Medical Coverage Policy | Prostate Cancer Detection with IsoPSA

EFFECTIVE DATE: 11|01|2024
POLICY LAST REVIEWED: 07|17|2024

OVERVIEW

IsoPSA® is a blood-based single parameter, structure-based assay for improved detection of high-grade prostate cancer. The test partitions isoforms of prostate-specific antigen with an aqueous two-phase reagent. The test aims to improve specificity by testing specific changes in PSA that arise specifically in cancer cells and would not be affected by conditions such as prostate hyperplasia, inflammation, or age that reduce the specificity of the standard PSA assays.

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

The IsoPSA® test is considered medically necessary when all the following are met:

- Testing of men 50 years of age and older who have a confirmed* moderately elevated PSA (greater than 4 and ≤ 25 ng/mL); and,
- No other relative contraindication for prostate biopsy including:
    - Less than a 10-year life expectancy

*PSA elevation should be verified after a few weeks under standardized conditions (e.g., no ejaculation, manipulations, and urinary tract infections) in the same laboratory or other CLIA approved laboratory before considering a biopsy.

PRIOR AUTHORIZATION

Prior authorization is required for Medicare Advantage Plans and is recommended for Commercial Products. **Note**: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The IsoPSA® test is considered medically necessary when the medical criteria above is met.

The IsoPSA® test is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products when the medical criteria above is not met as the evidence is insufficient to determine the effects on health outcomes.

Commercial Products
Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the Evidence of Coverage or Subscriber Agreement for applicable laboratory tests and applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

Screening modalities for prostate cancer (PCA) include digital rectal exam (DRE) and prostate-specific antigen (PSA) test at a frequency of every twelve months for men ages fifty and over in effort to detect increased risk for adenocarcinoma of prostate. PSA is a reliable immunocytochemical marker for adenocarcinoma of the prostate. However, screening and early treatment of prostate cancer have come under scrutiny due to concerns for over diagnosis of low-risk cancers. Guidelines have been updated due to studies to refine the use of PSA, which remains the primary screening test. Investigations into adjunctive testing may provide opportunities to avoid biopsies and reduce overdiagnosis.

IsoPSA® is a blood-based single parameter, structure-based assay for improved detection of high-grade prostate cancer. The test partitions isoforms of prostate-specific antigen with an aqueous two-phase reagent. The test aims to improve specificity by testing specific changes in PSA that arise specifically in cancer cells and would not be affected by conditions such as prostate hyperplasia, inflammation, or age that reduce the specificity of the standard PSA assays.

Klein et al. 2017 was an industry-sponsored multi-centered prospective study that included 261 men scheduled for prostate biopsy due to rising PSA level or suspicious digital rectal exam. The study was conducted at five different academic and community centers within the United States over 15 months. The primary study endpoint was the presence or absence of cancer and cancer grade as detected by ultrasound or MRI fusion biopsy. Exclusion criteria included serum PSA<2 ng/ml; recent (<72 hours) prostate manipulation, including DRE; recent (<2 weeks) urinary tract infection and/or prostatitis; recent (<30 days) prostate surgery, urinary catheterization, prostate infarction, or endoscopic evaluation; and other urinary tract malignancy. Out of 434 samples collected, 173 were excluded. Reasons for exclusion included prolonged storage greater than ninety days, canceled biopsies, the breach of sample collection protocol, shipping delays, or not meeting study protocol.

The research aimed to assess two clinical performance objectives: the discriminatory power between malignant and non-malignant prostate conditions and between high-grade and low-grade cancers versus benign pathology. This population had an overall prevalence of 53% for prostate cancer, with 33.7% of cancers considered high-grade. They utilized receiver operating characteristic analysis to determine the discriminatory power measurement. In this preliminary analysis, they utilized decision curve analysis to access the clinical utility of the models by comparing the two extremes, no biopsy to biopsy for all (current patient cohort), and comparison against the modified prostate cancer prevention trial risk calculator 2.0. They reported results were: "for cancer versus no cancer endpoint, the area under the curve (AUC) was 0.79 (95% CI 0.73–0.84) for IsoPSA® versus 0.61 (95% CI 0.54–0.67) for total PSA ($p < 0.001$). For high-grade cancer versus low-grade cancer/benign histology, the AUC was 0.81 (95% CI 0.74–0.86) for IsoPSA® versus 0.69 (95% CI 0.61–0.75) for total PSA ($p < 0.005$)". Using the pre-selected cutoff to recommend a biopsy, they reported a 48% reduction in false-positive biopsies with IsoPSA®. Utilizing a cutoff selected to identify men at low risk of high-risk disease, they reported a 45% reduction in the false-positive rate. They acknowledged

that the test was not yet validated. The authors conclude that IsoPSA® outperformed PSA in predicting prostate cancer risk.

The authors acknowledge that clinical and demographic parameters including age, race, and prostate volume could impact the clinical performance of the IsoPSA® test was not evaluated in this study which focused on the test's clinical performance. They also acknowledge weaknesses in the study, including lack of central or standardized pathology review of the biopsies, a lack of distinction between primary and repeat biopsies, and variability in the use of MRI for decisions on the need for in the technique used in biopsies. Additional weakness includes the study design was a prospective trial without controls. This was not designed or powered for superiority, although the authors suggest the test outperformed standard PSA test. Age, race, prostate volume, presence of benign prostatic hypertrophy (BPH) was not evaluated but could impact results. Various pathological labs and methods for biopsy may have some variability that was not controlled, introducing a risk of bias.

Stovsky et al. 2019 was an industry-sponsored multi-centered prospective validation study. Two hundred seventy-one men scheduled for prostate biopsy due to rising PSA or suspicious DRE over a ten-month period from seven academic and community centers were included. Biopsies were performed under ultrasound or MRI guidance. Exclusion criteria included: serum PSA less than 2 ng/ml; recent (less than 72 hours) prostate manipulation, including digital rectal examination; recent (less than two weeks) urinary tract infection and/or prostatitis; recent (less than 30 days) prostate surgery, urinary catheterization, prostate infarction or endoscopic evaluation; and any other urinary tract malignancy. Three hundred five samples were collected with thirty-four exclusions, including nine due to prolonged storage, forwarded canceled biopsies and fifteen due to PSA <2 (exclusion), and six unrelated, leaving a final cohort of 271.

The primary endpoint was the clinical performance of the test in discriminating power of IsoPSA® for the presence of high-grade prostate cancer versus low-grade cancer or benign pathology. Using the data from Klein et al. a cutoff value of 17% was selected as the predicted probability of high-grade prostate cancer. The authors concluded using a cutoff of 17% yielded 93% negative predictive value. They calculate that this would reduce unnecessary prostate biopsies by 43%. Using modeling, they estimate that out of 1000 subjects; the test would miss twenty-two high-grade cancers, of which seven would have been Gleason sum 4 + 3 or higher. A sub-analysis of the African American participants showed similar results to the original combined cohort.

Additional analysis on the biopsy technique segregated biopsies done by ultrasound compared to MRI guidance. They observed significant improvement in the IsoPSA® AUC when the biopsies were performed under MRI guidance. The number of biopsies done under MRI guidance increased from 4%4 to 41% in this study.

Strengths of the study include using a new patient cohort, the addition of sub-analysis for African Americans and based on biopsy type, test run in the same lab, and pre-specified fixed outcome measurements defined by the previously published study.

Weaknesses of this study include study design as a prospective trial without a control group. While the authors state the test had superior performance to PSA, the trial did not compare the performance of IsoPSA® to PSA directly, which would require an appropriately designed and powered superiority study or non-inferiority study to demonstrate at least equally accurate. While the study addressed the test's clinical performance (validity), it did not address the clinical utility. The lack of standardized biopsy technique and lack of central pathology review introduces a risk of bias. Age, prostate volume, presence of BPH were not evaluated but could impact results. The authors acknowledge a significant increase in MRI guidance for the biopsies, which is more accurate than the ultrasound guidance and cannot exclude selection bias.

Scovell et al. 2021 conducted a real-world observational study aimed to assess the impact of the IsoPSA® test for prostate cancer risk assessment on provider patient management decisions. A total of 38 providers enrolled 900 men being evaluated for prostate cancer. The inclusion criteria which were defined as age >50

years, total serum prostate specific antigen [PSA] >4 and <100 ng/ml and no history of prostate cancer and IsoPSA® indication for use. Of the 900 patients enrolled, 734 established the final study cohort. Providers recorded their intentions to recommend patients for biopsy and/or magnetic resonance imaging (MRI), informed by all clinical data available at the time prior to IsoPSA® testing. After IsoPSA® was obtained, results were reported above or below an index threshold of 6.0, where an index 6.0 has a 90% negative predictive value for the absence of high-grade cancer (Gleason grade group 2 or higher) and an index value >6.0 has a 48% positive predictive value for the presence of high-grade cancer. Upon review of IsoPSA® results, providers confirmed or updated their recommendations for biopsy and MRI.

The primary outcome was to determine the clinical utility of IsoPSA® based on two things. One, provider willingness to use the test (test utilization) and two, the change in provider behavior as assessed by how IsoPSA® influenced recommendations for biopsy and MRI. Consistency between IsoPSA® results and recommendations for prostate biopsy was also considered. Changes in recommendations (either for or against) in 60.2% (442/734) for decisions on prostate biopsy and 6.0% (44/734) for decisions on MRI resulted based on the utilization of IsoPSA®. Results included a 55% (284 vs 638) net reduction in recommendations for prostate biopsy for men with total PSA >4 ng/ml who underwent IsoPSA® testing. A 9% reduction in recommendations for MRI was observed. A correlation was observed between IsoPSA® results and provider recommendations for prostate biopsy, with 87% of patients with an IsoPSA® index above the threshold recommended for biopsy and 92% of patients with an IsoPSA® index below the threshold not recommended for biopsy.

Strengths of this study include a large number of providers representing real-world clinical practice including a broad range of practice styles, education and experience. Recruitment of patients ranged across varied practice settings, and participating providers served as intra-provider and intra-patient controls for both pre- and post-IsoPSA® clinical decision making. A standardized reporting module was utilized to record the influence of IsoPSA® on management decisions.

Limitations of this study include patient compliance with provider recommendations for or against biopsy post-IsoPSA® were not assessed, a lack of long-term outcome data, and lack of a control group. Cost analysis studies were excluded from evidence review.

Klein et al. 2022 conducted a prospective, multicenter study at eight academic and community sites between August 2015 and August 2020. IsoPSA® was performed in 888 men > 50 years with total PSA > 4ng/ml scheduled for prostate biopsy. The primary outcome of this study was to estimate the performance, sensitivity, specificity, and predictive characteristics of IsoPSA®. Secondary outcomes were to identify the risk of High-Grade prostate cancer (Gleason Score ≥ 7) and any PCa (Gleason Score ≥ 6) in men ≥ 50 years of age with a pre-biopsy total PSA ≥4 ng/ml undergoing diagnostic biopsy and to determine cancer status when tested per protocol. The secondary outcome was to compare the diagnostic accuracy of IsoPSA® to total PSA and percent free PSA based on receiver operating characteristic (ROC) analysis. Exploratory outcomes were to assess the performance of IsoPSA® using ROC analysis in subgroups with total PSA 4 to 10 ng/ml, total PSA > 10 ng/ml, and in relation to prior biopsy status.

Results included a disease prevalence of 35.6% (High-Grade PCA) and 58.9% (any PCA). The area under the ROC was 0.783 (High-Grade PCA) and 0.770 (any PCA). The High-Grade PCA endpoint, AUC was 0.783 (95% CI 0.752−0.814) for IsoPSA® vs. 0.672 (95% CI 0.639−0.706) for total PSA and 0.724 (95% CI 0.690 −0.758) for percent free PSA ($p < 0.001$). An estimated 46% (High-Grade PCA) and 42% (any PCA) of biopsies could be avoided in low-risk patients when utilizing IsoPSA® index cutoffs. Forty percent (354/888) subjects had a prior negative biopsy. In the group with at least one prior biopsy, IsoPSA® yielded a moderate AUC (0.82), a modest specificity (46%) and a good NPV (95%) for high-grade PCa on subsequent biopsy in 202 subjects with prior negative biopsies. These findings suggest IsoPSA® accuracy is not influenced by previous negative biopsy. The study suggests that IsoPSA® is unaffected by the use of alpha blockers or 5α-reductase inhibitors. The study data suggests that biopsy should be performed regardless of MRI findings for an IsoPSA® index >6 based on the information that MRI misses 20% of high-grade cancers.

The authors report that IsoPSA® maintained statical accuracy across a broad range of elevated total PSA ranging from 4-100 ng/mL in 888 subjects. 24% (217/888) of study subjects had a PSA >10 ng/mL. 54 subjects (14.8%) of the sub-set with PSA >10-25 ng/mL had a negative biopsy while 44 (21.3%) has low grade PCA and 96 (30.4%) had high-grade PCA. However, only 23 subjects or 2.5% (23/888) had total PSA values >25 ng/mL with 20 of those predictably having high grade PCA (Gleason >7). Specificity (SP) and NPV (negative predictive value) decreased modestly in the group with total PSA >10 ng/mL and further breakdown of the small sub-set with PSA> 25 (n=23) was not reported in the study.

Strengths of this study include the prospective, multicenter design, the large sample size, comparison of total and percent free PSA, and use of gold standard prostate biopsy pathology comparison in all study participates. Limitations include of this study include lack of standardized biopsy techniques, decentralized pathology review, failure to account for false positive IsoPSA® or false negative biopsy results, lack of a control group, lack of long-term follow-up and risk of bias due to funding by laboratory that produces the test.

Benidir et al. is a single center retrospective review of prospectively collected data from 2019-2021 following a consecutive cohort of 83 subjects with elevated IsoPSA levels (>6) and concerning PSA and/or digital rectal examination who had a prostate biopsy followed by radical prostatectomy (RP) within the same period. 44 subjects without pre-operative IsoPSA served as controls. Pre-operative prostate Magnetic Resonance Imaging (MRI) and adverse histopathologic and MRI features when comparing biopsy to RP histopathology were included in the analysis. Of the 83 subjects with elevated IsoPSA 82 had PCa (99%) on final pathology. There were no differences in concordance, downstaging, and upstaging GG rates from biopsy to RP between the IsoPSA group and control, however the IsoPSA group had statistically significant elevation in pre-operative PSA levels compared to the control group (7.8 ng/mL vs 5.2 ng/mL, respectively, P<.001). IsoPSA was not influenced by prostate MRI or pathological features suggesting IsoPSA is non-selective marker. The authors conclude elevated IsoPSA (>6) is a diagnostic tool that can detect clinically significant prostate cancer at the time of biopsy.

Limitations include study design of retrospective review at a single center, modest sample size for elevated IsoPSA outcomes, comparator group had significantly lower IsoPSA values and there was a lack of a comparator group of patients with low IsoPSA values who ended up undergoing biopsy and/or eventual RP.

National Comprehensive Cancer Network (NCCN) guidelines recommendations include consideration for the use of biomarker tests for men with persistent elevation in PSA between 3 to 10 ng/ml using a validated test (determined in peer-reviewed, multi-site studies using an independent cohort of patients) within the prostate cancer early detection algorithms. The algorithms breakdown the role of these test by age, risk factors for prostate cancer, and if the test is used to evaluate for possible initial biopsy versus management of biopsy results. As of 02/16/2022, they included percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, MPS, and IsoPSA® in the guidelines.

U.S. Preventive Service Task Force Guidelines updated in 2018 recommend PSA screening with a "C" recommendation and did not mention adjunctive screening test.

The American Urological Association (AUA) states that PSA derivatives and isoforms and novel urinary markers and biomarkers for screening with the goal of reducing prostate cancer mortality provide limited evidence to draw conclusions and should not be used for primary screening. Additionally, the use of these markers after PSA screening may be considered a secondary test for informed decisions making regarding the need for prostate biopsy or repeat biopsies, but "emphasized the lack of evidence that these tests will increase the ratio of benefit to harm".

IsoPSA® aims to improve the existing standard of care PSA testing for the detection of high-grade prostate cancer. One of the initial concerns was while the test offered a 93% sensitivity, resulting in approximately twenty-two missed cancers in 1000 patients based on the mathematical models, there was uncertainty if this would provide confidence to providers to be comfortable not performing a biopsy. In Scovell et al. changes

in recommendations were reported in 60.2% for decisions on prostate biopsy resulting in a 55% net reduction in recommendations for prostate biopsy demonstrating confidence in this real-world population to utilize the test in decision making. In addition, this study provides the clinical utility data that was previously lacking. As of June 2022, the impact of age, prostate volume, and comorbid conditions as well as use outside of the initial biopsy had not been investigated. Since this time, additional literature has been published that addresses the accuracy of IsoPSA® in men with BPH and on 5-APIs, prior initial biopsies, and a broader range of PSA levels. However, for baseline PSA range of 26-100 ng/mL, there is poor strength of data to support this range and concern for lack of long-term data on outcomes for missed cancers. The limited coverage criteria aligns with the population studied in the IsoPSA® literature.

CODING

Medicare Advantage and Commercial Products

The following code(s) are medically necessary when the medical criteria above is met:

The following CPT code(s) can be used for IsoPSA

0359U Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer

RELATED POLICIES

Biomarker Testing Mandate

Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)

PUBLISHED

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