

## **Identification of a Gene Expression Signature for Obstructive CAD in Whole Blood Using Precise Clinical Phenotyping and Paired Microarray Analysis**

### **Meeting:**

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### **Topic:**

Mechanisms of Atherosclerosis

### **Poster:**

P601

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### **Abstract:**

**Background:** We have previously identified genes in circulating cells that are differentially expressed in patients with coronary artery disease (CAD). To extend this work, given the significant effects of age and sex on CAD risk, we have combined rigorous eligibility criteria with precise CAD phenotyping in a paired case-control whole genome microarray experimental design.

**Methods:** Subjects were enrolled in PREDICT, a prospective multi-center clinical trial designed to compare peripheral blood gene expression with the gold standard of coronary angiography. Subjects had a history of chest pain, a suspected anginal equivalent to chest pain, or had a high risk of CAD, with exclusions for MI, high risk unstable angina, prior revascularization, systemic infection or inflammatory conditions. Angiograms were analyzed by quantitative coronary angiography (QCA) in a core laboratory (Cardiovascular Research Foundation, NY). RNA was isolated from 105 age and gender matched case:control pairs (cases > one stenosis  $\geq 50\%$  and controls no stenosis  $\geq 50\%$ ) and analyzed on whole genome microarrays. Selected significant genes discriminating CAD were further tested by RT-PCR in an independent validation cohort of 504 subjects.

**Results:** QCA yielded % diameter stenosis values that were 10-15 percentage points lower on average than clinical reads, with substantial variability in the differences. Logistic regression yielded 5935 significant genes ( $p < 0.05$ ); subsequent GO analysis showed involvement of the immune response, inflammatory signaling, apoptosis and other immunological processes. Based on

statistical significance and biological relevance, we selected 56 genes for further testing by qPCR in the validation cohort. Of these 56 genes, 32 (57%) were significant by PCR, ~11-fold higher than expected by chance.

**Conclusion:** We have identified a robust gene expression signal in whole blood that discriminates the presence of obstructive CAD. These results may yield a blood-based genomic test that will be useful in the management of chest-pain patients.