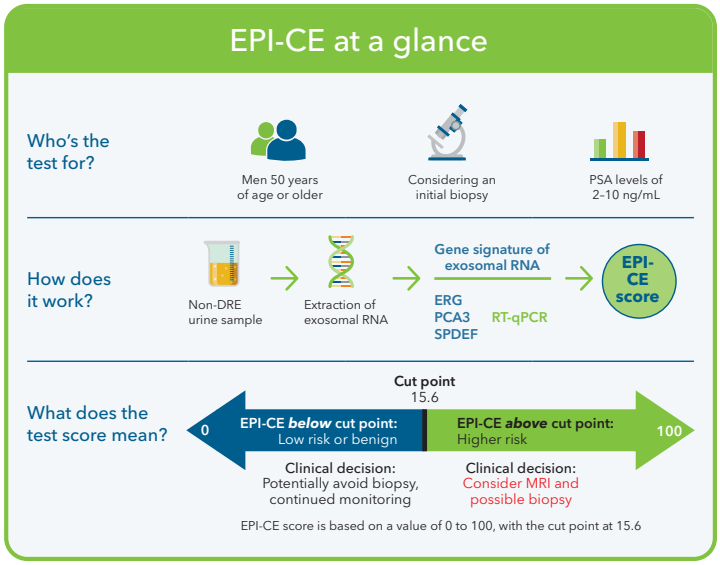
ExoDx™ Prostate *IntelliScore* (EPI-CE)

A simple urine test for risk assessment of high-grade prostate cancer (HGPCa)

Introducing the first and only exosomal molecular test that relies on genomic information to provide risk assessment for HGPCa. The EPI-CE Test was developed to assist physicians to reduce unnecessary biopsies,* and can be used as a risk assessment tool prior to MRI to determine if biopsy decision is warranted.

EPI-CE at a glance



The EPI-CE test is based on the well-established ExoDx™ Prostate Test that has successfully operated from ExoDx's CLIA facility in the U.S. since 2016, and is reimbursed by several leading insurance providers. Both tests share the same specimen requirements, exoRNA isolation methodology, RT-qPCR detection of biomarkers and algorithm for risk score calculation. The EPI-CE test has been further developed for distribution and use in third-party clinical laboratories in the EU and comprises a ready-to-use CE-IVD assay reagent kit and cloud-based CE-IVD software to facilitate risk score calculation.

The EPI-CE test was developed as a rule-out test 89% negative predictive value (NPV) and 92% sensitivity in the initial biopsy cohort) compared to the U.S. ExoDx Prostate test with a negative predictive value (NPV) of 91.3% of 92% sensitivity. Prostate cancer is the second leading cause of cancer in men, with over 1 million new cases and 300,000 deaths.[1] In Europe, PCa has now become the most frequently diagnosed cancer among men and the second leading cause of male cancer death.[2]

*Data on file, Exosome Diagnostics, 2021.

The unmet clinical need in prostate cancer.

Although Prostate Specific Antigen (PSA) screening is part of standard of care (SOC), its benefits have caused debate in recent years. The United States Preventive Services Task Force (USPSTF) changed its guidelines in 2018, advising men 55–69 years to make an informed choice and discuss with their doctor whether PSA screening is right for them, while recommending *against* screening for men over 70 years of age.[3] This change in guidance came about after a review of published data of 1.9 million men on the use of PSA testing to screen for cancer, based on the potential harms and benefits for PSA screening.

Limitations of PSA might include:

- Low sensitivity and specificity for prostate cancer
- PSA levels can be increased by benign prostatic hyperplasia (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 (DRE) factor into the shared decision-making discussion regarding prostatic biopsy
- PSA cannot distinguish high-grade from low-grade cancer and is not prostate cancer-specific.

FOR USE IN MEN WHO:

- Are age 50 and above
- Have PSA 2-10 ng/mL (Gray Zone)
- Are considering an initial biopsy
- Have not had an MRI performed

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Importantly, increased detection of prostate cancer has led to potentially unnecessary biopsies and overtreatment. The EPI-CE Test allows for greater confidence to identify high-grade prostate cancer (GS7 and above) in patients.

- Utilized in more than 60,000 patients in the U.S.
- The ExoDx Prostate test has been prospectively validated in two studies totaling 1,022 men
- Test algorithm independent of PSA and standard clinical parameters
- Complementary tool to clinical information
- Simple urine test that can be collected any time of day
- Publications in top-tier peer-reviewed journals: *JAMA Oncology*, *European Urology* and *Prostate Cancer and Prostatic Diseases*
- No DRE required prior to urine collection
- Excellent value for men interested in determining their personalized risk score prior to MRI
- Results quickly available in 2–3 business days

When there is uncertainty about proceeding with a biopsy, the EPI-CE Test may be a solution.
Clinical studies show The EPI-CE Test can potentially help avoid 34% of unnecessary biopsies.* EPI-CE results can be part of your best practices to send the ***right patient*** to the ***right intervention*** at the ***right time***.

In a European IVD validation study, the ExoDx Prostate EPI-CE Test was validated in a multi-center study with 109 patients enrolled from 11 clinical sites in Europe and the U.S.

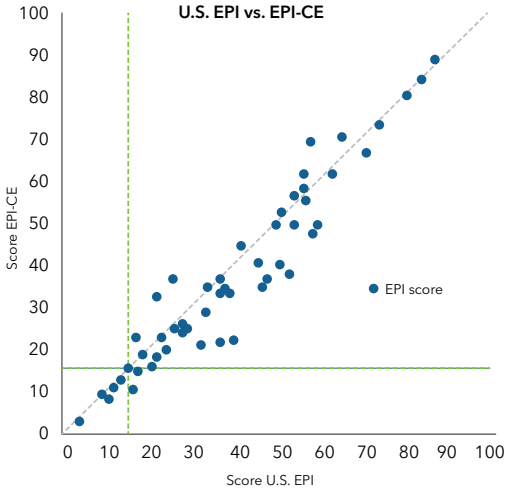
	EPI-CE (IVD) Mean (CI 95%)	EPI (U.S.)* Mean (CI 95%)
Sensitivity	**92%** (79–98)	**92%** (91–95)
Specificity	**34%** (23–46)	**30%** (27–33)
NPV	**89%** (71–98)	**91%** (87–94)
PPV	**43%** (32–54)	**37%** (34–39)

*Clinical performance from the ExoDx Prostate EPI-CE (IVD) European validation study, compared to a pooled analysis of two previously published U.S. studies:

Study 1: A Novel Urine Exosome Gene Expression Assay to Predict High-Grade Prostate Cancer at Initial Biopsy, *JAMA Oncology* | July 2016. Authors: McKiernan J, Donovan MJ, O'Neill V, Bentink S, Noerholm, M, Belzer Skog J, Kattan MW, Partin A, Andriole G, Brown G, Wei JT, Thompson IM Jr, Carroll P.

Study 2: 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 2–10 ng/ml at Initial Biopsy. *European Urology* | September 2018. Authors: McKiernan J, Donovan MJ, Margolis E, Partin A, Carter B, Brown G, Torkler P, Noerholm M, Skog J, Shore N, Andriole G, Thompson I, Carroll P.

Test performance was comparable to previous performance data published from U.S. studies. Publication of the European validation study is currently pending.

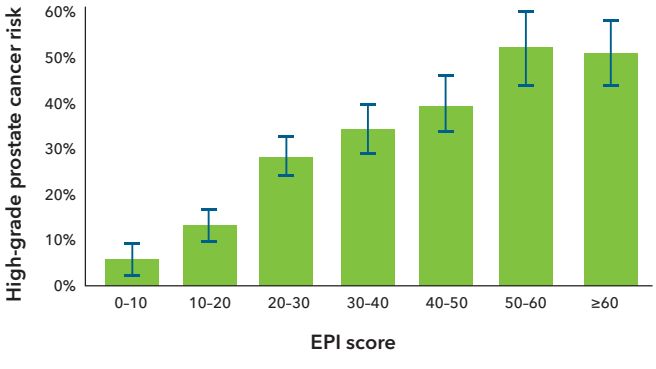


- Same EPI score for EPI-CE as the U.S. EPI available in the USA, which has been performed in >60,000 men
- EPI-CE uses an updated assay chemistry, but the same biomarkers as U.S. EPI
- The U.S. EPI has been extensively validated in >1,200 patients

Interpreting the EPI score

Scores from the ExoDx Prostate Test range from 0 to 100, with the cut point at 15.6. Score ranges are proportional to increased likelihood for HGPCa.

Likelihood of finding HGPCa on biopsy in intended use population[4,5]



Key points:

- Every patient in this data is in the intended use population (PSA 2–10ng/mL, presenting with initial biopsy, and 50 years and above)
- Consider age group and other standard of care factors when interpreting the results

Frequently asked questions

The EPI-CE Test came back at "Higher Risk" but a biopsy result came back negative. How should I interpret this result?	The purpose of The EPI-CE Test is to rule out patients who don't need a biopsy. If you are below the 15.6 cut point, you have a very low chance of finding high-grade cancer upon biopsy. The chance of finding high-grade cancer upon a biopsy is illustrated in the graph on the opposite page.
What is the Negative Predictive Value (NPV)?	Negative Predictive Value is a statistical measure that says how confident we are about a negative outcome. In the initial biopsy population, the NPV is 89%, at a cut point of 15.6.
What is the sensitivity of The EPI Test?	The sensitivity of The EPI-CE Test is 92% in the initial biopsy population. The sensitivity measures the proportion of high-grade prostate cancer (≥GS7) that are correctly identified as positive.
What is the cut-point used to determine high risk vs. lower risk?	The EPI-CE Test has been validated using a cut point of 15.6 to determine when patients are at lower risk for high-grade prostate cancer, defined as Gleason 7(3+4) or Grade Group 2 or higher. Patients with an EPI-CE score below this cut point have a very low risk of having high-grade prostate cancer.
Does The EPI-CE Test distinguish between GS6 and GS7 and higher prostate cancer?	Yes. The EPI Test is optimized as a rule-out test to distinguish high-grade prostate cancer (defined as GS7 and above) from low-grade prostate cancer. Patients above the cut point of 15.6 are associated with high risk of high-grade prostate cancer. Patients below the cut point of 15.6 are associated with lower risk of high-grade prostate cancer. Reference the graph on the opposite page to see the likelihood of finding HGPCa in the intended use population.
Is the score a percentage of risk?	Recent data presented on the U.S. EPI Test at ASCO GU 2019 clearly demonstrated that the EPI score is proportional to increased risk of finding HPGC upon biopsy. For example, an EPI score of 50 is associated with a 50% risk of finding HGPC upon biopsy (see the chart on the opposite page). The risk should be considered within the context of other patient parameters. A score of 60 or higher is not demonstrated to have higher risk of finding HPGC upon biopsy than a score of 50.
Should patients use your collection cup?	The prostate biomarkers we are looking for have the highest concentration in the "first catch" urine sample, which is the first 15 mLs of the void and is mostly from the prostate. Urine for isolation of exosomal RNA must be first catch (FC) with a minimum volume of 10 mL and a maximum volume of 50 mL, derived from the intended use population. To maximize urine input consistency, Exosome Diagnostics recommends collection of urine in a dedicated, validated FC collection device such as the ColliPee Device (Novosanis, Cat. #: N00055).
Which RNA biomarkers are analyzed?	PCA3, ERG and SPDEF.
What should I do if the patient voided 30 minutes ago?	Please have the patient wait at least one full hour before providing a new sample. The EPI-CE Test is most accurate when there is sufficient signal in the urine sample, which occurs with the first catch.

Experience the power of exosomes

Strength of the test	EPI-CE	Select MDx[6]	PCA3[7]
Based on proprietary algorithm	●	●	●
Risk assessment for prostate cancer	●	●	●
Non-invasive urine test	●	●	●
Genomic market test	●	●	●
PSA excluded from algorithm	●	●	●
Standard of Care (SoC) parameters/clinical risk factors excluded from algorithm	●	●	●
No DRE required	●	●	●

1. Ferlay, J et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015.
2. Van Poppel, H et al. Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission. European Association of Urology 2021.
3. USPSTF Final Recommendation Statement Prostate Cancer Screening: wwwuspreventiveservicestaskforce.org, 2018.
4. McKiernan J, Donovan M, et al. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. *JAMA Oncology*, July 2016.
5. McKiernan J., and Donovan, M. *et al.*, A Prospective Adaptive Utility Trial to Validate Performance of a Novel Urine Exosome Gene Expression Assay to Predict Exosome Gene High-grade Prostate Cancer in Patients with Prostate-specific antigen 2-10ng/ml at Initial Biopsy, *Eur Urol*, 2018.
6. Haese A. et al. Multicenter Optimization and Validation of a 2-Gene mRNA urine test for Detection of Clinically Significant Prostate Cancer before Initial Prostate Biopsy. *J Urol*. 2019.
7. Progensa PCA3 Assay Instructions For Use Rev002; https://www.hologic.com/sites/default/files/2018-11/502083-IFU-PI_002_01.pdf.

The EPI-CE test was developed by Exosome Diagnostics, Inc. according to the European Union directive for in-vitro diagnostic devices IVDD (98/79/EC) and the performance characteristics determined by Exosome Diagnostics, Inc. The test performance has been verified in Exosome Diagnostics GmbH's clinical laboratories in Martinsried, Germany. Exosome Diagnostics GmbH is accredited by Dakks to ISO 15189. Exosome Diagnostics and ExoDx are registered trademarks of Exosome Diagnostics, Inc

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