

# Don't Be Misled: Simon Criteria do not equal NCCN evidence



Hidden factors may significantly impact  
your patients' treatment recommendations

**Myriad**  
genetics®

**Prolaris®**

Prostate Cancer Prognostic Test

Report  
Patient Name: LUO, JING on 12/16/24 6:06 PM  
Accession #: 554-XR-24-0092  
MRN: [redacted]  
Acct #: [redacted]  
Report Date: 12/16/24 4:05 PM CDT  
Clinical Indication: DIRECT  
Tests: Fluoroscopic guidance  
Tests are housed in the [redacted]  
Limited examination  
Signed by: Philip Chy  
07/09/2024 3:40 pm

## GENERALIZED AND POTENTIALLY MISLEADING CRITERIA

*"We encourage investigators to judge nonrandomized research equally... and to cumulate evidence from multiple sources when judging causality between biomarkers and outcomes."*<sup>3</sup>

Susan Hankinson, ScD & Thomas P. Ahem, PhD, MPH

### HOW THESE GUIDELINE CRITERIA MAY SKEW TEST RECOMMENDATIONS<sup>3</sup>

1. Undue emphasis on studies via clinical trials, penalizing high-quality prospective observational studies
2. Even CAPRA, MSKCC and germline are not considered a Simon level 1
3. Creates confusion between Simon levels of evidence and NCCN levels of evidence

### STUDY OUTCOMES ARE CRITICAL TO CLINICAL UTILITY

0

There were 0 death in the AS cohort for Prolaris<sup>®</sup> Test's validation studies<sup>4</sup>



The Prolaris<sup>®</sup> Test aligns closest to the ProtecT study results out of all available biomarkers<sup>5-6</sup>



Patients under the test's multi-modal threshold received minimal benefit from treatment intensification<sup>7</sup>

# Simon Criteria: Found in **Only 1** of 67 Cancers in NCCN<sup>1</sup>

Cancer type	References Simon Criteria?
Acute Lymphoblastic Leukemia	No
Acute Myeloid Leukemia	No
Ampullary Adenocarcinoma	No
Anal Carcinoma	No
Basil Cell Skin Cancer	No
B-Cell Lymphomas	No
Biliary Tract Cancers	No
Bladder Cancer	No
Bone Cancer	No
Breast Cancer	No
Castleman Disease	No
Central Nervous System Cancer	No
Cervical Cancer	No
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	No
Chronic Myeloid Leukemia	No
Colon Cancer	No
Dermatofibrosarcoma Protuberans	No
Esophageal and Esophagogastric Junction Cancers	No
Gastric Cancer	No
Gastrointestinal Stromal Tumors	No
Gestational Trophoblastic Cancers	No
Hairy Cell Leukemia	No
Head and Neck Cancers	No
Hepatobiliary Cancers	No
Histiocytic Neoplasms	No
Hodgkin Lymphoma	No
Kaposi Sarcoma	No
Kidney Cancer	No
Melanoma: Cutaneous	No
Melanoma: Uveal	No
Merkel Cell Carcinoma	No
Mesothelioma: Peritoneal	No
Mesothelioma: Pleural	No
Multiple Myeloma	No
Myelodysplastic Syndromes	No
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase	No
Myeloproliferative Neoplasms	No
Neuroblastoma	No
Neuroendocrine and Adrenal Tumors	No
Non-Small Cell Lung Cancer	No
Occult Primary	No
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer	No
Pancreatic Adenocarcinoma	No
Pediatric Acute Lymphoblastic Leukemia	No
Pediatric Aggressive Mature B-Cell Lymphomas	No
Pediatric Central Nervous System Cancers	No
Pediatric Hodgkin Lymphoma	No
Penile Cancer	No
Primary Cutaneous Lymphomas	No
<b>Prostate Cancer</b>	<b>Yes</b>
Rectal Cancer	No
Small Bowel Adenocarcinoma	No
Small Cell Lung Cancer	No
Soft Tissue Sarcoma	No
Squamous Cell Skin Cancer	No
Systemic Light Chain Amyloidosis	No
Systemic Mastocytosis	No
T-Cell Lymphoma	No
Testicular Cancer	No
Thymomas and Thymic Carcinomas	No
Thyroid Carcinoma	No
Uterine Neoplasms	No
Vaginal Cancer	No
Vulvar Cancer	No
Waldenström macroglobulinemia/Lymphoplasmacytic Lymphoma	No
Wilms Tumor (Nephroblastoma)	No

# Fair Comparison: Treatment Implications for Decipher<sup>®</sup> and Prolaris<sup>®</sup> Tests

## PRINCIPLES OF RISK STRATIFICATION<sup>1</sup>

Table 3. Treatment Implications for Advanced Tools: 22-Gene Genomic Classifier (GC) Assay

Population	Score	Treatment Decision	Treatment Implications
NCCN Low-Risk	≥0.6	Active surveillance Intensity vs. Radical therapy	<p><b>Evidence:</b> In a prospective multicenter statewide registry, GC high risk (≥0.6) was associated with shorter time on active surveillance and shorter time to treatment failure (TTF) for those who underwent radical therapy.<sup>12</sup></p> <p><b>Evidence synthesis:</b> More intensive active surveillance frequency should be considered for patients with NCCN low-risk disease and a high GC score, given the higher probability of transitioning off active surveillance and subsequent progression.</p>
NCCN Intermediate-Risk	≤0.45 vs. ≥0.60	RT vs. RT with ST-ADT	<p><b>Evidence:</b> NRG/RTOG 0126 phase III randomized trial was profiled post-hoc with a prespecified analysis plan.<sup>13</sup> The study demonstrated the independent prognostic effect of GC on biochemical failure, secondary therapy, DM, PCSM, MFS, and OS. Patients receiving RT alone with low GC scores had 10-year DM rates of 4%, compared with 16% for GC high risk.</p> <p><b>Evidence synthesis:</b> RT alone should be considered for patients with a low GC score and NCCN intermediate-risk disease. The addition of ST-ADT should be considered for patients with a high GC score given their increased risk of DM and significant benefit of ST-ADT on DM, even with dose-escalated RT or brachytherapy boost.</p>
NCCN High-Risk	≤0.45 vs. ≥0.60	RT + LT-ADT vs. RT + ST-ADT	<p><b>Evidence:</b> A meta-analysis of three phase III randomized trials (NRG/RTOG 9202, 9413, and 9902) were profiled post-hoc with a prespecified analysis plan.<sup>14</sup> The study demonstrated the independent prognostic effect of GC on biochemical failure, DM, MFS, PCSM, and OS. Patients with low GC scores had 10-year DM rates of 6%, compared with 26% for GC high risk. The absolute benefit of LT-ADT over ST-ADT was 11% for patients with high GC scores (NNT of 9), and 3% for patients with low GC scores (NNT of 33).</p> <p><b>Evidence synthesis:</b> RT + LT-ADT should be recommended for most patients with NCCN high-risk disease regardless of the GC score outside of a clinical trial, even with dose-escalated RT or brachytherapy boost. However, patients with a GC low risk score should be counseled that the absolute benefit of LT-ADT over ST-ADT is smaller than for patients with GC high risk scores and when accounting for patient age, comorbidities, and patient preferences, it may be reasonable with shared decision-making to use a duration shorter than LT-ADT.</p>

NNT = number needed to treat, PCSS = prostate cancer-specific survival

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## Treatment Implications for Prolaris<sup>®</sup>

Threshold	Treatment Decision	Treatment Implications
≤3.2% 10-year risk of Disease-Specific Mortality (DSM)	Active Surveillance	<p><b>Evidence:</b> Prolaris's active surveillance threshold was developed and validated across 3 studies. The first two studies included 761 men with localized prostate cancer and demonstrated that the Prolaris Score was the strongest predictor of disease-specific mortality in both the univariate and multivariate analyses which included PSA and Gleason score. The third study included 2,283 biopsies from newly diagnosed, localized prostate cancer patients, out of which there were no prostate cancer-specific deaths below the Prolaris AS threshold.<sup>1-3</sup></p> <p><b>Evidence synthesis:</b> Patients with DSM risk at or below the Prolaris AS threshold (3.2%) may be considered candidates for active surveillance.</p>
>3.2% risk of DSM and ≤8.8% 10-year risk of Distant Metastasis (DM)	Single-Modal Treatment (surgery or RT)	<p><b>Evidence:</b> Prolaris's multi-modal threshold was developed and validated in two studies including 16,410 untreated intermediate/high-risk patients. The results established Prolaris as a better prognosticator of metastasis risk than CAPRA, NCCN risk category or CCP alone as well as prognosticating risk for those receiving RT alone or RT+ADT (sufficient or not).<sup>4-7</sup> Below the threshold, men on ADT of any duration did not significantly reduce this 10-year risk of metastasis. Further studies assessed CCP testing on biopsy specimens from a pooled cohort of men with low-risk prostate cancer treated by RP. Results showed that CCR was 2.5x more predictive of BCR than adverse pathology and that CCP score provides significant and independent prognostic information about risk to develop metastatic disease, in all men, irrespective of race, risk group, or treatment approach.<sup>5-7</sup></p> <p><b>Evidence synthesis:</b> Patients with DM risk at or below the Prolaris SM threshold (&lt;8.8%) may be considered candidates for single-modal treatment, and those above the MM threshold (&gt;8.8%) may be considered candidates for multi-modal treatment (RT+ADT).</p>
>8.8% 10-year risk of Distant Metastasis (DM)	Multi-Modal Treatment (surgery + RT or RT + ADT)	<p><b>Evidence:</b> In a study looking at the Prolaris multi-modal threshold across patients treated with RT alone and with RT + ADT, the average absolute risk reduction of adding ADT to RT was 0.86% in patients with CCR scores below the MMT, 8.2% for patients above the MMT, and 3.7% at the MMT. This demonstrates Prolaris can accurately predict the absolute risk reduction (ARR) in metastasis risk with the addition of ADT to RT versus RT alone across all NCCN<sup>®</sup> risk group categories.<sup>8</sup></p> <p><b>Evidence synthesis:</b> Patients get estimated 10-year metastasis risk reduction when androgen deprivation therapy is added to radiation therapy.</p>
Absolute Risk Reduction (ARR)	RT + ADT	<p><b>Evidence:</b> In a study looking at the Prolaris multi-modal threshold across patients treated with RT alone and with RT + ADT, the average absolute risk reduction of adding ADT to RT was 0.86% in patients with CCR scores below the MMT, 8.2% for patients above the MMT, and 3.7% at the MMT. This demonstrates Prolaris can accurately predict the absolute risk reduction (ARR) in metastasis risk with the addition of ADT to RT versus RT alone across all NCCN<sup>®</sup> risk group categories.<sup>8</sup></p> <p><b>Evidence synthesis:</b> Patients get estimated 10-year metastasis risk reduction when androgen deprivation therapy is added to radiation therapy.</p>

## References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Name V.4.2024. © National Comprehensive Cancer Network, Inc 2024. All rights reserved. Accessed [October 28, 2024]. To view the most recent and complete version of the guideline, go online to 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.
2. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst.* 2009 Nov 4;101(21):1446-52. doi: 10.1093/jnci/djp335. Epub 2009 Oct 8. PMID: 19815849; PMCID: PMC2782246.
3. Ahern, T. P., & Hankinson, S. E. (2011). Re: Use of archived specimens in evaluation of prognostic and predictive biomarkers. *JNCI Journal of the National Cancer Institute*, 103(20), 1558-1559. <https://doi.org/10.1093/jnci/djr327>.
4. DW, E. David Crawford, Keane T, et al. Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. *Urol. Oncol.* 2018;36(6):310.e7-310.e13. doi:<https://doi.org/10.1016/j.urolonc.2018.03.011>.
5. Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *NEJM*. Published online March 11, 2023. doi:<https://doi.org/10.1056/nejmoa2214122>.
6. Hu, J. C., et al. Clinical Utility of Gene Expression Classifiers in Men With Newly Diagnosed Prostate Cancer. *JCO Precision Oncology*, 2018; 1-15 doi:10.1200/po.18.00163.
7. Tward J, Lenz L, Flake DD, et al. The Clinical Cell-Cycle Risk (CCR) Score Is Associated With Metastasis After Radiation Therapy and Provides Guidance on When to Forgo Combined Androgen Deprivation Therapy With Dose-Escalated Radiation. *IJROBP*. 2022;113(1):66-76. doi:<https://doi.org/10.1016/j.ijrobp.2021.09.034>.
8. Myriad Urology. (2024). Prolaris Treatment Implications Table. Myriad Genetics [https://info.myriad.com/i/prktsYQlcOLD08yIPLUSSIGNH1bFnQ8\\_\\_PLUSSIGNbbiQ806JhbX1KbjU Xn7PLUSSIGNSIX8Dat9RtBEC1GHkNRVIDyh112QhhxQiN\\_\\_MI9\\_\\_pxeCpvqVopsqo1u3uWmJgXyAkbnwhgtn7fBxeJWoaOYU](https://info.myriad.com/i/prktsYQlcOLD08yIPLUSSIGNH1bFnQ8__PLUSSIGNbbiQ806JhbX1KbjU Xn7PLUSSIGNSIX8Dat9RtBEC1GHkNRVIDyh112QhhxQiN__MI9__pxeCpvqVopsqo1u3uWmJgXyAkbnwhgtn7fBxeJWoaOYU).



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