How I Use It: The Exosome Diagnostics (EPI) prostate cancer biomarker utility in urology and primary care

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Prostate-specific antigen (PSA) screening remains the mainstay for early detection of prostate cancer. Although PSA is a nonspecific prostate cancer biomarker, its specificity for high grade prostate cancer can be enhanced by pre-biopsy liquid biomarkers including the Exosome Dx Prostate IntelliScore (EPI) test.

EPI is a stand-alone urine genomic test that measures 3 exosome-derived gene expression signatures without the need for digital rectal examination (DRE) or inclusion of standard of care parameters in the test algorithm. EPI has broad clinical utility as a risk stratification tool for clinically significant high grade prostate cancer in men considering diagnostic prostate biopsy (MRI-targeted and systematic biopsy).

During the COVID-19 pandemic, the EPI At-Home Collection Kit was introduced and quickly became an important component of tele-urology. The EPI test has emerged as a prioritization tool for primary care referral to urologists and for prostate biopsy scheduling.

EPI provides an objective and actionable genomic risk assessment tool for high grade prostate cancer and is a critical part of the informed decision-making regarding biopsy (targeted, systematic or both) in both urology and primary care practices.

Key Words: ExoDx (EPI), prostate cancer, biomarkers, prostate-specific antigen (PSA) screening, primary care, urology, MRI

Introduction

Prostate cancer is the most common male solid organ cancer in the US and the second (after lung cancer) leading cause of cancer death in men. The American Cancer Society (ACS) estimates 268,490 new cases of prostate cancer with 34,500 deaths in 2022.[1]

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Widespread prostate-specific antigen (PSA) screening for prostate cancer followed the landmark *New England Journal of Medicine* publication in 1991[2] and resulted in an increase in prostate cancer incidence, decreased incidence of advanced/metastatic disease and a nearly 50% decline in prostate cancer deaths. Despite its known limitations, PSA testing remains the foundation of prostate cancer screening practices.

Multiple tests have been developed to improve the specificity of PSA as a screening test e.g., age-related PSA, free-to-total PSA ratio and PSA density. PSA screening continues to be somewhat controversial because of the potential for overdiagnosis and overtreatment of low-risk, clinically insignificant or

indolent Gleason 6 (Grade Group 1) prostate cancer. The United States Preventive Services Taskforce (USPSTF) 2012 Grade D recommendations against routine PSA screening resulted in less PSA screening, a reduction in the number of men diagnosed with prostate cancer and increased rates of metastatic prostate cancer and prostate cancer deaths.[3]

The American Cancer Society reports that distant-stage prostate cancer diagnoses more than doubled between 2007 and 2018 - from 3.9% to 8.2%.[1] These mortality trends are inconsistent with mortality trends observed with other cancers during the same period. The message from these data is clear - when you do not screen for prostate cancer, increased mortality follows.

Risk adapted/stratified screening and biomarkers

Despite the upgraded (Grade C) USPSTF recommendation in 2018 for PSA screening as part of shared decision making in men 55-69 years of age, lingering concerns continue regarding the value of PSA screening. This has led to development and adoption of a risk stratified prostate cancer screening algorithm as a clinical decision support tool in the Duke Primary Care Network[4] to limit over-detection and overtreatment of clinically insignificant prostate cancer. The increased adoption of active surveillance (AS) management for low-risk disease has mitigated the concerns regarding overtreatment that were cited by the USPSTF 2012 and 2018 recommendations.[5]

Biomarkers (blood vs. urine; genomic vs. non-genomic) provide pre-biopsy risk assessment of clinically significant prostate cancer. Biomarkers included in the NCCN guidelines include % Free PSA, Prostate Health Index (PHI), 4K Score, SelectMDx and the ExoDx (EPI) test.[6]

Herein, we describe the expanding clinical utility of the EPI liquid biomarker test in contemporary urology and primary care practice.

ExoDx (EPI) test – validation and clinical utility/decision impact studies

EPI is a Laboratory-Developed Test (LDT) developed by the Exosome Diagnostics CLIA (Clinical Laboratory Improvement Amendments) Certified Laboratory in Waltham, MA, USA. Prospective validation studies support the use of the EPI test to assess the risk of high grade prostate cancer (GG2 and higher) in men aged 50 plus with PSA levels 2-10 ng/mL undergoing biopsy (initial and repeat).

EPI is a first-catch urine exosome-based liquid biomarker assay that is independent of clinical variables and does not require a digital rectal examination (DRE) or prostatic massage. It is a genomic test that measures 3 prostate cancer specific, urinary exosome-derived RNA biomarkers (V-ets erythroblastosis virus E26 oncogene homologs) [ERG], prostate cancer antigen 3, and SAM-pointed domain-containing Ets transcription factor [SPDEF]) by quantitative polymerase chain reaction (PCR) and scores range from 0-100 with 15.6 being the "cut off" value that separates "low risk" from "intermediate/high risk". EPI has multiple points of differentiation from the other pre-biopsy biomarkers, Table 1.

Two large US multi-center (community and academic) prospective clinical validation studies

TABLE 1. **ExoDx (EPI) biomarker characteristics**

Defined "intended use" population
- 50 years plus
- PSA 2-10 ng/mL
Standalone pre-biopsy genomic molecular diagnostic
No digital rectal examination (DRE) or prostatic massage required
EPI algorithm
- 3 genes (PCA3, ERG, SPDEF)
- No standard of care features (age, PSA, prior biopsy etc.) in algorithm
Only biomarker with Level 1 Evidence Clinical Utility and Decision Impact Study
At-Home Collection Kit option
- broad adoption and utility
- easy integration into tele-health practice
- "meets patients where they are"

have been published[7,8] resulting in inclusion of EPI in the 2019 NCCN Prostate Cancer Early Detection Guidelines for initial and prior negative repeat biopsies. In a pooled meta-analysis (1212 patients) from three independent prospective validation studies, the area under the receiver-operating characteristic curve (AUC) for EPI was superior (0.70) to that of PSA (0.56), the Prostate Cancer Prevention Trial Risk Calculator (0.62) and the European Randomized Study of Screening for Prostate Cancer Risk Calculator (0.59). Using the validated 15.6 EPI cut point resulted in a 90.1% Negative Predictive Value (NPV) and a 92.3% Sensitivity.[9]

A real world, prospective randomized clinical utility study (Level 1 Evidence)[10] compared EPI to the standard of care and demonstrated high compliance rates with the urologist's biopsy recommendation – 92% for biopsy deferral when scores were less than 15.6 and 72% biopsy rate when scores were greater than 15.6. Sixty-eight percent (68%) of urologists reported that the EPI test influenced the biopsy decision and EPI resulted in diagnosis of 30% more high grade prostate cancer compared to the standard of care control group.[10]

EPI achieved a positive Final Local Coverage Decision (LCD) for Medicare Coverage from the National Government Services (NGS) Medicare Administrative Contractor (MAC) in December 2018 and was awarded the Veterans Administration (VA) General Services Administration (GSA) Award in 2020 which makes the test available in the VA Healthcare System.

EPI test in initial and repeat prostate biopsy

EPI is the pre-biopsy urinary risk stratification biomarker of choice in my practice based on its clinical validation and clinical utility study data.[9,10] In men with elevated PSA considering biopsy, an elevated EPI score provides a risk stratification data point that informs the decision making, reduces over-detection of clinically insignificant (Gleason 6/ Grade Group 1) cancer and increases the number of men diagnosed with clinically significant high grade prostate cancer.

The "standalone" EPI genomic test provides the physician and patient with an independent risk-stratification data as part of the biopsy discussion and diagnosis of "the right patient at the right time". The high compliance with the urologist recommendation to biopsy/not biopsy in the Clinical Utility Study led to 30% more high grade prostate cancer being diagnosed when EPI was utilized.[10]

About half of all men undergoing initial biopsy for an elevated PSA have a negative biopsy. Careful follow up of these men is important as the biopsy may have missed cancer due tissue under-sampling and the known heterogeneity/multifocality of prostate cancer. In a recent study of 229 men with prior negative biopsy undergoing repeat biopsy, EPI (at 15.6 cut point) achieved an NPV of 91.5% with a Sensitivity of 82.1% for diagnosis of high grade prostate cancer. AUC curves and Net Health Benefit Analyses showed enhanced performance over both PSA and the ERSPC clinical risk calculator.[11]

In our practice, EPI has demonstrated its utility as a risk stratification tool in men considering a repeat biopsy because of anxiety about missed diagnosis on initial biopsy, rising PSA levels or an abnormal DRE. EPI is included in the NCCN Guidelines for men undergoing both initial biopsy and repeat biopsy in men with a prior negative biopsy.

EPI test in prostate biopsy appointment no-shows and cancellations

Duke University serves a large underserved and considerably large African American patient population and noncompliance with biopsy recommendation or non-attendance (no show/cancellation) for the prostate biopsy procedure is common.[12] We have had a high biopsy compliance rate when EPI was added to the Duke Primary Care-Duke Cancer Institute prostate cancer screening algorithm (Publication pending).

In the EPI Clinical Utility Study only 39% of men in the "Standard of Care" control arm underwent biopsy compared to 58% in the EPI arm.[10] Similar high non-biopsy rates have been reported in both academic and large community urology group practices e.g., 34% in the University of California, San Francisco study and 48% from a retrospective review of Chesapeake Urology Electronic Medical Records.[10,13] No-shows and cancellations are costly, inefficient and may lead to delayed diagnosis with poor outcomes. High non-biopsy rates are of concern due to the increasing incidence of metastatic disease and prostate cancer deaths in the US.[1,3] If a patient misses a biopsy appointment, every effort is made to re-schedule the procedure after a discussion with the patient in person or via a telehealth consultation. The genomic risk score ("precision medicine") derived from the EPI test is highlighted and the increasing risk of high grade prostate cancer with rising EPI scores emphasized. Medico-legally, the above discussion needs to be documented along with the urologist's recommendation regarding biopsy.

EPI test for prostate biopsy prioritization

The COVID-19 pandemic led to widespread closure of physician offices and drastic limitation of elective surgical operating room (OR) and ambulatory surgical procedures including prostate biopsy.[14] At Duke, surgical procedures had to be prioritized by an OR Committee because of the reduced OR availability. Our Prostate Cancer Screening Clinic utilized the EPI score as a risk stratification measure for high grade prostate cancer and as a prioritization tool for scheduling of prostate biopsy procedures. EPI scores less than 20 were regarded as low priority whereas scores greater than 20 were deemed high priority for biopsy – the higher the score, the higher the scheduling priority.

EPI test utility in primary care practice

The 2012 USPSTF recommendation (Grade D) against PSA screening resulted in the joint development (urologists and primary care physicians) of a Duke risk-stratified screening and diagnostic algorithm based on the availability of new diagnostic tools including multi-parametric magnetic resonance imaging (mpMRI) and new prostate cancer molecular diagnostic biomarkers including EPI. The Duke Cancer Institute and the Duke Primary Care Network set up a Prostate Cancer Screening Clinic with a screening algorithm specifically tailored to the local and regional patient demographics, Figure 1a and 1b.[4]

EPI improves the specificity of PSA for clinically significant high grade prostate cancer and limits over-

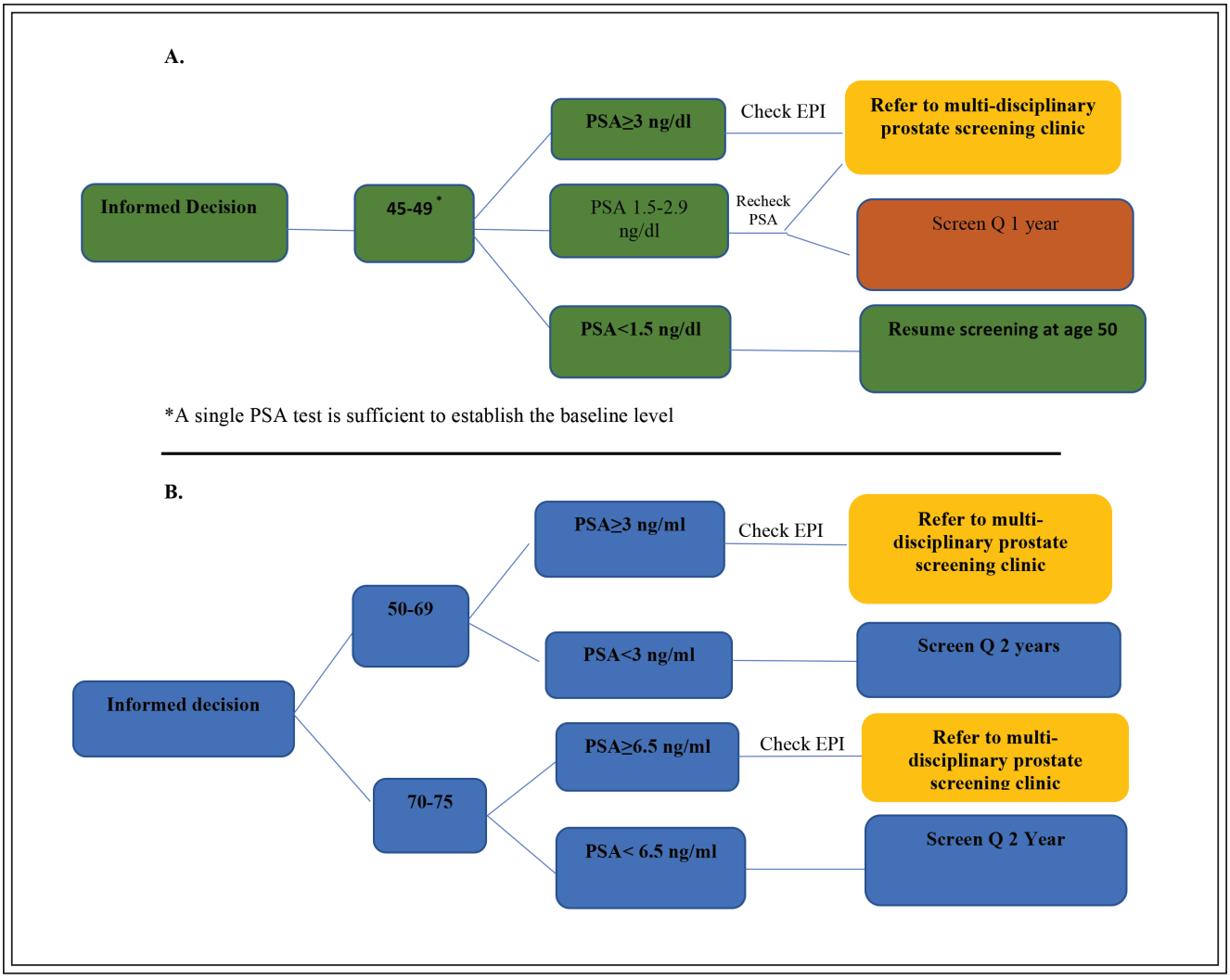

Figure 1. Screening algorithms. **A)** Long time pre-screening risk assessment. **B)** Prostate-specific antigen (PSA) screening.

detection of clinically insignificant Gleason 6 cancer and reduces the need for MRIs when EPI scores are less than 20. The ability to defer or avoid MRI is helpful in instances of MRI non-availability (rural or underserved areas), lack of prior authorization by the insurance company and/or lack of insurance coverage.

EPI testing early in the patient journey of men undergoing PSA screening helps the primary care physician to triage patients at high risk of high grade prostate cancer for prompt urologic referral. High risk EPI score results (above 20) helps the urologist to prioritize scheduling of diagnostic prostate biopsy procedures.

Availability of the EPI score together with the PSA level at the time of the initial urology consultation (in-person or tele-urology) results in an immediate and informed shared-decision making discussion regarding prostate biopsy. The EPI standalone genomic score contributes to a more informed biopsy decision, a shorter time to definitive diagnosis of prostate cancer and potential dollar savings to the healthcare system by avoidance of 1-2 urology specialty clinic visits.

EPI At-Home Collection Kit

The EPI At-Home Test kit was developed during the COVID-19 pandemic for patients who were unable to go for office testing because of office closures and/or lockdown and home quarantine policies.[14] After a successful pilot study at six US sites (including Duke), the customer-focused At-Home Test offering was made available nationwide to offer patients the ease, convenience, privacy, and choice of home testing. The test is ordered on-line by either the primary care physician or urologist and results are available within 3-5 days. The rapid uptake of the EPI home testing option during COVID (30%) continued thru successive pandemic waves and is now 35%-40%.

The EPI kit is mailed to the patient with instructions on (a) "first-catch" urine specimen collection in the privacy of their own home (b) specimen packaging and return shipping and (c) contact information for the Exosome Diagnostics Client Services Group in case of any patient/family questions. Home testing avoids the time and dollar costs of visiting the doctor's office for the test especially for men living in rural areas with limited access to urology specialty care. Once the EPI report is available, the physician (primary care, urology) can discuss it with the patient via a telehealth visit and a decision made for urology referral by the primary care physician or prostate biopsy by the urologist.

EPI test is complimentary to mp-MRI (pre-MRI and post-MRI)

Pre-MRI

The use of MRI as an imaging marker of high grade prostate cancer has increased in the US over the last 10 years. The 2021 NCCN Prostate Cancer Early Detection Guidelines for men with elevated PSAs suggested MRI be performed, if available, and biomarkers (including EPI) "considered" as a test to increase the specificity of PSA.

Recent studies have demonstrated the complimentary role of EPI to MRI in men undergoing PSA screening and diagnostic evaluation for prostate cancer.[15,16] Each test provides distinct information – a positive MRI informs targeted-biopsy planning ("where to biopsy") whereas EPI offers a molecular genomic risk assessment of the entire prostate gland ("who to biopsy"). Combination MRI and EPI pre-biopsy testing has been shown to be better than either alone[16] and "up-front" liquid biomarker testing (with an EPI threshold score of 19) followed by MRI and biopsy potentially reduces MRI imaging by nearly 40% and limits over-detection of Gleason 6 (Grade Group 1) prostate cancer.[15]

The widespread variability in technologist and radiologist expertise (steep learning curve, inter-observer variability) in multi-parametric MRI is a limiting factor in the broad adoption of MRI in the community and outside of the academic centers of excellence in MRI imaging. Furthermore, the cost of MRIs and the fragmented insurance payment system (State by State, Medicare/Medicaid vs. Commercial payers, variable insurance company policies and reimbursement) may result in MRI imaging not being available to some men undergoing prostate cancer screening and diagnostic work up. In this instance, EPI biomarker testing provides actionable risk assessment data that informs biopsy decision-making.

Post-MRI

MRI images of prostate cancer are scored according to the Prostate Imaging - Reporting and Data System (PI-RADS) on a scale of 1 to 5 with scores of 3 to 5 generally reported as positive. The percentage of negative MRIs (PI-RADS 1 and 2) in men referred for biopsy is significant with reported ranges between 19%-38%.[17]

Should a man with an elevated PSA and "negative" MRI (PI-RADS 1 and 2) be counselled to consider random biopsies or stop their evaluation? In men with negative "up-front" MRI imaging, systematic random biopsies reveal clinically significant high grade prostate cancer. The recently reported STHLM3 (Stockholm 3)-MRI Trial[17] showed that men with

negative MRIs and STHLM3 biomarker levels greater than 25 who underwent systematic biopsies had an 18% incidence of high grade prostate cancer. An earlier study had reported a 16% incidence of high grade prostate cancer in MRI-negative patients undergoing systematic biopsies.[18]

The recent exponential increase in use of MRI to evaluate men with elevated PSA levels has resulted in a sizeable number of men being seen in urology clinics with "negative" MRIs. In these men, an EPI biomarker score of greater than 20 is emerging as an actionable data point to trigger a recommendation for systematic biopsies.

EPI utility in active surveillance

Active surveillance (AS) for clinically insignificant, low risk Gleason 6 (Grade Group 1) prostate cancer has gained traction in the US over the last decade and the percent of men now choosing AS exceeds 50%.[5] Men on AS undergo close monitoring with PSA testing and interval prostate biopsies to check for pathologic upgrading or re-classification to a higher Gleason grade. Although AS protocol eligibility and patient follow up specifics vary by institution and geography, most men postpone active treatment (surgery, radiation etc.) for at least 5 years following their initial diagnosis.[5]

In a recent study, pre-biopsy EPI scores were correlated with pathologic upgrading/reclassification in men who underwent radical prostatectomy for Grade Group 1 (Gleason 6) prostate cancer. Although the overall upgrade rate was 56%, low risk EPI scores (less than 15.6) was associated with zero upgrades compared to 16% Grade Group 3 or higher upgrade risk when EPI scores were greater than 15.6.[19]

Because of the upgrading risk, men with high risk pre-biopsy EPI scores may not be good candidates for AS and the EPI score is now part of the shared decision making and counselling discussion with men considering AS.

Many AS protocols now incorporate imaging (MRI, micro-ultrasound) and biomarkers in patient monitoring. A prospective study is planned to assess the role of EPI as a risk assessment tool for AS biopsy pathologic upgrading/reclassification.

Conclusions

The EPI test provides actionable prostate cancer genomic information and is a widely utilized risk-stratification biomarker in both urology and primary care practices. It is a "standalone" non-invasive urine test that doesn't require a DRE or prostatic massage. The urine specimen can be collected in the privacy of the home and avoids the costs (time and money) associated with an office visit for the test.

The EPI biomarker test is easily integrated as a value-added test into primary care and urology practice and has broad clinical utility for triage and referral at the primary care level and for biopsy prioritization and informed biopsy decision-making in urology.

Disclosures

Judd Moul MD: Has received compensation in last 3 years for speaking and/or consulting: Exosome Diagnostics, Dendreon, Janssen, Sanofi, Myovant, Astellas, Bayer, Lantheus, Theralogix and Accord Biosciences.
Grannum Sant MD is a Medical Affairs Consultant to Exosome Diagnostics. □

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