHealth, Inc, detects an epigenetic field effect based on DNA methylation [43▪,44,45]. It is intended to distinguish patients who have a true negative biopsy from those who may have occult cancer with a 90% negative predictive value (NPV). MDx uses prostate core specimens collected during a 12-core biopsy (with a requirement of a minimum of eight cores from the left/right base, mid and apex and two additional

locations). Owing to molecular changes at the DNA level in cells that are adjacent to cancer foci, MDx is able to diagnosis PCa in specimens that are otherwise histologically benign because of a 'halo effect' that a cancerous lesion can have.

PROSTATE CORE MITOMIC TEST

The Prostate Core Mitomic Test (PCMT) is based on detecting large-scale mitochondrial DNA (mtDNA) deletions in prostate biopsy core specimens. PCMT purports detection of molecular changes at the mtDNA level in benign tissue that is adjacent to noninterrogated cancer tissue [46,47▪]. Clinical validation is based on 396 patients (143 were histologically benign and 253 were histologically malignant) and approximately 1700 prostate core specimens. Based on the discovery of a 3.4-kb mtDNA deletion, Mitomics is able to provide a test sensitivity of about 85% [46]. Additional studies are needed to validate the performance characteristics of this test.

OTHER POTENTIAL BIOMARKERS

The following are two additional tests that may be available clinically in the future.

4K Score (OPKO, Inc)

A panel of four kallikriens – total PSA, free PSA, intact PSA, and kallikrein-related peptide 2 (hK2), were combined to generate the 4K score [48,49▪▪,50]. Without hK2, the other three PSA isoforms are similar to the PSA isoforms used in the Prostate Health Index discussed earlier. Several recent European studies indicated that the 4K score could be used to distinguish between pathologically insignificant and aggressive disease and reduce unnecessary biopsies. In one of the studies, the AUC for 4K Score (0.83) improved over the AUC for total PSA (0.68) for the prediction of PCa at biopsy [49▪▪]. It is anticipated that this test will be available in 2014 in the United States from the CLIA-certified OURLab Urologic Reference Laboratory.

ProMark (Metamark Genetics)

ProMark is a biopsy-based PCa prognostic test detecting multiple protein biomarkers (n =8) using a fully automated immunofluorescent imaging platform. In a study presented at a recent meeting of the Society of Urologic Oncology, the combined eight biomarkers had an AUC of 0.72 (unpublished data). The test will be available in 2014 from the Metamark Genetics CLIA-certified laboratory.

CONCLUSION

In most cases, the new tests discussed are based on a combination of multiple genomic or proteomic biomarkers. Although the intended use of most of these tests is to distinguish PCa from benign prostatic conditions with better sensitivity and specificity than PSA, studies have shown that many of them are also useful in differentiation of aggressive from nonaggressive forms of PCa. In the next few years, we expect more new tests will become available to help clinicians in the prediction of aggressive PCa, and therefore help them make better clinical decisions for treating PCa patients.

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Dislaimer (D.A.S.): The view(s) expressed herein are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11–30. [PubMed: 23335087]
2. Clegg L, Li F, Hankey B, et al. Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology and End Results) Program population-based study. Arch Intern Med. 2002; 162:1985–1993. [PubMed: 12230422]
3. Martin DW, Starks AD, Ambs S. Biological determinants of health disparities in prostate cancer. Curr Opin Oncol. 2013; 25:235–241. [PubMed: 23399519]
4. Paquette E, Sun L, Paquette L, et al. Improved prostate cancer-specific survival and other disease parameters: impact of prostate-specific antigen testing. Urology. 2002; 60:756–759. [PubMed: 12429290]
5. Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer. PLoS One. 2010; 5:e9584. [PubMed: 20231893]
6. Marta GN, Hanna SA, da Silva JLF, Carvalho HdA. Screening for prostate cancer: an updated review. Expert Rev Anticancer Ther. 2013; 13:101–108. [PubMed: 23259431]
7. Trantham LC, Nielsen ME, Mobley LR, et al. Use of prostate-specific antigen testing as a disease surveillance tool following radical prostatectomy. Cancer. 2013; 119:3523–3530. [PubMed: 23893821]
8. Hewitt, M.; Greenfield, S.; Stovall, E. From cancer patient to cancer survivor: lost in transition. Washington, DC: National Academies Press; 2006.
9. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol. 2010; 28:1117–1123. [PubMed: 20124165]
10. Hansen J, Rink M, Graefen M, et al. Assays for prostate cancer. Mol Diagn Ther. 2013; 17:1–8. [PubMed: 23355098]
11. Lee YJ, Park JE, Jeon BR, et al. Is prostate-specific antigen effective for population screening of prostate cancer? A systemic review. Ann Lab Med. 2013; 33:233–241. [PubMed: 23826558]
12. Wong LM, Neal DE, Johnston RB, et al. International multicenter study examining selection criteria for active surveillance in men undergoing radical prostatectomy. Brit J Cancer. 2012; 107:1467–1473. [PubMed: 23037714]
13. Van Neste L, Herman JG, Otto G, et al. The epigenetic promise for prostate cancer diagnosis. Prostate. 2012; 72:1248–1261. [PubMed: 22161815]
14. Vickers AJ, Lilja H. We need a better marker for prostate cancer. How about renaming PSA. Urology. 2012; 79:254–255. [PubMed: 22196413]
15▪▪. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012; 157:120–134. The continued controversy toward the use of PSA as a cancer biomarker will support additional research for a new biomarker. [PubMed: 22801674]

16. NCCN. Clinical practice guidelines in oncology: prostate cancer. National comprehensive cancer network 2014; Version 1. Available from: NCCN.org. Detailed guidelines on the detection, prevention, risk stratification and treatment of patients

17. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994; 271:368–374. [PubMed: 7506797]

18▪. Füzéry A, Levin J, Chan MM, Chan DW. Translation of proteomic biomarkers into FDA approved cancer diagnostics: issues and challenges. Clin Proteom. 2013; 10:13–26. The article describes the steps required to translate discovery science to clinical diagnostics.

19. Hori S, Blanchet JS, McLoughlin J. From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. BJU Int. 2013; 112:717–728. [PubMed: 22759214]

20. Loeb S, Sokoll L, Broyles DL, et al. Prospective multicenter evaluation of the Beckman Coulter prostate health index using WHO calibration. J Uro. 2013; 189:1702–1706.

21▪▪. Lazzeri M, Abrate A, Lughezzani G, et al. Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [−2]proPSA (p2PSA), %p2PSA, and prostate health index in men with a total prostate-specific antigen of 4–10 ng/mL and normal digital rectal examination. Urology. 2014; 38:606–612. This is an important study that demonstrated the potential ability to distinguish PCa from chronic histologic prostatic inflammation (CHPI) or benign prostatic hyperplasia by analyzing [−2]proPSA. However, the authors also concluded that they could not distinguish between CHPI and benign prostatic hyperplasia from the serum result. [PubMed: 24315305]

22▪. Lazzeri M, Haese A, Abrate A, et al. Clinical performance of serum prostate specific antigen isoform [−2]proPSA (p2PSA) and its derivatives %p2PSA and the prostate health index (phi) in men with a family history of prostate cancer: results from a multicenter European study, the PROMEtheuS project. BJU Int. 2013; 112:313–321. The article demonstrated that %[−2]proPSA and phi more accurately predicted PCa in men with a family history of PCa. The test also correlates with aggressiveness of the disease. [PubMed: 23826841]

23. Heidegger I, Klocker H, Steiner E, et al. [−2]proPSA is an early marker for prostate cancer aggressiveness. Prostate Cancer and Prostatic Disease. 2014; 17:70–74.

24. 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. [PubMed: 23466239]

25. Sokoll LJ, Sanda MG, Feng Z, et al. A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [−2]proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. Cancer Epidemol Biomarkers Prev. 2010; 19:1193–1200.

26▪▪. Crawford ED, Rove KO, Trabulsi EJ, et al. Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1962 cases. J Urol. 2012; 188:1726–1731. When the authors used a higher PCA3 score of 35, the false-negative rate significantly increased (~2300%); however, when they used a lower PCA3 score of 10, the false-negative rate decreased to 5.6%. [PubMed: 22998901]

27. Vlaeminck-Guillem V, Ruffion A, André J, et al. Urinary prostate cancer 3 test: toward the age of reason? Urology. 2010; 75:447–453. [PubMed: 19586654]

28. Auprich M, Bjartell A, Chun FK-H, et al. Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. Eur Urol. 2011; 60:1045–1054. [PubMed: 21871709]

29▪▪. Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX prostate cancer assay – a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genom. 2013; 14:690–702. This study describes the validation of the multigene reverse transcription-polymerase chain reaction method on tissue as small as 1 mm.

30. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of cell cycle progression signature for a prostate cancer death in a conservatively managed needle biopsy cohort. Brit J Cancer. 2012; 106:1095–1099. [PubMed: 22361632]

31. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiation Oncol Biol Phys. 2013; 86:848–853.

32▪. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol. 2013; 31:1428–1434. The use of CCP may represent a new tool for the prediction of cancer stage from biopsy. This article helped to validate the CCP score and demonstrated that the score may help improve risk stratification. [PubMed: 23460710]

33▪▪. McDunn JE, Li Z, Adam KP, et al. Metabolomic signatures of aggressive prostate cancer. Prostate. 2013; 73:1547–1560. Using mass spectrometry to analyze the tissue samples, the authors were able to identify compounds that differentiate cancer from healthy tissue. [PubMed: 23824564]

34. Saylor PJ, Karoly ED, Smith MR. Prospective study of changes in the metabolomics profiles of men during their first three months of androgen deprivation therapy for prostate cancer. Clin Cancer Res. 2012; 18:3677–3685. [PubMed: 22589396]

35. Jung K, Reszka R, Kamlage B, et al. Tissue metabolite profiling identifies differentiating and prognostic biomarkers for prostate carcinoma. Int J Cancer. 2013; 133:2914–2924. [PubMed: 23737455]

36. Kami K, Fujimori T, Sato H, et al. Metabolomic profiling of lung and prostate tumor tissues by capillary electrophoresis time-of-flight mass spectrometry. Metabolomics. 2013; 9:444–453. [PubMed: 23543897]

37. Truong M, Yang B, Jarrad DF. Toward the detection of prostate cancer in urine: a critical analysis. J Urol. 2013; 189:422–429. [PubMed: 23017522]

38. Falzarano SM, Magi-Galluzzi C. ERG protein expression as a biomarker of prostate cancer. Biomarkers Med. 2013; 7:851–865.

39. Bhavsar T, McCue P, Birbe R. Molecular diagnosis of prostate cancer: are we up to age? Semin Oncol. 2013; 40:259–275. [PubMed: 23806492]

40▪▪. Salami SS, Schmidt F, Laxman B, et al. Combining urinary detection of TMPRSS2:ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. Urol Oncol. 2013; 31:566–571. A limited study that concluded that patients with a PSA less than 10 ng/ml should undergo a prostate biopsy only if they have a positive post-DRE urine Progrensa PCA3 or TMPRSS2:ERG. The study additionally demonstrated the utility of combining multiple biomarkers to increase specificity. [PubMed: 21600800]

41. Cornu JN, Cancel-Tassin G, Egrot C, et al. Urine TMPRSS2:ERG fusion transcript integrated with PCA3 score, genotyping, and biological features are correlated to the results of prostatic biopsies in men at risk of prostate cancer. Prostate. 2013; 73:242–249. [PubMed: 22821767]

42. Leyten GH, Hessels D, Jannick SA, et al. Prospective multicentre evaluation of PCA3 and TMPRSS2:ERG gene fusions as diagnostic and prognostic urinary biomarkers for prostate cancer. Eur Urol. 2014; 65:534–542. http://dx.doi.org/10.1016.j.eur-uro.2012.11.014. [PubMed: 23201468]

43▪. Heichman KA, Warren JD. DNA methylation biomarkers and their utility for solid cancer diagnostics. Clin Chem Lab Med. 2012; 50:1707–1721. A literature review covering six solid cancers that demonstrates the recent research and method development for DNA methylation biomarkers. [PubMed: 23089699]

44. Stewart GD, Van Neste L, Delvenne P, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: results of the MATLOC study. Urol. 2013; 189:1110–1116.

45. Desotelle J, Truong M, Ewald J, et al. CpG island hypermethylation frequently silences FILIP1L isoform 2 expression in prostate cancer. Urol. 2013; 189:329–335.

46. Parr R, Mills J, Harbottle A, et al. Mitochondria, prostate cancer, and biopsy sampling error. Discov Med. 2013; 15:213–220. [PubMed: 23636138]

47▪. Verschoor ML, Ungard R, Harbottle A, et al. Mitochondria and cancer: past, present, and future. Biomed Res Int. 2013; 2013:612369. A current review of mitochondrial mutations in the field of cancer research. Based on the current acceleration in the field, the potential to find new biomarkers in the future is significant. [PubMed: 23509753]

48. Voigt JD, Zappala SM, Vaughan ED, Wein AJ. The kallikrein panel for prostate cancer screening: Its economic impact. Prostate. 2014; 74:250–259.10.1002/pros.22746 [PubMed: 24166488]

49▪. Carlsson S, Machino A, Schröder F, et al. Predictive value of four kallikrein markers for pathologically insignificant compared to aggressive prostate cancer in radical prostatectomy specimens: results from the European randomized study of screening for prostate cancer section Rotterdam. Eur Urol. 2013; 64:693–699. This is a well defined retrospective study that combines four kallikrien markers to demonstrate the predictive value and ability to distinguish pathological insignificant from aggressive disease. [PubMed: 23683475]

50. Bjartell A. Next-generation prostate-specific antigen test: ready to use? Eur Urol. 2013; 64:700–702. [PubMed: 23850253]

KEY POINTS

- Recently two new tests have been approved by the US FDA that provide additional information on the need for performing a prostate biopsy.
- A number of LDTs are available by CLIA-certified labs using urine or tissue already obtained from a prostate biopsy. These tests should be used with caution and the clinician should judge the utility and acceptance of these tests based on their patients' needs and desires.
- Even though the United States Preventive Services Task Force recommends against the use of PSA as a first-line test, the two newly FDA-approved tests incorporate PSA into the algorithm that is used.