Author's response to reviews

Title: Investigation of 95 variants identified in a genome-wide study for association with mortality after acute coronary syndrome

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Version: 2 Date: 7 June 2011

Author's response to reviews: see over
May 23, 2011

To the Editor:

We are pleased to submit for your reconsideration our manuscript entitled, “Investigation of 95 variants identified in a genome-wide study for association with mortality after acute coronary syndrome.” This prognostic study derived from our recent collaborative work as members of the Myocardial Infarction Genetics Consortium, published in *Nature Genetics*, attempting to identify candidate genes for the occurrence of myocardial infarction. In brief, we were unable to validate genetic variants identified in the process of this GWAS studies as risk factors for all-cause mortality following acute coronary syndromes. However, we were intrigued by one particularly strong association in our initial discovery cohort of 811 white individuals with ACS.

We therefore embarked on an ambitious replication study, eventually including over 3,000 ACS patients in our combined analysis. In the manuscript that we initially submitted for your consideration, we present equivocal but nominally statistically significant evidence of an association between the rs6922269 variant in the *MTHFD1L* gene and mortality. In response to the reviewers of our initial work, we tripled our sample size in an effort to replicate our original finding, but ultimately, we found no association in over 9,000 patients and now report our work as a negative study. We also responded point-by-point to the suggestions of the three reviewers who helped us to improve our work, which we hereby resubmit to BMC Medical Genetics. In addition to valuable data that will be useful for future large-scale genetic meta-analyses, our work breaks ground in the field of cardiovascular genetic prognosis studies, highlighting the ongoing challenges of sample size requirements in the post-GWAS era.

In terms of disclosure of potential conflict of interest, Dr. Krumholz discloses that he has research contracts with the Colorado Foundation for Medical Care and the American College of Cardiology, serves on the advisory boards for Amgen, Alere and United Healthcare, is a subject matter expert for VHA, Inc., and is Editor-in-Chief of Journal Watch Cardiology of the Massachusetts Medical Society. Drs. Morgan and Spertus and the other authors have no conflicts of interest to report with regards to the subject matter of this paper. For completeness, Dr. Spertus discloses that he has received grant and contract support from the NIH, American Heart Association, American College of Cardiology Foundation’s National Cardiovascular Data Registry, Lilly, BMS/Sanofi, Amgen and EvaHeart. He has served as a consultant to United Healthcare, Quest Diagnostics and St. Jude and has an equity position in Health Outcomes Sciences.

We appreciate the opportunity to submit our work to *BMC Medical Genetics*. 
Sincerely,

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