

The Role of the ExoDx Prostate Test in Early Detection of Prostate Cancer

BY DAVID M. ALBALA, MD

PROSTATE CANCER IS the second leading cause of cancer in men globally, with more than 1 million new cases and 300,000 deaths attributed to this disease each year.¹ In 2021, an estimated 248,530 new cases of prostate cancer and approximately 34,130 prostate cancer deaths are expected in the United States.²

The COVID-19 pandemic resulted in unique clinical and real-world challenges in the screening, detection, and management of prostate cancer. Reductions in cancer screening in the United States led to delayed identification of men who may be at high risk of prostate cancer, leaving the population underdiagnosed and potentially undertreated.^{3,4} For example, estimates of new prostate cancer cases from the American Cancer Society (ACS) increased from 2020 to 2021 (191,930 and 248,530, respectively), suggesting lower detection, diagnoses, and treatment corresponding with COVID-19–related cancer screening deficits during the peak of the pandemic in 2020.^{2,5} Clinical care teams, from the primary care to urology settings, need to adopt and implement telehealth/telemedicine practices to address the cancer screening deficit associated with the COVID-19 pandemic.^{3,4}

There is an opportunity to implement prostate cancer biomarker testing to stratify patients into groups having high risk (combined Gleason Score ≥ 7 [3+4] or grade group 2+ [GG2+]) versus low risk of clinically significant prostate cancer. This risk stratification can help to overcome the lack of specificity of current prostate cancer screening tools (eg, prostate specific–antigen [PSA] testing, digital rectal examination [DRE]). This article highlights the ExoDx Prostate test, a urine liquid biomarker test that helps urologists identify patients who have a low versus high risk of clinically significant disease, independent of PSA testing and other standard of care parameters.⁶

UNMET CLINICAL NEEDS IN PROSTATE CANCER

PSA and DRE are primary tools used to screen men for prostate cancer; however, both have limitations.⁷ Whereas PSA screening may reduce prostate cancer mortality risk, it is associated with potential harm, including false-positive results,

overdiagnosis, and biopsy complications.⁸ Active surveillance has reduced rates of overtreatment, but serial biopsy follow-up can be burdensome, and contemporary screening strategies have focused on detecting clinically significant (GG2+) prostate cancers rather than indolent disease.^{8–10}

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The ACS recommends that PSA screening be considered; however, its benefits are debatable.^{8,11–14} The United States Preventive Services Task Force (USPSTF) and other organizations have expressed concern that use of PSA screening can lead to increased prostate cancer detection and overtreatment.^{8,11–13} In 2018, revised guidelines from the USPSTF recommended against PSA-based screening for prostate cancer in men aged 70 years and older and those who do not express a preference for screening. The guidelines also advised men aged 55 to 69 years to make an informed choice with their physicians by discussing whether PSA screening was right for them.⁸ The USPSTF and other organizations recommended against performing DRE in the primary care setting.^{8,11,12}

Limitations of PSA testing

PSA screening is not a standardized test that can be used in all circumstances to reliably indicate the presence of an aggressive prostate cancer (defined as GG2+).^{15,16} Often, other risk factors (eg, age, family history, ethnicity, DRE results)

are considered when a physician discusses prostatic biopsy with a patient to make a shared decision.^{17,18}

Notably, PSA screening has several other limitations. It does not distinguish between high- and low-grade prostate cancer.¹² It is not prostate cancer–specific; in fact, it offers low sensitivity and specificity for prostate cancer.^{15,19,20} Additionally, PSA levels can be elevated by noncancerous conditions, such as benign prostatic hyperplasia (enlargement), prostatic inflammation, and lower urinary tract infection and instrumentation.^{7,8,21}

COVID-19–related cancer screening deficits

Two recent peer-reviewed studies demonstrated a marked reduction in prostate cancer screening during the COVID-19 pandemic.^{3,4} These findings highlighted the unmet clinical need for improved identification of men at risk for a prostate cancer diagnosis. The investigators recommended that tools be adopted to help discriminate those at high risk from those at low risk of prostate cancer and prioritize them for diagnostic biopsy and treatment. In addition, they noted that screening biomarkers that do not require an in-person office visit are needed.³

A retrospective cohort study of single-payer United States administrative claims data from approximately 60 million people within Medicare Advantage and commercial health plans identified a reduction in prostate, breast, and colorectal cancer screening rates during the COVID-19 pandemic.³ When compared with screening rates in 2019, screening for all 3 cancers declined sharply from March 2020 to May 2020. A 63.4% reduction in prostate cancer screening was observed in April 2020 among the cohort of men aged 50 to 69 years identified to evaluate monthly prostate screening rates. Despite near-complete recoveries in monthly screening rates by July 2020 across these cancer types, an estimated screening deficit remained that affected 9.4 million Americans in 2020, including 1.6 million men for prostate

screening.³ A multivariable analysis of this data showed that telehealth use was associated with more cancer screening.³

A separate study reinforced the challenges noted during the COVID-19 pandemic that resulted in cancer screening deficits.⁴ During a 3-month primary pandemic study period from March 2020 to June 2020, there was a 63.4% reduction in prostate cancer screening when compared with 3 control periods.⁴ In addition, there was a 20% to 30% reduction in cancer diagnoses during the 3-month primary pandemic study period. A total of 1438 diagnoses of cancerous and precancerous lesions were “missed” when the primary pandemic period was compared with the control periods (1985 vs 3423 diagnoses, respectively).⁴ The percentage of positive PSA screening tests was 13.2% lower during the primary pandemic period (9.9%) than during the 3 control periods (22.7%).⁴

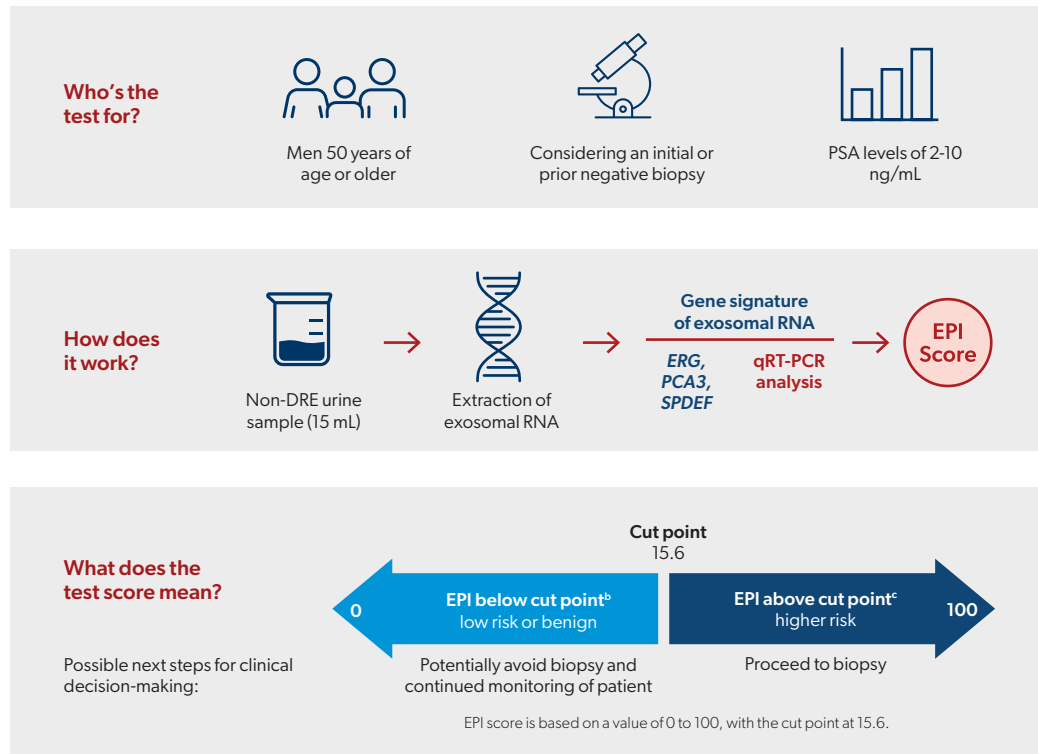
Overall, the results from this study highlighted the gap in the identification of men who may be at high risk of prostate cancer and remain underdiagnosed and potentially undertreated because of the COVID-19–driven screening deficit.³ These cancer screening deficits in the United States suggest that urologists should consider adopting telehealth/telemedicine practices, especially with progression of and/or status changes that may arise during the course of the continued COVID-19 pandemic, such as the emerging delta variant and its care complications.

EXODX PROSTATE TEST

The ExoDx Prostate test is a simple, non-DRE, urine-based, liquid biomarker test indicated for men aged 50 years and older with PSA levels between 2 and 10 ng/mL who are considering an initial biopsy or for men who received prior negative biopsy results and are considering a repeat biopsy.^{6,18}

The ExoDx Prostate test provides a personalized risk score to assess whether or not clinically significant prostate cancer will be found on biopsy. This risk assessment tool affords greater confidence for identifying high-grade prostate cancer than supplied by PSA screening alone. The ExoDx Prostate test is designed to alleviate clinical uncertainty by providing a standardized approach for assessing the risk of aggressive prostate cancer.¹⁵⁻¹⁸

FIGURE 1. ExoDx Prostate Test Clinical Workflow^{6,a}



DRE, digital rectal examination; EPI, ExoDx Prostate *IntelliScore*; PSA, prostate-specific antigen; qRT-PCR, quantitative reverse transcription–polymerase chain reaction.

^aThe test was developed as a rule-out test with 91.3% negative predictive value and 92% sensitivity in the initial biopsy cohort.

^bEPI result below cut point: Decreased likelihood of high-grade prostate cancer (Gleason Score <7).

^cEPI result above cut point: Increased likelihood of high-grade prostate cancer (Gleason Score ≥7).

The ExoDx Prostate test helps clinicians and patients to make a more informed prostate biopsy decision. It can be used in the primary-care setting to prioritize highest risk patients for early urologic referral for prostate biopsy. Moreover, the results can be used to support urologists and their patients to feel confident about decisions to proceed with a biopsy, to help reassure a patient about avoiding a prostate biopsy, and to improve patient compliance with physician recommendation for biopsy.^{6,15,16,18}

Risk assessment score

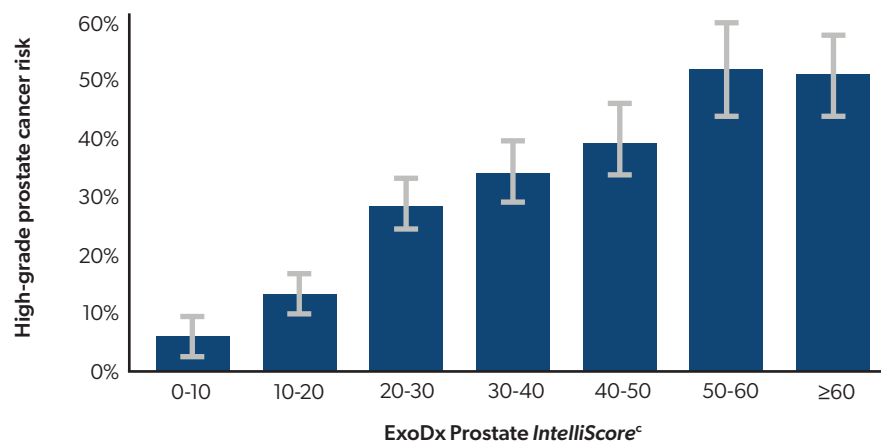
The ExoDx Prostate test provides unique, actionable information about risk stratification that is independent of PSA and other standard-of-care clinical features. This risk stratification liquid biomarker

is emerging as an important component of clinical practice and utility in the shared decision-making discussion about biopsy.^{15,16,18,19}

The ExoDx Prostate test analyzes 3 exosome-located genomic biomarkers that become elevated in high-grade prostate cancer.^{18,22} The ExoDx Prostate *IntelliScore* (EPI) gene signature measures exosome RNA levels of 3 genes—*PCA3*, *ERG*, and *SPDEF*—linked to high-grade, aggressive prostate cancer.^{18,22} The RNA expression levels of these 3 genes are incorporated into an equally weighted proprietary algorithm and a personalized risk score.¹⁸

The workflow for this test is provided in **Figure 1**.⁶ Advanced purification techniques are used to isolate RNA from exosomes in the “first-catch” urine specimen (15 mL) without the need for a prior DRE. Exosomes are small,

FIGURE 2. ExoDx Prostate *IntelliScore* Correlates With Incidence of Clinically Significant Prostate Cancer^{15,18,a,b}



^aPooled data collected from more than 1000 patients showed the likelihood of finding high-grade prostate cancer on biopsy in the intended-use population (males aged 50 years and older with a prostate specific-antigen level of 2-10 ng/mL who present with initial biopsy).

^bClinically significant is defined as a combined Gleason Score ≥ 7 (3+4) on prostate biopsy.

^cScores on a range from 0 to 100; cut-off point of 15.6.

double lipid-membrane vesicles (typically, 30-200 nm in diameter) that are a rich source of cellular protein, DNA, and RNA.^{18,22} RNA is extracted from urine exosomes to analyze the expression of *PCA3*, *ERG*, and *SPDEF*.^{18,22}

The ExoDx Prostate test returns a personalized risk score ranging from 0 to 100 to help assess a man's risk for high-grade, clinically significant prostate cancer.¹⁸ An EPI result below the cut-off point of 15.6 is associated with a lower likelihood of high-grade prostate cancer; on the other hand, an EPI result above the validated cut-off point of 15.6 is associated with an increased likelihood of high-grade prostate cancer.^{18,22}

As shown in **Figure 2**, pooled data collected from more than 1000 patients showed the likelihood of finding high-grade prostate cancer on biopsy in the intended-use population of males aged 50 years and older with a PSA level of 2-10 ng/mL who are presenting with initial biopsy. The EPI score correlates with the incidence of clinically significant prostate cancer (defined as a combined Gleason Score ≥ 7 [3+4] on prostate biopsy) and can be thought of as a percentage risk of high-grade clinically significant prostate cancer up to a maximum of ExoDx scores.^{15,18}

CLINICAL EVIDENCE

Peer-reviewed validation studies

The EPI gene signature was validated in 2 prospective, large-scale, clinical validation studies. First-catch urine samples were collected from more than 1000 biopsy-naive patients (men aged ≥ 50 years with a PSA of 2-10 ng/mL) who presented for initial biopsy across 28 clinical sites.^{15,18,22} The results were published in *JAMA Oncology* and *European Urology*.^{15,18}

The results from the ExoDx Prostate test were compared with those of PSA screening and 2 clinical risk calculators (ie, Prostate Cancer Prevention Trial Risk Calculator and European Randomized Study for Screening Prostate Cancer Risk Calculator). The ExoDx Prostate test outperformed PSA and both risk calculators for clinically significant prostate cancer and was shown to be an independent, stand-alone risk assessment tool.¹⁸ The ExoDx Prostate test score demonstrated improved accuracy in the test population; PSA level alone had an area under the curve (AUC) of 0.55 (95% confidence interval [CI], 0.49-0.60) compared with ExoDx Prostate test without standard of care, which had an AUC of 0.71 (95% CI, 0.66-0.75) in the same population.

Standard of care with ExoDx genomic testing had an AUC of 0.73 (95% CI, 0.68-0.77). The Prostate Cancer Prevention Trial Risk Calculator had an AUC of 0.62 (95% CI, 0.57-0.67), and the European Randomized Study for Screening Prostate Cancer Risk Calculator had an AUC of 0.58 (95% CI, 0.52-0.63).¹⁸

Results of the first validation study demonstrated that use of the ExoDx Prostate test was associated with improved identification of higher-grade prostate cancer among men with elevated PSA levels and could reduce the total number of unnecessary biopsies. It discriminated men with high-grade (Gleason Score ≥ 7 [3+4] prostate cancer on a biopsy) cancer from men with low-grade cancer and biopsy benign disease (Gleason Score = 6).¹⁸ An EPI score above the 15.6 cut-off point in the intended-use population identified clinically significant prostate cancer when compared with an EPI score below that cut-off point. With an EPI score cut-off point of greater than 15.6, the urine exosome gene expression assay demonstrated good clinical performance in predicting a prostate cancer of Gleason Score of 7 or more and showed that 27% of unnecessary biopsies would have been avoided with use of this diagnostic in patients with PSA levels of 2 to 10 ng/mL.¹⁸

In the second validation study, the ExoDx Prostate test helped to stratify risk among men given a diagnosis of prostate cancer of grade 2 or greater or grade 1 or benign disease.¹⁵ The ExoDx Prostate test was significantly more accurate than any individual clinical feature or combination of features. It was superior to optimized standard-of-care clinical models, results of 2 risk calculators, and PSA determination alone for predicting grade 2 prostate cancer.¹⁵ The test had a negative predictive value of 97% for ruling out disease having a combined Gleason Score of 7 or more (4+3) based on the findings of validation studies.^{15,18}

Clinical utility study

The ExoDx Prostate test was evaluated in a unique prospective, blinded, randomized, controlled, multicenter prostate cancer utility and decision impact study performed in partnership with CareFirst BlueCross/BlueShield (NCT03235687). This is the first prospective prostate biomarker trial to have a blinded control arm.¹⁶ This

real-world study involved 72 urologists across 24 clinical sites (ie, the Large Urology Group Practice Association Group) and more than 1000 subjects to evaluate the impact of the ExoDx Prostate test on shared clinical decision-making between patients and physicians.¹⁶

A total of 1094 men aged 50 years and older with a PSA level of 2 to 10 ng/mL scheduled for initial prostate biopsy were enrolled. Patients were randomized to either the ExoDx Prostate test arm (n=458) or the real-time, blinded, standard-of-care control arm (n=484).¹⁶ ExoDx Prostate test results were collected for the population of both arms. Urologists in the control arm were blinded to the ExoDx Prostate test results and used standard of care to make shared biopsy decisions. In the ExoDx Prostate test arm, results from the diagnostic were shared with both urologists and patients and used for shared decision-making about the need for biopsy. ExoDx Prostate test and biopsy results were collected, and patients were followed for up to 5 years to monitor decision-making and the impact of the diagnostic.¹⁶

The results demonstrated that use of the ExoDx Prostate test improved compliance with the urologist's biopsy recommendations. Patients demonstrated improved compliance with the physician's recommendation to defer prostate biopsy when the EPI score was below the cut-off point of 15.6 and to proceed with biopsy when the EPI score was above 15.6.¹⁶ In fact, 92% of patients in the group that had a test score below 15.6 complied with the urologist's recommendation to defer biopsy based on the EPI test result and physician-patient shared decision-making.¹⁶ In the group that had a test score above 15.6, 72% of patients complied with the physician's recommendation to proceed with biopsy based on both the EPI test results and physician-patient shared decision-making, resulting in a higher biopsy rate in the EPI arm vs the standard of care control arm (72% vs 39%, respectively).¹⁶

In the ExoDx Prostate test study arm, 30% more clinically significant cancer cases were detected among patients with higher EPI scores.¹⁶ Men with an ExoDx Prostate test score above the cut-off point of 15.6 were more likely to have clinically significant cancer when compared with those having a score below 15.6.¹⁶ In all, 72% of patients in the EPI arm and 39% of those in the control arm underwent biopsy; further, 30% more cases of clinically significant or high-grade prostate cancer were identified

among patients in the EPI arm than among those evaluated with standard of care.¹⁶

Overall, the results from this real-world clinical utility study showed that use of the ExoDx Prostate test was associated with improved identification of clinically significant cancer among men with elevated PSA levels.

“...72% of patients complied with the physician's recommendation to proceed with biopsy based on both the EPI test results and physician-patient shared decision-making, resulting in a higher biopsy rate in the EPI arm vs the standard of care control arm (72% vs 39%, respectively).”

ExoDx Prostate test performance in prior negative biopsy settings

Results using the 15.6 cut-off point of the ExoDx Prostate test also have helped to rule out high-grade prostate cancer in men with a PSA level of 2 to 10 ng/mL and a prior negative prostate biopsy.¹⁷

CONSIDERATIONS FOR UROLOGISTS

Whereas PSA testing is routine and a standard part of screening for prostate cancer, the 2018 USPSTF guidance against PSA testing and the conflicting outcomes of 2 clinical trials for PSA screening have created uncertainty about its usefulness in helping patients and their physicians decide to proceed with a prostate biopsy.⁷ The ExoDx Prostate test is a noninvasive urine assay that does not require a DRE and that can be used to assess the risk of high-grade prostate cancer in men aged 50 years and older who have a PSA level of 2 to 10 ng/mL and are considering initial or repeat prostate biopsy. Clinical validation and

utility studies support the effectiveness and value of the ExoDx Prostate test in assessing the risk of high-grade prostate cancer.⁶

In the urology setting, the ExoDx Prostate test enhances the specificity of PSA in identifying high-grade prostate cancer. The ExoDx Prostate test can help urologists decide whether biopsy is necessary independent of PSA results and other standard-of-care features. Results of the test can help urologists and their patients feel confident in their decision to proceed with a biopsy. In a clinical utility study, use of the ExoDx Prostate test improved compliance with physician recommendations, including the decision to undergo a biopsy.⁶ It may also be used in the primary setting to triage high-risk patients for referral to a urologist for help with the biopsy decision.⁶

In response to COVID-19 pandemic-related cancer screening deficits, it is important for urologists to consider telehealth strategies such as the ExoDx Prostate Test: At-Home Collection Kit to increase cancer detection and aid decision-making.^{3,6} Urine for this test can be collected at any time of the day without the need to visit an office or lab.⁶ Adoption of a telehealth solution may also help to reduce administrative burdens on urology office staff as well as various practical in-office health care staffing challenges (eg, workload, responsibilities) that were introduced as a result of the COVID-19 pandemic.

As part of the shared decision-making process, urologists can provide patients with downloadable resources and educational materials available at <https://www.exosomedx.com/> to support patient discussions and shared decision-making. These materials, which include a clinician brochure and 2 patient brochures that provide a high-level overview of the diagnostic, can help support patients in deciding whether use of the ExoDx Prostate test is the right choice for them. ●

AUTHOR BIO



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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-249. doi:10.3322/caac.21660
2. Prostate Cancer Research Highlights. American Cancer Society. Accessed September 20, 2021. <https://www.cancer.org/research/acs-research-highlights/prostate-cancer-research-highlights.html>
3. Chen RC, Haynes K, Du S, Barron J, Katz AJ. Association of cancer screening deficit in the United States with the COVID-19 pandemic. *JAMA Oncol.* 2021;7(6):878-884. doi:10.1001/jamaoncol.2021.0884
4. Bakouny Z, Paciotti M, Schmidt AL, Lipsitz SR, Choueiri TK, Trinh QD. Cancer screening tests and cancer diagnoses during the COVID-19 pandemic. *JAMA Oncol.* 2021;7(3):458-460. doi:10.1001/jamaoncol.2020.7600
5. Cancer Facts and Figures 2020. American Cancer Society. Revised June 2020. Accessed August 9, 2021. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf>
6. ExoDX Prostate Intelliscore (EPI) clinician brochure. Exosome Diagnostics. September 2020. Accessed August 26, 2021. https://www.exosomedx.com/sites/default/files/2020-09/Clinician%20brochure_September%202020.pdf
7. Mulhem E, Fulbright N, Duncan N. Prostate cancer screening. *Am Fam Physician.* 2015;92(8):683-688. <https://www.aafp.org/afp/2015/1015/p683.html>
8. Grossman DC, Curry SJ, Owens DK, et al; US Preventive Services Task Force. Screening for prostate cancer: US preventive services task force recommendation statement. *JAMA.* 2018;319(18):1901-1913. doi:10.1001/jama.2018.3710
9. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360(13):1310-1319. doi:10.1056/NEJMoa0810696
10. Schröder FH, Hugosson J, Roobol MJ, et al; ECRSP Investigators. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet.* 2014;384(9959):2027-2035. doi:10.1016/S0140-6736(14)60525-0
11. Clinical preventive service recommendation: prostate cancer. American Academy of Family Physicians. Published July 20, 2018. Accessed August 10, 2021. <https://www.aafp.org/family-physician/patient-care/clinical-recommendations/all-clinical-recommendations/prostate-cancer.html>
12. 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. doi:10.7326/0003-4819-158-10-201305210-00633
13. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol.* 2013;190(2):419-426. doi:10.1016/j.juro.2013.04.119
14. American Cancer Society recommendations for prostate cancer early detection. American Cancer Society. Updated April 23, 2021. Accessed August 26, 2021. <https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/acs-recommendations.html>
15. McKiernan J, Donovan MJ, Margolis E, et al. A prospective adaptive utility trial to validate performance of a novel urine exosome gene expression assay to predict high-grade prostate cancer in patients with prostate-specific antigen 2-10ng/ml at initial biopsy. *Eur Urol.* 2018;74(6):731-738. doi:10.1016/j.eururo.2018.08.019
16. Tutrone R, Donovan MJ, Torkler P, et al. 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 Prostatic Dis.* 2020;23(4):607-614. doi:10.1038/s41391-020-0237-z
17. McKiernan J, Noerholm M, Tädigotla V, et al. A urine-based exosomal gene expression test stratifies risk of high-grade prostate cancer in men with prior negative prostate biopsy undergoing repeat biopsy. *BMC Urol.* 2020;20(1):138. doi:10.1186/s12894-020-00712-4
18. McKiernan J, Donovan MJ, O'Neill V, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. *JAMA Oncol.* 2016;2(7):882-889. doi:10.1001/jamaoncol.2016.0097
19. Loeb S, Catalona WJ. The Prostate Health Index: a new test for the detection of prostate cancer. *Ther Adv Urol.* 2014;6(2):74-77. doi:10.1177/1756287213513488
20. Hoffman RM. Clinical practice. Screening for prostate cancer. *N Engl J Med.* 2011;365(21):2013-2019. doi:10.1056/NEJMcp1103642
21. Prostate-specific antigen (PSA) test. National Cancer Institute. Updated February 24, 2021. Accessed August 27, 2021. <https://www.cancer.gov/types/prostate/psa-fact-sheet>
22. Donovan MJ, Noerholm M, Bentink S, et al. A molecular signature of PCA3 and ERG exosomal RNA from non-DRE urine is predictive of initial prostate biopsy result. *Prostate Cancer Prostatic Dis.* 2015;18(4):370-375. doi:10.1038/pcan.2015.40