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Validation of a Cell-Cycle Progression Gene Panel to Improve Risk Stratification in a Contemporary Prostatectomy Cohort

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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A B S T R A C T

Purpose
We aimed to validate a previously described genetic risk score, denoted the cell-cycle progression (CCP) score, in predicting contemporary radical prostatectomy (RP) outcomes.

Methods
RNA was quantified from paraffin-embedded RP specimens. The CCP score was calculated as average expression of 31 CCP genes, normalized to 15 housekeeper genes. Recurrence was defined as two prostate-specific antigen levels $\geq$ 0.2 ng/mL or any salvage treatment. Associations between CCP score and recurrence were examined, with adjustment for clinical and pathologic variables using Cox proportional hazards regression and partial likelihood ratio tests. The CCP score was assessed for independent prognostic utility beyond a standard postoperative risk assessment (Cancer of the Prostate Risk Assessment post-Surgical [CAPRA-S] score), and a score combining CAPRA-S and CCP was validated.

Results
Eighty-two (19.9%) of 413 men experienced recurrence. The hazard ratio (HR) for each unit increase in CCP score (range, −1.62 to 2.16) was 2.1 (95% CI, 1.6 to 2.9); with adjustment for CAPRA-S, the HR was 1.7 (95% CI, 1.3 to 2.4). The score was able to substratify patients with low clinical risk as defined by CAPRA-S $\leq$ 2 (HR, 2.3; 95% CI, 1.4 to 3.7). Combining the CCP and CAPRA-S improved the concordance index for both the overall cohort and low-risk subset; the combined CAPRA-S + CCP score consistently predicted outcomes across the range of clinical risk. This combined score outperformed both individual scores on decision curve analysis.

Conclusion
The CCP score was validated to have significant prognostic accuracy after controlling for all available clinical and pathologic data. The score may improve accuracy of risk stratification for men with clinically localized prostate cancer, including those with low-risk disease.

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INTRODUCTION

Prostate cancer is the most common malignancy diagnosed in the United States and the second leading cause of cancer death among men.[1] Many prostate cancers, however, do not progress to a clinically meaningful stage even in the absence of treatment.[2] Randomized trials have confirmed an early survival advantage for surgery over observation for men with higher-risk disease but no difference for those with low-risk tumors.[3] Many men with high-risk disease may benefit from multimodal therapy, including, for example, adjuvant radiation after surgery.[4]

Decisions at diagnosis and other disease state transitions are made under varying degrees of uncertainty. Data available at diagnosis under current practice—prostate-specific antigen (PSA), biopsy Gleason score, clinical stage, and extent of biopsy involvement—can be combined in a variety of ways to yield validated risk-stratification systems with reasonably good predictive accuracy. However, even for those found to have low-risk cancers defined by clinical criteria, anxiety on the part of both patients and clinicians with respect to the likelihood of tumor undersampling and/or progression remains a significant driver of aggressive management.[5]

Thus, a clear need exists for novel biomarkers that can improve predictions and, therefore, decision making about treatment timing and intensity. One promising tool is a set of genes related to cell-cycle progression (CCP). Analysis of their expression yields a CCP score previously shown to add

independent information to standard clinical parameters in an earlier radical prostatectomy (RP) cohort from the Scott and White Clinic (SWC) in the United States and in conservatively treated transurethral resection of the prostate (TURP) and needle biopsy cohorts in the United Kingdom.[6,7] We aimed to validate the performance of the CCP score in a contemporary RP cohort and to integrate the score with an established risk assessment instrument.

METHODS

Validation of the CCP Score

This study conformed to the prospective specimen collection, retrospective blinded evaluation design for biomarker validation.[8] The first goal was validation of the CCP score, to which end patient cases were identified from the University of California, San Francisco Urologic Oncology Data Base (UCSF UODB). As of February 2011, the UCSF UODB included 3,630 men with prostate cancer, 2,495 of whom underwent RP without neoadjuvant or adjuvant therapy and consented to research under supervision of the local institutional review board. Of 600 eligible patients with ≥ 5 years follow-up, 489 with sufficient tissue available were identified in reverse sequential order. After an initial pilot study using 25 patients, 464 were identified for the analysis. These specimens were processed in the Myriad Genetics commercial laboratory with an overall failure rate of 7%. We excluded patients diagnosed before 1994, leaving 413 patients yielding CCP scores. Biochemical progression was defined as two consecutive PSA values ≥ 0.2 ng/mL[9] or any salvage treatment ≥ 6 months after RP. Those who died as a result of other causes or were lost to follow-up beyond 5 years were censored at the last follow-up date.

The CCP score was determined as previously described.[6] Briefly, samples were taken from the dominant tumor focus from archival paraffin-embedded RP specimens. RNA was extracted from these specimens using miRNeasy (Qiagen, Valencia, CA), and expression levels were determined using TaqMan low-density arrays (Applied Biosystems, Foster City, CA) for a set of 46 predetermined genes (31 CCP genes and 15 housekeeper genes). All genes were centered by their average expression in a set of commercial prostate tumor samples. The CCP score was defined as the average expression level of the CCP genes, normalized to the housekeeper genes such that a CCP score of 0 marked the middle of the distribution. Positive and negative CCP scores indicated over- and underexpression, respectively, of the CCP genes. Samples were processed in triplicate and were considered to fail analysis if greater than two housekeeper genes or greater than nine CCP genes were missing, or if the standard deviation of CCP scores across triplicates was > 0.5.

The prespecified primary analysis examined the CCP score, modeled as a continuous variable, as a predictor of time to progression using univariate Cox proportional hazards regression analysis in the UCSF cohort. Plots of scaled Schoenfeld residuals versus untransformed time were used to evaluate the appropriateness of the proportional hazards assumption for Cox regression. No evidence was found of time dependence for the CCP score hazard ratio (HR), and second- and third-order polynomials for CCP score tested in a Cox model were not statistically significant.

Development and Validation of the Cancer of the Prostate Risk Assessment post-Surgical Score + CCP Score

To characterize the independent value of the CCP signature given clinical variables, the CCP score was evaluated together with the Cancer of the Prostate Risk Assessment (CAPRA) post-Surgical (CAPRA-S) score, a validated instrument that predicts biochemical recurrence and cancer-specific mortality with good accuracy after RP. The CAPRA-S score, based on preoperative PSA, pathologic Gleason score, and pathologic staging parameters (extracapsular extension, seminal vesicle invasion, lymph node invasion, and surgical margin status), ranges from 0 to 12, and CAPRA-S scores can be grouped to stratify men into low (0 to 2), intermediate (3 to 5), and high (≥ 6) risk groups.[10]

Association between the CCP and CAPRA-S scores was examined using scatter plots and determination of Pearson correlation. Kaplan-Meier survival analysis was performed to illustrate the ability of the categorized CCP score to stratify outcomes both for the whole cohort and for men with low- and intermediate-/high-risk tumors. A new score combining CAPRA-S and CCP was generated with the coefficients of the two variables in a Cox proportional hazards model from the SWC RP cohort, including 353 patients from 1985 to 1995 as previously described.[6] This combined CAPRA-S + CCP score was then validated in the independent UCSF cohort.

Multivariable Cox regression was used to assess the utility of the CCP score after adjustment for clinical and pathologic variables in the UCSF cohort. This adjustment was performed using the CAPRA-S score as well as its component variables (age at diagnosis, year of surgery, PSA at diagnosis, pathologic Gleason score, extracapsular extension, seminal vesicle invasion, lymph node invasion, and surgical margin status). Prediction models were generated for 10-year likelihood of biochemical progression based on CAPRA-S score, CCP score, and the CAPRA-S + CCP model in both cohorts, and the concordance index was calculated. Decision curve analysis was used to compare the combined score with either the CCP or CAPRA-S score individually in the UCSF validation cohort. In this analysis, models are compared in terms of their net benefit—an expression of true positives minus false positives, with the latter weighted by a threshold probability term reflecting the clinical implication of a false-positive result.[11]

Statistical Analysis

Statistical analysis was performed in parallel by Myriad Genetics and UCSF according to a predetermined analysis plan. The test statistic was the partial likelihood ratio for the change in deviance from the full versus reduced model. All tests of significance were two sided. Data analysis was performed using R (version 2.12; R Foundation for Statistical Computing, Vienna, Austria) and STATA software (version 11; Stata, College Station, TX).

RESULTS

The final UCSF analytic cohort with calculable CCP scores included 413 patients. Table 1 summarizes the cohort characteristics. A wide range of CAPRA-S scores were observed, but a majority of patients (67%) were low risk based on CAPRA-S score 0 to 2. CCP scores ranged from −1.62 to 2.16. Overall, 82 men (19.9%) experienced progression. Median time to progression was 34 months (interquartile range [IQR], 13 to 60 months); among men not experiencing progression, median follow-up was 85 months (IQR, 72 to 109 months).

Median CAPRA-S and CCP scores were 2 (IQR, 1 to 3) and −0.37 (IQR, −0.71 to 0.10), respectively. CAPRA-S scores were skewed toward lower-risk scores, whereas CCP scores more closely approximated a normal distribution (Appendix Figs A1A and A1B, online only). CAPRA-S and CCP scores were weakly, though statistically significantly, correlated ($r = 0.21; P < .001$). At any given level of risk based on clinical and pathologic features, there was a broad range of CCP scores, demonstrating molecular heterogeneity among apparently similar-risk patients (Appendix Fig A1C, online only).

As illustrated in Figures 1A to 1C, in the primary validation analysis, the categorized CCP score stratified the UCSF cohort in terms of risk of biochemical recurrence ($P < .001$) and furthermore effectively substratified patients who were low risk (CAPRA-S score, 0 to 2) by clinical characteristics ($P = .003$ by partial likelihood ratio test). For clinically intermediate-/high-risk patients (CAPRA-S score ≥ 3), the categorized CCP score also stratified patients ($P = .01$ by partial likelihood ratio). In univariate Cox analysis, the continuous CCP score predicted recurrence with an HR of 2.1 (95% CI, 1.6 to 2.9) per unit increase in score. Among men with CAPRA-S scores of 0 to 2, the HR was 2.3 (95% CI, 1.4 to 3.7). At the extremes, the CCP score was uniformly predictive regardless of clinical risk group; no man with a CCP score < −1 experienced recurrence within 5 years, whereas for

Table 1. Characteristics of Patients in Both Radical Prostatectomy Cohorts

Characteristic	UCSF UODB		SWC	
	No.	%	No.	%
Age at diagnosis, years				
Median	59		67	
IQR	54-63		63-72	
Preoperative PSA, ng/mL				
≤ 6	215	52	154	43
> 6 to 10	135	33	98	28
> 10 to 20	56	13	66	19
> 20	7	2	35	10
Pathologic Gleason grade				
2 to 6	172	42	230	65
7	221	53	108	31
8 to 10	20	5	15	4
Positive margins				
No	345	84	274	78
Yes	68	16	79	22
Extracapsular extension				
No	320	77	254	72
Yes	93	23	99	28
Seminal vesicle invasion				
No	397	96	318	90
Yes	16	4	35	10
Pathologic N stage				
N0/x	407	99	340	96
N1	6	1	13	4
CCP score				
≤ −1	44	11	7	2
> −1 to 0	246	60	140	40
> 0 to 1	109	26	154	44
> 1	14	3	52	15
CAPRA-S score risk group				
Low (0 to 2)	276	67	209	59
Intermediate (3 to 5)	114	28	103	29
High (6 to 12)	23	6	41	12

Abbreviations: CAPRA-S, Cancer of the Prostate Risk Assessment post-Surgical; CCP, cell-cycle progression; IQR, interquartile range; SWC, Scott and White Clinic; UCSF UODB, University of California, San Francisco Urologic Oncology Data Base.

To ensure that these results were not dependent on the risk representation of the CAPRA-S score, a new model of the CCP score in the UCSF cohort was adjusted by the individual clinical and pathologic variables listed in the Methods. In this model, the HR for the CCP score was 2.0 (95% CI, 1.4 to 2.8), and adding the CCP score to the clinical variables again improved the model by partial likelihood ratio testing (P < .001). Table 2 summarizes the performance of the categorized CCP score in this model; the CCP score remained highly prognostic.

Figure 2B shows the effects of incorporating the CCP score together with the CAPRA-S score in terms of predicted outcomes. Figure 3 illustrates the model predictions of 10-year progression for the CAPRA-S + CCP score. The predicted risks of progression ranged from 5.5% to 94.1% for the CAPRA-S + CCP score. Figure 4 presents a forest plot analyzing the predictive accuracy of the CAPRA-S + CCP score stratified by various risk factors, indicating good performance and statistically significant values across a range of clinical risk subgroups. Again, the CAPRA-S + CCP score was predictive for those with low clinical risk as determined by a CAPRA-S score of 0 to 2 (HR, 5.2; 95% CI, 2.8 to 7.1 by Cox analysis). Appendix Figure A2 (online only) illustrates the results of the decision curve analysis; the CCP score was not superior to the CAPRA-S score, but the net benefit was greater for the CAPRA-S + CCP combined score than either score alone across the range of risk.

DISCUSSION

With early detection and treatment of aggressive prostate cancer in the PSA screening era, age-adjusted prostate cancer mortality rates in the United States have fallen roughly 40%, with a downward velocity matched only by lung cancer among cancers in men.[1] The price of this remarkable success, however, has been overtreatment of thousands of men who would not have experienced any symptoms or loss of life were their cancers never diagnosed.[13,14] Many of these men have experienced long-term adverse effects of treatments,[15] which ultimately were unnecessary, and the costs of these avoidable treatments are calculable in billions of dollars.[16]

Multiple trials, most recently the PIVOT (Prostate Intervention Versus Observation Trial) study, have demonstrated improved survival with early treatment of intermediate- to high-risk prostate cancer,[3,17] but a majority of men who today are diagnosed with low-risk disease face potential harms with minimal if any survival benefit.[3] Active surveillance remains underused as a primary treatment strategy,[13,18] in part because of acknowledged rates of undersampling by standard biopsy techniques,[19] but ultimately may prove safe and effective, even for carefully selected men with intermediate-risk clinical features.[20] Conversely, although trials have demonstrated a survival benefit with adjuvant radiation for men with adverse pathologic features,[4] this approach has not been widely adopted, in part because of fears of overtreatment of men who may not actually require additional therapy.[21]

A clear need therefore exists for new tools to improve prediction models for men at multiple decision points from diagnosis onward. Many candidate biomarkers have been proposed for this purpose. However, a majority are associated closely with established characteristics and offer little independent information.[22] Even among those

those with CCP scores > 1, 50% experienced recurrence within 5 years across CAPRA-S scores—even those in the low-risk group (CAPRA-S score, 0 to 2). With or without adjustment for clinical variables, increasing CCP score, both as a continuous and categorized variable, was associated with markedly higher hazards for progression (Table 2).

We used the SWC data set to create an optimized prediction model that incorporated both CCP and CAPRA-S scores. The clinical characteristics of the SWC cohort have been reported previously[12] and are compared with those of the UCSF cohort in Table 1. The combined score—0.38 × CAPRA-S + 0.57 × CCP—was highly prognostic in the SWC cohort (data not shown). This combined model was validated in the UCSF cohort by partial likelihood ratio testing and was more predictive than CAPRA-S score alone (P < .001). The concordance index for the combined model was 0.77 versus 0.73 for CAPRA-S score alone. Values of the combined CAPRA-S + CCP score ranged from −0.90 to 3.66 in the UCSF cohort, with a median of 0.51 (IQR, 0.04 to 1.01). The distribution is illustrated in Figure 2A.
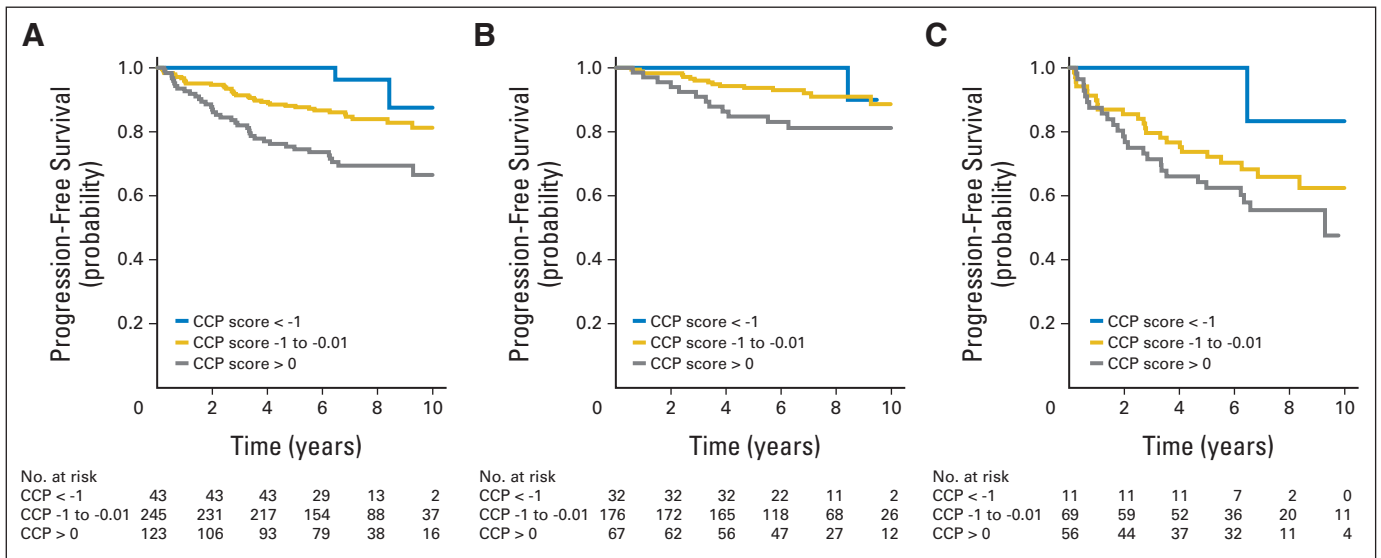
Fig 1. Kaplan-Meier plots of biochemical progression-free probability by cell-cycle progression (CCP) scores grouped by integers for (A) the overall cohort, (B) the subset of patients who were low risk by clinical criteria defined by Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score of 0 to 2, and (C) the subset of patients who were intermediate or high risk by clinical criteria defined by CAPRA-S score $\geq$ 3.

that have shown promise in initial studies, few have proven valuable on rigorous external validation.[23]

The CCP score was developed using the SWC RP specimens and additionally tested among 337 TURP specimens identified from men undergoing surgery in the United Kingdom from 1990 to 1996 who received no further local therapy. The CCP score predicted biochemical progression—in both univariate and multivariable analyses—in the RP cohort and cancer-specific mortality in the TURP cohort.[6] The score also predicted cancer-specific mortality from biopsy tissue in a cohort of conservatively managed patients in the United Kingdom.[7]

We aimed to validate the CCP score in an academic RP cohort in which both surgical technique and Gleason scoring reflected contemporary practice. The score performed well; the HR per unit change in CCP score of 2.1 for the continuous score on univariate analysis was comparable to 1.9 in the original RP cohort, as were the HRs of 1.7 (adjustment by CAPRA-S score) and 2.0 (adjustment by individual clinical and pathologic variables), compared with 1.7 in the original RP cohort.[6] As in the original analysis, the

CCP score did not associate closely with Gleason score or other clinical characteristics. Thus, in two disparate populations, the CCP score seemed similarly predictive.

In our analysis, the CCP score was able to substratify a large subset of patients who were relatively homogeneously low risk (CAPRA-S score, 0 to 2). Although there were comparably few patients with favorable clinical characteristics but adverse biology as indicated by the CCP score—or, conversely, higher-risk clinical features but a genetic signature reflective of indolence—these men were likely those who would benefit most from this test, and their tumors certainly bear further investigation. On the basis of its performance among men with intermediate- to high-risk clinical characteristics, the CCP score may also be helpful in selecting men for adjuvant therapy after RP and may prove valuable in stratifying men for future adjuvant studies.

Adding the CCP score to the CAPRA-S score or a de novo model of clinical and pathologic features improved discriminatory accuracy as assessed by the concordance index and improved both discrimination and calibration, as illustrated by the increased net benefit realized

		Univariate Analysis			Adjusted Model 1*			Adjusted Model 2†		
CCP Score	No. of Patients	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
$\leq$ −1‡	44									
> −1 to 0	246	3.7	0.9 to 15.2	.073	3.4	0.8 to 14.1	.09	3.0	0.7 to 12.6	.13
> 0 to 1	109	6.9	1.7 to 28.9	.008	5.2	1.2 to 21.7	.02	4.7	1.1 to 20.0	.04
> 1	14	15.2	3.2 to 71.9	.001	9.5	2.0 to 45.2	.005	13.5	2.7 to 67.3	.002
Continuous	413	2.1	1.6 to 2.9	< .001	1.7	1.3 to 2.3	< .001	2.0	1.4 to 2.8	< .001

Table 2. Validation of CCP Score in UCSF UODB Cohort

Abbreviations: CAPRA-S, Cancer of the Prostate Risk Assessment post-Surgical; CCP, cell-cycle progression; HR, hazard ratio; UCSF UODB, University of California, San Francisco Urologic Oncology Data Base.
*Adjusted model 1 included CCP and CAPRA-S scores.
†Adjusted model 2 included CCP score, prostate-specific antigen level at diagnosis, pathologic Gleason score, age at diagnosis, year of treatment, and presence or absence of extracapsular extension, seminal vesicle invasion, lymph node involvement, and surgical margin status.
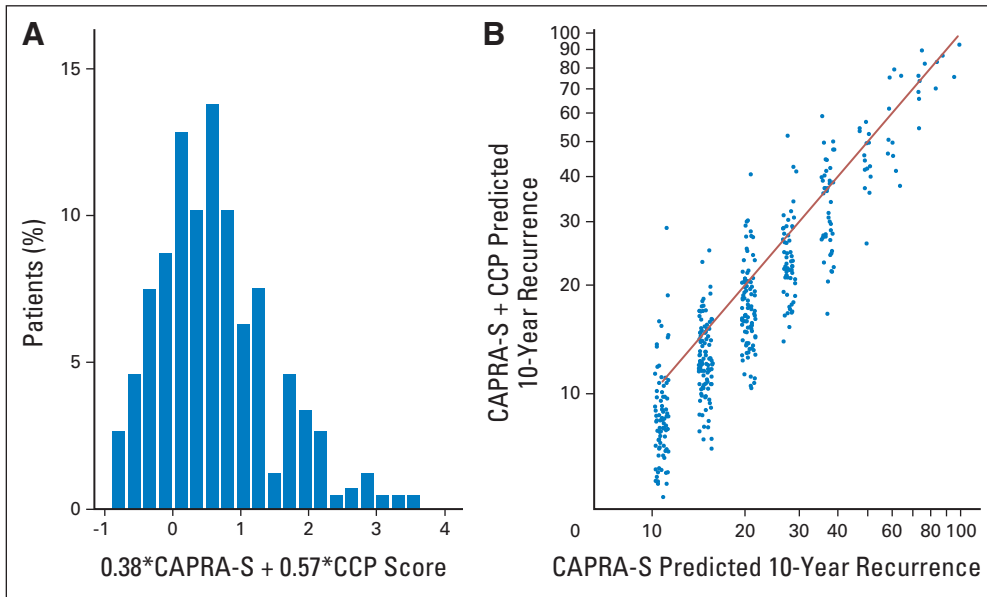‡Reference.

Fig 2. (A) Histogram of combined risk scores as defined by 0.38 × Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score + 0.57 × cell-cycle progression (CCP) score. (B) Comparison of the prediction of 10-year recurrence by CAPRA-S alone versus the combined score; line indicates CAPRA-S predictions represented on both axes for reference.

across the range of risk on decision curve analysis (Appendix Fig A2, online only). Furthermore, a model combining the CCP and CAPRA-S scores stratified the cohort in terms of risk of recurrence at 10 years across a broad range of risk from 5% to 94%, with relatively narrow CIs throughout this range (Fig 3). Examination of results from the SWC and UCSF cohorts side by side indicated generally good calibration; outcomes in the SWC cohort were consistently slightly worse at any given score compared with the UCSF cohort, which may reflect the earlier era of the SWC cohort, with, for example, different Gleason grading standards.

As noted, this study adhered to the principles of the prospective specimen collection, retrospective blinded evaluation design[8]; specimens were acquired consecutively and prospectively under uniform protocols from all consenting patients undergoing RP, regardless of a priori risk characteristics. Clinical data in the UCSF UODB likewise were consistently prospectively collected under

standardized protocols. Specimen processing and CCP score determination were performed with blinding to all clinical information, and CCP scores were matched to clinical data only after all patient cases had been processed.

These standards tend to minimize important sources of potential bias. Nonetheless, several caveats must be noted. Because the men in this cohort had mostly low- and intermediate-risk disease, too few have experienced metastases or cancer-specific mortality to allow analysis at these end points. Biochemical recurrence does not uniformly predict distal end points, but the association is strong.[24] Recurrence is, furthermore, the most relevant initial end point for most men after RP and drives both anxiety and further treatment. Of note, for the 3.3% of the SWC cohort who died as a result of prostate cancer, the univariate CCP score HR for mortality was higher at 3.0 than the HR of 1.9 for biochemical recurrence; the small number of events precluded multivariable
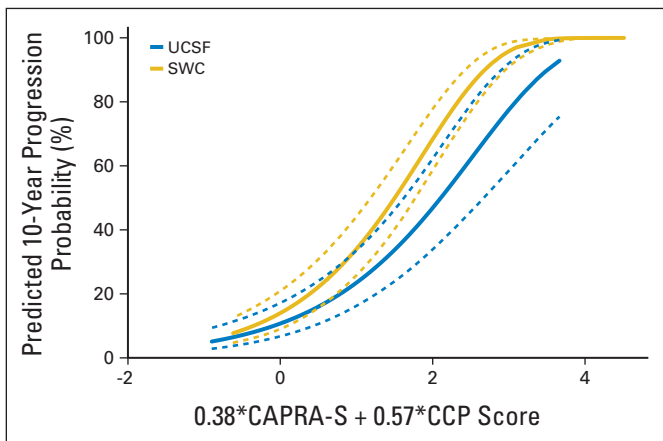

Fig 3. Prediction model for likelihood of 10-year progression probability for the University of California, San Francisco (UCSF) and Scott and White Clinic (SWC) cohorts based on the combined score defined by 0.38 × Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score + 0.57 × cell-cycle progression (CCP) score. Dashed lines represent 95% CI.
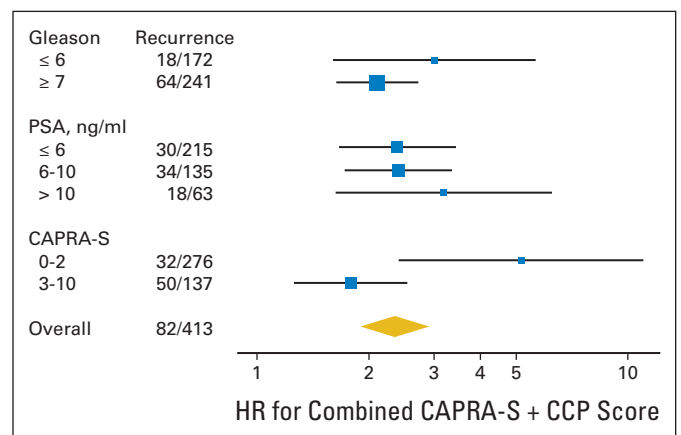

Fig 4. Forest plot illustrates hazard ratios (HRs) with CIs for recurrence for the Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) plus cell-cycle progression (CCP) combined score across a range of risk subgroups as defined by Gleason score, prostate-specific antigen (PSA) level, and CAPRA-S score.

analysis.[6] Conversely, markers that optimally predict recurrence after surgery may not be the same as those that predict progression under active surveillance. Additional validation studies are under way using biopsy specimens from preprostatectomy and active surveillance cohorts, which will help define the role of the CCP score in the pretreatment setting.

In this study, the CCP score was determined from the dominant tumor focus. Future studies will include explicit heterogeneity studies to compare CCP score findings between biopsy and prostatectomy tissues and from different samples taken from the same tumor. Although heterogeneity may have been a potential source of misclassification in our study, it would tend, if anything, to bias the results toward null. Furthermore, the real-world effectiveness of this assay depends on its applicability in the community setting, and sampling the dominant lesion is easier and less prone to interoperator variability than microdissection to ensure uniform grade. Postoperative risk prediction models may perform differently in academic and community-based settings,[10] so future validation in nonacademic cohorts will also be important. Finally, cost-effectiveness analyses will be necessary to help define the optimal role for emerging tests like the CCP score. Given the soaring costs of therapy for prostate cancer,[25] every treatment avoided would allow multiple tests to be purchased.

Despite these caveats, the performance of the CCP score in this validation study was excellent. The score provided independent prognostic information after RP and may prove useful in helping guide decisions with respect to adjuvant treatment and in stratifying men for future adjuvant therapy studies. The score had useful discriminatory performance among tumors that are low risk by clinical criteria, and if its performance is verified in studies of biopsy specimens currently under way, the CCP score will likely prove a valuable tool to aid decision making at time of diagnosis.

AUTHOR CONTRIBUTIONS

Conception and design: Matthew R. Cooperberg, Jeffry P. Simko, Janet E. Cowan, Julia E. Reid, Alexander Gutin, Jerry S. Lanchbury, Gregory P. Swanson, Steven Stone, Peter R. Carroll
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Data analysis and interpretation: Matthew R. Cooperberg, Janet E. Cowan, Julia E. Reid, Alexander Gutin, Gregory P. Swanson, Steven Stone, Peter R. Carroll
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

Active surveillance: An approach to management of suspected or proven malignancy felt to pose a low risk of progression in the short to intermediate term. Tumors are followed closely with blood tests, imaging, and/or serial biopsy, and intervention is undertaken if/when there is evidence of tumor growth or progression.

Cancer of the Prostate Risk Assessment (CAPRA) score: A 0 to 10 score based on a multivariable Cox model that predicts biochemical and clinical (metastasis and mortality) end points after primary treatment for prostate cancer. A postsurgical version (CAPRA-S) offers improved prediction of the same end points after radical prostatectomy.

Decision curve analysis: An approach to evaluating the discrimination and calibration of different prognostic tests or models. A decision curve plots net benefit for a given model across a range of threshold probabilities. Net benefit is calculated as true positives minus false positives, with the false-positive term weighted by the threshold probability. The threshold probability indicates the likelihood of a positive finding at which an intervention would be undertaken, given the results of the test or model.

Gleason score: A pathologic description of prostate cancer grade based on the degree of abnormality in the glandular architecture. Gleason patterns 3, 4, and 5 denote low, intermediate, and high levels of histologic abnormality and tumor aggressiveness, respectively. The score assigns primary and secondary numbers based on the most common and second most common patterns identified.