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Prostate cancer biomarkers and multiparametric MRI: is there a role for both in prostate cancer management?

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***Abstract*:** Several advancements have been made in recent years with regards to the detection and evaluation of prostate cancer (PCa). The low specificity of prostate specific antigen (PSA) has left much to be desired in a test, but a boom in novel biomarkers has made screening and surveillance more complicated. Several attempts at identifying a niche for these tests has helped somewhat, but much is still undetermined about the benefit that each test provides. In addition to laboratory tests, advancements in multiparametric magnetic resonance imaging (mpMRI) and PIRADSv.2 scoring have provided significant benefit to the evaluation of PCa. With the widespread use of prostate imaging, it is important to re-evaluate the impact of novel biomarkers in the context of furthering PCa screening and management. In this review, we aim to assess the influence mpMRI has on the role of nine different novel biomarkers in the detection and evaluation of PCa. We performed a review of current peer-reviewed literature to assess this question. Much data has been published on the role of these tests, allowing for their placement into one of three best-fit categories: tests for biopsy-naïve men (Prostate Health Index, Mi Prostate Score, 4K Score); tests for men with prior negative biopsies (ConfirmMDx, Progensa PCA3); and men on active surveillance (OncotypeDx, Prolaris, Decipher). Data on the role of these tests with the use of mpMRI have not been comprehensive and excludes several of the markers. More research is needed to determine the combined impact mpMRI and the novel biomarkers on the evaluation and management of PCa.

Keywords: Prostate Cancer, Biomarkers, Multiparametric MRI

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Background

Prostate cancer (PCa) persistently poses a large burden on our society. With one in nine men receiving a diagnosis of PCa in their lifetime, the search for an accurate diagnostic tool is well warranted.[1] Since 1986, prostate specific antigen (PSA) has served as the standard test for PCa screening and diagnostics[2]; however, controversy surrounds the use of PSA as it has led to overdiagnosis and overtreatment of clinically insignificant PCa. The implementation of PSA as the core diagnostic tool has led to an increase in the incidence of PCa and consequently the number of radical prostatectomies performed,[3,4] often for clinically insignificant cancer.[5] An elevated PSA can be secondary to non-cancerous conditions such as prostatitis and benign prostatic hyperplasia, or urinary tract instrumentation.[6] Due to these confounding causes, the positive predictive value (PPV) of PSA for PCa is only 25–40%.[7]

Conversely, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer study in 2009 did not show any significant improvement in mortality rates of PCa when PSA was used.[8] The European Randomized Study of Screening for Prostate Cancer (ERSCP) determined that the 1410 men would need to be screened to prevent one death from prostate cancer (csPCa).[9] Currently, the United States (US) Preventative Screening Task

Force (USPSTF) gives a Grade C recommendation for the use of PSA, and only then with shared decision-making.[6,10] In recent years, numerous biomarker tests have been developed to help account for the shortcomings of PSA. Ranging from blood-, to urine-, to tissue-based tests, these biomarkers aim to optimize the sensitivity and specificity of csPCa detection.

In recent years, the role of imaging the prostate has boomed as an adjunct to PSA for the evaluation of PCa. Multiparametric magnetic resonance imaging (mpMRI) has emerged as a useful tool not only for screening, but also for diagnosis and surveillance of PCa. mpMRI involves a combination of T1- and T2-weighted images, diffusion-weighted images (DWI), and dynamic contrast-enhanced images (DCE) to identify prostate lesions. From these sequences, lesions are graded using the PIRADS v2 grading system according to the risk of csPCa.[11] When comparing mpMRI with standard biopsy, studies have shown mpMRI to have a higher sensitivity for csPCa [93%; 95% confidence interval (CI) 88–96%].[12,13] From these findings, the authors concluded that the use of mpMRI as a screening tool would decrease the number of primary biopsies by 27%.[13] mpMRI has also been shown to be useful for the continued monitoring of men with previous negative biopsies or who are on active surveillance (AS), but who have continued rising PSA. Current American Urological Association (AUA) guidelines suggest the use of mpMRI for targeted biopsy of suspicious lesions in men with prior negative biopsies,[14] while the EAU guidelines strongly suggest the use of mpMRI for men with low-risk disease but suspicion for progression.[15] Additionally, the National Institute for Health and Care Excellence (NICE) guidelines published in 2019 recommend the use of mpMRI in all men suspected of having localized prostate cancer followed by MRI-influenced biopsy in men with Likert scale scores of 3 or more on MRI. The guidelines also recommend considering omitting a prostate biopsy altogether for low-risk MRI, but only after discussing the risks and benefits with the patient.[16]

Some even consider mpMRI of the prostate to represent another "biomarker" for PCa. In a systematic review of MRI-conspicuous lesions and the molecular patterns of the corresponding tissue, Norris *et al.* describe an association seen between genetic markers of disease aggressivity with lesions seen on mpMRI.[17] Genetic markers seen to be highly expressed in suspicious lesions included those for proliferation signaling, DNA damage, and inflammation.[17] Since MRI inherently provides information about the likelihood and location of csPCa, one could argue the addition of another biomarker to the current practice of MRI and PSA will yield incremental benefit.

Of the biomarkers reviewed, four(PSA, PHI, PCA3, and Prolaris) are approved by the US Food and Drug Administration (FDA), five are Clinical Laboratory Improvement Amendments (CLIA) approved (4Kscore, MiPS, ConfirmMDx, OncotypeDx, and Decipher), while miRNA has not received institutional approval for use in prostate cancer.

In this article, we examine alternative diagnostic tests to PSA. Specifically, we aim to stratify the utility of these tests based on their needs in different populations: repeat screening for previous negative biopsies, AS, and biopsy naïve men, and evaluate their utility within the context of widespread mpMRI.

Tests for men with prior negative biopsies

ConfirmMDx

ConfirmMDx is a tissue-based gene assay that analyzes a set of epigenetic changes seen in a prostate tissue sample. By detecting alterations of DNA methylation in key tumor suppressor genes (GSTP1, GASSF1, and APC), this tool helps risk-stratify men with prior negative biopsies.[6] It was shown that prostate biopsies have a high false-negative rate, leading to repeat biopsies in more than 50% of men with negative pathology due to suspicious PSA levels and DRE exams.[18] ConfirmMDx has been shown to augment the negative predictive value (NPV) of a negative biopsy to 90%.[18,19] In a blind multicenter observational study ($N = 138$), Wojno *et al.* discovered that implementation of ConfirmMDx led to a 10-fold decrease in the number of biopsies performed.[20] In a study with 350 subjects, Partin *et al.* validated the test to be a significant, independent predictor of prostate cancer detection in a repeat biopsy due to its NPV of 88% ($p = 0.0227$).[19] Also, a 2019 cross-sectional study ($N = 211$) of the efficiency of ConfirmMDx in an African American cohort demonstrated that this tool can be utilized successfully in multiple races with equal value ($p = 0.235$ for sensitivity and $p = 0.697$ for specificity).[21] With the low NPV of

initial prostate biopsies, ConfirmMDx can be implemented to decrease significantly the number of unnecessary repeat biopsies. This test is limited, however, in that it requires a biopsy sample and thus would only be of use to patients undergoing a biopsy or who have access to their previous tissue samples.

A recent study by Artenstein *et al.* ($N=113$) of mpMRI results after ConfirmMDx showed that a negative ConfirmMDx test correlated reasonably with negative MRI results (71.4%).[22] However, it was seen that PIRADS 5 lesions tended to be located in the anterior base of the prostate, a region not well sampled on systematic biopsy.[22] Due to these results, it is reasonable to suggest that ConfirmMDx may be more suitable after mpMRI, as a targeted biopsy would be more sensitive. More studies are needed to assess the role of ConfirmMDx after fusion biopsy specifically, to determine if there is an additive benefit of the test to mpMRI.

Progensa PCA3 assay

Progensa PCA3 uses a post-DRE urine sample to quantify mRNA that is overexpressed in PCa tissue.[23] The downstream product of the targeted mRNA was found to play a role in the cell survival of tumor tissue, likely by modulating androgen receptor signaling.[24] In 2012, the FDA approved PCA3 as a PCa diagnostic test to be used after prior negative biopsy but before obtaining a second biopsy.[6] This test quantifies the risk of a PSA elevation being related to PCa. In a case control study ($N=466$) Gittelman *et al.*[25] showed that a NPV of 90% can be achieved using a cut-off score of 25. Several studies went on to demonstrate that men with a lower score were more likely to have a negative repeat biopsy when compared with men with a higher score,[25–27] further demonstrating the utility of PCA3 when ruling out csPCa. In another prospective randomized study ($N=859$), Wei *et al.* determined that a high PCA3 score increased the probability that an initial prostate biopsy would identify high-grade cancer.[27] Therefore, PCA3 primarily plays a role in reducing the number of repeat biopsies for men suspected to have PCa with prior negative biopsy, but does show utility for biopsy naïve men.

Alkasab *et al.* evaluated PCA3 in combination with MpMRI in patients with two prior negative biopsies.[28] Alone, PCA3 has a NPV for PCa of 40% and mpMRI has an NPV of 83%. However, adding mpMRI to high PCA3 scores augments the NPV to 95%.[28] These data suggests that, in patients with clinical suspicion of PCa, both PCA3 and mpMRI can be used to help decide to biopsy.

The most critical limitation of PCA3 comes from the lack of an established standard for providers and the inconsistency of DRE exams across providers. This is further complicated by patients with atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasia (HGPIN) who were found to have higher scores than their healthy control counterparts.[29]

Tests for men on active surveillance

OncotypeDx

Developed in 2013, OncotypeDx utilizes a prostate tissue sample to calculate a Genomic Prostate Score (GPS). Quantifying mRNA of 17 genes known to be associated with PCa tumorigenesis, a GPS score from 0 to 100 is calculated, such that higher scores are associated with more aggressive PCa. Determination of the GPS allows for individual risk stratification and aids treatment decision making for patients and providers. This test has proven useful specifically for low- and low-intermediate risk PCa patients,[6] specifically those with a life expectancy of 10–20 years. GPS can also be combined with the National Cancer Comprehensive Network (NCCN) clinical risk group to assess disease aggressiveness.[6] In addition, several studies have shown that OncotypeDx can lower the NCCN risk group, most notably from low- to very low-risk cancer.[30–32] Badani *et al.* showed in a prospective study ($N=158$) that a change in the NCCN group was seen in 39% of men,[31] with 36% of men having their risk downstaged. Lowering risk categorization led to a decrease in the invasive treatment utilized, with more patients qualifying for AS.[32–34] A systematic review by Olleik *et al.* showed that OncotypeDX plays a role in the determination of the appropriateness of AS in patients with a positive prostate biopsy.[34]

When studying the longevity of usefulness for OncotypeDx, Cedars *et al.* showed that changes in GPS score aid physicians in upgrading PCa lesions and transitioning from AS to treatment.[35] Therefore, the value of this marker is best noted in long-term surveillance of men with known low-risk PCa.

In the current climate of widespread imaging of the prostate as a tool for tracking PCa, the utility of OncotypeDx has been re-evaluated. In a study comparing the GPS signature of lesions with mpMRI findings ($N = 100$), a weak correlation of higher GPS was seen with more suspicious mpMRI lesions.[36] However, significant variation in GPS scores was noted across all mpMRI categories, suggesting that OncotypeDx may not provide accurate and reliable information on lesions seen on mpMRI. In a cross-sectional study by Salmasi *et al.*, the role of the GPS in the context of mpMRI was again evaluated.[37] In their study, a multivariate model containing mpMRI, GPS was still an independent predictor of adverse pathology. Therefore, we believe that there is a role for both OncotypeDx and mpMRI in the evaluation of men with prior positive biopsies; however, they should be used in parallel to one another.

Prolaris

Prolaris is a test that analyzes 46 genes from a prostate biopsy tissue sample to arrive at a risk score used to predict the probability of aggressive disease.[38] Because Prolaris relies on tissue from a biopsy rather than blood or urine, it is primarily used to decide the course of treatment when prostate cancer is suspected or confirmed. While this may be a limitation, Prolaris can still benefit patients by decreasing the need for unnecessary treatment.[39] Additionally, it can aid in patient risk stratification. A pooled cohort ($N = 1062$) found that men with higher scores were significantly more likely to show progression to metastatic disease in 10 years (hazard ratio = 2.93, $p < 0.001$).[40] This is especially helpful for patients who are diagnosed with low- or moderate-risk cancer and can help determine if intervention is warranted.[41] However, Prolaris has limited utility in patients where prostate cancer is only suspected or under investigation. Furthermore, it is unknown if intensive treatment in response to a high Prolaris score will provide additional benefit *versus* standard treatment.[40] While there is sufficient evidence to justify the use of Prolaris, the requirement for a biopsy and established diagnosis of prostate cancer limits its utility as a screening tool.

Due to the novelty of both Prolaris and MRI advancements, few studies exist that compare the two. In a study addressing features of PCa on MRI and the cell cycle genes assessed in Prolaris, Wibmer *et al.* found that both methods were able to find aggressive forms of prostate cancer ($N = 118$).[42] However, a higher risk score from Prolaris was also associated with extracapsular extension. Because of this, MRI in conjunction with Prolaris may be helpful when evaluating extracapsular extension in smaller lesions or low-grade lesions that are more difficult to evaluate with MRI alone. Ultimately, more studies are still needed to identify possible utilization for Prolaris in combination with or instead of MRI.

Decipher

Similar to Prolaris, Decipher is a test that seeks to risk stratify patients who have undergone radical prostatectomy (RP).[43,44] From the prostatectomy specimen, the test examines 22 RNA markers to better predict the risk of metastasis and mortality after prostatectomy. This can help minimize aggressive treatment when a patient has low-risk PCa. One study showed a downgrade of treatment modality to AS for 27% of patients with low Decipher scores.[43] Furthermore, a retrospective case-cohort study ($N = 260$) concluded that Decipher correlates strongly with biochemical recurrence, metastasis, and mortality ($p < 0.01$).[45] Decipher has also been shown to be predictive of metastasis when used on biopsy samples, with a c-index of 0.80 (95% CI, 0.58–0.95) compared with 0.75 (95% CI, 0.64–0.87) of NCCN risk stratification.[43]

The original dependence of Decipher on RP narrows its use in decision making until after surgery, preventing its utility as a screening tool. Recent studies, however, demonstrate Decipher tests done on biopsy samples have a high concordance with RP, seen as high as 86%.[46] Therefore, running tests on biopsy samples has potential as a valuable instrument for pre-treatment prognostication.[43] Furthermore, as local therapy becomes more widely used for PCa, the destruction of prostatic tissue further limits the role of Decipher. Overall, Decipher remains useful for risk stratification, only after the initial diagnosis of prostate cancer.

Despite MRI advancements, imaging does not appear to be superior to Decipher testing. In a study by Purysko *et al.* ($N = 72$),[47] it was found that MRI missed some intermediate and high-risk lesions as characterized by Decipher. However, most (82.6%) of the MRI-invisible lesions from the study were low risk based on Decipher testing, suggesting the addition of Decipher to MRI may not yield significantly more detection of CS cancer.[48]

Tests for biopsy-naïve men

Prostate health index

In 2012 the FDA approved the use of a different isoform of PSA, proenzyme PSA (proPSA), to be used as a novel biomarker for the detection of csPCa. Serum PSA alone is not specific for csPCa at 4–10 ng/ml, whereas a PSA > 10 ng/ml often indicates advanced disease.[49] The Prostate Health Index (PHI) score, calculated using proPSA, has been correlated to a risk of Gleason 7 or higher lesions on prostate biopsy.[49] It was shown to be the best predictor of biopsy grade in men with negative DRE, especially those with a serum PSA 4–10 ng/ml.[50,51] This correlation allows PHI to be useful as a decision-making tool to limit the need for unnecessary biopsies.[50,51]

PHI's relevance stems from studies that have illustrated proPSA to be associated with PCa, with high levels expressed by PCa tissue on biopsy.[52–54] These findings of the clinical usefulness of PHI were further proven in a 16-study meta-analysis showing a sensitivity of 0.85 and specificity of 0.70.[55] Additionally, when discriminating between high (⩾7) *versus* low (<7) Gleason lesions, PHI had a sensitivity of 0.90.[55]

With PHI's strength for predicting aggressive lesions, this diagnostic tool is most useful when determining the need for prostate biopsy.[55] Several studies examining PHI have looked for a cutoff to maximize the sensitivity and specificity of the marker while minimizing missing csPCa. A multicenter trial of men with a PHI cutoff of 24 had a sensitivity of 95% and led to a 58% decrease of unnecessary biopsies in men with no cancer or clinically insignificant cancer.[56]

When studied for its role in the context of MRI, the PRIM study demonstrated PHI as an independent predictive factor of a positive MRI.[57] The combination of PHI with mpMRI, however, shows much promise for the detection of cancer. Using a threshold of a PHI score of 30 for referral for mpMRI and only obtaining biopsies on men with suspicious imaging reduces the number of men biopsied by 23% while only missing 6% of clinically significant lesions.[57] Furthermore, using both PHI and MRI together before deciding to biopsy resulted in a 40% reduction in unnecessary biopsies.[57] A recent retrospective study by Schwen *et al.* demonstrates that the combination of PHI with mpMRI raises the NPV for PCa to 98%,[58] exceeding that for PSA density with mpMRI and mpMRI alone (95.4 and 91.6%, respectively). These studies thus provide evidence that PHI and mpMRI are complementary, such that more information can be obtained from the use of both tests before proceeding to biopsy.

Mi prostate score

The Mi Prostate Score (MiPS) urine test is a non-invasive test that utilizes a combination of three biomarkers: T2-ERG gene fusion, PCA3, and serum PSA. Using these markers, and validated models, the test estimates individualized risk.[59] T2-ERG is a protein formed when TMPRSS2 and ERG abnormally fuse and is a strong indicator of prostate cancer. A validation cohort ($N = 1225$) where 80% of men were biopsy naïve found that incorporation of T2:ERG better predicted the presence of any prostate cancer or high grade (GS⩾7) compared with either PSA alone or PSA with PCA3 ($p < 0.01$ for both groups).[59] The ability to stratify risk makes MiPS useful in patients for initial screening.[60]

In contrast, there is some evidence to promote the use of PSA and PCA3 over T2-ERG. A 2019 study concluded T2-ERG was not able to significantly predict biopsy score,[60] calling into question the utility of MiPS. Furthermore, the addition of T2-ERG did not improve the prediction of prostate cancer compared with just PSA with PCA3 but instead assisted with the validation of the test.[61] It is for these reasons that MiPS can be considered as a screening tool but there is not sufficient evidence to recommend its use over PSA and PCA3. While the addition of T2-ERG in MiPS did not negatively impact treatment, the added cost of another test component may not provide additional benefit.

Currently, there is no literature comparing the use of MiPS with MRI. This is also true of the T2-ERH gene fusion, but available data regarding PCA3 and PSA can suggest possible utility.

4K score

The 4Kscore test uses a combination of biomarkers and clinical findings to determine a percent risk of finding high-grade prostate cancer on biopsy.[62] The biomarkers include total PSA, free PSA, intact PSA, and human kallikrein 2 (kH2), while the clinical data includes age, prior biopsy status, and digital rectal exam. One study ($N = 1012$) demonstrated that 4Kscore could

detect Gleason score ⩾7 while preventing 30–58% of unnecessary biopsies.[63] When compared with the Prostate Cancer Prevention Trial Risk Calculator 2.0 (PCPTRC), the 4Kscore better discriminated when detecting GS⩾7 prostate cancer ($p < 0.0001$). This study also showed a rate of only 1.3–4.7% for delayed diagnosis of PCa.[63] Additionally, a systemic review using data from over 16,000 patients demonstrated that the 4Kscore could serve as a method of detecting both overall and high-grade prostate cancer.[64] Therefore, the 4Kscore may have a role in the initial workup of PCa, delaying biopsies, and preventing unnecessary procedures. However, before this is done, a longitudinal cohort study is recommended to confirm previous results.

The strong diagnostic capability of the 4Kscore test also allows for the decrease of healthcare costs and unnecessary biopsies.[65] While it is unlikely to replace biopsy entirely, this test further demonstrates the potential biomarkers have to reduce the economic burden associated with prostate cancer screening and diagnosis.

Several studies have also looked at the use of 4Kscore in conjunction with mpMRI. Marzouk *et al.* demonstrated the use of 4Kscore before mpMRI could reduce the need for MRI in some men.[66] In particular, men with a 4Kscore of 5–23% could benefit most from imaging. However, because this study describes a conceptual approach, validation with a prospective study may further strengthen these initial findings. Additionally, Falagario *et al.* analyzed biopsy-naïve patients that received MpMRI ($N = 266$),[67] 4Kscore, and prostate biopsy, finding that using 4Kscore and mpMRI together resulted in avoiding 34.2% of biopsies. These results, however, were produced when the biopsy was done with a 4Kscore ⩾7.5% and mpMRI found PIRADS 3–5 lesions. From these studies, the use of both 4K score and MpMRI together can be useful to decrease the need for additional biopsies and both tests can complement each other.

Markers with an undetermined role

microRNA

MicroRNAs (miRNAs) are an emerging area with utility in the diagnosis and treatment of various cancers, including prostate cancer.[68] Because miRNAs encompass a diverse range of molecules, there are numerous targets available for prostate cancer screening.

Some promising miRNA biomarkers include miRNA-21, miRNA-139-5p, miRNA-141, miRNA-375, and miRNA-1290.[69–72] Prior studies have found an association with miRNA-375 and cancer metastasis, while miRNA-1290 levels correlate with cancer severity.[72] One study concluded that miRNA-141, miRNA-21, and miRNA-375 can be elevated in the serum of patients with PCa compared with a healthy population. These three markers were combined into a model that provided a more accurate prediction of cancer compared with any marker alone, but the study population was very small ($N = 20$), limiting the conclusions that can be drawn from this as well as other studies for the role of miRNA in the detection and surveillance of PCa.[70] Regarding miRNA-139-5p, it was found to be elevated in the blood of patients with PSA > 20ng/mL ($p < 0.05$), prostate cancer tumor stages 3 and 4 ($p < 0.05$), and Gleason score ⩾7 ($p < 0.001$).[69] This study was also rather small though ($N = 45$), further displaying the limitations of the literature on miRNA.

Despite the potential miRNA holds, it does not seem to have a well-defined role.[73] This is largely due to numerous markers being discovered, but few large-scale trials evaluating potential implementation. It remains unclear when to utilize miRNA as a biomarker in the workup and several logistical and economic obstacles impede their value. Another aspect to consider is that while there are several miRNAs found to be associated with prostate cancer, their presence outside of the prostate is not always observed, indicating a urine or blood test may not be sufficient for their detection.[74]

Conclusion

The field of PCa screening and detection is ever-changing with the continued development of novel diagnostic tests. However, each category of men has unique requirements, and tests will be better suited to various scenarios. While it is encouraging to see research exploring numerous options for PCa assessment, PSA remains the gold standard due to its standardization, being inexpensive, and a large volume of research. Furthermore, the limitations of PSA are well-documented and understood by clinicians. Even still, these tests

may, with time, have a place in the decision-making process, given they are used in appropriate situations. Additionally, with the improvements in MRI quality and standardization of interpretations with PIRADS v2, mpMRI has taken its place at the forefront of PCa detection, surveillance, and management. Organizations such as NICE and the AUA recommend the use of mpMRI for cancer detection in men clinically suspected of having localized PCa.[16,75] The EAU, meanwhile, strongly recommends against its use as a primary screening tool.[15] A summary of the biomarkers reviewed is described in Table 1.

In addition, there are still more biomarker assays with roles that are not yet established. This is an exciting prospect for the future of prostate cancer diagnostics. However, it is important to recognize that the largest limitation facing all the tests discussed here is the lack of

Table 1. Summary of the biomarkers reviewed.

Test	Source	Description	Endpoint	Target	Evidence for utility with mpMRI
ConfirmMDx (MDx Health, Irvine, CA, USA)	Prostate biopsy	Quantitative methylation-specific polymerase chain reaction of 3 key tumor suppressor genes	Augment NPV of biopsy	Prior negative biopsy	Y
Progensa PCA3 (Hologic Gen-Probe, Marlborough, MA, USA)	Post-DRE urine	Prostate-specific mRNA quantification	Risk of a positive repeat biopsy	Prior negative biopsy* Biopsy naïve men	Y
OncotypeDx (Genomic Health, Redwood City, CA, USA)	Prostate biopsy	Score calculated from DNA quantification of 17 genes involved in tumorigenesis	Risk stratification of positive biopsies	Men on active surveillance	Y
Prolaris (Myriad Genetic Laboratories, Salt Lake City, UT, USA)	Prostate biopsy	Measures 46 PCa-related proliferation genes	Prediction of cancer aggressiveness	Men on active surveillance	Y
Decipher (GenomeDx Biosciences, Vancouver, British Columbia, Canada	Radical prostatectomy or prostate biopsy	Examines 22 RNA markers to predict risk of cancer metastasis and prognosis	Risk of tumor metastasis	Men on active surveillance	Y
Prostate Health Index (Beckman Coulter, Brea, CA, USA)	Serum	Calculated score based on isoforms of serum PSA	Risk of Gleason 7 or higher cancer	Biopsy naïve men* Prior negative biopsy	Y
Mi Prostate Score (University of Michigan MLabs, Ann Arbor, MI, USA)	Urine and serum	Risk calculated using T2-ERG, PCA3, and PSA	Risk of any cancer	Biopsy naïve men* Prior negative biopsy	N
4K Score (OPKO Health, Miami, FL, USA)	Serum	Measurement of 4 kallikrein markers: total PSA, free PSA, intact PSA, and kH2	Risk of high grade (Gleason $\geqslant$7) cancer	Biopsy naïve men	Y
miRNA	Serum	Quantification of serum miRNAs	Variable	Variable	N

kH2, human kallikrein 2; miRNA, microRNA; mpMRI, multiparametric magnetic resonance imaging; N, no; NPV, negative predictive value; PCa, prostate cancer; PSA, prostate specific antigen; Y, yes.
*Primary use of the biomarker test.

standardization and limited data supporting their use. With the growing role of prostate mpMRI in the detection and surveillance of PCa, these biomarker tests need to be evaluated more closely. Recent studies have shown that the majority of the tests discussed here add to mpMRI, whether to decrease the number of unnecessary biopsies or to help describe the extent of disease. More studies are needed to fully understand the impact that all of these tests have on imaging and disease monitoring. The tests discussed here, however, are likely to remain secondary to PSA for the foreseeable future. Moving forward, it is possible that additional testing can augment decision-making as further consensus and standardization are established. With time, additional methods of testing will hopefully lead to better outcomes and more informed decision-making for clinicians and their patients.

Author contributions

Abhinav Sidana devised the idea for this manuscript. Anna Saltman and Joseph Zegar were involved in concept development and refinement. Anna Saltman, Joseph Zegar, and Monzer Haj-Hamed wrote the manuscript with input from Sadhna Verma and Abhinav Sidana.

Conflict of interest statement

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