Executive Summary

Over 260,000 American men are diagnosed with prostate cancer every year, making it the second leading cause of male cancer death in the U.S. Fortunately, about 84% of these cancers are discovered in the localized stage, before spreading to other parts of the body.¹ A recent study found that 20% of newly-diagnosed men met the criteria for low-risk disease, and AS is likely appropriate for around 80% of this population. The number of low-risk patients opting for active surveillance (AS) is headed in the right direction, doubling from 29.6% in 2014 to about 60% in 2021.² However, researchers identified “excessive variation” of AS rates across urology providers, causing concern that overtreatment remains a problem.³

NCCN Guidelines® recommend various types and intensities of treatments across the range of very low-risk to very high-risk localized prostate cancer.⁴ Accurate risk stratification is critical for creating individualized treatment plans, and for avoiding overtreatment of men with low-risk tumors that would not have led to death. Diagnostic tools, such as prostate-specific antigen (PSA) and Gleason score, are effective in determining the stage of cancer, but limited in their ability to distinguish tumor aggressiveness. The Prolaris® test provides physicians with consistent data that allows them to make personalized treatment plans.

Prolaris doubles the predictive power of disease-specific mortality (DSM) when compared to Gleason and PSA, and demonstrates a nearly 2-fold increase in low-risk men safely pursuing active surveillance when compared to the national average.⁵⁻⁷

Prolaris influences treatment strategies, with 34 – 50% reduction in planned surgical interventions and 30 – 39% reduction in planned radiation treatments.⁸⁻⁹

Prolaris supports cost-effective healthcare management. After accounting for the cost of the test, Prolaris is projected to reduce treatment costs by $1,894 per patient over three years when used for AS decision-making.¹⁰
Test Description
Prolaris is a prognostic test that measures tumor biology to more precisely stratify patients with localized prostate cancer according to disease aggressiveness. The test combines the RNA expression levels of 31 genes involved in cell cycle progression (CCP) and 15 housekeeping genes to generate a Prolaris molecular score. Prolaris is a genomic test that estimates how fast tumor cells are proliferating to determine the risk of DSM and metastasis.

Intended Use Population
Prolaris is intended for men with biopsy-confirmed, localized prostate cancer, who have not received prior intervention. The assay is performed using tumor tissue from an existing biopsy sample.

Analytical Validity
The analytical validation studies for this test indicate that the Prolaris gene signature is robust and reproducible with a standard deviation of 0.1 units, representing only 1.6% of the range of scores seen in clinical validation studies for formalin-fixed paraffin-embedded prostate biopsy and radical prostatectomy samples.\(^6\)\(^{11}\)\(^{12}\)

Clinical Validity
In more than 20 patient cohorts, Prolaris has been shown to be a strong predictor of oncologic outcomes and adds a substantial amount of independent prognostic information not captured by standard clinical features alone.\(^6\) (See Table 1.) The amount of prognostic information provided by Prolaris is consistent across all of the studies, indicating there was not a cohort or sample bias.

### Table 1.
The Prolaris CCP molecular score, in combination with PSA and Gleason, is 2x more predictive of a patient’s risk variables (DSM and Mets) than PSA and Gleason alone.
Prolaris is the only biomarker test on the market with both an active surveillance (AS) and a multi-modal (MM) threshold. The AS threshold was validated in a study (Lin et al., 2018) using an unselected, conservatively-managed cohort. The threshold dichotomized low- and high-risk groups for 10-year prostate cancer mortality, and may enable more appropriate identification of patients for AS.¹³

The Prolaris MM threshold was validated in two studies by Tward et al. (2021) using a cohort of patients with NCCN intermediate- and high-risk prostate cancer and a known clinical cell-cycle risk (CCR). The first study validated the prognostic ability of the CCR score to help determine which patients may safely forego multimodality therapy in a cohort of patients treated with surgery or radiation.¹⁴ The second study validated the ability of the CCR score to prognosticate the risk of metastasis in men receiving dose-escalated radiation therapy (RT), with or without androgen deprivation therapy (ADT).¹⁵

(See Table 2.)

Table 2. The Prolaris AS and MM thresholds help physicians to tailor treatment and patients to avoid unnecessary additional treatments.

CCR is a validated model that combines the CCP score with the University of California San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score to determine the risk of progressive disease for men with prostate cancer.
Clinical Utility
Prolaris demonstrates clear clinical utility across all risk groups and treatment decisions in localized prostate cancer. Shore et al. (2016) reported that 47.8% of patients had a treatment modification after their Prolaris test. Of these, 72.1% were reductions and 26.9% were increases in treatment. In another clinical utility study, Crawford et al. (2014) there was a 40.0% reduction and a 24.9% increase in therapeutic burden from pre- to post-test. Lin et.al (2018) looked at 19,215 men who had clinical testing, 68.8% had CCR scores suggesting they were good candidates for AS vs. 42.6% who would be considered AS candidates based on clinical and pathologic features alone.8,9,13 (See Table 3.)

Prolaris® is the industry leader for proven clinical utility

In two clinical utility studies, Prolaris results led to change in management in up to 65% of patients

Prolaris extends active surveillance candidate population by 62% compared to clinical and pathologic features alone

Table 3. Prolaris results led to a change in treatment8 and an increase in AS13.

Medical Society Guidelines
An American Society of Clinical Oncology (ASCO) multidisciplinary Expert Panel, with representatives from the European Association of Urology, American Urological Association, and the College of American Pathologists, has stated that molecular biomarkers improve risk stratification and patient management; therefore, endorsing their use in situations where the results may affect a clinical decision.16

NCCN prostate cancer treatment guidelines recommend considering tumor molecular biomarker analysis, specifically including Prolaris, in the initial risk stratification and staging workup for clinically localized prostate cancer in men with a life expectancy of 10 years or more and who have low-, favorable intermediate-, unfavorable intermediate- or high-risk disease.4
The American Academy of Clinical Urologists (AACU) released a position statement on genomic testing in prostate cancer that has been endorsed by the Large Urology Group Practice Association (LUGPA). The AACU references the NCCN practice guidelines, stating that it “support[s] the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making.”

Additionally, the Washington State Health Care Authority determined that use of gene expression profiling tests can impact treatment decisions and therefore supports the use of Prolaris for men with low- and favorable intermediate-risk disease. Prolaris has also received a favorable technical assessment by MolDX, resulting in a positive Local Coverage Determination for Medicare beneficiaries across all localized prostate cancer risk groups.

**Health Economics**

Data published in Future Oncology demonstrate potential cost savings driven by Prolaris utilization in American Urological Association (AUA) low- and intermediate-risk patients. A health economic model estimates impact of test adoption on US commercial health plans, and projects that Prolaris adoption and use of the AS threshold would drive cost savings, regardless of time after diagnosis, in a 1 to 10-year timeframe. (See Table 4.)

![Modeled savings in 3-year period](image-url)

**Table 4.** After accounting for the cost of the test, Prolaris is projected to reduce costs by $1,894 per patient.
Sample Reports
The Prolaris report explains the behavior of the tumor to provide the risk of disease-specific mortality (DSM) and metastasis.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2022.© National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [June 2, 2022]. To view the most recent and complete version of the guideline, go online to https://www.nccn.org/. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.