A 17-Gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling


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BACKGROUND: Prostate tumor heterogeneity and biopsy undersampling pose challenges to accurate, individualized risk assessment for men with localized disease.

OBJECTIVE: To identify and validate a biopsy-based gene expression signature that predicts clinical recurrence, prostate cancer (PCa) death, and adverse pathology.

DESIGN, SETTING, AND PARTICIPANTS: Gene expression was quantified by reverse transcription-polymerase chain reaction for three studies—a discovery prostatectomy study (n=441), a biopsy study (n=167), and a prospectively designed, independent clinical validation study (n=395)—testing retrospectively collected needle biopsies from contemporary (1997-2011) patients with low to intermediate clinical risk who were candidates for active surveillance (AS).

OUTCOME MEASURES AND STATISTICAL ANALYSIS: The main outcome measures defining aggressive PCa were clinical recurrence, PCa death, and adverse pathology at prostatectomy. Cox proportional hazards regression models were used to evaluate the association between gene expression and time to event end points. Results from the prostatectomy and biopsy studies were used to develop and lock a multigene-expression-based signature, called the Genomic Prostate Score (GPS); in the validation study, logistic regression was used to test the association between the GPS and pathologic stage and grade at prostatectomy. Decision-curve analysis and risk profiles were used together with clinical and pathologic characteristics to evaluate clinical utility.

RESULTS AND LIMITATIONS: Of the 732 candidate genes analyzed, 288 (39%) were found to predict clinical recurrence despite heterogeneity and multifocality, and 198 (27%) were predictive of aggressive disease after adjustment for prostate-specific antigen, Gleason score, and clinical stage. Further analysis identified 17 genes representing multiple biological pathways that were combined into the GPS algorithm. In the validation study, GPS predicted high-grade (odds ratio [OR] per 20 GPS units: 2.3; 95% confidence interval [CI], 1.5-3.7; p<0.001) and high-stage (OR per 20 GPS units: 1.9; 95% CI, 1.3-3.0; p=0.003) at surgical pathology. GPS predicted high-grade and/or high-stage disease after controlling for established clinical factors (p<0.005) such as an OR of 2.1 (95% CI, 1.4-3.2) when adjusting for Cancer of the Prostate Risk Assessment score. A limitation of the validation study was the inclusion of men with low-volume intermediate-risk PCa (Gleason score 3+4), for whom some providers would not consider AS.
CONCLUSIONS: Genes representing multiple biological pathways discriminate PCa aggressiveness in biopsy tissue despite tumor heterogeneity, multifocality, and limited sampling at time of biopsy. The biopsy-based 17-gene GPS improves prediction of the presence or absence of adverse pathology and may help men with PCa make more informed decisions between AS and immediate treatment.

PATIENT SUMMARY: Prostate cancer (PCa) is often present in multiple locations within the prostate and has variable characteristics. We identified genes with expression associated with aggressive PCa to develop a biopsy-based, multigene signature, the Genomic Prostate Score (GPS). GPS was validated for its ability to predict men who have high-grade or high-stage PCa at diagnosis and may help men diagnosed with PCa decide between active surveillance and immediate definitive treatment.