Reviewer's report

Title: Development of a Blood-based Gene Expression Algorithm for Assessment of Obstructive Coronary Artery Disease in Non-Diabetic Patients

Version: 1 Date: 14 January 2011

Reviewer: Damien Chaussabel

Reviewer's report:

This work describes the development of a validated biomarker signature for the assessment of the likelihood of obstructive coronary artery disease in non-diabetic patients. This study benefits from access to a large collection of clinical samples and a rigorous analytic approach. The biomarkers identified are likely to be of clinical benefit.

Specific comments:

1) As pointed out by the authors other studies have identified signatures associated with CAD (e.g. refs 12 and 13); how do these previous finding compare with the signatures associated with the signature described in this manuscript? It would seem logical to factor this information in the selection process.

2) The approach employed here for the development of a diagnostic signature of CAD is principled but also "myopic". Given the large number of samples available it would have been straightforward during the training/discovery phase to compare the performance of several competing prediction models. Is the algorithm presented here – that is rather convoluted – truly constitutes the best approach for classifying cases vs controls? It might turn out to be unnecessarily complicated or arcane. The authors need to benchmark other approaches and report their performance.

3) The manuscript lacks clarity on some key points. The authors should define clearly how this algorithm can be applied, in other words what it can do and cannot do. The language used throughout the manuscript is not always consistent and can easily lead to confusion. For instance the authors state that the signature can be employed for the “Assessment of CAD” or “Identification of CAD” or “Association with CAD” or “Diagnosis of CAD” or “assess the likelihood of obstructive CAD”. Different people can interpret these claims differently. Please state clearly what the intended use for this test is, what it can and cannot do. Basic details are also lacking in the result section, which requires going back and forth between this section and material and methods (e.g. what type of sample what used – whole blood, PBMCS, ??; whether multiple testing corrections were applied, the type of array).

4) The choice of controls is also critical and the authors should provide more details on this point. Are all control subjects with complaints of chest pain? Does
the choice of the control population limit the application of this test in any way? Would the test be able to distinguish between early stage and late stage disease?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests