

## Highlights of the Development of the Corus<sup>®</sup> CAD Gene Expression Test Algorithm

**CORUS<sup>®</sup> CAD**  
Gene Expression Test By CardioDx

Development of a Blood-Based Gene Expression  
Algorithm for the Assessment of Obstructive  
Coronary Artery Disease in Non-Diabetic Patients

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**CARDIODX<sup>®</sup>**

# Highlights of the Development of the Corus<sup>®</sup> CAD Gene Expression Algorithm

Elashoff MR, Wingrove JA, Beineke P, et al. Development of a Blood-Based Gene Expression Algorithm for Assessment of Obstructive Coronary Artery Disease in Non-Diabetic Patients. *BMC Med Genomics*. 2011;4:26.

## BACKGROUND

Corus CAD is a blood-based gene expression test that uses peripheral blood to quickly and safely assess whether or not a patient's symptoms are due to obstructive coronary artery disease (CAD)\* by measuring the RNA levels of 23 genes that significantly correlate with obstructive CAD.<sup>1</sup> Alterations in gene expression in peripheral blood cells have been shown to be sensitive to the presence and extent of obstructive CAD.

In 2010, Rosenberg et al. published results from the PREDICT Trial, a prospective trial at 39 centers to validate the Corus CAD gene expression test for the assessment of obstructive CAD in stable non-diabetic patients with symptoms suggestive of CAD clinically referred for elective invasive coronary angiography (N=526).

Key finding from the PREDICT Trial:<sup>2</sup>

- Corus CAD demonstrated high sensitivity at 85% and negative predictive value (NPV) at 83% for excluding obstructive CAD as the cause of patient's symptoms

## CORUS CAD ALGORITHM DEVELOPMENT

The Corus CAD algorithm was developed via a combination of microarray and RT-PCR gene expression data analysis, collected from age and sex-matched patients with symptoms suggestive of CAD who were clinically referred for invasive coronary angiography. Actual obstructive CAD status was then measured at angiography for each of these patients.

(SEE FIGURE 1)

The resulting CAD gene expression algorithm was then validated in the PREDICT Trial. The Corus CAD test incorporates patient-specific gene expression, age, and sex data. The resulting Corus CAD score aids clinicians in assessing whether or not an individual patient's symptoms are due to obstructive CAD.

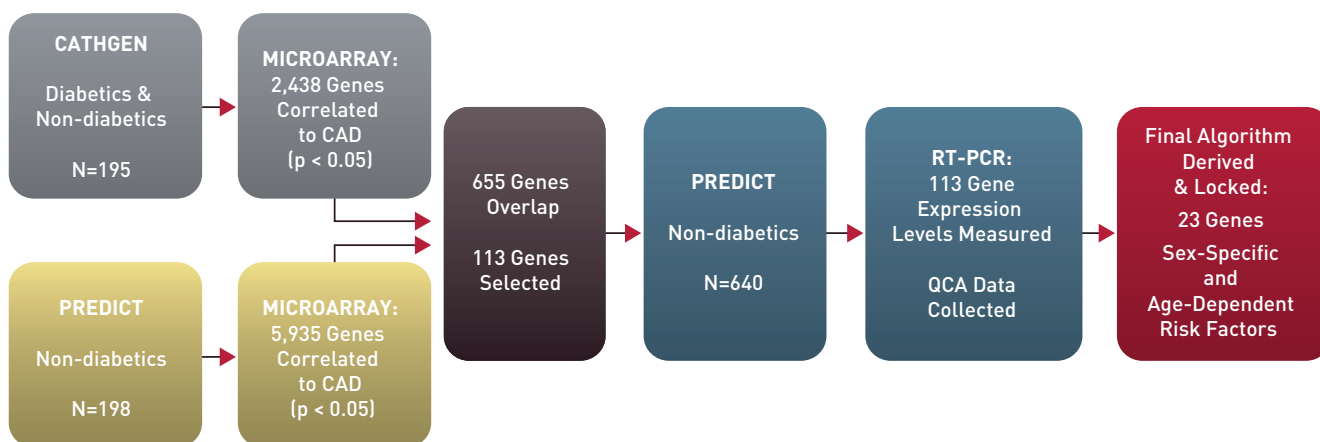


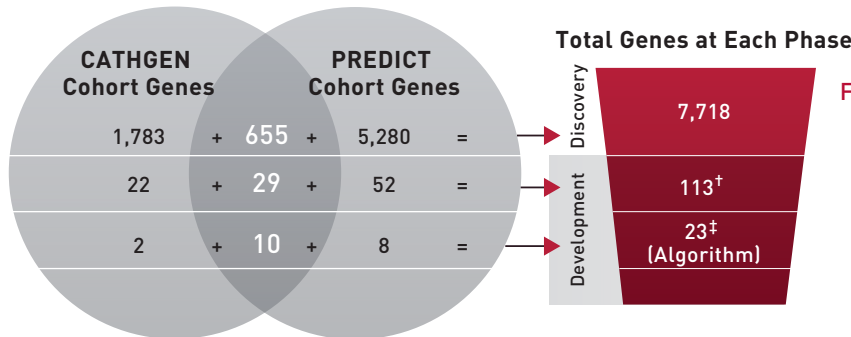
FIGURE 1: Patient flow diagram for Corus CAD algorithm discovery and development

\* Obstructive CAD was defined in the study as at least one atherosclerotic plaque causing  $\geq 50\%$  luminal diameter stenosis in a major coronary artery ( $\geq 1.5\text{mm}$  lumen diameter) as determined by quantitative coronary angiography (QCA).

## KEY FINDINGS

### Independent Patient Cohorts Contributed to the Discovery and Development of a Robust, High-Performance Corus CAD Algorithm

- Independent patient cohorts (from CATHGEN & PREDICT) identified gene expression biomarkers significantly correlated to obstructive CAD (SEE FIGURE 2)

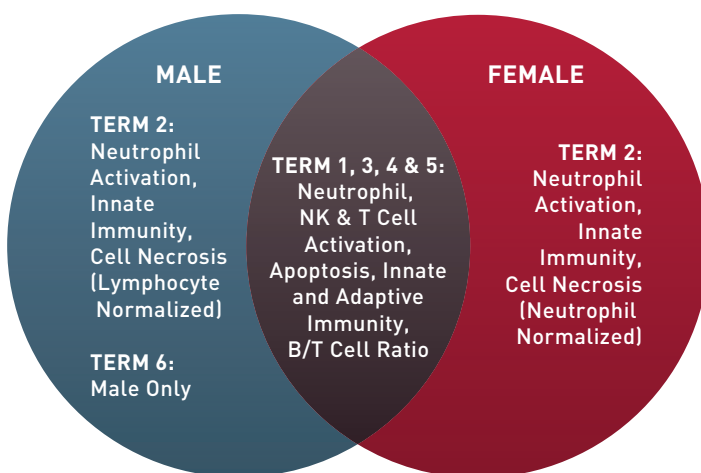


**FIGURE 2:** Corus CAD algorithm gene selection process. All selected genes include biologically relevant genes and cell types significantly correlated to the clinical presentation of obstructive CAD, as measured at invasive coronary angiography

### Corus CAD Algorithm is Comprised of Age, Sex, and the Gene Expression Pattern of Patients

Age, sex, and gene expression are weighted and incorporated into the Corus CAD algorithm

- The 23 genes included in the Corus CAD score include biologically relevant genes and cell types involved in key inflammatory pathways (e.g. T cells, B cells, neutrophils, and NK cells) that correspond to the presence and extent of coronary plaque in obstructive CAD (SEE FIGURE 3)
- Corus CAD is the only sex-specific test for obstructive CAD that accounts for critical biological differences between men and women



**FIGURE 3:** The 23 genes included in the Corus CAD algorithm are grouped into 6 terms and weighted by sex, contributing to the sex-specific diagnostic power of the test. Additional sex-specific and age-dependent variables factor into the final Corus CAD score, increasing the test's sensitivity and negative predictive value

<sup>†</sup> 10 normalization genes were added from Wingrove et al.<sup>1</sup> gene expression data to form a development set of 113 genes for analysis by RT-PCR.  
<sup>‡</sup> 3 normalization genes were added from Wingrove et al.<sup>1</sup> gene expression data to form a final algorithm that included 23 genes.

## CardioDx®

CardioDx, Inc., a pioneer in the field of cardiovascular genomic diagnostics, is committed to developing clinically validated tests that empower clinicians to better tailor care to each individual patient. Strategically focused on coronary artery disease, cardiac arrhythmia and heart failure, CardioDx is poised to expand patient access and improve healthcare quality and efficiency through the commercialization of genomic technologies.

## Corus® CAD Intended Use

The Corus CAD test is a quantitative in vitro diagnostic test performed in a single laboratory, using the gene expression profile of cells found in peripheral blood specimens to be used as an aid to identify patients who are likely to have coronary artery stenosis of at least 50%. The test should be performed on patients with a history of chest pain, with suspected anginal equivalent to chest pain, or with a high risk of coronary artery disease, but with no known prior myocardial infarction or revascularization procedures. The test is not intended for patients with acute myocardial infarction, high risk unstable angina, systemic infectious or systemic inflammatory conditions, diabetes, and/or who are currently taking steroids, immunosuppressive agents, or chemotherapeutic agents.

The test is performed on a blood specimen obtained from the patient. The test incorporates the expression levels of multiple genes using an algorithm with weighted functions to generate a quantitative score. The results of the test should be used by clinicians in conjunction with other tests and clinical information in their assessment of a patient's coronary artery disease.

The Corus CAD test is for prescription use only. The test is not intended to be used to screen for stenosis among patients who are asymptomatic and not considered at high risk for coronary artery disease, to predict or detect response to therapy, or to help select the optimal therapy for patients.

### REFERENCES:

- 1 Wingrove JA, Daniels SE, Sehnert AJ, et al. Correlation of Peripheral-Blood Gene Expression With the Extent of Coronary Artery Stenosis. *Circ Cardiovasc Genet*. 2008;1:31-38.
- 2 Rosenberg S, Elashoff MR, Beineke P, et al. Multicenter Validation of the Diagnostic Accuracy of a Blood-Based Gene Expression Test for Assessing Obstructive Coronary Artery Disease in Nondiabetic Patients. *Ann Intern Med*. 2010;153:425-434.

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