Prolaris®
Prostate Cancer Prognostic Test

Personalize prostate cancer treatment decisions based on consistent data

Myriad genetics

Health. Illuminated.

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Introduction

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend various treatment types and intensities across the range of very low-risk to very high-risk localized prostate cancer[1]. This can include Active Surveillance (AS), which involves close monitoring as an option for some lower-risk patients, as well as active treatments (e.g., surgery, radiation, or hormone therapy administered alone or combined with radiation) for higher-risk patients. Accurate risk stratification of patients with prostate cancer is critical for treatment decision-making. Providers recognize the limitations of existing tools, such as prostate-specific antigen (PSA) and Gleason score. With the goal to improve the personalization of risk stratification, there has been a rise in the proportion of patients who undergo biopsy tissue-based molecular testing. This white paper supplies urologic providers with the data needed to evaluate the validity and utility of Prolaris®, a biopsy tissue-based biomarker.

Background

Patients with prostate cancer can have indolent or aggressive tumors, and there are limitations in the ability of clinicopathologic features to distinguish well between the two[2,3,4]. As a result, many providers are looking for more direction to inform the most appropriate treatment of localized prostate cancer in each individual patient.

Clinicopathologic features like Gleason score or blood PSA levels have been used as the basis of prostate cancer risk stratification. However, new technology is available to improve existing stratification so that it is more personalized to the individual patient. NCCN Guidelines® recommend biopsy tissue-based biomarkers when "they have the ability to change management"[1] (PROS-C, 1 of 3). Evaluating data in support for prognostic molecular testing in prostate cancer plays an essential role in healthcare providers' decision-making to adopt the newer technology and decide which to order.

Demand for prognostic information is driven in part by:

- The need for accurate risk stratification
- Limitations in the ability of clinicopathologic features to distinguish tumor aggressiveness
- Pathology subjectivity
- The need for decision support to avoid patient regret

PSA testing has been used as a guide to determine when prostate biopsies should be performed. The pathology depends upon the pathologist's interpretation of the specimen, and different pathologists may categorize the same tumor in different ways. The diagnosis of prostate cancer, particularly on biopsies, is challenging, especially where only a limited amount of tissue is seen[5]. Some patients' prognoses turn out to be far worse—or better—than expected based on PSA and Gleason score.

Decisional regret about a treatment path is not uncommon among patients diagnosed with localized prostate cancer. Prostate cancer biomarkers may provide additional prognostic information to aid in the decision to seek AS or treatment, while inspiring confidence in the final decision. Without such information, a significant proportion of patients who initially choose AS decide to pursue active treatment shortly after starting AS. For example, AS was the initial management strategy in a Canadian study of 8,541 patients with prostate cancer. After a median follow-up of 48 months, 4,337 (51%) patients had discontinued[6]. In another study, of 6,775 patients included in an analysis, 2,260 (33.4%) converted to treatment at a median follow-up of 6.7 years[7].

The Prolaris® prognostic test from Myriad Genetic Laboratories, Inc. meets the challenge of identifying which patients have less aggressive cancers and can safely go on AS, versus which patients have more aggressive cancers and may benefit from various degrees of active treatment. Prolaris is a powerful prognosticator of disease-specific mortality and metastasis risk in prostate cancer and provides information that extends and improves current practice, thereby increasing confidence in patient-risk classification. NCCN Guidelines recommends Prolaris testing for patients with a life expectancy ≥10 years across low- to high-risk groups[1] (PROS-C 2 of 3).

Case Study 1 – Favorable Intermediate patient with AS Result

Variables used for risk assessment

Prolaris molecular score:	**2.6**
Patient age at biopsy:	**67**
PSA prior to this biopsy:	**7.2**
Clinical t stage:	**T2a**
% Positive cores:	**< 34%**
Gleason score:	**3+4=7 (Group 2 ISUP)**
NCCN risk:	**Favorable Intermediate**

Prolaris test result summary

Based on a 10-year Disease Specific Mortality (DSM) risk of 2.3% with conservative management, this patient is a candidate for Active Surveillance.

This patient → Active surveillance | Single-modal treatment | Multi-modal treatment

Defined as either radiation with androgen deprivation or surgery with intensified therapy per guideline recommendations.

Understanding Prolaris Scores: Cell-Cycle Proliferation (CCP) and Clinical Cell-Cycle Risk (CCR)

One study evaluated five sets of different gene pathways in breast cancer and identified cell-cycle proliferation (CCP) genes to carry the most prognostic power. The expression levels of CCP genes measure the rate of cancer growth and provide valuable information about the aggressiveness of cancer. Signatures containing multiple pathways, even those including CCP genes, have been shown to lose prognostic ability when CCP pathway genes are removed[8]. Another study looking at genome-wide survival models from 10,884 patients, found the strongest adverse bio-markers represent widely expressed cell-cycle and housekeeping genes across multiple cancer types[9]. Prolaris, which is a CCP gene-based test, has introduced this concept to the treatment of prostate cancer.

Cell-Cycle Proliferation (CCP): independent molecular score

Clinical Cell-Cycle Risk (CCR): CCP combined with clinical features

Prolaris, the CCP score, was developed and validated to provide prognostic information to patients with prostate cancer in all risk groups. In clinical validation studies, only weak interactions were found between CCP and clinicopathologic variables, demonstrating that the effect is independent of clinical variables. Prolaris is a molecular test that is performed on prostate tumor biopsy tissue which measures the expression levels of 31 CCP genes, along with 15 housekeeping genes to serve as a baseline expression level for comparison. The CCP score refers to the measurement of gene expression alone and is reported as a continuous value, ranging from approximately 1.8 to 8.7. Prolaris test results can be used to stratify patient risk more precisely, according to disease aggressiveness in patients with clinically localized biopsy-proven prostate cancer who have not received prior intervention or treatment.

The 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. Prolaris provides an understanding of the tumor's biology at the molecular level, an element of information not currently available through standard clinicopathologic measures.

To further improve upon the prognostic power of CCP, the molecular score was added to the Cancer of the Prostate Risk Assessment (CAPRA) score, a previously validated prognostic risk model comprised solely of clinicopathologic variables, resulting in the combined clinical cell-cycle risk (CCR) score. The CCR score was validated to be the best possible prognostic in numerous studies. The CCR score correlates to a personalized risk for 10-year disease-specific mortality (DSM) and 10-year metastasis risk.

Clinical studies support Prolaris validation

Extensive research has been conducted to validate the Prolaris test. Table 1 displays the clinical validation studies for Prolaris. Validation has been demonstrated comprehensively through peer-reviewed, published studies across more than 20 patient cohorts (Table 1).

These metrics are valuable in planning and monitoring treatment. The endpoints displayed in the Prolaris Report (i.e., DSM and metastasis) mirror endpoints recommended in NCCN Guidelines[1] (PROS-C 1 of 3). The presence of predicted adverse pathology (AP) is not included in that list and is considered a short-term outcome.

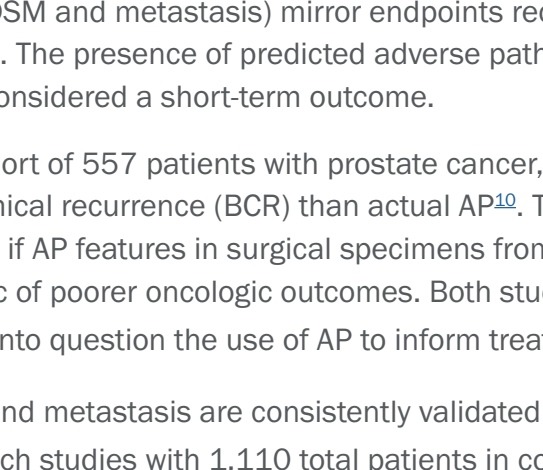
Prolaris Clinical Validations:

- Consistent hazard ratios >1 for CCP
- Strong oncologic endpoints of DSM and metastasis risk
- Appropriately designed (e.g., all risk groups, patient treatment type, and sample type)

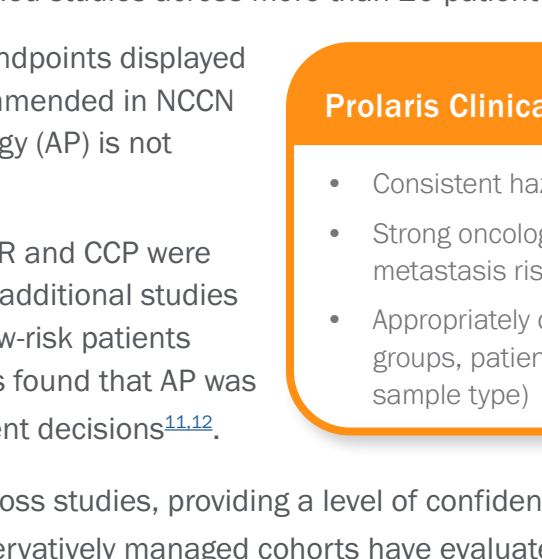
Based on a study with a cohort of 557 patients with prostate cancer, CCR and CCP were better predictors of biochemical recurrence (BCR) than actual AP[10]. Two additional studies were designed to determine if AP features in surgical specimens from low-risk patients eligible for AS are prognostic of poorer oncologic outcomes. Both studies found that AP was not informative, and called into question the use of AP to inform treatment decisions[11,12].

Prolaris endpoints of DSM and metastasis are consistently validated across studies, providing a level of confidence and quality with reproducible results. Two such studies with 1,110 total patients in conservatively managed cohorts have evaluated DSM as an oncologic endpoint[13,14], while two studies with 912 total patients who were definitively treated were followed for the development of metastatic disease[15,16].

Disease-specific mortality with **conservative management** studies[13,14]



Metastatic disease with **definitive treatment** studies[15,16]



When selecting a molecular test for an individual patient, it is essential to select a test that has been validated in a population that specifically represents the patient who will receive the test. It is also critical that the endpoints have been validated in the patient risk group, treatment type, and sample type that is relevant to the patient who is receiving the result (see Table 1). Prolaris has been validated in all risk groups, conservatively managed patients, patients treated with single-modal therapies (e.g., surgery or radiation), and patients treated with multiple modes of therapy (e.g., surgery/radiation + hormone therapy). Prostate cancer molecular tests also need to be validated in whichever sample types the provider intends to send for testing. Prolaris has been validated in biopsy, post-radical prostatectomy, and transurethral resection of the prostate (TURP) samples. Most of the validation studies (in over 7,400 patients) have been performed using biopsy samples.

Prolaris threshold validation publications

The Prolaris report displays two validated thresholds to provide actionable information aiding in the treatment decision-making process, the AS Threshold, and the Multi-Modal Threshold. These thresholds were created based on strong endpoints, DSM/metastasis, and were deliberately trained and validated in separate cohorts, making them statistically more robust than biomarkers that have used cross-validation, which may perpetuate biases as the data sets are not independent.

Why Train and Validate in Separate Cohorts:

By training and validating thresholds in separate, independent cohorts, the validation more accurately measures the performance of the threshold. Together they characterize how the thresholds are expected to work in the real clinical setting. This is different from cross-validation, where a data set is split into two parts; one for training and the other for validation. Those data sets are not independent and likely contain the same biases. This means that a validation performed through cross-validation is likely to overestimate the performance of the threshold.

Active Surveillance Threshold

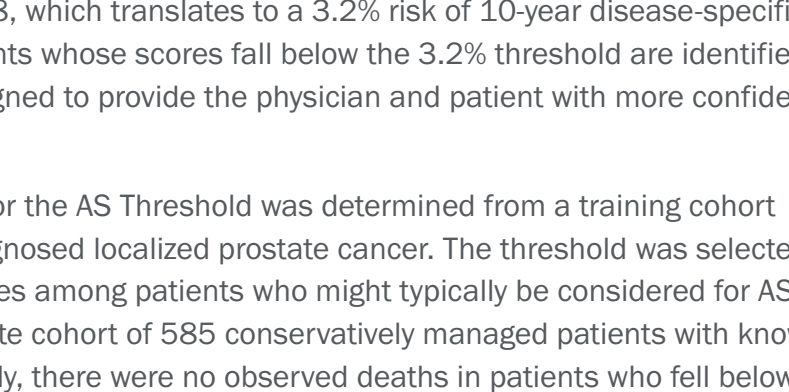
The AS Threshold is at a CCR score of 0.8, which translates to a 3.2% risk of 10-year disease-specific mortality without active treatment. Patients whose scores fall below the 3.2% threshold are identified as candidates for AS. This threshold is designed to provide the physician and patient with more confidence in selecting AS.

Active Surveillance (AS) Threshold Studies:

- Lin et al - AS Threshold training and validation
- Kaul et al - AS Threshold safety, real world application
- Hu et al - AS Threshold compared to other tests

In the validation study[17], the CCR score for the AS Threshold was determined from a training cohort of 1,718 biopsy samples from newly diagnosed localized prostate cancer. The threshold was selected based on the 90th percentile of CCR scores among patients who might typically be considered for AS. The threshold was then validated in a separate cohort of 585 conservatively managed patients with known long-term mortality outcomes. Importantly, there were no observed deaths in patients who fell below the AS Threshold[17]. Patients with scores above the threshold had significantly different risk profiles compared to those below the threshold.

Prostate cancer mortality over time in conservatively managed patients above and below the AS Threshold[17]



Additionally, this study demonstrated that Prolaris improved outcomes by broadening the group of patients considered appropriate for AS. Of 19,215 patients evaluated, only 42.6% met AS criteria based on clinicopathologic criteria alone; however, once the AS Threshold was incorporated, this population of eligible patients increased to 68.8%. Of the patients who did not qualify for AS based on clinicopathologic criteria alone, 52.2% scored below the AS Threshold indicating this treatment path was viable. This group would not have been considered for AS previously[17].

A publication by Kaul, et al. evaluated clinical outcomes with the use of Prolaris testing and the AS Threshold in a real-world clinical setting of 664 patients with low-risk prostate cancer[18]. The data showed 82.4% of low-risk patients who also scored below the AS Threshold selected AS, which is comparatively higher than the national average of low-risk patients who select AS (59.6%)[19]. Only 0.4% of the patients who chose AS experienced disease progression, confirming that AS informed by a Prolaris result is safe[18]. At 3 years, 70% of patients who initially selected AS remained on AS, showing durability of treatment when guided by Prolaris[18].

In another independent study, 3,996 patients with newly diagnosed localized prostate cancer were tracked through the Michigan Urological Surgery Collaborative (MUSIC) registry[20]. A total of 747 (18.8%) underwent testing with tissue-based gene expression classifiers. The study found that patients classified as low-risk by molecular testing were more likely to be managed with AS than those who did not undergo molecular testing. The Prolaris AS threshold was found to incorporate more candidates with favorable-risk prostate cancer for AS compared with competing molecular tests. In the subgroup of patients with Gleason 6 prostate cancer, 86% of patients tested with Prolaris were below the low-risk threshold vs. only 40-60% in other tests (P < .001)[20].

Multi-Modal Threshold

A second threshold, the Multi-Modal (MM) Threshold, (CCR=2.112, which translates to 8.9% 10-year metastasis risk with active treatment) was validated in a cohort of patients with NCCN intermediate- and high-risk prostate cancer[15]. In this study the MM Threshold was trained by examining a cohort of 15,669 patients with NCCN unfavorable intermediate- and high-risk prostate cancer and a known CCR score. Among these individuals, 4,615 (29.5%) patients were classified as having NCCN high-risk. The threshold was set at CCR=2.112, such that the proportion of individuals with a score above the threshold would not exceed 29.5%. The threshold was then validated in a separate multicenter cohort of 718 patients with NCCN intermediate- and high-risk prostate cancer who had primary treatment with radiation or surgery, known outcomes, and CCR scores.

Multi-Modal (MM) Threshold Studies:

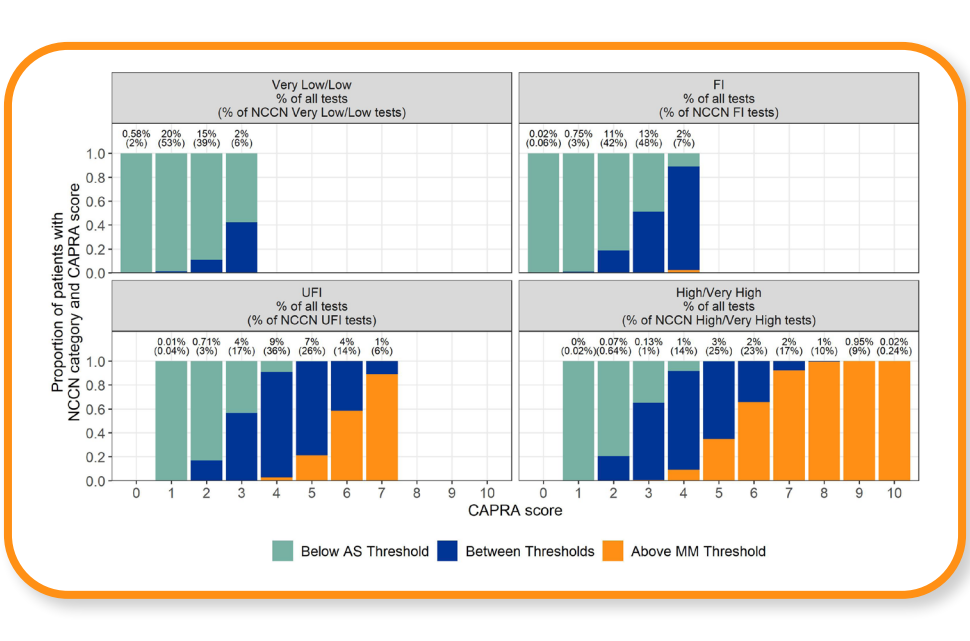
- Tward et al - MM Threshold training and validation in pooled radiation and surgery cohort
- Tward et al - MM Threshold validation in radiation cohort

This validation study found that CCR was a significant prognosticator of metastasis, even when stratified by treatment type or single-modality versus multi-modality treatment. Patients treated with single-modality therapy with CCR scores above the threshold had nearly a 16-fold higher risk of developing metastasis compared to those with scores below the threshold. When examining patients with scores below the threshold, 27% of patients with NCCN high-risk and 73% with NCCN unfavorable intermediate-risk have minimal to no absolute benefit when treated more intensely with multimodal treatments. CCR has been shown to prognosticate metastasis in patients undergoing single- or multi-modality treatment more accurately than NCCN risk groups, CAPRA, or CCP alone. There was little to no benefit of multi-modal therapy in men with CCR scores below the threshold, whereas those above the threshold demonstrated a significant increase in the risk of developing metastatic disease.

In another study, researchers further validated the Prolaris MM Threshold in 741 patients with NCCN intermediate-, high- and very high-risk prostate cancer to help identify individual patients who may benefit from the addition of androgen deprivation therapy (ADT) to radiation therapy (RT) or who might consider treatment with RT alone, potentially mitigating toxicities and quality-of-life impairment associated with adding ADT[16]. Patients treated with RT alone with scores above the MM threshold had >6-fold higher predicted risk of metastasis than those below the threshold. The 10-year risk of metastasis was 3.7% and 14.4% in patients below or above the threshold, respectively. For patients below the threshold, ADT of any duration did not significantly reduce this 10-year risk.

Prolaris clinical utility across risk groups

Using the two thresholds, Prolaris demonstrates clear clinical utility across all risk groups and treatment decisions in localized prostate cancer. An analysis of commercial tests has been performed, stratifying data by NCCN risk group, CCR category, and CAPRA score[21]:



Approximately 10% of CAPRA 2 low-risk patients and approximately 40% of CAPRA 3 low-risk patients have CCR scores above the AS threshold and would be recommended as candidates for single-modal treatment on Prolaris reports. There is a spread of risk stratification across all NCCN risk groups and CAPRA scores. This shows that risk stratification with Prolaris provides more granular and personalized information than CAPRA or NCCN risk groups.

Case Study 2 – Unfavorable Intermediate patient with Single Modal Result

Variables used for risk assessment

Prolaris molecular score:	**2.5**
Patient age at biopsy:	**68**
PSA prior to this biopsy:	**6.7**
Clinical t stage:	**T2a**
% Positive cores:	**< 34%**
Gleason score:	**4+3=7 (Group 3 ISUP)**
NCCN risk:	**Unfavorable Intermediate**

Prolaris test result summary

Based on a 10-year Metastasis (Mets) risk of 2.5% with active treatment, this patient is a candidate for single-modal treatment.

Active surveillance | This patient → Single-modal treatment | Multi-modal treatment

Defined as either radiation with androgen deprivation or surgery with intensified therapy per guideline recommendations.

PCR technology selected over microarray for Prolaris

Prolaris studies evaluating CCP gene expression have used quantitative real-time polymerase chain reaction (qRT-PCR) technology to measure expression levels, which is generally considered the 'gold-standard' for measuring RNA expression. A study comparing qRT-PCR with microarray was performed. Expression of CCP genes, as determined by microarrays, compared poorly with expression as measured by qRT-PCR, because the range of CCP scores is limited in microarray analysis limiting the accuracy of the score. As a result, microarray-generated CCP scores should not be assumed to be a valid surrogate for qRT-PCR generated scores for prediction of patient outcome[22].

Prolaris works with MRI

Multiparametric Magnetic Resonance Imaging (mpMRI) and Prostate Imaging and Reporting and Data System (PI-RADS) have become more widely used in urology practice. One retrospective study analyzed the prognostic ability of Prolaris, mpMRI and PI-RADS scoring, and clinicopathologic features. The study included 222 patients with localized prostate cancer who were either newly diagnosed or had been on AS. Small but statistically significant correlations were found between PI-RADS and CCP, PI-RADS and CAPRA score, as well as PI-RADS and CCR score. These small correlations suggest that the prognostic information captured by these variables is somewhat independent. The study also found that mpMRI and PI-RADS scoring may be useful in the diagnosis of prostate cancer but did not support the utility of these methods as prognostic indicators. CCP was a better predictor of both tumor grade and subsequent patient management than was PI-RADS on subsequent biopsies. Even within the context of targeted biopsy, molecular information remains essential to ensure precise risk assessment for patients with newly diagnosed prostate cancer[23].

Conclusion

Prolaris addresses the limitations of clinicopathologic features and provides carefully validated scores and thresholds to aid in treatment decisions, as demonstrated by the studies summarized in this white paper. The improved risk stratification can lead to more personalized decisions that may reduce over- and under-treatment of localized prostate cancer and give patients confidence in the joint patient-physician decision. Providers should consider the Prolaris test to help define a personalized treatment path through the numerous treatment options available.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2022.© National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [June 2, 2022]. To view the most recent and complete version of the guideline, go online to https://www.nccn.org/. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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Table 1

Endpoint	Description	Results: MVA Effect Size (95% CI, p-value) Prolaris (CCP)	Sample Type	Cohort Treatment	Risk Groups
Prostate Cancer-Disease Specific Mortality	Cuzick (2011) *Lancet Oncology* N=703	TURP HR – 2.57 (1.93-3.43, p=8.2x10^{-11})	TURP	Conservatively Managed	Low, Intermediate, High
		RP HR – 1.77 (1.40–2.22, p=4.3×10^{-6})	RP	RP	
	Cuzick (2012) *Br. J. Cancer* N=349	HR 1.65 (1.31-2.09, p=3x10^{-5})	Biopsy	Conservatively Managed	Low, Intermediate, High
	Cuzick (2015) *Br. J. Cancer* N=761	HR 1.76 (1.44-2.14, p<10^{-6})	Biopsy	Conservatively Managed	Low, Intermediate, High
	Lin (2018) *J Urol* N=585	AS Threshold Validation	Biopsy	Conservatively Managed	Low, Intermediate, High
	Cuzick (2021) *Cancer Reports* N=305	CCR HR 4.36 (2.65-7.16, p=1.3 × 10^{-8})	TURP	Conservatively Managed	Low, Intermediate, High
Metastasis	Swanson (2021) *The Prostate* N=360	CCR Post-RP: HR 3.03 (1.49-6.20, p = 0.003)	RP	RP	Low, Intermediate, High
		CCP Post-BCR: HR 1.70 (1.14-2.53, p=0.012)			
	Tward (2021b) *International Journal of Radiation Oncology, Biology, Physics* N=741	HR 1.71 (1.23-2.35, p=0.0017)	Biopsy	Single- or Mult-modal Active Treatment (RT +/- ADT)	Favorable intermediate, Unfavorable intermediate, High, Very High
	Tward (2021a) *Clinical Genitourinary Cancer* N=718	CCR RT: HR 4.30 (2.23-8.30, p=6.2x10^{-5}) CCR Surgery: HR 4.08 (1.90-8.78, p=5.7x10^{-4})	Biopsy	Single- or Mult-modal Active Treatment (RT +/- ADT; RP +/- adjuvant RT or ADT)	Favorable Intermediate, Unfavorable Intermediate, High
	Canter (2019a) *Eur Urology* N=767	HR 2.03 (1.47-2.78, p<0.001)	Biopsy	Active Treatment and Deferred Treatment	Low, Intermediate, High
	Canter (2019b) *Prostate Cancer Prostatic Disease* N=1,062	HR 2.21 (1.64-2.98, p=1.9x10^{-6})	Biopsy	Active Treatment	Low, Intermediate, High
	Koch (2016) *Cancer Biomarkers* N=47	OR 3.64 (1.27-10.5, p=0.0056)	RP	RP	Low, Intermediate, High
Biochemical Failure	Tosoian (2017) *BJU International* N=236	Full Cohort: HR 1.41 (1.02-1.96, p=0.039)	Biopsy	RP	Low
		Low Risk Cohort: HR 1.77 (1.21-2.58, p=0.003)			
	Freedland (2013) *Int. J. Radiat. Oncol. Biol. Phys.* N=141	HR 2.11 (1.05-4.25, p=0.034)	Biopsy	Primary EBRT	Low, Intermediate, High
	Leon (2018) *World J Urol* N= 652	Full Cohort: HR 1.28 (1.03-1.59, p=0.026)	RP	RP	Low, Intermediate, High
		High Risk Cohort: HR 1.55 (1.17-2.04, p=0.0019)			
	Cooperberg (2013) *Journal of Clinical Oncology* n=413	HR 1.7 (1.3-2.4, p<0.001)	RP	RP	Low, Intermediate, High
	Kaul (2019) *Personalized Medicine* N=664	Saftey of AS Threshold	Biopsy	Conservatively Managed	Low
Biochemical Failure and Metastases	Bishoff (2014) *J. Urology* N=585	BCR HR 1.47 (1.23-1.76, p=4.7x10^{-5}) METS HR 4.19 (2.08-8.45, p=8.2x10^{-6})	Biopsy	RP	Low, Intermediate, High
Adverse Pathology	Cooperberg (2020) *Eur Urol* N=641	Minor upgrade/upstage: OR 1.62 (1.05-2.49, p = 0.03) Major upgrade/upstage: OR 2.26 (1.05-4.90, p=0.04)	Biopsy	RP	Low
	Morris (2020) *Urologic Oncology* N=222	OR 3.72 (1.39-11.88, p=7.9x10^{-3})	Biopsy	Conservatively Managed or Newly Diagnosed	Low, Favorable Intermediate, Unfavorable Intermediate, High

CCP = Cycle-Cycle Proliferation; CCR = Combined Clinical Cycle-Cycle Risk; MVA = multivariable analysis; CI = confidence interval; HR = hazard ratio; OR = odds ratio; ref = reference group; NR = not reported; RT = radiation therapy; RP = Radical Prostatectomy; AS = Actice Surveillance; ADT = androgen deprivation therapy; TURP = Transurethral Resection of the Prostate; EBRT = External Beam Radiation Therapy

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