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The Development and Validation of a 17-Gene Genomic Prostate Score (GPS) as a Predictor of Outcome in Newly Diagnosed Prostate Cancer

Background: The development of a molecular diagnostic assay involves a series of feasibility and analytic studies; clinical adoption requires a suitable level of clinical evidence (McShane JCO 2012; Simon JNCI 2009). Our goal was to develop a robust, fit-for-purpose gene expression assay that could be performed on RNA from diagnostic needle biopsies, and provide improved risk stratification in early-stage prostate cancer (PCa). We summarize the development and validation of the 17-gene Onco*type* DX® Prostate Cancer Assay (Genomic Health, Inc., Redwood City, CA), a biopsy-based RT-PCR assay that yields a Genomic Prostate Score (GPS, scale 0 -100), as a biologic measure of tumor aggressiveness. The assay includes 12 cancer-related genes representing four biologic pathways.

Methods: To date, feasibility, development and validation studies have included >1,500 patients from four academic centers. In the development and validation studies, archival tissues were assayed following prospectively designed protocols with pre-specified methods and statistical analysis plans.

Results: Feasibility studies confirmed that gene expression can be measured in small amounts of RNA obtained from formalin-fixed needle biopsies. Development studies identified genes whose expression was predictive of clinical recurrence, biochemical recurrence (BCR), prostate cancer death, and adverse pathology (AP) at surgery in the face of tumor heterogeneity and multifocality. Analytic validation studies showed that the assay provided robust, reproducible results over a wide range of RNA inputs, different operators, instruments, and reagent lots. The first clinical validation study established GPS as an independent predictor of AP in men with NCCN very-low, low, and low-intermediate-risk PCa. Exploratory analyses showed that GPS is a robust predictor of AP despite inter-observer differences in pathologic grade and stage assessment. A second clinical validation study in a racially diverse population confirmed the assay as a predictor of AP and validated the assay as a strong predictor of BCR (HR/20 GPS units=2.9; $p<0.001$). GPS was also significantly associated with metastatic disease (HR/20 units=3.8; $p=0.032$). Other exploratory analyses showed that the assay can predict 1) likelihood of clinical recurrence after BCR, regardless of salvage therapy, and 2) tumor aggressiveness when assessed in adjacent normal-appearing tissue. All four gene groups contribute to the predictive value of the assay.

Conclusions: The development program for the assay addressed challenges of small sample size, tumor heterogeneity, multifocality, and biopsy under-sampling. Validation in two large contemporary cohorts of men with PCa in two prospectively designed studies provides level IB clinical evidence for GPS as a predictor of adverse pathology.