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Applying Prolaris Data to an Evidentiary Framework

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ALTERNATIVE FRAMEWORK FOR ASSESSING CLINICAL UTILITY OF PROGNOSTIC TUMOR BIOMARKERS

New biomarker tests can achieve the "gold standard" Level of Evidence (LOE) I for clinical utility by demonstrating improved outcomes through prospective randomized controlled trials (PRCTs), with subjects assigned to receive either the new test or standard of care. However, Simon et al. and others have acknowledged that challenges such as variable medical care, small treatment effects, and long outcome timeframes can present obstacles to timely validation in a PRCT of prognostic tumor biomarkers for clinical utility (Simon et al., 2009; CMTP 2013; NICE 2017). Addressing these challenges, Simon et al. presented an alternative framework for using archived tumor specimens to establish LOE I or II, with studies that meet LOE II serving as adequate evidence of clinical utility in "particularly compelling circumstances." This revised framework accepts the use of archived specimens from previous prospective observational studies with known outcomes, provided that the studies meet certain requirements and that the study cohort represents a defined medical indication for use of the particular biomarker.

Despite the emergence of alternative frameworks, payers have been reluctant to apply them to their review of the data, leading to continued lack of coverage. The result is limited patient access to testing that can inform medical management, improve outcomes, and reduce costs. The American Medical Association (AMA) recently presented new policy regarding genetic and genomic testing, encouraging transparent coverage and payment policies "that are evidence-based and take into account the unique challenges of traditional evidence development through RCTs, and work with test developers and appropriate clinical experts to establish clear thresholds for acceptable evidence" (American Medical Association, 2017).

This white paper aligns the Prolaris® prostate cancer (PCa) prognostic test with the widely cited and accepted Simon et al. evidentiary framework of 2009, positioning it for favorable payer coverage decisions. Analysis across six published studies with non-overlapping patient cohorts showing notably consistent and significant results places Prolaris firmly within LOE II – which stands as a practical, real-world benchmark for clinical utility for a disease with a long natural history and that is regularly over treated.

THE SIMON et al. EVIDENTIARY FRAMEWORK

Recognizing the complexity of establishing the clinical utility of tumor biomarkers, Simon et al. proposed a refined system for biomarker evaluation (Simon et al., 2009). This system ranks the types and quantities of evidence available for clinical utility within a hierarchical Level of Evidence Scale originally developed through the American Society of Clinical Oncology (Hayes et al., 1996).

The scientific "gold standard" is demonstrating clinical utility through one or more large-scale, prospective randomized clinical trials (PRCTs); these are required to reach Level of Evidence I, the highest rating which indicates that a biomarker can change clinical decision making and improve outcomes (Table 1). Practically speaking, however, PRCTs for cancer biomarkers often require unrealistic study sizes to achieve statistical significance. By taking as many as 15-20 years to complete, they also prove time-inefficient and cost prohibitive. These factors, plus ethical considerations encouraging more timely advances in patient treatment, point strongly to alternate validation paths. The Simon et al. Level of Evidence II allows for practical, real-world and timely demonstration of clinical utility, through the use of archived specimens from previously completed prospective trials (Table 1; Category B) or observational registries (Table 1; Category C).

TABLE 1

Simon et al. Level of Evidence (LOE) descriptions and requirements.

Levels of evidence in the Simon et al. evidentiary framework		
LOE	DESCRIPTION	REQUIREMENTS
I	Practice-changing. The biomarker reliably influences clinical treatment decisions.	**One "Category A" study:** PRCT designed to test the biomarker's prognostic or predictive value. -or- **At least two "Category B" studies with consistent results:** • Utilizes archived samples from a prospective clinical trial not specifically designed to test the biomarker. • Both studies must be designed, conducted, and analyzed in a similar manner.
II	Category C studies meeting LOE II could be sufficient to change practice under "particularly compelling circumstances."	**One "Category B" study** -or- **Three* or more independent "Category C" studies that provide consistent results** • Utilizes archived samples from patients enrolled in a prospective observational registry with specimen collection, treatment, and follow-up dictated by standard of care. • Requires careful assessment to rule out confounding or selection bias. • At least two validation studies must be designed, conducted, and analyzed in a similar manner.

*One development study + two validation studies

Since 2009, more than 200 research publications have cited the Simon et al. evidentiary framework, and it is recognized by a number of medical societies and guideline recommendations for tumor prognostics. This signifies widespread acceptance of the framework over the past decade. Moreover, organizations including the Center for Medical Technology Policy (CMTP) and the U.K. National Institute for Health Care and Excellence (NICE) have recognized the challenges in evaluating clinical utility for oncology molecular diagnostics and the clear need for alternate frameworks that link relevant data from multiple sources and elicit expert opinion to develop compelling cases for support (CMTP 2013; NICE 2017).

SIMON et al. APPLIED TO PROSTATE CANCER

Two "compelling circumstances" qualify PCa as a condition warranting practice change using a validated LOE II prognostic biomarker (as interpreted by Myriad):

1

Overtreatment: In the United States, providers lack trust in current clinicopathologic measures to guide selection between active surveillance (AS) and interventional treatment, i.e., radical prostatectomy or radiation therapy (Maurice et al., 2016). This often results in interventional treatment for patients who do not need it (Andriole et al., 2009; Chou et al., 2011; Welch et al., 2009)

2

Long natural history of PCa: The indolent, slow-growing nature of most prostate tumors presents challenges to completing prospective, randomized biomarker trials in a time-efficient, cost-efficient, and ethical manner. LOE I is not achievable for PCa prognostics within the current paradigm. Based on an 80% power to detect a statistically significant 25% difference in PCa death, it is estimated that a 5-year study would require between 33,000 and 43,000 subjects with low-risk PCa (Myriad internal analysis).

A reliable prognostic marker for PCa has the potential to reduce overtreatment substantially, while helping providers and patients make sound medical management decisions over the typically lengthy course of PCa.

PROGNOSTIC TOOLS NEEDED IN PCa TREATMENT SELECTION

Guideline-based treatment selection for newly diagnosed, localized PCa involves several considerations, including:

- **Patient medical history**
- **Prognosis**
- **Balancing treatment effectiveness against harmful side effects**
- **Patient preference**
- **Cost**

A validated molecular prognostic test that improves predictive accuracy over clinicopathologic parameters alone can bring providers and patients extra confidence in selecting appropriate, cost-effective treatments that maximize benefit-to-harm ratio (Crawford et al., poster 2015). Such assurance often is needed to consider AS in lieu of definitive intervention in favorable-risk cases, avoiding overtreatment. Thus, validated molecular prognostic tools for PCa merit careful consideration for positive payer coverage.

PROLARIS HAS PROGNOSTIC VALUE FOR PATIENTS WITH LOCALIZED PCa

Introduced in 2012, Prolaris is a PCa prognostic test that measures tumor biology in biopsy tissue to stratify patient risk precisely, according to disease aggressiveness. The test is intended for men who have clinically localized, non-metastatic PCa, confirmed by biopsy, and who have not received prior intervention or treatment. Prolaris test results include a prognostic score that estimates the patient's 10-year PCa mortality risk if conservatively managed, alongside the estimated risk of metastasis following a curative intervention. Providers and patients use this score to select among treatment choices, including AS and more invasive interventions such as radical prostatectomy (RP) or radiation treatment (RT).

PROLARIS ADDS NEW PREDICTIVE POWER TO TRADITIONAL PCa RISK ASSESSMENT METHODS

Because Prolaris combines molecular analysis with clinicopathologic data to generate 10-year mortality and post-intervention metastasis risk assessments, it adds new information and significant predictive power to traditional PCa risk assessment methods. Substantial published evidence demonstrates the analytical and clinical validity of Prolaris in correlating a patient's tumor molecular status with long-term outcomes and shows that Prolaris is a better predictor of oncologic endpoints than standard cliniocopathologic features (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). Two of the published validation studies include prediction of prostate cancer specific mortality in conservatively managed patients, confirming Prolaris' ability to be used in the intended use population; that is, men who have clinically localized, non-metastatic prostate cancer who are trying to decide between conservative management or intervention (Cuzick et al., 2012; Cuzick et al., 2015).

PROLARIS MEETS SIMON et al. LEVEL OF EVIDENCE II

The Simon et al. evidentiary framework is intended to evaluate biomarker clinical utility. Specifically, is the test actionable to the point where it will reliably influence treatment decisions, resulting in improved outcomes? Six studies measured the ability of Prolaris to predict long-term outcomes such as PCa-specific mortality using archival PCa tumor specimens, conforming to elements for "Category C" studies as set forth by Simon et al. (Table 2) (Cuzick et al., 2011; Cuzick et al., 2012; Freedland et al., 2013; Cooperberg et al., 2013; Bishoff et al., 2014; Cuzick et al., 2015). These six studies show consistent and statistically significant results across different populations, treatments and endpoints, thereby reducing likely influence of chance with the results. The Prolaris Score's prognostic ability is further validated across a range of designs, time periods, and patients. Prolaris also demonstrates clinical utility by identifying a significant group of patients with low risk of biochemical recurrence and PCa-specific mortality that can avoid potential overtreatment.

TABLE 2:

Prolaris conforms to Simon et al. elements for multiple "Category C" studies (prospective observational registry), plus PCa being a "compelling circumstance," reaching LOE II

CATEGORY ELEMENT (as cited in Simon et al.)	WHY PROLARIS MEETS ELEMENTS OF TUMOR MARKER STUDIES
Prospective observational registry, treatment and follow-up not dictated	All six studies examined patients who were entered prospectively into an observational (non-randomized) registry. The patients included in the studies were representative of the larger population of patients receiving the treatments described in the studies during that time period. This indicates a lack of selection bias across the study populations. Analysis of treatment and follow up procedures indicates that patients included in the study were treated at the provider's discretion, according to the standard of care recommended for the tumor clinical stage at the time of patient enrollment.
Specimens collected, processed, and archived prospectively using generic SOPs; assayed after trial completion	Pathological tissue specimens were derived from prostate needle biopsy or RP, processed and stored according to institutional standard operating procedure. Assays were conducted retrospectively after all patients were registered and specimens collected. The specimens were representative of tumors found in the larger population of patients receiving the treatments described in the studies during that time period. Analysis across the six studies indicated that selection bias, based on patient or tumor characteristics such as tumor size, stage or grade, was unlikely to have significantly biased the results of the studies, or impacted the tissue quality needed for a successful biochemical assay (Trock, 2017).
Study not prospectively powered at all; retrospective study design confounded by selection of specimens for study	Simon notes that a concern with retrospective studies of archived samples from observational studies is that the necessary sample size is not determined ahead of time, resulting in studies that may be too small and results that may be confounded by selection bias. Patients included in the Prolaris studies were prospectively entered into registries according to the clinical volume at the participating institutions, without a specific study design or target sample size. Subsequently, when Prolaris studies were initiated, most studies obtained tissue specimens and data from as many registry patients fitting eligibility criteria as possible. Prolaris studies were designed retrospectively, and eligibility criteria were similar across all six studies ("elements" listed in column 1 of Table 2). All studies showed statistically significant associations between the Prolaris prognostic score and measured outcomes. Therefore, studies were large enough despite not being prospectively powered, and the retrospective study design was unlikely to produce bias based on selection of specimens for study.
Focused analysis plan for marker question developed before doing assays	All six studies produced prognostic Prolaris Scores in a manner that was blinded to patient outcomes and other study data. Study protocols were developed before any assays were performed. Study publications indicated that pre-specified analysis plans were followed. Therefore, analyses plans were independent of patient outcome data.
Requires subsequent validation studies	Level of Evidence II based on studies from a prospective observational registry ("Category C") requires an initial "discovery" study plus two or more independent validation studies that provide consistent results. A total of six studies demonstrated Prolaris clinical validity with remarkably consistent and statistically significant results across different populations, treatments and endpoints. This reduces the likelihood that the results reflected the influence of chance. Thus, the studies (1) validate the Prolaris Score's prognostic ability across a range of designs, time periods, and patients, and (2) demonstrate clinical utility by identifying a significant group of patients with low risk of biochemical recurrence and PCa-specific mortality that can avoid potential overtreatment.

An additional meta-analysis of six independent, non-overlapping peer-reviewed and published studies of Prolaris has placed the prognostic test firmly within the Simon et al. Level of Evidence II category (Trock, 2017). Each of the six studies used tumor biospecimen sets that conformed to Simon et al. conditions for evidence generation (summarized in Table 2) (Cuzick et al., 2011; Cuzick et al., 2012; Freedland et al., 2013; Cooperberg et al., 2013; Bishoff et al., 2014; Cuzick et al., 2015).

TABLE 3:

Prolaris studies used archived biospecimen sets that exceed Simon et al. conditions for studies to establish biomarker utility.

Conditions for archived biospecimens in studies to establish biomarker utility	
LOE II REQUIREMENT	WHY PROLARIS MEETS LOE II REQUIREMENT
Three* or more "Category C" studies with consistent results	Prolaris clinical validity demonstrated in six studies, with remarkably consistent and statistically significant results across different populations, treatments, and endpoints.
CONDITIONS FOR EVIDENCE GENERATION	WHY PROLARIS MEETS CONDITIONS
Archived tissue must be available on a sufficient number of patients to (a) permit appropriately powered analyses and (b) ensure that patients and tissue samples evaluated are representative of those in the original prospective studies.	All six studies showed statistically significant associations between the Prolaris prognostic score and measured outcomes. The specimens were processed according to existing clinical standard of care. Tumors were representative of those found in the larger population of patients receiving the treatments described in the studies during that time, and were evaluated in the majority of patients prospectively enrolled in each study; thus, selection bias most likely did not play a role.
Substantial data on analytical validity of the test must exist.	Analytic validity demonstrated across 7,725 tissue samples that were representative of clinical test conditions (Warf et al., 2015).
Analysis plan must be completely developed before performing the assay.	Prolaris assays were blinded to patient outcomes and other study data. Study publications indicated that pre-specified analysis plans were followed.
Results of original study validated in at least two similarly designed studies using the same assay techniques.	Analysis across six studies with consistent and statistically significant results makes it very unlikely that the results reflect play of chance, confounding, or selection biases.

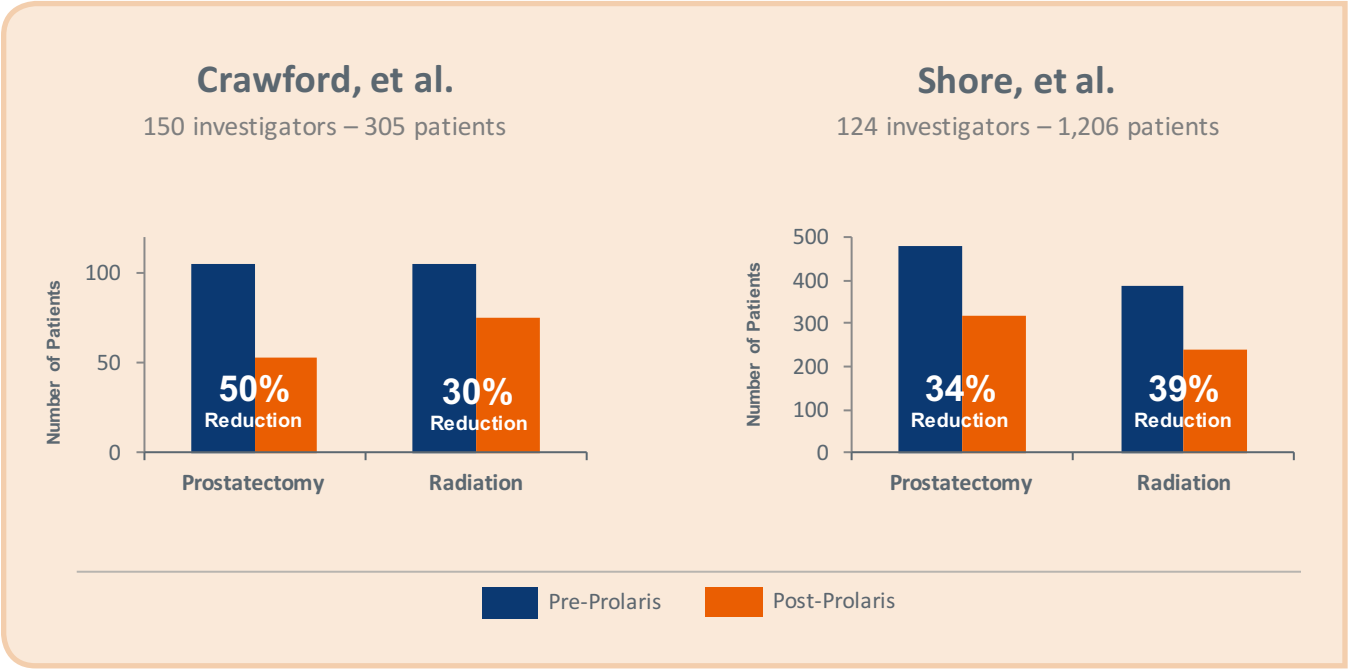
*One development study + two validation studies

PROLARIS IMPROVES NET HEALTH OUTCOME BY REDUCING MORBIDITIES, CHANGING CLINICAL MANAGEMENT

Clinical utility studies, including physician and patient decision impact studies, show that Prolaris not only provides new and meaningful PCa risk assessment information for physicians, but also that test results prompt medical decision changes and clinical follow-through by providers and patients alike (Crawford et al., 2014; Shore et al., 2016). These prospective, real-world studies involved over 1,500 patients and showed marked changes in interventional treatment that aligned with PCa risk specified by the test (Table 4).

TABLE 4:

Decision impact studies demonstrate behavior change.



Risk-appropriate selection of AS provides value to patients by avoiding the well-established and significant functional side effects of RP and RT, including sexual, urinary and bowel dysfunction (Resnick et al., 2013; Jeldres et al., 2015; Donovan et al., 2016; Hamdy et al., 2016; Barocas et al., 2017; Chen et al., 2017; Wilt et al., 2017).

Cost modeling demonstrates that using Prolaris can produce significant financial savings for insurance payers, due to a predicted shift from interventional therapy to AS – thereby avoiding unnecessary treatments and their related side effects (Crawford et al., poster 2015).

CHAIN OF EVIDENCE FOR PROLARIS

Extending upon Simon et al., a "chain of evidence" (CMTP 2013) can be employed to show that Prolaris improves PCa outcomes by reducing unnecessary interventions, thereby reducing treatment-related morbidity without decreasing survival. This chain of evidence is summarized as follows:

- Localized prostate cancer is over treated (Draisma et al., 2009; Ollendorf et al., 2010; Wilt et al., 2017).
- Prolaris significantly improves prediction of oncologic endpoints beyond that achieved with standard clinicopathologic features (Cuzick et al., 2011; Cuzick et al., 2012; Freedland et al., 2013; Cooperberg et al., 2013; Bishoff et al., 2014; Cuzick et al., 2015).
- Prolaris meets Simon et al. LOE II for clinical utility.
- Prolaris results in more appropriate treatment based on a better estimate of risk.
- Prolaris changes medical management and decreases overtreatment (by reducing RP and RT by 30-50%, while increasing AS) (Crawford et al., 2014; Shore et al., 2016)
- Reduced over treatment helps patients avoid unnecessary morbidities such as sexual, urinary and bowel dysfunction, other treatment-related adverse events, and negative impacts on quality of life (Jeldres et al., 2015; Donovan et al., 2016; Barocas et al. 2017; Chen et al., 2017; Wilt et al., 2017).
- Reducing definitive therapies does not increase mortality for low-risk patients (Hamdy et al., 2016; Wilt et al., 2017).

EVIDENCE SUPPORTS COVERAGE OF PROLARIS

By virtue of six "Category C" studies meeting the conditions set forth by Simon et al., Prolaris more than meets the requirement for Level of Evidence II in this widely accepted and time-proven evidentiary framework. Additionally, prospective decision impact studies document changes in practice, and those changes lead to improved outcomes by reducing morbidity, as demonstrated by a chain-of-evidence. Economic modeling projects significant cost savings for patient, provider and payer alike, adding a further dimension of clinical utility (Crawford et al., poster 2015).

In October 2015, Prolaris received a favorable technical assessment for National Comprehensive Cancer Network® (NCCN) very low- and low-risk men from Palmetto GBA MolDx, indicating that it meets Medicare reasonable and necessary criteria. A second LCD was issued in 2017 for NCCN favorable intermediate-risk men. Palmetto GBA was the first Centers for Medicare and Medicaid Services (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 (Peabody et al., 2014; MolDx 2015 and 2017).

The NCCN® 2018 prostate cancer treatment guidelines recommend consideration of molecular testing, including Prolaris, of a patient's tumor post-biopsy when prostate cancer presents as low- or favorable intermediate-risk and life expectancy is greater than or equal to 10 years (NCCN v2.2018). 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 above mentioned NCCN practice guidelines for prostate cancer (v2.2018) 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" (AACU 2018).

In summary, alignment of Prolaris with Simon et al. LOE II, combined with positive decision impact studies demonstrating value across PCa stakeholders and Medicare coverage across many NCCN risk categories, provides compelling support for positive payer coverage decisions. In addition, this body of evidence positions Prolaris as a reference model for the AMA's recommendation to adopt transparent and clear guidelines and value assessments for determining payer coverage of genetic tests (AMA 2017).

PROLARIS BIOMARKER TEST MEDICALLY NECESSARY

- ✓ Simon et al. provides evidentiary framework to evaluate the medical utility of a prognostic biomarker
- ✓ Multiple category C studies provide LOE II for Prolaris; LOE I is not achievable for prostate cancer prognostics within the current paradigm
- ✓ Prostate cancer is a compelling circumstance, and therefore LOE II is acceptable
- ✓ Prospective decision impact studies document changes in practice in > 1,500 patients that lead to improved outcomes by reducing morbidity, as demonstrated by a chain-of-evidence
- ✓ Reaching LOE II, coupled with management change, supports medical value of biomarker
- ✓ Medicare covers Prolaris for very low-, low- and favorable intermediate-risk men
- ✓ NCCN guidelines support the use of Prolaris

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