Validation of a Gender-Dependent Blood-Based Gene Expression Test for Diagnosis of Obstructive Coronary Artery Disease in Non-diabetic Patients

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Abstract:
Background: The current diagnosis of significant coronary artery disease (CAD) in stable chest pain patients without prior known disease follows a varied clinical path, and is especially challenging in women. Using whole blood samples from the PREDICT trial, a clinical angiographic population, a gender-specific gene expression test, has been developed.

Methods: Total blood RNA was isolated from PAXgene® tubes drawn from subjects undergoing coronary angiography participating in the PREDICT multicenter trial. Cases had ≥50% stenosis in >1 major coronary artery; controls had < 50% luminal stenosis as determined by quantitative coronary angiography. A 23 gene RT-PCR and demographics based classifier was developed from data on 640 patients in the PREDICT trial. The algorithm consists of gender and age specific gene-expression terms, gene-expression- ratios and is reported on a 1-40 scale. The performance characteristics of the test were prospectively determined in 526 non-diabetic patients (192 cases and 334 controls; 57% male).

Results: ROC analysis yielded an overall AUC = 0.70, (p=10^-16) with significant performance in both the male and female subsets, (p < 0.001 in each gender). The algorithm was significantly additive to clinical variables (Diamond-Forrester method (AUC 0.72 vs. 0.66, p < 0.01) in ROC analysis; classification of clinically defined patient disease status was also significantly improved (p = 0.004). At a threshold algorithm score of 14.75, the test sensitivity was 85% with a specificity of 43%. In this population, 34% of the patients had scores below this threshold.

Conclusion: This whole blood gene expression test provides clinicians with a new and novel, non-invasive diagnostic approach in assessing stable chest pain in non-diabetic patients. It incorporates age and gender in the diagnostic algorithm and appears to improve upon the personalized risk stratification for obstructive CAD.