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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

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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

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aggressiveness, as measured by GPS, and outcomes were similar in AA and Caucasian men in this equal-access health care system.

Patient summary: Predicting outcomes in men with newly diagnosed prostate cancer is challenging. This study demonstrates that a new molecular test, the Genomic Prostate Score, which can be performed on a patient's original prostate needle biopsy, can predict the aggressiveness of the cancer and help men make decisions regarding the need for immediate treatment of their cancer.

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 Tumour 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.

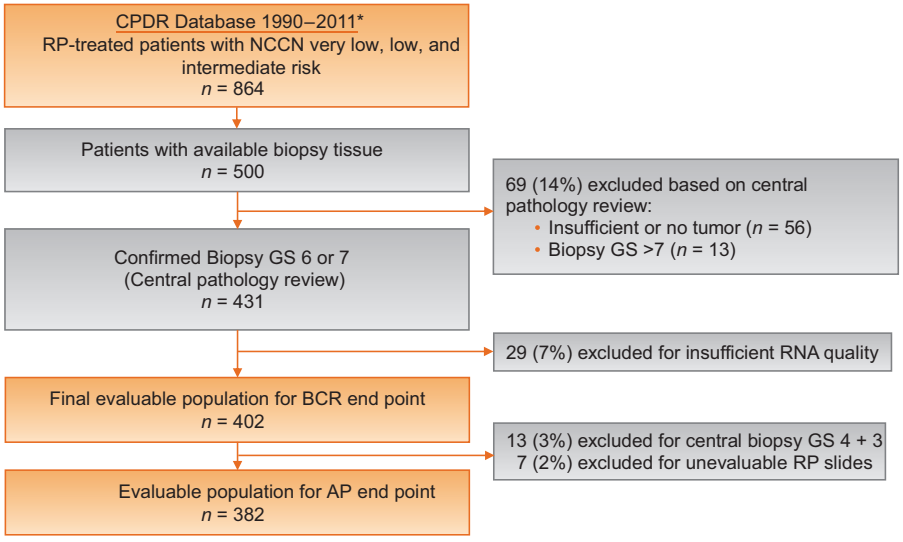

Fig. 1 – REMARK diagram detailing study cohort.
*** Walter Reed National Military Medical Center: 2001–2011; Madigan Army Medical Center: 1990–2011.**
AP = adverse pathology; BCR = biochemical recurrence; CPDR = Center for Prostate Disease Research; GS = Gleason score, RP = radical prostatectomy; NCCN = National Comprehensive Cancer Network; REMARK = Reporting Recommendations for Tumor Marker Prognostic Studies [10].

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