HALŌ DIAGNOSTICS

# Advances in Diagnosing and Treating Prostate Cancer

## Improved Outcomes and Patient Experience.


**SUMMARY**

- Prostate-specific antigen (PSA) testing alone results in unnecessary biopsies which have real risks including hospitalization.
- When combined, PSA along with high quality prostate mpMRI, targeted biopsies, and genomic tests have shown to miss 0% of clinically significant prostate cancer and help patients make a data-driven decision to undergo biopsy.
- Real time MRI-guided biopsies miss ≤10% of clinically significant cancers versus the standard of care transurethral ultrasound (TRUS) biopsies which miss 30-40%.
- A radical prostatectomy (part of the current standard of care) is the most commonly recommended treatment by urologists and carries a 50% risk of erectile dysfunction (ED) and a 25% risk of incontinence. Laser focal therapy at HALO centers resulted in ≤1% ED and incontinence.


The United States Preventive Services Task Force (USPSTF) recommends prostate cancer screening in men aged 55-69 years annually based on individual decision.  Recent data also suggests a baseline serum prostate specific antigen test (PSA) at age 40 – 54 among men with a higher risk of disease, including those with a family history of prostate cancer. The USPSTF also recommends against screening in men older than 70 as the harmful effects of screening and side effects from treatment may  outweigh the benefits in these individuals.

High serum PSA levels may indicate the likelihood of prostate cancer, although the test is not a definitive diagnostic tool. If the prostate gland volume is known (through MRI or ultrasound), it can be used to derive a patient's PSA density, a known predictor of clinically significant prostate cancer.

The PSA test was approved by the U.S. Food and Drug Administration (FDA) for prostate cancer screening in 1994., However, the FDA disapproves of PSA screening as a standalone test, and physicians often combine it with a digital rectal exam (DRE) for risk assessment. A DRE is best at detecting posterior peripheral prostate tumors and will most often completely miss tumors in the anterior gland. Though both the PSA test and DRE lack specificity, when combined they would provide a more holistic view in consideration with other risk factors, including family history and ethnicity.

The PSA test has proven controversial over the years, receiving no shortage of negative publicity. PSA is not specific to prostate cancer, and individual levels fluctuate due to a variety of reasons. Physical and sexual activity, and conditions such as benign prostatic hyperplasia (BPH), prostatitis, infection, inflammation, etc., can increase serum PSA levels. Certain medications, such as statins (medications that lower cholesterol) and alpha-reductase inhibitors can significantly lower PSA levels.

## Defining Threshold Values for Population-Based Screening

Fundamentally, screening differs from diagnostics in that screening is population-based and targeted to healthy at-risk individuals with no symptoms, or prior disease history who may or may not pursue a medical prognosis. Diagnostic testing is performed on individuals who screened positive for abnormalities to determine presence or absence of disease.

Population-wide screening requires a clear threshold or cut-off point for precise evaluation. The threshold value for serum PSA tests is widely debated. Most cases of prostate cancer screening are recommended for biopsy if the PSA level is 4ng/ml or higher. The Prostate Cancer Prevention Trial (PCPT) demonstrated that a cutoff of 1.6 ng/ml of PSA was required to achieve a sensitivity of 84% in predicting prostate cancer.

## The Role of Primary Care Providers In Screening

Primary Care Providers (PCPs), often internal medicine and family care practitioners, are responsible for the vast majority of serum PSA test referrals (nearly 90%). Patient education is still far from ideal, and most men in the susceptible age range may only opt for screening if their PCPs recommend doing so. Perhaps further complicating matters, the minimum age for screening is based on familial history and ethnicity.

Based on this data, it stands to reason that clarity on prostate cancer screening guidelines is needed to help guide patients through the decision-making process.

Recent recommendations and guidelines published by different associations:

1. **1. The USPSTF** made a final recommendation (May 2018) about PSA-based screening in men between 55 and 69 years of age, using individual decision making based on a conversation between the patient and their physician regarding the risks and benefits of PSA screening. This significantly increases the workload of the physician, and oftentimes, these conversations do not happen.
2. **The American Cancer Society (ACS)** recommends men make an informed decision with their PCP or other healthcare provider whether to be screened after considering the following risk factors:
    - Age 50 for average-risk individuals
    - Age 45 for high-risk individuals, African American men, and men with first-degree relatives with prostate cancer (at less than 65 years of age)
    - Age 40 for very high-risk men, with more than one first-degree relative affected by prostate cancer at an early age.
3. **The American Urological Association (AUA)** recommends PSA-based screening in men 55-69 years of age at least once every 2 years, strictly for men who have participated in a shared decision-making process. The AUA recommends against screening in men below 40 and for average-risk individuals aged 40-54.

Based on these recommendations, it is clear there is no definitive consensus among associations when it comes to guidelines for serum PSA screening. Moreover, there are concerns about the test producing false positive results leading to the overdiagnosis and overtreatment of clinically insignificant prostate cancer, or conversely yielding false negative results with the potential to delay necessary treatment.

## The HALO Dx Solution

HALO Diagnostics brings a new and far more comprehensive approach to prostate cancer screening, diagnosis, and monitoring. With an ensemble of advanced screening and diagnostic tools, HALO Dx is committed to greatly reducing the ambiguity and margin of error inherent in the current standard diagnostic protocol. In order to provide patients and physicians with detailed and more robust risk assessment, HALO Dx offers a comprehensive solution aligned with National Comprehensive Cancer Network (NCCN) guidelines on radiological imaging and prostate cancer biomarker analysis.

## NCCN Guidelines for Prostate Cancer Screening

Traditional screening protocol dictates that a patient with an elevated PSA and a positive DRE undergo a non-targeted transrectal ultrasound (TRUS) or transperineal-guided biopsy. A TRUS or transperineal-guided biopsy is ordered to obtain 12 to 24 needle core samples of prostate tissue and is known to carry a risk of side effects including infection. The NCCN's guidelines also call for more non-invasive screening methods prior to a biopsy. After a PSA test and DRE, NCCN guidelines recommend a biomarker risk assessment and non-invasive multiparametric MRI (mpMRI) of the prostate gland.

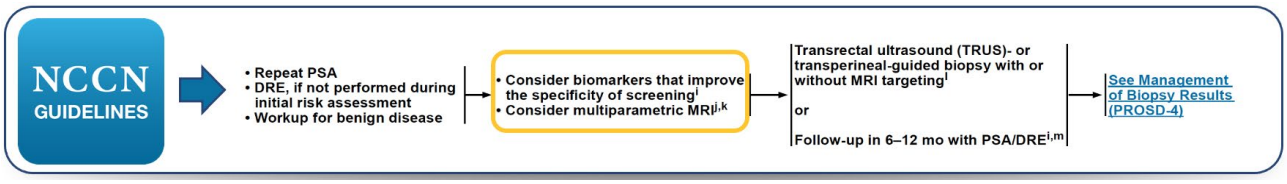


Fig.2. NCCN Guidelines on Prostate Cancer Screening (Suggested Pre-biopsy Work-up for High PSA Levels)

### Biomarker Analysis with The ExoDxTM Intelliscore Test

In addition to advanced radiological imaging services, HALO provides non-invasive biomarker tests, known as liquid biopsies. The ExoDx Prostate Test (Bio-Techne, Inc.) is a simple urine-based test that helps predict the presence of clinically significant prostate cancer by evaluating the expression of 3 genes associated with high-grade disease. This test provides a predictive score independent of PSA, family history, and other standard workup data to help determine if a biopsy is needed. The test is recommended for men 50 years and older with a PSA between 2-10 ng/mL.

### Understanding Inherited Risk - ProstateNext Test

5-10% of prostate cancer is hereditary, and for individuals with a personal or family history, it is not uncommon for the disease to be early on-set (occurring before the age of 55). The ProstateNext test (Ambry Genetics, Inc.) analyzes and detects mutations in 14 genes linked to an increased lifetime risk for clinically significant prostate cancer, including the BRCA1 and BRCA2, and HOXB13 genes.

## Imaging in Prostate Cancer Screening and Diagnostics

As identified by the NCCN and American Urological Association (AUA), magnetic resonance imaging (MRI) is critical in prostate cancer screening, akin to mammography in breast cancer screening and computed tomography (CT) scans for detecting lung cancer. In patients with a primary suspicion, the use of MRI has demonstrated high levels of sensitivity in detecting clinically significant prostate cancer. Multiple studies, including the Prostate MR Imaging Study (PROMIS), have indicated sensitivities ranging from 91% to nearly 100% as an in-bore diagnostic screening method. Most studies compare the efficacy of MRI-guided screening/biopsy versus TRUS-guided biopsy for diagnosing prostate cancer, with template mapping or saturation mapping biopsy as the reference. Prostate MRI also ensures precise anatomic localization of lesions, measures the prostate gland volume, and allows for greater precision of tumor staging.

## Prostate MRI Before Biopsy

The AUA updated its policy in October, 2019 to recommend a prostate MRI for biopsy-naive individuals at risk of prostate cancer and those with at least one negative biopsy prior to undergoing an invasive TRUS-guided biopsy.

The recent advancements in the field of prostate multiparametric magnetic resonance imaging (mpMRI) led to a policy update on prostate gland imaging. The statement from the AUA, published in Urology Today read, “Utility of prostate MRI in the risk stratification, diagnosis, and treatment pathway of men with prostate cancer is expanding. When a quality prostate MRI is obtained, current evidence now supports its use in men at risk of harboring prostate cancer before their first biopsy, as well as in men with a rising PSA following an initial negative standard prostate biopsy procedure.” A recent study indicates that when a liquid biopsy test, specifically the ExoDx Prostate Test is paired with mpMRI, the accuracy of cancer detection improves significantly. In one study published by the University of California, San Francisco, researchers were able to demonstrate 0% clinically significant prostate cancers were missed with these tests were combined.

## Conventional Prostate Biopsy and Related Side Effects

Despite often missing clinically significant prostate cancers, overdiagnosing clinically insignificant prostate cancers, and having a plethora of risks, transrectal ultrasound-guided biopsy (TRUS) remains the most commonly used approach for biopsying individuals with elevated serum PSA levels. The procedure is performed using an ultrasound device that is inserted either transrectally and requires 12-24 punctures into multiple areas of the prostate gland to collect tissue for pathological evaluation. TRUS biopsies are non-specific and miss 30-35% of aggressive cancers, either by hitting clinically insignificant tumors or

missing them altogether.xvi TRUS biopsies are associated with post-procedural side effects including pain, fever, severe infections (septicemia), hematuria, and even death (0.4%).

Epidemiological surveillance and Medicare-linked data show that in the United States, TRUS biopsy-related hospitalizations increased from 0.5% to 1.3% between 2007 and 2015. Emergency room visits rose from 0.2% to 0.5% and intensive care unit (ICU) visits increased from 0.1% to 0.3% 12. Based on these findings, HALO Dx believes it is imperative that individuals are provided with far more adequate and actionable information during the screening process prior to making a decision to undergo an invasive biopsy. Should a biopsy be deemed necessary, how then can it be performed with precision and a reduced risk of dangerous side effects?

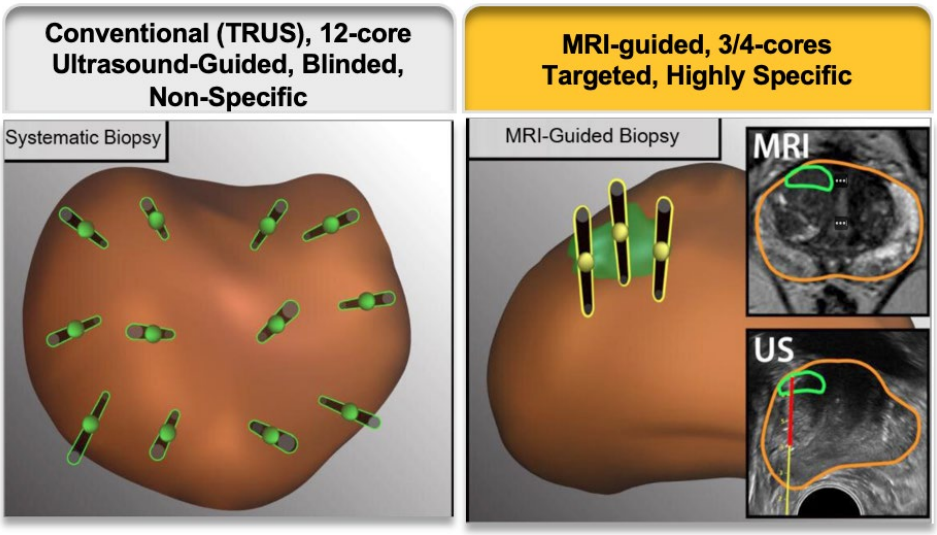


Fig. 3. TRUS vs. MR/Ultrasoud (US) FusionBiopsy

## The HALO Dx Solution: MRI-Guided Biopsy

An MRI-guided biopsy is performed with the patient in-bore in real time. In contrast to the 12-24 non-targeted needle cores collected during a TRUS biopsy, MRI-guided biopsy requires only 3-4 tissue cores. The real-time imaging allows the physician and radiologist to guide the needle straight to tumor suspicious lesion(s), as opposed to a non-targeted approach during which samples are taken from zones spread across the entire prostate gland. The greatly improved sensitivity and specificity of an MRI-targeted biopsy has shown to greatly reduce overtreatment and misdiagnosis, as well as significantly reducing a patient's risk of infection and/or rectal toxicities.

## Predicting Metastatic Risk Through Biopsy

In addition to targeted MRI-guided biopsy, we use tissue genomics to help predict the metastatic risk. The Decipher Prostate Biopsy (Decipher Biosciences, Inc.) is a personalized genomic test performed on prostate biopsy tissue that has been confirmed to be cancerous. The test works by identifying how the individual cells in the cancerous tissue are mutating to predict how the tumor(s) will likely evolve. From the cellular level up, it provides a risk assessment that helps predict the likelihood of metastasis as well as the associated risk of mortality.

Another non-invasive liquid biopsy offered by HALO is the Biocept Liquid Biopsy (Biocept, Inc.). It is a prognostic test performed using a simple blood sample, and it does not require a formal biopsy as a precursor. The Biocept Liquid Biopsy captures and detects the amount of circulating tumor cells (CTCs), which are cells shed from the primary tumor(s). CTCs have the potential to travel to other organs and create metastases. The test can be performed at any stage of diagnosis or treatment, though like most cancer screening methods is best utilized early. It can be used to detect disease progression in newly diagnosed patients, as well as monitor for recurrence.  Based on the results of the test, doctors are better able to recommend current and future screening and treatment accordingly.

## Laser Focal Therapy

Laser Focal Therapy (LFT) also known as Focal Laser Ablation (FLA) uses precisely targeted heat to eradicate cancerous tumor(s) within the prostate. Under real-time in-bore MRI guidance, a laser fiber is positioned within a tumor and used to heat it to a temperature that kills cancer cells. The surgical team monitors the temperature within and around the treatment area to protect healthy tissue, especially areas near critical structures such as the urethra, the neurovascular nerve bundles responsible for erectile function, the external urinary sphincter responsible for urinary control, and the rectal wall.  Special software places safety boundaries over vital structures to help protect them and minimize non-target tissue destruction. Given that the prostate gland is encapsulated by and separated from those vital structures by only millimeters, the extreme precision afforded by in bored, real time MRI guided laser focal therapy (LFT) has shown a significantly lower incidence of side effects in comparison with whole gland therapies. Furthermore, unlike other treatments, laser focal therapy does not limit the option to treat with radiation therapy or surgery if needed later.

Since 2010, HALO Dx has offered laser focal therapy as part of an ongoing 20-year clinical trial.  10-year follow-up studies have now been published indicating the efficacy and advantages of laser therapy compared to conventional, standard-of-care measures such as whole gland surgical removal (radical prostatectomy) and whole or partial gland radiation therapy. In January 2021, the procedure was launched in the commercial setting and the 200 research subjects from the Phase II Clinical Trial will continue their follow-up protocol for 20 years.

## Key highlights from the interim 10-year study:

- **Precise, safe, controllable "sculpted" therapy**
- <1% risk of erectile dysfunction and incontinence
- 1% infection (vs 4% with whole gland therapy)
- Reduced cost ($25K, no general anesthesia, outpatient procedure vs the average $50K cost of a hospital operation)
- 94% avoided whole gland therapy and associated morbidity
- Rapid recovery: most patients can return to work within days
- Superior accuracy compared to other focal approaches, e.g., high intensity focused ultrasound guided (HIFU) therapy
- 100% prostate cancer specific survival
- >1% rate of metastasis

After 10 years of diligent practice, successful execution, and the acquisition of a growing number of invaluable resources, HALO Dx remains committed to improving the course of standard prostate cancer management. . By building on the PSA test next-generation machine-learning-enhanced imaging software and genomic tests, HALO Dx is creating the opportunity for a future defined by drastically improved patient outcomes and experience.

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www.halodx.com

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