Prostate Cancer

A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer

Jennifer Cullena,*, Inger L. Rosnerb, Timothy C. Brandc, Nan Zhangd, Athanasios C. Tsiatisd, Joel Moncurb, Amina Ali, Yongmei Chena, Dejan Knezevicd, Tara Maddalad, H. Jeffrey Lawrence, Phillip G. Febbo, Shiv Srivastava, Isabell A. Sesterhenn, David G. McLeod

a Center for Prostate Disease Research, Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD, USA; b Walter Reed National Military Medical Center, Bethesda, MD, USA; c Madigan Army Medical Center, Tacoma, WA, USA; d Genomic Health, Inc., Redwood City, CA, USA; e Joint Pathology Center, Silver Spring, MD, USA

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Abstract

Background: Biomarkers that are validated in independent cohorts are needed to improve risk assessment for prostate cancer (PCa).

Objective: A racially diverse cohort of men (20% African American [AA]) was used to evaluate the association of the clinically validated 17-gene Genomic Prostate Score (GPS) with recurrence after radical prostatectomy and adverse pathology (AP) at surgery.

Design, setting, and participants: Biopsies from 431 men treated for National Comprehensive Cancer Network (NCCN) very low-, low-, or intermediate-risk PCa between 1990 and 2011 at two US military medical centers were tested to validate the association between GPS and biochemical recurrence (BCR) and to confirm the association with AP. Metastatic recurrence (MR) was also evaluated.

Outcome measurements and statistical analysis: Cox proportional hazards models were used for BCR and MR, and logistic regression was used for AP. Central pathology review was performed by one uropathologist. AP was defined as primary Gleason pattern 4 or any pattern 5 and/or pT3 disease.

Results and limitations: GPS results (scale: 0–100) were obtained in 402 cases (93%); 62 men (15%) experienced BCR, 5 developed metastases, and 163 had AP. Median follow-up was 5.2 yr. GPS predicted time to BCR in univariable analysis (hazard ratio per 20 GPS units [HR/20 units]: 2.9; p < 0.001) and after adjusting for NCCN risk group (HR/20 units: 2.7; p < 0.001). GPS also predicted time to metastases (HR/20 units: 3.8; p = 0.032), although the event rate was low (n = 5). GPS was strongly associated with AP (odds ratio per 20 GPS units: 3.3; p < 0.001), adjusted for NCCN risk group. In AA and Caucasian men, the median GPS was 30.3 for both, the distributions of GPS results were similar, and GPS was similarly predictive of outcome.

Conclusions: The association of GPS with near- and long-term clinical end points establishes the assay as a strong independent measure of PCa aggressiveness. Tumor
1. Introduction

Men with low-risk prostate cancer (PCa) are increasingly counseled to consider active surveillance as a safe alternative to immediate therapy [1]. However, clinical and pathologic features at diagnosis do not sufficiently anticipate clinical behavior of the tumor, and concerns about tumor heterogeneity and undersampling associated with needle biopsies create doubt that biopsy findings truly reflect tumor aggressiveness [2,3]. Validated molecular biomarkers that provide objective measures of tumor biology and improve risk stratification are needed [4,5]. Clinical adoption of biomarkers requires that they (1) be analytically validated to provide robust, reproducible results; (2) be validated to predict clinically relevant end points; and (3) offer equivalent performance across a spectrum of disease including race and age [6–8].

This study sought to confirm the ability of a biopsy-based 17-gene assay to predict adverse pathology (AP), an actionable near-term measure of disease aggressiveness, and to validate its association with longer term outcomes after radical prostatectomy (RP; ie, biochemical recurrence [BCR]) in an independent, racially diverse cohort with National Comprehensive Cancer Network (NCCN) clinically very low-, low-, and intermediate-risk PCa in an equal-access health care system [9].

2. Materials and methods

2.1. Study design

All investigators agreed to the protocol and statistical analysis plan for this prospectively designed study of archival specimens that conformed to Reporting Recommendations for Tumor Marker Prognostic Studies guidelines [10]. The study was approved by institutional review boards (IRBs) at all sites, and data were locked prior to analysis.

2.2. Study population

Eligible patients included men treated with RP for NCCN very low-, low-, and intermediate-risk PCa between 1990 and 2011 at two US military medical centers (Walter Reed National Military Medical Center [WRNMMC] and Madigan Army Medical Center) and enrolled in the Center for Prostate Cancer Research (CPDR) longitudinal study [9], maintained under an IRB-approved protocol. Inclusion criteria for the BCR end point included biopsy Gleason score (GS) 6 or 7, prostate-specific antigen (PSA) <20 ng/ml, clinical stage T2 or lower, and RP within 6 mo of diagnosis. Exclusion criteria included adjuvant therapy, <1 mm biopsy tumor length, and inadequate RNA quality. For the AP end point, patients with biopsy GS 4 + 3 were excluded (Fig. 1).

Blinded review of aggregate tissue block availability and laboratory data revealed that >90% of eligible WRNMMC patients treated before 2001 could not be evaluated due to unavailable biopsies, lack of residual tumor, or inadequate RNA quality, and they were excluded prior to database lock.

Fig. 1 – REMARK diagram detailing study cohort.


AP = adverse pathology; BCR = biochemical recurrence; CPDR = Center for Prostate Disease Research; GS = Gleason score, RP = radical prostatectomy; NCCN = National Comprehensive Cancer Network; REMARK = Reporting Recommendations for Tumor Marker Prognostic Studies [18].
2.3. Pathology

Fixed paraffin-embedded biopsy and RP specimens were centrally reviewed by one uropathologist (I.A.S.) blinded to clinical outcomes and using the 2005 International Society of Urological Pathology Consensus guidelines [11]. Biopsy review was performed blinded to RP specimen review and vice versa. Biopsy tissue sections submitted to the Genomic Health laboratory were manually microdissected as previously described [12,13].

2.4. Assay methods

An analytically validated 17-gene quantitative reverse transcription-polymerase chain reaction assay provides a Genomic Prostate Score (GPS) as a measure of tumor aggressiveness [12]. The assay is validated to predict AP at surgery in men with clinically localized PCa [13].

All analytical methods were predefined and performed as previously described [12,13]. Expression of 12 cancer genes was normalized to five reference genes and used to calculate the GPS (scaled from 0 to 100).

2.5. Statistical methods

All analyses were detailed in a prespecified statistical analysis plan. BCR was defined as two successive PSA levels >0.2 ng/ml [14] or initiation of salvage therapy for rising PSA. Univariable and multivariable Cox proportional hazards (PH) models were used to evaluate the association of GPS with BCR-free interval (bRFI; time from biopsy to BCR) and metastasis-free interval (time from biopsy to metastasis). Losses to follow-up and non–cancer-related deaths were censored at the time of the last observation.

AP was defined as high-grade (primary Gleason pattern 4 or any pattern 5) and/or non–organ-confined disease (pT3). Capsular incision (pT2+ ) was considered non–organ-confined disease [15]. The association of GPS with AP was evaluated using binary logistic regression models after adjustment for biopsy GS.

For Cox PH models, the PH assumption was evaluated [16], and linearity assumption for the predictors was assessed by Martingale residuals [17], GPS was treated as a continuous variable. As with the first validation study [13], hazard ratios (HRs) and odds ratios (ORs) for GPS were calculated per 20 units, representing the difference between the average GPS of the highest and lowest 25th percentiles of patients. A p value <0.05 was considered significant based on a likelihood ratio test.

The C-statistic was used for time to event analyses and for binary outcomes area under the curve (AUC) for receiver operating characteristic (ROC) curves. Analyses were performed independently by CPDR and Genomic Health using SAS v.9.2 and SAS Enterprise Guide v.6.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

Among 864 eligible patients, 500 (57.9%) had available biopsies; 56 (11%) were excluded for insufficient tumor and 13 (3%) for biopsy GS ≥8. Of the remaining 431, GPS was obtained for 402 (93%), the final evaluable population for BCR. Of these, 382 were evaluable for AP after excluding patients with biopsy GS 4 + 3 (n = 13 [3%]) or unavailable RP slides (n = 7 [2%]) (Fig. 1).

Baseline characteristics in the evaluable population were representative of a contemporary cohort of patients with low-risk PCa and similar to the unevaluable population of 462 patients except that the unevaluable population had a higher percentage of GS 6 tumors and very low-risk/low-risk tumors (Supplementary Table 1). Median age was 62 yr; the distribution of NCCN clinical risk groups was very low, 11%; low, 54%; and intermediate risk, 35%. Overall, 76% were Caucasian and 20% African American (AA). Baseline characteristics were similar between the two sites, except for race and patient age (Table 1).

Median follow-up was 5.2 yr; 62 patients (15.4%) had BCR and 5 patients had metastases. In univariable models, diagnostic PSA, central biopsy GS, and NCCN risk group were significantly associated with BRFI (p < 0.05); race was not (HR: 0.77 for AA vs Caucasian; 95% confidence interval [CI], 0.37–1.46; p = 0.42) (Supplementary Table 2).

A total of 163 patients (43%) had AP; 80 (21%) had high-grade and 130 (34%) had non–organ-confined disease (including 39 pT2+ cases) (Supplementary Table 3). Age, PSA, central biopsy GS, and NCCN risk group were significantly (p < 0.05) associated with the likelihood of AP in univariable analysis (Supplementary Table 2).

Median GPS increased with higher NCCN risk and age, and GPS had a modest but statistically significant correlation with both (NCCN, r = 0.37, p < 0.001; age, r = 0.26, p < 0.001). However, a broad and overlapping range of GPS results was observed in all NCCN risk and age groups (Fig. 2).

3.2. Biochemical recurrence and metastasis

In the prespecified primary univariable analysis, GPS was significantly predictive of bRFI (HR/20 GPS units: 2.93; 95% CI, 2.03–4.15; p < 0.001). PH and linearity assumptions were deemed to be valid (data not shown), and the HR remained constant over time. The association between bRFI was as strong for men with bRFI ≤2 yr (HR: 2.85; 95% CI, 1.69–4.61; p < 0.001) as those with bRFI >2 yr (HR: 3.01; 95% CI, 1.78–4.96; p < 0.001). Modifying the definition of BCR by (1) including only men with two successive PSA levels >0.2 ng/ml (n events = 57), (2) including patients receiving salvage therapy without a rise in PSA (n events = 69), or (3) defining bRFI based on time to the second elevated PSA instead of the first had a minimal impact on the association between GPS and bRFI (data not shown).

GPS was the only significant predictive factor of bRFI in multivariable analyses after adjustment for baseline characteristics (Table 2), and it was a consistent predictor of bRFI within various clinical subgroups (Fig. 3A). For each 20-unit increase in GPS, the HR was 2.73 (95% CI, 1.84–3.96; p < 0.001) adjusted for NCCN risk group and 2.65 (95% CI, 1.80–3.83; p < 0.001) in a multivariable analysis adjusted for all significant factors from the univariable analysis.

Although there were only five metastases, GPS was significantly predictive of metastasis-free interval (HR/20 units: 3.83; 95% CI, 1.13–12.60; p = 0.032) in univariable analysis. The small number of events precluded multivariable analysis.

3.3. Analysis of the adverse pathology end point

After adjusting for central biopsy GS, GPS was significantly associated with AP (OR/20 units: 3.23; 95% CI, 2.14–4.97;
p < 0.001) (Table 3) and high-grade (OR/20 units: 2.60; 95% CI 1.65–4.15; p < 0.001) and non–organ-confined disease (OR/20 units: 3.55; 95% CI, 2.33–5.54; p < 0.001) separately. GPS was a consistent predictor of AP within various clinical subgroups (Fig. 3B) and remained significantly associated with AP (OR/20 units: 2.74; p < 0.001) after adjustment for age and NCCN risk group. GPS remained strongly predictive of AP when cases of capsular incision (pT2+) were excluded (OR/20 units: 3.53; 95% CI, 2.25–5.53; p < 0.001).

A subset analysis in 337 patients whose biopsy pathology criteria (biopsy GS 3 + 3 and low volume ≤33% positive cores) GS 3 + 4) matched the prior clinical validation study [13] showed that the association between GPS and AP remained significant (OR/20 units: 2.97; 95% CI, 1.94–4.67; p < 0.001) after adjusting for biopsy GS, and after adjustment for age and NCCN risk group (Supplementary Table 4).

### 3.4. Individual genes and gene groups

The 12 cancer-related genes in the GPS are divided into four groups, representing androgen signaling, stromal response, cellular organization, and proliferation [13]. Downregulation of androgen signaling and upregulation of stromal response gene groups were most strongly associated with bRFI (Fig. 4A). All four gene groups were significant predictors of AP (Fig. 4B).

### 3.5. Comparisons between African American and Caucasian patients

There was a broad range of GPS results within each racial group. GPS distribution and median GPS results were similar between AA (GPS median: 30.3; interquartile range [IQR]: 23–38) and Caucasian (GPS median: 30.3; IQR: 23–40) patients (Fig. 2C). No correlation was observed

<table>
<thead>
<tr>
<th>Table 1 – Distribution of baseline characteristics overall (n = 402) and by site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Age at diagnosis, yr</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Minimum</td>
</tr>
<tr>
<td>Maximum</td>
</tr>
<tr>
<td>Race, n (%)</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Diagnostic PSA, ng/ml, n (%)</td>
</tr>
<tr>
<td>&lt;4</td>
</tr>
<tr>
<td>4–9.99</td>
</tr>
<tr>
<td>10–20</td>
</tr>
<tr>
<td>Clinical T stage, n (%)</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>Biopsy Gleason score, n (%)</td>
</tr>
<tr>
<td>3 + 3</td>
</tr>
<tr>
<td>3 + 4</td>
</tr>
<tr>
<td>4 + 3</td>
</tr>
<tr>
<td>NCCN risk group, n (%)**</td>
</tr>
<tr>
<td>Very low</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
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<tr>
<td>Surgical Gleason score, n (%)***</td>
</tr>
<tr>
<td>3 + 3</td>
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<tr>
<td>3 + 4</td>
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<tr>
<td>Any major pattern 4 or pattern 5</td>
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<tr>
<td>Pathologic T stage, n (%)***</td>
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<td>T2</td>
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<tr>
<td>T2+</td>
</tr>
<tr>
<td>T3a</td>
</tr>
<tr>
<td>T3b</td>
</tr>
</tbody>
</table>

MAMC = Madigan Army Medical Center; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; SD = standard deviation; WRNMMC = Walter Reed National Military Medical Center.

* The \( p \) value was calculated by analysis of variance for continuous covariates, and the chi-square test or Fisher exact test was used for categorical covariates where appropriate.

** NCCN risk category could not be assigned for 10 men.

*** Surgical Gleason score and pathologic T stage data were available for 382 men with biopsy Gleason score 3 + 3 and 3 + 4: MAMC, \( n = 237 \); WRNMMC, \( n = 145 \).
between GPS and race ($r = -0.04; p = 0.45$). There were no differences in the expression of individual genes or gene groups between AA and Caucasian men (data not shown).

The association between GPS and bRFI or AP was similarly strong and statistically significant in both Caucasian and AA men in univariable analysis (bRFI HR/20 units: 2.97 vs 3.50; AP OR/20 units: 4.05 vs 2.86, respectively) (Fig. 3).

### 3.6 Clinical significance

In ROC analysis of AP, incorporation of GPS improved the AUC from 0.63 (NCCN alone) to 0.72 (GPS and NCCN) (Supplementary Fig. 1). In the subset with biopsy GS $3 + 3$ and low-volume $3 + 4$ disease, AUC for NCCN alone was 0.60 compared with 0.50 without risk factors, and it further improved to 0.69 by adding GPS ($p = 0.001$) (Supplementary Fig. 1b and 1c). Thus AUC when GPS is combined with NCCN is improved by an additional 90% relative to AUC with NCCN risk stratification alone.

Risk profiles and ROC analyses were performed to describe how GPS improves the accuracy of prediction of BCR. The risk profile curve for predicting BCR (Supplementary Fig. 2).

### Table 2 – Genomic Prostate Score (GPS) predicts biochemical recurrence after radical prostatectomy alone or with adjustment for the clinical/pathology covariates ($n = 402$)

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GPS/20 units</td>
<td>2.93</td>
<td>2.03–3.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>GPS/20 units</td>
<td>2.73</td>
<td>1.84–3.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>NCCN risk group: low vs very low</td>
<td>1.88</td>
<td>0.56–11.71</td>
<td>0.349</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs very low</td>
<td>2.17</td>
<td>0.63–13.72</td>
<td>0.249</td>
</tr>
<tr>
<td>3</td>
<td>GPS/20 units</td>
<td>2.65</td>
<td>1.80–3.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>WRNMMC vs MAMC</td>
<td>0.58</td>
<td>0.31–1.03</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>NCCN risk group: low vs very low</td>
<td>2.01</td>
<td>0.60–12.56</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs very low</td>
<td>2.41</td>
<td>0.69–15.21</td>
<td>0.187</td>
</tr>
</tbody>
</table>

CI = confidence interval; GPS = Genomic Prostate Score; HR = hazard ratio; MAMC = Madigan Army Medical Center; NCCN = National Comprehensive Cancer Network; WRNMMC = Walter Reed National Military Medical Center.

$n = 392$ (NCCN risk category could not be assigned for 10 patients).

### Table 3 – Genomic Prostate Score predicts adverse pathology at radical prostatectomy with adjustment for the clinical/pathology covariates ($n = 382$)

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
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<tr>
<td>1</td>
<td>GPS/20 units</td>
<td>3.23</td>
<td>2.14–4.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Biopsy Gleason score 3 vs 4</td>
<td>1.89</td>
<td>1.12–3.18</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>biopsy Gleason score $3 + 3$ vs $3 + 4$</td>
<td>1.89</td>
<td>1.12–3.18</td>
<td>0.016</td>
</tr>
<tr>
<td>2</td>
<td>GPS/20 units</td>
<td>3.25</td>
<td>2.12–5.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>NCCN risk group: low vs very low</td>
<td>3.17</td>
<td>1.33–8.81</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs very low</td>
<td>4.52</td>
<td>1.81–13.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age at diagnosis, yr</td>
<td>2.74</td>
<td>1.77–4.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>NCCN risk group: low vs very low</td>
<td>3.44</td>
<td>1.43–9.65</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Intermediate vs very low</td>
<td>5.20</td>
<td>2.05–15.18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; GPS = Genomic Prostate Score; OR = odds ratio; WRNMMC = Walter Reed National Military Medical Center.

$n = 372$ (NCCN risk category could not be assigned for 10 patients).
Fig. 3 – (A) Univariable hazard ratios (HRs) for Genomic Prostate Score (GPS) in predicting biochemical recurrence (BCR) after radical prostatectomy (RP) within different clinical subgroups. The size of the each box is proportional to the number of patients within that patient subgroup. The thin horizontal lines indicate the 95% confidence interval (CI) for each HR. The solid vertical line indicates the HR for GPS for the entire cohort. The dashed vertical line indicates a HR of 1 (no association). Due to the low number of BCR events in the subgroups of patients aged <56 yr or Walter Reed National Military Medical Center (WRNMMC) patients, the CIs for the HR of GPS were wider and included 1. (B) Univariable odds ratios (ORs) for GPS in predicting adverse pathology at RP within different clinical subgroups. The size of the each box is proportional to the number of patients within that patient subgroup. The thin horizontal lines indicate the 95% CI for each OR. The solid vertical line indicates the OR of GPS for the entire cohort. The dashed vertical line indicates an OR of 1 (no association).

CI = confidence interval; NCCN = National Comprehensive Cancer Network; MAMC = Madigan Army Medical Center; PSA = prostate-specific antigen; Q = quartile; WRNMMC = Walter Reed National Military Medical Center.
demonstrates a wide range of 5-yr risk of BCR as GPS increased. Average 5-yr risk was 7.5% (95% CI, 4.0–11.0) for men in the lowest quartile of GPS results (GPS/C20/23) and 33.6% (95% CI, 25.3–41.9) in the highest quartile (GPS/C21/39). Incorporation of GPS improved the C-statistic for NCCN risk from 0.59 (NCCN alone) to 0.68 (Supplementary Fig. 1c).

4. Discussion

The strong independent association of GPS with multiple clinical end points—BCR and AP—establishes the assay as a robust measure of PCa aggressiveness. This study confirms and extends findings of the prior validation study [13]. In both studies, using identical criteria for AP and centralized pathology review, GPS was significantly associated with AP after adjustment for clinical and pathologic factors, and it was predictive of both high-grade and non–organ-confined disease. ROC analyses from this study indicate that the added predictive value of the GPS is comparable with that provided by the NCCN risk category.

This study also validates the assay as a strong predictor of both early and late BCR, which has clinical relevance because early BCR is associated with a higher risk of systemic recurrence, whereas late BCR suggests local recurrence [18]. The association between GPS and metastases was also statistically significant, not a surprising finding given that genes in GPS were selected primarily based on their association with clinical recurrence [13].

Several molecular diagnostic assays have become available for PCa [4,5,19]. NCCN guidelines now include these assays as an option for clinically localized PCa to improve prediction of AP at surgery or the likelihood of BCR and PCa-specific mortality following surgery [20]. Although three of these assays (the 17-gene GPS assay validated here, a 46 cell cycle gene signature, and a 22-gene assay) have been shown to predict longer term outcomes such as BCR and metastases, only GPS has been validated to predict AP [19]. Growing evidence indicates that use of these assays provides physicians with greater confidence in treatment recommendations [21].

The appropriate use of genomic assays requires understanding their performance within specific patient populations. Several studies have highlighted molecular differences in PCa in AA and Caucasian men [22] including prevalence of transmembrane protease, serine 2/ets avian erythroblastosis virus E26 oncogene homolog (TMPRSS2-ERG) fusions [23] and phosphatase and tensin homolog (PTEN) deletions [24], and gene expression patterns [25]. Studies also suggest that increased androgen signaling is seen in AA men [26]. In this study within an equal-access health care system, AA and Caucasian men had similar outcomes, similar distributions and median values for GPS, and similar distribution of individual gene groups and genes including the androgen gene group. These findings suggest that the tumor biology captured by GPS is similar between Caucasian and AA men. Importantly, GPS was an equally strong predictor for near- and longer term outcomes for both AA and Caucasian men.

Limitations of the study should be noted. The number of metastatic events was small, as expected in low- and intermediate-risk patients with a 5-yr median follow-up. The representation of other racial groups was too low to assess the assay’s performance in other populations. Finally, because of the limited amount of biopsy tissue available and

Fig. 4 – Performance of gene groups and individual genes that make up the Genomic Prostate Score. (A) Univariable hazard ratios (HRs) and 95% confidence interval for gene groups and individual genes for predicting biochemical recurrence. (B) Univariable odds ratios (ORs) and 95% CI for gene groups and individual genes for predicting adverse pathology. Each square represents the standardized HR or OR for each individual gene or gene group. The thin horizontal lines indicate the 95% CI for each HR or OR. Standardized HR or OR indicates the HR or OR per 1-standard deviation increase in gene expression measured on the log scale. Standardized HR >1 or OR >1 indicates that higher expression is associated with worse outcome.

CI = confidence interval.
degradation of RNA with time, very low-risk and low-risk GS 6 tumors appeared more likely to be excluded for technical reasons. Nonetheless, the final evaluable population remained representative of a contemporary cohort.

The strength of association between GPS and AP was notable in the face of considerable tumor heterogeneity. Although the impact of heterogeneity was not measured in this study, the previously described strategy of selecting genes predictive of outcome across spatially distinct regions of the tumor including adjacent normal–appearing tissue [27] likely captured an underlying field effect [28] and contributed to the successful validation of the assay.

The robustness of the GPS assay is in part due to inclusion of genes representing multiple, distinct biologic pathways involved in prostate tumorigenesis. In the development studies for the assay, we found that a test including these four pathways was a more robust predictor of outcome than genes representing any single pathway [13], an observation consistent with the complex biology underlying the malignant process [29].

5. Conclusions

This prospectively designed study has validated the biopsy-based GPS as a strong, independent predictor of an actionable near-term end point (AP) and longer term clinical outcome (BCR) in Caucasian and AA men with very low-, low-, or intermediate-risk PCas. This establishes GPS as a robust measure of tumor aggressiveness that can provide more accurate risk assessment to guide treatment decisions for men with newly diagnosed disease.

This work was presented in part at the 2014 Congress of the European Society of Medical Oncology (ESMO), September 2014, Madrid, Spain.

Author contributions: Jennifer Cullen 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.

Study concept and design: Cullen, Rosner, Zhang, Tsiasis, Knezevic, Maddala, Lawrence, Srivastava, Sesterhenn, McLeod.

Acquisition of data: Cullen, Brand, Zhang, Tsiasis, Moncur, Ali, Knezevic, Maddala, Lawrence, Febbo, Sesterhenn.

Analysis and interpretation of data: Cullen, Zhang, Tsiasis, Knezevic, Maddala, Lawrence, Febbo, Sesterhenn.

Drafting of the manuscript: Cullen, Zhang, Tsiasis, Knezevic, Maddala, Lawrence, Febbo, Sesterhenn.

Critical revision of the manuscript for important intellectual content: Cullen, Zhang, Tsiasis, Lawrence, Maddala, Febbo, Srivastava, Sesterhenn.

Statistical analysis: Cullen, Zhang, Chen, Maddala.

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Appendix A. Supplementary data

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References


