Patient-specific Meta-analysis of 2 Clinical Validation Studies to Predict Pathologic Outcomes in Prostate Cancer Using the 17-Gene Genomic Prostate Score

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OBJECTIVE To perform patient-specific meta-analysis (MA) of two independent clinical validation studies of a 17-gene biopsy-based genomic assay as a predictor of favorable pathology at radical prostatectomy.

MATERIALS AND METHODS Patient-specific MA was performed on data from 2 studies (732 patients) using the Genomic Prostate Score (GPS; scale 0-100) together with Cancer of the Prostate Risk Assessment (CAPRA) score or National Comprehensive Cancer Network (NCCN) risk group as predictors of the likelihood of favorable pathology (LFP). Risk profile curves associating GPS with LFP by CAPRA score and NCCN risk group were generated. Decision curves and receiver operating characteristic curves were calculated using patient-specific MA risk estimates.

RESULTS Patient-specific MA-generated risk profiles ensure more precise estimates of LFP with narrower confidence intervals than either study alone. GPS added significant predictive value to each clinical classifier. A model utilizing GPS and CAPRA provided the most risk discrimination. In decision-curve analysis, greater net benefit was shown when combining GPS with each clinical classifier compared with the classifier alone. The area under the receiver operating characteristic curve improved from 0.68 to 0.73 by adding GPS to CAPRA, and 0.64 to 0.70 by adding GPS to NCCN risk group. The proportion of patients with LFP >80% increased from 11% using NCCN risk group alone to 23% using GPS with NCCN. Using GPS with CAPRA identified the highest proportion—31%—of patients with LFP >80%.

CONCLUSION Patient-specific MA provides more precise risk estimates that reflect the complete body of evidence. GPS adds predictive value to 3 widely used clinical classifiers, and identifies a larger proportion of low-risk patients than identified by clinical risk group alone. UROLOGY 89: 69–75, 2016.

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A number of new tissue-based molecular assays have been developed to provide improved risk stratification for men with newly diagnosed, clinically localized prostate cancer to help guide therapeutic decisions, such as immediate definitive therapy vs active surveillance. These prognostic assays must meet a suitable level of clinical validation before gaining widespread adoption into clinical urological practice. Studies using archival specimens can provide level I evidence if a suitable "prospective-retrospective" study design is used.[1]

One such assay is the Onco*type* DX Prostate Cancer Assay, a biopsy-based test that measures the expression of 17 genes (12 cancer-related and 5 reference) to provide a Genomic Prostate Score (GPS; scaled 0-100) as a measure of biologic aggressiveness. Two "prospective-retrospective" clinical studies have validated GPS as a strong and independent predictor of adverse pathology (AP) at radical prostatectomy (RP), thus, providing level I evidence.[2,3]

Using GPS together with National Comprehensive Cancer Network (NCCN) clinical risk group, the test currently provides an estimate of the likelihood of favorable pathology (LFP), which is furnished in the patient report of a commercial-grade assay, based on data from the first validation study. The second validation study confirmed the association between GPS and LFP. Although the baseline characteristics of both cohorts were similar, there were some differences, including the inclusion criteria for intermediate risk patients, the percentage of African American patients, and the pathologist responsible for the central pathology review. To provide more broadly representative and precise estimates of LFP, we combined information from both studies and examined predictive models using GPS with other clinical risk-stratifying tools.

To take full advantage of the combined data from these studies, which comprise a total of 732 patients, a patient-specific meta-analysis (MA) was performed.[4] Patient-specific MA combines predictions for individual patients from multiple studies, with weighting based on the precision of each prediction, thereby permitting more precise risk estimates with narrower confidence intervals that reflect the complete body of evidence collected across these studies.[4] Patient-specific MA was applied previously to the prognostic information provided by Onco*type* DX Breast Cancer Assay Recurrence Score together with pathology and clinical covariates in 2 studies of early stage breast cancer.[5] An educational tool providing estimates of distant recurrence risk of breast cancer based on the patient-specific MA calculation is available online.

Using the patient-specific MA, we sought (1) to determine if GPS added predictive value to 3 widely used clinical risk stratification tools (Cancer of the Prostate Risk Assessment [CAPRA] score, NCCN risk group, and American Urology Association/European Association of Urology [AUA/EAU] risk group), and (2) to provide a better estimate of the proportion of patients identified for whom the risk of aggressive disease is very low than is identified by clinical risk group alone.

MATERIALS AND METHODS

Patients and Study Design

The patient selection criteria and study design for the University of California San Francisco (UCSF) and the Uniformed Services University Center for Prostate Disease Research (CPDR) clinical validation studies of GPS have been described previously.[2,3] Both studies included patients who were potential candidates for active surveillance under relatively broad inclusion criteria at diagnosis—(ie, biopsy Gleason score [GS] 3 + 3 or 3 + 4 disease [Gleason 4 + 3 disease was permitted in the CPDR study]), prostate-specific antigen (PSA) ≤20, and clinical stage ≤T2—but who elected RP within 6 months of diagnosis. Patients were identified from the institutional review board-approved clinical databases and biobanks at each institution. The UCSF study patients were diagnosed from 1997 to 2011 and the CPDR study patients were diagnosed from 1990 to 2011. Exclusion criteria included any neoadjuvant therapy, <1 mm total biopsy tumor length, missing prostatectomy or biopsy tissue for central pathology review, and inadequate ribonucleic acid (RNA) quality for analysis. All biopsies and prostatectomies were centrally reviewed by academic urologic pathologists (Jeffry P. Simko for UCSF study, Isabell A. Sesterhenn for CPDR study), following the 2005 International Society of Urological Pathology Consensus guidelines.[6] Pathology review of biopsies was performed blinded to the review of RP and vice versa. Patients from these validation studies were excluded from the MA if they were found to have biopsy GS 4 + 3 disease at diagnosis or pathologic pT2$^+$ (because capsular incision renders the true tumor status with regard to organ confinement indeterminate) at RP upon central pathology review.

GPS Assay and End Point

The Onco*type* DX Prostate Cancer Assay (GPS assay) has been described previously, and analyzes the expression levels of 17-genes (12 cancer-related and 5 reference) to provide the GPS, which is scaled from 0 to 100.[7] The end point of AP at RP for both studies was defined as high-grade (primary GS pattern 4 or any pattern 5) or non–organ-confined disease (pT3).[7] Favorable pathology (FP) at RP is defined as low-grade (surgical GS 3 + 3 or 3 + 4 with no pattern 5) and organ-confined disease (pT2).

Statistical Methods

The analyses performed included GPS plus each of 3 widely used clinical risk assessment tools: CAPRA score,[8] NCCN risk group,[9] and AUA/EAU risk group.[10,11] For each of the combinations, multivariable logistic regression models with factors for the clinical risk assessment tool and GPS were fit separately to each study, with AP as the end point. The CAPRA score, which ranged from 0 to 5 across the 2 study populations, was treated as a continuous numerical variable in the logistic regression models. Patients classified as having clinical T2c disease were excluded from the patient-specific MA of GPS plus AUA/EAU risk group, because these patients are considered to have high-risk disease using the AUA/EAU risk classification system.

Both studies enrolled patients with NCCN very low, low, and intermediate risk disease. However, the enrollment of intermediate-risk patients in the UCSF study was restricted to patients with low volume (≤3 positive biopsy cores or ≤33% of positive cores) Gleason score 3 + 4 disease[2]; the CPDR study enrolled all intermediate-risk patients, regardless of tumor volume.[3] The patient-specific MA method can accommodate the "special population" of NCCN intermediate-risk patients with high tumor volume, who were included only in the CPDR study, provided 2 assumptions are met[4]: (1) there is no interaction between NCCN