REVIEWS IN UROLOGY

Incorporation of IsoPSA Into Clinical Practice in the Management of Elevated Prostate-Specific Antigen Based on Current Guidelines

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Abstract

Prostate cancer is a highly prevalent malignancy among men worldwide. Optimal management depends on early detection and accurate surveillance. Several screening and surveillance tools are available to men with prostate cancer, including prostate-specific antigen (PSA) testing, digital rectal examination, prostate biopsy, imaging modalities, and a plethora of biomarkers. Prostate-specific antigen, though widespread in its use, is limited in its specificity. Many adjunctive tests to PSA have been developed. One such test is IsoPSA (Cleveland Diagnostics), a novel PSA assay that focuses on structural differences among PSA isoforms to aid in detecting clinically significant prostate cancer. With an improved understanding of the capability and uses of IsoPSA, physicians can enhance patient outcomes through more accurate risk assessment and save costs by reducing the number of unnecessary prostate biopsies and imaging generated resulting from a nonspecific elevation in serum PSA. This review describes the performance and use of IsoPSA.

Introduction

Prostate cancer ranks as the fourth-most diagnosed cancer globally and the second-most diagnosed cancer in men.[1] Early detection and surveillance are critical for effective management. Prostate-specific antigen (PSA) was first identified in the 1960s, was first approved as a test for prostate cancer by the US Food and Drug Administration in 1986, and has been a first-line screening treatment for prostate cancer since the early 1990s.[2] The American Urological Association (AUA) recommends regular prostate cancer screening using serum PSA testing every 2 to 4 years for men aged 50 to 69 years; the National Comprehensive Cancer Network (NCCN) guidelines recommend screening for prostate cancer using PSA testing from ages 45 to 75 years, with follow-up testing contingent on PSA results.[3,4] In both guidelines, digital rectal examination can be used as an adjunct to assess the risk of prostate cancer. Though widely used, traditional PSA testing has substantial limitations. Prostate-specific antigen is often elevated in response to prostatic neoplasm, but PSA can also rise in response to benign prostatic hyperplasia (BPH), inflammatory or infectious prostatitis, surgical manipulation, digital manipulation, or trauma.[5] Further reflecting this lack of specificity, a recently published

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systematic review and meta-analysis found that the sensitivity of PSA for prostate cancer was 0.93, while its specificity for prostate cancer was 0.20.[6]

The Prostate Health Index, SelectMDx (MDxHealth), 4Kscore Test (OPKO Health), ExoDx Prostate test (Bio-Techne), and MyProstateScore 2.0 (Lynx Dx) have been developed in recent years to address the PSA specificity issue and guide further prostate cancer treatment.[7] Many of these tests are limited, though, by highly technical and challenging analytical techniques and often require qualifiers for advanced testing use, such as previous prostate biopsy, prostate size measurements based on imaging, or PSA within a confined range.[8] An ancillary test that is showing clinical promise, however, is IsoPSA (Cleveland Diagnostics), described in a 2017 preliminary report by Klein et al.[9] IsoPSA results are provided as the IsoPSA Index (see "What Is IsoPSA?"). Using this technique, Stovsky et al[10] found that the ratio of PSA isoforms was significantly more sensitive and specific at predicting malignancy than total PSA. IsoPSA was then compared with PSA in a multicenter prospective study setting in 2017 in which IsoPSA was found to statistically significantly outperform standard PSA in differentiating between no prostate cancer and prostate cancer and in differentiating between low-grade and high-grade prostate cancer, mainly because of a 3-fold increase in specificity (48% vs 15%).[9]

Since its inception, IsoPSA has been shown in various contexts to predict clinically significant prostate cancer more accurately than standard PSA testing. Additional studies have evaluated how incorporating IsoPSA can spare patients additional costs, particularly costs related to prostate magnetic resonance imaging (MRI) or prostate biopsy. This review describes key contemporary findings concerning IsoPSA as a screening tool for diagnosing clinically significant prostate cancer and how IsoPSA can be incorporated into everyday practice.

What Is IsoPSA?

IsoPSA is a novel assay for prostate cancer that measures structural changes in PSA by calculating the ratio between total and free PSA among the different phases of the system. This approach differs from a standard PSA assay, which solely measures PSA concentrations. IsoPSA provides its result as the IsoPSA Index, which is derived from differences in total and free PSA concentrations between structurally distinct isoforms.

By analyzing the different PSA isoforms, clinicians can appreciate structural differences in PSA expression to stratify patients more likely to have malignancy and patients more likely to have high-grade malignancy. IsoPSA has been shown to correlate with prostate cancer and strongly with high-grade prostate cancer.[11]

ABBREVIATIONS

AUA	American Urological Association
BPH	benign prostatic hyperplasia
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PI-RADS	Prostate Imaging Reporting and Data Systems
PSA	prostate-specific antigen

How Does IsoPSA Fare in Predicting Prostate Cancer?

Much of the existing literature on IsoPSA compares the predictive power of IsoPSA with standard PSA testing in detecting prostate cancer. The IsoPSA Index is validated in men older than 50 years of age with a PSA of 4 to 100 µg/L (4-100 ng/mL). (Note that the Medicare criterion for payment is 4-25 µg/L [4-25 ng/mL].) In a prospective multicenter study of more than 850 men, IsoPSA was more accurate than both total PSA and free PSA in predicting high-grade prostate cancer (Gleason Grade ≥7) and any prostate cancer (Gleason Grade ≥6).[12] The receiver operating characteristic curve from this study is shown in Figure 1. In a single-center retrospective study of more than 1500 patients, an initial IsoPSA score of at least 6 was found to be a strong predictor of clinically significant prostate cancer (Gleason Grade Group ≥2) on biopsy, with a sensitivity of 94.1% and a negative predictive value of 89.3%.[13]

IsoPSA has been evaluated as a surveillance tool, as well. In a single-center retrospective review spanning 5 years, only 1.1% of patients with low IsoPSA scores were found to have clinically significant prostate cancer on biopsy at 18-month follow-up compared with 28.5% of patients with high IsoPSA scores. Patients with an IsoPSA score greater than 10 were 7 times more likely to have clinically significant prostate cancer.[14]

Prostate-specific antigen values are known to be affected by medications that affect prostate volume, such as 5-α-reductase inhibitors.[15] IsoPSA, however, is unaffected in its ability to detect clinically significant prostate cancer in patients taking α-blockers or 5-α-reductase inhibitors for BPH.[16] IsoPSA has demonstrated enhanced prediction of malignancy and clinically significant malignancy (which may influence the decision to perform a prostate biopsy) and is an independent variable of risk, regardless of MRI or biopsy findings.[17]

When studied in tandem with prostate MRI, a negative MRI finding with a low IsoPSA score (<6) was associated with a lower risk of clinically significant prostate cancer (2% vs 15%), whereas an MRI finding of a lesion with a Prostate Imaging Reporting and Data System (PI-RADS) score of 4 or 5 and an elevated IsoPSA score (>6) was associated with a higher risk of clinically significant prostate cancer (49% vs 19%) (Figure 2). Magnetic resonance imaging and IsoPSA, in combination, had the highest area under the curve in predicting prostate cancer.[18] The combination of IsoPSA and PI-RADS scores provides meaningful predicted probabilities for the likelihood of detecting clinically significant prostate cancer at biopsy. For a lesion with a PI-RADS score of 3 or less with a low IsoPSA, the likelihood of clinically significant prostate cancer is less than 5% (Figure 2). Regardless of IsoPSA Index score, lesions with PI-RADS scores of 4 or 5 should be biopsied in most circumstances because of the high likelihood of malignancy irrespective of the IsoPSA Index.

Current Guidelines and Incorporation of IsoPSA Into Clinical Practice

Both the AUA and the NCCN recommend PSA testing as the first-line test in screening for prostate

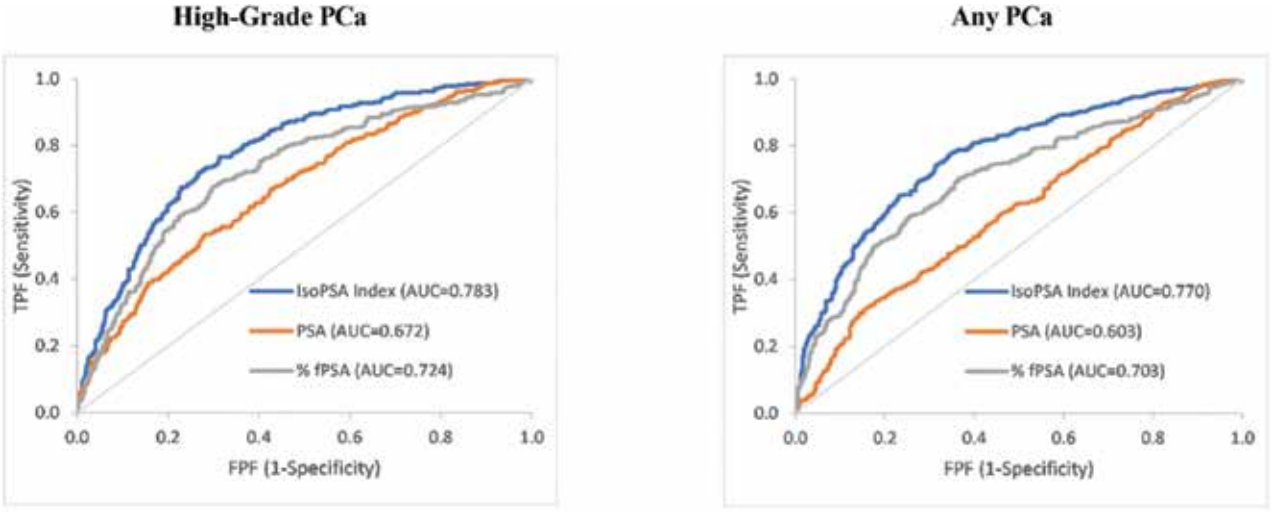

Figure 1. Receiver operating characteristic curves are shown for (**A**) high-grade prostate cancer and (**B**) any prostate cancer.
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Abbreviations: AUC, area under the curve; FPF, false-positive fraction; fPSA, free prostate-specific antigen; PCa, prostate cancer; PSA, prostate-specific antigen; TPF, true-positive fraction.

cancer.[3,4] Both guidelines further suggest that patients with newly elevated PSA should undergo repeat PSA testing before procuring a secondary biomarker test, diagnostic image, or biopsy. Repeating PSA testing before secondary forms of testing underscores the wide availability and low cost of standard PSA testing. American Urological Association and NCCN guidelines suggest the probability of high-grade cancer (Gleason score ≥3 + 4, Grade Group ≥2) may be further defined by using adjuvant markers such as the Prostate Health Index, SelectMDx, 4Kscore Test, ExoDx Prostate test, MyProstateScore 2.0, and IsoPSA. Many of these tests, however, are limited by preexisting conditions, such as previous prostate biopsy, the use of BPH medications, or PSA within a confined range (Table 1).

The IsoPSA test always reports a serum PSA result along with the IsoPSA Index, potentially reducing unnecessary blood draws and testing. Adjunctive tests such as IsoPSA are currently recommended as part of the shared decision-making process between patients and clinicians for high-risk patients and patients with negative biopsy results.

The AUA states that clinicians may use adjunctive urine or serum markers to aid in deciding whether to perform a prostate biopsy.[19] The AUA also recommends that an MRI be performed before the initial biopsy to increase the detection of clinically significant prostate cancer (Gleason score ≥3 + 4, Grade Group ≥2). Given the improved ability of IsoPSA to detect clinically significant prostate cancer over standard PSA testing, these statements support the use of IsoPSA as a potential adjunct before more extensive testing, such as prostate biopsy or prostate MRI.

Based on the published literature and guidelines, IsoPSA can be incorporated into clinical practice through multiple pathways (Figure 3). The development of these pathways will vary from practice to practice and may be affected by coverage, cost, and the quality of MRI scans as well as by shared decision-making between clinicians and their patients.

The Use of IsoPSA and Its Impact on Patient Care

In a single-system study of 900 men 50 years of age and older with a PSA greater than 4 and no history of prostate cancer, IsoPSA testing resulted in a 55% net reduction in physician recommendations for prostate biopsy and a 9% reduction in recommendations for MRI compared with standard PSA testing.[20] Prostate biopsy is an invasive procedure with known complications and may cause patients substantial distress before or after the procedure.[21] In addition to its cost and availability, MRI is subject to variability among interpreters, and its results are therefore not as reproducible as biomarker results.[22] A cost analysis performed in 2021 projected that the use of IsoPSA instead of transrectal ultrasound–guided biopsy for men with suspected missed prostate cancer would generate a savings of $533 per patient undergoing prostate cancer screening.[23]

Though initial studies on IsoPSA demonstrate

	IsoPSA ≤ 6	IsoPSA > 6
PI-RADS 1-2	2%	15%
PI-RADS 3	4.5%	16%
PI-RADS 4-5	19%	49%

Figure 2. Risk of clinically significant prostate cancer using a combination of IsoPSA and PI-RADS scoring.
Adapted from Benidir et al. *Journal of Clinical Oncology.* 41(6_suppl), abstract 388. Used with permission from *Journal of Clinical Oncology* (Copyright ©2023). ASCO Publications. All Rights Reserved.
Abbreviation: PI-RADS, Prostate Imaging Reporting and Data Systems.

Table 1. Indications for Adjuvant Testing, by Marker

	IsoPSA	Prostate Health Index[a]	SelectMDx[b]	4Kscore Test[c]	ExoDx Prostate test[d]	MyProstateScore 2.0[e]
Specimen source	Blood	Blood	Urine	Blood	Urine	Urine
PSA, ng/mL; age eligibility, y	4-100; >50	4-10; >50; normal digital rectal exam	3-10; ≤75 and 4-10; >75 or abnormal digital rectal exam	≥2.0; 45-54 ≥3.0; 55-75 ≥4.0; ≥76	2-10; ≥50	Eligibility criteria if no prior biopsy PSA, ng/mL: 3-10; Patient age, y: ≤75; Digital rectal exam findings: Any; MRI status: Any PSA, ng/mL: ≤3; Patient age, y: ≤75; Digital rectal exam findings: Abnormal; MRI status: Any PSA, ng/mL: 4-10; Patient age, y: >75; Digital rectal exam findings: Any; MRI status: Any PSA, ng/mL: <4; Patient age, y: >75; Digital rectal exam findings: Abnormal; MRI status: Any Eligibility criteria if prior negative biopsy PSA, ng/mL: 3-10; Patient age, y: ≤75; Digital rectal exam findings: Any; MRI status: Any PSA, ng/mL: ≤3; Patient age, y: ≤75; Digital rectal exam findings: Abnormal; MRI status: Any PSA, ng/mL: 4-10; Patient age, y: >75; Digital rectal exam findings: Any; MRI status: Any PSA, ng/mL: <4; Patient age, y: >75; Digital rectal exam findings: Abnormal; MRI status: Any PSA, ng/mL: >10; Patient age, y: Any; Digital rectal exam findings: Any; MRI status: Negative (if performed)
Algorithm requires clinical information	No	No	Yes: age, PSA, digital rectal exam, and prostate volume (MRI or transrectal ultrasound only)	Yes, prior biopsy status, digital rectal exam, and age	No	Yes, based on biopsy history but can also include PSA, PSA density, age, family history, and having African ancestry
Affected by use of 5-α-reductase inhibitor	No	Yes	Unknown, not validated	Yes, 5-α-reductase inhibitor use within 6 mo of test	No	No
Requires digital rectal exam	No	Normal digital rectal exam	Yes, modified 3 strokes per lobe	No digital rectal exam within 96 h of test	No	Yes
Post-digital rectal exam specimen	No	No	Yes, patient urinates with funnel device	No	No, home testing kits available	Yes, patient urinates in urine collection device within 1 h of digital rectal exam

Abbreviations: MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

SI conversion factor: To convert ng/mL to µg/L, multiply by 1.

[a] More information about the Prostate Health Index can be found at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P090026.

[b] More information about SelectMDx can be found at https://mdxhealth.com/select-mdx-for-physicians.

[c] More information about the 4Kscore Test can be found at https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190022B.pdf.

[d] More information about the ExoDx Prostate test can be found at https://www.exosomedx.com/physicians/exodx-prostate-test.

[e] More information about MyProstateScore 2.0 can be found at https://www.lynxdx.com/my-prostate-score/providers.

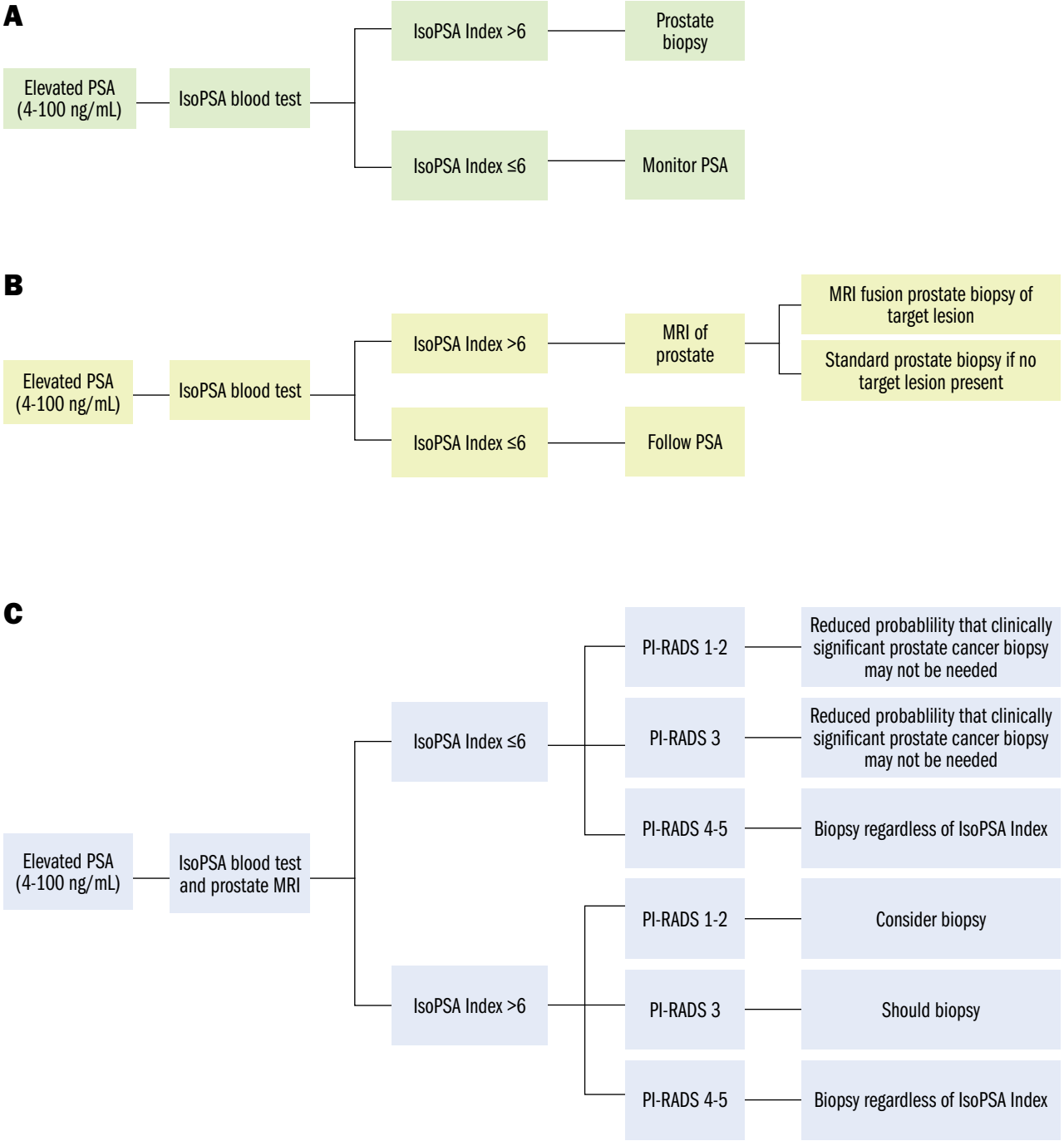

Figure 3. Potential clinical pathways based on the use of IsoPSA, including (**A**) a potential clinical pathway without MRI of the prostate; (**B**) a potential clinical pathway in which IsoPSA is ordered before prostate MRI; and (**C**) a potential clinical pathway with IsoPSA and MRI ordered at the same time. In all cases, baseline risk (PSA and PSA analogs, family history, digital rectal examination findings, MRI PI-RADS, race and ethnicity) should be an important component of decision-making. SI conversion factor: To convert ng/mL to µg/L, multiply by 1.
Abbreviations: MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data Systems; PSA, prostate-specific antigen.

excellent potential for this diagnostic tool (see the callout box "Advantages of the IsoPSA Index"), many questions remain, such as how IsoPSA is affected by BPH surgery; how IsoPSA functions as a long-term prognostic tool for active surveillance; and how IsoPSA differs among patients with varying demographic factors, such as age and ethnicity. Findings from studies currently underway may provide answers to such questions.[13,14]

Conclusion

Many ancillary tests are available today for patients with an elevated PSA level. Among them, IsoPSA is a promising novel blood-based assay that more accurately detects prostate cancer and high-grade prostate cancer than standard PSA testing. By improving the negative predictive value of PSA testing, IsoPSA can reduce the need for MRI and prostate biopsy for patients with elevated PSA levels. Streamlining the use of IsoPSA may spare patients unnecessary costs and procedures while better identifying patients for prostate biopsy with or without a prostate MRI.

Advantages of the IsoPSA Index

- **Serum blood test**
- **Indicated for men older than 50 years of age with PSA levels of 4 to 100 µg/L (4-100 ng/mL)**
- **Not affected by 5-α-reductase inhibitors**
- **More sensitive and specific than standard PSA and free PSA testing**
- **Increased negative and positive predictive value, identifying MRI-invisible high-grade prostate cancer lesions with PI-RADS scores of 1 to 2**
- **Provides additional information to aid in biopsy decision-making for lesions with PI-RADS 3 scores**
- **May reduce unnecessary biopsy of the prostate**
- **Validated in biopsy-naive patients and in patients being considered for repeat biopsy**

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Data Availability Statement: Data sources are publicly available.