EUROPEAN UROLOGY 75 (2019) 515–522

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Comparison of the Prognostic Utility of the Cell Cycle Progression Score for Predicting Clinical Outcomes in African American and Non-African American Men with Localized Prostate Cancer

Daniel J. Canter[a,b,*], *Julia Reid*[c], *Maria Latsis*[a], *Margaret Variano*[a], *Shams Halat*[a], *Saradha Rajamani*[c], *Kristen E. Gurtner*[a], *Zaina Sangale*[c], *Michael Brawer*[c], *Steven Stone*[c], *Stephen Bardot*[a,b]

[a] *Department of Urology, Ochsner Clinic, New Orleans, LA, USA;* [b] *Queensland School of Medicine, Brisbane, Australia;* [c] *Myriad Genetics, Salt Lake City, UT, USA*

Article info

Article history:
Accepted October 12, 2018

Associate Editor:
Matthew Cooperberg

Keywords:
Localized prostate cancer
Biomarker
Prognostic assay
Ancestry-based risk

Abstract

Background: Better prostate cancer risk stratification is necessary to inform medical management, especially for African American (AA) men, for whom outcomes are particularly uncertain.
Objective: To evaluate the utility of both a cell cycle progression (CCP) score and a clinical cell-cycle risk (CCR) score to predict clinical outcomes in a large cohort of men with prostate cancer highly enriched in an AA patient population.
Design, setting, and participants: Patients were diagnosed with clinically localized adenocarcinoma of the prostate and treated at The Ochsner Clinic (New Orleans, LA, USA) from January 2006 to December 2011. CCP scores were derived from archival formalin-fixed, paraffin-embedded biopsy tissue. CCR scores were calculated as the combination of molecular (CCP score) and clinical (Cancer of the Prostate Risk Assessment [CAPRA] score) components.
Intervention: Active treatment (radical prostatectomy, radiation therapy alone, or radiation and hormone therapy) or watchful waiting.
Outcome measurements and statistical analysis: The primary outcome was progression to metastatic disease. Association with outcomes was evaluated via Cox proportional hazards survival analysis and likelihood ratio tests.
Results and limitations: The final cohort included 767 men, of whom 281 (36.6%) were AA. After accounting for ancestry, treatment, and CAPRA in multivariable analysis, the CCP score remained a significant predictor of metastatic disease (hazard ratio [HR] 2.04; $p < 0.001$), and there was no interaction with ancestry ($p = 0.20$) or treatment ($p = 0.09$). The CCR score was highly prognostic (HR 3.86; $p < 0.001$), and as with the CCP score, there was no interaction with ancestry ($p = 0.24$) or treatment ($p = 0.32$). Limitations include the retrospective study design and the use of self-reported ancestry information.
Conclusions: A CCR score provided significant prognostic information regardless of ancestry. The findings demonstrate that AA men in this study cohort appear to have similar prostate cancer outcomes to non-AA patients after accounting for all available molecular and clinicopathologic variables.

* Corresponding author. Department of Urology, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121, USA. Tel. +1 504 8424083.
E-mail address: daniel.canter@ochsner.org (D.J. Canter).

https://doi.org/10.1016/j.eururo.2018.10.028
0302-2838/© 2018 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Patient summary: In this study we evaluated the ability of a combined molecular and clinical score to predict the progression of localized prostate cancer. We found that the combined molecular and clinical score predicted progression to metastasis regardless of patient ancestry or treatment. This suggests that the combined molecular and clinical score may be a valuable tool for determining the risk of metastasis in men with newly diagnosed prostate cancer in order to make appropriate treatment decisions.

© 2018 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Localized prostate cancer has a highly variable natural history. This leads to significant clinical uncertainty regarding appropriate management for patients with newly diagnosed low-risk disease, with options ranging from radical intervention to surveillance with the potential for deferred treatment [1,2]. Prognostic molecular biomarkers in the postbiopsy and postsurgical settings have recently emerged as important clinical adjuncts to standard clinicopathologic features for evaluating the aggressiveness of newly diagnosed localized disease [1,3]. The goal of such markers is to improve clinical management by providing prognostic information that is independent of clinicopathologic variables.

The need for better prognostic markers is especially urgent for African American (AA) men, who are more frequently diagnosed with prostate cancer [4,5], have higher prostate-specific antigen (PSA) levels [6], and are 2.5 times more likely to die from their disease than non-AA men in the USA [4,5]. Although this disparity has been well documented [7], it remains unclear whether the difference reflects underlying biology or non-disease-related factors. Thus, there is an acute information gap in our understanding of the behavior of prostate cancer in AA men, and the need for better risk discrimination potentially afforded by prognostic markers is particularly acute in this population.

The American Urologic Association (AUA) and American Cancer Society (ACS) guidelines on prostate cancer screening both identify AA ancestry as an indicator of poor prognosis [8,9]. Recent studies have also indicated that very low-risk AA men are at higher risk of adverse pathology after radical prostatectomy compared to risk-matched counterparts of other ancestries [10,11]. Because ancestry may impact disease outcome, it is critical that the performance of prostate cancer prognostic markers is carefully validated in AA patients. This need is especially urgent given the recent rapid adoption of active surveillance protocols for many low-risk prostate cancer patients, regardless of ancestry [12,13].

The cell cycle progression (CCP) score is a well-validated prognostic RNA expression signature that is based on expression levels of 31 CCP genes [14]. Previous studies have demonstrated the ability of this score to predict prostate cancer outcomes in numerous clinical settings and patient cohorts [14–17]. The molecular CCP score has also been combined with the Cancer of the Prostate Risk Assessment (CAPRA) score in a validated prognostic model [18,19]. It has been shown that this combined clinical cell-cycle risk (CCR) score provides better prediction of adverse outcomes compared to clinical or molecular components in isolation [19]. However, evidence that the CCP or CCR scores provide useful prognostic information in AA patients is relatively sparse [20]. In addition, it has been shown that PTEN expression provides prognostic information in some clinical settings [21], with emerging evidence that the frequency of PTEN loss in prostate cancer varies by ancestry [17].

Given the importance of improving risk discrimination among AA patients, we evaluated the prognostic utility of the CCP score and PTEN expression in predicting clinical outcomes in a cohort of men with localized prostate cancer highly enriched in AA patients.

2. Patients and methods

2.1. Patients

This retrospective study included patients diagnosed with clinically localized adenocarcinoma of the prostate who were treated at The Ochsner Clinic (New Orleans, LA, USA) between January 1, 2006 and December 31, 2011 with available biopsy formalin-fixed, paraffin-embedded (FFPE) tumor block (IRB #2013.243.A). Biopsies had been prospectively collected in a curated tissue bank. Patients were excluded from the study if they had any prior prostate therapy, a presurgical PSA level >100 ng/ml, histology on diagnostic biopsy other than adenocarcinoma of prostate, or nonlocalized disease (clinical T4 or M1). We also excluded patients who were treated with transurethral resection of the prostate, cryosurgery, or laser vaporization of the prostate.

Clinical and demographic data at the time of diagnosis were collected for each patient via chart review and included all the variables required to calculate a CAPRA score (presurgical serum PSA, biopsy Gleason scores, clinical stage, percent needle cores positive, and age at diagnosis) [18]. Self-reported ancestry was categorized as either AA or non-AA. In this study population, almost all non-AA patients were non-Hispanic Caucasians. Initial treatment type, progression of prostate cancer, subsequent treatment, vital status, cause of death, and the dates associated with these events were collected from The Ochsner Clinic tumor registry and/or medical chart review.

2.2. Patient outcomes

The primary clinical outcome was progression to metastatic disease, as confirmed by imaging. Disease-specific mortality (DSM) was an exploratory clinical outcome. Date and cause of death were sought from the Louisiana State Cancer Registry and National Death Index, and were used if prostate cancer death occurred within 6 mo of last patient contact with The Ochsner Clinic Department of Urology.

Time to clinical outcomes was measured in days elapsed since date of diagnosis. All non-events were censored at the date of last follow-up with The Ochsner Clinic or 10 yr from the date of diagnosis, whichever occurred first. Patients without follow-up were censored at the date of last contact with the clinic.

2.3. Biomarker testing

All molecular testing was completed blinded to patient outcomes at Myriad Genetics. CCP testing was performed as previously described with the exception that quality criteria were modified to allow for lower RNA content and greater RNA degradation in the archival tissue [14,19]. A board-certified pathologist (Z.S.) identified carcinoma tissue for analysis from FFPE biopsy samples. Selected tissue regions were macrodissected and deparaffinized (Deparaffinization Solution; Qiagen, Valencia, CA, USA) and RNA extraction was performed using miRNeasy (Qiagen). The expression of 31 CCP genes and 15 housekeeper genes was quantified in triplicate using TaqMan Low Density Arrays (Applied Biosystems, Foster City, CA, USA).

The CCP score was calculated as the average expression of the CCP genes normalized by the expression of the housekeeper genes [14]. CCP scores were considered not passing if the expression for more than nine CCP genes was missing or if the standard deviation for the triplicate score was >0.5. The CCR score was calculated as a linear combination of the CCP and CAPRA scores ($0.39 \times \text{CAPRA} + 0.57 \times \text{CCP}$) [19].

PTEN immunohistochemistry was performed using rabbit monoclonal antibody 138G6 (Cell Signaling Technology, Danvers, MA, USA) as previously described [22]. Negative PTEN expression was defined as no staining in ≥90% of tumor cells, and positive PTEN expression as staining in >10% of tumor cells.

2.4. Statistical analysis

Analyses are detailed in the Supplementary material and followed a prespecified statistical analysis plan. The main goal of the study was to test the interaction between race and CCP or CCR with metastasis as the outcome. The interaction between race and CCP or CCR scores was tested under the null hypothesis that there is no interaction between the variables of interest. All molecular data were generated blinded to patient outcome. Descriptive statistics for continuous variables included patient count, median, and interquartile range (IQR) and were compared between ancestral subgroups (AA vs non-AA). A multivariable Cox proportional hazards model was used to evaluate the prognostic value of the CCP score after accounting for other clinical covariates.

A predicted risk curve for metastatic disease within 7 yr of diagnosis as a function of the CCR score was produced for the range of CCR scores observed. All p values are two-sided and $p \leq 0.05$ was considered statistically significant unless otherwise indicated. Analyses were performed using R v.3.0.2 or later (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient cohort

The cohort included 969 eligible cases. Passing CCP scores were generated for 772 men (80%), five of whom were missing clinical information. The final cohort consisted of 767 men with complete molecular and clinical information for subsequent analyses, including 281 AA men (36.6%). There were no significant differences in demographic and

Table 1 – Demographic and clinical characteristics by ancestry

Parameter	Non-African American		African American		p value [a]
	Men (n)	Median (IQR) or %	Men (n)	Median (IQR) or %	
Median age at diagnosis (yr)	486	66 (59–73)	281	63 (58–70)	<0.001
Median prebiopsy PSA (ng/ml)	486	5.8 (4.4–8.3)	281	6.9 (5.0–11.7)	<0.001
Biopsy Gleason score					
<7	249	51.2	140	49.8	0.23
3 + 4 = 7	106	21.8	77	27.4	
4 + 3 = 7	51	10.5	29	10.3	
>7	80	16.5	35	12.5	
Clinical stage					
T1	342	70.4	214	76.2	0.22
T2	122	25.1	56	19.9	
T3	22	4.5	11	3.9	
Clinical node status					
N0	231	98.7	136	100	0.30
N1	3	1.3	0	0	
Median positive cores (%)[b]	486	42.9 (25.0–66.7)	281	46.2 (30.8–66.7)	0.24
Median number of cores	486	12.0 (11.0–13.0)	281	12.0 (11.0–13.0)	0.45
PTEN					
Positive	391	88.9	247	96.5	<0.001
Negative	49	11.1	9	3.5	
Median CCP score	486	0.3 (−0.2 to 1.0)	281	0.3 (−0.2 to 0.8)	0.52
Median CAPRA score	486	3 (2–5)	281	3 (2–5)	0.06
Median CCR score	486	1.3 (0.7–2.2)	281	1.4 (0.8–2.3)	0.38

IQR = interquartile range; PSA = prostate-specific antigen; CAPRA = Cancer of the Prostate Risk Assessment; CCP = cell cycle progression; CCR = clinical cell-cycle risk.

[a] Calculated using Fisher's exact test or a Wilcoxon test.

[b] The exact number of positive cores was missing for 46 patients. However, the percentage positive cores was inferred to be ≤34% or >34% for these patients.

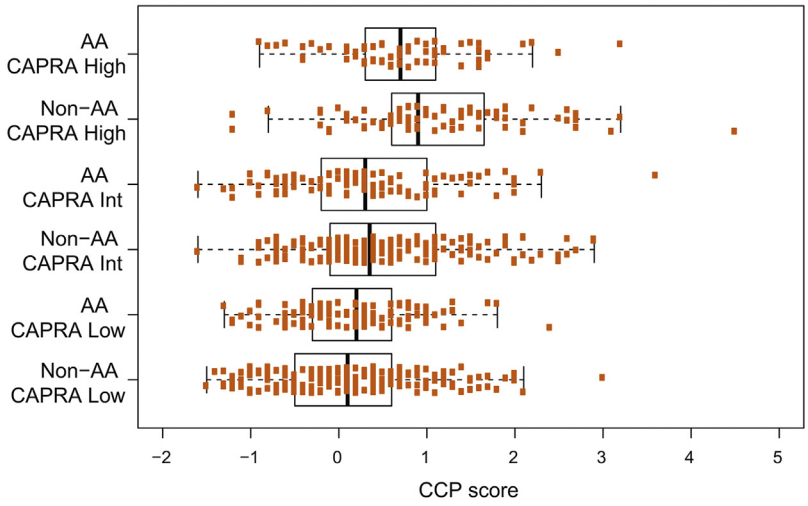

Fig. 1 – Cell cycle progression (CCP) score according to ancestry and Cancer of the Prostate Risk Assessment (CAPRA) score. CAPRA × interaction, $p = 0.035$. AA = African American; Int = intermediate.

clinical characteristics between non-AA and AA men (Table 1), with the exception of age at diagnosis (66 vs 63 yr; $p = 0.00019$), median PSA (5.8 vs 6.9 ng/ml; $p < 0.001$), and loss of PTEN expression (11.1% vs 3.5%; $p < 0.001$). There were no ancestry-based differences in CCP score distribution within each CAPRA risk category (Fig. 1).

The majority of men ($n = 646$; 84.2%) received definitive treatment, defined as radical prostatectomy, radiation therapy alone, or radiation and hormone therapy. Other primary treatments included hormone therapy only ($n = 50$; 6.5%) and watchful waiting ($n = 49$; 6.4%). Treatment was unknown for 22 men (2.9%). There were no differences in primary treatment by ancestry (Supplementary Table 1). Clinical and demographic characteristics by treatment are shown in Supplementary Table 2.

Clinical outcomes by ancestry and treatment type are given in Supplementary Table 3. The median follow-up time for men without metastatic disease who were alive at last follow-up was 5.6 yr (IQR 4.2–6.8) and did not differ by ancestry (non-AA: 5.6 yr, IQR 4.2–6.8; AA: 5.7 yr, IQR 4.4–6.9).

3.2. Association of clinical and molecular variables with metastatic disease

In univariate analyses, the CCP score was a significant predictor of progression to metastatic disease (hazard ratio [HR] per unit score 2.74, 95% confidence interval [CI] 2.08–3.55; $p < 0.001$). CAPRA score and primary treatment were also significant predictors, while PTEN expression was not (HR 0.48, 95% CI 0.20–1.41; $p = 0.16$). The rate of metastatic disease was positively correlated with the CCP score (Fig. 2A). Specifically, the Kaplan-Meier estimate of the probability of progression to metastatic disease was 2% among men with CCP scores <1 and increased to 18% for CCP scores of 1–2 and 38% for CCP scores >2.

In the preplanned multivariable analysis, CCP score was a highly significant predictor of metastatic disease after adjusting for CAPRA score, ancestry, and treatment (HR per unit score 2.04, 95% CI 1.47–2.79; $p < 0.001$; Table 2). There was no evidence of interaction between CCP score and ancestry ($p = 0.20$), initial treatment (overall $p = 0.094$), or CAPRA scores ($p = 0.84$), indicating

Table 2 – Multivariable Cox regression models of progression to metastatic disease

Variable [a]	HR [b] (95% CI)	*p* value
CCP score	2.03 (1.47–2.78)	<0.001
CAPRA score	1.71 (1.46–2.02)	<0.001
Ancestry (African American/non-African American)	0.52 (0.23–1.06)	0.072
Primary treatment		
Radical prostatectomy	Reference	0.25
Radiation	2.92 (1.10–7.72)	
Radiation with adjuvant hormone therapy	1.00 (0.38–2.65)	
Hormone therapy only	1.72 (0.60–4.99)	
Watchful waiting	1.05 (0.0081–8.63)	
Unknown	2.30 (0.23–11.20)	

CI = confidence interval; HR = hazard ratio; CAPRA = Cancer of the Prostate Risk Assessment; CCP = cell cycle progression.
[a] The clinical cell-cycle risk was not included in multivariable analyses because it is a multivariable combination of CAPRA and CCP.
[b] HR calculated per unit score.

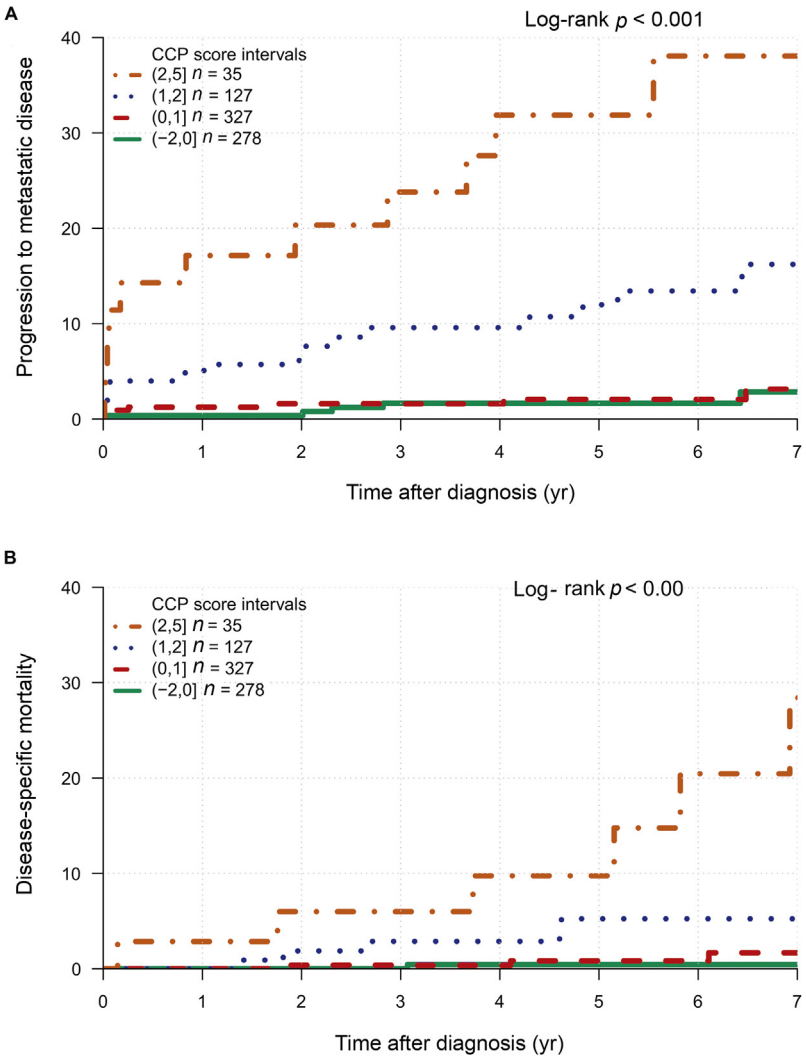

Fig. 2 – (A) Progression to metastatic disease and (B) disease-specific mortality by cell cycle progression (CCP) score risk category.

that the HR for CCP is independent of these variables. Results did not differ materially when the subset of patients for whom treatment was unknown were excluded (Supplementary Table 4). The *c*-index for the CCP-only model in predicting metastatic disease was 0.774. The *c*-index for the CAPRA-only model improved from 0.88 to 0.90 on addition of CCP scores. This provides supporting evidence that the CCP score adds prognostic information to that provided by clinical variables alone. Furthermore, the CCR includes approximately 20% more information than a CAPRA-only model (Supplementary Fig. 1).

The CCR score was highly prognostic in univariate analysis (HR per unit score 3.86, 95% CI 2.91–5.23; $p < 0.001$) and properly accounted for all the prognostic clinical variables included (Supplementary Fig. 1). There was no interaction between CCR and treatment ($p = 0.32$) or ancestry ($p = 0.24$). The CCR-based estimated risk for progression to metastatic disease did not differ significantly by ancestry (Fig. 3), and the CCR score distributions were similar (median 1.41 for AA vs 1.34 for non-AA; $p = 0.38$; Supplementary Fig. 2). The CCR score was also prognostic in the subset of men who had definitive therapy ($n = 646$), defined as radical prostatectomy, primary radiation therapy alone, or primary radiation therapy and androgen deprivation therapy (Supplementary Fig. 3). The amount of new prognostic information provided by the CCR score can be illustrated by comparing the difference in predicted risk between CCR-only and CAPRA-only prognostic models (Fig. 4). In addition, most men who progressed to metastatic disease had substantially higher estimated risks after addition of the CCP score to the prediction model.

3.3. *Association of clinical and molecular variables with DSM*

The association between CCP and DSM was highly significant in univariate analysis (HR per unit score 3.10, 95% CI 2.01–4.72; $p < 0.001$). The Kaplan-Meier estimated probability of the progression rate to DSM was 1.7% for those with CCP scores <1 and increased to 5% and 28% for CCP scores of 1–2 and >2, respectively (Fig. 2B). The *c*-index for a CAPRA-

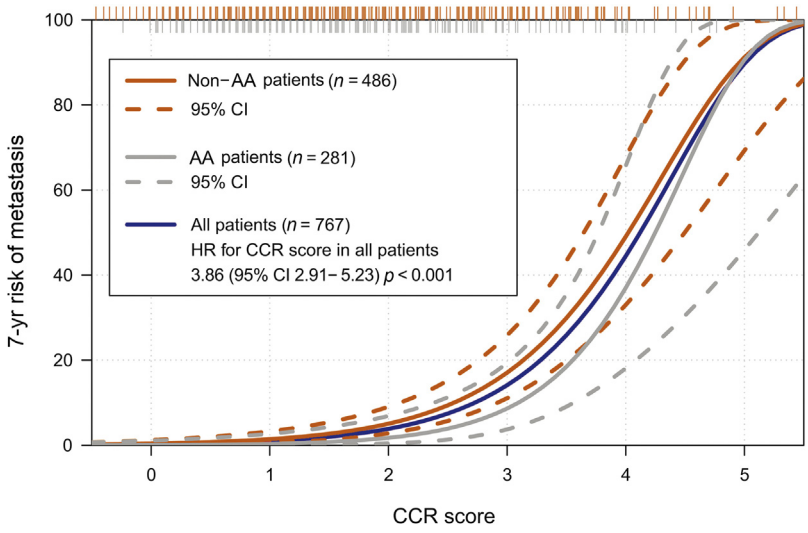

Fig. 3 – The 7-yr risk of metastasis by ancestry. AA = African American; CCR = clinical cell-cycle risk; HR = hazard ratio; CI = confidence interval.

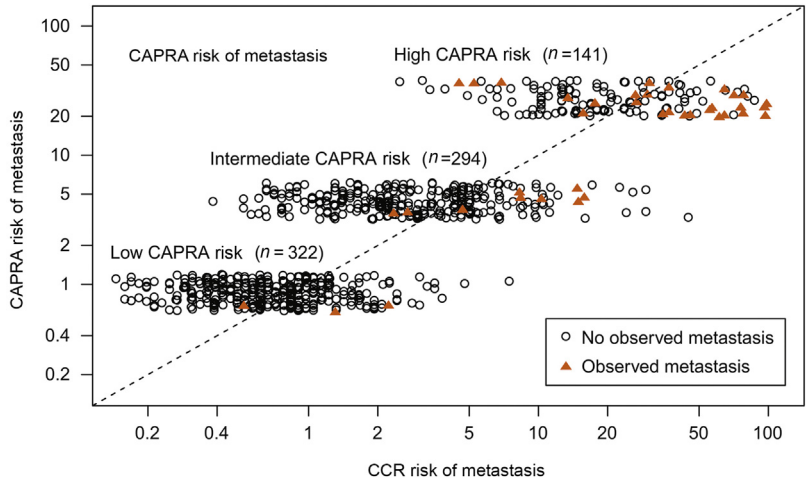

Fig. 4 – Clinical cell-cycle risk (CCR) score and progression to metastatic disease according to Cancer of the Prostate Risk Assessment (CAPRA) risk category.

only model was 0.91 and this improved to 0.94 after addition of CCP. However, the limited number of DSM events ($n = 15$) precludes a rigorous evaluation of this endpoint.

4. Discussion

An important application of personalized medicine is tailoring the aggressiveness of clinical intervention based on an assessment of patient prognosis. It has become evident that some early-stage cancers are indolent and can be safely monitored, while others require immediate intervention [23,24]. However, applying this strategy in the clinical setting requires accurate risk discrimination, especially in prostate cancer, for which physicians can use a myriad of treatment options ranging from deferred treatment to multimodal interventions.

Clinical uncertainty about the prognosis of newly diagnosed prostate cancer among AA men is particularly acute [25]. Previous studies have documented numerous differences in prostate cancer between AA and non-AA men [7,11,26]. These differences include disease presentation, diagnosis, treatment, and distant oncologic outcomes, all suggesting a more aggressive disease phenotype in AA men. The reasons underlying these observations are unclear, but could be driven by a combination of biologic, socioeconomic, and/or cultural factors. To this point, the disparities in outcomes between AA and non-AA patients tend to be reduced in studies that either focused on intensively screened populations or that were conducted at institutions where patient access to the health system was equal [27,28].

In this study, the higher frequency of PTEN loss among AA men was confirmed [17]. However, this did not impact

risk discrimination, as PTEN expression was not significantly associated with progression to metastatic disease. The study also showed that ancestry does not appear to impact the prognostic information provided by the CCP score, with no significant differences in HRs according to ancestry ($p = 0.20$). This is consistent with a previous study that showed equivalent CCP HRs in a cohort that included 81 AA men [20]. Furthermore, the predicted risk for metastatic disease did not differ between AA and non-AA patients after accounting for all available molecular and clinicopathologic prognostic information in this study cohort (Fig. 3). These data may indicate that both the molecular score and the derived predicted risk (based on the CCR score) could be used to help in guiding appropriate clinical management of both AA and non-AA patients with newly diagnosed prostate cancer.

This study has several limitations. First, ancestry was self-reported. This may introduce error and limit the generalizability of the conclusions, as population-based genetic heterogeneity was not addressed [29]. Although obtaining genetic information for this patient population could have provided more precise ancestry information, this was impractical within the scope of the study. Second, the study was retrospective in nature. To minimize the sample bias that can occur in retrospective studies, we studied a population-based disease cohort that was prospectively collected and molecular testing was performed for as many evaluable men as possible. This design conforms to best practice as defined by several peer-reviewed guidelines for biomarker validation [30]. In addition, patients were not randomly assigned to treatment regimens. Although clinical information is available, factors that might have guided treatment choices remain unknown and no conclusions can be drawn about the relative efficacy of different therapies. The clinical follow-up is also somewhat limited (median 5.6 yr) and conclusions regarding late metastatic events require caution. Finally, the men in this study were mostly treated, and therefore the data presented add little to the evidence that the CCP score can help in selecting men for deferred treatment. However, the study expands the evidence that the test can identify men at high risk of failing on standard therapy.

5. Conclusions

Appropriate clinical management of newly diagnosed prostate cancer depends on accurate risk discrimination. This is the first study to robustly evaluate the impact of ancestry on the prognostic performance of this molecular test. The study indicates that the prognostic information provided by the CCP score is independent of ancestry and therefore could be used to improve risk discrimination among both AA and non-AA men with localized prostate cancer.

Author contributions: Daniel J. Canter had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Canter, Reid, Halat, Gurtner, Sangale, Brawer, Stone, Bardot.
Acquisition of data: Canter, Latsis, Variano, Halat, Gurtner, Sangale, Brawer, Stone, Bardot.
Analysis and interpretation of data: Canter, Reid, Halat, Rajamani, Gurtner, Sangale, Brawer, Stone, Bardot.
Drafting of the manuscript: Canter, Reid, Halat, Rajamani, Gurtner, Sangale, Brawer, Stone, Bardot.
Critical revision of the manuscript for important intellectual content: Canter, Reid, Latsis, Variano, Halat, Rajamani, Gurtner, Sangale, Brawer, Stone, Bardot.
Statistical analysis: Reid, Rajamani.
Obtaining funding: Reid, Sangale, Brawer, Stone.
Administrative, technical, or material support: Latsis, Variano.
Supervision: Canter, Halat, Gurtner, Sangale, Stone, Bardot.
Other: None.

Financial disclosures: Daniel J. Canter certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Julia Reid, Zaina Sangale, Michael Brawer, and Steven Stone were employed by Myriad Genetic Laboratories at the time of this study. The remaining authors have nothing to disclose.

***Funding/Support and role of the sponsor*:** This work was supported by Myriad Genetic Laboratories, Inc. The sponsor played a role in the design and conduct of the study; data management, analysis, and interpretation; and preparation, review, and approval of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.028.

References

[1] Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate Cancer V2.2017. National Comprehensive Cancer Network clinical practice guidelines in oncology. 2017. www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
[2] Sanda MG, Chen RC, Crispino T, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline.. 2017. www.auanet.org/Documents/education/clinical-guidance/Clinically-Localized-Prostate-Cancer.pdf
[3] Colicchia M, Morlacco A, Cheville JC, Karnes RJ. Genomic tests to guide prostate cancer management following diagnosis. Expert Rev Mol Diagn 2017;17:367–77.
[4] Brawley OW. Trends in prostate cancer in the United States. J Nat Cancer Inst Monogr 2012;2012:152–6.
[5] Powell IJ. Epidemiology and pathophysiology of prostate cancer in African-American men. J Urol 2007;177:444–9.
[6] Vollmer RT. Race and the linkage between serum prostate-specific antigen and prostate cancer: a study of American veterans. Am J Clin Pathol 2004;122:338–44.
[7] Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. Prostate 2011;71:985–97.
[8] Carroll P, Albertsen PC, Greene K, et al. PSA testing for the pretreatment staging and posttreatment management of prostate cancer.

American Urological Association. 2013. www.auanet.org/documents//education/clinical-guidance/Prostate-Specific-Antigen.pdf
[9] Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin 2010;60:70–98.
[10] Maurice MJ, Sundi D, Schaeffer EM, Abouassaly R. Risk of pathological upgrading and up staging among men with low risk prostate cancer varies by race: results from the National Cancer Database. J Urol 2017;197:627–31.
[11] Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol 2013;31:2991–7.
[12] Chung MS, Lee SH. Current status of active surveillance in prostate cancer. Investig Clin Urol 2016;57:14–20.
[13] Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976–83.
[14] Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245–55.
[15] Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: a straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer 2011;117:5039–46.
[16] Koch MO, Cho JS, Kaimakliotis HZ, et al. Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. Cancer Biomarkers 2016;17:83–8.
[17] Tosoian JJ, Chappidi MR, Bishoff JT, et al. 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. BJU Int 2017.
[18] Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005;173:1938–42.
[19] Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer 2015;113:382–9.
[20] Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys 2013;86:848–53.
[21] Jamaspishvili T, Berman DM, Ross AE, et al. Clinical implications of PTEN loss in prostate cancer. Nat Rev Urol 2018;15:222.
[22] Sangale Z, Prass C, Carlson A, et al. A robust immunohistochemical assay for detecting PTEN expression in human tumors. Appl Immunohistochem Mol Morphol 2011;19:173–83.
[23] Klotz L. Cancer overdiagnosis and overtreatment. Curr Opin Urol 2012;22:203–9.
[24] Haymart MR, Miller DC, Hawley ST. Active surveillance for low-risk cancers—a viable solution to overtreatment? N Engl J Med 2017;377:203–6.
[25] Vijayakumar S, Henegan JC, Zhang X, et al. Enriching gene expression profiles will help personalize prostate cancer management for African-Americans: a perspective. Urol Oncol 2017;35:315–21.
[26] Mahal BA, Chen YW, Muralidhar V, et al. Racial disparities in prostate cancer outcome among prostate-specific antigen screening eligible populations in the United States. Ann Oncol 2017;28:1098–104.
[27] Daskivich TJ, Kwan L, Dash A, Litwin MS. Racial parity in tumor burden, treatment choice and survival outcomes in men with prostate cancer in the VA healthcare system. Prostate Cancer Prostat Dis 2015;18:104–9.
[28] Powell IJ, Vigneau FD, Bock CH, Ruterbusch J, Heilbrun LK. Reducing prostate cancer racial disparity: evidence for aggressive early prostate cancer PSA testing of African American men. Cancer Epidemiol Biomarkers Prev 2014;23:1505–11.
[29] Han E, Carbonetto P, Curtis RE, et al. Clustering of 770,000 genomes reveals post-colonial population structure of North America. Nat Commun 2017;8:14238.
[30] Pepe MS, Feng Z, Janes H, Bossuyt PM, Potter JD. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. J Natl Cancer Inst 2008;100:1432–8.