Reviewer’s report

Title: Genotype-Informed Risk of Coronary Heart Disease Based on Genome-Wide Association Data Linked to the Electronic Medical Record

Version: 1 Date: 9 March 2011

Reviewer: Stanley Shaw

Reviewer’s report:

I applaud the authors for tackling a critical problem – how genotype alters traditional risk stratification -- using a creative EMR-based approach.

My major concern with the manuscript is that the major findings are essentially calculations with no validation from a patient cohort, EMR-based or conventional. The authors state (in the second-to-last sentence of the manuscript) that the structure of their EMR study does not allow them to ascertain CHD phenotypes, which is what a reader might be expecting from an EMR approach.

Major Revisions:
1. p. 10: The authors state that the genetic risk scores did not correlate with traditional risk factors or the Framingham risk score. However, 3 of the 11 SNP loci are related to lipid phenotypes (PCSK9, LDLR, SORT1). Does the genotype at these loci (either one locus at a time, or in aggregate) correlate with the lipid values (esp LDL) extracted from the EMR? This in and of itself would be an interesting contribution to the EMR-based genetics literature, and would potentially help validate their overall approach in this manuscript and their phenotype ascertainment.

2. The lack of EMR validation of the revised risk scores should be made clearer.
   - For instance, the title should be modified to something along the lines of: “Genotype-informed calculations of risk of …” or “Genotype-informed calculated risk of …”
   - The need for validation in traditional or EMR cohorts should be added to Table 5 (Limitations)
   - The absence of empiric validation should be stated more prominently in the Discussion, e.g. at the end of the first paragraph.

Minor Revisions:
1. In the Methods section, it would be helpful to briefly summarize what methods were used in the prior PVD publication to determine that the current study subjects did not have CHD, given the centrality of this to the current study.

2. Some discussion of why the authors chose to use an additive model would be informative (especially since they note in the Discussion that others use multiplicative models).
Level of interest: An article whose findings are important to those with closely related research interests

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