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Validation of the Decipher Test for Predicting Distant Metastatic Recurrence in Men with High-risk Nonmetastatic Prostate Cancer 10 Years After Surgery

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Abstract

Background: Decipher is a genomic classifier designed to predict the development of distant metastases after surgical treatment of prostate cancer (PC). Its long-term prognostic role in a high-risk PC population has not been investigated previously.

Objective: To determine the prognostic role of the Decipher genomic classifier in two high-risk PC case-control studies.

Design, setting, and participants: Patients who developed distant metastases after surgery for high-risk, nonmetastatic PC in a European tertiary referral center from 1991 to 2011 were matched to patients not developing distant metastases ($n = 54$). A validation study ($n = 298$) was performed using a similar US case-control cohort. Formalin-fixed, paraffin-embedded tissue blocks from the index PC lesion were used for RNA extraction and gene expression analysis.

Outcome measurements and statistical analysis: The outcome investigated was the development of distant metastasis within 10-yr follow-up. Multivariable logistic regression analysis was performed, with statistical significance considered at $p < 0.05$.

Results and limitations: In both the European and US case-control studies, the median Decipher scores were higher in the population that developed metastases. In the multivariable analysis, each 10% increase in Decipher score translated to an increase in the risk of distant metastases within 10-yr follow-up, with an odds ratio of 1.53 (95% confidence interval [CI] 1.06–2.22; $p = 0.025$) and 1.58 (95% CI 1.31–1.92; $p < 0.001$) for the European and US cohorts, respectively. Median follow-up for the European cohort was 12 yr (interquartile range 8–12). The study limitation is the small size of the European cohort.

Conclusions: Our study validates Decipher as a predictor for metastatic recurrence even in patients with high-risk, nonmetastatic PC within 10-yr follow-up.

Patient summary: Decipher is a test based on gene expression profiles in primary tumors in prostate cancer. It has already been proven to predict cancer recurrence after surgery, but this has not yet been shown for patients with high-risk prostate cancer. This is the first study confirming that Decipher predicts a patient's risk of developing cancer recurrence after surgery for high-risk prostate cancer.

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1. Introduction

Patients with high-risk prostate cancer (PC) are at the highest risk of metastatic progression and death from PC after primary treatment. However, despite being at high risk of disease progression, only 12% and 22% of patients develop distant metastases and only 2.8% and 8% of patients will die from PC by 5- and 10-yr follow-up, respectively [1]. For patients classified as having the highest risk of PC progression, these rates remain relatively low, suggesting that the classification systems currently used are inaccurate.

Because distant metastases are associated with PC mortality and suitable therapies have a major deleterious impact on quality of life [2,3], the ability to predict a PC patient's risk of developing metastatic recurrence after surgical treatment is essential should there be a need to tailor individualized follow-up schedules and secondary therapies. The Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) score is a postsurgical clinical scoring system that is considered the gold standard for PC prognostication. However, risk stratifications based on clinical data remain insufficiently accurate. We hypothesized that genetic and genomic markers that directly reflect tumor biology have an additive value in clinical decision-making [4–8].

We analyzed the value of Decipher, a genomic classifier based on expression patterns for 22 biomarkers in radical prostatectomy (RP) specimens, in predicting patient outcomes within 10-yr follow-up. Although this classifier has been validated in multiple cohorts, it has not been validated in a very high-risk PC cohort. The prognostic potential of a biomarker largely depends on variability between groups, which obviously is best when group differences are large. However, there is probably limited added value of a biomarker in differentiating patient groups with clear differences in clinical outcomes (eg, low- vs high-risk PC) [9]. A biomarker that can differentiate between clinical outcomes within patient groups with similar outcome predictions based on clinical features is of much more interest. We challenged the prognostic power of Decipher in carefully selected patients with very high-risk nonmetastatic PC. Our aim was to determine whether Decipher could predict which patients would develop distant metastatic recurrence in a cohort already judged to be at the highest risk of developing recurrent disease.

2. Patients and methods

2.1. Discovery study design

The University Hospitals Leuven High-Risk Prostate Cancer database, a retrospective database of all patients who underwent RP for high-risk PC in a single center, was queried. Patients were included if they had undergone RP and pelvic lymph node dissection (PLND) between 1991 and 2011 for clinically nonmetastatic high-risk PC as defined according to the European Association of Urology guidelines (prostate-specific antigen [PSA] >20 ng/ml or $\geq$ cT3a or biopsy grade group 4–5) [9]. Patients were excluded if they were preoperatively diagnosed with clinical M+ or N+ disease or if they were known to have another active malignancy at the time of PC diagnosis.

As systemic progression is relatively infrequent, we designed a nested case-control study (referred to as the Leuven cohort study). Patients who developed distant metastatic recurrence were identified and were pair-matched 1:1 (for pathologic T stage, RP grade group, surgical margin status, and lymph node invasion status) with patients who did not develop distant metastases despite even longer follow-up (Fig. 1). The study size was limited by the number of patients suffering from distant metastases, as confirmed by in-house imaging modalities at long-term follow-up.

For each patient ($n = 70$), a representative formalin-fixed, paraffin-embedded (FFPE) tissue block from the index PC lesion, defined as the lesion with the highest Gleason score and the highest percentage tumor involvement, was identified by a dedicated uropathologist (T.G.). Patients with unavailable/incomplete RP tissue blocks ($n = 9$) or follow-up of <10 yr ($n = 7$) were excluded, resulting in a final cohort of 54 patients (Fig. 1). The study followed the prospective-specimen-collection, retrospective-blinded-evaluation (PROBE) and REporting recommendations for tumour MARKer prognostic studies (REMARK) guidelines for evaluation and analysis of prognostic biomarkers [10,11]. All laboratory analyses were blinded to clinical outcomes.

2.2. Sample preparation and processing

For the Leuven cohort, two 1.5-mm punch cores were obtained from the FFPE block from the area delineated by the uropathologist on the corresponding hematoxylin and eosin slide for RNA extraction. RNA was amplified using the Ovation WTA FFPE system (NuGen, San Carlos, CA, USA) and subsequently labeled and hybridized to Human Exon 1.0 ST microarrays (Thermo Fisher, Carlsbad, CA, USA). Processing of oligonucleotide microarray data for analysis and the generation of signature scores were performed as previously described [12]. Quality control was verified using Affymetrix power tools [13] and data normalization was performed via the Single Channel Array Normalization (SCAN) algorithm [14].

The expression values for the 22 prespecified biomarkers that constitute Decipher were extracted from the normalized data matrix and entered into the locked random forest algorithm with tuning and weighting parameters as previously defined [12]. The Decipher readout is a continuous risk score between 0 and 1, with higher scores indicating a greater probability of disease progression or metastasis. Decipher results were also stratified into low (<0.45), intermediate (0.45–0.60), and high (>0.60) risk groups on the basis of previously developed and validated cut points [15].

2.3. Design of the validation study

To further investigate the high-risk subset, we selected genome-wide expression profiles for 1118 patients with available metastatic outcome data from the Decipher Genomics Resource Information Database (GRID) trial (NCT02609269). We pooled patients from four case-control or cohort designed studies. Patients came from five institutions: Thomas Jefferson University ($n = 139$) [16], Johns Hopkins Medical Institutions ($n = 260$) [15], Mayo Clinic ($n = 216$) [7], MD Anderson Cancer Center ($n = 279$) [17], and Kaiser Permanente Northwest ($n = 224$) [18]. After pooling the data, we simulated a nested case-control cohort (the GRID cohort) from a subset of these patients with similar characteristics to patients from the University Hospitals Leuven study (Table 1). To this end, we filtered patients with complete post-RP clinical information and with a CAPRA-S score ≥ 3 , 193 of whom experienced distant metastases. Patients with and without metastasis were then matched using nearest-neighbor matching with a caliper of 0.5 on study and CAPRA-S in a 1:1 ratio [19].

2.4. Definition of variables

Clinical data consisted of patient age at RP (in years), preoperative PSA level (ng/ml), year of surgery, clinical T stage (T2, T3, or T4), biopsy

Fig. 1 – CONSORT diagram showing the study design and the patient selection process for the Leuven cohort. Bx = biopsy; EAU = European Association of Urology; PC = prostate cancer; PLND = pelvic lymph node dissection; PSA = prostate-specific antigen.

Table 1 – Descriptive characteristics for patients treated with RP and pelvic lymph node dissection in the Leuven University Hospitals cohort and the Decipher GRID cohort

Variable	Leuven University Hospitals study				Decipher GRID cohorts			
	Total cohort	Recurrent cohort	Nonrecurrent cohort	p value	Total cohort	Recurrent cohort	Nonrecurrent cohort	p value
Patients (n)	54	29	25		298	149	149	
Median age, yr (IQR)	64 (58–70)	64 (57–67)	68 (59–70)	0.4	61 (56–66)	61 (56–66)	62 (56–67)	0.4
pPSA, n (%)				0.4				0.7
<10 ng/ml	23 (42.6)	13 (44.8)	10 (40)		147 (49.3)	77 (51.7)	70 (47.0)	
10–20 ng/ml	14 (25.9)	8 (27.6)	6 (24)		101 (33.9)	48 (32.2)	53 (35.6)	
>20 ng/ml	17 (31.5)	8 (27.6)	9 (36)		50 (17.3)	24 (16.1)	26 (17.4)	
RP GG, n (%)				0.7				0.02
Group 1	0 (0)	0 (0)	0 (0)		3 (1)	0 (0)	3 (2)	
Group 2	17 (31.5)	8 (27.6)	10 (40)		78 (26.2)	31 (20.8)	47 (31.5)	
Group 3	0 (0)	0 (0)	0 (0)		74 (24.8)	36 (24.2)	38 (25.5)	
Group 4	24 (44.4)	13 (44.8)	10 (40)		50 (16.8)	24 (16.1)	26 (17.4)	
Group 5	13 (24.1)	8 (27.6)	5 (20)		93 (31.2)	58 (38.9)	35 (23.5)	
pT stage, n (%)				0.8				0.09
T2	4 (7.4)	2 (6.9)	2 (8)		73 (24.5)	28 (18.8)	45 (30.2)	
T3a	16 (29.6)	7 (24.1)	9 (36)		93 (31.2)	48 (32.2)	45 (30.2)	
T3b	27 (50)	16 (55.2)	11 (44)		106 (35.6)	59 (39.6)	47 (31.5)	
T4	7 (13)	4 (13.8)	3 (12)		1 (0.3)	0 (0)	1 (0.7)	
NA	0 (0)	0 (0)	0 (0)		25 (8.4)	14 (9.4)	11 (7.4)	
LNI, n (%)	12 (22.2)	9 (31)	3 (12)	0.1	60 (20.1)	38 (25.5)	22 (14.8)	0.03
Median score (IQR)								
CAPRA-S	7 (5–10)	8 (6–9)	7 (5–9)	1	6 (5–8)	6 (5–8)	6 (4–8)	0.2
Decipher	0.61 (0.45–0.77)	0.72 (0.50–0.80)	0.55 (0.44–0.68)	0.016	0.49 (0.31–0.63)	0.55 (0.39–0.70)	0.42 (0.24–0.56)	<0.001
Median FU, yr (IQR)	12 (8–14)	9 (4–11)	14 (13–16)	<0.001	7 (5–10)	7 (5–10)	7 (5–10)	0.5

CAPRA-S = Cancer of the Prostate Risk Assessment postsurgical; FU = follow-up; GG = grade group; IQR = interquartile range; LNI = lymph node invasion; pPSA = preoperative prostate-specific antigen; RP = radical prostatectomy.

International Society of Urological Pathology (ISUP) grade group (grades 1–5), RP ISUP grade group (grades 1–5), pathological T stage (T2, T3a, T3b, or T4) and lymph node invasion status (yes or no). The extent of PLND was at the discretion of the treating physician. CAPRA-S scores were calculated as described previously [4].

2.5. Definition of outcomes

The study outcome was the development of distant metastasis within 10-yr follow-up. Patients who did or did not develop distant metastases were defined as the recurrent and nonrecurrent subgroups, respectively. Distant metastases in bones, parenchymal organs, or soft tissues were identified via radiological imaging or histologically confirmed at the discretion of the treating physician. Follow-up time was defined as the period from RP until the development of distant metastasis or last follow-up.

2.6. Statistical analysis

Statistical analyses, reporting, and interpretation of the results were performed following guidelines proposed by Vickers et al. [20]. Patients were censored at death due to other causes when their PC was nonmetastatic or at final follow-up. Because of the nested case-control patient selection strategy, multivariable logistic regression analyses were performed to evaluate the performance of Decipher in predicting distant metastases at 10-yr follow-up. For the GRID cohort, since not all patients had at least 10 yr of follow-up, a sensitivity analysis was performed in addition to logistic regression analysis using the generalized linear mixed model with random effects (GLMM) approach and logistic regression after exclusion of patients with <10 yr of follow-up. Since the 1:1 matching in the Leuven cohort was not perfectly balanced (owing to the unavailability of tumor blocks; see above) and to ensure the robustness of the multivariable model of the Leuven cohort, a penalized least absolute shrinkage and selection operator (LASSO) regression method was used to identify the most predictive variables [21]. Variables considered in the LASSO regression analysis were preoperative PSA (log2 converted continuous variable), age at RP (continuous), RP grade group (4 or 5 vs 2), pathologic T stage (T4, T3b, or T3a vs T2), lymph node invasion (yes vs no), and the Decipher score. The University Hospitals Leuven model was then tested in the GRID cohort. To test the association of the Decipher score with continuous clinicopathological variables, Spearman rank correlation was performed. For categorical variables, the Mann-Whitney *U* test (for binary variables) and Kruskal-Wallis test (for variables with more than two groups) were performed. Comparison of patient characteristics was performed using the χ^2 test. Statistical analyses were performed using R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria) with statistical significance set at $p < 0.05$.

3. Results

Patient characteristics for the Leuven cohort ($n = 54$) and the GRID cohort ($n = 298$) are shown in Table 1. For the Leuven cohort, clinical determinants did not significantly differ between the recurrent and nonrecurrent subgroups, while median patient follow-up was significantly longer for the nonrecurrent (14 yr, interquartile range [IQR] 13–16) than for the recurrent subgroup (9 yr, IQR 4–11; $p < 0.0001$). The use of adjuvant therapies was similar between the subgroups (0.32% for nonrecurrent vs 0.45% for recurrent; $p = 0.9$). For the GRID cohort there was a significant difference in RP grade group distribution ($p = 0.02$) and

lymph node invasion status ($p = 0.03$), with more patients in the recurrent group having grade group 5 tumors and lymph node invasion. However, the CAPRA-S score was very similar between the recurrent and nonrecurrent groups ($p = 0.2$). For the Leuven cohort, 72% (21/29) of patients with recurrent disease eventually died due to their disease. For both cohorts, it is not possible to discriminate between recurrent and nonrecurrent patients on the basis of clinical features; hence, it remains impossible to identify patients with lethal disease.

For the Leuven cohort, the median Decipher score of 0.61 (IQR 0.45–0.77) was significantly higher in the recurrent (median 0.72, IQR 0.50–0.80) than in the nonrecurrent group (median 0.55, IQR 0.44–0.68), as shown by discrimination box plots (Fig. 2A; $p = 0.016$). For the GRID cohort, the median Decipher score was 0.49 (IQR 0.31–0.63) and was higher in the recurrent (0.55, IQR 0.39–0.70) than in the nonrecurrent group (0.42, IQR 0.24–0.56) as well ($p < 0.001$).

When patients were stratified by Decipher score into low (<0.45), intermediate (0.45–0.60), and high (>0.60) risk groups, the recurrent subgroup had a higher proportion of

Fig. 2 – Decipher score distribution plots. (A) Decipher score distributions among cases and controls. Horizontal lines denote the median scores and interquartile range. Whiskers of the boxplot represent all of the values included. Dashed lines represent the cut points for the Decipher risk groups. (B) Decipher risk-group distributions among cases and controls.

Fig. 3 – Cumulative incidence analysis: incidence of metastatic recurrence stratified according to Decipher score groups. Time from radical prostatectomy (RP) to distant metastases (Mets), with time zero representing the date of surgery.

high-risk Decipher scores (Fig. 2B). The cumulative incidence of metastatic recurrence for patients with low- or intermediate-risk Decipher scores ($n = 26$) was 66%, compared to 35% for those with high-risk scores ($n = 28$) at 12.5-yr follow-up ($p = 0.02$; Fig. 3).

For the Leuven cohort, none of the clinical variables considered for multivariable analysis showed a significant correlation with the Decipher score, although there is some evidence of a higher Decipher score in the RP ISUP grade 5 group (Supplementary Fig. 1). According to the LASSO regression analysis, Decipher score, lymph node invasion, and age at RP were included in the multivariable model (Supplementary Fig. 2), with the Decipher score being the only significant predictor of distant metastases within 10-yr follow-up (Table 2). For every 10% increase in Decipher score, the odds of metastases at 10-yr follow-up increased by 53% (odds ratio [OR] 1.53, 95% confidence interval [CI] 1.06–2.22; $p = 0.025$). For the GRID cohort, logistic regression analysis showed that when adjusting for the same clinical risk factors, for every 10% increase in Decipher score, the odds of metastases increased by 31% (OR 1.31, 95% CI 1.17–1.48; $p < 0.001$). A similar result was obtained via

GLMM with institution site as the random effect (OR 1.36, 95% CI 1.19–1.55; $p < 0.001$). This was further confirmed in a sensitivity analysis that excluded 103 patients who were censored for metastasis with < 10 yr of follow-up (OR 1.58, 95% CI 1.31–1.92; Table 3).

4. Discussion

Decipher is a genomic classifier with a score based on the expression profile of 22 biomarkers in the primary prostate tumor (PC biopsy and RP specimens). On the basis of this score, a patient's risk of developing distant metastases following RP at 5- and 10-yr follow-up can be estimated. This test was designed and externally validated in US studies, and its use is covered by Medicare, a US federal health insurance program. Although the Decipher test has been extensively validated, it has never been validated in a very high-risk PC surgical population with long-term follow-up [12,15,22]. The prognostic potential of a biomarker largely depends on variability between groups, which obviously is best when group differences are large. However, there appears to be only limited added value of a biomarker in differentiating patient groups with clear differences in clinical outcomes (eg, low- vs high-risk PC) [9]. Theoretically, when a population is clinically homogeneous, the prognostic power of a biomarker could be expected to be lower. However, at the clinician level, a biomarker would add the most benefit in a homogeneous high-risk population in which the clinician cannot predict a patient's outcome. This is the first study to validate the role of the Decipher test in predicting the development of distant metastases 10 yr after surgery in a high-risk PC population.

Table 2 – Multivariable logistic regression analysis predicting distant metastases-free survival at 10-yr follow-up after RP and pelvic lymph node dissection for the Leuven University Hospitals cohort

Variable	Odds ratio (95% CI)	p value
RP Decipher score (per 10% increment)	1.53 (1.06–2.22)	0.025
Age at RP	0.92 (0.84–1.02)	0.1
Lymph node invasion	3.14 (0.64–15.34)	0.16

CI = confidence interval; RP = radical prostatectomy.

Table 3 – Multivariable logistic regression analysis predicting distant metastases-free survival after RP and pelvic lymph node dissection for the Decipher GRID study using LRA, GLMM, and LRA excluding patients with metastases and follow-up of <10 yr

Variable	LRA		GLMM		ALRA	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
RP Decipher score ^a	1.31 (1.17–1.48)	<0.001	1.36 (1.19–1.55)	<0.001	1.58 (1.31–1.92)	<0.001
Age at RP	0.98 (0.95–1.01)	0.15	0.98 (0.94–1.01)	0.13	0.99 (0.94–1.03)	0.52
LNI	1.51 (0.081–2.80)	0.19	1.42 (0.76–2.68)	0.27	1.36 (0.53–3.55)	0.52

ALRA = adjusted LRA (exclusion of patients with metastases and follow-up of <10 yr); CI = confidence interval; GLMM = generalized linear mixed models; LNI = lymph node invasion; LRA = logistic regression analysis; OR = odds ratio; RP = radical prostatectomy.

^a Per 10% increment in score.

Some important observations can be derived from this study. Because of the nested case-control design, clinical patient characteristics in the recurrent and nonrecurrent subgroups were highly similar and, despite drastically different outcomes, clinically indistinguishable. Furthermore, it has been shown that metastatic recurrence correlates very well with overall survival among PC patients and is a good surrogate endpoint [23]. As a result, it would be impossible for a clinician to identify patients from these two cohorts with actual lethal PC. Although patients with high-risk nonmetastatic PC generally have the highest risk of developing recurrent disease, this clinical entity remains very heterogeneous in outcome. On the basis of clinical patient and tumor characteristics, patients can be stratified as having good, intermediate, or poor prognosis at 10-yr follow-up, with PC survival rates of 95.4%, 88.3%, and 79.7%, respectively [8]. However, these data also imply that current patient stratification systems based on clinical features lack specificity, since 79.7% of patients in the poor prognosis group survive, whilst 4.6% in the good prognosis group die, as do 11.7% of patients in the intermediate prognosis group. Again, prognostic models based on clinical patient and tumor characteristics remain too inaccurate and need to be complemented with biomarkers reflecting tumor biology, such as Decipher.

The median Decipher scores were 0.61 (IQR 0.45–0.77) and 0.49 (IQR 0.31–0.63) in the Leuven and GRID cohorts, respectively. The differences can most likely be attributed to the higher risk profile in the Leuven cohort, as reflected by CAPRA-S scores. Still, these scores remain comparable to studies reporting Decipher scores in patient populations at the highest risk of metastatic progression [15,22]. The Decipher score was significantly higher among patients who developed metastatic recurrence than among patients who did not develop them in both cohorts.

A recent meta-analysis by Spratt et al. [24] based on a pooled analysis of 855 patients with 82 events validated the prognostic ability of the Decipher score for metastatic recurrence, with a hazard ratio of 1.52 (95% CI 1.39–1.67). Our analyses further validate the robustness of the Decipher score in separating subgroups of men at the highest risk of distant metastases at 10-yr follow-up with odds ratios of 1.53 (95% CI 1.06–2.22, $p = 0.025$) and 1.31 (95% CI 1.19–1.55, $p < 0.001$) even in patient populations with known prognostic poor tumor features [25]. On exclusion of

patients with <10 yr of follow-up in the GRID cohort, multivariable analysis showed an odds ratio of 1.58 (95% CI 1.31–1.92, $p < 0.001$). This means that for PC patients with high-risk nonmetastatic disease, for every 10% increase in the Decipher score, an individual patient has a 53–58% greater risk of developing metastatic disease within 10 yr.

The results of this study validate the potential of Decipher to identify patients at the highest risk of metastatic recurrent disease, even within a highly selected high-risk population with nonmetastatic PC. Biomarkers such as Decipher allow us to intensify follow-up schedules or decide on the need for adjuvant therapies. It has been shown that the Decipher score is not only a prognostic marker but also a predictive biomarker, identifying with high accuracy which patients would benefit from adjuvant or salvage radiotherapy [26–28]. Furthermore, biomarkers such as Decipher are attracting increasing interest in prospective clinical trials investigating their potential to identify patients at the highest risk of poor outcome (NCT03070886, NCT03371719) and specifically including these patients in clinical trials. This strategy was proposed by the SPECTA program of the European Organization for Research and Treatment of Cancer to improve clinical trial results by preselecting patients on the basis of molecular alterations (NCT02834884).

Our study has several strengths. First, we used a robust, extensively validated biomarker expression assay [12,15,22]. Second, all laboratory analyses were blinded to clinical outcomes. Importantly, this study also meets the PROBE and REMARK criteria for studies reporting on biomarkers [10,11]. Finally, we were able to validate our findings in a separate, larger, multi-institutional validation study.

There are also some limitations to be reported. First, not all patients underwent extended PLND, so lymph node status might not be accurate in the Leuven cohort. Second, the sample size of the cohort is small. Finally, the follow-up time in the GRID cohort was similar for the recurrent and nonrecurrent subgroups, which might introduce some missed cases in the nonrecurrent subgroup. However, we feel that the combination of the small Leuven cohort with long-term follow-up and the validation of these findings in the GRID cohort with shorter follow-up data is a robust analysis that underlines the reproducibility of the power of the Decipher test, even in small populations.

5. Conclusions

The study results show that Decipher remains prognostic even in a homogeneous, high-risk PC cohort, with a 53% (Leuven cohort) and 58% (GRID cohort) increase in the risk of distant metastases at 10-yr follow-up per 10% increase in Decipher score. These data confirm the clinical applicability of Decipher for prognostication in patients with high-risk PC and suggest that it could guide clinicians in their decision-making regarding follow-up and secondary therapeutic strategies.

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

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.euo.2018.12.007](https://doi.org/10.1016/j.euo.2018.12.007).

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