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ORIGINAL REPORT

Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer

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ABSTRACT

Purpose
It is clinically challenging to integrate genomic-classifier results that report a numeric risk of recurrence into treatment recommendations for localized prostate cancer, which are founded in the framework of risk groups. We aimed to develop a novel clinical-genomic risk grouping system that can readily be incorporated into treatment guidelines for localized prostate cancer.

Materials and Methods
Two multicenter cohorts (n = 991) were used for training and validation of the clinical-genomic risk groups, and two additional cohorts (n = 5,937) were used for reclassification analyses. Competing risks analysis was used to estimate the risk of distant metastasis. Time-dependent c-indices were constructed to compare clinicopathologic risk models with the clinical-genomic risk groups.

Results
With a median follow-up of 8 years for patients in the training cohort, 10-year distant metastasis rates for National Comprehensive Cancer Network (NCCN) low, favorable-intermediate, unfavorable-intermediate, and high-risk were 7.3%, 9.2%, 38.0%, and 39.5%, respectively. In contrast, the three-tier clinical-genomic risk groups had 10-year distant metastasis rates of 3.5%, 29.4%, and 54.6%, for low-, intermediate-, and high-risk, respectively, which were consistent in the validation cohort (0%, 25.9%, and 55.2%, respectively). C-indices for the clinical-genomic risk grouping system (0.84; 95% CI, 0.61 to 0.93) were improved over NCCN (0.73; 95% CI, 0.60 to 0.86) and Cancer of the Prostate Risk Assessment (0.74; 95% CI, 0.65 to 0.84), and 30% of patients using NCCN low/intermediate/high would be reclassified by the new three-tier system and 67% of patients would be reclassified from NCCN six-tier (very-low– to very-high–risk) by the new six-tier system.

Conclusion
A commercially available genomic classifier in combination with standard clinicopathologic variables can generate a simple-to-use clinical-genomic risk grouping that more accurately identifies patients at low, intermediate, and high risk for metastasis and can be easily incorporated into current guidelines to better risk-stratify patients.

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INTRODUCTION

Clinicians have at their disposal numerous methods to determine the aggressiveness of a patient's localized prostate cancer. These include risk grouping systems (eg, National Comprehensive Cancer Network [NCCN][1] or D'Amico[2]), staging systems,[3] risk assessment scoring systems,[4,5] tables,[6] and nomograms.[7] Arguably, the most commonly used system worldwide is the simplified three-tier (low-, intermediate-, and high-risk) NCCN risk groups, on the basis of categorical groupings of pretreatment prostate-specific antigen (PSA), Gleason score, and clinical T stage. Beyond their simplicity, NCCN risk groups are routinely used in clinical trial design and reporting of clinical trial data. Thus, treatment

ASSOCIATED CONTENT

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Appendix

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recommendations have largely been put in the framework of these risk groups to guide clinical management.

NCCN risk groups, which were generated from the original D'Amico risk groups, have the primary intent to predict a patient's pretreatment risk of biochemical recurrence and were not optimized for survival outcomes or surrogates, such as distant metastases (DM). Recently, the Intermediate Clinical Endpoints in Cancer of the Prostate initiative[8] has demonstrated that biochemical recurrence does not serve as a surrogate end point of more meaningful survival outcomes, further supporting the need to optimize risk groups to predict for clinically meaningful end points. Furthermore, there has been a recent emergence of validated genomic classifiers,[9-11] many of which are supported by NCCN and reimbursed through Medicare for routine clinical use. However, these tissue-based prognostic biomarkers report a continuous scale of the absolute numeric risk of the outcome reported (eg, 5-year metastasis). It is unclear how to consistently incorporate these continuous scale results into treatment recommendations that have been generated for NCCN risk groupings rather than the numeric risk of recurrence.

Given the clinical utility, widespread use, and inherent link to treatment decision making of the NCCN risk grouping system, we present a novel clinical-genomic risk grouping system that incorporates genomic and clinicopathologic risk of DM and prostate cancer-specific mortality (PCSM) into three new simple-to-calculate risk groups that more accurately assign the risk of recurrence and can be readily incorporated into existing NCCN and treatment guidelines.

MATERIALS AND METHODS

Study Cohort

Institutional review board approval was obtained from each participating institution before conducting this study. Four multicenter cohorts (all with 22-gene Decipher scores) were used to identify, characterize, and validate the clinical-genomic risk grouping system. A flow diagram outlining the four multicenter cohorts is shown in Figure 1A. This was performed by using two multicenter retrospective cohorts with long-term clinical outcomes to identify and validate the clinical-genomic risk grouping system, which consisted of 756 radical prostatectomy (RP) samples (retrospective training cohort comprising patients treated at Mayo Clinic, Thomas Jefferson University, Johns Hopkins School of Medicine, Duke University, Cleveland Clinic, and Kaiser Permanente) and 235 pretreatment biopsy samples (retrospective validation cohort comprising patients treated at Dana-Farber Cancer Institute, MD Anderson Cancer Center, University of Miami, University of Michigan, Johns Hopkins School of Medicine, University of California San Diego, and Cleveland Clinic)[12] from formalin-fixed paraffin-embedded tissue. For both training and validation cohorts, patients were limited to those with baseline PSA $<$ 200 ng/mL, clinical stage T1c to T3b, and clinical N0. In the training cohort, patients who received neoadjuvant treatment before RP were excluded.

In addition, two prospective cohorts were used for reclassification analyses consisting of 4,960 RP samples (prospective cohort I) and 977 pretreatment biopsy samples (prospective cohort II) that included demographic and baseline clinical and pathologic information. These patients were deidentified and aggregated from routine clinical use of the Decipher prostate cancer classifier test (GenomeDx Biosciences Laboratory, San Diego, CA) in the genomic resource information database (GRID; NCT02609269).[13] The currently endorsed International Society of Urological Pathology grading was used for all patients.

Biomarker Selection

Numerous gene expression–based prognostic signatures have been developed that could be combined with clinicopathologic variables. Decipher was selected for generation of the clinical-genomic risk groups on the basis of prior work comparing the performance of 34 previously published signatures, and the 22-gene genomic classifier had the highest c-index for predicting 10-year metastasis.[14]

Selection of NCCN Risk Groups

Rather than using the classic three-tier NCCN risk groups (low, intermediate, and high), NCCN has recently supported a subdivision of intermediate-risk into favorable-intermediate and unfavorable-intermediate categories, which was used for all comparisons.[15] Very-low–risk and very-high–risk groups were used only for reclassification analyses, primarily given that only 1.5% of the training cohort was NCCN very-high–risk. For the training cohort, unfavorable-intermediate risk was defined as the presence of two or more intermediate risk factors and/or the presence of primary pattern 4. For the validation cohort, the percentage of positive core information was available and was used to define the favorable-intermediate and unfavorable-intermediate subgroups per Zumsteg et al.[15]

Identification and Validation of the Clinical-Genomic Risk Grouping System

To generate a new risk grouping system that could be readily incorporated into NCCN guidelines, we used two approaches using the retrospective training cohort: (1) a model-generated method to optimally combine NCCN and Decipher (see statistics section for detailed description of this model), and (2) a simple summation method of NCCN and Decipher groups (Fig 1B). The model-generated and the summation methods were quantitatively compared using the c-index, and the performance was similar in predicting DM and PCSM; therefore, the summation method was chosen, given the simplicity and ease of clinical use. Summing points given for each NCCN risk group and Decipher categories yields the new six-tier clinical-genomic risk grouping system, analogous to a new very-low–, low-, favorable-intermediate–, unfavorable-intermediate–, high-, and very-high–risk group. This six-tier system was then converted for simplicity into a three-tier risk grouping system, analogous to the low-, intermediate- and high-risk groups of NCCN.

The retrospective training and validation cohorts used pretreatment PSA, clinical T stage, and biopsy Gleason score. However, the genomic analyses from the training cohort were performed on tissue from the RP specimen. Therefore, to extend the applicability of this system into patients' pretreatment, validation of the new clinical-genomic risk grouping system was performed on the retrospective validation cohort where the genomic analyses were performed on the pretreatment biopsy samples.

Statistics

Decipher risk categories were defined using previously locked cut points as low ($<$ 0.45), intermediate (0.45 to 0.60), and high ($>$ 0.6). DM was defined as either bone, viscera, or nonpelvic lymph node metastasis documented radiographically by computed tomography or bone scan. Missing data were believed to be at random, and patients whose NCCN risk group could not be calculated were removed from analysis, and no imputation was done. In time-to-event analyses, event times were defined as the time from initial treatment to metastasis or PCSM. Fine-Gray competing risks analysis was used to estimate the risk of both end points over time when constructing cumulative incidence curves. Survival receiver operating characteristic curves were constructed using the approach described by Heagerty et al.[16] The c-index of the combined model was estimated by subjecting the model to bootstrapping with 500 resamples. CIs for survival c-indices were computed via the bootstrap. Cox proportional hazards models were used to compare the clinical-genomic risk grouping system and clinical-only models for predicting DM and PCSM for both retrospective cohorts. Firth's penalized bias reduction method for

Cox proportional hazards models was implemented to account for the low event rate. Sensitivity analysis fitting a multivariable Cox proportional hazards model, adjusting for treatment as covariables and institution as a stratification variable, was performed (Appendix Table A1, online only). Statistical analyses were performed in R v3.3, and all statistical tests were performed using a 5% significance level.

RESULTS

The baseline patient characteristics of the four multicenter cohorts (prospective cohort I and II, and the retrospective training and validation cohorts) are listed in Table 1. Second-line treatment information for patients in the training cohort is listed in Appendix Table A2 (online only).

Prognostic Performance of the NCCN Risk Groups

Because the NCCN risk groups were developed to prognosticate biochemical recurrence, we first tested the prognostic performance of NCCN risk groups on development of DM. Using the retrospective training cohort (n = 756), which had a median follow-up of 8 years (Table 1), DM at 10-years for the four-tier NCCN risk groups were 7.3% (95% CI, 1.9% to 12.8%), 9.2% (95% CI, 4.3% to 14.0%), 38.0% (95% CI, 29.5% to 46.6%), and 39.5% (95% CI, 33.0% to 46.1%) for low-, favorable-intermediate–,

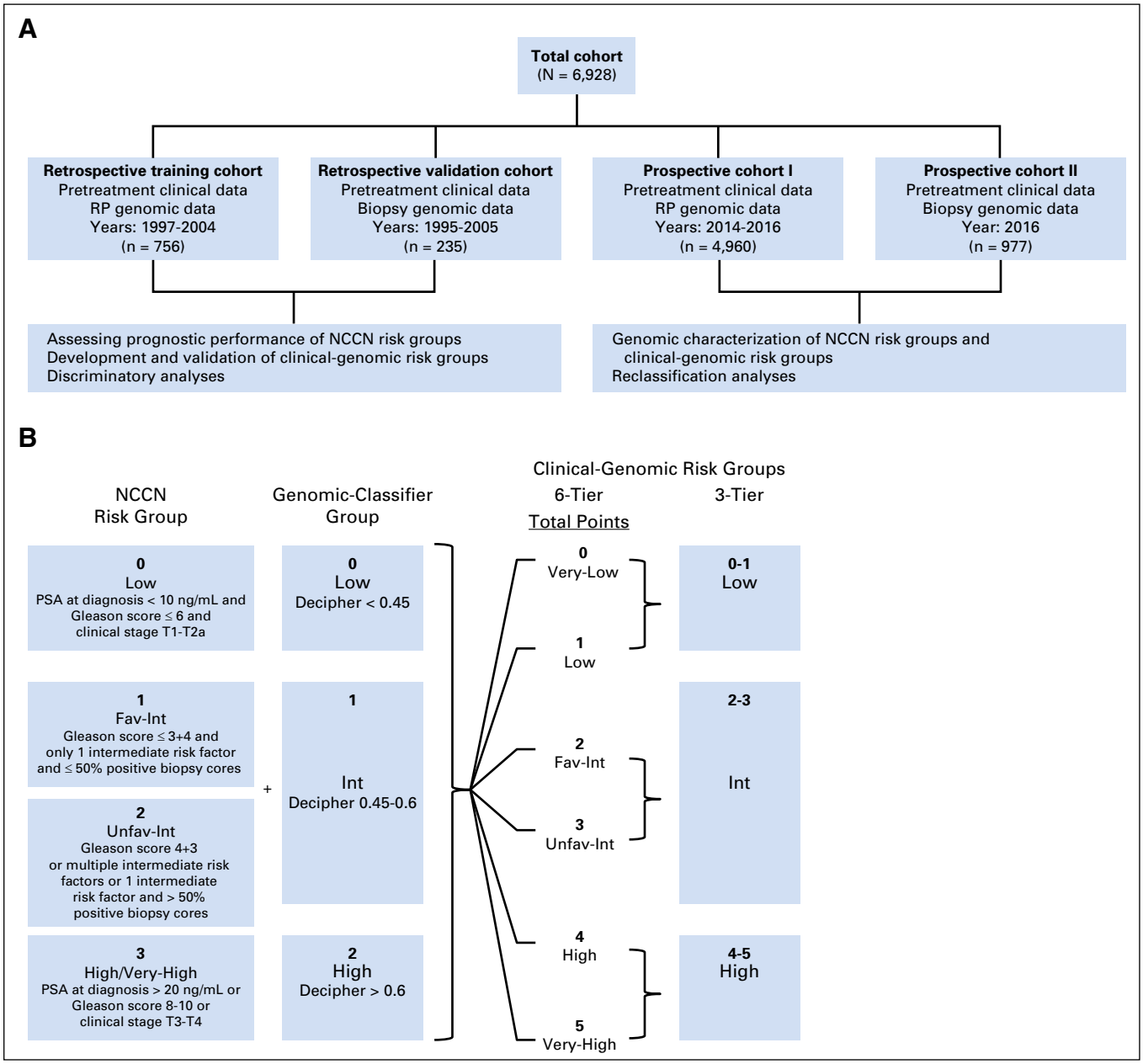

Fig 1. (A) Flow diagram of the study cohort details and analyses performed by cohort and (B) schema of how to combine National Comprehensive Cancer Network (NCCN) risk groups with Decipher groups to develop the clinical-genomic point system and the resulting clinical-genomic risk groups. fav, favorable; int, intermediate; PSA, prostate-specific antigen; RP, radical prostatectomy; unfav, unfavorable.

Table 1. Patient Characteristics

Variables	Retrospective Training and Validation Cohorts		Prospective Genomic Characterization Cohorts	
	Training Cohort (RP)	Validation Cohort (Bx)	Prospective Cohort I (RP)	Prospective Cohort II (Bx)
	No. (%)/Median (IQR)	No. (%)/Median (IQR)	No. (%)/Median (IQR)	No. (%)/Median (IQR)
Total	756 (100)	235 (100)	4,960 (100)	977 (100)
Year of RP or Bx	2000 (1997-2004)	2000 (1995-2005)	2015 (2014-2016)	2016 (2016-2016)
Age at RP or Bx, years*	61.0 (55.0-66.0)	64.0 (58.0-70.0)	65.1 (59.5-68.9)	67.4 (61.8-72.5)
Race				
African American	37 (4.9)	32 (13.6)	.	.
Caucasian	704 (93.1)	167 (71.1)	.	.
Other	14 (1.9)	10 (4.2)	.	.
Unknown	1 (0.1)	26 (11.1)	.	.
PSA at diagnosis, ng/mL	8.6 (5.6-14.9)	7.0 (4.6-13.2)	6.5 (4.8-9.7)	6.3 (4.6-9.3)
< 10	424 (56.1)	149 (63.4)	3,788 (76.4)	758 (77.6)
10-20	209 (27.6)	59 (25.1)	874 (17.6)	149 (15.3)
> 20	121 (16)	27 (11.5)	298 (6.0)	70 (7.2)
Unknown	2 (0.3)	0 (0)	0 (0)	0 (0)
Grade group (GS)				
1 (GS 3 + 3)	267 (35.3)	44 (18.7)	320 (6.5)	390 (39.9)
2 (GS 3 + 4)	131 (17.3)	65 (27.7)	2,030 (40.9)	315 (32.2)
3 (GS 4 + 3)	61 (8.1)	59 (25.1)	1,496 (30.2)	135 (13.8)
4 (GS 8)	129 (17.1)	32 (13.6)	465 (9.4)	79 (8.1)
5 (GS 9-10)	60 (7.9)	35 (14.9)	649 (13.1)	58 (5.9)
Unknown†	108 (14.3)	0 (0)	0 (0)	0 (0)
Tumor stage‡				
T1	293 (38.8)	108 (46.0)	.	748 (76.6)
T2	375 (49.6)	104 (44.2)	1,893 (38.2)	212 (21.7)
T3/4	36 (4.8)	19 (8.1)	2,786 (56.2)	17 (1.7)
Unknown	52 (6.9)	4 (1.7)	281 (5.7)	0 (0)
NCCN risk group§				
Low	115 (15.2)	21 (8.9)	203 (4.1)	315 (32.2)
Intermediate-favorable	157 (20.8)	35 (14.9)	948 (19.1)	198 (20.3)
Intermediate-unfavorable	172 (22.8)	93 (39.6)	634 (12.8)	284 (29.1)
High/very-high	312 (41.3)‖	83 (35.3)	3,175 (64.0)	180 (18.4)
Unknown¶	0 (0.0)	3 (1.3)	0 (0)	0 (0)
Percentage of positive cores	.	45.4 (27.3-66.7)		33.3 (16.7-50.0)
< 50	.	112 (47.7)		645 (66.0)
≥ 50	.	102 (43.4)		332 (34.0)
Unknown	.	21 (8.9)		0 (0.0)
First-line treatment				
RP	756 (100)	107 (44.7)		
RT with or without ADT	.	130 (55.3)		
Unknown	3 (0.4)			

Abbreviations: ADT, androgen deprivation therapy; Bx, biopsy; GS, Gleason Score; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation treatment.

*Age of RP was used for training and prospective cohort I; age of Bx was used for other cohorts.

†For the training cohort, 22 patients had missing GSs, and 86 patients were GS 7 but had unknown primary GS; therefore, unable to categorize into Gleason Grade Group.

‡Pathologic stage was used for tumor stage for prospective cohort I; clinical stage was used for all other cohorts.

§Percentage of positive Bx cores was considered in definition of NCCN risk groups in prospective cohort I and validation cohort patients and other cohorts.

‖For training and validation cohorts, 11 (1.5%) and 11 (4.7%) patients, respectively, were classified to NCCN very high risk.

¶Includes three NCCN intermediate patients from the validation cohort with unknown favorable/unfavorable status.

unfavorable-intermediate–, and high-risk groups, respectively (Fig 2A). There were no significant differences between low- and favorable-intermediate–risk groups, as well between unfavorable-intermediate– and high-risk groups. Compared with the NCCN low-risk group, the hazard ratio (HR) of developing DM was 1.2 (95% CI, 0.5 to 3.0; $P = .64$), 5.5 (95% CI 2.8 to 12.1; $P < .001$), and 6.0 (95% CI, 3.2 to 13.0; $P < .001$) for favorable-intermediate–, unfavorable-intermediate–, and high-risk groups, respectively (Table 2).

PCSM at 10 years for the four-tier NCCN risk groups were 5.8% (95% CI, 0.5% to 11.0%), 2.7% (95% CI, 0% to 5.9%), 15.9% (95% CI, 9.2% to 22.5%), and 16.8% (95% CI, 11.7% to 22.0%) for low-, favorable-intermediate–, unfavorable-intermediate–, and high-risk groups, respectively (Fig 2B). Compared with the NCCN low-risk group, the HR for PCSM was 0.4 (95% CI, 0.1 to 1.7; $P = .231$), 2.9 (95% CI, 1.2 to 8.3; $P = .013$), and 3.6 (95% CI, 1.6 to 9.7; $P < .001$) for the favorable-intermediate–, unfavorable-intermediate–, and high-risk groups, respectively.

Prognostic Performance of the Clinical-Genomic Risk Groups

After combining the NCCN risk groups and the genomic-classifier groups, the resulting six-point system yielded 10-year DM

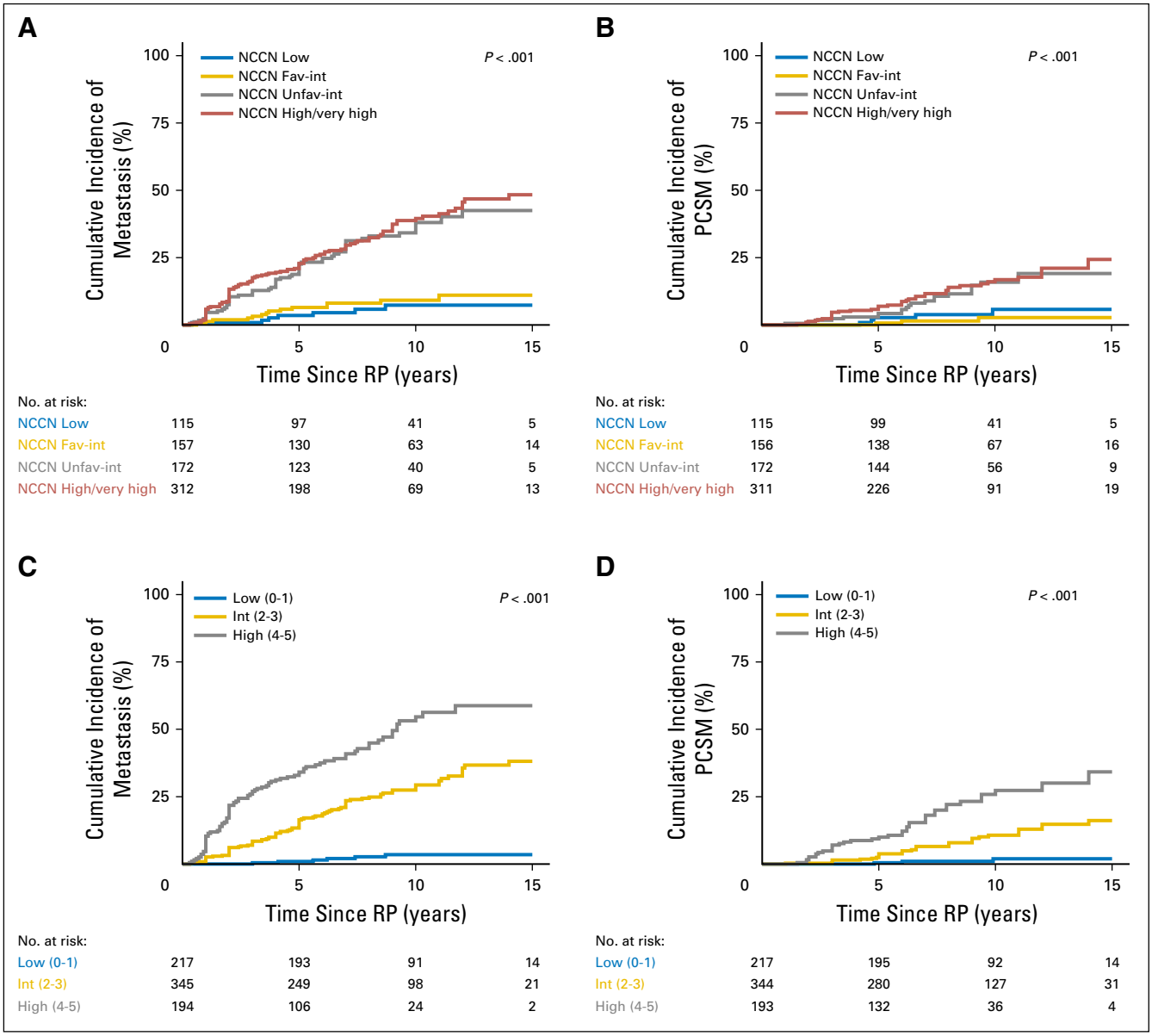

Fig 2. Cumulative incidence curves using the training cohort for (A) distant metastasis by National Comprehensive Cancer Network (NCCN) risk group, (B) prostate cancer-specific mortality (PCSM) by NCCN risk group, (C) distant metastasis by clinical-genomic risks, and (D) prostate cancer–specific mortality by clinical-genomic risk groups. fav, favorable; int, intermediate; RP, radical prostatectomy; unfav, unfavorable.

rates of 3.1% (95% CI, 0% to 7.6%), 3.7% (95% CI, 0.1% to 7.3%), 25.9% (95% CI, 17.0% to 34.8%), 31.7% (95% CI, 24.4% to 39.0%), 49.7% (95% CI, 38.2% to 61.3%), and 61.9% (95% CI, 46.9% to 76.9%) for very-low–, low-, favorable-intermediate–, unfavorable-intermediate–, high-, and very-high–risk groups, respectively (Appendix Fig A1, online only). When converting the six-tier clinical-genomic risk groups into the three-tier clinical-genomic risk groups, the 10-year DM rates of low-, intermediate-, and high-risk were 3.5% (95% CI, 0.7% to 6.3%), 29.4% (95% CI, 23.8% to 35.0%), and 54.6% (95% CI, 45.6% to 63.6%), respectively (Fig 2C). Compared with the clinical-genomic low-risk group, the HR for DM was 9.3 (95% CI, 4.8 to 21.5; $P < .001$) and 21.9 (95% CI, 11.1 to 50.4; $P < .001$) for the intermediate- and high-risk groups, respectively (Table 2).

The 10-year PCSM rates for the clinical-genomic risk grouping system for low-, intermediate-, and high-risk were 2.0% (95% CI, 0% to 4.3%), 10.7% (95% CI, 6.8% to 14.7%), and 27.3% (95% CI, 19.0% to 35.6%), respectively (Fig 2D). Compared with clinical-genomic low-risk, the HR for PCSM was 6.5 (95% CI, 2.5 to 14.0; $P < .001$) and 18.9 (95% CI, 7.2 to 69.3; $P < .001$) for the intermediate- and high-risk groups, respectively.

These findings were then validated for metastasis using our retrospective validation cohort. The three-tier clinical-genomic risk grouping system had 10-year DM rates for low-, intermediate-, and high-risk of 0% (95% CI, 0% to 0%), 25.9% (95% CI, 8.8% to 43.0%), and 55.2% (95% CI, 33.9% to 76.6%), respectively (Fig 3A).

Table 2. Performance Comparison of NCCN and Clinical-Genomic Risk Grouping System

Grouping System	NCCN		Clinical-Genomic Risk Grouping System: Training		Clinical-Genomic Risk Grouping System: Validation	
10-year metastasis rate, % (95% CI)	Low	7.3 (1.9 to 12.8)	Low	3.5 (0.7 to 6.3)	Low	0.0 (0.0 to 0.0)
	Fav-int	9.2 (4.3 to 14.0)	Int	29.4 (23.8 to 35.0)	Int	25.9 (8.8 to 43.0)
	Unfav-int	38.0 (29.5 to 46.6)				
	High	39.5 (33.0 to 46.1)	High	54.6 (45.6 to 63.6)	High	55.2 (33.9 to 76.6)
C-index for 10-year metastasis (95% CI)		0.68 (0.64 to 0.73)		0.77 (0.72 to 0.81)		0.84 (0.61 to 0.93)
HR for metastasis (95% CI)	Low	Ref	Low	Ref	Low	Ref
	Fav-int	1.2 (0.5 to 3.0)	Int	9.3 (4.8 to 21.5)*	Int	21.3 (2.8 to 2,727.6)*
	Unfav-int	5.4 (2.8 to 12.0)*				
	High	6.0 (3.2 to 13.0)*	High	21.9 (11.1 to 50.4)*	High	62.5 (8.5 to 7,969.6)*

Abbreviations: fav, favorable, HR, hazard ratio; int, intermediate, NCCN, National Comprehensive Cancer Network; Ref, reference level; unfav, unfavorable.
*Significant at .001 level.

Discriminatory Analyses

Within the retrospective training cohort, c-index analyses demonstrated that the six-tier clinical-genomic risk grouping system (0.77; 95% CI, 0.72 to 0.81) had greater ability to discriminate 10-year rates of DM than either the three-tier (0.65; 95% CI, 0.60 to 0.69) or four-tier NCCN risk groups (0.68; 95% CI, 0.64 to 0.72), the Cancer of the Prostate Risk Assessment (CAPRA) continuous score (0.68, 95% CI, 0.62 to 0.74), or CAPRA risk groups (0.64, 95% CI, 0.59 to 0.70; Appendix Fig A2, online only). Similarly, within the retrospective validation cohort, the six-tier clinical-genomic risk grouping system had a c-index of 0.84 (95% CI, 0.61 to 0.93) to discriminate 10-year rates of DM (Appendix Fig A3, online only). The longitudinal area under the curve over time (Fig 3B) demonstrated that the c-index was greater at each time point for both the three- and six-tier clinical-genomic risk grouping systems compared with NCCN risk groups in both the training and validation cohorts.

Reclassification of NCCN to Clinical-Genomic Risk Groups

In the prospective cohort I, a total of 33.4% of patients (n = 1,655 of 4,960) would be reclassified using the three-tier clinical-genomic risk grouping system compared with NCCN risk groups (Appendix Fig A4, online only). Specifically, 12.8%, 48.4%, and 27.2% of NCCN low-, intermediate-, and high-risk, respectively, would be reclassified. Using the expanded four-tier NCCN system, 56.8% and 36.0% of favorable- and unfavorable-intermediate–risk, respectively, would be reclassified (Fig 4A). Likewise, in the prospective cohort II, 29.9% of patients (n = 292 of 977) would be reclassified using the clinical-genomic risk grouping system compared with NCCN. Similarly, 17.1%, 44.4%, 40.5%, and 19.4% of NCCN low-, favorable-intermediate–, unfavorable-intermediate–, and high-risk, respectively, would be reclassified (Fig 4B).

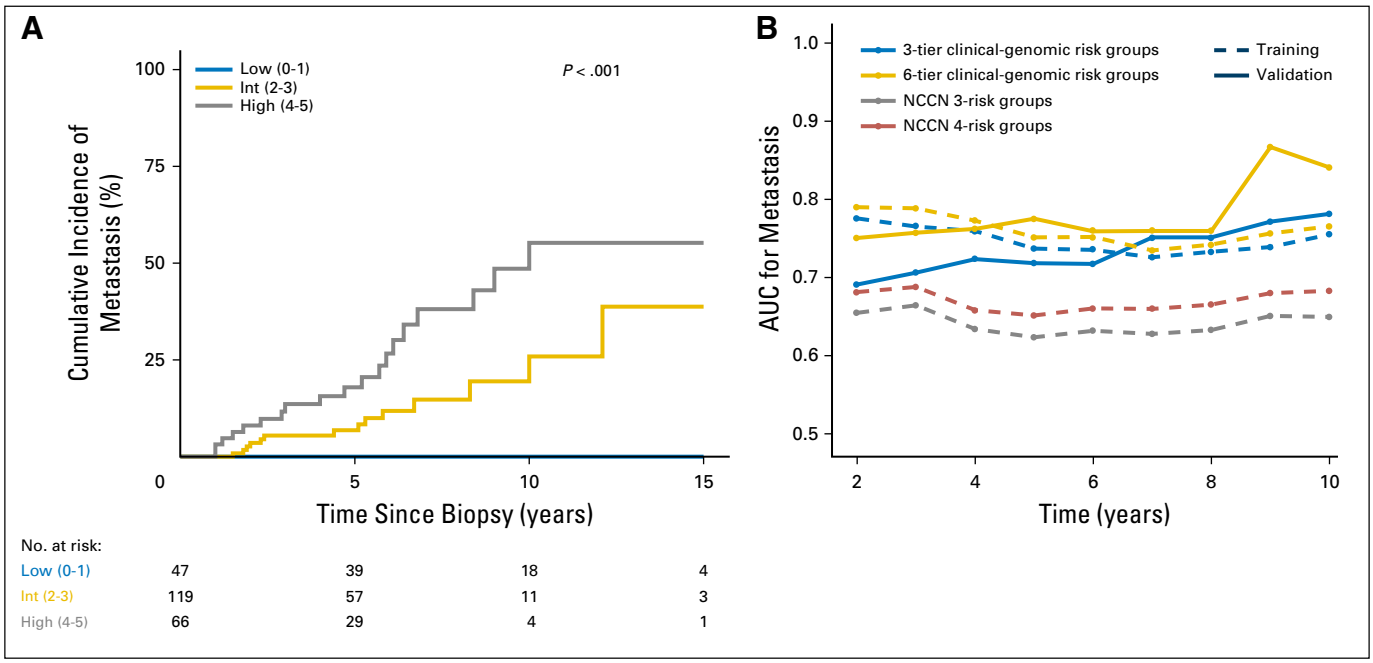

Fig 3. (A) Cumulative incidence curves using the validation cohort for distant metastasis by the clinical-genomic risk groups. (B) Discriminatory analysis of c-indices over time for metastasis of the training and validation cohorts comparing National Comprehensive Cancer Network (NCCN) and clinical-genomic risk groups. AUC, area under the curve.

When comparing the six-tier NCCN risk groups (very-low– to very-high–risk) with the new six-tier clinical-genomic risk groups, there was extensive reclassification (Fig 4C). Of patients classified by NCCN risk groups, 43% of very-low–, 70% of low-, 71.7% of favorable-intermediate–, 75.4% of unfavorable-intermediate–, 83.8% of high-, and 20% of very-high–risk would be reclassified by the new clinical-genomic risk groups. In total, 66.6% of patients classified by the NCCN six-tier system would be reclassified using the new six-tier clinical-genomic risk groups.

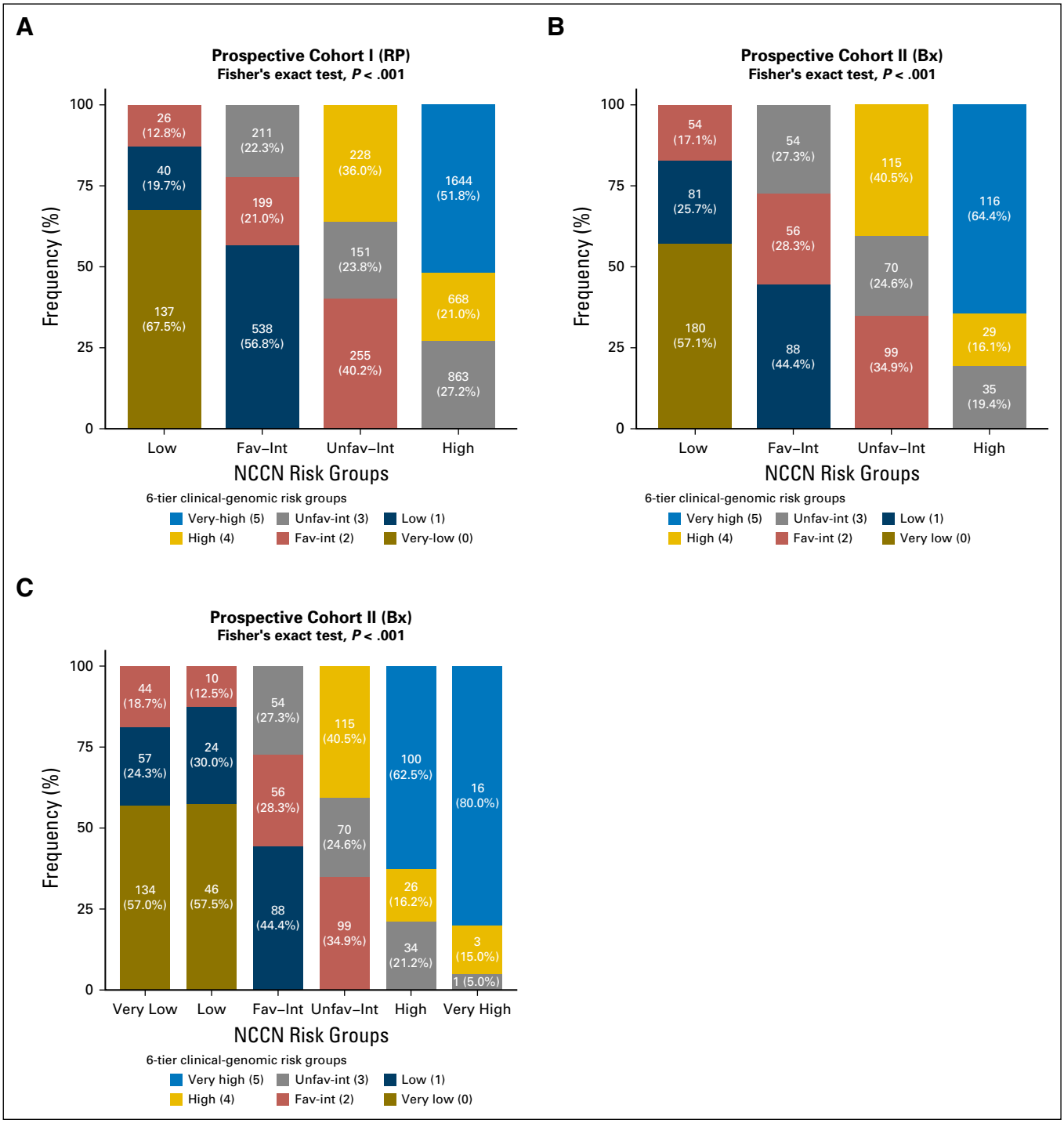

Fig 4. Reclassification of National Comprehensive Cancer Network (NCCN) risk groups to clinical-genomic risk groups within (A) prospective cohort I using the NCCN four-tier system, (B) prospective cohort II using the NCCN four-tier system, and (C) prospective cohort II using the expanded NCCN six-tier system (very-low–, low-, favorable-intermediate–, unfavorable-intermediate–, high-, and very-high–risk groups). Bx, biopsy; fav, favorable; int, intermediate; RP, radical prostatectomy; unfav, unfavorable.

DISCUSSION

The current study aimed to build on the framework of the NCCN risk groups by integrating it with a highly prognostic genomic-classifier score to allow for rapid incorporation into existing treatment guidelines and improved prognostication of patients. The results show that the newly developed clinical-genomic risk grouping system has improved performance over both the current NCCN risk groups and other systems, such as CAPRA, for both metastasis and PCSM. The clinical-genomic risk grouping system was able to identify patients at very low risk for DM (5-year rate of 1% and 0% in the retrospective training and validation cohorts, respectively) and very high risk for DM (10-year rate of 58% and 63% in the training and validation cohorts, respectively). Furthermore, patients originally classified by NCCN were frequently reclassified by our clinical-genomic risk groups.

The goal of staging and risk classification schemas are to serve as a prognostic stratification system to assign an accurate risk of recurrence to each individual patient. Using clinicopathologic variables alone has been shown in multiple contexts to yield inferior prognostic ability compared with the combination of prognostic biomarkers.[17,18] Despite the prognostic capability of genomic classifiers to predict outcomes, it is less clear how to incorporate these results into practice. It has been demonstrated that clinicians have a poor ability to predict the absolute risk of recurrence in their patients without the use of detailed nomograms.[19] Therefore, understanding whether the results from genomic classifiers are congruent or incongruent with the predicted pretreatment clinicopathologic risk of recurrence is currently not readily available. These complexities are simplified by using our clinical-genomic risk grouping system, which simultaneously integrates the genomic and clinicopathologic risk together to yield a highly prognostic risk grouping system. Although we created a simple-to-use three-tier system that may be ideal for clinical trial design and discussion with patients, a more accurate system for use in clinical practice and decision making is the six-tier system we generated, from very-low– to very-high–clinical-genomic risk. This system may allow for more nuanced decision making regarding the use of active surveillance (AS) or treatment intensification.[20]

The implications and benefits of the clinical-genomic risk grouping system are multiple. The new three- or six-tier risk grouping system can readily be incorporated into current NCCN guidelines for those with access to the genomic-classifier. This could improve adoption of AS for low-risk patients. For example, currently patients with very-low, low, and select patients with favorable-intermediate risk are eligible to undergo AS.[21] However, current practice patterns suggest that a large subset of patients at low risk and most of those with intermediate risk do not undergo AS.[22] One of the suggested reasons is the uncertainty that these patients are truly at a low risk for recurrence. Our data demonstrate that approximately 15% of patients with NCCN who are at low risk would be reclassified to intermediate risk by the clinical-genomic risk grouping system and may not be the ideal candidates for AS. This is almost identical to an independent study of low-risk AS candidates, where Cooperberg et al[23] demonstrated that 13% of patients at low risk had more aggressive genomic features. Furthermore, 42% to 56% of patients with NCCN and favorable-intermediate risk would be reclassified as low risk by the clinical-genomic risk groups and could increase the confidence of clinicians and patients that the subset of those with favorable-intermediate–risk may be candidates for AS. In contrast, the new clinical-genomic risk groups identify a very-high–risk cohort that is at dramatically increased risk for metastasis. Therefore, this subset of patients needs to be the focus of treatment intensification and multimodality clinical trials.[20]

Although our new clinical-genomic risk groups unquestionably outperform standard risk grouping metrics, there are added upfront costs of the genomic-classifier. The use of Decipher in the post-operative setting has demonstrated cost effectiveness, given its ability to help guide the use of adjuvant therapies, and has already demonstrated the ability to affect adjuvant radiotherapy use.[24,25] The clinical-genomic risk groups require pretreatment biopsy analysis, and cost-effectiveness studies are ongoing. Given that AS has been shown to be more cost effective than immediate radical therapy for patients at low risk for recurrence, a biomarker that increases the use of AS may be cost effective.[26] In contrast, patients with NCCN who are at intermediate risk are often treated with RP or radiation treatment with or without androgen deprivation therapy. We demonstrate that many of these patients who have high genomic-classifier scores will develop metastatic disease within 10 years, an extremely costly burden to society. The costs of recurrence have been shown to be significantly greater than upfront treatment intensification[27] and thus may also prove to be cost effective.

Notably, we did not include a separate NCCN very-high–risk category in our model for several reasons. First, although these men have poor oncologic outcomes, there is a lack of consensus for the definition of very-high–risk disease and thus, it is not included in American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology 2017 guidelines. Second, only 1.5% of our training cohort was NCCN very high risk. In contrast, 25.7% of our training cohort was clinical-genomic high risk, which has significantly worse outcomes than the NCCN high-risk group, and thus, we have identified a much larger group of patients with very poor outcomes.

Lastly, a potential source of bias that is present in our retrospective cohort is that the samples analyzed were typically older than 10 years. Thus, it is possible that samples with larger tumor burden were more likely to be analyzed successfully.[12] This may explain why our event rates were generally higher than comparable clinical trial series. This is in contrast to normal clinical use tissue, which has a high pass rate, even for patients with NCCN at very-low risk.[23] Given constant stage and grade migration, it is challenging to simultaneously have modern patients who also have long-term outcomes. For example, 12-year outcomes were recently reported from Radiation Therapy Oncology Group (RTOG) 9601, a trial that started over 20 years ago.[28] Despite this, it will be important for continued validation of our clinical-genomic risk system.

In conclusion, the use of a commercially available genomic-classifier in combination with standard NCCN clinicopathologic variables can generate a simple-to-use three-tier or six-tier clinical-genomic risk grouping system that is highly prognostic for DM; more accurately identifies patients at low, intermediate, and high risk of recurrence; and can be easily incorporated into current NCCN guidelines to help inform treatment decisions.

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Disclosures provided by the authors are available with this article at jco.org.

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Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer

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Appendix

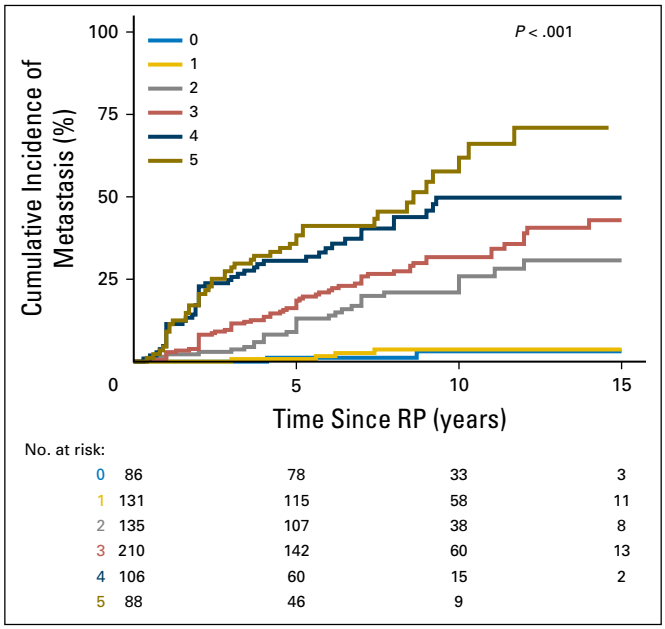

Fig A1. Cumulative incidence curves using the training cohort for distant metastasis by six-tier clinical-genomic risk groups. RP, radical prostatectomy.

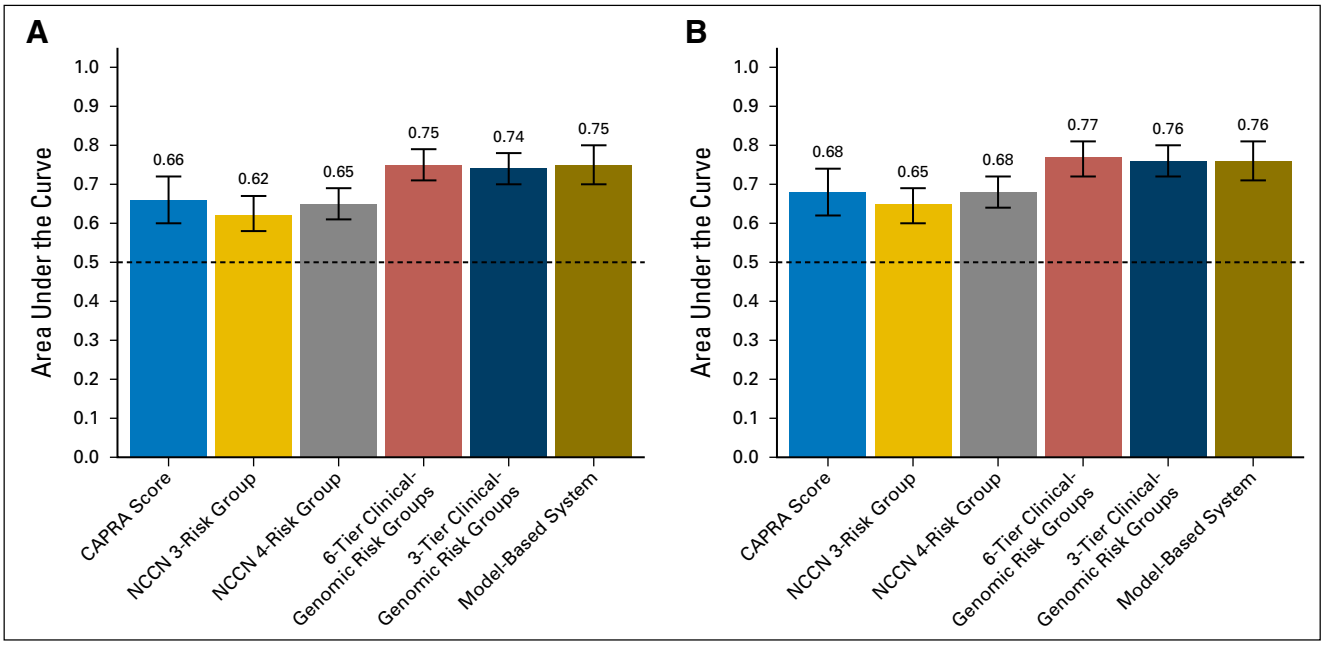

Fig A2. C-indices of all risk grouping systems in the retrospective training cohort: (A) metastasis at 5 years and (B) metastasis at 10 years. CAPRA, Cancer of the Prostate Risk Assessment; NCCN, National Comprehensive Cancer Network.

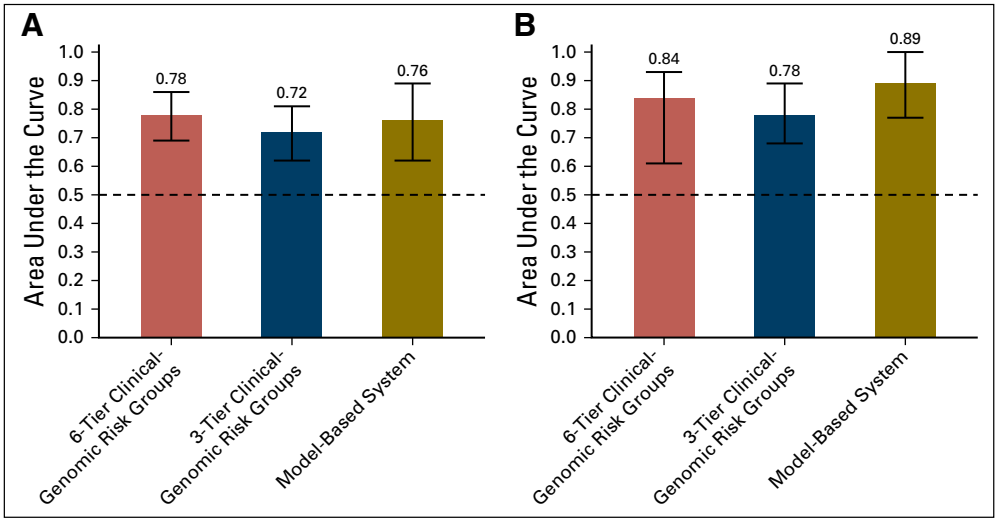

Fig A3. C-indices of clinical-genomic risk grouping systems in the retrospective validation cohort. (A) Metastasis at 5 years and (B) metastasis at 10 years.

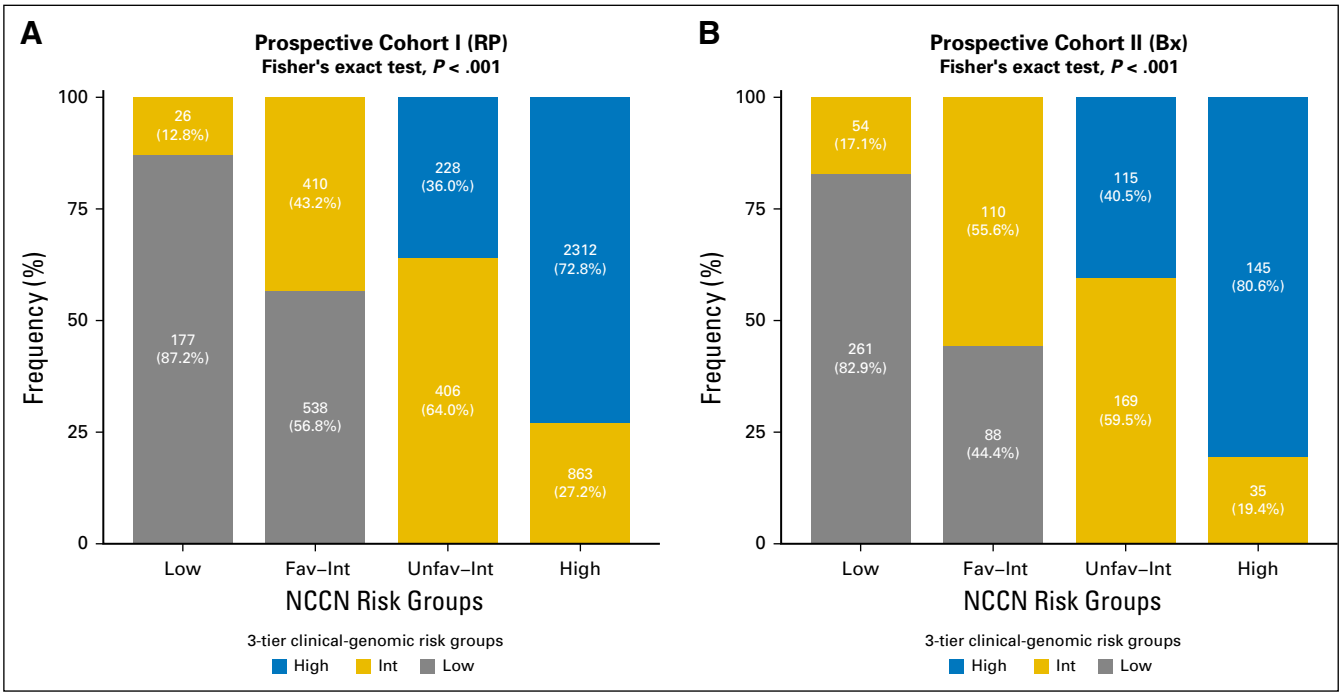

Fig A4. Reclassification of National Comprehensive Cancer Network (NCCN) risk groups to clinical-genomic risk groups within (A) prospective cohort I and (B) prospective cohort II. Bx, biopsy; fav, favorable; int, intermediate; RP, radical prostatectomy; unfav, unfavorable.

Table A1. Performance Comparison of NCCN and Clinical-Genomic Risk Grouping System Adjusting for Treatment and Institution

Grouping System	NCCN		Clinical-Genomic Risk Grouping System			
			Training		Validation	
10-year metastasis rate, % (95% CI)	Low	7.3 (1.9 to 12.8)	Low	3.5 (0.7 to 6.3)	Low	0.0 (0.0 to 0.0)
	Fav-int	9.2 (4.3 to 14.0)	Int	29.4 (23.8 to 35.0)	Int	25.9 (8.8 to 43.0)
	Unfav-int	38.0 (29.5 to 46.6)				
	High	39.5 (33.0 to 46.1)	High	54.6 (45.6 to 63.6)	High	55.2 (33.9 to 76.6)
C-index for 10-year metastasis (95% CI)	0.68 (0.64 to 0.73)		0.77 (0.72-0.81)		0.84 (0.61-0.93)	
HR for metastasis* (95% CI)	Low	Ref	Low	Ref	Low	Ref
	Fav-int	1.4 (0.6 to 3.4)	Int	3.5 (1.5 to 8.3)†	Int	22.3 (2.9 to 2863.8)‡
	Unfav-int	2.5 (1.1 to 5.6)§				
	High	2.5 (1.1 to 5.4)§	High	6.1 (2.6 to 14.4)‡	High	61.6 (8.1 to 7914.9)‡

Abbreviations: fav, favorable; HR, hazard ratio; int, intermediate; NCCN, National Comprehensive Cancer Network; Ref, reference level; unfav, unfavorable.
*In retrospective training cohort, Cox proportional hazards model was used, adjusting for androgen deprivation therapy and radiation treatment as covariables, institution as a stratification variable; in retrospective validation cohort, penalized Cox proportional hazards model was used, adjusting for first-line treatment as a covariable.
†Significant at .01 level.
‡Significant at .001 level.
§Significant at .05 level.

Table A2. Second-Line Treatment Information in the Training Cohort

Treatment Modality	Training (n = 756), No. (%)
Prostatectomy alone	476 (63)
Adjuvant RT	50 (7)
Salvage RT	101 (13)
Adjuvant ADT	53 (7)
Salvage ADT	139 (18)

Abbreviations: ADT, androgen deprivation therapy; RT, radiation treatment.