

Development and Validation of a Blood-based Gene Expression Algorithm for Assessment of Obstructive Coronary Artery Disease in Nondiabetic Patients

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Abstract:

Background: We have previously identified genes in circulating blood cells that are differentially expressed in patients with coronary artery disease (CAD). To extend this work, we have developed a gene expression and demographics based algorithm for assessment of obstructive CAD in non-diabetic patients.

Methods: We first analyzed gene expression in 393 whole blood samples from 2 independent cohorts (195 patients from Duke CATHGEN registry; 198 patients from the PREDICT trial) using whole genome microarrays. From this analysis, 113 candidate genes were chosen and their expression levels measured by RT-PCR in 640 non-diabetic PREDICT patient samples to assess the relationships between gene expression, obstructive CAD likelihood, age and gender, and to analyze cell type-gene expression correlations. Meta-genes and sex-specific age functions of CAD likelihood were input for algorithm derivation by forward stepwise logistic and Ridge regression to yield a final algorithm, consisting of 6 meta-genes (23 genes) and sex-specific age functions.

Results: The final algorithm was validated against an independent set of 526 PREDICT patients, yielding an AUC = 0.70 ± 0.02 , ($p=10^{-16}$) with independently significant performance in men and women, ($p < 0.001$ for each). The classifier added to clinical variables alone (Diamond-Forrester method) in ROC analysis (AUC 0.72 with classifier vs 0.66 without, $p = 0.003$, see figure), and showed significant reclassification relative to clinical models.

Conclusions: We have developed and validated a non-invasive whole blood classifier based on gene expression, age and sex for the assessment of obstructive CAD in non-diabetic patients. Due to its relatively high sensitivity, clinical use of this test may reduce further testing of patients with suspected CAD and low test scores. In addition, due to its ease of use, patients for whom current non-invasive testing modalities yield less accurate results, including obese patients and women, may especially benefit.

