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ORIGINAL ARTICLE

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Cell-cycle risk score more accurately determines the risk for metastases and death in prostatectomy patients compared with clinical features alone

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Abstract

Background: Prostate cancer treatment aims to prevent metastases and disease-specific mortality. Pathologic parameters have limited ability to predict these outcomes, but biomarkers can improve risk discrimination. We evaluated the ability of cell-cycle progression and combined cell-cycle risk scores to predict metastases and disease-specific mortality after prostatectomy.

Methods: Eligibility included (1) treatment with radical prostatectomy (1985–1997); (2) cell-cycle progression score; (3) preoperative prostate-specific antigen; (4) no neoadjuvant therapy; and (5) clinical follow-up ($N = 360$). Cancer of the prostate risk assessment postsurgical score was combined with cell cycle progression into the prespecified combined cell-cycle risk score. Hazard ratios (HRs) are reported per unit score.

Results: In total, 11% (41/360) developed metastases and 9% (33/360) experienced disease-specific mortality. Combined cell-cycle risk score predicted metastases and disease-specific mortality post-radical prostatectomy ($p < 1 \times 10^{-8}$). Adjusting for cancer of the prostate risk assessment postsurgical score, the combined cell-cycle risk score remained a predictor of metastases (HR = 3.03 [95% confidence interval (CI): 1.49, 6.20]; $p = .003$] and disease-specific mortality (HR = 3.40 [95% CI: 1.52, 7.59]; $p = .004$). Of patients with biochemical recurrence, 25% (41/163) developed metastases. Cancer of the prostate risk assessment postsurgical score was predictive of metastases postbiochemical recurrence but was improved by the addition of cell cycle progression (HR = 1.70 [95% CI: 1.14, 2.53]; $p = .012$). The combined cell-cycle risk was also prognostic of metastases post-biochemical recurrence (HR = 1.56 [95% CI: 1.20, 2.03]; $p = .001$).

Conclusion: Combined cell-cycle risk and cell cycle progression scores predict metastases and disease-specific mortality post-radical prostatectomy and should help identify patients at greatest risk of treatment failure who might benefit from earlier intervention.

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KEYWORDS
cell cycle progression, clinical cell-cycle risk, disease progression, prostate cancer, radical prostatectomy

1 | INTRODUCTION

The primary goal in the treatment of any cancer is the prevention of disease-specific mortality (DSM). Metastatic disease is difficult to treat and usually incurable, resulting in DSM unless the patient dies of intercurrent disease or fatal accident.[1–4] Practically, cancer does not necessarily have to be totally eradicated by the primary intervention; rather the goal is to significantly delay progression to metastatic disease and, therefore, DSM. To accomplish this goal, patients at risk for disease progression must be identified before it occurs.

Depending on the risk of disease progression, a number of primary interventions may be available for patients. For men with prostate cancer at low risk of disease progression, active surveillance rather than immediate definitive treatment may be appropriate. Radical prostatectomy (RP), on the contrary, is a standard treatment for men with localized prostate cancer at intermediate or high risk of disease progression and a life expectancy of at least 10 years.[4] Traditionally, postsurgical factors such as prostate-specific antigen (PSA), Gleason score, and pathological stage have been used to provide prognostic information regarding the risk of DSM post-RP. For these factors, rising PSA (i.e., biochemical recurrence [BCR]) has primarily been used as a surrogate for DSM to accommodate for the long natural history of prostate cancer and the inherent difficulties associated with following patients for extended time periods.[5] Although all patients with prostate cancer who experience DSM exhibit a rising PSA, the correlation between the two is actually fairly weak.[6] For example, a recently published post-RP cohort of men with prostate cancer and a median follow-up time of 23.9 years found that 36% had rising PSA, but only 8% had died from their disease.[7]

With the increased ability to define the molecular characteristics of prostate cancer, there is a pervasive interest in using molecular markers to differentiate cancer severity.[8] Indeed, the patient cohort published by Swanson et al.[7] was previously used to evaluate the first validated panel of molecular markers in prostate cancer (Prolaris®, Myriad Genetics Inc.).[9] This panel includes 31 genes involved in cell cycle progression (CCP) and produces a CCP score, which informs the risk of disease progression. This CCP score was shown by Cuzick et al.[9] to be the single-most powerful predictor of BCR post-treatment, exceeding that of Gleason score, pathological stage, including seminal vesicles and lymph node involvement, and PSA. When CCP gene expression was added to other clinicopathologic features, the combined model was a significantly better predictor of recurrence than clinicopathologic features alone.[9] This observation has subsequently been validated in many independent cohorts,[10–14] including in patients following radical prostatectomy.[15,16] In fact, Cooperberg et al.[15] validated a predefined model (clinical cell-cycle risk [CCR] score) that combines the CCP score and the postsurgical Cancer of the Prostate Cancer Risk Assessment (CAPRA-S) for determining patient prognosis post-prostatectomy.[15] However, in all previous studies of disease progression following RP, the endpoint was BCR, and while this is widely accepted as a surrogate for treatment failure, it is poorly correlated to DSM or progression to metastatic disease.

The goal in this reanalysis of a previously published cohort[9] was to determine if, with longer follow-up, the CCP and CCR scores can be used to improve the ability to identify patients at risk for progression to metastatic disease and DSM after RP. We also evaluated whether both scores can be used to help identify men at the highest risk of progression to metastatic disease after BCR.

2 | MATERIALS AND METHODS

2.1 | Cohort

As previously reported,[9] this cohort consists of consecutive patients that underwent radical retropubic prostatectomy between 1985 and 1997 at Scott and White hospital (Temple, TX). Of the total of 754 patients who underwent RP, 360 were eligible for this analysis after applying inclusion criteria (see Figure S1 for details of cohort selection). Patients were followed routinely with PSA level measurement and urology clinic visits. Ultimately, follow-up was released to the managing physicians, varying by the urologist, at which point routine PSA measurement became less systematic. As other medical issues became more urgent and/or the patients' health declined, such testing often ceased. The patients were tracked at various intervals to obtain information on survival and cancer status. For patients no longer seen in Scott and White hospital clinics, contact was attempted with the home physician and/or the patient. For patients that were deceased without clear outcome information, death certificates were requested. The endpoints for this study were progression to metastatic disease and progression to DSM. Events regarding metastatic disease and death were recorded. Prostate cancer death was recorded as such only when cancer contributed to the death.

2.2 | Formalin-fixed paraffin-embedded (FFPE) tumor tissue

The prostatectomy specimens were originally processed by inking the external surface. The glands were randomly sectioned into multiple sections from areas of known or gross disease and areas suspicious for cancer extension. Additional sections were taken from the apex and base with careful attention to the bladder neck and

urethral margin.[7] As per the 2005 International Society of Urological Pathology revised the Gleason scoring system; all samples were re-scored using contemporary standards.[7]

2.3 | Molecular testing

All molecular testing was completely blinded to the patient outcomes at Myriad Genetics Inc. (Salt Lake City, UT). CCP testing was performed as previously described.[9] A board-certified pathologist identified carcinoma tissue for analysis from FFPE post-RP tissue samples. Selected tissue regions were macrodissected and deparaffinized (Deparaffinization Solution; Qiagen), and RNA extraction was performed using miRNeasy (Qiagen). The expression of 31 CCPs (*ASF1B*, *ASPM*, *BIRC5*, *BUB1B*, *C18orf24*, *CDC2*, *CDC20*, *CDCA3*, *CDCA8*, *CDKN3*, *CENPF*, *CENPM*, *CEP55*, *DLGAP5*, *DTL*, *FOXM1*, *KIAA0101*, *KIF11*, *KIF20A*, *MCM10*, *NUSAP1*, *ORC6L*, *PBK*, *PLK1*, *PRC1*, *PTTG1*, *RAD51*, *RAD54L*, *RRM2*, *TK1*, *TOP2A*) genes and 15 housekeeper genes (*CLTC*, *MMADHC*, *MRFAP1*, *PPP2CA*, *PSMA1*, *PSMC1*, *RPL13A*, *RPL37*, *RPL38*, *RPL4*, *RPL8*, *RPS29*, *SLC25A3*, *TXNL1*, *UBA52*) was quantified in triplicate using TaqMan Low Density Arrays (Applied Biosystems).

The CCP score was calculated as the average expression of the CCP genes normalized by the expression of the housekeeper genes. The CCR score for post-RP was calculated as a linear combination of the CCP and University of California, San Francisco (UCSF) Cancer of the Prostate Risk Assessment (CAPRA-S) score ($0.38 \times \text{CAPRA} + 0.57 \times \text{CCP}$).[15] CAPRA-S stratifies patients risk based on the recognized predictive markers of Gleason score, preoperative PSA, and the pathological findings of extracapsular extension, margins, seminal vesicle involvement, and lymph node positivity.[17]

2.4 | Statistical methods

All available follow-up data were used to calculate Kaplan–Meier estimates and to fit Cox proportional hazard models to determine the significance of molecular and clinical factors in predicting progression events. Hazard ratios (HR) with 95% profile likelihood-based confidence intervals (CIs) and p values from partial likelihood ratio tests are reported for all Cox proportional hazards models. All risk estimate CIs are based on the log–log transformation. $p < .05$ is considered to indicate statistical significance.

In cohort-optimized prognostic models, there was a time-dependent effect of the CCP for predicting metastasis ($p = .033$) and DSM ($p = .019$) following RP, which was accounted for in the optimized models with CCP and CAPRA-S using identity transformation. There was no significant time dependence seen in the combined CCR score on the prediction of metastasis ($p = .21$) or DSM ($p = .13$) following RP, or in CCP, CAPRA-S, or CCR in predicting metastasis (CCP: $p = .22$, CAPRA-S: $p = .53$, CCR: $p = .99$) or DSM (CCP: $p = .07$, CAPRA-S: $p = .68$, CCR: $p = .68$) after BCR. All analyses were carried out with the use of R software, version 3.5.0 or higher (R Core Team).

3 | RESULTS

The study cohort included 360 patients (Figure S1) evaluated with a median follow-up time of 16 years, 163 (45%) of whom developed BCR, 41 (11%) developed metastatic disease, and 33 (9%) experienced DSM. Overall, at the time of analysis, 80% of this cohort were deceased. The 73 patients who were alive at the time of analysis had a median follow-up of 23.5 years. There were 167 (46%) patients considered to have a low risk of disease progression, 126 (35%) to have an intermediate risk, and 67 (19%) to have high risk according to CAPRA-S. A summary of postsurgical clinicopathologic variables is provided in Table 1. The median CCP score for the cohort was 0.2 (interquartile range [IQR]: −0.3, 0.7).

3.1 | Risk post-RP

The post-RP CCR score was a highly significant predictor of metastasis after RP (HR per unit score, 2.03 [95% CI: 1.66, 2.48]; $p = 2.1 \times 10^{-10}$). The CCR score remained a significant predictor of metastasis after adjusting for CAPRA-S (HR per unit score, 3.03 [95% CI: 1.49, 6.20]; $p = .003$), indicating that the CCP score provides significant prognostic information, which is not captured by CAPRA-S. The CCP score also added significant prognostic information to CAPRA-S in a model that was optimized for this cohort and accounted for time dependence

TABLE 1 Patient characteristics

	Median (IQR) or *N* (%)
Age at surgery (years)	67.5 (63.3, 71.5)
Gleason Score	
<7	95 (26.4%)
7	227 (63.1%)
>7	38 (10.6%)
Pre-RP PSA	6.90 (4.5, 11.2)
<10	253 (70.3%)
10–20	66 (18.3%)
>20	41 (11.4%)
Seminal vesical+	40 (11.1%)
Lymph node+	16 (4.4%)
Surgical margin+	85 (23.6%)
Extracapsular extension+	106 (29.4%)
CAPRA-S	3 (1, 5)
Low (0–2)	167 (46.4%)
Intermediate (3–5)	126 (35.0%)
High (6–12)	67 (18.6%)
CCP, median (IQR)	0.2 (−0.3, 0.7)
CCR, median (IQR)	1.140 (0.494, 2.033)

Abbreviations: CAPRA-S, cancer of the prostate risk assessment; CCP, cell cycle progression; CCR, cell-cycle risk; IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy.

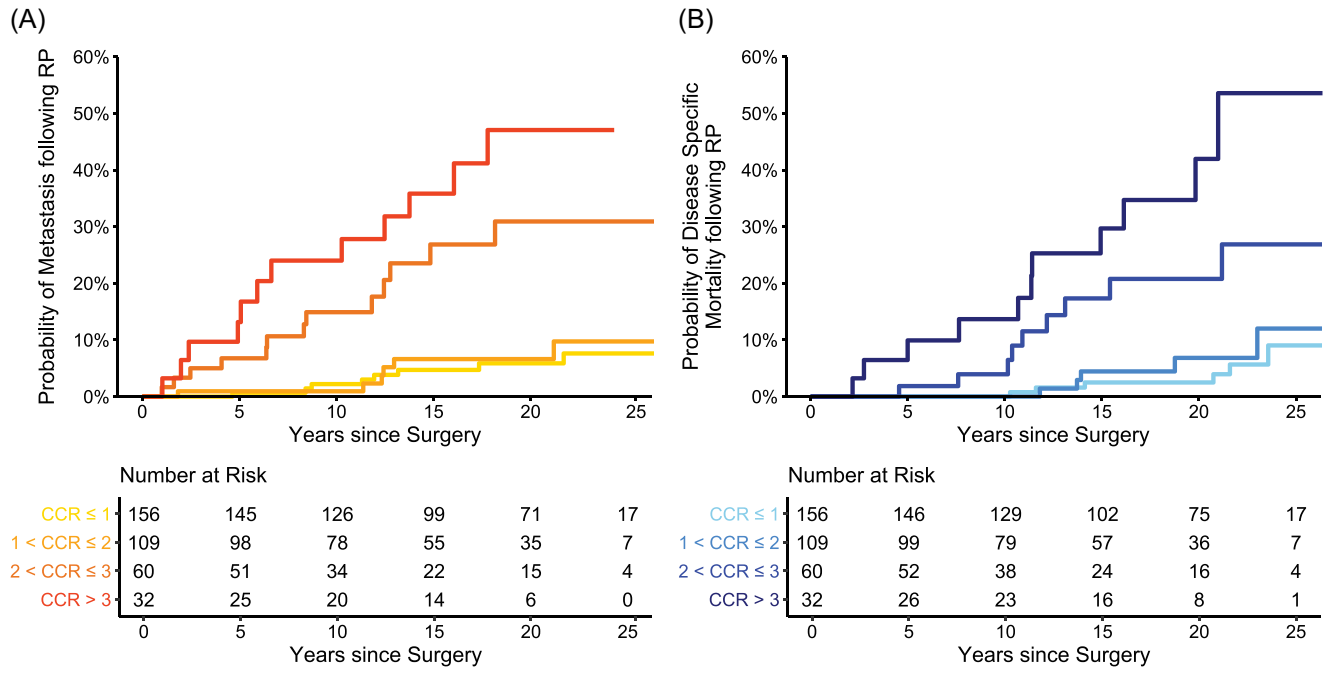

FIGURE 1 Kaplan–Meier plots for (A) risk of metastasis following RP; (B) risk of disease-specific mortality following RP. CCR, cell-cycle risk; RP, radical prostatectomy [Color figure can be viewed at wileyonlinelibrary.com]

($p = .001$). Kaplan–Meier analysis was used to illustrate the impact of CCR score on the risk of progression to metastatic disease (Figure 1A) with CCR scores >3 having about 45% risk of progression to metastatic disease by 20 years post-RP. CCR-based risk models were calculated at 10, 15, and 20 years post-RP (Figure 2). Additionally, we compared individual patient predicted risks using CCR score to risks predicted by a CAPRA-S only model (Figure 3 and Table S1). CCR score offered further risk stratification for all three CAPRA-S risk groups at all time periods for predicting progression to metastatic disease after surgery. As the CCR score is a combination of CAPRA-S and the CCP molecular score, the additional risk stratification, as illustrated by the spread along the *x* axis, is due to the molecular component of the score.

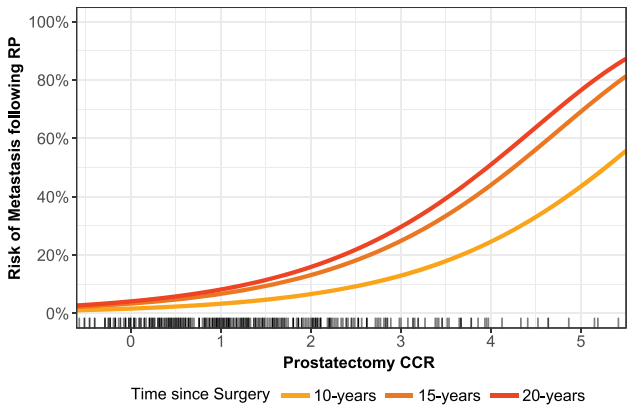

FIGURE 2 Risk of metastasis at 10, 15, and 20 years after RP. CCR, cell-cycle risk; RP, radical prostatectomy [Color figure can be viewed at wileyonlinelibrary.com]

The CCR score was highly prognostic of DSM after RP (HR per unit score, 2.11 [95% CI: 1.68, 2.65]; $p = 1.7 \times 10^{-9}$) and remained significant after accounting for the information in CAPRA-S (HR per unit score, 3.40 [95% CI: 1.52, 7.59]; $p = .004$). Kaplan–Meier analysis was used to illustrate the impact of CCR score on the risk of progression to DSM (Figure 1B). The CCP score was also significant ($p = .001$) when combined with CAPRA-S in a prognostic model that was optimized for this cohort and included a factor for time dependence. As with predicting metastatic disease, the added value of CCR for predicting DSM was illustrated by comparing patients' predicted risk using CCR to risks predicted by a CAPRA-S-only model (Figure S2 and Table S1). Interestingly, CAPRA-S low-risk patients have higher CCR predicted risks and, conversely, CAPRA-S intermediate-risk patients have lower CCR predicted risks than would have been predicted by CAPRA-S alone.

3.2 | Risk post-BCR

Of the 163 men who developed BCR, only 41 (25%) developed metastases. In univariate analysis, both CAPRA-S (HR per unit score, 1.16 [95% CI: 1.04, 1.29]; $p = .010$) and the CCP score (HR per unit score, 1.75 [95% CI: 1.18, 2.59]; $p = .008$) were significant predictors of progression to metastatic disease after BCR. Time from surgery to BCR was not prognostic (HR, 0.98 [0.89, 1.08; $p = .69$]). In multivariable analysis, the CCP score added significant information to CAPRA-S (HR per unit score, 1.70 (95% CI: 1.14, 2.53); $p = .012$; Table 2) and the C-index improved to 0.64 compared with 0.60 in the CAPRA-S only model. The CCR score was also highly prognostic (HR per unit score, 1.56 [95% CI: 1.20, 2.03]; $p = .001$).

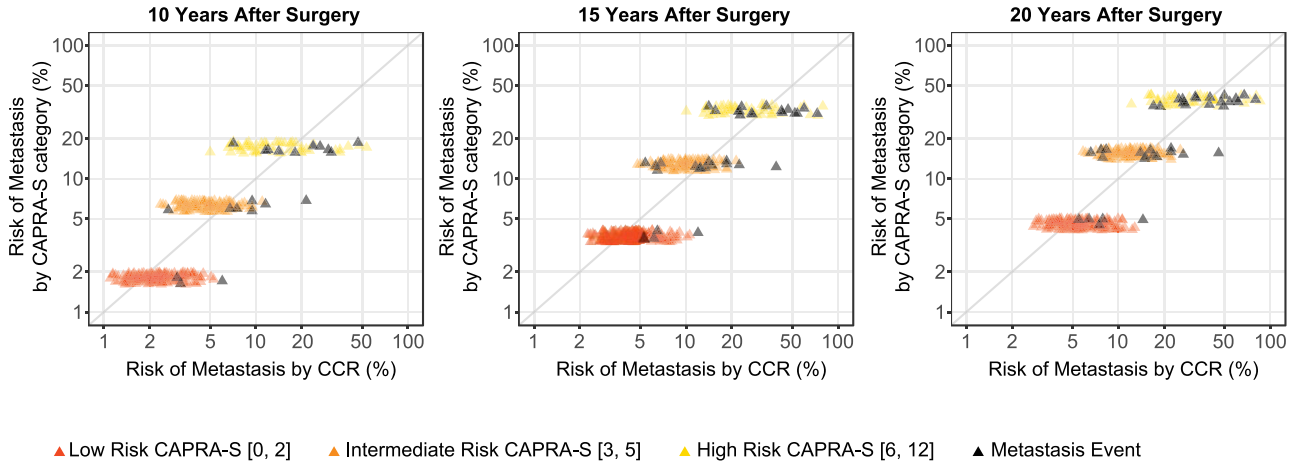

FIGURE 3 Risk stratification for metastasis after radical prostatectomy (RP) patients who experienced metastasis within the timeframe indicated in each graph (10, 15, and 20 years post-RP) are denoted using the black triangles within each CAPRA-S (cancer of the prostate risk assessment) risk category. Predicted risk using CAPRA-S only is plotted on the *y* axis and the risk predicted by cell-cycle risk (CCR) is on the *x* axis. The spread along the *x* axis is due to the information cell cycle progression (CCP) score adds to CAPRA-S when combined as CCR. Time to the event or last follow-up is not indicated. For the numerical representation of these patients as a ratio of the total group, please see Table S1 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Predicting time to metastasis following BCR

	Univariate				Multivariate			
	HR (95% CI)	χ^2 test statistic	*p* value	C-index	HR (95% CI)	χ^2 test statistic	*p* value	C-index
CCP	1.75 (1.18, 2.59)	7.12	.008	0.58	1.70 (1.14, 2.53)	6.25	.012	0.64
CAPRA-S	1.16 (1.04, 1.29)	6.67	.01	0.60	1.15 (1.03, 1.28)	5.80	.016	
CCR	1.56 (1.20, 2.03)	10.91	.001	0.63				

Abbreviations: BCR, biochemical recurrence; CAPRA-S, cancer of the prostate risk assessment; CCP, cell cycle progression; CI, confidence interval; CCR, cell-cycle risk; HR, hazard ratio.

CCR-based risk curves for progression to metastatic disease following BCR are shown for 5, 10, and 15 years after BCR (Figure 4). Similar data were observed for the association of both CCR and CCP with progression to DSM after BCR (data not shown).

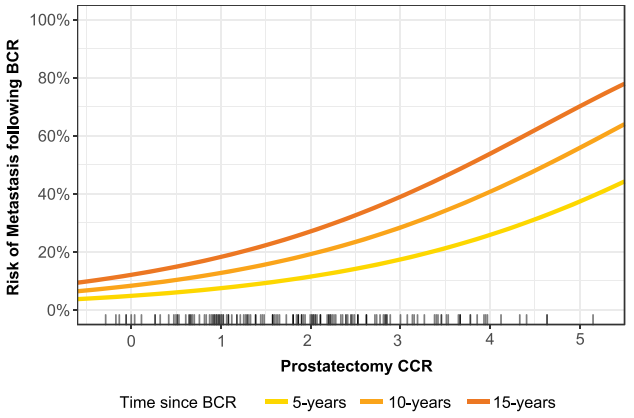

FIGURE 4 Risk of metastasis at 5, 10, and 15 years after BCR. BCR, biochemical recurrence; CCR, cell-cycle risk [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The real goal of determining the risk of failure after RP is to identify at-risk patients and intervene early to prevent metastatic disease and DSM. There is some evidence that administering chemotherapy before patients have failed androgen ablation increases survival, though the results were modest.[18] In general, the longstanding indication for adjuvant systemic therapy in oncology is a risk of metastatic disease of >10%.[19] Unfortunately, using that criteria, Stage III randomized studies of men with prostate cancer selected based on clinical criteria alone with adjuvant chemotherapy have not shown a survival advantage.[20,21] The results of these trials, and perhaps of multimodality therapy in clinical practice, would likely be improved if more accurate risk discrimination was used to identify patients at the highest risk of disease progression.

Attempts have been made to combine standard prognostic variables, such as PSA, Gleason score, and pathological findings, to create more discriminative classifications. Many schemes, such as risk groups and nomograms, have been developed based on combinations of these basic parameters, but almost all rely on prognosticating BCR as a surrogate endpoint for DSM. When applied to more distal oncologic outcomes, these schemes tend to lack the

desired discrimination. For example, CAPRA-S applied to the present study cohort identified about 20% of the cohort as high-risk patients (CAPRA-S scores, 6–12) with a predicted risk for progression to metastatic disease by 10 years of about 17%. Therefore, even within the highest risk group defined by CAPRA-S, the vast majority of men will never experience disease progression after surgery.

The hope was that molecular markers would add significant prognostic information beyond what was provided by clinicopathologic variables. Indeed, the ability of the CCP score to improve risk discrimination by itself or in combination with other factors has been well documented.[9,11–15,22–24] It has also been included in several professional guidelines (i.e., ASCO, NCCN) as an important tool for improving risk discrimination in patients with newly diagnosed localized disease.[25–27] We previously evaluated the CCP in the present study cohort, and with a median of 9.4 years of follow-up were able to show that the CCP score was prognostic of BCR.[9] Here, because of increased follow-up time (median, 23.5 years), we were able to extend our previous analysis of the CCP and CCR scores to evaluate their association with metastatic disease and DSM after RP. Both scores were highly prognostic, and importantly, the molecular information added significant prognostic information after accounting for CAPRA-S. Additionally, adding molecular information to CAPRA-S substantially changed predicted risks for individual patients. For example, within the CAPRA-S high-risk group with a predicted 10-year metastasis risk post-RP of 17%, CCR-based risks ranged from 5% to about 50%, showing that the CCR score was better able to discriminate, including identifying very high-risk patients who may be candidates for clinical trials. In addition, in men with BCR, the CCR score identified those with the highest risk of metastatic disease. The ability to identify patients that are highly likely to fail salvage treatment could be invaluable for the selection of patients that may benefit from treatment beyond standard radiation and/or androgen ablation.

This study is primarily limited by the age of the cohort. This cohort received treatment with RP between 1985 and 1997. Increased understanding of the biology of prostate cancer has resulted in changes in the management of the disease in the intervening decades. Therefore, changes in treatment paradigms since the initial treatment of this cohort may result in a different composition of patient risks than a modern cohort. However, the age of this cohort is also one of the greatest strengths as it allows for a significantly longer clinical follow-up time. Additionally, patients in this study cohort receive a variety of post-RP treatments before metastasis or DSM, which reflects the current treatments in standard clinical practice. This treatment heterogeneity should have no impact on the overall conclusions of this study relating to the performance of the CCP and CCR scores and, in fact, indicates that the prognostic scores are robust to this variability.

5 | CONCLUSION

Here, with the benefit of long-term follow-up, enabling the evaluation of the meaningful oncologic endpoints of metastatic disease and DSM, the CCP score has proven to be a powerful predictor of these events. When combined with CAPRA-S into the CCR score, the resultant model is even more prognostic. These scores provide tools to more reliably identify those patients at the highest risk for disease progression after RP. This should improve both clinical decision-making for treatment intensification and the selection of appropriate patients for clinical trials intended to lower prostate cancer mortality.

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CONFLICT OF INTERESTS

Lauren Lenz, Steve Stone, and Todd Cohen are employed by Myriad Genetics Inc. and receive salary and stock options as compensation.

ETHICS STATEMENT

Institutional review board approval was obtained from the Scott and White Clinic. This protocol was approved with a waiver of consent.

DATA AVAILABILITY STATEMENT

Data is available upon reasonable request to the authors.

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SUPPORTING INFORMATION

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