original reports

17-Gene Genomic Prostate Score Test Results in the Canary Prostate Active Surveillance Study (PASS) Cohort

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abstract

PURPOSE The 17-gene Onco*type* DX Genomic Prostate Score (GPS) test predicts adverse pathology (AP) in patients with low-risk prostate cancer treated with immediate surgery. We evaluated the GPS test as a predictor of outcomes in a multicenter active surveillance cohort.

MATERIALS AND METHODS Diagnostic biopsy tissue was obtained from men enrolled at 8 sites in the Canary Prostate Active Surveillance Study. The primary endpoint was AP (Gleason Grade Group [GG] ≥ 3, ≥ pT3a) in men who underwent radical prostatectomy (RP) after initial surveillance. Multivariable regression models for interval-censored data were used to evaluate the association between AP and GPS. Inverse probability of censoring weighting was applied to adjust for informative censoring. Predictiveness curves were used to evaluate how models stratified risk of AP. Association between GPS and time to upgrade on surveillance biopsy was evaluated using Cox proportional hazards models.

RESULTS GPS results were obtained for 432 men (median follow-up, 4.6 years); 101 underwent RP after a median 2.1 years of surveillance, and 52 had AP. A total of 167 men (39%) upgraded at a subsequent biopsy. GPS was significantly associated with AP when adjusted for diagnostic GG (hazards ratio [HR]/5 GPS units, 1.18; 95% CI, 1.04 to 1.44; $P = .030$), but not when also adjusted for prostate-specific antigen density (PSAD; HR, 1.85; 95% CI, 0.99 to 4.19; $P = .066$). Models containing PSAD and GG, or PSAD, GG, and GPS may stratify risk better than a model with GPS and GG. No association was observed between GPS and subsequent biopsy upgrade ($P = .48$).

CONCLUSION In our study, the independent association of GPS with AP after initial active surveillance was not statistically significant, and there was no association with upgrading in surveillance biopsy. Adding GPS to a model containing PSAD and diagnostic GG did not significantly improve stratification of risk for AP over the clinical variables alone.

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INTRODUCTION

Active surveillance (AS) is recognized as the preferred management strategy for men diagnosed with low-risk prostate cancer (PCa).[1] However, widespread adoption of AS has been tempered,[2,3] in part, because of uncertainty about the possibility of occult aggressive cancer. There also may be a small but significant number of men with apparent low-risk disease who experience disease progression during monitoring who might benefit from immediate treatment.[4] Additionally, optimal surveillance schedules and triggers for intervention have not yet been established,[5] resulting in substantial variation in the practice of AS.[6] Biomarkers that improve stratification of risk for harboring or progressing to high-grade, high-stage PCa could improve both the use and practice of AS.

The biopsy-based 17-gene Onco*type* DX Genomic Prostate Score (GPS; Genomic Health, Redwood City, CA) test has been shown to predict adverse surgical pathology and recurrence in men diagnosed with low- and intermediate-risk PCa treated with immediate surgery.[7-10] It has been used as a tool to inform the decision making of immediate treatment versus AS in men newly diagnosed with low- or favorable intermediate-risk PCa and was recently included in National Comprehensive Cancer Network (NCCN) guidelines.[11] However, studies of the predictive value of the GPS test in men initially managed with AS have been limited.

In the current study, we used a multicenter AS cohort to examine the association of GPS results with outcomes relevant to AS. We examined the association of GPS with adverse pathology (AP) in men who had surgery after initial management with AS. We also evaluated whether GPS was associated with upgrading at surveillance biopsy. Importantly, we assessed the association of GPS with adverse outcome when

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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adjusted for commonly available clinical variables. We used a prospective-retrospective study design[12] to evaluate GPS at initial diagnosis as part of the Canary Prostate Active Surveillance Study (PASS).

MATERIALS AND METHODS

Canary PASS (ClinicalTrials.gov identifier: NCT00756665) is a prospective cohort enrolling men eligible for AS who provide informed consent under institutional review board supervision.[13,14] In PASS, prostate-specific antigen (PSA) is measured every 3 months, clinic visits occur every 6 months, and ultrasound-guided biopsies are performed 6-12 and 24 months after diagnosis, then every 2 years; 76% of the biopsies were per protocol.[15] Other tests, including magnetic resonance imaging (MRI), are performed at the clinician's discretion. For the current study, tissue blocks from the initial diagnostic biopsy were collected from men enrolled between 2008 and 2016 at 8 PASS sites (Beth Israel Deaconess Medical Center, Eastern Virginia Medical School, Stanford University, University of British Columbia, University of Michigan, University of Texas Health Sciences Center San Antonio, University of Washington, Veterans Affairs Puget Sound Health Care Systems). Participants were excluded if they received treatment within 6 months of diagnosis, diagnostic PSA $>$ 20 ng/mL, $<$ 6 cores in the diagnostic biopsy, or Gleason Grade Group (GG) $\geq$ 3 on central pathology review of the diagnostic biopsy.

Pathology and Assay Methods

Fixed paraffin-embedded biopsy tissue from initial diagnosis was collected. Hematoxylin and eosin–stained slides from radical prostatectomies (RPs) and recuts of the diagnostic biopsy tissue were centrally reviewed by 1 uropathologist (J.K.M.) blinded to clinical outcomes and using the 2016 International Society of Urologic Pathology Consensus guidelines.[16] Local pathology data were used for surveillance biopsies. Unstained biopsy tissue sections were manually microdissected, and the GPS assay was performed at Genomic Health Laboratory as previously described.[7,17] GPS testing was performed retrospectively, and treating physicians were blinded to the GPS results.

Statistical Analysis

The statistical analyses were delineated in a prespecified statistical analysis plan. The primary objective of this study was to evaluate the association between the GPS result and AP in the subset of AS patients who underwent RP after a period of surveillance, after adjusting for diagnostic GG. AP was defined as Gleason GG $\geq$ 3 and/or $\geq$ pT3a and/or N1. Key secondary objectives were to (1) evaluate the association between GPS and AP after adjusting for important clinical and pathologic features and (2) evaluate the association between GPS and reclassification, or upgrading, on surveillance biopsy. Reclassification was defined as any increase in biopsy GG from the diagnostic GG; major upgrading was defined as an increase to GG $\geq$ 3. Follow-up clinical data were collected through February 2018. Other covariables considered in modeling were age (continuous or $>$ 65 *v* $\leq$ 65 years), race (nonwhite *v* white), diagnostic Gleason GG (1 or 2), ratio of positive/total biopsy cores, log (PSA), log (prostate size) or $\log_2$ PSA density (PSAD), cT stage, body mass index (BMI; kg/m^2), family history of PCa (yes/no), and year of diagnosis.

GPS and AP at RP after period of surveillance. The association between GPS and AP was assessed in the 101 participants who had RP. Time to AP was interval censored between diagnosis and time of RP if AP was observed on RP or right censored at time of RP if AP was not observed. Parametric survival models for interval-censored data with Weibull distribution were used, with inverse probability of censoring weighting applied to adjust for informative censoring[18] (Data Supplement). Variance estimation was based on 1,000 bootstrap replications drawn before data lock. Hazard ratios (HRs) were estimated from the fitted Weibull distribution parameters and reported for continuous GPS per 20-unit and 5-unit increase, which is approximately the difference between the median and first quartile. CIs were derived using the bootstrap quantile method. An individual's estimated risk of AP within 2 years given GPS and/or other factors was calculated based on the fitted risk models. The distribution of risks was shown by the predictiveness curve[19]: the risks were ordered from lowest to highest and their values were plotted. Because of the limited sample size for the primary outcome, we did not further evaluate the discriminatory performance of the prediction model.

GPS and upgrading at surveillance biopsy. The association between GPS at diagnosis and the biopsy reclassification was modeled in the full cohort of 432 participants using Cox proportional hazards models, stratified by enrollment before or after the first surveillance biopsy. Participants without reclassification were censored at date of last study contact, treatment, or 2 years after last biopsy, whichever came first. The proportional hazards assumptions were tested with the Schoenfeld residuals.[20] A 2-sided *P* value $<$ .05 was considered significant for all analyses, which were performed using SAS version 9.4 (SAS Institute, Cary, NC) or R version 3.3.0.

RESULTS

Study Population

Among 1,041 Canary PASS participants using AS, 634 (61%) had available tissue from their diagnostic biopsy (Fig 1). Of these, 7 (1%) did not meet inclusion criteria, 174 (27%) had insufficient residual tumor tissue for GPS testing, 10 (2%) had Gleason GG $\geq$ 3 on central pathology review, and 11 (2%) had insufficient RNA quality, resulting in 432 (68%) with a valid GPS result. Of the 432 with GPS results, 106 (25%) underwent RP; 77 (73%) had RP after biopsy upgrade, and 29 (27%) had surgery with no biopsy

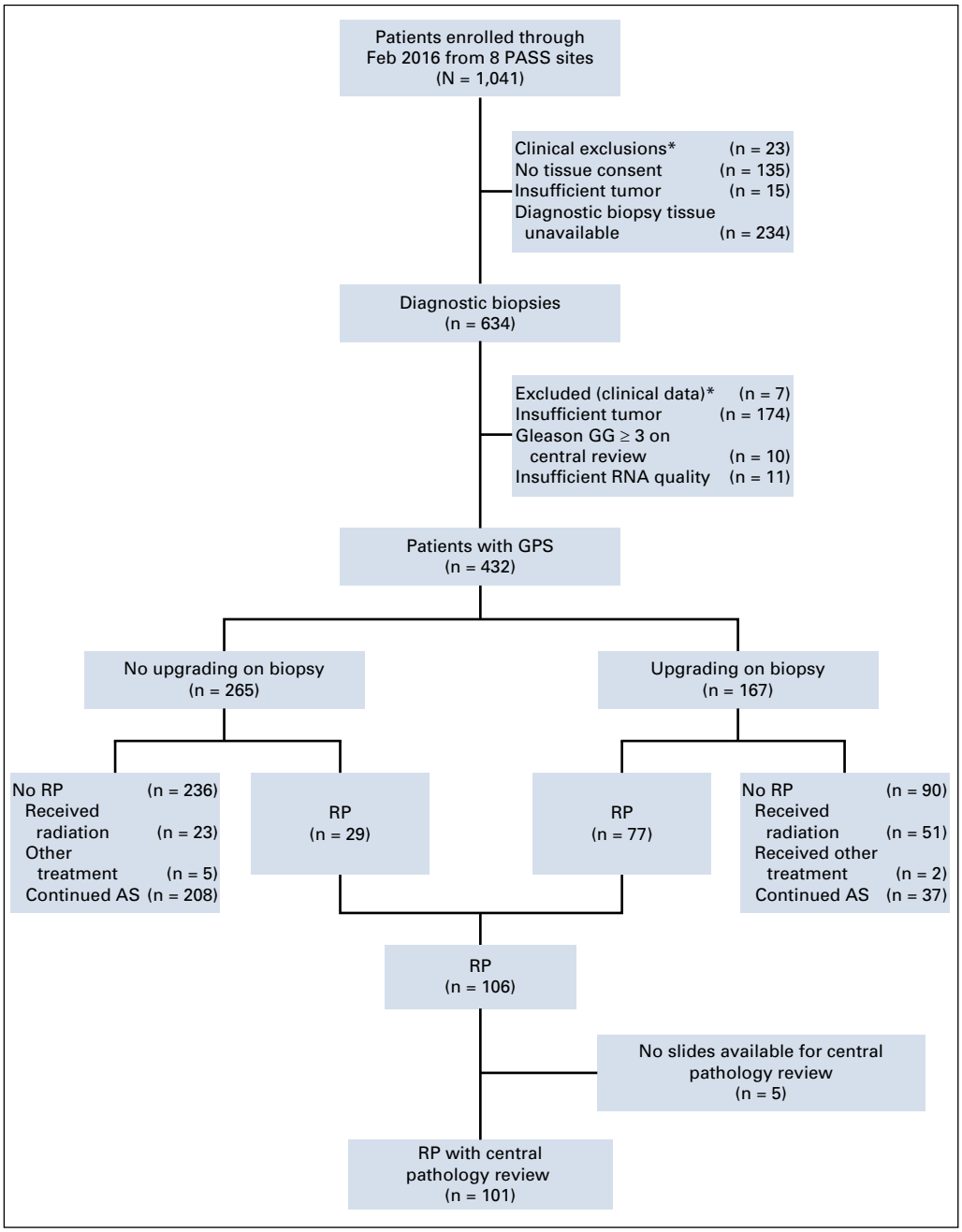

FIG 1. CONSORT diagram detailing the study cohort. (*) Treatment within 6 months of diagnosis; diagnostic prostate-specific antigen > 20 ng/mL; < 6 cores in the diagnostic biopsy. AS, active surveillance; PASS, Prostate Active Surveillance Study; GG, Gleason Grade Group; GPS, Genomic Prostate Score; RP, radical prostatectomy.

upgrade during initial surveillance. After excluding 5 participants with no RP slides available for central pathology review, 101 participants were available for evaluation of the AP endpoint.

Participant characteristics at diagnosis were similar for the 634 participants for which tissue blocks could be obtained and the 432 fully evaluable participants compared with the full Canary PASS (Table 1.) Median follow-up in participants with no reclassification at biopsy was 4.6 years (interquartile range [IQR], 2.9-6.2 years) with 167 (39%) who experienced upgrading at a surveillance biopsy, 51 (12%) to Gleason GG ≥ 3. Median time from diagnosis to surgery was 2.1 years (IQR, 1.3-4.3 years), and 52 men (51%) had AP at surgery with the pathologic features shown in the Data Supplement. Median GPS result in the full cohort (N = 432) was 21 (IQR, 15.4-27.3; range, 0-67) and 20.5 (IQR, 14.6-27.3; range, 6-67) in the RP cohort (n = 101).

TABLE 1. Participant Characteristics at Diagnosis

Characteristic	Enrolled Through Feb 2016 (n = 1,041)	Available FFPE Blocks (n = 634)	With GPS Result (N = 432)	Radical Prostatectomy (n = 101)
GPS result (IQR)	N/A	N/A	21.0 (15.4-27.3)	20.5 (14.6-27.3)
Age, years (IQR)	63 (58-67)	63 (59-67)	63 (59-67)	62 (57-65)
Race				
Asian	25 (2)	18 (3)	12 (3)	5 (5)
Black	74 (7)	36 (6)	24 (6)	5 (5)
Other	11 (1)	8 (1)	6 (1)	0
White	931 (89)	572 (90)	390 (90)	91 (90)
Hispanic ethnicity	42 (4)	28 (4)	19 (4)	3 (3)
BMI (kg/m^2; IQR)	27 (25-30)	27 (25-30)	27 (25-30)	27 (25-30)
Year of diagnosis (IQR)	2011 (2009-2012)	2011 (2009-2013)	2011 (2009-2013)	2011 (2009-2013)
Family history of PCa (first degree)	284 (27)	165 (26)	109 (25)	25 (25)
T-stage				
T1	929 (89)	573 (90)	385 (89)	91 (90)
T2a	103 (10)	56 (9)	42 (10)	10 (10)
T2b	7 (1)	4 (1)	4 (1)	0
T2c	2 (< 1)	1 (< 1)	1 (< 1)	0
Diagnosis biopsy Gleason score[a]				
GG 1	958 (92)	584 (92)	374 (87)	81 (80)
GG 2	77 (7)	46 (7)	58 (13)	20 (20)
GG 3	6 (1)	4 (1)	0	0
Percent of positive biopsy cores (IQR)	8.3 (8.3-16.7)	10.0 (8.3-16.7)	12.5 (8.3-16.7)	16.7 (8.3-21.4)
PSA (ng/mL; IQR)	5.0 (3.8-6.5)	4.9 (3.8-6.6)	4.8 (3.7-6.5)	4.8 (4.1-6.1)
Prostate size (cm^3; IQR)	43 (31-59)	42 (31-58)	40 (31-57)	35 (26-47)
PSA density (ng/cm^3; IQR)	0.11 (0.08-0.16)	0.11 (0.08-0.16)	0.11 (0.08-0.15)	0.14 (0.10-0.19)
NCCN risk group[b]				
Very low	470 (45)	310 (49)	202 (47)	37 (37)
Low	411 (39)	228 (36)	142 (33)	39 (39)
Intermediate	160 (15)	96 (15)	88 (20)	25 (25)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; FFPE, formalin-fixed paraffin-embedded; GG, Gleason Grade Group; GPS, Genomic Prostate Score; IQR, interquartile range; N/A, not available; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PSA, prostate-specific antigen.

[a]Biopsy Gleason score for entire Prostate Active Surveillance Study cohort and available FFPE blocks by clinical site pathology report, and Gleason score of patients with GPS and RP by central review.

[b]NCCN risk group determined for entire Prostate Active Surveillance Study cohort and available FFPE blocks using Gleason score from clinical site review of diagnostic biopsy and for patients with GPS and RP using Gleason score from central review.

AP at RP After a Period of AS

In univariable analysis of the 101 men who had RP, GPS was not significantly associated with AP (HR, 1.14; 95% CI, 1.00 to 1.34; $P = .062$); PSAD was the only variable significantly associated with AP (both log-transformed; $P = .017$; and per 0.1 unit; $P = .025$; Table 2). In bivariable analysis, GPS was significantly associated with AP when adjusted for diagnostic GG (Table 3; HR, 1.18; 95% CI, 1.04 to 1.44; $P = .030$). In multivariable models that included PSAD and diagnostic GG, GPS did not reach statistical significance (HR, 1.17; 95% CI, 1.00 to 1.43; $P = .066$), whereas $\log_2$ PSAD was significantly associated with AP (HR, 1.75; 95% CI, 1.11 to 3.21; $P = .025$). Results were similar in a sensitivity analysis of only those with GG 1 at diagnosis (data not shown).

Models containing PSAD and diagnostic GG, with or without GPS, may stratify risk of AP better than a model with only GG and GPS (Fig 2). For example, given an AP within 2-year

TABLE 2. Univariable HRs for Association of Variables at Diagnosis With AP in Men Who Had Radical Prostatectomy (n = 101) After a Period of Surveillance and Biopsy Upgrade in Men Using AS (N = 432)

Variable	Adverse Pathology HR (95% CI) (n = 101)	*P*	Biopsy Upgrade HR[a] (95% CI) (N = 432)	*P*
GPS (per 5 units)	1.14 (1.00 to 1.34)	.062	1.00 (0.93 to 1.08)	.93
GPS (per 20 units)	1.70 (1.01 to 3.26)	.062	1.02 (0.75 to 1.38)	.93
Age (per year)	1.01 (0.95 to 1.05)	.84	1.00 (0.97 to 1.02)	.70
Age > 65 *v* ≤ 65, years	1.07 (0.49 to 2.16)	.85	0.85 (0.61 to 1.17)	.31
Nonwhite *v* white race	0.94 (0.26 to 2.58)	.98	1.12 (0.68 to 1.85)	.66
Gleason GG 2 *v* 1	0.85 (0.34 to 1.77)	.68	0.70 (0.37 to 1.34)	.29
Percent of positive cores	1.02 (0.99 to 1.05)	.29	1.04 (1.02 to 1.05)	< .001
Log PSA	1.65 (0.79 to 4.29)	.21	1.14 (0.88 to 1.46)	.32
Log prostate size	0.61 (0.24 to 1.45)	.29	0.44 (0.32 to 0.61)	< .001
PSA density (per 0.1 ng/mL^2)	1.69 (1.13 to 3.07)	.025	1.16 (1.08 to 1.25)	< .001
Log_2 PSA density	1.78 (1.14 to 3.11)	.017	1.52 (1.29 to 1.79)	< .001
Clinical stage T2 *v* T1	2.48 (0.92 to 13.80)	.14	0.97 (0.59 to 1.61)	.92
BMI (kg/m^2)	1.05 (0.96 to 1.13)	.24	1.04 (1.00 to 1.07)	.049
Family history of PCa	0.81 (0.38 to 1.59)	.57	1.12 (0.79 to 1.59)	.52
Diagnosis year (per year)	1.09 (0.98 to 1.25)	.15	1.14 (1.05 to 1.24)	.002

Abbreviations: AP, adverse pathology; AS, active surveillance; BMI, body mass index; GG, Gleason Grade Group; GPS, Genomic Prostate Score; HR, hazard ratio; PCa, prostate cancer; PSA, prostate-specific antigen.

[a]Univariable HRs are shown using enrollment before or after the first surveillance biopsy as a stratification variable.

prevalence of 49% in the cohort, if patients with a risk level exceeding 70% are considered as high risk, models with GPS, PSAD, and diagnostic GG or with PSAD and GG put 16% (95% CI, 3% to 31%) and 8% (95% CI, 0% to 30%) of patients, respectively, at or above a threshold of 70% risk of AP within 2 years, whereas GPS adjusted for GG put only 4% (95% CI, 0% to 21%) of patients in the high-risk range.

Upgrading at Surveillance Biopsy

In univariable analysis of the 432 men on AS, GPS was not associated with upgrade at surveillance biopsy (HR, 1.00; 95% CI, 0.93 to 1.08; *P* = .93), whereas % positive biopsy cores, prostate volume, PSAD, BMI, and year of diagnosis were significantly associated with reclassification (Table 2). In a multivariable model including GPS, % positive biopsy cores, PSAD, and year of diagnosis, there was no significant association of GPS with upgrading in the cohort of 432 patients or in a subset including only the 395 men initially diagnosed with GG 1 cancer (adjusted HR, 0.97; 95% CI, 0.90 to 1.05; *P* = .48; or HR, 0.99; 95% CI, 0.92 to 1.07; *P* = .81, respectively; Table 4). Similar results were observed for a sensitivity analysis using an endpoint of major upgrade (to GG ≥ 3) on surveillance biopsy (Data Supplement). No significant departure from the proportional hazards assumption was found.

TABLE 3. Multivariable Models for Adverse Pathology (n = 101)

Variable	HR[a] (95% CI)	*P*
Model 1		
GPS (per 5 units)	1.18 (1.04 to 1.44)	.030
Gleason GG 2 *v* 1	0.62 (0.24 to 1.33)	.26
Model 2		
GPS (per 5 units)	1.17 (1.00 to 1.43)	.066
Gleason GG 2 *v* 1	0.61 (0.24 to 1.24)	.24
Log_2 PSA density	1.75 (1.11 to 3.21)	.025

Abbreviations: GG, Gleason Grade Group; GPS, Genomic Prostate Score; HR, hazard ratio; PSA, prostate-specific antigen.

[a]Log hazard ratio = regression parameter × Weibull shape parameter. CIs calculated using the bootstrap quantile method.

DISCUSSION

In this multicenter AS study, we evaluated the ability of the GPS test, performed on the biopsy tissue from initial diagnosis, to predict AP and biopsy upgrading for men initially managed with AS, and we evaluated the performance of the GPS test in the context of commonly available clinical variables that have been reported to predict outcomes in AS.[14,21-24] We showed GPS was associated with AP when adjusted for diagnostic GG. However, GPS was not significantly associated with AP after adjustment for diagnostic GG and PSAD. Notably, GPS was not associated with biopsy upgrade on subsequent surveillance biopsy.

We recognize that a larger study may result in smaller CIs and a significant independent association of GPS with AP, although we also anticipate that clinical parameters, such

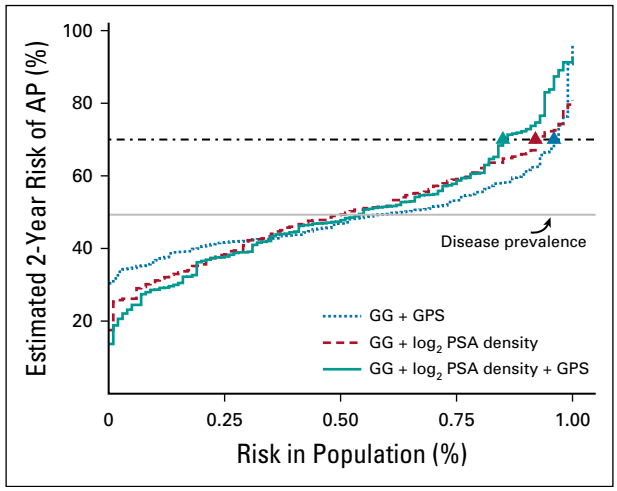

FIG 2. Predictiveness curves for risk of adverse pathology (AP) at 2 years, in which the cumulative percentage of the cohort at risk is plotted against the risk estimated from models. The solid gray line shows the prevalence of AP. The dashed black line shows a risk threshold of ≥ 70% for high risk of AP with triangles at the percent of the population stratified as high risk at that threshold. For well-calibrated models, the model with a curve further away from the prevalence line may be helpful for more individuals in making an unequivocal decision on active surveillance (AS). GG, Gleason Grade Group; GPS, Genomic Prostate Score; PSA, prostate-specific antigen.

as PSAD, would continue to significantly improve the predication of AP in modeling. Indeed, a single-center study was recently performed in which the association of GPS with AP was evaluated in 215 patients who were initially managed with AS.[25] In this study, GPS was an independent predictor of AP, with a statistically significant HR that was similar to our present report. However, that single-center study not only combined GPS results from a research study that included central pathology review with GPS results from routine clinical practice, but also used GPS test results from either diagnostic biopsy samples or subsequent surveillance biopsies. Notably, strong predictors of AP were study group (ie, research study *v* clinical care samples) and whether the test was performed on diagnostic versus subsequent surveillance biopsy tissue, suggesting that caution be exercised when interpreting their results because of potential bias introduced in study design.

GPS has been shown to be an independent predictor of AP and biochemical recurrence in patients with low- and intermediate-risk PCa who were treated with immediate surgery.[7,8] The test is covered by Medicare, and guidelines state that molecular tests such as the GPS assay may be considered in men with localized disease as a decision aid for patients considering immediate treatment versus AS.[11] To our knowledge, this is the first study to address performance of the GPS test in a prospectively accrued AS cohort in which all available residual tissue from the initial diagnostic biopsy was collected, with endpoints that included both AP at surgery and upgrading on surveillance biopsy, the latter of which is arguably the most actionable endpoint in management of AS patients. Importantly, the characteristics of the participants with available tissue at diagnosis were similar to those in the full PASS cohort, suggesting a representative set was used for the present analyses.

We addressed the potential clinical utility of the GPS test using predictiveness curves.[19] Risk models that included PSAD and diagnostic GG, or PSAD, GG, and GPS stratified more men as being at high risk for having AP than a model with only GPS and GG, suggesting that the GPS test, or any molecular diagnostic, should be used in combination with other clinical variables, such as PSAD. Our study is one of the first to consider GPS in the context of PSAD or prostate volume, which are only incorporated in the commonly used NCCN guidelines as part of the definition of very low risk. Although our study was not designed to address clinical utility, our results do suggest that risk models including PSAD and other clinical variables may stratify patients at high risk for AP better than GPS alone.

There is no indication that GPS is associated with upgrading or major upgrading on surveillance biopsy. It is possible that GPS detects tumor biology associated with substantially more aggressive disease but does not detect minor changes in Gleason score (eg, GG1 to GG2). Furthermore, undersampling of prostate biopsy is well established, with significantly more upgrading than downgrading at RP (Data Supplement), and GPS may have an association with major upgrading at surgery. Our findings contrast with recently published single-center results in which GPS tests performed in the setting of clinical practice were shown to have a significant association with biopsy upgrade.[26] However,

TABLE 4. Multivariable Analysis for Biopsy Upgrade

Variable	Full Cohort (No. of events, 167 of 432) HR (95% CI)	*P*	Diagnosis With Gleason 6 (No. of events, 157 of 395) HR (95% CI)	*P*
GPS (per 5 units)	0.97 (0.90 to 1.05)	.48	0.99 (0.92 to 1.07)	.81
Log_2 PSA density	1.44 (1.21 to 1.71)	< .001	1.45 (1.21 to 1.72)	< .001
Percent of positive cores	1.03 (1.02 to 1.04)	< .001	1.04 (1.02 to 1.05)	< .001
Year of diagnosis	1.13 (1.04 to 1.23)	.003	1.11 (1.03 to 1.21)	.010

Abbreviations: GPS, Genomic Prostate Score; HR, hazard ratio; PSA, prostate-specific antigen.

data from that single institution were retrospectively abstracted from clinical records, the GPS tests were performed on diagnostic and surveillance biopsies within 5 years of diagnosis from patients who were chosen at the treating provider's discretion, and the intensity of monitoring could have been tailored to clinical characteristics, including the knowledge of the GPS result, all of which may introduce selection and ascertainment bias.

Strengths of this study include that it used a prospective-retrospective design in a multicenter AS cohort with a defined surveillance protocol using tissue from original diagnostic biopsy tissue, a design that eliminates many potential sources of bias. Central pathology review was performed on all the diagnostic biopsies and RP tissues for the primary endpoint. Additionally, statistical modeling included all clinical and pathologic factors that are readily available in routine patient care. There are, however, limitations to this study that should be noted. First, the sample size for the AP endpoint was small. The study was designed with a higher number of AP events, but was limited in part because of the higher than expected rate of patients with insufficient tumor for molecular testing, likely due to smaller volume tumors in men on AS compared with men undergoing immediate prostatectomy. We focused on studying associations, given the smaller than anticipated sample size. Second, this study does not address the discriminatory performance of prediction models including GPS or validate the use of GPS testing in clinical care. Such validation would require an independent cohort, with likely a much larger sample size than the current study, in which GPS is found to be statistically significant in a multivariable model with other significant clinical and pathologic covariables, and performance of models with and without GPS can be compared. Third, MRI imaging was variably performed in this cohort, primarily because many patients entered the study before widescale multiparametric MRI use. Approximately 28% of the cohort described here had undergone MRI imaging, with a similar distribution of use between those who reclassified by biopsy and those who did not. An analysis of MRI in PASS is forthcoming and consistent with publications that report modest sensitivity and applicability of MRI in AS.[27,28] Fourth, PCa is known to be heterogeneous, and any biopsy-based test may not adequately sample all tumors.[29]

Despite these limitations, our findings have important implications for the use of tissue-based molecular markers for risk assessment in early-stage PCa. First, multiple clinical and pathologic features are known to contribute to the prediction of outcomes in men managed with AS, and together, provide a robust base model. For a new molecular marker to be clinically useful in this setting, it should add significant predictive power to these clinicopathologic models. Specifically, no factor can or should be used in isolation and should instead be used within the context of a risk model or tool that encompasses all known clinical and pathologic parameters. Second, low-volume disease in typical AS patients and insufficient RNA for molecular analyses in the current study represent a potential limitation of tissue-based genomic assays in this population. Third, our study was not designed to address optimal use of GPS or variables in clinical practice, and additional studies are needed to evaluate the incremental value of GPS relative to other factors for clinical utility in risk stratification and in cost-benefit calculations.

In conclusion, this multicenter cohort of men using AS, GPS was significantly associated with AP when adjusted for diagnostic GG, but not when adjusted for GG and PSAD. Adding GPS to a model containing PSAD and diagnostic GG did not significantly improve stratification of risk for AP over the clinical variables alone. GPS was not associated with upgrading in surveillance biopsies during AS, and previously described clinical variables (PSAD and % positive biopsy cores) remained significantly associated with upgrading.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

17-Gene Genomic Prostate Score Test Results in the Canary Prostate Active Surveillance Study (PASS) Cohort

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