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Development and validation of the biopsy-based genomic prostate score (GPS) as a predictor of high grade or extracapsular prostate cancer to improve patient selection for active surveillance

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Introduction and Objectives New pretreatment tools are needed to improve selection of prostate cancer (PCa) patients for active surveillance (AS) but are challenged by multifocality of PCa and under-sampling with needle biopsies. To overcome these challenges, we conducted 2 large development studies: first to identify genes predictive of clinical recurrence and adverse pathology across multiple tumor foci within patient, and second to confirm predictive value of these genes in prostate biopsies. The 17-gene GPS, developed from these data, was then validated as a predictor of true grade and stage over clinical criteria alone in an independent validation study of biopsies from patients suitable for AS.

Methods In development studies, gene expression was quantitated by RT-PCR from manually microdissected FPE PCa tissue for each patient from two spatially distinct tumor specimens from radical prostatectomy (study 1) or from needle biopsies (study 2). For the validation study, GPS was assessed on 30 µm FPE tissue from a single needle biopsy for each patient using a prespecified gene list and algorithm. Association with clinical recurrence and adverse pathology (high grade and/or pT3) was analyzed by Cox PH or logistic regression.

Results Analysis of 732 candidate genes in development study 1 (n=441 pts) identified 288 genes predictive of clinical recurrence regardless of Gleason patterns in separately-sampled specimens. 81 genes taken forward into needle biopsy study of low/int-risk patients (development study 2, n=167 pts) confirmed strong association of the genes with adverse pathology. Multivariate analysis of both development studies yielded 17 genes across multiple biological pathways (3 stromal response, 4 cellular organization, 3 androgen, 1 proliferation, and 5 reference genes) and a GPS algorithm. In the validation study (n=395 pts), GPS, assessed in biopsies with as little as 1mm tumor length from patients suitable for AS, strongly predicted ($p<0.005$) high grade and/or pT3 disease after adjusting for CAPRA or other standard pretreatment factors.

Conclusions The 17-gene GPS, specifically developed to overcome tumor heterogeneity and biopsy under-sampling, has been validated as a biopsy-based predictor of high grade and/or pT3 disease, addressing a pressing clinical need by substantially improving risk assessment at diagnosis. Incorporating GPS enables more accurate identification of a larger population of patients who can more confidently choose AS for initial management.