The ExoDx™ Prostate Test *(EPI)* and Primary Care Providers

The ***right*** intervention, with the ***right*** patient, at the ***right*** time.

exosomedx™
a bio-techne® brand

The role of the primary care provider*, or PCP, in the early detection of prostate cancer is critical. Prostate cancer is the second most common cancer in men, and primary care physicians are the first line of defense for recognizing the signs and symptoms of the disease. Primary care physicians begin having conversations with men around the age of 40 years about prostate cancer incidence and options for screening. Prostate-specific antigen, or PSA, and digital rectal examination, or DRE, are the primary tools used to screen men for prostate cancer, but both have inherent limitations. Ideally, the primary care physician should have adequate tools to identify the highest-risk patients, but existing tools fall short of guideline recommendations in the primary care setting.

Inside

**Primary care provider* is generally defined as an internal medicine or primary care physician, nurse practitioner or physician's assistant.*

"(The) harms of screening include adverse effects from prostate biopsy, overdiagnosis and overtreatment, and anxiety. One-half of screen-detected prostate cancers will not cause symptoms in the patient's lifetime, and 80% to 85% of men who choose observation will not die from prostate cancer within 15 years. Adverse effects of radical prostatectomy include perioperative complications, erectile dysfunction, and urinary incontinence. Radiation therapy can cause acute toxicity leading to urinary urgency, dysuria, diarrhea, and rectal pain; late toxicity includes erectile dysfunction, rectal bleeding, and urethral stricture. Despite variations across guidelines, no organization recommends routine PSA testing, and all endorse some form of shared decision-making before testing. If screening is performed, it should generally be discontinued at 70 years of age."

— American Academy of Family Practice PSA testing guidelines

Limits of PSA

Limitations can lead to overtreatment

PSA, although widely used, is a nonspecific biomarker for prostate cancer. The United States Preventive Services Task Force (USPSTF) and other organizations have expressed concern that PSA use can lead to increased prostate cancer detection and overtreatment. Guidelines from the American Academy of Family Practice (AAFP) and USPSTF actually recommend *against* using PSA as a routine screening tool for men age 55 to 69 years, advising that "Clinicians and their patients should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs." The AAFP also recommends that clinicians not use PSA to screen men who do not express a preference for screening, and men age 70 years and over.

PSA has a number of limitations, but most importantly:

- PSA is not cancer-specific and PSA levels can be increased by non-cancerous conditions such as benign prostatic enlargement (BPH) and prostatic inflammation or lower urinary tract infection.
- When PSA results are in the "gray zone," other factors such as age, family history, ethnicity and digital rectal examination factor into the shared decision-making discussion regarding prostatic biopsy.
- PSA does not distinguish high-grade from low-grade prostate cancer and is not prostate cancer-specific.

When PSA testing is requested by a patient in the primary care setting, an elevated PSA number typically prompts referral to a urologist (internal data) and an additional workup that may include repeat PSA testing, DRE (digital rectal examination), and other laboratory and prostate imaging tests such as an MRI or ultrasound before a decision on biopsy is made.

Digital rectal examination (DRE)

Widely used, but limitations exist

The digital rectal exam is used in conjunction with PSA, but it is limited by the subjective nature of the assessment and may vary with physician experience and specialty. A meta-analysis of 8,217 studies looked at DRE clinical value in the primary care setting and found that although DRE has low sensitivity of 0.51 (95% CI, 0.36-0.67; I2 = 98.4%) and low specificity 0.59 (95% CI, 0.41-0.76; I2 = 99.4%)[1]. In fact, AAFP recommends against its use:

"There are limited data on the value of DRE alone or in combination with PSA testing. Some RCTs evaluated DRE with PSA, but none evaluated DRE alone. Even in patients with elevated PSA levels, DRE did not influence the chance of detecting prostate cancer after eight years of follow-up.[2] Harms from DRE include discomfort and rectal bleeding".[3]

PSA prompts urology referral

Refer patients more accurately with more information

While PSA and DRE are screening tools for early detection of prostate cancer, their use is limited in the primary care setting due to lack of guideline recommendations from AAFP and USPSTF. When PSA is utilized as screening tool, it often prompts a urology visit, and it can be a bit of a guessing game as to who is the most appropriate for urology referral. Interestingly, urologists report seeing a high number of low-risk patients, including those who are unlikely to need immediate urology care. This leads to urologists spending too much time with patients who do not require treatment or procedures compared to high-risk patients who need urgent attention.

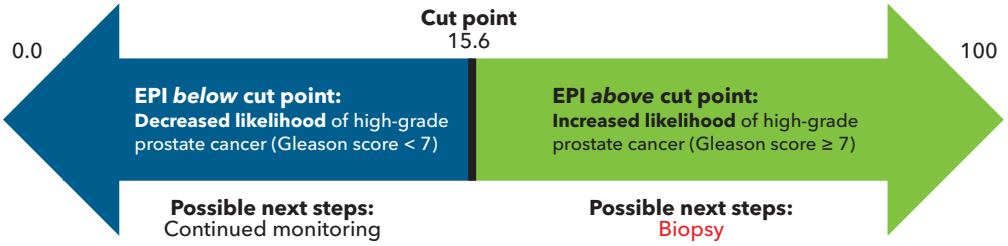
It's clear that primary care physicians would benefit from more specific tools to assist them in identifying men at highest risk of prostate cancer. The USPSTF and other guideline organizations, state that biomarkers, such as EPI, can improve the specificity of PSA in cancer detection for patients/physicians who wish to further define risk (*NCCN – National Comprehensive Cancer Network Guidelines 2019*).

The ExoDx™ Prostate Test (EPI)

Making more informed decisions

Eliminating the guesswork can be resolved with the ExoDx Prostate Test. The test analyzes prostate gene expression in very small extracellular vesicles called *exosomes*. These vesicles contain DNA, RNA and proteins, and are produced and secreted in large quantities from every cell in the body and can be found in urine and other bodily fluids. The ExoDx Prostate test is a risk assessment tool that assesses the risk of aggressive prostate cancer, with a result between 0 and 100 (*Figure 1 on the next page*)

Figure 1:
Interpreting the ExoDx Prostate Test score



Test scores range from 0 to 100, and are separate from standard of care factors to help assess a patient's risk for high-grade prostate cancer. The test has a sensitivity of 92% and NPV of 91.3%.

The ExoDx Prostate test is a non-invasive urine assay that does not require a digital rectal examination and analyzes three exosome-located genomic markers that are elevated in high grade prostate cancer (HGPCa). As reviewed in the National Comprehensive Cancer Network (NCCN) guidelines, the ExoDx Prostate Test is intended for use in men considering initial biopsy or repeat biopsy due to a prior negative biopsy, who are 50 years or older and have PSA levels between 2–10ng/mL. ExoDx Prostate helps make more informed decisions on which patients may likely benefit – or not – from a prostate biopsy.

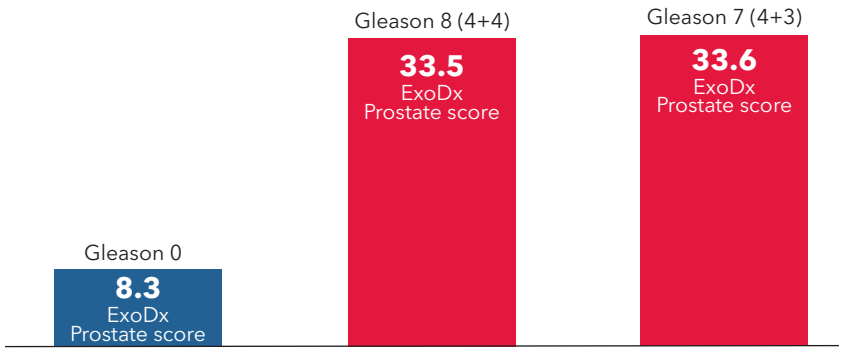
ExoDx Prostate Test value to the primary care physician

Refer patients likely to benefit

Currently, primary care physicians use PSA and existing clinical features such as age, ethnicity and family history to decide which patients should be referred to a urologist for a biopsy. However, PSA is notoriously nonspecific, and although other clinical features provide limited incremental value, it is often difficult to appropriately select patients for referral.

ExoDx Prostate can help PCPs make more informed urology referral decisions. Patients who look clinically identical will have different ExoDx Prostate scores with different levels of risk, which will result in different patient conversations and, ultimately, more informed shared decision-making (*Figure 2*).

Figure 2:
ExoDx Prostate Test scores of three clinically identical patients



All patients were biopsied.
No suspicious DRE.
No family Hx.

ExoDx Prostate Test validation

Robust, peer-reviewed data

The ExoDx Prostate Test gene signature was developed to examine exosome gene expression from three genes: PCA3 (prostate cancer antigen 3), ERG (V-ets erythroblastosis virus E26 oncogene homologs) and SAM-pointed domain-containing Ets transcription factor (SPDEF). The ExoDx Prostate Test was validated in two prospective large scale clinical validation studies – urine samples were collected from more than 1,000 biopsy-naive patients across 28 clinical sites, and the results were published in both the *Journal of the American Medical Association* and in *European Urology*.

ExoDx Prostate Test accuracy

Superior performance compared to existing clinical information

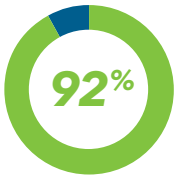
The ExoDx Prostate Test is significantly more accurate than any individual clinical feature or combination of features. In both clinical validation studies, the ExoDx Prostate Test was compared to PSA, an optimized standard of care model, and clinical risk calculators such as PCPT (Prostate Cancer Prevention Trial) and ERSPC (European Randomized study of Screening for Prostate Cancer). ExoDx Prostate testing was significantly more accurate than either optimized standard of care clinical models, risk calculators or PSA. Critically important, adding standard of care to ExoDx genomics did not improve test accuracy, meaning that the majority of prognostic information is captured by ExoDx Prostate gene expression.

ExoDx Prostate Test clinical utility

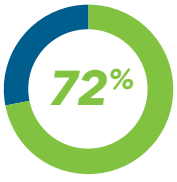
The right intervention for the right patient at the right time

The clinical utility of the ExoDx Prostate Test was studied in a unique prospective, blinded, randomized, controlled, multi-center prostate cancer utility trial, (NCT03235687) in partnership with CareFirst BlueCross/BlueShield. This real-world study included more than 1,090 patients and 72 urologists across 24 clinical sites with the goal of evaluating the ExoDx Prostate impact on shared clinical decision making between patients and physicians. The study had an ExoDx Prostate arm as well as a real-time, blinded standard of care control arm. ExoDx Prostate results were collected on all patients but physicians in the control arm were not provided ExoDx Prostate results: they used standard of care information to make shared biopsy decisions.

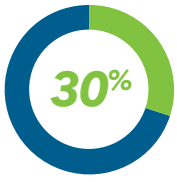
ExoDx Prostate Test use resulted in a significant increase in patient compliance with the physician biopsy recommendations and demonstrated the following key points:[4]



of patients complied to physician recommendation to defer biopsy due to The EPI Test based on the physician-patient shared decision



of patients complied to physician recommendation to proceed to biopsy due to The EPI Test based on the physician-patient shared decision making, compared to only 39% in the SOC control arm



more cases of clinically significant or high-grade prostate cancer were detected by physicians due to increased compliance, compared to the standard of care control arm

Expected impact on Accountable Care Organizations (ACOs)

Enhanced shared decision-making results in higher-quality care

ACOs might be especially interested due to the need for referring the right patients at the right time:

- ACOs provide coordinated care to ensure that patients get the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors.
- When an ACO succeeds both in delivering high-quality care and spending health care dollars more wisely, the ACO will share in the savings it achieves for the Medicare program.
- Health plans (payors such as Aetna, Cigna, etc.) own ACOs.

Conclusion

Right *patient*, right *intervention*, right *time*

PCPs are the gatekeepers for prostate cancer screening and first line of defense in the diagnosis and treatment of prostate cancer patients, but the tools at their disposal are limited. The ExoDx Prostate Test is a well validated urine genomic test that provides important risk assessment data that can help guide the right patient, at the right time for a prostate biopsy and can help with timely urology referral.

1. Naji L, Randhawa H, Sohani Z, Dennis B, Lautenbach D, Kavanagh O, Bawor M, Banfield L, Profetto J. Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A Systematic Review and Meta-Analysis. *Ann Fam Med.* 2018 Mar;16(2):149-154. doi: 10.1370/afm.2205. PMID: 29531107; PMCID: PMC5847354.
2. Gosselaar C, Roobol MJ, van den Bergh RC, Wolters T, Schröder FH. Digital rectal examination and the diagnosis of prostate cancer—a study based on 8 years and three screenings within the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. *Eur Urol.* 2009;55(1):139–146.
3. Qaseem A, Barry MJ, Denberg TD, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med.* 2013;158(10):761–769.
4. Tutrone R, Donovan MJ, Torkler P, Tadigotla V, McLain T, Noerholm M, Skog J, McKiernan J. Clinical utility of the exosome based ExoDx Prostate (IntelliScore) EPI test in men presenting for initial Biopsy with a PSA 2–10ng/mL. *Prostate Cancer and Prostatic Diseases.* May, 2020.

Exosome Diagnostics, Inc.
266 Second Ave., Suite 200
Waltham, MA 02451
www.exosomedx.com
844-EXOSOME (844-396-7663)
MKT 169

exosomedx™
a bio-techne® brand