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RESEARCH HIGHLIGHT

# A genomic approach to active surveillance: a step toward precision medicine

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**In the last 25 years, Prostate Specific Antigen (PSA) screening has resulted in a large gap between the likelihood of being diagnosed with and of dying of prostate cancer, leading to the clinical problems of overdiagnosis and overtreatment. Despite the favorable outcomes reported for active surveillance, its clinical use is limited, with >90% of men in the US diagnosed with potentially indolent disease undergoing immediate treatment with radiation or surgery. We have designed a novel strategy of molecular profiling of prostate cancers, allowing an assessment of tumor aggressiveness to be based on tumor tissue obtained at biopsy. The results have led to a soon-to-be clinically available test that will allow improved selection of men for active surveillance.**

Although there is agreement in urologic circles that early detection and aggressive treatment of higher grade cancers reduces prostate cancer-specific mortality, the widespread overtreatment of low grade, nonaggressive disease led the US Preventative Services Task Force to recommend against routine screening.[1] There are accumulating data from several institutions on an alternative management strategy called 'active surveillance'.[2] Active surveillance is defined as expectant management with curative intervention delayed until signs of tumor progression; its main advantage is that it avoids overtreatment of indolent disease, thereby restricting the cost and morbidity of curative-intent treatments only to those who have potentially life-threatening cancers. Despite the favorable outcomes reported for surveillance, its clinical use is limited, with >90% of men in the US diagnosed with potentially indolent disease undergoing immediate treatment with radiation or surgery.[2]

There are several reasons that surveillance has not been more widely adopted—legal (fear of being sued if the window of curability is missed), economic (doctors get paid to intervene, not watch) and emotional (patient and family anxiety over not treating a known cancer). However, the major limitation to wider use of surveillance is the lack of a tool that can distinguish indolent from aggressive prostate cancer at the time of diagnosis, and that can be used on subsequent biopsies to determine if someone on surveillance has true biological progression.

Working with Genomic Health, Inc., we have designed a novel strategy built upon the approach used to successfully develop molecular profiling of breast and colon cancers,[3,4] and designed to address the challenge of tumor heterogeneity inherent in prostate cancer. Results from the first two studies in this strategy were recently presented at the 2012 American Society of Clinical Oncology Annual Meeting (Klein EA *et al*,[5] abstract 4560). We first conducted a gene discovery study in fixed, paraffin-embedded tumor tissue from patients treated by radical prostatectomy (RP), where the relationship between gene expression and clinical tumor recurrence in two separate tumor foci selected to represent the primary and highest Gleason patterns were examined. We found a group of 288 genes in six biological pathways that predict for clinical recurrence expressed in common by both the primary and highest Gleason patterns. We then conducted a second study to demonstrate that the majority of the most highly predictive genes identified in RP specimens in the first study, when assayed in tumor from prostate needle biopsies, could also predict adverse pathology at the time of prostatectomy.

## METHODS

For the gene identification study, we sampled 441 tumor specimens from a large pool of approximately 2600 men treated by RP between 1987 and 2004 at the Glickman Urological and Kidney Institute. For the biopsy study, fixed, paraffin-embedded prostate needle biopsy specimens were selected from an additional 167 patients (92 low-risk and 75 intermediate-risk) who had both a prostate biopsy and RP at our institution. All specimens were re-reviewed and assigned Gleason pattern and score using the 2005 International Society of Urological Pathology Consensus guidelines.[6] In the RP study, we sampled two spatially distinct tumor specimens which represented the primary Gleason and highest or secondary Gleason patterns. For the biopsy study, representative tissue blocks were selected for each patient.

For the gene discovery study, 727 candidate genes selected from a meta-analysis of publicly available DNA microarray datasets were analyzed. Candidate genes were assayed for expression by quantitative RT-PCR assays. Eighty-one candidate genes identified in the gene discovery study were assayed using the same methods in the needle biopsy study.

## STATISTICS METHODS

For the gene discovery study, the primary objective was to identify genes associated with time to clinical recurrence (local recurrence or distant metastases), and for the needle biopsy study, the presence of adverse pathology (high-grade or non-organ confined disease) in the RP specimen. Cox proportional hazards regression and logistic regression models were used to evaluate associations between genes and outcome variables. The false discovery rate was controlled at 10%.

## RESULTS

In data presented at the 2012 American Society of Clinical Oncology Annual Meeting, we identified 288 genes that were similarly predictive of clinical recurrence (as assessed by standardized hazard ratios) in both primary and highest Gleason pattern.[5] This result demonstrated that certain genes could predict tumor aggressiveness regardless

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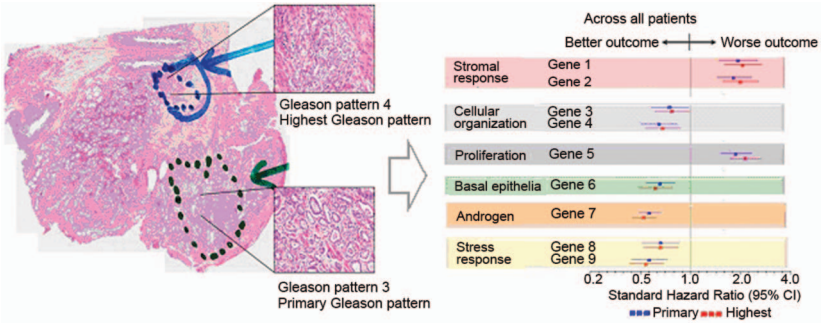


**Figure 1** Gene identification study in RP specimens: novel design to assess gene expression in the context of tumor heterogeneity. RP, radical prostatectomy.

of the Gleason pattern tumor in which they were assessed (**Figure 1**). These genes span multiple pathways that are differentially associated with aggressiveness—for example, higher expression of the stromal response and proliferation genes is associated with higher risk of clinical recurrence, while for other groups (cellular organization, basal epithelial, androgen and stress), higher expression is associated with lower recurrence risk. After adjustment for American Urological Association risk group (based on pretreatment PSA, T stage and PSA), 198 genes, including representative genes from the six groups identified in univariable analyses, remained strongly associated with clinical recurrence in tumor taken from either the primary or highest Gleason pattern. Importantly, in the second study, expression patterns in these groups were also predictive of adverse pathology on RP in tumor samples taken from needle biopsy specimens (**Figure 2**). Overall, 58 of 81 (72%) tested genes predicted high-grade and/or non-organ-confined disease (false discovery rate $<10\%$).[5]

## DISCUSSION

In 2011, the Institute of Medicine issued a call for the development of a new system of disease classification that would link molecular data to health outcomes in order to allow more precise clinical decision making that is tailored to individual patients, a concept termed 'precision medicine'.[7] The overdiagnosis of non-lethal prostate cancer by PSA screening coupled with recent advances in genomic profiling of prostate and other human cancers represents a significant opportunity to apply the concept of precision medicine to the management of prostate cancer. The major question that most newly diagnosed men today face is no longer 'What is the best treatment for my cancer', but rather 'Does my cancer need to be treated at all?'. Current clinical predictors, including nomograms, lack the discriminative ability to answer this question for most newly diagnosed tumors. We have attempted to address this limitation by studying the biology of prostate cancer as revealed by gene expression profiling from both RP specimens and prostate biopsies. The capacity to predict clinically meaningful outcomes from biopsies is essential for those considering active surveillance, since it is the only material available on which to make a judgment.

Our studies, as presented at the 2012 American Society of Clinical Oncology Annual Meeting, have revealed that sampling the expression of genes contained in multiple biological families has the ability to predict outcomes in ways that can be used in inform clinical decision making. The study identified 288 genes that can predict for the development of metastasis or prostate cancer death whether they are assayed in the primary or highest Gleason pattern present in prostatectomy specimens; a subset of these genes assayed on biopsy samples also predicted for adverse pathology at RP. Altogether, these observations suggest that meaningful information on outcomes is contained in the small amounts of tissue obtained at biopsy. The fact that this information can be obtained from either the primary or highest Gleason pattern tumor suggests that the sampling error inherent with needle biopsy consequent to tumor multifocality and heterogeneity may be overcame with this approach (although this conclusion requires a great deal more studies). A multigene assay developed from this work is now undergoing validation using biopsy specimens from an independent cohort of patients from another center. If our initial findings are confirmed, gene expression profiling of biopsy samples at the time of diagnosis and subsequently in those initially managed by surveillance could have major clinical impact, bringing precision medicine to the prostate cancer clinic in the near future (**Figure 3**).

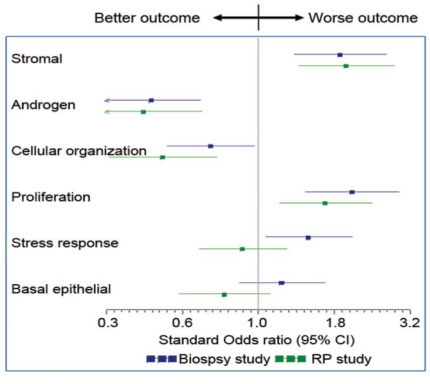


**Figure 2** Expression of most key gene groups/pathways is similarly predictive of adverse pathology in the RP and the needle biopsy studies. RP, radical prostatectomy.

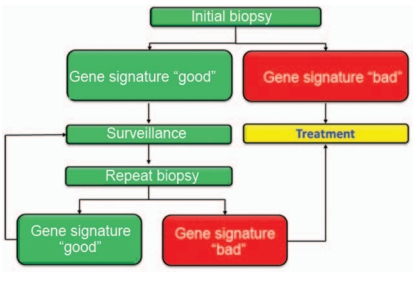


**Figure 3** Clinical algorithm of a biopsy-based gene expression signature for choosing and managing active surveillance patients.

## ACKNOWLEDGMENTS

Genomic Health, Inc. provided research funding to the Cleveland Clinic for performance of this study. A patent application for the development of a genomic assay based on the genes identified in this study has been submitted by Genomic Health, Inc.

1 Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012; **157**: 120–34.
2 Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. *J Clin Oncol* 2011; **29**: 3669–76.
3 O'Connell MJ, Lavery I, Yothers G, Paik S, Clark-Langone KM *et al*. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. *J Clin Oncol* 2010; **28**: 3937–44.
4 Paik S, Shak S, Tang G, Kim C, Baker J *et al*. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; **351**: 2817–26.
5 Klein EA, Maddala T, Millward C, Cherbavaz DB, Moscovita Falzarano S *et al*. Development of a needle biopsy-based genomic test to improve discrimination of clinically aggressive from indolent prostate cancer. *J Clin Oncol* 2012; **30** (Suppl): abstr 4560. Presented at the 2012 Annual Meeting of the American Society of Clinical Oncology.
6 Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2005; **29**: 1228–42.
7 Committee on a Framework for Development a New Taxonomy of Disease; National Research Council. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC: The National Academies Press; 2011. http://www.nap.edu/openbook.php?record_id=13284