LCD - Biomarker Testing for Prostate Cancer Diagnosis (L37733)

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Issue

Issue Description

Prostate cancer is the most diagnosed, non-cutaneous malignancy, and the third leading cause of cancer-related deaths in American men (behind lung and colorectal cancer). Approximately 165,000 men are expected to be diagnosed with prostate cancer in 2018, with approximately 18% dying of the disease (2). However, prostate cancer is a heterogeneous disease with a clinical course ranging from indolent to life-threatening.

The provision of limited coverage for Biomarker Testing for Prostate Cancer Diagnosis has the potential to not only decrease biopsies (and associated risks), but also of reducing detection of indolent disease (and the attendant risks of overtreatment). The primary aim is to increase specificity compared with PSA without decreasing the sensitivity to diagnose high-risk prostate cancer.

CMS National Coverage Policy

Language quoted from Centers for Medicare and Medicaid Services (CMS), National Coverage Determinations (NCDs) and coverage provisions in interpretive manuals is italicized throughout the policy. NCDs and coverage provisions in interpretive manuals are not subject to the Local Coverage Determination (LCD) Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See Section 1869(f)(1)(A)(i) of the Social Security Act.

Unless otherwise specified, *italicized* text represents quotation from one or more of the following CMS sources:

Title XVIII of the Social Security Act (SSA):
Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Section 1862(a)(7) excludes routine physical examinations, unless otherwise covered by statute.

CMS Publications:
CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.1 – Laboratory services must meet applicable requirements of CLIA

CMS Publication 100-04, *Medicare Claims Processing Manual*, Chapter 16, Section 40.7 Billing for Noncovered Clinical Laboratory Tests Section and 120.1 Clarification of the Use of the Term “Screening” or “Screen”

CMS Publication 100-04, *Medicare Claims Processing Manual*, Chapter 30, Section 50 Advance Beneficiary Notice of Noncoverage (ABN)

CMS Publication 100-08, *Medicare Program Integrity Manual*, Chapter 13, Local Coverage Determinations

CMS National Correct Coding Initiative (NCCI) *Policy Manual for Medicare Services*, Chapter 10, Pathology/Laboratory Services, (A) Introduction

CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.6. 5 which describes the Surgical/Cytopathology Exception.

CMS National Correct Coding Initiative (NCCI) *Policy Manual for Medicare Services*, Chapter 10 Pathology/Laboratory Services which addresses reflex testing.

Code of Federal Regulations:
42 CFR, Section 410.32, indicates that diagnostic tests may only be ordered by the treating physician (or other treating practitioner acting within the scope of his or her license and Medicare requirements) who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician (or other qualified non-physician provider) who is treating the beneficiary are not reasonable and necessary (see Sec. 411.15(k)(1) of this chapter).

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

One biomarker test, ordered by a physician or other qualified health care professional (i.e., NP, CNS, PA) is covered ONCE per year.

PRIOR to potential biopsy, for men >/ 45 years old covered testing includes **%fPSA, PHI, Select MDx, 4K Score or MyProstate score**; in men >/ 50 with a PSA > than 4ng/ml covered testing additionally includes **EPI and isoPSA.** Must have both of the following:

1. No other relative indication for prostate biopsy including **ANY** of the following:
    a. DRE suspicious for cancer (e.g., nodules, induration, or asymmetry)
    b. Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] ≥3) (if available)
    c. Positive prior biopsy (cancer Grade Group ≥1, intraductal carcinoma (IDC), atypical intraductal proliferation (AIP))
    d. Other major risk factor for prostate cancer including:
        i. Ethnicity at higher risk for prostate cancer^
        ii. First-degree relative with prostate cancer^
        iii. High-penetrance prostate cancer risk gene(s) per NCCN (if known)^
2. No other relative contraindication for prostate biopsy including **ANY** of the following:
    a. <10 year life expectancy, or otherwise not a candidate for prostate cancer treatment
    b. Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 mo.
    c. Active prostatitis on antibiotics

*PSA elevation should be confirmed after a few weeks under standardized conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory before considering a biopsy (1).

^Limitation does not apply to EPI

Those men, who need a REPEAT BIOPSY in the setting of patients thought to be at higher risk despite a prior negative biopsy, covered testing includes **%fPSA, PHI, 4K Score, PCA 3, EPI, Confirm Dx, MyProstate Score and isoPSA** with confirmed * moderately elevated PSA (>3ng/ml and <10ng/ml; or PSA >/4ng/ml and < 10ng/ml in men > 75 years of age) with BOTH of the following:

3. No other relative indication for prostate biopsy including **ANY** of the following:
    a. DRE suspicious for cancer (e.g., nodules, induration, or asymmetry)
    b. Positive multiparametric MRI (Prostate Imaging Reporting and Data System [PI-RADS] ≥3) (if available)
    c. Positive prior biopsy (cancer Grade Group ≥1, intraductal carcinoma (IDC), atypical intraductal proliferation (AIP))
    d. Other major risk factor for prostate cancer including:
        i. Ethnicity at higher risk for prostate cancer
        ii. First-degree relative with prostate cancer
        iii. High-penetrance prostate cancer risk gene(s) per NCCN (if known)
4. No other relative contraindication for prostate biopsy including **ANY** of the following:
    a. <10 year life expectancy, or otherwise not a candidate for prostate cancer treatment
    b. Invasive treatment for benign prostatic disease or taking medications that influence serum PSA levels within 6 mo.
    c. Active prostatitis on antibiotics

*PSA elevation should be confirmed after a few weeks under standardized conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory before considering a biopsy (1).

Summary of Evidence

Prostate cancer is the most diagnosed, non-cutaneous malignancy, and the third leading cause of cancer-related deaths in American men (behind lung and colorectal cancer). Approximately 165,000 men are expected to be diagnosed with prostate cancer in 2018, with approximately 18% dying of the disease (2). However, prostate cancer is a heterogeneous disease with a clinical course ranging from indolent to life-threatening. Prostate-specific antigen (PSA) screening, introduced around 1990 (3), resulted in a marked drop in the incidence of metastatic disease at diagnosis, and probably, but not definitely, reduced prostate cancer-specific mortality (1,4). However, a concomitant over-diagnosis (via prostate biopsy) and over-treatment of early-stage and indolent disease occurred as well (5-9). Only about 25% of men with PSA in the 4-10 ng/mL range have prostate cancer on biopsy, and of those, about 20-50% are indolent, disease that would not be a problem if undetected or untreated (10,11). As noted in a recent editorial, "in a biological sense, of course, screening does not cause prostate cancer, but in a practical sense, it does (12)." The results of three major PSA screening trials involving hundreds of thousands of men, the US Prostate, Lung, Colorectal and Ovarian Cancer Screening (PCLO) trial, the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, and the Cluster Randomized Trial of PSA Testing or Prostate Cancer (CAP), all show the risk-benefit ratio to be a close call (6,13,14). Because screening seemed to be doing more harm than good, the US Preventive Services Task Force (USPSTF) advised against PSA testing in 2012, though this is under reconsideration for men aged 55 to 69 years (10,15).

However, ample evidence has shown survival benefits associated with treatment of intermediate- and high-risk, early-stage prostate cancer (6,16). A Gleason score of 2 to 5 is regarded as normal prostate tissue; 6 is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. Ten-year survival rates stratified by Gleason score have been estimated from the Surveillance, Epidemiology, and End Results registry to be about 98% for scores 2 through 6, 92% for a score of 7 with primary pattern 3 and secondary pattern 4 (3+4), 77% for a score of 7 (4+3), and 70% for scores between 8 and 10 (17).

Unfortunately, PSA is not even specific to prostate cancer, much less clinically significant prostate cancer. Therefore, the current focus is on finding a more nuanced approach (beyond PSA and digital rectal exam (DRE)), by reserving biopsy and treatment for men with clinically significant, higher-grade (Gleason score ≥ 3 + 4, Grade Group 2 or higher) prostate cancer (HGPC). Such testing would represent secondary or reflex testing, rather than screening, effectively allowing for risk stratification and a more targeted response to PSA screening results (18). This strategy has the potential to not only decrease biopsies (and associated risks), but also of reducing detection of indolent disease (and the attendant risks of overtreatment). The primary aim is to increase specificity compared with PSA without decreasing the sensitivity to diagnose high-risk prostate cancer.

Percent Free PSA (%fPSA)

Unbound or free PSA (fPSA), expressed as a ratio of total PSA (tPSA), is significantly lower in men with prostate cancer. In 1998, a large, prospective, multicenter study showed that a 25% %fPSA cutoff detected 95% of prostate cancers (of any grade) while avoiding 20% of unnecessary biopsies (11).

In 2003, the FDA approved %fPSA for use "as an aid in distinguishing prostate cancer from benign prostate conditions in men 50 years or older with total PSA 4-10 ng/mL, and DRE findings not suspicious for cancer (19)."

In a recent publication, among 417 men with a PSA>2, using a 25% cutoff, 83 (20%) would have avoided a biopsy (20). %fPSA has since become widely adopted more for active surveillance post prostate biopsy (1).

Prostate Health Index (PHI)

The PHI adds [-2]proPSA (p2PSA) (a fPSA isoform associated with PCa) to tPSA and fPSA in an algorithm that calculates a score that has demonstrated a correlation with HGPC. The test was initially validated in 2011 in a multi-institutional, prospective trial evaluating 892 men (with no history of PCa, a normal DRE, and PSA of 2-10 ng/mL) for the presence of Gleason ≥4+3 prostate cancer (21). The receiver-operating characteristic curve (AUC) for PHI (0.724) exceeded that of %fPSA (0.670) in discriminating between Gleason ≥4+3 vs. lower Gleason grade PCa or negative biopsies. No optimal PHI cutoff was defined, however. Shortly thereafter, in 2012, PHI was FDA approved with identical indications to %fPSA (22).

A subsequent, prospective multi-center study of 658 men with a PSA of 4-10 ng/mL and normal DRE showed AUCs of 0.707 for PHI, 0.661 for %fPSA, and 0.551 for PSA, potentially sparing 30.1% of unnecessary biopsies with a PHI cutpoint of 28.6 (23). Another prospective multi-center studied two independent cohorts of 561 (primary) and 395 (validation) biopsy naive men (24). The primary and validation cohorts demonstrated an AUC for the detection of high-grade (GS ≥7) prostate cancer of 0.815 and 0.783, respectively. The study determined the optimal cutoff of PHI to be a score of 24, reducing unnecessary biopsies by 36% and only missing 2.5% of high-grade cancers. A subsequent publication by the same group showed that PHI significantly improved the performance of the Prostate Cancer Prevention Trial (PCPT) and ERSPC risk calculators in men with a PSA 2-10 ng/mL for predicting HGPC (25).

In a prospective, single-center observational study in 188 men with elevated PSA (> 2ng/mL) and negative DRE, PHI had a higher discriminative ability for clinically significant PCa (AUC 0.76) compared to PSA (AUC 0.52) or %fPSA (AUC 0.75%) (51). However, the authors focus seems to be on something called PHI density rather than PHI.

In another prospective observational study, 506 men over 50 years old, with PSA in the 4-10 ng/mL range, a negative DRE, and receiving a PHI test, were compared with a historical control group of 683 similar men (52). Men receiving a PHI test showed nearly a 24% reduction in biopsy procedures performed compared to the historical control group (36.4% versus 60.3%, respectively, $p<0.0001$). "Based on questionnaire responses, the phi score

impacted the physician's patient management plan in 73% of cases, including biopsy deferrals when the phi score was low, and decisions to perform biopsies when the phi score indicated an intermediate or high probability of prostate cancer (phi ≥36)." The authors conclude that the study "supports the routine use of PHI testing for men presenting with elevated serum total PSA and non-suspicious DRE findings."

Of note, there is conflicting data on the optimal PHI cutoff, with another study claiming poor results using a cutoff of 25-30 (26). The study, comparing 4K and PHI, is described in more detail in the 4Kscore section.

4Kscore

The 4Kscore combines data from serum levels of four kallikrein proteins (fPSA, tPSA, iPSA, human kalilkrein 2 (hK2)), along with clinical information (age, DRE, prior negative biopsy) to estimate the percent likelihood of HGPC on biopsy using a proprietary algorithm.

In a population-based study involving 2914 men with elevated PSA >3 ng/mL, addition of free PSA, intact PSA, and hK2 to a model containing total PSA and age improved the AUC from 0.64 to 0.76 and 0.70 to 0.78 for models without and with digital rectal examination results, respectively (P <.001 for both) (27). The authors claim application of the panel could reduce biopsies by 51.3% and miss 12% of high-grade cancers.

In a multi-center prospective study of 1012 subjects scheduled for prostate biopsy, the predictive accuracy of the 4Kscore was compared to a modified Prostate Cancer Prevention Trial (PCPT) Risk Calculator 2.0 and showed superior discrimination in detecting HGPC (AUC 0.82 versus 0.74, p < 0.0001) (28). It was estimated that, depending on the 4Kscore cutoff (≥6% to ≥15%), biopsies avoided would range from 30% to 58%, and the number of HGPC missed would range from 1.3% to 4.7%.

In a study of 6129 men with elevated PSA (≥ 3 ng/mL), the 4Kscore AUC for predicting HGPC was 0.820 (95% CI = 0.802 to 0.838) vs 0.738 (95% CI = 0.716 to 0.761) for PSA and age alone (29). Using a 6% risk of high-grade cancer as a cutoff, the model would reduce biopsies by 42.8% and delay diagnosis in 14 of 133 (10.5%) of HGPC.

A multi-institutional clinical utility study was performed to evaluate the effect of the 4Kscore test in lieu of prostate biopsy for males referred to urologists for atypical PSA and/or DRE results (30). The study involved 611 subjects in 35 United States academic and community settings. Results for the patients were stratified into low risk (< 7.5%), intermediate risk (7.5%-19.9%), and high risk (≥ 20%) for aggressive prostate cancer. Performing the 4Kscore Test resulted in a 64.6% reduction in prostate biopsies in patients; the actual percentage of cases not proceeding to biopsy were 94.0%, 52.9%, and 19.0% for men who had low-, intermediate-, and high-risk 4Kscore results, respectively.

When comparing PHI and the 4K score, the two tests appear to demonstrate similar discriminatory ability in predicting high-risk prostate cancer in men with a PSA between 3 and 15 ng/mL (AUC 4Kscore 0.718 vs. PHI 0.711); both tests had a higher AUC than PSA and age alone (p<0.0001 for both) (26). Of note, the 4K panel showed net benefit when the cutoff for biopsy exceeds 8% risk for HGPC. The clinical utility of PHI was also strongly dependent on the cut-off used. PHI cutoffs of 25–30 had poor clinical utility compared to higher cutoffs (30-40). According to the study authors, the tests save almost 30% of the biopsies to the cost of missing 10% high grade cancers if using 10% risk of high grade cancer as predicted by the 4K panel or a PHI cutoff of 39.

However, a subsequent meta-analysis of twelve 4Kscore studies (N = 11,134), yielded an overall AUC of 0.81 (0.79-0.83), and found the Nordstrom study to be an outlier (AUC 0.72 vs. around 0.8 for others) (45). Excluding Nordstrom (a possible methodological flaw was admitted to by the Nordstrom authors (46)) increased this to 0.82

(0.80-0.84), and heterogeneity was no longer significant (p = 0.08). Interestingly, the authors also cite the lack of a specific "arbitrary" cutoff as a positive, saying "a continuous risk score from <1% to >90% that allows the physician and patient to act according to their own desired risk threshold."

A prospective, multi-institutional study of 366 men (56% African American) showed better discrimination (AUC 0.81 vs. 0.74, p <0.01) than standard-of-care (SOC) (age, PSA, DRE) (47). There was no significant AUC difference for detecting clinically significant prostate cancer between African American and non-African Americans. In a retrospective study of 749 men referred for biopsy due to elevated PSA (≥3 ng/mL), low %fPSA (<20%), or suspicious DRE, the use of the 4Kscore (in conjunction with age and DRE) improved discrimination compared with SOC (age and PSA) for high-grade cancer (0.78 vs. 0.72; p = 0.002) (48). At a threshold of > 8%, 24% of biopsies would have been avoided and 13 high-grade cancers missed.

Two similarly designed retrospective, case-control studies address the question of whether biopsy outcome is a good proxy for long-term prostate cancer morbidity and mortality. A case-control studied 12,542 men enrolled at ages 40-60 and followed for >15yr; 1,423 developed incident PCa, 235 with distant metastasis (49). PSA and 4Kscore were measured in cryopreserved blood. Among those with a PSA ≥3ng/mL (2,432), 62% had a 4Kscore ≥7.5% and a 16.36% (95% CI: 12.44-20.74) risk at 20 years of distant metastasis, versus a 1.82% (95% CI: 0.47-4.99) risk among the 38% with a 4Kscore <7.5%. The authors conclude that the 4Kscore "can be used as a reflex test to aid biopsy decisions." Another case-control studied 11,506 men enrolled at ages 45-73 and followed for >15yr; 1,223 developed incident PCa, 235 prostate cancer deaths (50). PSA and 4Kscore were measured in cryopreserved blood. Among men aged 60-73 with a PSA ≥2ng/mL (1,822), 54% had a 4Kscore ≥7.5% and a 24.21% (95% CI: 20.62-27.98) risk at 20 years of prostate cancer death, versus a 4.24% (95% CI: 2.64-6.40) risk among the 38% with a 4Kscore <7.5%. The authors conclude that "men with elevated PSA but low 4Kscores can be monitored rather than being subject to biopsy."

The 4K score is not FDA approved, but rather a Laboratory Developed Test (LDT) through one CLIA-accredited testing laboratory in Nashville, TN.

ExoDx Prostate IntelliScore (EPI)

EPI is a urine-based 3-gene exosomal RNA expression assay. The EPI gene signature and score incorporates levels of PCA3 (PCa antigen 3), ERG (v-ets erythroblastosis virus E26 oncogene homologs) and SPDEF (SAM-pointed domain-containing Ets transcription factor). EPI uses a proprietary algorithm to translate the level of expression of these three genes into an individualized risk score that predicts the presence of HGPC, with a higher EPI score indicative of a higher probability of high-grade disease. EPI does not incorporate PSA and other SOC factors into the score, but is intended to be used in conjunction with SOC elements such as age, family history, PSA level and DRE results.

A study in men over 50 years without a prior biopsy and a PSA 2-10 ng/mL demonstrated a correlation with HGPC significantly better than SOC alone (31). In 255 men in the training target population (median age 62 years and median PSA level 5.0 ng/mL, and initial biopsy), EPI plus SOC was associated with improved discrimination of HGPC: AUC 0.77 (95%CI, 0.71-0.83) vs SOC AUC 0.66 (95%CI, 0.58-0.72) (P <.001). Results were similar in the independent validation of 519 patients; EPI plus SOC AUC 0.73 (95%CI, 0.68-0.77) was superior to SOC AUC 0.63 (95%CI, 0.58-0.68) (P <.001). Using a predefined cut point, 138 of 519 (27%) biopsies would have been avoided, missing 8% of HGPC cases, but only 5% of patients with dominant pattern 4 high-risk GS7 disease. An accompanying editorial indicates EPI has the advantage over other biomarkers in being the least invasive (requires neither DRE or phlebotomy) (32).

In a second prospective, nonrandomized, controlled clinical study of 503 men 50 years or older with a PSA between 2-10 ng/mL, EPI AUC 0.70 (95%CI, 0.65-0.75) was superior to both the Prostate Cancer Prevention Trial Risk

Calculator (PCPTRC2.0) AUC 0.63 (95%CI, 0.58-0.68) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator AUC 0.59 (95%CI, 0.54-0.64) (53). Using the test's predefined cut point (15.6), 101 of 503 (20%) biopsies would have been avoided, missing 7% of HGPC cases (11 ≥ GG2, of which 7 were ≥ GG3). The authors concluded "EPI is a noninvasive, easy-to-use, gene expression urine assay, which has now been successfully validated in over 1000 patients across two prospective validation trials to stratify risk of ≥GG2 from GG1 cancer and benign disease. The test improves identification of patients with higher grade disease and would reduce the total number of unnecessary biopsies."

In a prospective, randomized, blinded study of 1048 patients considered for initial prostate biopsy based on an elevated PSA (2-10 ng/mL), while all patients had an EPI test, only those in the EPI arm received results for their biopsy decision (33). The sole objective primary metric was reduction of initial prostate biopsy by 15%. The EPI arm (N=458) had a median age of 64 years and PSA of 4.8 ng/mL, similar to the SOC control arm (N=484) with a median age of 65 years and PSA of 4.8 ng/mL. This was a "real-world" exercise in that the EPI score potentially influenced but did not necessarily determine the physician biopsy recommendation, and the recommendation likewise met with variable patient compliance. Unfortunately, control arm physician recommendations are not reported, precluding comparisons of patient compliance.

Ninety-three (20%) EPI group patients had a low risk EPI score of <15.6; of these, 59 (63%) were recommended to defer biopsy (54 (92%) complied) and 69 (74%) deferred overall. Three hundred sixty-five (80%) EPI group patients had a high risk EPI score of ≥15.6; of these, 318 (87%) were recommended for biopsy (229 (72%) complied) and 240 (66%) underwent biopsy overall. Of the 484 control patients, although physician recommendations are not detailed, ultimately only 190 (39%) underwent biopsy. Thus overall, the EPI arm had a higher (264/458; 57.6%) rather than lower biopsy rate than the control group (190/484; 39.3%). This translated to finding 30% more HGPC compared to the control arm (78 vs. 60). Among African-Americans, representing a significant 22% and 24% of patients in the EPI and control arms, respectively, 81% more HGPCs were found in the EPI arm (29 vs. 16). Using HGPC prevalence in the corresponding biopsied groups, the authors project that there were 46 presumed missed HGPC in the EPI cohort, and 94 presumed missed HGPC in the control cohort, a 48% reduction.

Unlike the validation studies which had no control group and assumed every low risk score was a biopsy deferred, the control group here demonstrated the focus perhaps should be on greater physician recommendation accuracy and patient compliance, rather than an absolute drop in biopsy rate. Compared to the control group biopsy rate of 39.3% (190/484), knowledge of EPI results stratified the biopsy rate between 65.8% (240/365) in the high risk group, and 25.8% (24/93) in the low risk group, resulting 18 more HGPC identified. Including both EPI and control groups, 10.3% (7/68) low EPI risk patients had HGPC, whereas 33.9% (131/386) high EPI risk patients had HGPC. The EPI arm physician recommendations experienced 73.8% (338/458) compliance; as noted previously, comparable control arm physician recommendations are not described. Overall 68% of urologists in the study reported that the EPI test influenced their biopsy decision, and 23% said they recommended biopsy deferral due to the EPI result.

In men with a prior negative biopsy, a prospective clinical validation study of 229 men undergoing repeat biopsy found that the EPI test had a NPV of 92% and would have avoided 26% of unnecessary biopsies while missing 2.1% of HGPC (54).

NCCN Prostate Cancer Early Detection V1.2023-January 9, 2023. Accessed 2/6/2023 include the following corrections of NCCN technical errors:

- PROSD4: "Footnote u modified: Tests that improve specificity in the post-biopsy setting including percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA should be considered in patients thought to be higher risk despite a negative prostate biopsy (See PROSD-3)."
- MS-19: "%f PSA, PHI, 4Kscore, EPI, PCA3, and ConfirmMDx may also be considered for those who have had at

least one prior negative biopsy and are thought to be at higher risk."

Mi-Prostate Score (MiPS)-Also known as MyPRostate Score

The MiPS assay measures tPSA and post-DRE urine expression of PCA3 and the TMPRSS2:ERG fusion gene. A validation study of 1244 men with planned biopsy (80% initial) found the AUC for the prediction of HGPC was 0.772 for MiPS compared with 0.651 for PSA alone (34). Using a predicted risk cutoff of ≥30%, 35% of biopsies could have been avoided, and only 1% of HGPC missed.

A multicenter prospective validation study of 561 men found a sensitivity and specificity for HGPC of 93% and 33%, respectively (35). The authors calculate that 42% of unnecessary biopsies could be avoided at the cost of only 7% missed HGPC.

SelectMDx

SelectMDx is a gene expression assay measuring mRNA levels of homeobox C6 (HOXC6) and distal-less hemeobox 1 (DLX1) in post-DRE urine; both HOXC6 and DL1 may be involved in the onset of prostate cancer and are associated with HGPC (36). A prospective, multicenter study involved a training cohort (n=519) and validation cohort (n=386) in men scheduled for prostate biopsy (PSA ≥ 3ng/mL, abnormal DRE, or family history of prostate cancer) (37). Using a cut-off of 27.5 for the prediction of HGPC, the expression of DLX1 and HOXC6 alone resulted in an AUC of 0.76 and 0.73 for the two cohorts, respectively. Combined with other SOC risk factors, the AUC increased to 0.90 in the training set and 0.86 in the validation set.

ConfirmMDx

ConfirmMDx is a tissue-based, multiplex epigenetic assay intended to improve risk-stratification of men being considered for repeat biopsy. The test uses prostate biopsy tissue to assess the methylation status of 3 biomarkers (GSTP1, RASSF1, APC) associated with prostate cancer. The test is performed in one CLIA-certified laboratory, and not FDA approved. The performance of this assay in large, blinded clinical validation studies using archived tissue from 848 patients with negative biopsies, demonstrated a NPV of 88-90% for all prostate cancer (56,57). Multivariate analysis in both studies showed the test to be predictive of patient outcome.

PCA3

PCA3 is an mRNA expression assay tested from post-DRE urine. The FDA has approved the PCA3 assay to help decide whether a repeat biopsy in men aged 50 years or older with one or more previous negative prostate biopsies is necessary. In a prospective multicenter study of 466 men with a least one prior negative prostate biopsy scheduled for repeat biopsy based on best clinical judgement, a PCA3 score cutoff of 25 showed a sensitivity of 77.5%, specificity of 57.1%, NPV of 90%, and PPV of 33.6% (55). Those with a score of <25 were 4.56 times more likely to have a negative repeat biopsy.

isoPSA

isoPSA is a blood based, structure focused assay which predicts risk by partitioning the isoforms of prostate specific antigen that are linked to cancer in an aqueous 2-phase reagent system. If 1000 patients were biopsied, the assay would have reduced the number of unnecessary biopsies from 705 to 402 with only 22 missed high grade cancers, of which 7 would have been Gleason sum 4+3 or higher.

Analysis of Evidence (Rationale for Determination)

The number of assays purported to serve as a useful adjunct to PSA in HGPC prediction is mounting rapidly. NCCN recommends (level 2A) "consideration" of a biomarker test (one that has been validated in peer-reviewed, multi-site studies using an independent cohort of patients) to better define the probability of HGPC in patients who meet PSA standards for consideration of prostate biopsy (1). For biopsy-naïve patients, the guideline discussion cites %fPSA, PHI, SelectMDx, 4Kscore, MyProstate Score, isoPSA, or EPI, while adding %fPSA, PHI, 4K Score, PCA3, MyProstate Score, isoPSA, and ConfirmMDx in the setting of a prior negative biopsy and patient thought to be at higher risk. Secondary to small study sample size and varied results, NCCN eschews recommending any biomarker over another. They caution that these tests can be complex and urge both specialist referral and shared decision-making.

Other organizations also seem to imply at least some support for biomarkers to help determine when an initial or repeat biopsy is needed, including the American Cancer Society (ACS) (38), as well as the European Association of Urology (EAU), European Society for Radiotherapy & Oncology (ESTRO), and International Society of Geriatric Oncology (SIOG) (39). However, more recent EAU-EANM-ESTRO-ESURE-SIOG guidelines have downgraded their recommendation ("weak") in favor of multi-parametric MRI (mpMRI) ("strong") (58). The American Urological Association (AUA) state that "approaches subsequent to a PSA test (e.g., urinary and serum biomarkers, imaging, risk calculators) are available for identifying men more likely to harbor a prostate cancer and/or one with an aggressive phenotype. The use of such tools can be considered in men with a suspicious PSA level to inform prostate biopsy decisions (41)." UpToDate notes that they "may provide information which is complementary to PSA and PSA density as well as magnetic resonance imaging (MRI) findings. How they best perform in providing prognostic information is still being evaluated (59)."

The Canadian Urological Association (CUA) distinguishes %fPSA from both 4Kscore and PHI, concluding that "percent free PSA can be useful in estimating the risk of underlying disease in men with elevations in PSA (Level of evidence: 2; Grade of recommendation: C) (40)." In contrast, 4Kscore and PHI "in men with moderately elevated PSA…may improve the prediction of clinically significant prostate cancer and provide additional information over PSA alone; however, … At the present time, based upon the available data, the CUA does not encourage the widespread use of these tests." The American Society of Clinical Oncology (ASCO) considers ancillary radiologic and genomic tests (during active surveillance) investigational, noting that "prospective validation of these tests is needed to assess their impact on patient outcomes such as survival", but may have a role in patients with discordant clinical and/or pathologic findings (42). While a different patient population, the concerns would apply equally to the pre-diagnosis biomarker literature.

In general, biomarker studies suffer from one or more limitations, including lack of independent validation, false negatives, short follow-up, lack of randomized trials or outcome results, cut-point standardization, undetected cancers (up to 25%) with a single negative prostate biopsy, and the potential for upgrading (32%-49) that occurs in patients with Gleason 6 at biopsy. The concern implicit in the last two issues is that biomarker validations studies, which correlate biomarker test results only with biopsy findings, may be underestimating the risk of missing clinically significant cancer, hence the need for longer follow-up. Another limitation is that they predate the mpMRI era. In serving as both an alternative risk-assessment and biopsy optimization tool, routine use of mpMRI may diminish the need for biomarker testing. Whereas NCCN guidelines originally recommended to "consider" both mpMRI or biomarker testing, in 2021 the word "consider" was struck from mpMRI only, noting "it is recommended that MRI should precede biopsy and image-guided biopsy techniques be employed routinely" (1). This adjustment is consistent with the change to the latest EAU-EANM-ESTRO-ESURE-SIOG guidelines cited above (58).

In addition, the case against early diagnosis of low-risk prostate cancer is weakening. There is increasing uncoupling of over-diagnosis and over-treatment due to the emerging use of active surveillance. The most recent AUA/ASTRO/SUO, ASCO, and NICE guidelines recommend active surveillance (serial PSA, DRE, prostate biopsy) for most low risk localized prostate cancer patients (PSA <10, Gleason score ≤ 7, and clinical stage T1-T2a) (42-44). This trend toward active surveillance (instead of treatment) of low-risk prostate cancer could lower the harm

associated with diagnosis. Active surveillance of low-risk cancer also ameliorates the risks associated with misclassification on biopsy.

In summary, while the results of the mostly industry-sponsored validation studies are promising, benefits remain theoretical, namely, that fewer biopsies of men with moderately elevated PSA is inherently a good thing. Certainly, it is good in the short term for men who avoid an "unnecessary" prostate biopsy. Not good, however, are necessary biopsies missed due to false negatives. Moreover, even the definition of "unnecessary" may be evolving. Also, some studies overrepresented men for whom the information is less likely to be helpful (a positive DRE, PSA levels outside the gray zone, or older men not candidates for surgery), or underrepresented others (e.g., high risk groups such as African Americans, etc.). Comparative studies of the many biomarkers are lacking and it is unclear how to use the tests in practice, particularly when test results are contradictory (1). For all these reasons, the long-term benefit of these tests to net health outcomes (i.e., mortality, morbidity, or quality of life) is not yet clear.

Given the state of flux of PSA screening in general, combined with arguably tentative, and in some ways diminished, guideline support (secondary to the almost complete absence of Level I or outcome studies), of adjunctive biomarker testing, NGS will provide very circumscribed coverage. Coverage will be limited to patients with moderately elevated PSA levels, but with no other, even relative, indication for or against biopsy (largely based on NCCN guidelines). These are men for whom the decision about whether to proceed with prostate biopsy is most ambiguous, and therefore for whom the information is most likely to impact clinical decision making. Criteria for the EPI test are somewhat more liberal given the RCT patient mix and results. Nevertheless, none of these assays are recommended for routine use as they have not been prospectively tested or shown to improve long-term outcomes (e.g., quality of life, need for treatment, or survival).

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
03/01/2023	R4	- Based on the National Comprehensive Cancer Network (NCCN) January 9, 2023 technical correction in NCCN, Prostate Cancer Early Detection, Version 1.2023, NGS has corrected the technical error in LCD L37733 accordingly. The NCCN guidelines now include coverage for EPI for men with at least one prior negative biopsy and when a repeat biopsy in patients thought to be at higher risk despite a prior negative biopsy. - Added the following language to the Summary of Evidence: NCCN Prostate Cancer Early Detection V1.2023-January 9, 2023. Accessed 2/6/2023 includes the following corrections of NCCN technical errors: • PROSD4: "Footnote u modified: Tests that improve specificity in the post-biopsy setting including percent-free PSA, 4Kscore, PHI, PCA3, ConfirmMDx, ExoDx Prostate Test, MPS, and IsoPSA should be considered in patients thought to be higher risk despite a negative prostate biopsy (See PROSD-3)." • MS-19: "%f PSA, PHI, 4Kscore, EPI, PCA3, and ConfirmMDx may also be considered for those who have had at least one prior	• Other (Request for technical correction, based on NCCN Prostate Cancer Early Detection, Version 1.2023-January 9, 2023 update which corrected guideline errors.)

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		negative biopsy and are thought to be at higher risk.”	
11/01/2022	R3	Based on a request for Reconsideration, the LCD was revised to allow a physician or other qualified health care professional (i.e., NP, CNS, PA) to order the EPI test as well as other biomarkers as discussed in the LCD. Added two additional biomarkers: the MyProstateScore and the isoPSA test. Clarified which biomarker tests are recommended for use prior to prostate biopsy and what tests are recommended for use after biopsy of the prostate. The language concerning biomarker testing was updated and the information in the Rationale for Determination section was clarified.	• Provider Education/Guidance • Reconsideration Request
08/01/2021	R2	Based on a Reconsideration Request, the Indication of Coverage for EPI test was expanded, based on the review of recently published literature, effective for services rendered on or after August 1, 2021.	• Provider Education/Guidance • Reconsideration Request
12/01/2019	R1	Consistent with Change Request 10901, all coding information, National coverage provisions, and Associated Information (Documentation Requirements, Utilization Guidelines) have been removed from the LCD and placed in the related Billing and Coding Article, A56609. Based on a reconsideration request, coverage for EPI (0005U) was added for patients with moderately elevated PSA levels.	• Provider Education/Guidance • Reconsideration Request

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A56609 - Billing and Coding: Biomarker Testing for Prostate Cancer Diagnosis

A59220 - Response to Comments: Biomarker Testing for Prostate Cancer Diagnosis

Related National Coverage Documents

N/A

Public Versions

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02/15/2023	03/01/2023 - N/A	Currently in Effect (This Version)
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Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.		

Keywords

N/A