May 3, 2021

Craig Haug, MD
Medical Director
National Government Services, Inc.
P.O. Box 7111
Indianapolis, IN 46207-7111
New LCD Request: Biomarker Testing for Men with Prior Negative Prostate Biopsies

Dear Dr. Haug,

I am writing on behalf of Exosome Diagnostics, Inc. to formally request of National Government Services, Inc.'s (NGS') a new Local Coverage Decision (LCD) for Biomarker Testing for men with Prior Negative Prostate Biopsies.

Clinical Background

EPI is a non-DRE urine-based liquid biomarker test for the assessment of the risk of high-grade prostate cancer on biopsy in men 50 years of age and older with Prostate Specific Antigen (PSA) results of 2-10 ng/mL, and has received NGS coverage for initial biopsy. We now request that EPI receive an LCD for men with a prior negative biopsy under consideration for repeat biopsy. Men with a prior negative prostate and a PSA in the gray zone (2-10 ng/mL) are especially challenging for two reasons .

First, many men go through a 'repeat' biopsy, with its attendant morbidity and cost, when the repeat biopsy could have been avoided. These "unnecessary" biopsies can result in complications such as bleeding, incontinence, impotency, and in 3 to 4% of cases, severe infection. Second, many other men opt out of repeat prostate biopsy because they are apprehensive about having the invasive procedure a second time. These men may have clinically significant cancer that could benefit from earlier diagnosis and subsequent treatment. In 2012 and again in 2017 the United States Preventive Services Task Force (USPSTF) expressed concerns about the imprecise nature of PSA screening, noting the potential harms of screening and false positive results. In 2018, the USPSTF updated these recommendations for men 55 to 69 years, but continued to emphasize the limitations and potential harms of PSA screening (JAMA 2018).
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EPI was developed in collaboration with the Prostate Cancer Foundation and top academic and community urologists to address these clinical concerns and reduce the frequency of over-biopsy and the overtreatment of indolent prostate cancer by ruling out the possibility of clinically significant disease into the biopsy decision process. It is a multianalyte assay with algorithmic analysis (MAAA) test that uses reverse transcription polymerase chain reaction (RT-PCR) to analyze exosomal RNA expression for three genes associated with high-grade prostate cancer.

The stand-alone EPI urine test translates the level of expression of these three genes into an individualized risk score that predicts the presence or absence of high-grade (Gleason score (GS) ≥ 7) prostate cancer, with a higher EPI score indicative of a higher probability of high-grade disease, and a lower EPI score indicative of a lower probability of high-grade disease. The test utilizes a single cut point to simplify interpretation and facilitate understanding by both urologists and their patients, with a score below the cut point representing low risk for high-grade prostate cancer. Notably, while many other tests incorporate PSA and other standard of care factors, that the doctor already knows, into their scores - EPI does not incorporate these factors to provide a test result and instead provides unique information to which the doctor does not otherwise have access.

EPI has been assigned the Proprietary Laboratory Analyses (PLA) code 0005U by the American Medical Association (AMA) CPT Editorial Panel and is nationally priced on the Clinical Laboratory Fee Schedule.

Analytical Validity

EPI's analytical validation comprises extensive internal validation studies characterizing all analytical performance specifications required under the Clinical Laboratory Improvement Amendment (CLIA). The test is performed in Exosome Diagnostics' CAP (College of American Pathologists)-accredited and CLIA-certified laboratory in Waltham, MA, which is licensed for high complexity testing in all 50 states, including New York. Extensive analytical validations have evaluated the performance of EPI over a series of studies and sub-investigations, including two independent prospective multi-center validation studies in the US involving over 1,000 patients. These clinical validation analyses, together with extensive analytical validation, which are the basis of our CLIA certification, are summarized below, with greater detail available on request, if desired:

- EPI is highly reproducible, even when including variation from, for example, different operators, instruments, batches, and reagent lots.
- The analytical specificity of the assay was assessed in multiple experiments, including tests for both endogenous (e.g., microorganisms, genomic DNA, blood in urine) and exogenous (e.g., alcohol or detergent) interfering substances.

In summary, extensive analytical validation studies were conducted to evaluate the performance characteristics of EPI under a variety of experimental and clinical conditions, demonstrating highly accurate and reproducible results.

Validation Studies

The ExoDx Prostate assay was validated in two separate prospective clinical studies (NCT02702856 and NCT03031418). Urine samples were collected from more than 2,000 patients from more than twenty-four clinical sites and the results were published in - Journal of the American Medical Association Oncology and in European Urology. EPI demonstrated significantly superior performance to current standard of care as well as a high negative predictive value (NPV) of 91.3% and a sensitivity of 92% at a cut point of 15.6.

Clinical Utility

EPI has completed a prospective, randomized, blinded, clinical utility and decision impact trial utilizing a groundbreaking trial design involving 1,094 patients and 72 urologists across 24 urology practices in Maryland. The trial was conducted in collaboration with CareFirst BlueCross BlueShield and one of the nation's largest urology group practices, Chesapeake Urology Associates. The data from this study was published in the peer-reviewed Prostate Cancer and Prostatic Diseases urology journal.

Key findings include:

- Avoid unnecessary biopsies in patients unlikely to have clinically significant cancer and increased compliance to biopsy in the high-risk patients.
- Utilization of EPI detected 30% more cases of high-grade, clinically significant prostate cancers that were missed in the standard of care setting without EPI.
- Significantly, improved patient compliance with urologist's recommendation to defer (92% compliance) or proceed to biopsy (72% compliance)

The EPI score is intended to be used and is being used in conjunction with other standard of care factors, such as age, race, family history, PSA level, and digital rectal examination (DRE) results to inform the decision to proceed or defer biopsy. The validation studies did not exclude subjects based on DRE and/or family history and/or ethnicity. The ethnic demographics of these studies are representative of the general population in the United States and the reported performance of the test is for this population.

Additional Published Evidence and NCCN Guidelines for Coverage Determination

a) Support Coverage for Beneficiaries with Prior Negative Biopsy

Recently published evidence supports that EPI coverage not be limited to beneficiaries prior to initial biopsy, because the test is reasonable and necessary for beneficiaries with previous negative biopsy results who are being considered for another biopsy. A recent publication in *BMC Urology* (McKiernan et al.,(2020), analyzed EPI's performance in men undergoing repeat biopsy after a prior negative biopsy (N=229). These men represented a subset of a large, prospective multi-center clinical trial. The study objective was to assess ExoDx Prostate performance metrics in a repeat biopsy setting (McKiernan, 2020, BMC Urol). All men fit existing inclusion criteria (PSA 2-10ng/mL and >50 years) for which ExoDx Prostate was previously validated for initial biopsy. Also, the repeat biopsy evaluation employed the same risk assessment threshold (15.6) as the previously published validation study (McKiernan, 2016, JAMA).

This study, when compared to EPI's validation in patients prior to initial biopsy, showed that EPI's performance (negative predictive value (NPV), sensitivity) is similar in patients with prior negative biopsies as in biopsy naïve patients and can be used to stratify risk in patients considering a repeat biopsy. Specifically, in both the initial biopsy validation and the repeat biopsy study, the EPI Test demonstrated a much better performance (AUC) than comparative clinical tools. The NPV for ruling out high-grade prostate cancer (≥GG2) was 91.5% for repeat biopsy and 91.3% for initial biopsy. Net benefit analysis (conducted in both studies) demonstrated that EPI provided significantly improved clinical benefit than existing clinical standard of care methods, both in biopsy naïve and prior negative biopsy populations.

b) National Comprehensive Cancer Network (NCCN) Guidelines – Prostate Cancer Early Detection

The ExoDx™ Prostate(IntelliScore) or EPI test was included in the 2019 NCCN Guidelines for Prostate Cancer Early Detection (NCCN V2.2019, May 31, 2019) and does not limit the use of EPI to patients presenting for their first biopsy. The NCCN guidelines recommendation was based on the two US prospective multi-center (academic and community urologists) validation studies published in major peer-reviewed oncology and urology journals. The validation studies included data also for men presenting with a prior negative biopsy.

As NGS reviews the new LCD consideration for Biomarker Testing for Prior Negative Biopsies in Prostate Cancer Diagnosis, the additional clinical evidence supports coverage of the ExoDx Prostate

Test. Also, based on the previously submitted data, the NCCN Guidelines do not limit EPI testing to patients who have not previously been tested using a biomarker test.

As with all biomarkers, urologists find value in longitudinal measurements of prostate biomarkers to monitor patient health. Having access to longitudinal measurements of a biomarker that does not rely on PSA or other standard of care parameters for the score may help the decision-making process for biopsy. A patient can develop prostate cancer over time. Doctors need to continue to monitor their patients over time, especially as their PSA or other clinical factors and symptoms change. For these reasons, doctors need to use biomarkers more than once, and the NCCN Guidelines likewise do not limit their recommendation to a single EPI test per lifetime.

Exosome Diagnostics is seeking coverage for patients with prior negative biopsy to have access to the ExoDx (EPI) Prostate Test and allow the use more than once. We thank you for your review of this reconsideration request and will be reaching out to set up a meeting in the next few weeks. If you have any questions, please contact me at (617) 588-0522 or Steven.Silverman@bio-techne.com if you have any questions or need additional information.

Thank you,

Steven Silverman