INTRODUCTION

There is widespread concern that the early detection of prostate cancer through screening programs has led to the overtreatment of localized disease. Approximately 90% of all localized prostate cancer patients receive definitive treatment, including radical prostatectomy, radiation therapy, androgen deprivation therapy, or some combination. This occurs despite the high risk of treatment-related complications and the fact that the vast majority of prostate cancers do not cause death even when initial management is conservative. 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

Myriad Genetic Laboratories, Inc. has developed Prolaris, 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™, which has been proven in eight 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. 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. The Prolaris test report is used by the patient and physician as a decision support tool to make rational 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.
**CLINICAL VALIDITY**

In eight 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.\(^{11-19}\) 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 treated conservatively, representing the intended use population. In the first study,\(^{11}\) multivariate analysis demonstrated that the Prolaris Score was the dominant variable in predicting 10-year mortality from prostate cancer (HR=1.65, \(p=3\times10^{-5}\)), adding prognostic information not captured by Gleason score or PSA level. In the more recent study,\(^{12}\) 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)\(^{23}\) demonstrated that the **Prolaris Score** was one of the **strongest variables for predicting** disease-specific mortality (HR=1.76, \(p<10^{-9}\)), and provided more independent prognostic information than any other variable. In both studies,\(^{11,12}\) 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 (\(p=3.7\times10^{-16}\)).\(^{24}\) 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 \(p<10^{-20}\).\(^{12}\)

**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.\(^{25,26}\) 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**:\(^{27,28}\)
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.27

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.28

When the number of interventional therapies are reduced, common therapy-related complications such as urinary incontinence, fecal incontinence and erectile dysfunction5,6 are also reduced. 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,7 and that other major management options produce similar survival outcomes.29 The nature of prostate cancer (long natural history with 10-year mortality rate of less than 3.2%20) precludes conducting a prospective trial in which patients are randomized with or without Prolaris and followed for 10-15 years to evaluate outcomes. Rather, a “chain of evidence”30 can be employed to conclude that Prolaris improves outcomes for localized prostate cancer by reducing unnecessary interventions, thereby reducing treatment-related morbidity, without decreasing survival.

MEDICARE COVERAGE AND SOCIETAL GUIDELINES

Prolaris received a favorable technical assessment by MolDX, resulting in a positive Local Coverage Determination for Medicare beneficiaries with NCCN very low-, low-, and favorable intermediate-risk prostate cancer.31,32 The NCCN 2016 prostate cancer treatment guidelines include the use of Prolaris in the initial clinical assessment of localized prostate cancer, regardless of risk category, in men who are symptomatic or have a life expectancy of greater than 5 years.33 The NCCN emphasizes the importance of more clearly defining risk for men with localized prostate cancer in order to formulate optimal management decisions; it also encourages the use of molecular assays such as Prolaris to help reduce overtreatment by increasing active surveillance, when appropriate.10

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.27,28 This net reduction in unnecessary therapies produces an overall cost savings to the healthcare system.34
REFERENCES


