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How should radiologists incorporate non-imaging prostate cancer biomarkers into daily practice?

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Abstract

Objective: To review the current body of evidence surrounding non-imaging biomarkers in patients with known or suspected prostate cancer.

Results: Several non-imaging biomarkers have been developed and are available that aim to improve risk estimates at several critical clinical junctures. For patients with suspicion of prostate cancer considering first-time or repeat biopsy, blood and urine-based assays can improve the prediction of harboring clinically-significant disease and may reduce unnecessary biopsy. Blood and urine-based biomarkers have been evaluated in association with prostate MRI, offering insights that might augment decision-making in the pre and post-MRI setting. Tissue based genomic and proteomic assays have also been developed that provide independent assessments of prostate cancer aggressiveness that may complement imaging.

Conclusion: A growing number of non-imaging biomarkers are available to assist in clinical decision-making for men with known or suspected prostate cancer. An appreciation for the intersection of imaging and biomarkers may improve clinical care and resource utilization for men with prostate cancer.

Keywords

Prostate cancer; biomarkers; molecular markers; MRI; prostate biopsy non-imaging biomarkers

Introduction

Prostate cancer is a major contributor to the global burden from cancer, with an estimated 1,276,000 new cases and 359,000 deaths each year.[1] Although prostate cancer is highly prevalent, it is also heterogeneous, remaining confined to the prostate in some while proving

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capable of rapid metastatic spread in others. As a result, efforts to estimate cancer aggressiveness hold value in improving the quality of care for patients by allowing expedient treatment (or observation) to be tailored to an individual's cancer risk, life expectancy, and preferences. Historically the measures used to predict disease outcome have been relatively rudimentary and included digital rectal examination (DRE), prostate-specific antigen (PSA) measurement, and systematic prostate biopsy.[2,3] However, over the past four decades incremental progress in early detection, staging, and treatment have led to demonstrable improvements in disease outcome.[4,5] In particular, advancements in imaging such as multi-parametric prostate magnetic resonance imaging (mpMRI), have catalyzed a shift in the management of the disease by refining localization, as well as estimates of cancer grade and stage.[6–11] Parallel developments in the understanding of the molecular foundation of prostate cancer have also given rise to a generation of prognostic biomarkers that add independent value in assessing prostate cancer risk. Therefore, an appreciation of the intersection of these technologies—including potential areas of synergy— may further improve the precision with which the disease is managed.

In this work, we aim to review the current state of common biomarkers aimed at estimating prostate cancer risk that have entered the arena of clinical practice. Radiologists may not routinely be the provider to order biomarker studies as a component of patient counseling. Nonetheless, there are several potentially important applications of their results that can be relevant. These include refining the pool of patients undergoing initial imaging, improving pre and post-test probability through the incorporation of biomarker results, and tailoring the intensity of imaging for patients electing observation for their cancer. Given the increasingly central role of radiologists in the diagnosis and staging of prostate cancer, we have focused on practical considerations for non-imaging biomarkers relating to: (1) non-invasive biomarkers performed prior to prostate biopsy, (2) tissue-based genomic and proteomic assays that estimate cancer aggressiveness, and (3) the intersection of these tests with prostate MRI, including questions of resource utilization and clinical integration.

Non-Invasive Biomarkers Available Prior to Prostate Biopsy

Limitations of Conventional Biomarkers

PSA is a reliable although imperfect marker of clinically significant prostate cancer. For example, at conventionally used cut-offs (e.g. 3 or 4 ng/ml) PSA demonstrates modest performance for detecting for high-grade (Gleason ≥3+4) disease (at a cutoff of 4 ng/mL: sensitivity 31%, specificity 90.5%).[12,13] The majority of men with an elevated PSA who undergo a prostate biopsy will have not have evidence of prostate cancer, leading to potentially avoidable morbidity, anxiety, discomfort and expense.[13,14] In addition, PSA testing alone may also lead to delayed detection of aggressive prostate cancer in a minority of men with PSA ≤4 ng/mL[15,16]. To address these limitations, non-imaging biomarkers have been developed to improve the early detection of the disease—with the aim of both reducing unnecessary biopsy and identifying those whose cancers would be undetected by PSA driven approaches.

Commercially Available Assays Prior to Prostate Cancer Diagnosis

a. Blood-based biomarkers—*Prostate Health Index* (*phi*; Beckman Coulter, Brea, California, USA) is a three-analyte assay that combines the results of free PSA (fPSA), total PSA, and [–2]proPSA, an isoform of PSA, into a mathematical formula ([–2]proPSA/fPSA × √PSA). The output is a continuous score that estimates the probability of detecting prostate cancer on a prostate biopsy. The test is intended to be used in men aged ≥50 with PSA levels of 4–10 ng/mL, who are undergoing first-time or repeat prostate biopsy.[17–19] Since the initial introduction, *phi* has been validated in multiple large cohort studies. For example, Catalona et al., prospectively evaluated the discrimination of *phi* for prostate cancer in men undergoing systematic biopsy. For the detection of prostate cancer (any grade), *phi* (area under the curve, AUC: 0.703) outperformed free-to-total PSA ratio (AUC: 0.648) and PSA alone (AUC: 0.525). For the detection of high-grade prostate cancer (Gleason score≥ 4+3), the AUC *for* phi alone was 0.724.[17] In a separate prospective study, the diagnostic accuracy of *phi* was tested on the FDA-recommended sample cohort (50 years or older, 4–10 ng/ml PSA, normal DRE).[19] The assay was a robust predictor of Gleason score ≥3+4 cancer (AUC: 0.707) with a better performance than its individual components (AUCs: %fPSA 0.661, [−2]proPSA 0.558, PSA 0.551). At 90% sensitivity for Gleason 3+4 or higher disease, *phi* (28.9 cut-off) was more specific than PSA (29.7% vs. 7.8%, $p<0.05$). Moreover, in multivariable analysis (MVA), adjusted for previous biopsy status and gland volume, log-transformed *phi* was independently associated with the detection of clinically significant prostate cancer. 4Kscore® (OPKO, Elmwood Park, New Jersey, USA), is a blood-based kallikrein panel, that combines PSA, free PSA, intact PSA (iPSA), and human kallikrein 2 (hK2) as well as the information contributed by age, DRE and prior biopsy status.[20] The score estimates the probability of detecting high-grade (Gleason ≥3+4) on a prostate biopsy, and is reported on a 0–100% continuous scale.[20–23] The initial validation study was derived from a cohort of patients enrolled in a randomized trial of prostate cancer screening in Europe (n=740).[21] Combining the baseline clinical model (age, PSA, DRE) with Kallikrein markers resulted in an improvement in diagnostic accuracy with an AUC of 0.87 to 0.90 for the Gleason score ≥3+4 disease.[21] In the first prospective study assessing the panel performance in an independent multi-center U.S. cohort (n=1,012), the 4Kscore® was a better predictor of clinically significant prostate cancer, than a commonly used risk calculator derived from clinical features (AUCs: 0.82 vs 0.74, $p<0.0001$).[22] Furthermore, the analysis indicated that thresholds for intervention may be altered for patients based on clinically-relevant factors such as age. For example, individuals with longer life expectancy generally derive greater benefit from early detection, resulting in a lower threshold in this population. As a result, fewer biopsies would be avoided with the use of 4KScore® in younger patients (30–40%), while still capturing the majority of high-grade disease (90–94%). Contrary, for older patients or those with higher comorbidity burden, a higher 4Kscore® cutoff (e.g. ≥15%) may be reasonable, leading to a reduction of 58% of biopsies while identifying 79% of high-grade prostate cancers.[22]

Stockholm-3 (STHLM3): The STHLM3 is a prognostic model that has been evaluated to detect high-grade prostate cancer. The model incorporates plasma protein biomarkers [including PSA, free PSA, intact PSA, hK2, beta-microseminoprotein (MSMB), macrophage inhibitory cytokine-1 (MIC1)], genetic single nucleotide polymorphisms

(SNPs), and relevant clinical variables (age, family history, previous biopsy status, prostate volume, and digital rectal exam findings). In a prospective, population-based diagnostic study of men without known prostate cancer aged 50–69 years, the STHLM3 model (AUC 0.74, 95% CI 0.72–0.75) outperformed PSA alone (AUC 0.56, 95% CI 0.55–0.60) for the detection of Gleason grade 3+4 or higher prostate cancer.[24] Based on this performance, implementation of the STHLM3 model could reduce the number of total prostate biopsies by 32% (including those detecting Gleason 3+3 cancer) and avoid 44% of benign biopsies. Therefore, the STHLM3 model has been proposed as reflex test for patients with an elevated PSA prior to biopsy.[25]

b. Studies Comparing Prostate MRI and Blood-Based Biomarkers—An expanding body of literature has evaluated the diagnostic performance of mpMRI and commonly used blood-based biomarkers. In a study that assessed the results of *phi* and mpMRI among men undergoing a repeat prostate biopsy, the use of mpMRI and PSA alone demonstrated an AUC for the detection of clinically-significant prostate cancer of 0.69. In comparison, the incorporation of *phi* improved the performance for both any-prostate cancer and clinically-significant prostate cancer (AUC 0.71 and 0.75, respectively). Moreover, at a threshold of ≥35, *phi* and mpMRI demonstrated a negative predictive value (NPV) of 0.97, suggesting strong potential for using these tools to identify a subset of patients with elevated PSA who may avoid prostate biopsy. Moreover, in patients without a visible lesion on MRI, *phi* also improved the prediction of significant cancer on a systematic biopsy, with an AUC of 0.76 versus 0.63 with PSA level alone.[26] In another study of 57 men who underwent mpMRI-ultrasound fusion biopsy, no individuals with Prostate Imaging Reporting and Data System (PIRADS) ≤3 studies and *phi*<27 were found to have Gleason ≥3+4 prostate cancer on biopsy. By comparison, among the small subset of men with PIRADS ≤ 3 and *phi* scores above 27, 29% were found to have Gleason ≥3+4 cancer.[27] Further evidence indicates that the *phi* assay may further refine selection for biopsy among patients who have undergone a prostate MRI. In a study of 102 patients, limiting biopsy to those with a PIRADS-5 lesion, or those with PIRADS 3–4 with *phi* scores ≥ 30 would reduce biopsy by 50% at the expense of missing one clinically significant cancer.[28] However, to date, no cutoff of *phi* has been universally accepted or integrated into major clinical practice guidelines to modify the interpretation of outcome of prostate MRI.

The 4Kscore® has also been studied in conjunction with prostate MRI to evaluate selection for both initial MRI and biopsy. In a cohort of 266 biopsy-naïve patients who underwent mpMRI and subsequent MRI-ultrasound fusion biopsy, the diagnostic yield of mpMRI was improved by integration of the 4Kscore®. For example, the NPV for mpMRI among patients with low or intermediate biomarker results was 96.9 and 97.1% respectively. Moreover, the positive predictive value (PPV) was negligible for PIRADS 3–5 lesions with low 4Kscore® results. These findings also indicated that biomarkers such as 4KScore® could be operationalized to select patients who are most likely to benefit from a prostate MRI. For example, offering an MRI to those with a 4Kscore® greater than 7.5, and further restricting biopsy to those with PIRADS scores of 3 or greater would avoid nearly a third of prostate biopsies, while missing 2.7% of clinically significant cancers.[29] Similar to the *phi* test, no

clinical practice guidelines currently endorse a specific 4Kscore® cutoff to select patients for prostate MRI or prostate biopsy.

Take Home Message: Blood-based biomarkers have been developed and widely validated that improve the prediction of prostate cancer in the pre-biopsy setting. These tests appear to add independent information that could modify selection for MRI as well as prostate biopsy. At present, no clear consensus or guideline statements are available to inform how best to integrate biomarkers and MRI to refine biopsy selection, however this is a potential avenue for future development.

c. Urine Based Biomarkers Available Prior to Biopsy—Several urinary-based assays have been developed and are commercially-available that predict the risk of harboring prostate cancer. These tests, although analytically distinct from blood-based biomarkers, aim to answer similar questions regarding the likelihood of detecting prostate cancer if a biopsy is performed.

Urinary Exosome Assay: ExoDx™ Prostate IntelliScore (EPI), is an exosome-based gene expression urinary assay, which has been developed and studied to predict the presence of high-grade prostate cancer.[20,30] Extracellular bilayer vesicles (exosomes) are released by both normal and cancer cells, and transfer proteins, lipids, and nucleotide acids.[31,32] The ExoDx™ signature is derived from urinary exosomal *ERG* and *PCA3* mRNA normalized to the expression level of *SPDEF*. In the developmental study, the diagnostic performance of the exosomal assay was assessed in 195 biopsy-naive men aged ≥40yr with PSA 2–10 ng/mL[33]. The marker had robust predictive accuracy for any (AUC: 0.715) and high-grade prostate cancer (AUC: 0.764).[33] In a subsequent study, the algorithm was optimized and validated in 1,064 men using a ≥15.6 threshold (scale 0–30). For the prediction of Gleason 3+4 disease or higher, the assay alone showed favorable accuracy (AUC: 0.71) and added value to the clinical standard of care, SOC (AUCs; ExoDx™ + SOC 0.73 vs SOC 0.63, $p<0.001$). For example, it was estimated that clinical integration of this assay could avert 27% of unnecessary biopsies while missing 8% of Gleason 3+4 and 5% of Gleason 4+3 disease.[30] Moreover, the assay also appears to maintain high negative predictive value in the context of both first-time and repeat prostate biopsy. Currently, no studies exist to compare the utility or diagnostic interpretation of this assay among patients receiving prostate MRI.

SelectMDX® (MDxHealth, Irvine, CA, USA) is a diagnostic molecular urinary assay for men considered for initial and repeat biopsy.[9,34,35] The assay measures mRNA expression among a panel of genes (*HOXC6, DLX1, TDRD1*) that were derived from patients treated with radical prostatectomy and transurethral resection of the prostate.[34] The signature was validated among 358 men undergoing initial and re-biopsy and demonstrated favorable accuracy for the prediction of Gleason score ≥3+4 cancer (AUC: 0.77).[34] Incorporating gene expression and clinical variables, including age, PSA, PSAD, DRE, family history and prior biopsy, improved the prediction of high-grade prostate cancer (AUC: 0.86). Notably, the model was more accurate without the results of a digital rectal examination, and also surpassed the performance of standard clinical nomograms. Based on these estimates, it was estimated that 53% of unnecessary biopsies could be avoided at a cut-point adjusted to a NPV of 98%.[35] The association between the SelectMDx® assay and mpMRI of the prostate

has been evaluated in a study of 172 patients undergoing prostate biopsy. Among a study cohort who underwent evaluation in the Netherlands, SelectMDx® scores were higher among those with suspicious lesions (PI-RADS 4–5). Moreover, SelectMDx® results also outperformed PSA(AUC 0.83 versus 0.66) for the prediction of possessing a suspicious lesion on MRI.[36] These findings suggest that the SelectMDx® assay may also provide value in identifying patients who may benefit from further testing although no diagnostic cutoff has been validated.

Prostate Cancer Antigen-3 (PCA3) is a prostate-specific, long non-coding RNA (lncRNA) that can be detected in the urine.[37] In 2012, the Food and Drug Administration (FDA) approved the Progensa ™ PCA3 test (Gen-Probe Inc., San Diego, CA, USA) which measures PCA3 mRNA relative in the urine relative to PSA expression. The assay is clinically intended for men ≥50, with previous negative biopsy.[9,38–40] Among 859 patients, who underwent initial (n=562) and repeat (n=297) biopsy the PCA3 score (at a cutoff score of 60) had PPV of 80%, 42% sensitivity and specificity of 91%. Among patients undergoing repeat biopsy, PCA3 (had NPV of 88%, sensitivity of 76% and specificity 52%. The combined utility of prostate MRI and the PCA3 assay in avoiding repeat prostate biopsy after an initial negative evaluation has been evaluated in several studies. Recently, Perlis et al. examined a cohort of 470 men who underwent mpMRI and PCA3 testing, and found that PI-RADS score and PCA3 score were independently associated with the presence of clinically significant prostate cancer on a repeat biopsy. Notably, there were no patients with a normal MRI and PCA3 score who had prostate cancer identified on a subsequent biopsy (NPV 100%).

Mi-Prostate Score (MiPS) (MLabs, Ann Arbor, MI): The TMPRSS2:ERG (T2:ERG) fusion gene is a genetic aberration that is commonly observed in prostate cancer.[41,42] The MiPS assay which incorporates serum PSA level and urinary expression levels of T2:ERG, PCA3 and PSA mRNA provides an estimate of prostate cancer risk that is expressed on a 0–100% scale.[43,44] In a prospective study of 443 men prior to biopsy, the inclusion of T2:ERG and PCA3 scores into a standard clinical nomogram improved the accuracy of prostate cancer detection from 0.799 to 0.842.[43] Among 1,225 men, including 80% undergoing a first-time biopsy, MiPS had higher predictive accuracy than PSA for any (AUC: 0.751 vs. 0.585, $p<0.001$) and high-grade prostate cancer (AUC: 0.772 vs. 0.651, $p<0.001$).[44] The algorithm was further optimized to reach >95% sensitivity (T2:ERG score >8; PCA3 score >20; PSA >10 ng/ml) and then validated in a cohort of 561 patients. Using these cutoffs, a potential decision algorithm could lead to avoidance of 42% of unnecessary biopsies while missing 7% GS ≥7 cancers. Notably, results of cost analysis indicated that the assay clinical implementation compared with theoretical standard care (abnormal PSA-driven biopsy in all patients) may lead to $1200–2100 cost savings per patient.[45] To our knowledge, the association between the MiPS assay and prostate MRI has not been evaluated.

d. Tissue-based tests of histologically negative prostate biopsy tissue:

ConfirmMDx® (MDxHealth, Irvine, CA, USA) is a multiplex epigenetic assay that predicts the likelihood of detecting prostate cancer in a subsequent biopsy among men with an initial negative biopsy. Historically, more than one third of patients with an initial negative prostate biopsy undergo a repeat prostate biopsy due to persistent suspicion for

prostate cancer.[46] Therefore, tools that improve confidence in the status of a first negative biopsy can reduce unnecessary subsequent biopsies, or identify patients at risk for harboring occult prostate cancer. ConfirmMDx® examines the methylation status of three genes (*APC, GSTP1* and *RASSF1)* associated with the presence of prostate cancer as a field effect. Across two cohorts of patients with prior negative systematic prostate biopsies, the methylation assay demonstrated 96% NPV for the presence of high-grade (Gleason 3+4 or higher) prostate cancer.[47] Although prostate MRI has demonstrated utility for the management of patients with prior negative biopsies, no published studies have directly compared the performance of the ConfirmMDx® assay with MRI-ultrasound targeted biopsy.[48] =

Take Home Message: Urine-based biomarkers have been developed to improve the discrimination of prostate cancer in the pre-biopsy setting. Correlative studies have been performed that suggest potential cut-points that may help improve selection for prostate biopsy.

III. Tissue-based prognostic tests

Prognostic tissue-based genomic and proteomic assays have been validated and entered clinical care for patients with prostate cancer.[9,49] Currently, several tests are available that estimate cancer aggressiveness and aim to improve decision-making in multiple clinical scenarios. Broadly these include: (1) selection of active surveillance or definitive treatment for men with clinically localized prostate cancer, and (2) use of adjuvant radiation therapy after definitive treatment.[49,50] Commercially-available tests are performed on formalin-fixed paraffin embedded (FFPE) prostate tissue, and therefore are derived from either prostate biopsy or radical prostatectomy. Recently, the use of these tests have been incorporated into the National Comprehensive Cancer Network's prostate cancer guideline for men with low or favorable-intermediate risk prostate cancer considering active surveillance or for patients who are considering subsequent radiation therapy after radical prostatectomy.[9] Moreover, given the dissemination of prostate MRI in the diagnostic pathway for prostate cancer, there is a growing number of patients who undergo testing both modalities, raising questions regarding their optimal positioning, comparative performance, and cost.

a. Clinically directed genomic tests—

Prolaris® (Myriad Genetics, Inc., Salt Lake City, Utah), is a 46-mRNA (31 cycle cell progression [CCP] genes, 15 housekeeping genes) panel that has been associated with numerous clinical endpoints including biochemical recurrence, metastasis, and cancer-specific survival.[51,52] Unit increases in the CCP score have been independently associated with the risk of biochemical recurrence after prostatectomy and death from prostate cancer among patients who elect conservative management[51,52]. Integrating clinical information such as the Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) and CCP improved accuracy (c-index: 0.77) compared to clinical classification alone (c-index: 0.73, $p<0.001$).[52] Moreover, a biopsy-based CCP score predicted 10-yr prostate cancer mortality in patients with prostate cancer who did not undergo initial treatment, suggesting clinical utility in refining decisions about definitive treatment versus observational approaches (active surveillance or watchful waiting).[53,54]

Oncotype DX Genomic Prostate Score (GPS) (Genomic Health, Redwood City, CA, USA), is a tissue-based 17-gene expression signature. The assay measures the mRNA expression of 12 cancer-related genes normalized to five housekeeping genes, and the results are presented as a scaled score (0–100) reflecting increasing aggressiveness. The test has been clinically validated to predict numerous endpoints including the risk of adverse surgical pathology (high-grade and/or high stage), biochemical recurrence, metastasis, and death from prostate cancer.[55–57] For example, among patients with favorable clinical risk prostate cancer who may be candidates for active surveillance, increases in GPS are independently associated with the risk of adverse surgical pathology. These findings suggest that the GPS assay may have clinical utility in substratifying risk among patients with ostensibly low and intermediate clinical risk prostate cancer.[58–61] The GPS assay has also been associated with distant oncologic endpoints including distant metastasis and prostate cancer specific mortality.[62]

Decipher® (GenomeDx Biosciences, Inc., Vancouver, British Columbia) is a 22-gene genomic classifier (GC), that has been developed and validated to predict numerous prostate cancer endpoints.[63,64] The assay uses high-density transcriptome wide microarrays to analyze 1.4 genomic features representing 46,000 coding and non-coding RNA sequences. Although initially studied as a predictor of metastasis and prostate cancer mortality among high-risk patients undergoing radical prostatectomy, this assay has also been studied as a predictor of adverse surgical pathology (high grade and/or high stage), biochemical recurrence, metastasis and cancer-specific mortality among patients who are considering definitive therapy.[56,63–68] Although the Decipher classifier has been independently associated with numerous prostate cancer endpoints, it is worth emphasizing that the performance of the classifier is improved with the integration of clinical information such as Gleason score, cancer stage, PSA levels.[69]

ProMark® (Metamark Genetics, Inc., Waltham, Massachusetts) is a biopsy-based prognostic assay that evaluates the status of eight proteomic biomarkers associated with prostate cancer aggressiveness.[70,71] The score is scaled 0–100, reflecting increasing probability of high-grade and/or high-stage disease. The test has been clinically validated among patients with low and intermediate-risk prostate cancer by clinical features who were treated with radical prostatectomy. The ProMark® assay demonstrated an AUC of 0.68 for the detection of favorable pathology (organ confined and Gleason score ≤3+4). However, the predictive accuracy was improved with integration of clinical information (AUC 0.75). Using the lower cut-off (≤0.33) in very-low, low and intermediate NCCN clinical risk groups, the PPV reached 95% and 81.5% and 75%, respectively, which outperformed clinical criteria alone. Furthermore, 76.9% of patients with ProMark® assay scores greater than 0.8 were found to have adverse surgical pathology.[71] As a result, the test is marketed towards patients with localized low and favorable-intermediate risk Gleason ≤3+4 prostate cancer to aid in decision making.

Take Home Message: Prognostic assays derived from prostate cancer specimens obtained from biopsy or radical prostatectomy provide independent clinical information regarding several prostate cancer endpoints that may improve decision-making.

b. Association between MRI and Genomic Testing—Several recent studies have examined the associations between prostate MRI and tissue-based gene expression tests. Among 100 men who underwent prostate MRI and OncotypeDX GPS testing at the University of California San Francisco, GPS results differed by MRI suspicion groups. However, there was a wide distribution of GPS values, suggesting heterogeneity within categories of prostate MRI findings. Examining specific pathways within the panel, the authors found that expression levels reflecting stromal response (p=0.015) and cellular organization (p=0.045) differed significantly by MRI findings, but no differences were seen among androgen signaling or proliferation genes.In addition, GPS results were weakly correlated with mean apparent diffusion coefficient (ADC, rho=−0.151).[72] Stoyanova et al. correlated radio-genomic features among 17 MRI-targeted prostate biopsies profiled using the Decipher classifier, noting associations between imaging findings and gene expression.[73] In another study, including 102 men with low and intermediate risk prostate cancer who underwent MRI-ultrasound fusion biopsy and Decipher® testing, the authors noted that high-risk genomic profiles were seen across categories of MRI findings. Moreover, 25% of men with PI-RADS 5 and Gleason grade 3+4 disease had low Decipher scores, highlighting the presence of molecular heterogeneity within even highly suspicious MRI lesions.[74]

Studies have also examined the association between MRI-visibility and gene expression profiling. For example, among 72 patients who underwent radical prostatectomy who received pre-operative MRI whole-mount correlative assessment, the authors identified foci of malignant tissue with aggressive genomic profiles in areas that were not evident on MRI. [75] In another recent study, Parry et al. characterized genomic, epigenomic, and transcriptomic features of MRI visible and non-visible prostate cancer among patients treated with prostatectomy. Using fresh tissue obtained from 43 cores collected from six patients with intermediate to high-risk prostate cancer the authors noted intratumoral heterogeneity among MRI visible lesions, raising concerns for incompletely characterizing disease risk if genomic testing is performed on a single biopsy core. Moreover, the authors also detected adverse genomic alterations (copy number changes, *MYC* amplification) present in MRI-nonvisible lesions, highlighting the potential to under-sample and misclassify prostate cancer risk if an MRI-fusion biopsy-only approach is employed without systematic biopsy.[76]

Take Home Message: Studies examining the results of prostate MRI and tissue-based gene expression testing reveal that estimates of cancer aggressiveness are largely aligned, however, heterogeneity among MRI results suggests a complementary role for these to modalities.

Conclusions: How Should Radiologists Incorporate Prostate Cancer Biomarkers into Practice?

Over the past decade there has been a remarkable expansion of tools that aim to improve risk stratification for patients with known or suspected prostate cancer. In parallel to the refinements of both performance and interpretation of prostate MRI, a host of non-imaging biomarkers have been developed and clinically implemented to improve clinical decision-

making. Given the ongoing transformation of the prostate cancer diagnostic pathway, radiologists play an increasingly important role in the identification and staging of the disease which is poised to be offered in an increasingly multidisciplinary manner. From this context, a greater appreciation of the information contributed by non-imaging biomarkers by radiologists has several practical applications.

Non-invasive blood and urine-based biomarkers that improve prediction of prostate cancer among patients with clinical suspicion may help reduce unnecessary biopsies, or more promptly identify patients harboring aggressive disease. These tests may also one day be applied to better inform the selection pathway for prostate MRI, potentially improving resource utilization and cost-effectiveness.[11,77,78] For example, if blood-based biomarkers are routinely employed as a reflex test for patients with an elevated PSA, a subset of men might be identified who can forego additional evaluation, including MRI however further validation of such an approach would be required. Close collaboration between radiologists and urologists therefore holds value in designing and clinically implementing such approaches.

In addition, integration of available biomarker information can improve the diagnostic performance of imaging alone for clinically meaningful endpoints. Prostate MRI is increasingly used among men with low and favorable-intermediate risk prostate cancer who are considering or being managed with active surveillance. The use of genomic testing may fill in important insights about disease biology that are not conveyed by imaging parameters alone, suggesting a complementary role. Furthermore, given the growing prevalence of men who are being managed with active surveillance the use of genomic testing may also help refine the intensity of monitoring – potentially indicating pathways of less vigilant MRI imaging for certain individuals at lower risk, and more frequent monitoring for those with greater risk. Lastly, prostate MRI and genomic tests are both associated with considerable expense to patients and payment systems. As comparative study continues, efforts are also valuable to understand cost-effective approaches to implementing these tools.

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Table 1.

Summary of commercially-available biomarkers used in clinical decision making for men with known or suspected prostate cancer.

Name	Substrate	Clinical Scenario	Outcomes Examined	Studied in Comparison with MRI?
Prostate Health Index®	Blood	Before prostate biopsy; after initial negative biopsy	Prostate cancer at biopsy	Yes
4KScore®	Blood	Before prostate biopsy; after initial negative biopsy	Prostate cancer at biopsy	Yes
ExoDX®	Urine	Before prostate biopsy; after initial negative biopsy	Prostate cancer at biopsy	No
SelectMDX ®	Urine	Before prostate biopsy; after initial negative biopsy	Prostate cancer at biopsy	No
PCA3	Urine	After initial negative biopsy	Prostate cancer at biopsy	Yes
Mi-Prostate®	Urine	Before prostate biopsy	Prostate cancer at biopsy	No
Prolaris®	Prostate cancer Tissue	After prostate cancer diagnosis or radical prostatectomy	Cancer recurrence; metastasis; death from prostate cancer	Yes
OncotypeDX ® Genomic Prostate Score (GPS)	Prostate cancer Tissue	Low and intermediate risk prostate cancer after biopsy	Adverse pathology at biopsy; cancer recurrence; metastasis; death form prostate cancer	Yes
Decipher®	Prostate cancer Tissue	After prostate cancer diagnosis or radical prostatectomy	Adverse pathology; cancer recurrence; metastasis, death from prostate cancer	Yes
Promark®	Prostate cancer Tissue	Low and intermediate risk prostate cancer after biopsy	Adverse surgical pathology	No
ConfirmMDx®	Histologically benign tissue	After negative prostate biopsy	Probability of cancer on subsequent biopsy	No