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## Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease.

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# Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease

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## A B S T R A C T

### Purpose

To perform the first meta-analysis of the performance of the genomic classifier test, Decipher, in men with prostate cancer postprostatectomy.

### Methods

MEDLINE, EMBASE, and the Decipher genomic resource information database were searched for published reports between 2011 and 2016 of men treated by prostatectomy that assessed the benefit of the Decipher test. Multivariable Cox proportional hazards models fit to individual patient data were performed; meta-analyses were conducted by pooling the study-specific hazard ratios (HRs) using random-effects modeling. Extent of heterogeneity between studies was determined with the  $I^2$  test.

### Results

Five studies (975 total patients, and 855 patients with individual patient-level data) were eligible for analysis, with a median follow-up of 8 years. Of the total cohort, 60.9%, 22.6%, and 16.5% of patients were classified by Decipher as low, intermediate, and high risk, respectively. The 10-year cumulative incidence metastases rates were 5.5%, 15.0%, and 26.7% ( $P < .001$ ), respectively, for the three risk classifications. Pooling the study-specific Decipher HRs across the five studies resulted in an HR of 1.52 (95% CI, 1.39 to 1.67;  $I^2 = 0\%$ ) per 0.1 unit. In multivariable analysis of individual patient data, adjusting for clinicopathologic variables, Decipher remained a statistically significant predictor of metastasis (HR, 1.30; 95% CI, 1.14 to 1.47;  $P < .001$ ) per 0.1 unit. The C-index for 10-year distant metastasis of the clinical model alone was 0.76; this increased to 0.81 with inclusion of Decipher.

### Conclusion

The genomic classifier test, Decipher, can independently improve prognostication of patients postprostatectomy, as well as within nearly all clinicopathologic, demographic, and treatment subgroups. Future study of how to best incorporate genomic testing in clinical decision-making and subsequent treatment recommendations is warranted.

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## INTRODUCTION

Stratifying patients' risk of localized prostate cancer (PCa) continues to be clinically challenging.<sup>1,2</sup> Fundamentally, National Comprehensive Cancer Network risk stratification is based on the serum prostate-specific antigen (PSA) level, staging primarily from a digital rectal examination, and the Gleason score (originally described approximately 40 years ago).<sup>3</sup> Growing molecular evidence has

raised discussion around the solitary use of routine clinicopathologic risk factors and nomograms for predicting disease progression.<sup>4,5</sup>

Decipher (GenomeDx Biosciences, Vancouver, British Columbia, Canada) is a 22-gene genomic classifier that has been developed to aid in prognostication of patients who have undergone radical prostatectomy (RP).<sup>6</sup> It has been shown that the Decipher post-RP test discriminates risk of metastasis and PCa-specific mortality, improves accuracy of risk stratification

### ASSOCIATED CONTENT



See accompanying Editorial on page 1976



Appendix  
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above and beyond clinicopathologic risk factors or commonly used models, and impacts physician and patient post-RP treatment decisions.<sup>6-15</sup> However, the cohort size and event rate in the previous validation studies did not allow for a thorough investigation into the performance of Decipher, especially within individual clinicopathologic, demographic, or treatment subgroups.

Therefore, the present meta-analysis with individual patient-level genomic and clinicopathologic data was conducted to better understand the performance of Decipher to prognosticate risk of metastases. Additionally, by pooling studies, we aimed to explore the correlation and performance of Decipher in multiple clinically relevant subgroups within a multi-institutional and multiethnic cohort of patients with adverse pathology at time of RP.

## MATERIALS AND METHODS

### Study Selection

Systematic literature searches were performed (July 1, 2016) using two databases (MEDLINE [via PubMed] and EMBASE) for all studies published from January 1, 2011, through July 1, 2016. Controlled vocabulary was used in the formation of the search strategy.

The search strategy contained two major components linked together with the AND operator: (1) genomic classifier AND (2) prostate. All search results were imported into a bibliographic management tool and duplicates were removed. Then, leveraging the Decipher genomic resource information database, 1,692 patients from seven independent studies of the

Decipher test who underwent RP were identified.<sup>6-12</sup> These studies were all present in the previous bibliographic search strategy and duplicates were removed electronically.

**Data extraction.** Two investigators (K.Y. and D.E.S) independently reviewed each manuscript. Studies eligible for inclusion were required to (1) have used the Decipher genomic test, (2) been performed in men postprostatectomy, (3) have assessed rates of development of metastatic disease, and (4) include only patients who reached an undetectable PSA level after surgery (Fig 1). Of the seven eligible studies, patients from Erho et al<sup>6</sup> were excluded because this study was used to discover the Decipher genomic classifier. In addition, the Klein et al<sup>9</sup> study was excluded because of its case-control design, which is not compatible with survival analysis (Appendix Table A1, online only). After application of these requirements, five studies remained, comprising 975 patients. Patients who were not randomly selected from the case-cohort studies (n = 120) were excluded from the individual patient-level analysis to avoid bias in estimation of the hazard ratios [HRs].<sup>7,10,16</sup> Individual patient genomic and clinicopathologic data were gathered from each study group (n = 855) after institutional review boards at the participating institutions approved the research protocol under which the data were collected. Finally, the genomic data from all prior published studies were deposited into the genomic resource information database.<sup>7,8,10-12</sup> Approval to obtain long-term clinical outcomes data were obtained from each study's authors, and these data were then linked to the genomic and clinical information.<sup>7,8,10-12</sup> Data extraction and study selection followed the PRISMA-IPD (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data) statement.<sup>17</sup>

**End points.** The primary end point of the study was to determine the performance of Decipher using individual patient data (n = 855) to predict

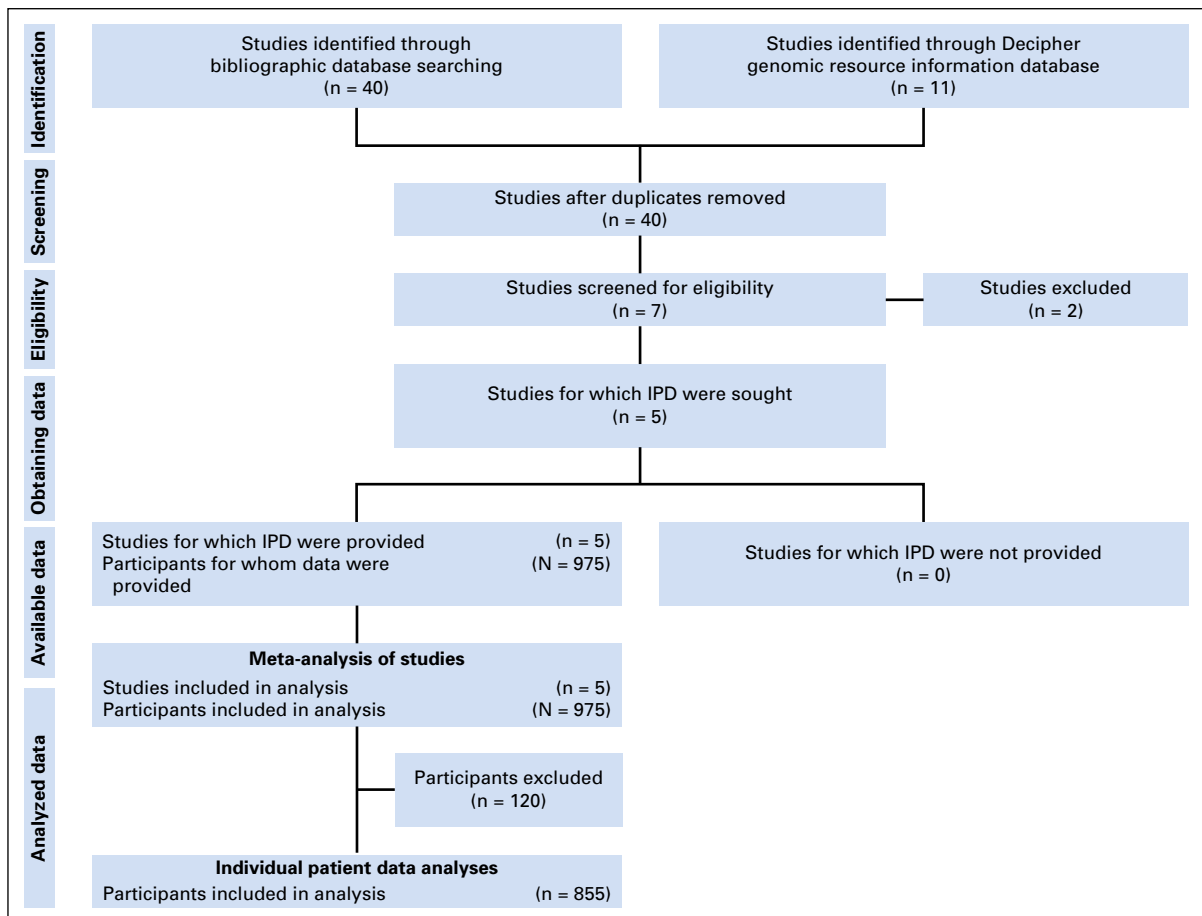


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of the study selection process. IPD, individual patient data.

time to regional or distant metastases on multivariable analyses while adjusting for pre-RP PSA level, RP Gleason score, margin status, extracapsular extension (ECE), seminal vesical invasion (SVI), and lymph node invasion (LNI). Metastasis end point was defined as either bone, viscera, or LN metastasis documented radiographically by computed tomography or bone scan. The secondary end point was to assess the performance of Decipher to predict time to metastases by pooling study-specific HRs across all five studies (N = 975).

Preplanned analyses using the individual patient level data (n = 855) included (1) determining the correlation of Decipher with pre-RP PSA, RP Gleason score, margin status, ECE, SVI, and LNI; and (2) determining the ability of Decipher to prognosticate time to regional or distant metastases in subgroups by race, pre-RP PSA, RP Gleason score, margin status, ECE, SVI, LNI, and adjuvant/salvage treatment modality (androgen deprivation therapy [ADT] or radiation therapy [RT]).

Patients received either no postoperative treatment before metastasis onset or were treated with adjuvant RT, salvage RT, adjuvant ADT, or salvage ADT. Adjuvant RT and salvage RT were defined by initiation of therapy at PSA levels of < 0.2 and ≥ 0.2 ng/mL, respectively. Adjuvant RT or salvage RT was performed using three-dimensional conformal RT or intensity modulated radiation therapy. Adjuvant ADT and salvage ADT were defined by initiation of therapy within 12 months and after 12 months post-RP, respectively.

**Calculation of Decipher Score**

The expression values for the 22 prespecified biomarkers that constitute Decipher were extracted from the normalized data matrix and entered into the random forest algorithm that was locked with defined tuning and weighting parameters as previously described.<sup>6</sup> The Decipher score read-out is a continuous score between 0 and 1, with higher scores indicating greater risk of metastasis. Previously established and locked cut points of 0.45 and 0.60 were used to categorize patients into low-, intermediate-, and high-risk groups.<sup>10,12</sup>

**Statistical Analysis**

Association of Decipher with individual clinicopathologic variables was assessed using the Spearman rank correlation coefficient. In time-to-event analyses, event times were defined as the time from RP to metastasis. Cumulative incidence curves were constructed using Fine-Gray competing risks analysis to estimate the risk of metastasis over time, with deaths from other causes as a competing risk.<sup>18</sup> Time-dependent C indices were constructed using the approach described by Heagerty et al.<sup>19</sup> The C index of the combined model was estimated by subjecting the model to bootstrapping with 100 resamples. Analysis of individual patient data used stratified Cox univariable analysis (UVA) and multivariable analysis (MVA) proportional hazards models to evaluate the association of Decipher with time to metastasis, where deaths from other causes was considered as a competing risk.<sup>20</sup> In these analyses, institution was modeled as a stratification variable to allow for variation of underlying hazard functions by stratification levels due to the varying patient populations and referral patterns.<sup>21</sup> In a sensitivity analysis, we fitted an MVA Cox proportional hazards model adjusting for RT and ADT as time-dependent covariates. Study-specific HRs were pooled using a random effects model according to the inverse variance method described by DerSimonian and Laird.<sup>22</sup> Heterogeneity between studies was assessed using the I<sup>2</sup> statistic. Egger's regression test was used to evaluate publication bias. All statistical tests were two-sided and analyses were performed in R version 3.1 (R Foundation, Vienna, Austria).

**RESULTS**

**Study and Patient Characteristics**

Patient and study selections following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data statement are shown in Fig 1. Of the 855 patients with

**Table 1.** Demographic and Clinical Characteristics of Included Patients and Studies

Variables	All Patients	Karnes et al <sup>7</sup>	Den et al <sup>8</sup>	Ross et al <sup>10</sup>	Glass et al <sup>11</sup>	Freedland et al <sup>12</sup>
Patients, No.	855*	235	139	260	224	117
Race						
White	730 (85.4)	235 (100.0)	118 (84.9)	231 (88.8)	210 (93.8)	49 (41.9)
Black	106 (12.4)	0 (0.0)	18 (12.9)	21 (8.1)	5 (2.2)	66 (56.4)
Other	17 (2.0)	0 (0.0)	3 (2.2)	5 (1.9)	9 (4.0)	2 (1.7)
Unknown	2 (0.2)	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Patient age, years (median [Q1, Q3])	60 (55, 65)	63 (58, 69)	60 (56, 64)	60 (56, 64)	57 (46, 64)	61 (57, 64)
Preoperative PSA level, ng/mL (median [Q1, Q3])	7.6 (5.3, 12.1)	9.3 (6.2, 15.6)	6.9 (4.9, 12.2)	9.5 (6.2, 14.2)	6.1 (4.7, 8.9)	7.6 (5.3, 10.8)
RP Gleason score, No. (%)						
≤ 3+4	459 (53.7)	96 (40.9)	61 (44.2)	96 (36.9)	143 (63.8)	82 (68.3)
4+3	171 (20)	41 (17.4)	37 (26.8)	50 (19.2)	45 (20.1)	20 (16.7)
≥ 8	222 (26)	98 (41.7)	38 (27.3)	114 (43.8)	36 (16.1)	15 (12.5)
Unknown	3 (0.4)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Extraprostatic extension, No. (%)	359 (42.0)	99 (42.1)	114 (82.0)	184 (70.8)	19 (8.5)	34 (28.3)
Seminal vesicle invasion, No. (%)	238 (27.8)	84 (35.7)	53 (38.1)	73 (28.1)	73 (32.6)	21 (17.5)
Positive surgical margins, No. (%)	499 (58.4)	135 (57.4)	105 (75.5)	72 (27.7)	136 (60.7)	100 (83.3)
Lymph node invasion, No. (%)	49 (5.7)	33 (14)	2 (1.4)	53 (20.4)	0 (0.0)	3 (2.5)
Treatment modality, No. (%)						
Prostatectomy alone	421 (49.2)	71 (30.2)	0 (0)	260 (100)	158 (70.5)	0 (0.0)
Adjuvant RT	140 (16.4)	29 (12.3)	57 (41.3)	0 (0.0)	23 (10.3)	46 (38.3)
Salvage RT	213 (24.9)	68 (28.9)	70 (50.7)	0 (0.0)	35 (15.6)	71 (59.2)
Adjuvant ADT	44 (5.1)	55 (23.4)	8 (5.8)	0 (0.0)	0 (0)	8 (6.7)
Salvage ADT	116 (13.6)	81 (34.5)	21 (15.2)	0 (0.0)	30 (13.4)	17 (14.5)
Follow-up of censored patients, years (median [Q1, Q3])	8 (5, 11)	7 (5, 9)	7 (4, 12)	9 (6, 12)	9 (6, 12)	9 (6, 12)
Patients with metastasis, No.	82	76	10	99	12	5

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; Q1, quarter 1; Q3, quarter 3; RP, radical prostatectomy; RT, radiation therapy. \*A total of 120 patients with metastasis who were not randomly selected from the case-cohort studies were excluded from the individual patient level meta-analysis.

individual patient data, the median follow-up time for censored patients was 8 years (interquartile range [IQR], 5 to 11 years). Patients were treated with RP between 1990 and 2010. The median age of patients at the time of RP was 60 years (IQR, 55 to 65 years); 41.9% had ECE, 27.8% had SVI, and 26% had an RP Gleason score of 8 to 10 (Table 1). Overall, 51.3% of the patients received only prostatectomy with no additional second-line therapy.

The median Decipher score for the cohort ( $n = 855$ ) was 0.37 (IQR, 0.24 to 0.54). Of these patients, 60.9% ( $n = 520$ ), 22.6% ( $n = 193$ ), and 16.5% ( $n = 141$ ) were categorized as being at, respectively, low, intermediate, and high risk by Decipher.

### Correlation of Decipher With Clinicopathologic Features

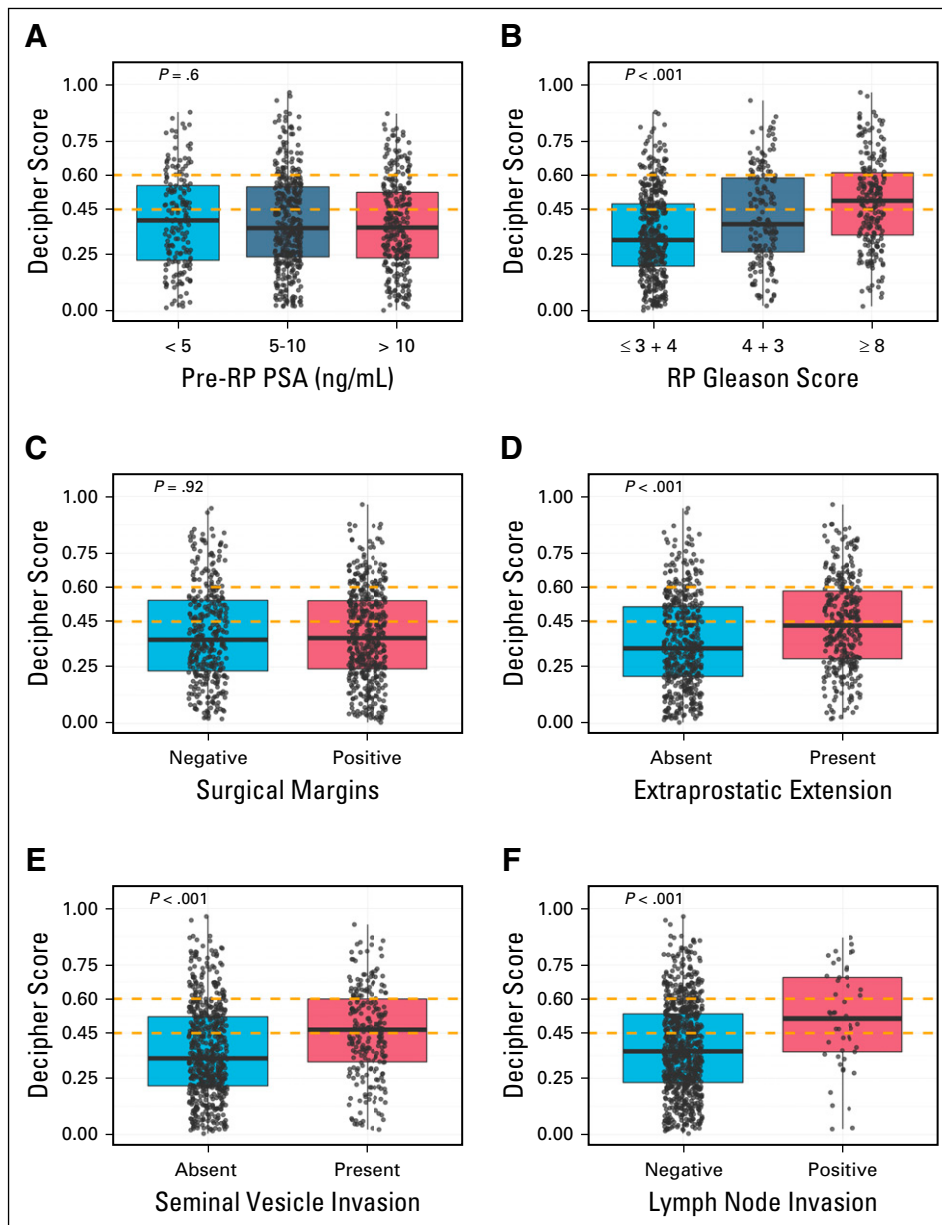
Decipher was significantly, albeit only low to moderately, correlated with RP Gleason score ( $r = 0.27$ ), EPE ( $r = 0.20$ ), SVI

( $r = 0.19$ ), and LNI ( $r = 0.13$ ; all  $P < .001$ ). Decipher was not significantly correlated with preoperative PSA or surgical margin status (Fig 2).

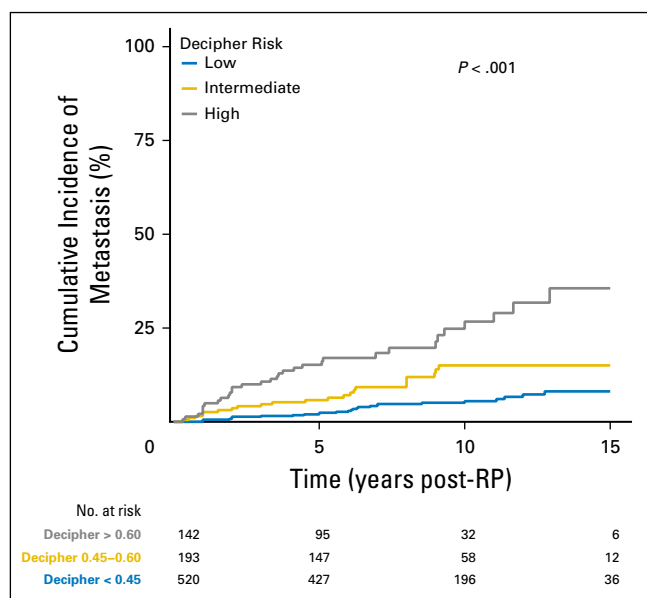
### Decipher As a Predictor of Metastasis

During the study, 82 patients experienced metastasis. Cumulative incidence curves demonstrated that Decipher categories significantly stratified risk of metastasis ( $P < .001$ ; Fig 3). Patients categorized as low, intermediate, and high risk by Decipher had a 5-year cumulative incidence of metastasis of 2.4%, 5.8%, and 15.2%, respectively; and a 10-year rate of 5.5%, 15.0% and 26.7%, respectively.

On UVA, all variables except pre-RP PSA showed significant association with time to metastasis (Table 2). On MVA, Decipher remained a significant predictor of metastasis ( $P < .001$ ). Decipher



**Fig 2.** Correlation of the genomic-risk score (Decipher Score) to the following clinicopathologic variables: (A) preoperative prostate-specific antigen (PSA), (B) radical prostatectomy (RP) Gleason score, (C) surgical margins, (D) extraprostatic extension, (E) seminal vesicle invasion, and (F) lymph node invasion.



**Fig 3.** Individual patient-level analysis for the cumulative incidence of metastasis over time stratified by genomic-risk groups (also referred to as the Decipher risk categories): low, intermediate, and high. RP, radical prostatectomy.

had a HR of 1.30 (95% CI, 1.14 to 1.47) per 0.1 unit increase in score. Analyzing Decipher as a categorical variable (low risk as reference), Decipher high-risk patients had the greatest hazard for metastases (HR, 3.31; 95% CI, 1.86 to 5.88;  $P < .001$ ), even compared with Gleason score 8-10 (Gleason  $\leq$  3+4 as reference; HR 3.23; 95% CI, 1.75 to 5.93;  $P < .001$ ). In a sensitivity analysis, adjusting for RT and ADT as time-dependent covariates, Decipher remained a significant predictor of metastasis (Appendix Table A2, online only). The C-index for 10-year distant metastases of the clinical model alone was 0.76 and increased to 0.81 with inclusion of Decipher.

Pooling study-specific HRs across the five studies (N = 975) demonstrated that the Decipher score was significantly associated with time to metastasis (HR, 1.52; 95% CI, 1.39 to 1.67) per 0.1-unit increase;  $I^2 = 0\%$ ; Fig 4A).

### Performance of Decipher Within Individual Subgroups

Decipher significantly predicted risk of metastasis irrespective of pre-RP PSA levels, RP Gleason score, surgical margin status, and ECE, SVI, and LNI status (Fig 4B; Appendix Figs A1A-A1C, online only). Additionally, Decipher was associated with risk of metastasis in subgroups of white men, men treated with RP alone, those treated with RP and salvage RT, and those treated with RP and ADT (Fig 4B). For black patients (n = 106) and those of any race treated with adjuvant RT (n = 140) or ADT (n = 44), Decipher approached, but did not reach, statistical significance for predicting risk of metastasis (HR, 1.43 [95% CI, 0.95 to 2.15]; HR, 1.86 [95% CI, 0.92 to 5.62]; and HR 1.52 [95% CI, 0.97 to 2.39], respectively).

### Assessment of Publication Bias

A funnel plot of the five included studies demonstrated excellent symmetry (Appendix Fig A2, online only). In this analysis, Egger regression test resulted in a P value of .60, indicating a low probability of publication bias (Appendix Fig 2).

## DISCUSSION

Accurately understanding the risk of recurrence after initial therapy for cancer is critical to determine goals of care, therapeutic recommendations, and the design of future clinical trials. Men with PCa often have a long natural history after RP or definitive RT, even for disease categorized as high risk according to the National Comprehensive Cancer Network, with an estimated median time to metastatic disease of 5 to 8 years after biochemical recurrence.<sup>23,24</sup> However, the subset of men who will eventually develop metastatic disease is poorly understood and not fully captured by clinicopathologic variables. For this reason, there have been efforts to develop companion genomic tests to provide clarity to classic phenotypic risk factors (ie, Gleason score, PSA level, and T stage) and add independent prognostic value.

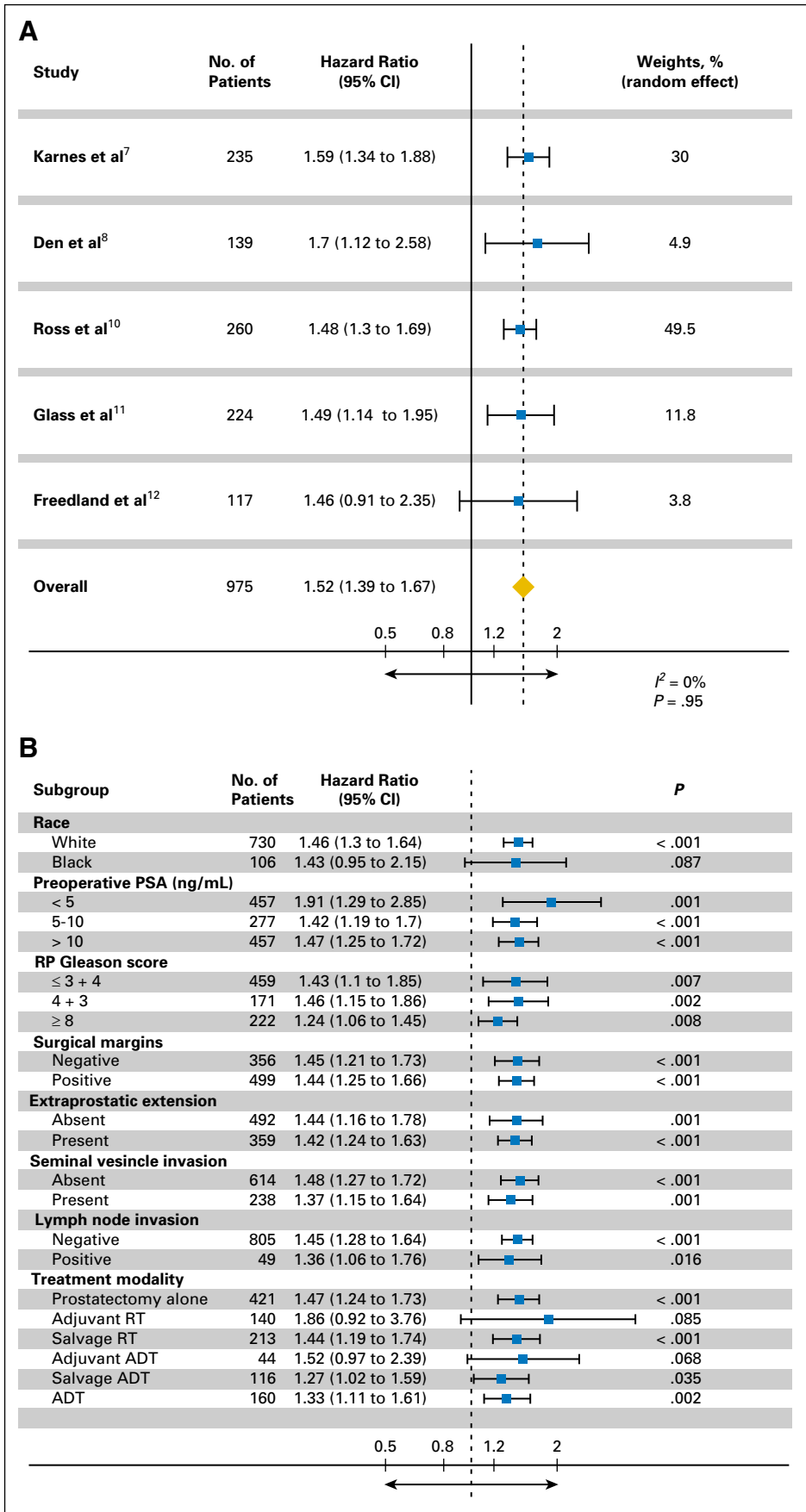
Over the past several years, one of the commercially available genomic tests (Decipher) has been externally validated as

**Table 2.** Univariable and Multivariable Analysis of Metastasis Including Decipher and Clinicopathologic Risk Factors

Variables	UVA		MVA (Decipher as continuous)		MVA (Decipher as categorical)	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Log2 preoperative PSA level, ng/mL	1.21 (0.97 to 1.51)	.088	1.10 (0.88 to 1.38)	.417	1.12 (0.89 to 1.41)	.322
RP Gleason score $\leq$ 3 + 4	ref	1	ref	1	ref	1
RP Gleason score 4 + 3	3.18 (1.64 to 6.14)	.001	2.40 (1.22 to 4.72)	.011	2.45 (1.25 to 4.81)	.009
RP Gleason score $\geq$ 8	5.47 (3.10 to 9.66)	< .001	2.97 (1.60 to 5.51)	.001	3.23 (1.75 to 5.93)	< .001
Positive surgical margins	1.67 (1.02 to 2.73)	.041	1.57 (0.96 to 2.58)	.075	1.48 (0.91 to 2.43)	.12
Extraprostatic extension	4.01 (2.24 to 7.17)	< .001	1.92 (0.99 to 3.75)	.054	2.03 (1.05 to 3.93)	.04
Seminal vesicle invasion	3.30 (2.11 to 5.16)	< .001	1.91 (1.18 to 3.11)	.009	1.87 (1.15 to 3.04)	.01
Lymph node invasion	4.08 (2.36 to 7.04)	< .001	1.78 (0.98 to 3.26)	.06	1.73 (0.94 to 3.15)	.08
Decipher*	1.48 (1.32 to 1.65)	< .001	1.30 (1.14 to 1.47)	< .001	—	—
Decipher low (< 0.45)	ref	1	—	—	ref	1
Decipher intermediate (0.45-0.60)	2.67 (1.51 to 4.72)	.001	—	—	1.77 (0.98 to 3.21)	.06
Decipher high (> 0.60)	6.19 (3.65 to 10.51)	< .001	—	—	3.31 (1.86 to 5.88)	< .001

Abbreviations: —, not applicable; MVA, multivariable analysis; PSA, prostate-specific antigen; RP, radical prostatectomy; UVA, univariable analysis.

\*Decipher is reported per 0.1-unit increase.



**Fig 4.** Forest plot of the Decipher score's hazard ratio for metastasis for (A) the study-specific hazard ratio pooled across all five studies, and (B) individual patient data in preplanned demographic, treatment, and clinicopathologic subgroups. Hazard ratios are reported per 0.1 unit increase in Decipher score. Weights in (A) were calculated based on the inverse variance formulation by DerSimonian and Laird.<sup>22</sup> Higher weights were assigned to studies with larger sample size and event rate. ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.



a prognostic tool to predict time to metastasis in multiple independent studies.<sup>6-12</sup> However, the sample size of each individual study limited the ability to robustly assess the correlation of Decipher with clinicopathologic risk factors, to assess the overall performance of Decipher above standard clinicopathologic risk factors, and to determine the performance of Decipher within relevant individual clinicopathologic risk groups. Our analysis provides numerous findings into the association of genomic and clinicopathologic risk and demonstrates how they are complementary and impart unique biologic information.

First, Decipher has a low-to-moderate correlation with RP Gleason score, ECE, SVI, and LNI. Additionally, there was no correlation of pre-RP PSA nor surgical margin status with Decipher score. These results demonstrate that select clinicopathologic variables trend with Decipher scores; however, there is a wide overlapping distribution of Decipher scores within each subset (ie, Gleason  $\leq 3+4$   $\nu$   $\geq 8$ ; Fig 2). Furthermore, it is rational that surgical margin status, a function partially dependent on the surgical procedure rather than the intrinsic biology of the disease, would not correlate with the genomic classifier results.

Second, in the present cohort of men with adverse pathology after RP, 61% were classified as low risk by Decipher, whereas only 17% were classified as high risk. Metastases rates could readily be discriminated by the Decipher score (5 year: 2.4%  $\nu$  15.2% for low and high Decipher score, respectively;  $P < .001$ ). Importantly, this prognostication was maintained on MVA adjusting for pre-RP PSA, RP Gleason score, margin status, ECE, SVI, and LNI (HR, 1.30 for each 0.1 increase in Decipher score). Although clinicopathologic variables perform reasonably well to predict who is at very low or very high risk of recurrence, Decipher independently improves upon this to further discriminate metastatic risk within these clinical risk groups. This observation has important implications for designing clinical trials for men with high-risk disease; use of Decipher as an entry criterion or for stratification would enrich the study population for meaningful clinical events (metastasis), thereby increasing the event rate, decreasing the needed sample size, and perhaps shortening trial length.

Last, given the large sample size of the present meta-analysis, we were able to test the prognostic benefit of Decipher in numerous preplanned analyses of distinct clinicopathologic subgroups. Decipher improved the ability to predict the cumulative incidence of metastases in nearly all subgroups based on clinicopathologic factors, treatment factors, and demographic factors. All subgroups reached statistical significance except the adjuvant RT subgroup (HR, 2.25; 95% CI, 0.90 to 5.62;  $P = .082$ ) and the black race subgroup (HR, 1.43; 95% CI, 0.95 to 2.15;  $P = .087$ ). Both exhibited elevated HRs associated with Decipher, and the marginally nonsignificant tests may reflect the small sample size of the subgroups. Given the recently demonstrated disparities that exist for minorities undergoing genomic sequencing, it will be important to have dedicated efforts to increase tumor profiling for racial minorities.<sup>25</sup> Despite this, it appears that the added benefit of using the Decipher genomic classifier does not appear to be limited to a particular

subgroup; rather, it appears to add consistent benefit across all subgroups (HR of all subgroups, 1.24 to 2.25).

The strength of our study is driven by the meta-analysis methodology with individual patient-level genomic and clinicopathologic data from large multi-institutional cohorts, use of a meaningful survival end point (ie, metastasis), and long-term follow-up. However, this study is not without limitations. First, the analysis is subject to the limitations associated with the retrospective design of the individual studies (Appendix Table A3, online only). Second, adjuvant and salvage treatments were not randomized and thus differed based on institutional and patient preferences. Third, our selection criteria included only patients with adverse clinicopathologic features, thus utility of Decipher in lower-risk PCa remains to be investigated. Fourth, use of imaging for restaging post-treatment was not standardized and, therefore, ascertainment bias is a potential limitation of the current analyses. Last, there are further potential social (eg, insurance and socioeconomic) factors, patient-level factors (eg, comorbidities), treatment factors (eg, duration of ADT and RT dose/field size), and tumor level factors (eg, PSA kinetics) that were not accounted for but could impact our results.

In conclusion, this study was performed to evaluate the performance of Decipher to predict metastases in men with PCa after RP. The results suggest that though Decipher only moderately correlates with clinicopathologic variables, it independently adds prognostic benefit over routine clinicopathologic variables to predict metastases and appears to add benefit across a number of clinically relevant subgroups. Decipher should be considered an additive validated test to improve prognostication in high-risk men after RP and to aid clinical decision-making and future clinical trial design.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease**

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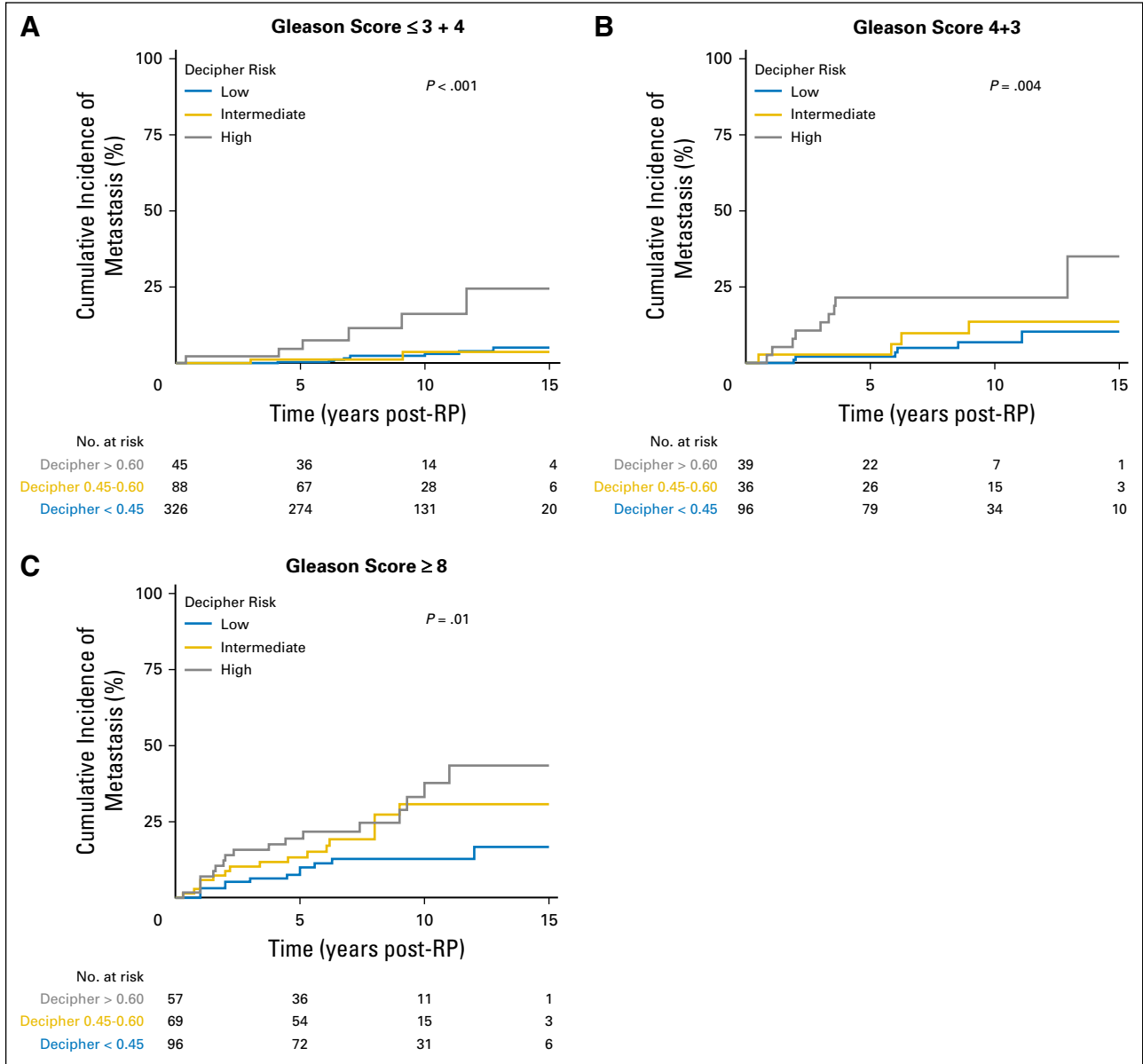
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Appendix



**Fig A1.** Individual patient level analyses for the cumulative incidence of metastasis over time stratified by Decipher risk categories (low, intermediate, and high) among patients with (A) radical prostatectomy (RP) Gleason score  $\leq 3+4$ , (B) RP Gleason score 4+3, and (C) RP Gleason score 8 to 10.

Meta-Analysis of Decipher Postprostatectomy

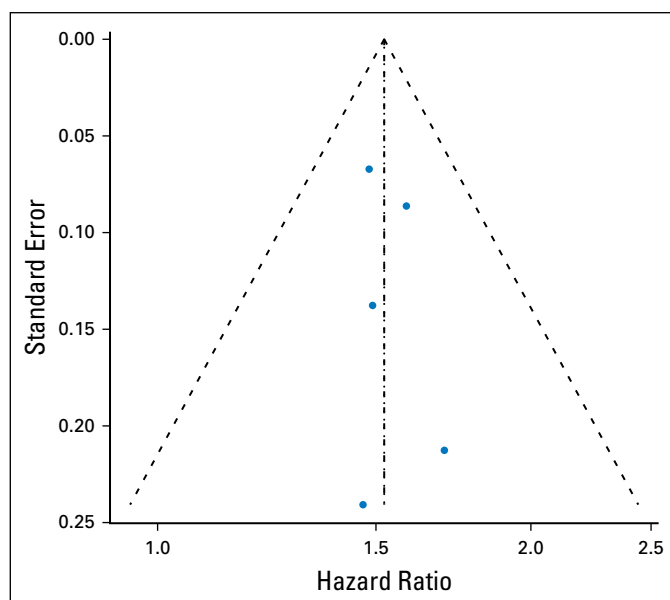


Fig A2. Funnel plot for publication bias.

Table A1. Demographic and Clinical Characteristics of Excluded Patients and Studies

Variables	Studies	
	Erho et al <sup>6</sup>	Klein et al <sup>9</sup>
Patients, No.	545	169
Race, No. (%)		
White	Unknown	152 (89.9)
Black	Unknown	14 (8.3)
Other	Unknown	3 (1.8)
Unknown	545 (100.0)	0 (0.0)
Patient age, years (median [Q1, Q3])	66 (61, 70)	62 (58, 67)
Preoperative PSA level, ng/mL (median [Q1, Q3])	9.4 (6, 19.7)	6.5 (4.8, 10.7)
RP Gleason score, No. (%)		
≤ 3+4	Unknown*	100 (59.2)
4+3	Unknown*	28 (16.6)
≥ 8	211 (38.7)	41 (24.3)
Extraprostatic extension, No. (%)	273 (50.1)	124 (73.4)
Seminal vesicle invasion, No. (%)	176 (32.3)	30 (17.8)
Positive surgical margins, No. (%)	266 (48.8)	84 (49.7)
Lymph node invasion, No. (%)	73 (13.4)	0 (0.0)
Treatment modality, No. (%)		
Prostatectomy alone	225 (41.3)	138 (81.6)
Adjuvant RT	54 (9.9)	0 (0.0)
Salvage RT	82 (15.0)	18 (10.6)
Adjuvant ADT	124 (22.7)	0 (0.0)
Salvage ADT	172 (31.6)	28 (16.6)
Follow-up of censored patients, years (median [Q1, Q3])	15 (13-18)	8 (6-11)
Reason for exclusion	Discovery set	Case-control

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; Q1, quarter 1; Q3, quarter 3.  
\*Gleason score breakdown by primary and secondary Gleason grade was not available.

**Table A2.** Multivariable Analysis of Decipher and Clinicopathologic Risk Factors Adjusting for Radiation Treatment and Androgen Deprivation Therapy as Time-Dependent Covariates

Variables	MVA (Decipher as continuous)		MVA (Decipher as categorical)	
	Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>
Log <sup>2</sup> preoperative PSA, ng/mL	1.06 (0.84 to 1.34)	.602	1.07 (0.85 to 1.36)	.549
RP Gleason score ≤ 3 + 4	ref	1	ref	1
RP Gleason score 4 + 3	1.65 (0.83 to 3.29)	.152	1.68 (0.84 to 3.34)	.139
RP Gleason score ≥ 8	2.50 (1.34 to 4.68)	.004	2.75 (1.49 to 5.08)	.001
Positive surgical margins	1.22 (0.73 to 2.04)	.450	1.16 (0.70 to 1.94)	.567
Extraprostatic extension	1.69 (0.89 to 3.22)	.108	1.78 (0.94 to 3.36)	.076
Seminal vesicle invasion	1.94 (1.18 to 3.18)	.009	1.87 (1.14 to 3.07)	.013
Lymph node invasion	2.10 (1.13 to 3.90)	.019	2.08 (1.12 to 3.87)	.020
RT	7.47 (3.19 to 17.49)	< .001	7.71 (3.29 to 18.06)	< .001
ADT	3.26 (1.62 to 6.57)	.001	3.21 (1.59 to 6.48)	.001
Decipher*	1.24 (1.09 to 1.42)	.001	—	—
Decipher low (< 0.45)	—	—	ref	1
Decipher intermediate (0.45-0.60)	—	—	1.56 (0.84 to 2.88)	.157
Decipher high (> 0.60)	—	—	2.77 (1.53 to 5.03)	.001

Abbreviations: —, not applicable; ADT, androgen deprivation therapy; MVA, multivariable analysis; PSA, prostate-specific antigen; ref, reference; RP, radical prostatectomy; RT, radiation therapy.

\*Decipher is reported per 0.1-unit increase

**Table A3.** National Institutes of Health Level of Evidence Scale\*

Study	Year	Level of Evidence
Karnes et al <sup>7</sup>	2013	3C
Den et al <sup>8</sup>	2014	3C
Ross et al <sup>10</sup>	2016	3C
Glass et al <sup>11</sup>	2016	3C
Freedland et al <sup>12</sup>	2016	3C

\*National Cancer Institute: Levels of Evidence for Adult and Pediatric Cancer Treatment Studies: Strength of Study Design. <http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/HealthProfessional/page2>