INTRODUCTION

There is widespread concern that the early detection of prostate cancer through screening programs has led to the overtreatment of localized disease.\(^1\) \(^3\) Approximately 87% of all localized prostate cancer patients receive definitive treatment, including radical prostatectomy, radiation therapy, androgen deprivation therapy, or some combination.\(^4\) \(^5\) This occurs despite the high risk of treatment-related complications\(^6\) \(^7\) and the fact that the vast majority of prostate cancers do not cause death even when initial management is conservative.\(^8\) It is estimated that $1.32 billion could be saved annually in the U.S. by avoiding unnecessary treatment of men who will never die of their prostate cancer.

THE PROLARIS TEST

Prolaris is a novel prognostic test that directly measures tumor biology, in order to more precisely stratify patients with localized prostate cancer according to disease aggressiveness. The Prolaris test combines the RNA expression levels of 31 genes involved in cell cycle progression and 15 housekeeping genes to generate a Prolaris Score\(^\text{TM}\), which has been proven in 12 published studies to be a powerful predictor of prostate cancer outcomes, providing information that is new and independent of standard clinicopathologic features, such as PSA and Gleason score.\(^1\) \(^2\) \(^3\) \(^4\) \(^5\) \(^6\) \(^7\) \(^8\) \(^9\) The patient’s 10-year prostate cancer-specific mortality is reported and shown graphically, compared to a cut-point which can be used to guide patient selection for active surveillance or definitive treatment.\(^2\) \(^1\) The Prolaris test report is used by the patient and physician as a decision support tool to make improved treatment choices based on the patient’s 10-year risk of dying from prostate cancer.

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.\(^16\) \(^24\) \(^25\)

CLINICAL VALIDITY

In 12 published studies on more than 2,900 patients from multiple cohorts, using prostatectomy, transurethral resection of the prostate (TURP) and biopsy samples, Prolaris has been shown to be a strong predictor of oncologic outcomes and adds a substantial amount of independent prognostic information that is not captured by standard clinicopathologic features, such as PSA and Gleason score.\(^1\) \(^2\) \(^3\) \(^4\) \(^5\) Across all of these studies, the amount of prognostic information provided by Prolaris is consistent, indicating that there was not a cohort or sample bias in the studies.
Two of these validation studies were performed on diagnostic needle-biopsy samples from men with localized prostate cancer who were previously untreated, representing the current intended use population. In the first study, multivariate analysis demonstrated that the Prolaris Score was the dominant variable in predicting 10-year mortality from prostate cancer (HR=1.65, p=3x10^-5), adding prognostic information not captured by Gleason score or PSA level. In the second study, multivariate analysis including CAPRA (a validated prediction model that incorporates age at diagnosis, PSA at diagnosis, Gleason score of the biopsy, clinical stage and percent of biopsy cores involved with cancer) demonstrated that the Prolaris Score was one of the strongest variables for predicting disease-specific mortality (HR=1.76, p<10^-6), and provided more independent prognostic information than any other variable. In both studies, hazard ratios were calculated for Prolaris and other available clinicopathologic variables in order to conduct the comparison; further, Prolaris was found to more than double the amount of prognostic information provided by PSA level and Gleason score when predicting death from disease (p=3.7x10^-15). In the Prolaris test report, the final estimate of death from disease combines the Prolaris Score with CAPRA for the most predictive combination of all variables. This combination of the Prolaris Score with CAPRA, referred to as the CCR score, has a hazard ratio of 2.17 with p<10^-20.

The Prolaris active surveillance threshold was validated by Lin et al. using 10-year disease-specific mortality in an unselected, conservatively managed cohort. The threshold significantly dichotomized low- and high-risk disease (p=1.2×10^-5) and there were no prostate cancer-specific deaths in men with scores below the threshold.

**CLINICAL UTILITY AND IMPACT OF PROLARIS ON PATIENT CARE**

The Prolaris result directly impacts clinical management by providing physicians with an accurate measure of the indolence or aggressiveness of an individual’s prostate cancer and the chance of dying of prostate cancer within 10 years. Urologists use this information to guide initial treatment decisions, which may include active surveillance, prostatectomy, radiation therapy and/or hormone therapy, according to current guidelines.

Hu et al., an independent, non-industry funded study, reported that patients classified as low risk by a gene expression test – most often, Prolaris – were more likely to be managed by AS than those without testing, with an odds ratio of 1.84 (p=0.006). This finding demonstrates the clinical utility of Prolaris in confirming low-risk disease and increasing rates of AS, thus reducing overtreatment and its associated morbidities.

Another recent publication by Kaul et al. directly evaluated clinical outcomes with the use of Prolaris. Data showed 82.4% of men with low-risk prostate cancer, who also scored below the Prolaris active surveillance threshold, selected AS, compared to the national average of 42.1% for low-risk men selecting active surveillance. The clinical outcome showed a low rate of progression of only 0.4% in the men who chose this pathway, confirming that active surveillance informed by a Prolaris result is safe. Clinical outcomes were improved because there was a low rate of progression, and the increase in AS compared to usual care meant that treatment-related morbidities were reduced or avoided. At 3 years, 70% of men who initially selected active surveillance remained on this treatment pathway, showing that this modality was durable when guided by Prolaris.
The Lin et al. study demonstrated that Prolaris improves outcomes by broadening the group of patients considered appropriate for active surveillance. In this study, only 42.6% of men met AS criteria based on clinicopathologic criteria alone; however, once the validated Prolaris active surveillance threshold was incorporated, this population increased to 68.8%. Of the men who did not qualify for AS based on clinicopathologic criteria alone, 52.2% scored below the Prolaris active surveillance threshold indicating this treatment path was viable. This group would not have been considered for AS previously.

Two prospective, real-world clinical utility studies involving over 1,500 patients demonstrated the significant impact Prolaris has on the management of localized prostate cancer. Crawford et al. reported that 65% of patients had modifications to their planned treatment strategies after reviewing the Prolaris result, with a 50% reduction in surgical interventions and a 30% reduction in radiation treatment. Shore et al. reported that 48% of patients had a modification to their treatment approach after Prolaris, with a 34% reduction in radical prostatectomies and a 39% reduction in primary radiation.

The nature of prostate cancer (long natural history with 10-year mortality rate of less than 3.2%) precludes conducting a prospective trial in which patients are randomized with or without Prolaris and followed for 10-15 years to evaluate long-term outcomes. Prolaris has been shown to increase AS rates and reduce unnecessary interventional therapies. This results in a reduction of common therapy-related complications such as urinary incontinence, fecal incontinence and erectile dysfunction. Prolaris improves short-term outcomes by reducing treatment-related morbidity. The increase in AS rates associated with Prolaris has been shown to be safe and durable. By a chain-of-evidence argument, a reduction in interventional therapies is not expected to decrease survival, since randomized controlled studies have demonstrated that men with low-risk localized prostate cancer receive no overall survival benefit from prostatectomy or radiation, and that other major management options produce similar survival outcomes.

**SOCIETAL GUIDELINES AND MEDICARE COVERAGE**

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, conducted a systematic literature review of localized prostate cancer biomarker studies between January 2013 and January 2019 and made recommendations regarding the clinical use and indications of certain prostate cancer biomarkers. Specifically, the Panel stated that molecular biomarkers improve risk stratification and patient management, endorsing their use in situations where the results may affect a clinical decision.

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. 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 for prostate cancer and states that it “support[s] the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making.”

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 with very low-, low-, and favorable intermediate-risk prostate cancer as defined by NCCN risk groups.

**SUMMARY**

Physicians use the Prolaris test for men with localized prostate cancer to add precision to their clinical risk assessment. The unique information provided by Prolaris drives optimal treatment decisions, by identifying patients who can safely choose active surveillance and thereby reduce morbidities associated with unneeded interventions. This net reduction in unnecessary therapies produces an overall cost savings to the healthcare system.