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The Wide World of Molecular Profiling for Tumor Classification

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As the past millennium was coming to an end and we were about to enter a new one, the National Cancer Institute (NCI) director issued a request for applications in which the scientific community was challenged to submit proposals "to harness the power of comprehensive molecular analysis technologies to make the classification of tumors vastly more informative." The director invited investigators to form multidisciplinary research groups with proposals to exploit 1 or a related set of comprehensive molecular analysis technologies for the examination of tumor specimens. Together with a group of investigators at the University of Michigan, we submitted a proposal to exploit comprehensive gene expression and proteomic technologies to profile 3 epithelial tumor types: lung, colon, and ovarian. The rationale for 3 tumor types was to determine features that were distinctive to each tumor and that were predictive of clinical behavior that may or may not cut across tumor types (1, 2). The rationale for combining gene expression and proteomics was that gene expression levels might be predictive of neither protein concentrations (3) nor subcellular location or posttranslation modifications that may impact function.

The design of our study was based on a training and testing approach in which the training was based on data from biospecimens obtained at 1 institution and testing was done with gene-expression data obtained from a completely independent sample set. The training set resulted in a 50-gene index that identified low-risk and high-risk stage I lung adenocarcinoma subgroups that differed substantially with respect to survival and that was validated in the independent set.

The question of why this particular set of genes formed a risk index for survival in early-stage lung adenocarcinoma was of interest. The genes had little in common. They were not restricted in their expression to lung cancer and did not appear to be enriched in particular signaling pathways or gene families in a manner that was obvious. Next, we turned to proteomic profiling of adenocarcinomas (4). A leave-one-out cross-validation procedure using the top 20 survival-associated proteins identified by Cox modeling indicated that protein profiles could predict survival in patients with stage I tumors. Interestingly, the combined analysis of the mRNA and protein data revealed 11 components of the glycolysis pathway as associated with poor survival, pointing to glycolysis as an important feature of

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tumors likely to progress and to the merits of integrating datasets derived from different platforms (5). The protein profiling article has been far less cited than the mRNA profiling article, and this has been rather puzzling.

A follow-up study was published that involved the Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma (6). A large, training-testing, multisite, blinded validation study was done to assess the performance of several prognostic models based on gene expression for 442 lung adenocarcinomas. Several models examined produced risk scores that substantially correlated with actual subject outcome. Performance was improved with the inclusion of clinical data.

To date, the acceptance of prognostic gene expression signatures in clinical practice has been rather slow. This has been attributed in part to the fact that most studies have been developed without a clear definition of the intended clinical application and without rigorous independent validation to demonstrate the clinical utility (7). At present, there is an embarrassment of riches of technologies and platforms for molecular profiling for predictive and prognostic markers. Which approach will emerge that will be widely adopted in the clinic with the prerequisite performance characteristics and ease of implementation remains to be determined.

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[2]This article has been cited more than 1150 times since publication.