Applying the Center for Medical Technology Policy’s (CMTP) Chain of Evidence for Clinical Utility to Prolaris, a Prognostic Prostate Cancer Test Developed by Myriad Genetic Laboratories
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The rapidly expanding knowledge base generated by genomic medicine research has opened promising avenues for molecular diagnostic testing in health care. If thoroughly validated and sagely applied, such testing can indeed provide more, different and better diagnostic and prognostic information to clinicians and patients than can current practice standards. Appropriate use of these technologies can lead to improved health outcomes and patient quality of life, at a reduced cost both to the patient and across the healthcare system.

Ongoing challenges and debate exist, however, around evaluating molecular diagnostic tests for clinical use, coverage and reimbursement (Joseph et al., 2016). Traditional reliance on long-term, randomized clinical study data for positive insurance coverage decisions is less appropriate in cases where: (1) a long-term study design puts patient health and quality of life at risk; (2) statistical challenges require inordinately large cohort sizes or long study periods; and (3) available surrogate data supply robust and sufficient clinical evidence to support a diagnostic coverage decision.

Test developers bear the burden of evidence for proving the clinical suitability and cost effectiveness of molecular diagnostics. In the early 2000s, the U.S. Centers for Disease Control’s ACCE framework guided the early adoption of tests by establishing the concepts of analytic validity, clinical validity and clinical utility: (Haddow and Palomaki, 2003)

- Analytic validity: Ability of a test to measure, accurately and reliably, the genetic information it is designed to analyze.
- Clinical validity: How well the genetic information measured by the test correlates with the defined health status or outcome of interest.
- Clinical utility: The usefulness of a test in clinical practice to improve health outcomes through test-informed decisions about treatment.

Building upon the ACCE framework, the Center for Medical Technology Policy (CMTP) in 2013 established best practices for test developers to generate evidence of clinical utility. Through its “Chain-of-Evidence” guidance, CMTP integrates analytic and clinical validity with an expanded definition of clinical utility, demonstrating that a diagnostic test not only improves patient health outcomes, but also quality of life and cost effectiveness. (http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf).

We employ the CMTP chain-of-evidence format in a strong case for coverage and reimbursement of the Prolaris® prostate cancer prognostic test from Myriad Genetic Laboratories, Inc. Evidence detailed herein supports a high level of clinical utility for Prolaris in giving a more precise prognosis of prostate cancer risk, to guide provider and patient decisions about treatment. Put into practice, Prolaris test information should result in quick and demonstrable improvement in care and quality of life for men with prostate cancer, while at the same time reducing cost to patients, providers and payers.
Current Prostate Cancer Treatment: Outcomes, Cost and Challenges

Concern about the overtreatment of men with localized prostate cancer has spurred the need for better ways to classify newly diagnosed tumors.

Currently, about 90% of men diagnosed with localized prostate cancer receive some form of interventional treatment, in the form of radical prostatectomy (RP), radiation treatment (RT), hormone therapy (HT), or a combination of methods (Maurice et al., 2016). This occurs despite the fact that current practice guidelines recommend active surveillance (AS), which involves a regimen of regular follow-up (periodic PSA test, digital rectal exam and needle biopsy), as an option for most patients with low- or favorable-intermediate risk, localized prostate cancer (Thompson et al., 2007; Mohler et al., 2016). Debate in the field centers on the true need for such interventions, given the following factors:

1. **Even with conservative, non-interventional management, most prostate cancers do not cause death.** Regardless of age, race or coexisting medical conditions, men are far more likely to die from causes other than their prostate cancer (Wilt et al., 2017; Wilt et al., 2012; Tosoian et al., 2015; Klotz et al., 2015; Hamdy et al., 2016; Musunuru et al., 2016).

2. **Interventions such as RP and RT produce significant and lasting complications, including sexual, urinary and bowel dysfunction, in a large proportion of men who undergo treatment** (van den Bergh et al., 2012; Resnick et al., 2013). These occur in addition to adverse effects that can immediately follow procedures, requiring medical follow-up. Such complications compromise quality of life for patients and add to the cost burden of disease management (Tables 1 and 2).

<table>
<thead>
<tr>
<th>TABLE 1: Complications Associated with Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Complication</strong></td>
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<tr>
<td>Radiation Therapy (RT) / Radical Prostatectomy (RP)</td>
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<tr>
<td>Bowel Urgency</td>
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<tr>
<td>Sexual Dysfunction</td>
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<tr>
<td>Urinary Incontinence</td>
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<tr>
<td>Depression</td>
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(Table 1 Resnick et al., 2013; van den Bergh RCN et al., 2012)

<table>
<thead>
<tr>
<th>TABLE 2: Adverse Effects of Surgery</th>
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</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
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<tr>
<td>Any</td>
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<tr>
<td>Pneumonia</td>
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<tr>
<td>Wound infection</td>
</tr>
<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Deep-vein thrombosis</td>
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<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
</tr>
<tr>
<td>Bowel injury requiring surgical repair</td>
</tr>
<tr>
<td>Additional surgical repair</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
</tr>
<tr>
<td>Urinary catheter present &gt; 30 days after surgery</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

(Table 2 Wilt et al., 2012)
Therefore, while the vast majority of men receive interventional treatment for localized prostate cancer, they might not need it, and they will likely suffer adverse effects from it. An expanding body of research shows that management through AS can produce equal or better health and quality-of-life outcomes and reduce management costs, compared to interventional treatment (Barocas et al., 2017; Chen et al., 2017; Donovan et al., 2016; Klotz et al., 2015; Tosoian et al., 2015; Jeldres et al., 2015).

That said, uncertainty remains among providers about taking a more conservative approach to localized prostate cancer. Newly diagnosed men can have aggressive or indolent tumors, and current clinicopathologic measures do not distinguish well between the two. This complicates decisions about medical management (Carter et al., 2013; Cooperberg et al., 2006; Welch and Albertsen, 2009). The decision to pursue AS in lieu of immediate intervention is weighty for patients and their providers, whose most pressing concern is preventing death from the disease.

For insurance payers, effective AS management of prostate cancer translates into substantial near- and long-term cost savings. It is estimated that improved adherence to clinical guidelines for pursuing AS in lieu of intervention in men with low-risk disease whose life expectancy is less than 10 years would save $58 million annually (Aizer et al., 2015). Further, more precise methods for tumor risk classification, such as a validated molecular test, could spare most men unnecessary treatment and translate into $1.32 billion in annual cost savings. (Aizer et al., 2015). Therefore, investing in such methods to select and tailor treatment can eliminate considerable unnecessary cost.

The pressing charge to all stakeholders, then, is determining with the greatest possible confidence which patients fit a disease risk profile that is best suited to an AS management approach. The Prolaris® prognostic test from Myriad Genetic Laboratories, Inc. (Myriad) meets this challenge. A powerful predictor of prostate cancer outcomes, Prolaris provides information that extends and improves current practices, increasing confidence in patient risk classification.

**Current Practice in Diagnosis, Risk Profiling and Outstanding Needs**

Prostate cancer is diagnosed and classified into the American Urological Association (AUA) risk categories of low, intermediate and high based on standard clinical and pathological features (http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-staging). These features include:

- Prostate-Specific Antigen (PSA) test value
- Gleason Score: The pathologist’s grading scale for tumors in biopsy tissue. (Range from 2, “most normal,” to 10, “most abnormal.”)
- Clinical T Stage: The provider’s best estimate of disease extent, based on physical exam and laboratory results. (Range from T1, less advanced, to T4, more advanced.)

These and other clinical features, along with the patient’s age, can be combined to generate the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score, a validated measurement tool to assist with assessment of risk status (https://urology.ucsf.edu/research/cancer/prostate-cancer-risk-assessment-and-the-ucsf-capra-score).

National Comprehensive Cancer Network® (NCCN) practice guidelines recommend AS in the very low-, low- and favorable-intermediate-risk cases (Mohler et al., 2016; NCCN version 2.2017). The AUA clinical practice guideline suggests its use in all risk groups (Thompson et al., 2007). Despite these guidelines, however, most patients are treated aggressively, with interventional procedures such as RP, RT and HT. Across all risk categories, AS is the least-chosen management option.

Long-term studies have shown AS to be a useful management route, but diagnosis and risk classification remains an inexact science. Unlike other cancer types, prostate cancer is slow growing and indolent in nature. Its rate of progression is difficult to predict using existing clinicopathologic measures. In addition, these measures do not directly address the question of great concern to patients and providers as they evaluate treatment modalities: What is the risk of dying from one’s prostate cancer? Patients and physicians need a more precise and reliable answer to this question.
Prolaris: A Validated Prognostic Test for Patients with Localized Prostate Cancer

To address this clinical uncertainty, Myriad developed Prolaris as a prognostic test for patients with localized prostate cancer. Introduced in 2012, Prolaris is a molecular test that measures prostate tumor biology in biopsy tissue to stratify patient risk more precisely, according to disease aggressiveness. The Prolaris test is intended for men who have clinically localized, non-metastatic prostate cancer, confirmed by biopsy, and who have not received prior intervention or treatment. Providers and patients use Prolaris test results to make rational treatment choices based on the patient’s 10-year risk of dying from prostate cancer.

Specifically, Prolaris measures the expression of 46 genes: 31 cell cycle progression (CCP) genes and 15 “housekeeping” genes (as a control measure for sample quality and test success). CCP genes regulate the growth and proliferation of cells (Cuzick et al., 2011). Overexpression of CCP genes indicates that cells in the tumor are dividing rapidly, whereas lower expression levels indicate slower growth and a less aggressive tumor. Therefore, Prolaris provides an understanding of the tumor’s biology at the molecular level—a dimension of information not currently available through standard clinicopathologic measures.

The Prolaris test report (Figure 1a and 1b) includes the following components:

- Clinical and pathologic features: Provided by the physician’s office
- Prolaris Score: Laboratory result that is expressed as a number between 1 and 10, representing the average expression of the 31 CCP genes.

On the report, the Prolaris Score is rated as higher than, lower than, or consistent with other men’s scores within the same AUA risk group, and includes the distribution within the group. The patient’s 10-year disease specific mortality is calculated using a validated prognostic model that appropriately weights the Prolaris Score, Gleason score and other clinical features.

The report depicts graphically the “Active Surveillance Threshold,” with a zone from 0 to 3.2%, representing the percent risk of 10-year disease specific mortality without interventional treatment. Men who fall below the 3.2% threshold are recommended eligible for AS. Myriad developed this threshold to provide the physician and patient more confidence in opting for AS. A “3.2% risk” reflects a prediction of three deaths among 100 men with similar diagnostic characteristics; however, in several studies, whenever a patient had a 3.2% or less risk of dying from prostate cancer, according to Prolaris analysis, there were no observed deaths (Cuzick et al., 2012; Cuzick et al., 2015). Myriad validated the threshold in two independent cohorts of conservatively managed men (combined n=765); the average risk for 10-year mortality was 2.6% for men whose CCR scores fell below the threshold, contrasted with 21.4% for men above it (Cuzick et al., 2012; Cuzick et al., 2015). Moreover, there were no deaths in 10 years of follow up for men below the threshold. Evaluation of a commercially tested cohort of 4,218 men showed that 60% would fall below the AS threshold with Prolaris information, whereas only 36% of these men would have qualified for AS based on clinical parameters alone (Cuzick et al., AUA poster 2015).

Because the Prolaris test combines molecular analysis with clinicopathologic data to generate a mortality risk assessment, it adds new information and significant predictive power to traditional risk assessment methods. Through eight published clinical validity studies and with 10 patient cohorts, the Prolaris Score has proven an independent and powerful predictor of prostate cancer outcomes (Cuzick et al., 2011; Cuzick et al., 2012; Cooperberg et al., 2013; Freedland et al., 2013; Bishoff et al., 2014; Cuzick et al., 2015; Koch et al., 2016; Tosoian et al., 2017). Here we present detailed data confirming the analytic validity, clinical validity and clinical utility of the Prolaris test.
The Prolaris test report gives quick, easily absorbed and actionable information that can assist in decision-making and patient counseling. The test report provides the clinician with:

1) **The Prolaris Score™**: Reported from 1 to 10 (technical range), representing the average expression of 31 CCP genes. Each 1-unit increase in the Prolaris Score represents an approximate doubling of risk. Higher Prolaris Scores represent more aggressive cancers.

2) **Mortality Risk**: The U.S. Distribution Percentile indicates where the patient’s Prolaris Score falls (percentile) within a U.S. distribution of Prolaris Scores of patients in the same National Comprehensive Cancer Network (NCCN) risk category.
   - The patient’s 10-year prostate cancer-specific mortality risk (under initial conservative management) is estimated based on the addition of his Prolaris Score to the CAPRA (Cancer of the Prostate Risk Assessment) score, using clinical and pathological features of the biopsy, provided by the physician.

3) **Active Surveillance (AS) Threshold**: A zone from 0 to 3.2%, representing the percent risk of 10-year disease specific mortality without interventional treatment. Patients who fall below the 3.2% threshold are recommended eligible for AS.

4) **NCCN Risk Analysis**: The report displays how the patient’s Prolaris Score compares to that of other tested patients within the same NCCN risk category. Each of the graph’s bars represents a risk category with the triangle centered at the median of Prolaris Scores for patients in this category.

5) **Metastasis Risk**: Predicts the 10-year risk of metastases in men treated for prostate cancer (Bardot et al., AUA 2017).
Support for Prolaris as a Molecular Diagnostic and Clinical Decision Tool

As a result of its validation in research and clinical studies, Prolaris has received support from societal guideline entities and earned payer coverage.

NCCN emphasizes the importance of more clearly defining risk for men with localized prostate cancer in order to formulate optimal management decisions. Recently, the network clarified its suggested endpoints for molecular prostate cancer prognostic utility to include disease-specific mortality, biochemical recurrence and metastasis after treatment (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Prolaris has been validated across all of these endpoints. NCCN also added a selection of favorable intermediate-risk patients as candidates for AS in its Clinical Practice Guidelines. Prolaris has been validated across all risk categories, including intermediate and favorable-intermediate risk with proven utility.

NCCN also encourages the use of molecular assays to help reduce overtreatment by increasing AS, when appropriate. The NCCN v2.2016 guidelines list Prolaris for the initial clinical assessment of prostate cancer, regardless of risk category, in men who are symptomatic or who have life expectancy of greater than five years.

Of the three prognostic tests with a NCCN recommendation, only Prolaris has been studied extensively and validated against all oncologic endpoints and in all risk categories of both treated and conservatively managed patients, and performed using post-RP as well as diagnostic biopsy tissue.

In October 2015, Prolaris received a favorable technical assessment from Palmetto GBA MolDx, indicating that it meets Medicare reasonable and necessary criteria (MolDX L36350). Palmetto GBA was the first CMS carrier to require examination of all evidence of clinical validity and clinical utility for a diagnostic test as criteria for CMS coverage and reimbursement. The favorable assessment for Prolaris resulted in the award of Medicare coverage for NCCN “low” and “very low” risk patients (Peabody et al., 2014). In July 2017, a second favorable assessment for Prolaris resulted in the award of Medicare coverage for NCCN “favorable intermediate” patients (MolDX L37082).
Applying the CMTP’s Chain of Evidence for Clinical Utility to Prolaris®

We have collected extensive evidence supporting the utility of Prolaris in providing better care and quality of life for men with prostate cancer, while at the same time reducing cost to patients, providers and payers. In 2013, the Center for Medical Technology Policy (CMTP) published the Effectiveness Guidance Document (EGD), Evaluation of Clinical Validity and Clinical Utility of Actionable Molecular Diagnostic Tests in Adult Oncology. This document establishes a common framework for developing and validating clinical molecular tests, to facilitate evaluation of the tests by post-regulatory stakeholders, including insurance payers, providers and patients (http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf).

Here we present robust data establishing the analytic and clinical validity and clinical utility of Prolaris in the CMTP EGD-recommended “chain-of-evidence” format, which comprises four phases (Figure 2). Our summary includes studies conducted by Myriad and its research partners as well as those from independent investigators across the prostate cancer field.

Chain of Evidence to Support Payer Coverage of Prolaris

FIGURE 2: CMTP “Clinical Phases of Test Development”

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>PHASE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Test Performance &amp; Assay Refinement</td>
<td>Test Validation &amp; Generalizability</td>
<td>Components of Clinical Test Performance &amp; Health Impacts</td>
<td>Comparison with Standard of Care</td>
</tr>
<tr>
<td>Determine test performance of defined assay in targeted population</td>
<td>Determine how well test predicts clinically relevant phenotypes in the intended use population</td>
<td>Select the components to measure how test affects clinical decision-making (benefits and harms) and related health outcome</td>
<td>Determine the net impact on health outcomes &amp; added value compared to current patient management without MDx testing (clinical utility)</td>
</tr>
<tr>
<td><strong>Recommendation 1:</strong> Follow standard reporting guidelines to document analytic validity has been established</td>
<td><strong>Recommendation 2:</strong> Study patient population intended for clinical use of test</td>
<td><strong>Recommendation 4:</strong> Anticipate clinical pathways related to test use</td>
<td><strong>Recommendation 6:</strong> RCT design selection OR <strong>Recommendation 7:</strong> Prospective-retrospective study OR <strong>Recommendation 8:</strong> Single-arm study OR <strong>Recommendation 9:</strong> Prospective observational study OR <strong>Recommendation 10:</strong> Modeling techniques (e.g., decision-analytic)</td>
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<tr>
<td><strong>Recommendation 3:</strong> Choose appropriate metrics for clinical validation</td>
<td><strong>Recommendation 5:</strong> Select outcomes to measure net benefit from the patient perspective</td>
<td><strong>Recommendation 8:</strong></td>
<td><strong>Recommendation 9:</strong></td>
</tr>
</tbody>
</table>
**Analytic Validity: Initial Test Performance and Assay Refinement**

The Prolaris test is performed in Myriad’s state-of-the-art molecular diagnostics facility in Salt Lake City, Utah, under CLIA and CAP accreditation. The test also has gained approval from the New York State Department of Health.

Prolaris measures the expression of 31 CCP genes with known correlation to cell cycle progression in actively dividing cells, along with 15 housekeeping genes to control for sample quality. A valid “CCP score” (also called the “Prolaris Score”) requires successful measurement of both the housekeeping genes and the CCP genes and confirms the quality of the sample. The CCP score refers to the measurement of cell cycle gene expression alone, with no clinicopathologic data included.

Myriad scientists demonstrated analytic validity for Prolaris on formalin-fixed, paraffin-embedded (FFPE) prostate biopsy and RP samples; the standard deviation of the signature was 0.1 score units, representing 1.6% of the range of scores observed within previous clinical validation studies (Warf et al., 2015). In a study across 7,525 samples, 99.8% of the biopsy and 100% of the RP samples produced sufficient RNA for testing. In addition, RNA samples were able to reproduce measured CCP scores up to eight weeks after preparation. Finally, the linear and dynamic range of the CCP gene expression signature exceeded the parameters used in clinical testing.

**Clinical Validity: Test Validation and Generalizability**

Clinical validity for Prolaris has been demonstrated comprehensively through eight peer-reviewed, published studies across 10 patient cohorts, along with an internal study using samples submitted to Myriad for commercial testing and a scientific poster (Tables 3 and 4) (Cuzick et al., 2011; Cuzick et al., 2012; Cooperberg et al., 2013; Freedland et al., 2013; Bishoff et al., 2014; Cuzick et al., 2015; Koch et al., 2016; Tosoian et al., 2017; Scardino et al., 2016 - poster; Bardot et al., 2017 - poster).

- The patient population intended for clinical use of the test is men who have been newly diagnosed with localized prostate cancer. The test provides prognostic information based on molecular evaluation of biopsy tissue collected for clinical diagnostic purposes.
- Metrics for clinical validation include clinical endpoints (likelihood of 10-year mortality, metastatic disease, or biochemical recurrence [BCR]) that are valuable in planning and monitoring treatment. These mirror the endpoints recommended by NCCN.
- The impact of Prolaris on patient care will be proportionate to its ability to more accurately reclassify patient outcomes relative to existing parameters.
### TABLE 3: Summary of Prolaris Clinical Validation Studies

<table>
<thead>
<tr>
<th>Cohort, Specimen Type</th>
<th>Primary Endpoint</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis with Clinical Covariates</th>
<th>Ability of Prolaris to Predict Endpoint*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cuzick 2012</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cohort 3, Biopsy:</td>
<td>Disease specific mortality</td>
<td>HR=2.02 p=8.6x10^-10</td>
<td>HR=1.65 p=2.6x10^-3</td>
<td>Prolaris most predictive</td>
</tr>
<tr>
<td><strong>Cuzick 2015</strong></td>
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<tr>
<td>Cohort 9, Biopsy:</td>
<td>Disease specific mortality</td>
<td>HR=2.08 p=6.0x10^-14</td>
<td>HR=1.76 p=4.2x10^-7</td>
<td>Prolaris most predictive</td>
</tr>
<tr>
<td><strong>Cuzick 2011</strong></td>
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<tr>
<td>Cohort 1, Post-prostatectomy: U.S. men, radical prostatectomy from 1985-95; tumor registry. N=353</td>
<td>Biochemical recurrence</td>
<td>HR=1.89 p=5.6x10^-9</td>
<td>HR=1.77 p=4.3x10^-4</td>
<td>Prolaris and PSA were most predictive</td>
</tr>
<tr>
<td>Cohort 2, Transurethral resection of the prostate: Conservatively managed U.K. patients diagnosed after TURP from 1990-1996. N=337</td>
<td>Disease specific mortality</td>
<td>HR=2.92 p=6.1x10^-22</td>
<td>HR=2.57 p=8.2x10^-11</td>
<td>Prolaris most predictive</td>
</tr>
<tr>
<td><strong>Cooperberg 2013</strong></td>
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<tr>
<td>Cohort 4, Post-prostatectomy: Contemporary cohort of U.S. men, radical prostatectomy from 1994-2008. N=413</td>
<td>Biochemical recurrence</td>
<td>HR=2.13 p=2.2x10^-6</td>
<td>HR=2.01 p=5.7x10^-5</td>
<td>Prolaris most predictive</td>
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<tr>
<td><strong>Freedland 2013</strong></td>
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<tr>
<td>Cohort 5, Biopsy: U.S. men, external beam radiation therapy (EBRT) from 1991-2006. N=141</td>
<td>Biochemical recurrence</td>
<td>HR=2.55 p=0.0017</td>
<td>HR=2.11 p=0.034</td>
<td>Prolaris most predictive</td>
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<tr>
<td><strong>Bishoff 2014</strong></td>
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<tr>
<td>Combined Cohorts 6-8</td>
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<tr>
<td>Combined Cohorts 6-8</td>
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<tr>
<td>Cohort 6, Biopsy: German men, radical prostatectomy from 2005-2006. N=283</td>
<td>Biochemical recurrence</td>
<td>HR=1.60 p=2.4x10^-7</td>
<td>HR=1.47 p=4.7x10^-5</td>
<td>Prolaris and PSA were most predictive</td>
</tr>
<tr>
<td><strong>Koch 2016</strong></td>
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<tr>
<td>Cohort 10, Post-prostatectomy: Contemporary cohort of U.S. men, biochemical recurrence after radical prostatectomy from 1995-2010. N=47</td>
<td>Metastatic disease</td>
<td>OR=3.72 p=0.0060</td>
<td>OR=10.4 p=0.0031</td>
<td>Prolaris and pathologic Gleason score most predictive</td>
</tr>
<tr>
<td><strong>Tosoian 2017</strong></td>
<td></td>
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<tr>
<td>Combined Cohort of NCCN low-risk patients. N=188</td>
<td>Biochemical recurrence</td>
<td>HR=1.77 p=0.0022</td>
<td>HR=1.77 p=0.0030</td>
<td>Prolaris most predictive</td>
</tr>
</tbody>
</table>

*In multivariate analysis. Variables retaining their predictive significance in multivariate analysis provide information not captured by other variables.*
Synopses of Clinical Validation Publications

<table>
<thead>
<tr>
<th>Publication</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Prognostic Value of a Cell Cycle Progression Signature for Prostate Cancer Death in a Conservatively Managed Needle Biopsy Cohort (Cuzick 2012)</td>
<td>This study addressed the need to predict outcome in patients diagnosed with prostate cancer by needle biopsy (Cuzick et al., 2012). Prostate Scores were generated for 349 conservatively managed prostate cancer patients who were diagnosed by needle biopsy. The Prostate Score correlated only weakly with standard clinicopathologic measures, indicating that it provided unique information. In a multivariate analysis, the Prostate Score was the dominant variable in predicting 10-year mortality from prostate cancer (HR=1.65; p=2.6x10^-7). Adding prognostic information not captured by Gleason score or PSA level. For conservatively managed patients, the Prostate Score was the strongest independent predictor of prostate cancer death.</td>
</tr>
<tr>
<td>Validation of an RNA Cell Cycle Progression Score for Predicting Death from Prostate Cancer in a Conservatively Managed Needle Biopsy Cohort (Cuzick 2015)</td>
<td>This study validated both the CCP score and the combined clinical cell-cycle risk (CCR) score for predicting disease specific mortality (DSM) in a cohort of conservatively managed patients diagnosed with prostate cancer by needle biopsy (Cuzick et al., 2015). The study evaluated needle biopsies from 757 men in the U.K. diagnosed with clinically localized prostate cancer between 1990 and 2004 who pursued watchful waiting. The mean clinical follow-up was 10.6 years and 18% of patients died from prostate cancer. In a multivariate analysis (n=586) including CAPRA, the CCP score proved the most important variable for predicting DSM (hazard ratio=1.76; p=4.2x10^-1). It provided more independent prognostic information than any other variable. The combined CCR score was highly predictive and captured virtually all currently available prognostic information (hazard ratio = 2.17; p=10^-16).</td>
</tr>
</tbody>
</table>

Prognostic Value of an RNA Expression Signature Derived from Cell Cycle Proliferation Genes in Patients with Prostate Cancer: A Retrospective Study (Cuzick 2011) | This study describes the selection process for the genes that comprise the CCP score, referred to as the “Prostate Score,” and the initial clinical validation in two patient cohorts (Cuzick et al., 2011). The predefined Prostate Score was calculated from the expression levels of 31 cell cycle and 15 housekeeping genes, and its usefulness in predicting disease outcome was assessed. The Prostate Score was assessed retrospectively in one cohort of patients who had undergone RP (n=353) and in a second cohort of men with localized prostate cancer, diagnosed by use of a transurethral resection of the prostate (TURP), who were managed conservatively via a “watchful waiting” approach (n=337). In the RP cohort, the Prostate Score was useful in multivariate analysis for predicting the primary endpoint of BCR. The hazard ratio (HR), reflecting the fold increase in risk for the defined endpoint with one each one-increase in Prostate Score, was 1.77 (p=4.3x10^-5). The Prostate Score and PSA concentration were the most important variables and were more significant than any other clinical variable. In the TURP cohort, the Prostate Score was the most important variable in multivariate analysis for predicting the primary endpoint of time to death from prostate cancer (HR=2.57; p=8.2x10^-16), and was stronger than all other prognostic factors. |

Validation of a Cell-Cycle Progression Gene Panel to Improve Risk Stratification in a Contemporary Prostatectomy Cohort (Cooperberg 2013) | The purpose of this study was to validate the test in predicting BCR from a contemporary RP cohort (Cooperberg et al., 2013). The Prostate Score was assessed for independent prognostic utility beyond that of a standard clinicopathologic risk measure (the CAPRA-S score), and a score that combined the Prostate and CAPRA-S scores was validated. Of 413 men in the cohort, 82 (19.9%) men experienced recurrence. The Prostate Score proved to be the dominant variable in multivariate analysis for the prediction of BCR (HR=2.01; p<5.7x10^-7). Among patients in the study with low-risk Prostate Scores, there was no recurrence of prostate cancer within the five-year study period. However, prostate cancer did recur in 50% of the patients with high-risk Prostate Scores. The test was found to predict the risk of prostate cancer recurrence more accurately than did the current clinical parameters used in risk assessment. |

Prognostic Utility of Cell Cycle Progression Score in Men With Prostate Cancer After Primary External Beam Radiation Therapy (Freedland 2013) | This study evaluated the prognostic utility of the Prostate Score for predicting BCR in men with prostate cancer treated with external beam radiation therapy (EBRT) as their primary curative therapy (Freedland et al., 2013). The Prostate Score was derived retrospectively from diagnostic biopsy specimens of men diagnosed with prostate cancer from 1991 to 2006. All patients were treated with definitive EBRT, approximately half of the cohort was African American. Of 141 patients, 19 (13%) had BCR. In a multivariate analysis that included Gleason score, prostate-specific antigen, percent positive cores, and androgen deprivation therapy, the HR (2.11) for the Prostate Score remained significant (p=0.034). Among men treated with EBRT, the Prostate Score significantly predicted outcome and provided greater prognostic information than was available with clinical parameters. |

Prognostic Utility of the CCP Score Generated from Biopsy in Men Treated with Prostatectomy (Bishoff 2014) | This study evaluated the prognostic utility of the Prostate Score in three cohorts of men who had undergone RP, predicting patients who would have a favorable outcome following surgical therapy (N=283; N=176; N=123) (Bishoff et al., 2014). Prostate Scores were derived from simulated or diagnostic biopsy tissue and evaluated for association with BCR and metastatic disease. In all three cohorts, the Prostate Score was associated with both BCR and metastatic disease. Combined analysis of all three cohorts (N=582) showed that the Prostate Score was a strong predictor of BCR following RP in the multivariable analyses (HR=1.47; p=4.7x10^-5). The Prostate Score was the strongest predictor of metastatic disease after adjusting for clinical variables (HR=4.19; p=8.2x10^-16). This study evaluated the association between the Prostate Score and BCR after surgery, but used only the amount of tumor tissue that is available in prostate needle biopsies in the analysis to generate the Prostate Score. The similarities in the hazard ratios between this study and others suggests that the score derived from limited tissue in a needle biopsy is no less prognostic than the score derived after surgery. This suggests that the sampling bias inherent in needle biopsies has limited impact on the Prostate Score’s prognostic performance. |

Use of the Cell Cycle Progression (CCP) Score for Predicting Systemic Disease and Response to Radiation of Biochemical Recurrence (Koch 2016) | This study evaluated the ability of the CCP score to discriminate between the presence of systemic disease and local recurrence in patients with BCR after RP (Koch et al., 2016). The CCP score proved a significant predictor of outcome in 47 patients over a median follow up time of 113 months (odds ratio 3.72; p=0.006). Consistent with previous results, this study found only a weak correlation between the CCP score and other clinical variables, further supporting the hypothesis that highly proliferative tumors are not easily identifiable based on standard clinicopathologic measures. These results raise the possibility that, in addition to aiding initial management decisions, the CCP score might also be useful in predicting which tumors will respond to radiotherapy or other interventions after failing radical prostatectomy. |

Prognostic Utility of biopsy-derived Cell Cycle Progression Score in Patients with National Comprehensive Cancer Network Low-risk Prostate Cancer Undergoing Radical Prostatectomy: Implications for Treatment Guidance (Tosoian 2017) | This study evaluated the prognostic utility of the Prostate Score in men with National Comprehensive Cancer Network (NCCN)-defined low-risk prostate cancer (PCA) undergoing radical prostatectomy (RP) (N=236). In this cohort, the Prostate Score improved clinical risk stratification of men who were at increased risk of biochemical recurrence (BCR), which suggests the Prostate Score could improve the assessment of candidacy for active surveillance and guide optimum treatment selection in these patients with otherwise similar clinical characteristics. |

Internal Analysis: Application of AS Threshold to Submitted Samples (Scardino 2016) | Studies described to this point were conducted by independent laboratories in partnership with Myriad. To further evaluate and extend the clinical validity of the Prostate test, Myriad evaluated a series of samples submitted to its laboratories for commercial testing (Scardino et al., ASCO-GU poster 2016). This study applied the Prostate Score AS Threshold to a series of 11,885 patient samples submitted for testing. This threshold was validated in a large cohort with known outcomes, with no deaths in low-risk men (Cuzick et al., 2012; Cuzick et al., 2015). The Prostate Score for each sample was generated using the Prostate Score with the CAPRA score obtained through clinicopathologic data submitted with the sample. Of the 11,885 patients included in the analysis, 7,325 (62.8%) qualified for AS based on their Prostate Scores. Nearly half of these patients (3,368; 45.1%) would not have qualified for AS based on their clinical characteristics alone. Again, these results suggest strongly that the Prostate Score provides significant clinical utility. |

Comparing the Prognostic Utility of the CCP Score for Predicting Metastatic Disease in African American and Non-African American Men with Prostate Cancer (Bardot 2017) | This study evaluated the utility of the Prostate Score generated from diagnostic biopsy to predict metastatic disease in a large cohort of treated patients that is highly enriched with an African American patient population. Consistent with previous reports, the Prostate Score was a strong predictor of metastatic disease. In this analysis, there was no evidence of an interaction between the Prostate Score and either race or treatment (i.e., the Prostate Score hazard ratio was not significantly different). Contrary to expectation, this study provided no evidence that African American men have more aggressive disease than non-African American men after accounting for all available molecular and clinicopathologic prognostic information. |
Phase 2 Summary

The ten clinical validity studies for Prolaris demonstrated the following:

- RNA derived from biopsies produced valid Prolaris Scores for the majority of the archival FFPE samples examined. Notably, all samples had been preserved for about 10 years. Therefore, the technology used is biochemically robust and appropriate for diagnostic analysis of needle biopsy tissue.

- The Prolaris Score provides significant prognostic information for death from prostate cancer. It was the strongest predictor of 10-year prostate cancer-specific mortality, as compared with other clinicopathologic measures, including Gleason score and PSA.

- Information provided by the Prolaris Score is fully objective in nature — unlike Gleason grading, which has a subjective component.

- The Prolaris Score is combined with the CAPRA risk assessment score in a validated algorithm to produce the 10-year risk of prostate cancer mortality, which is reported to the physician.

- The Prolaris Score provides significant pre-treatment prognostic information that cannot be provided by clinical variables. This information is useful for determining which newly diagnosed men can be managed safely through conservative approaches such as AS.

- Prolaris is the only test available currently that includes conservatively managed cohorts in its validation studies. Indeed, Prolaris is the only test that is validated against all three NCCN recommended endpoints, in all three treatment modalities, in all three risk categories, and in all three sample types.

Physician and Patient Decision Making:
Components of Clinical Test Performance and Health Impacts

The anticipated clinical pathway for Prolaris begins with physicians providing care for men with newly biopsy-diagnosed localized prostate cancer. The physician orders the Prolaris test as a standard component of a decision-making protocol for disease management. A portion of the needle biopsy used for the diagnosis would be submitted with clinicopathologic data for Prolaris testing. Evidence of clinical utility is a change in the patient’s treatment pathway as a result of using Prolaris as part of the diagnostic and decision-making process.

The selected outcomes to measure net benefit from the patient perspective involve the straightforward estimation of 10-year disease-specific mortality risk. This information addresses directly the patient’s important question: What is the risk of dying from one’s prostate cancer? If the Prolaris test is useful, one would expect physicians and patients to apply test result information in their decisions on disease management, possibly changing the decisions based on Prolaris results. Successful long-term disease management (health maintenance, avoiding treatment-related adverse effects/functional complications and improved quality of life) and cost savings to the patient, provider and payer complete the list of desired outcomes for Prolaris clinical utility.
Phase 3 Summary

Components of Clinical Test Performance and Health Impacts

Evidence of Clinical Utility
Change in the patient’s management pathway after incorporating Prolaris test results. This aligns specifically with three Blue Ribbon Panel Research Recommendations for the Obama Administration’s Cancer Moonshot initiative (https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel).

- Minimize cancer treatment’s debilitating side effects
- Expand use of proven prevention and early detection strategies
- Mine past patient data to predict future patient outcomes

Outcomes to Measure Net Benefit From the Patient Perspective
- Accurate estimation of 10-year disease-specific mortality risk
- Change in the patient’s management pathway after incorporating Prolaris test results
- Successful long-term health maintenance
- Avoiding treatment-related adverse effects or lasting functional complications such as sexual, urinary or bowel dysfunction
- Improved quality of life
- Demonstrated cost savings for prostate cancer care as a result of Prolaris-informed management.

Clinical Utility: Comparison With Standard of Care
CMTTP provides a number of recommendations for addressing Phase 4. Those most relevant to establishing the clinical utility of Prolaris include Recommendation 9: Prospective/Longitudinal Observational Studies (such as Decision Impact Studies) and Recommendation 10: Modeling Techniques. Rationale pertinent to Reporting Recommendation 6: Randomized Controlled Trials is discussed below.

Change in Prostate Cancer Management: Decision Impact Studies as a Validated Outcome
Phase 4 was first addressed by documenting the clinical utility of the Prolaris test in two published decision impact studies involving physicians and patients in community-based urology offices (Crawford et al., 2014; Shore et al., 2016). Substantial literature supports the use of decision impact studies as a clinical utility measure for diagnostics in scenarios where medical management outcomes are important and clearly differentiated (Staub et al., 2012).
Prospective Decision Impact Study 1: Physicians
This study evaluated the impact of the Prolaris report on treatment recommendations made by physicians ordering the test commercially for patients in their practices (Crawford et al, 2014). This study followed 331 untreated patient cases following diagnosis; the main endpoints of the study were “percentage change in treatment options selected,” and the “overall direction of change in the treatment burden before and after the test.” Physicians completed surveys regarding their treatment recommendations before and after receiving the test results and discussing them with patients. They also rated how Prolaris influenced their treatment decisions.

Most patients in the cohort (87.6%) fell within the low or intermediate AUA risk categories based on clinicopathologic measures. Actual treatment selections were confirmed via a third-party audit of patient charts at least 45 days following final survey responses, which was at least 90 days post diagnosis. The ordering physicians came from 31 U.S. states, and 89.3% specialized in urology. Among the patients, 52% had fee-for-service Medicare coverage, 10.6% were participants in managed Medicare plans, and 37.4% had private insurance.

Study results showed a substantial impact of the Prolaris report on physician recommendations for patient treatment:

- Overall, 65% of cases showed a change between intended therapy options pre- and post-Prolaris test reporting, including a 49.5% reduction in surgical interventions and a 29.6% reduction in RT.
- Changes in treatment recommendations were also measured in a binary format, i.e., between interventional (radical prostatectomy, radiation therapy, hormone therapy) and non-interventional (AS or watchful waiting) options.
  - Recommendations for interventional therapy (RP, RT or some combination) dropped by 37.2% in favor of non-interventional management.
  - In 23.4% of cases, recommendations shifted in the opposite direction, from non-interventional to interventional.
- 80% of AUA low-risk and 39% of AUA intermediate-risk patients ended up in the non-interventional or AS group, corresponding to significant reductions in both RP and RT.
- Back-end chart reviews showed 80.2% concordance between physician recommendation and actual treatment. Among study participants, the Prolaris test was found to impact clinical decision-making in 97.8% of the respondents.

In summary, the study showed that the Prolaris test provided meaningful new information to localized prostate cancer risk assessment by physicians, and that test results led to treatment changes, aligned with the prostate cancer risk specified by the results.

Prospective Decision Impact Study 2: Physicians and Patients
This study added a necessary component – patient preference – to the design, representing the first large-scale prospective biomarker study to include both physician and patient consensus on prostate cancer treatment decisions. In a cohort of 1,206 patients, most of whom were initially categorized as AUA low (40.3%) or intermediate (42%) risk, the study surveyed physicians and patients during four sequential steps in the decision-making process:
• Prior to the Prolaris test
• After return of Prolaris results, before consult between physician and patient regarding intended treatment
• After return of Prolaris results and patient consult regarding intended treatment
• After actual treatment (minimum three months of clinical follow-up).

Results again showed a substantial impact of the Prolaris report on treatment decisions:
• In almost half (47.8%) of cases, treatment decisions changed based on receipt and review of Prolaris results. Decisions shifted to a reduction in treatment in 72.1% of these.
• Within each AUA risk category, there was a significant change in treatment (intervention versus non-intervention). After the Prolaris test, 57% of low-risk and 24% of intermediate-risk patients decided to pursue non-interventional (AS) management. This corresponded to significant reductions in both RP and RT intervention.

Myriad’s studies demonstrate that: (1) prognostic discrimination at disease diagnosis is improved with the addition of Prolaris (clinical validity studies); and (2) physicians appropriately use the information to change clinical management (clinical utility studies). Therefore, it follows a priori that men will be better managed as a result of using Prolaris with less overtreatment for indolent disease and less undertreatment for aggressive disease.

Physician/Patient Impact Summary
Results of these real-world physician and physician/patient impact studies support each other with closely concordant results:
• Prolaris provides meaningful information to prompt behavior change regarding intended therapy options in a substantial number of cases.
• Incorporating Prolaris results into physician and patient decision-making resulted in significant reductions in interventional treatments (RP and RT).
• Decisions to change treatment included patients in both AUA low-risk and intermediate-risk groups.
• Prolaris stratified risk for physicians and patients beyond that assigned by clinicopathologic features alone. There was an observed shift from intervention to non-interventional management. Some AUA low-risk patients chose instead to pursue intervention following receipt of Prolaris results.

Prospective Randomized Controlled Trials
For the foreseeable future, clinical decision impact is the only Prolaris outcome measure that will be available. Given the lengthy natural history of localized prostate cancer (a 10-year mortality rate of 3.2%), it is neither practical nor feasible to conduct prospective trials in which patients are randomized with or without Prolaris and followed for 10 to 20 years to evaluate survival and metastatic disease outcomes.
• Because prostate cancer mortality is low to begin with and because prostate tumors grow slowly, it is difficult to show a statistically significant change in disease-specific mortality. Our modeling shows that a 10-year prospective study randomizing NCCN low to favorable-intermediate risk patients to Prolaris testing would require 3,672 patients in each arm to show a 50% increase in disease-specific mortality, or 10,367 patients in each arm to show a 25% decrease.
The time lag associated with conducting such a large randomized controlled study would result in an unacceptable number of missed opportunities to use the test on patients diagnosed during the extended study period.

This is particularly concerning given research showing that men with low-risk disease have limited benefit from interventional treatment such as RP, and the published data herein demonstrating that the use of Prolaris reduces the number of prostatectomies in these men (Wilt et al., 2017; Crawford et al., 2014; Shore et al., 2016; Hamdy et al., 2016).

CMTP recognizes that prospective randomized controlled trials for molecular diagnostic tests in oncology may not be necessary when evidence exists to link treatment choices to patient outcomes. They support the use of prospective observational studies (e.g., decision impact studies) to demonstrate clinical utility when “there is genuine uncertainty on the part of the expert medical community regarding the preferred clinical pathway” (http://www.cmtpnet.org/docs/resources/MDX_EGD.pdf). This is the case for the treatment of localized prostate cancer, as a clinician may choose surgery, radiation, or AS for men regardless of risk, as no preferred treatment paths currently exist based on societal guidelines from NCCN, AUA and the American Society of Clinical Oncology (ASCO).

Also in the case of prostate cancer, society benefits from the existing results from long-term prospective studies that demonstrate the respective impacts of interventional treatment or conservative management on mortality and functional outcomes. These reports, discussed below, serve as suitable surrogates for evaluating the potential impact of Prolaris test-informed treatment decisions on long-term outcomes for localized prostate cancer.

**Impact on Long-Term, Disease-Specific Mortality**

Long-term prospective studies show that conservative management (AS and observation) perform just as well as medical intervention, in the form or RT or RP, with regard to long-term mortality outcomes in men diagnosed with localized prostate cancer. Here we highlight three such studies.

The PIVOT study, a randomized prospective study launched in the mid-1990s, compared long-term outcomes in men treated with RP with those followed through observation (Wilt et al., 2017 and 2012). A cohort of 731 men (mean age = 67 years) was followed for nearly 20 years. In this cohort, 40% had low-risk, 34% intermediate-risk and 21% high-risk prostate cancer. The primary outcome measured was mortality from all causes, and the secondary outcome measured was prostate cancer-specific mortality.

- Through nearly 20 years of follow up, RP was not associated with significantly lower all-cause or prostate-cancer mortality than observation among men with localized prostate cancer.
- The study concluded that RP surgery may have been associated with lower all-cause mortality than observation among men with intermediate-risk disease but not among those with low-risk disease or high-risk disease, although the differences remained nonsignificant.
- On the other hand, men in the study did report adverse events as a result of RP surgery: 17.1 percent reported urinary incontinence, 81.1 percent reported erectile dysfunction, and 12.2 percent reported bowel dysfunction.
- Furthermore, 21 percent of the patients who underwent surgery reported perioperative complications within 30 days after the procedure.
A larger study (Hopkins) followed men with favorable-risk prostate cancer through a prospective study of AS (n=1,298 men, median age 66 years; AS involved a semiannual PSA measurement, digital rectal examination and an annual prostate biopsy) (Tosoian et al., 2015). Primary outcomes measured were overall, cancer-specific and metastasis-free survival. Secondary outcomes were cumulative incidence of tumor reclassification and curative intervention. The median follow-up time for these 1,298 men was 5 years, though some were followed for up to 18 years. The study showed:

- Survival rates of 93% overall, 99% cancer-specific and 99.4% metastasis-free at 15 years.
- Cumulative tumor grade reclassification was 26% at 10 years and 31% at 15 years.
- Median treatment-free survival of 8.5 years, with factors associated with reclassification being older age, PSA score, and greater number of biopsy cores.

The third study, ProtecT, examined 10-year outcomes in 1,643 men diagnosed with clinically localized prostate cancer between 1999 and 2009 using PSA testing and other clinical measures (Hamdy et al., 2016). These men (median age 62 years) were randomized into three clinical management groups: active monitoring (545 men), surgery (553) and radiotherapy (545). In the active-monitoring group, PSA levels were measured every three months in the first year, followed by testing every 6-12 months thereafter. The primary trigger for considering alternative clinical management in this group was a change in PSA score. At baseline, there were no meaningful differences in Gleason score or tumor grade among the three groups. The primary outcome, measured at a median of 10 years follow-up, was prostate cancer mortality. Secondary outcomes included rates of disease progression, metastases, and all-cause deaths.

- At a median of 10 years follow-up, prostate cancer mortality was low regardless of treatment type with no significant difference in mortality among the three groups.
- All-cause mortality also was low, at approximately 10%, with no significant differences seen among the three groups.
- Disease progression and metastasis events did occur more frequently in the active-monitoring group as compared with the other two groups. Although these differences highlight the known effectiveness of immediate intervention, the treatments themselves have not translated into significant differences in disease-specific or all-cause mortality. This result highlights the need for improved risk discrimination at diagnosis (i.e., some men on AS would have benefited from treatment).
- Almost half (44%) of the men in the active-monitoring group received no further intervention during the 10-year follow-up period and thus avoided treatment side effects. For those who did ultimately pursue intervention, the change of management might have occurred for reasons other than disease progression.

Evidence supporting the findings of these three major studies continues to build (Klotz et al., 2015; Musunuru et al., 2016). Combined, these data highlight the importance of using the most precise measures possible, including Prolaris, to improve risk discrimination among patients. This in turn will lead to better treatment choices at diagnosis for each individual, helping ensure improved outcomes.
Applying the CMTP's Chain of Evidence for Clinical Utility to Prolaris®

### Long-Term Disease-Specific Mortality Summary

- Large, long-term prospective studies show that conservative management (AS and observation) performs just as well as intervention for low-risk and favorable-intermediate men, with regard to long-term mortality outcomes.
- Outcomes for men diagnosed with localized prostate cancer may depend more on the proper selection of candidates for conservative management than on the type and intensity of monitoring.
- Using the most precise measures available will improve risk discrimination among patients. This in turn will lead to better treatment choices at diagnosis, be they for more conservative management or intervention, helping to ensure improved outcomes.

### Quality of Life and Functional Impacts of Conservative Management

For the patient, improved functional outcomes add great value to a risk-appropriate selection of conservative disease management when appropriate. Sexual, urinary and bowel dysfunction are well-established and significant functional side effects of RP and RT. A long-term study following 1,655 men who had undergone these interventional treatments showed significant functional declines after up to 15 years post-diagnosis (Resnick et al., 2013).

RP outcomes after two to 15 years of follow-up included:
- Urinary incontinence in 9.6-18.3% of cases
- Erectile dysfunction in 78.8-87.0% of cases
- Bowel dysfunction in 13.6-21.9% of cases

RT outcomes after two to 15 years of follow-up included:
- Urinary incontinence in 3.2-9.4% of cases
- Erectile dysfunction in up to 93.9% of cases
- Bowel dysfunction in 34.0-35.8% of cases

Another study compared sexual function among men with low-risk prostate cancer who chose AS with those who received RT, RP or both (van den Bergh et al., 2012). Patient follow-up at 6 months and 12-18 months post diagnosis showed significantly less impact of disease and treatment choice on sexual function in men managed through AS (comprised of PSA screen, digital rectal exam, repeat biopsies). This study found that men with localized cancer on AS were more sexually active than men who had undergone interventional treatment; in men who were not sexually active, the causes were less often attributable to erectile dysfunction. Sexual inactivity as a result of erectile dysfunction occurred in:
- 20-30% of AS cases
- 86-90% of RP cases
- 56-60% of RT cases
- 71-76% in combined RP + RT cases

Treatment-related morbidities are documented in more recent, modern cohorts, as well. In these, treatment such as RP and RT resulted in an increase in urinary incontinence and irritation, erectile dysfunction, and bowel dysfunction (Donovan et al., 2016; Barocas et al., 2017; Chen et al., 2017; Jeldres et al., 2015). In contrast, AS resulted in better urinary function, less urinary incontinence and better sexual function, and quality of life was similar to men without prostate cancer (Vanderbos et al., 2016 - poster).
Cost Savings Associated with Prolaris-Informed Management

Cost modeling has demonstrated that using Prolaris can produce significant cost savings for insurance payers, due to the expected shift from intervention to AS (Crawford et al., poster 2015). We estimated the cost impact of Prolaris testing in prostate cancer management through economic modeling for a hypothetical cohort of men with localized disease. The model extended out 10 years, with assumptions about management and disease progression based on published observations and physician interviews. We calculated the total cost of care for two groups of men in the model: a group managed according to current clinical practice (Table 5) and a group whose management was altered based on Prolaris test results (Table 6).

### Quality of Life and Functional Impact Summary

- Conservative management (AS) of localized prostate cancer helps men avoid critical functional impacts caused by interventional treatments, including sexual, urinary and bowel dysfunction.
- Shifting from interventional to conservative disease management when appropriate adds great value for patients in the form of improved functional outcomes and quality of life.

### TABLE 5: Reference Scenario Clinical Treatment Paradigm

<table>
<thead>
<tr>
<th>AUA Risk Group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tbody>
<tr>
<td>Active Surveillance</td>
<td>15%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Radical Prostatectomy Only</td>
<td>45%</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>Radiation Therapy Only</td>
<td>35%</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Androgen Deprivation Therapy Only</td>
<td>5%</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>Radical Prostatectomy and Radiation Therapy</td>
<td>0%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Radiation Therapy and Androgen Deprivation Therapy</td>
<td>0%</td>
<td>3%</td>
<td>25%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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### TABLE 6: Test Scenario Clinical Treatment Paradigm

<table>
<thead>
<tr>
<th>AUA Risk Group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>Active Surveillance</td>
<td>69%</td>
<td>27%</td>
<td>0%</td>
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<tr>
<td>Radical Prostatectomy Only</td>
<td>16%</td>
<td>31%</td>
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<tr>
<td>Radiation Therapy Only</td>
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<td>21%</td>
<td>5%</td>
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<tr>
<td>Androgen Deprivation Therapy Only</td>
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<td>10%</td>
<td>25%</td>
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<td>5%</td>
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<tr>
<td>TOTAL</td>
<td>100%</td>
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</tr>
</tbody>
</table>

In these models, Prolaris reduced costs by up to $2,850 per patient tested over 10 years, after accounting for test cost. For a health plan with 10 million members, this translates to savings of more than $16 million, with two-thirds of those savings realized in the first year following diagnosis and testing (Table 7).
TABLE 7: Economic Impact of Test on Costs to Payer

<table>
<thead>
<tr>
<th></th>
<th>Number of Localized Prostate Cancer Patients</th>
<th>Number of Tests Modeled</th>
<th>Cumulative Cost at Year 10 in Reference Scenario</th>
<th>Cumulative Cost at Year 10 in Test Scenario</th>
<th>Cumulative Savings at 10 Years per CCP Test-Eligible Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Patient Tested</td>
<td>1</td>
<td>1</td>
<td>$64,464</td>
<td>$61,849</td>
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<tr>
<td>Health Plan – 5 Million Members</td>
<td>3,078</td>
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<td>Health Plan – 10 Million Members</td>
<td>6,156</td>
<td>5,648</td>
<td>$396,840,241</td>
<td>$380,741,648</td>
<td>$16,098,593</td>
</tr>
</tbody>
</table>

These initial savings stem from foregoing RP, RT or other medical interventions, and associated follow-up medical costs, in lieu of AS. Additional cost savings would be realized over the longer term based on reduced progression to metastatic disease, resulting from identification and appropriate treatment for patients with more aggressive disease. Even in the most conservative scenarios modeled, no circumstances caused the model to show that the test was no longer cost saving.

Cost Savings Summary

- Modeling shows that Prolaris can reduce costs by up to $2,850 per patient tested over 10 years, after accounting for test cost. These cost savings include low, intermediate and high risk men in the analysis.
- For a health plan with 10 million members, this translates to savings of more than $16 million, with two-thirds of those savings realized in the first year following diagnosis and testing.
- Additional cost savings would be realized over the longer term based on reduced progression to metastatic disease.
- When only low and intermediate risk men are included in the analysis, the per patient savings in the initial year of diagnosis and treatment equals $7,510.
Phase 4 Summary

Comparison with standard of care:

- Decision impact studies are a valid clinical utility measure for diagnostics in scenarios where medical management outcomes are important and clearly differentiated.

- Two decision impact studies have shown that the Prolaris test influences physician and patient selection of treatment options.

- Given the long natural history of localized prostate cancer (a 10-year mortality rate of 3.2%), it is impractical to conduct long-term, randomized prospective trials in which patients are randomized with or without Prolaris and followed for 10 to 20 years to evaluate survival and metastatic disease outcomes.

- CMTP recognizes that prospective randomized controlled trials for molecular diagnostic tests in oncology may not be necessary when evidence exists to link treatment choices to patient outcomes.

- Proper, well-informed selection of favorable risk candidates for conservative disease management (AS) will produce long-term mortality outcomes similar to or better than those resulting from interventional (RP, RT or combination) treatment. Prolaris provides improved risk discrimination at diagnosis and has been validated against outcomes; thus, when a patient is managed by his physician according to his Prolaris Score, the patient experiences a better and more predictable treatment outcome.

- Shifting from interventional to conservative disease management when appropriate adds value for patients in the form of improved functional outcomes and quality of life.

- Prolaris provides clinically valid and clinically useful information to aid in the appropriate selection of treatment; this information complements and extends the accuracy of clinicopathologic data alone.

- Economic modeling indicates that Prolaris will generate substantial near- and long-term cost savings for management of localized prostate cancer.
Conclusion

Prolaris addresses a currently unmet need in prostate cancer by improving accuracy in predicting disease aggressiveness and outcome. The Prolaris Score is the most powerful prognostic variable at disease diagnosis and in the contemporary post-surgical patient, providing additional, unique information about the individual patient’s tumor biology. The addition of Prolaris to the prostate cancer clinical pathway has been proven to drive rational treatment decisions consistent with the disease aggressiveness indicated by their underlying tumor biology and with widely accepted national guidelines (NCCN, AUA). Indeed, Prolaris is the only test validated against all three NCCN recommended oncologic endpoints, in all three treatment modalities, and in all three risk categories. Further, because Prolaris was validated against proven outcomes, medical decisions made in alignment with Prolaris results lead to better patient outcomes. In the advent of precision medicine and the Cancer Moonshot initiative, Prolaris is a key biomarker for use in localized prostate cancer, helping urologists determine the right treatment, at the right time, for the right patient.

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Publications


Applying the CMTP’s Chain of Evidence for Clinical Utility to Prolaris®

**Posters**


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