



A 17-gene Panel for Prediction of Adverse Prostate Cancer Pathologic Features: Prospective Clinical Validation and Utility

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OBJECTIVE	To validate the 17-gene Oncotype DX Genomic Prostate Score (GPS) biopsy-based gene expression assay as a predictor of adverse pathology (AP, Gleason score [pGS] $\geq 4+3$ and/or $\geq pT3$) in a prospectively enrolled cohort.
METHODS	Between July 2014 and September 2015, 1200 men with very low-, low-, and favorable intermediate-risk prostate cancer enrolled in a multi-institutional prospective study of the GPS assay (NCT03502213). The subset who proceeded to immediate radical prostatectomy (RP) after GPS testing was included in a prespecified subanalysis of GPS on biopsy and its association with surgical AP on RP using logistic regression and receiver operating characteristic curves. The effect of GPS testing on physicians' and patients' attitudes about decision making was assessed with the Decisional Conflict Scale.
RESULTS	One hundred fourteen patients (treated by 59 physicians from 19 sites) elected RP and 40 (35%) had AP. GPS result was a significant predictor of AP (odds ratio per 20 GPS units [OR/20 units]: 2.2; 95% CI 1.2-4.1; $P = .008$) in univariable analysis and remained significant after adjustment for biopsy Gleason score, clinical T-stage, and logPSA (OR/20 units: 1.9; 95% CI 1.0-3.8; $P = .04$), or NCCN risk group (OR/20 units: 2.0; 95% CI 1.1-3.7; $P = .02$). Mean pre-GPS Decisional Conflict Scale score was 27 (95% CI 24-31), which improved significantly after GPS testing to 14 (95% CI 11-17) ($P < .001$).
CONCLUSION	In this real-world multi-institutional study, the GPS assay was prospectively confirmed as an independent predictor of AP at surgery. GPS testing was associated with reduced patient decisional conflict. UROLOGY 126: 76–82, 2019. © 2019 The Authors. Published by Elsevier Inc.

Selection of the optimal management for clinically localized prostate cancer (PCa) is dependent on accurate risk assessment.¹ Adverse surgical pathology (AP), as defined as pathologic Gleason score (pGS) $\geq 4+3$ and/or $\geq pT3$, has been validated as a strong predictor of disease progression after treatment.^{2,3} Men with

organ-confined, low-grade PCa very rarely progress to metastasis and are unlikely to benefit from definitive treatment.⁴

Accurate assessment of AP risk in low- and intermediate-risk PCa patients is essential in candidate selection for active surveillance (AS). Unfortunately, in some cases there is substantial discordance between biopsy Gleason score (bGS) and final pathologic grade and stage.⁵ A large series indicated 64% of bGS 3+3 patients had pGS 3+3 confirmed at time of radical prostatectomy (RP) while only 50% of bGS 3+4 were confirmed with pGS 3+4 at RP.⁶

These findings underscore the limitations of standard clinical tools for accurate risk assessment in low-risk PCa. Uncertainty regarding diagnostic accuracy undermines confidence and may prompt men with low-risk, potentially indolent cancers to proceed to definitive treatment with radiation and/or surgery. The potential for overtreatment is particularly high in men with bGS 3+3=6; it is also potentially high in bGS 3+4=7, as approximately 25% may be downgraded at surgery.⁶ PCa treatment

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carries significant cost and risk,^{7,8} and thus establishing a means to identify and treat only men who are most likely to benefit is a long-standing goal in PCa management.

In recent years, traditional tools for PCa risk grouping have been augmented by tissue-based molecular assays that are increasingly recognized by guidelines including the National Comprehensive Cancer Network (NCCN).^{1,9} These tests provide additional information that, in conjunction with clinical and pathologic parameters, can improve risk estimation and subsequent management recommendations.⁹ The Oncotype DX Genomic Prostate Score (GPS, Redwood City, CA) test is a 17-gene RT-PCR-based genomic assay validated as an independent predictor of AP, as well as time to biochemical recurrence (BCR), metastases, and PCa-specific mortality (PCSM) within 10 years using archived samples from men treated with RP.¹⁰⁻¹³ Use of the GPS assay has been demonstrated to individualize risk estimates, enhance physician confidence,¹⁴ and increase utilization of AS in contemporary PCa patients.¹⁵⁻²⁰

Here, we describe a prospective clinical validation study and utility analysis of the GPS assay in a cohort of men from a multi-institutional study who received the test and elected immediate RP.

MATERIAL AND METHODS

Study Design

The protocol was approved by the Institutional Review Board at all sites, and data were locked prior to analysis. Our prespecified objectives were to (1) prospectively evaluate the association of GPS testing with AP in the pathologic specimen in men with very low-, low-, and favorable intermediate-risk prostate cancer who elected RP and (2) understand the perceived value of the GPS test on physician and patient treatment decisions. A subset analysis of the GPS assay as a predictor of AP was also conducted in the NCCN intermediate-risk subset and also in the subset of patients who met criteria for NCCN favorable intermediate-risk disease according to the 2017 NCCN definitions.²¹ Favorable intermediate-risk patients were men with <50% of cores positive and a single intermediate-risk factor: (1) Gleason Grade Group (GGG) 2 (i.e., bGS 3+4), (2) PSA 10-20 ng/mL, or (3) cT2_{b-c}. An analysis of the study participants who did not elect RP as initial management is not included in this report.

At initial visit, eligible patients were offered study participation and a GPS assay was ordered. Written informed consent was obtained from all participants. Patients were informed of management options per practice standard, provided decision aids, and an assessment of decisional conflict was collected. A personalized estimation of AP risk derived from the GPS test and clinical factors was discussed at the second visit. At a third visit, a PCa management decision was made and recorded. For patients who elected RP, surgical pathology details were collected.

Physician and patient perceived utility of the GPS assay were measured with a 7 point-Likert scale. Responses of "somewhat helpful/more confident," "helpful/more confident," and "very helpful/much more confident" were treated as positive for test utility/increased confidence. Patient decisional conflict was measured before and after GPS testing using the Decisional Conflict Scale (DCS).²² The DCS is a validated survey that measures: (1) uncertainty about treatment options; (2) factors that drive uncertainty

(e.g. feeling uninformed, lack of clarity on personal values, feeling unsupported in decision making); and (3) effective decision making. Low decisional conflict is defined as a DCS score of 25 or less on a 0-100 point scale.²² The change in the proportion of patients with low decisional conflict pre- and post-GPS test was assessed using McNemar's test.

Site Selection and Patient Eligibility

Physicians were selected for participation if they practiced at a center with experience in AS and annually managed at least 25 newly diagnosed PCa patients with NCCN very low-, low-, or intermediate-risk disease. All participating physicians were provided information about the GPS test.

Study enrollment was initiated in July 2014 and completed in September 2015; target enrollment was 1200 men from US community-based urology practices, with no investigator contributing more than 50 patients. This report analyzes patients who incorporated GPS results into their shared management decision, elected RP, and had all relevant data available for the primary aim of this analysis. Patient inclusion and exclusion criteria are summarized in Table S1. Biopsy specimens were reviewed by board-certified GHI pathologists prior to tissue processing as per standard protocol. The RP specimens were not centrally reviewed.

Data Capture and Statistical Methods

The clinical data, including the local assessment of Gleason score and pathologic stage, were captured using the Electronic Data Capture system eClinicalOS, compliant with 21CFR11. AP was defined as high-grade (primary Gleason pattern 4 or any pattern 5) and/or non-organ-confined disease (\geq pT3 or nodal involvement at RP). Analyses were conducted based on a prespecified statistical plan including univariable and multivariable logistic regression models to evaluate the association of AP with GPS result and other clinical and pathologic variables; for analyses including PSA, the logarithmic value of PSA (logPSA) was used. As with previous studies, the GPS result was treated as a continuous variable and odds ratios (ORs) for the GPS result were calculated per 20 units. A *P* value <.05 was considered significant based on a likelihood ratio test. Area under the curve (AUC) for the receiver operating characteristic (ROC) were calculated based on the logistic regression models.²³ We used the nonparametric method described by DeLong, DeLong, and Clark-Pearson²⁴ to compare the areas under the ROC curves. Descriptive analyses were used to report demographics and clinicopathologic characteristics. The difference between the pre- and post-GPS result for the DCS was assessed using the Wilcoxon signed-rank test. Analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Overall, 1200 patients were enrolled from 26 centers. Of these men, 143 elected immediate RP. Median time from diagnostic biopsy to surgery was 3.3 months (IQR 2.6-4.4 months). Of men who elected RP, 114 (treated by 59 physicians from 19 sites) had surgical pathology and all other relevant data for the primary analysis (Fig. 1). Compared to men from the overall cohort, the 114 evaluable patients tended to have higher Gleason score, clinical stage, NCCN risk group, and median GPS result. Other

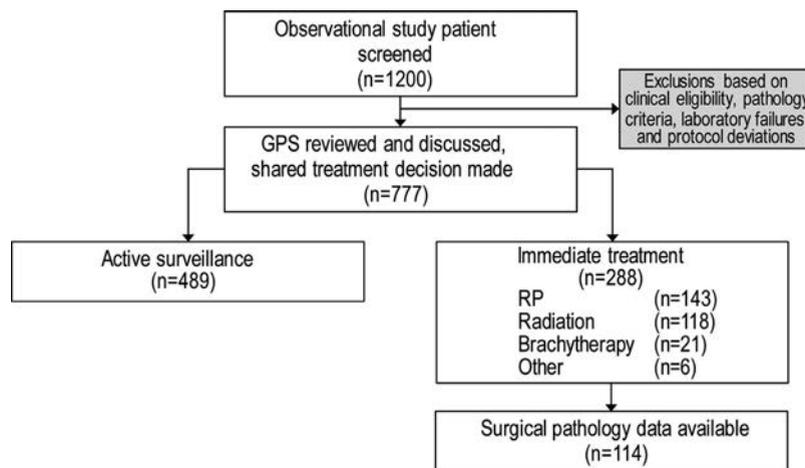


Figure 1. Consort diagram depicting patient disposition in this study.

demographic and clinical characteristics (Table 1) were similar to those of the overall cohort of patients who did not elect RP (i.e., patients who opted for surveillance or an alternate definitive treatment). Median age was 63 (range 50-79) with 62% of men younger than 65 years; 49% had biopsy Gleason score 3+4, and 58% had NCCN intermediate-risk disease. Mean (SD) and median (range) GPS results were 31 (13.8) and 30 (8-82), respectively. There was a broad range of GPS results within each NCCN risk group (Fig. 2A).

Prospective Validation of Adverse Pathology at Radical Prostatectomy

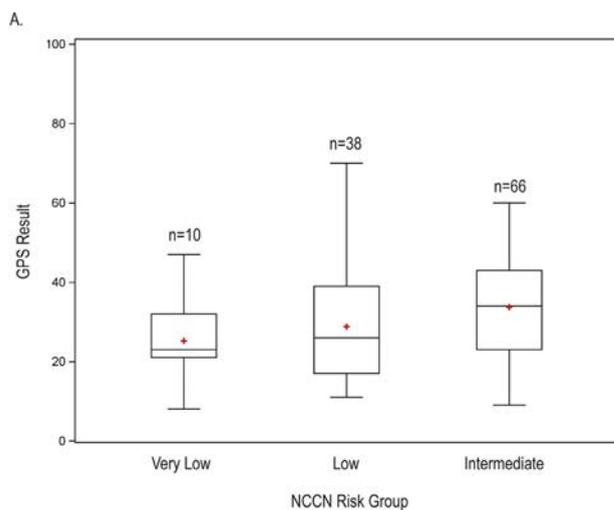
Forty (35%) patients had AP at RP. Specifically, AP was present in 1 in 10 (10%) men with NCCN very low-risk

disease, 11 in 38 (29%) with low-risk disease, and 28 in 66 (42%) with intermediate-risk disease (Fig. 2B). In the univariable analysis, GPS result was a significant predictor of AP (OR/20 units: 2.2; 95% CI 1.2-4.1; $P = .008$) as was biopsy Gleason score and NCCN clinical risk group (Table 2). The GPS result remained a significant predictor of AP after adjusting for biopsy Gleason score, logPSA and clinical T-stage (OR/20 units: 1.9; 95% CI 1.0-3.8; $P = .041$) or adjusting for NCCN risk group (OR/20 units: 2.0; 95% CI 1.1-3.7; $P = .024$; Table 3). The average predicted risk of AP by NCCN risk group and GPS result (range 0-82), based on the multivariable results, was 5.9% (GPS 0-19), 11.2% (GPS 20-40), and 27.5% (GPS 41-82) among very low-risk patients; 16.9% (GPS 0-19), 29.0% (GPS 20-40), and 54.1% (GPS 41-82) among

Table 1. Patient demographic and clinical characteristics

		RP Cohort (n = 114)	Non-RP Patients (n = 634)
Age	Median (IQR)	63 (58-66)	65 (60-70)
	Range (min, max)	50-79	50-86
	<65	71 (62%)	284 (45%)
	≥65	43 (38%)	350 (55%)
Ethnicity	Hispanic or Latino	7 (6%)	23 (4%)
	Not Hispanic or Latino	107 (94%)	610 (96%)
Race	White	107 (94%)	547 (87%)
	Black or African American	5 (4%)	76 (12%)
	Asian	1 (1%)	6 (1%)
	American Indian or Alaska Native	1 (1%)	2 (<1%)
PSA (ng/mL)	0 to <4 ng/mL	19 (17%)	117 (18%)
	4 to <10 ng/mL	79 (69%)	460 (73%)
	10-20 ng/mL	16 (14%)	57 (9%)
Biopsy Gleason Score	3+3	58 (51%)	523 (82%)
	3+4	56 (49%)	111 (18%)
Clinical T-stage	T1c	88 (77%)	546 (86%)
	T2a	23 (20%)	79 (12%)
	T2b	2 (2%)	6 (1%)
	T2c	1 (1%)	3 (<1%)
NCCN risk group	Very low	10 (9%)	169 (27%)
	Low	38 (33%)	315 (50%)
	Intermediate	66 (58%)	150 (24%)

Percentages are column percent within each clinical feature. The 29 patients who underwent RP but did not have surgical pathology data available are not included in this table.



B.

	Very Low	Low	Intermediate
Adverse Pathology	1 (10%)	11 (29%)	28 (42%)
Favorable Pathology	9 (90%)	27 (71%)	38 (58%)

Figure 2. A. GPS result distribution by NCCN risk groups. The outer edges of the boxes define the first and third quartiles. The whiskers are 1.5 times the IQR \pm quartiles. The line in the middle represents the median and the red cross represents group mean. B. Percentage of patients with favorable or adverse pathology per NCCN risk group. (Color version available online.)

low-risk patients; and 24.4% (GPS 0-19), 39.2% (GPS 20-40), and 64.7% (GPS 41-82) among intermediate-risk patients (Table S2).

Furthermore, in a subset analysis, the GPS assay was a significant and independent predictor of AP at RP after adjusting for biopsy Gleason score, clinical T stage and logPSA within the NCCN intermediate-risk subset (OR/20 units: 3.0; 95% CI 1.2-8.1; $P = .014$) and the favorable intermediate-risk group (OR/20 units: 3.9; 95% CI 1.5-12.8; $P = .006$; Table 3).

To determine the relative contribution of the GPS result to the accurate prediction of AP, ROC analysis was performed. The AUC for CAPRA score alone was 0.633,

which increased to 0.726 for GPS and CAPRA score ($P = .039$). The AUC for NCCN alone in prediction of AP was 0.605; the AUC increased to 0.675 with the addition of the GPS result ($P = .114$).

In order to assess the relative contribution of the GPS result to the prediction of AP for the intermediate NCCN risk group, a model including the clinical components of NCCN criteria (bGS, clinical stage, and logPSA) was developed. Within the NCCN intermediate-risk subset ($n = 66$), the baseline AUC with clinical factors was 0.668 and increased to 0.760 with inclusion of GPS result ($P = .061$).

Clinical Utility of GPS Assay

Physicians reported GPS testing useful and a source of increased confidence in 90% of cases, while GPS testing was reported as useful for decision making by 90% of patients. Mean patient decisional conflict was 27 (95% CI: 24-31) prior to GPS testing and 14 (95% CI: 11-17) after GPS testing ($P < .001$). Using the previously validated threshold of DCS <25 to indicate low decisional conflict, 42% of men had low decisional conflict before GPS testing. After GPS testing and physician-patient shared decision making, 68% of men reported low decisional conflict ($P < .001$).

COMMENT

Among geographically diverse large community practices, we prospectively validated the GPS assay as an independent predictor of AP at RP, a clinically meaningful measure of outcome, in newly diagnosed low- and intermediate-risk PCa patients. This finding mirrors prior validations that employed a prospective-retrospective design²⁵ (prespecified prospective study design with archived samples) in academic and military healthcare systems,^{11,12} and demonstrates that GPS testing provides prognostic information that substantially and consistently improves on the diagnostic accuracy of clinical parameters alone. GPS testing also increased physician confidence and decreased decision conflict in patients who elected RP as initial management.

The Prostate Cancer Intervention vs Observation Trial and the Prostate Cancer for Testing and Treatment (Protect) trial both demonstrated 10-year PCSM does not differ significantly between clinically low-risk men managed conservatively or receiving definitive treatment.^{26,27} However, treatment-related morbidities including urinary incontinence and erectile and sexual dysfunction were each significantly greater with surgery compared to observation at 10 years.²⁷ Taken together, these data suggest that increasing AS among low-risk men will improve quality of life without negatively impacting longitudinal outcomes.

Based on the collective body of evidence, numerous practice guidelines support AS as a recommended management strategy for the majority of men with very low- and low-risk PCa.^{1,4,28,29} In 2016, the NCCN expanded the

Table 2. Univariable analyses of GPS result and clinical/pathology covariates for prediction of adverse pathology (AP) at RP in NCCN risk groups ($n = 114$)

Model	Variable	Odds Ratio (95% CI)	P Value
1	GPS (per 20 units)	2.2 (1.2, 4.1)	.008
2	Biopsy Gleason 3+4 vs 3+3	3.2 (1.5, 7.4)	.004
3	Clinical T-stage (T2 vs T1)	1.2 (0.5, 3.0)	.683
4	Age (continuous)	1.0 (1.0, 1.1)	.615
5	PSA (log)	1.2 (0.6, 2.6)	.541
6	NCCN risk group		
	Low vs very low	3.7 (0.6, 71.7)	.185
	Intermediate vs very low	6.6 (1.1, 125.9)	.032

Table 3. Multivariable analyses of GPS result and clinical/pathology covariates for prediction of adverse pathology (AP) at RP

Model	Subgroup	Effect	Odds Ratio	95% CI	P Value
1	All RP patients (n = 114)	GPS by 20 units	1.9	(1.0, 3.8)	.041
		Biopsy GS 3+4 vs 3+3	2.7	(1.2, 6.4)	.021
		PSA (log)	1.2	(0.6, 2.7)	.654
		Clinical T-stage T2 vs T1	1.1	(0.4, 3.0)	.911
2	All RP patients (n = 114)	GPS by 20 units	2.0	(1.1, 3.7)	.024
		NCCN risk group low vs very low	3.3	(0.5, 64.3)	.241
		NCCN Intermediate vs very low	5.2	(0.9, 99.0)	.076
3	NCCN intermediate (n = 66)	GPS by 20 units	3.0	(1.2, 8.1)	.014
		Biopsy GS 3+4 vs 3+3	14.9	(2.0, 320.8)	.006
		PSA (log)	3.3	(1.0, 12.3)	.054
		Clinical T-stage T2 vs T1	1.0	(0.2, 4.3)	.991
4	NCCN favorable intermediate (n = 56)	GPS by 20 units	3.9	(1.5, 12.8)	.006
		Biopsy GS 3+4 vs 3+3	6.4	(0.6, 161.9)	.135
		PSA (log)	1.3	(0.2, 8.5)	.799
		Clinical T-stage T2 vs T1	0.5	(0.1, 2.9)	.438

AS-eligible pool to include men with favorable intermediate-risk disease, defined as bGS \leq 3+4 or less with 1 intermediate-risk factor and fewer than 50% of biopsy cores positive.²¹ Despite the inclusion of AS in guidelines and demonstrated improvements in quality of life with AS, AS uptake has been met with challenges.^{30,31} Physicians lack confidence in traditional risk stratification approaches (e.g., PSA testing, systematic 12-core biopsies) and have looked to both genomic testing and imaging for refinement. To this end, the NCCN has included consideration of genomic testing for men with low- or favorable intermediate-risk PCa and a >10-year life expectancy.¹

Adverse pathology is a surrogate marker of PCa aggressiveness and has been shown to be a strong predictor of disease progression, including BCR and 15-year PCSM after RP.^{2,3} Predictions of AP augmented by biopsy-based genomic profiling or MRI are used to determine whether to treat and how extensively; patients with predicted risk of AP (pGS \geq 4+3 and/or \geq pT3) are known to be at higher risk for adverse outcomes and would not typically be candidates for AS, whereas patients with predicted favorable pathology are generally considered AS-eligible. Previous studies validated the GPS assay for prediction of AP, BCR, metastases, and PCSM within 10 years among low- and intermediate-risk men using archived samples,¹⁰⁻¹³ and thus a major strength of the current study is the validation of GPS for AP in a prospectively enrolled contemporary cohort of men. As part of the study, we demonstrated the capacity of the GPS assay to enhance prediction of AP among men with intermediate-risk disease, suggesting the assay may be particularly useful for AS selection in this patient subset. These findings in combination with extensive data showing AS is pursued more often when GPS testing is incorporated into the decision-making process, provide utility for the GPS assay in routine practice and align with guideline-based care.^{1,16-20}

To gain a better understanding of how incorporation of the GPS assay leads to higher rates of AS, we assessed the effect of GPS testing on physicians' and patients' attitudes

about decision making. We report that patient decisional conflict, as measured by the DCS, significantly declined after receiving GPS testing, suggesting that genomic testing not only helped predict an individual's likelihood of having AP, but also gave patients greater certainty about their chosen management strategy and empowered them to make effective choices regarding their care. We also report that physicians found GPS testing useful and a source of increased confidence in 90% of cases, findings that build on previous data.¹⁴ Taken together, these data suggest that both patients and doctors perceive GPS testing as a value-added component of their decision-making process and indicate GPS testing may increase satisfaction regarding the care men with PCa receive.

The data presented here are not without limitations. RP was performed by 59 surgeons from 19 centers and providers were not coached on how to address PCa decision making in a uniform fashion. In addition, biopsy and prostatectomy specimens were evaluated locally without central review. While the lack of standardization across sites introduces the potential for site-specific variation and interobserver variability in grading/staging, the fact that these results are derived from diverse practices may increase the external validity and relevance of our findings for routine use of GPS testing in practice. Although there were only 40 AP events, there was a strong and significant association between the GPS result and AP and it is unlikely additional data points would have substantively modified the result. This study did not include patients managed with initial AS or radiation therapy; assessments of the GPS assay in men managed with initial AS or radiation therapy are ongoing.³²

Despite these limitations, this prospective analysis highlights the added value of GPS testing for prediction of AP in a contemporary, AS-eligible PCa cohort. The added potential for genomic testing to inform management decisions may help to increase the pool of men who are eligible and appropriate for AS, while identifying men with more aggressive disease who may consider definitive treatment.

CONCLUSION

For men diagnosed with very low-, low-, or favorable intermediate-risk PCa, the Oncotype DX Genomic Prostate Score assay provides more precise estimates of disease aggressiveness beyond clinical factors. This information helps guide patient and physician discussions on appropriate disease management and improves confidence in decision making.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.11.050>.

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EDITORIAL COMMENT



Accurate pretreatment risk stratification plays a central role in optimizing management decisions for patients with clinically-localized prostate cancer. Nonetheless, the current approach to initial risk stratification is rapidly evolving, as novel tools such as tissue-based genomic assays are introduced.¹ While an ideal biomarker would be highly sensitive, specific, cost-effective, quantifiable, and reproducible, clinical tests often fall short of this standard.² As such, it is critical to establish the situational utility of emerging modalities in order to employ them efficiently and appropriately.

Based on a prospective multi-institutional study of the Oncotype DX Genomic Prostate Score (GPS), the authors report a prespecified subanalysis demonstrating that GPS provides both prognostic information and decisional reassurance to patients with favorable-risk prostate cancer electing surgery. First and foremost, the authors should be commended for their approach to this important question; prospective studies provide the optimal assessment of new clinical biomarkers but remain the exception in this space. At the same time, unanswered questions highlight the difficulty of conducting a truly definitive study of this type. For 1, how do we know that similar improvements in decisional conflict could not have been achieved through the use of free, publicly-available decision aids?³ Furthermore, as the authors acknowledge, the current report does not include men who elected active surveillance. While men electing treatment could be expected to experience some level of relief after simply making this decision, the more pertinent question may be how GPS impacts patients pursuing a less definitive, more anxiety-associated approach such as surveillance.⁴

It is also important to consider the manner in which biomarker data are reported. Odds ratios (OR) are traditionally used to convey the magnitude of associations, but, importantly, can vary greatly based on units and observed clinical range.⁵ While the current study reports an OR of 2.2 per 20 GPS units and a GPS range of 8-82, it is difficult to capture the clinical significance of the OR without a clear illustration of the overall GPS distribution. Furthermore, as illustrated by Pepe et al,⁵ ORs traditionally considered strong in the research setting are not adequate for discriminating between subjects who do and do not

experience the outcome at the individual level. One challenge of prognostic tests that report on a continuum of risk is the lack of a clear, singular threshold that can rule in or out the projected outcome.⁶ Moving forward, it may be useful for authors to additionally report threshold values with very high specificity and sensitivity observed in the study population. Clinical utility in this setting will continue to be challenged by a need to identify such thresholds for reliable, individual-level decision making.

Ultimately, the current study provides important prospective data while also drawing attention to the difficulties inherent to furthering our understanding of prostate cancer biomarkers. Additional studies will help to clarify the optimal clinical scenarios for implementing this test and others in this rapidly-evolving arena.

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