Disclosure of the Genetic Risk of Alzheimer's Disease:
A Rejoinder to Green et al.'s Response to Our Critique

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As many as 5.3 million people in the United States are estimated to be afflicted by Alzheimer's disease, with the overall costs of Alzheimer's and other dementias to Medicare, Medicaid and businesses estimated at upwards of $148 billion each year.[1] Issues related to treatment, care, and research into the disease have, understandably, had a high public policy profile and attracted considerable public attention. One such issue is the desirability of genetic testing of relatives of Alzheimer's patients for their own predisposition to Alzheimer's. A key concern in the debate is the possible psychological effects of the test: does knowing that one is genetically predisposed have harmful psychological consequences apart from those that may be wrought by the onset of the disease itself? And in light of those potential consequences, should testing be encouraged?

In a much publicized article in the *New England Journal of Medicine*, Green et al.[2] present the results of a randomized study that they argue show that at least in the short-run, the genetic testing has no appreciable harmful effects with respect to the standard measures of anxiety and depression. Their article was followed by our exchange with the authors in a later issue of the same journal.[3] Below is our rejoinder to the authors' reply.

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In our January 13, 2010 correspondence to the *New England Journal of Medicine*, we argue that the conclusions reached by Green et. al. in their July 16, 2009 article were based on a flaw in the study's research design: the use of the wrong control group. In a reply, the authors dispute this contention. Their arguments are unconvincing.

First, the authors state, "Our design was focused on isolating the effect of disclosure of genetic risk on persons who were motivated to learn about their own risk of Alzheimer's disease. A comparison group of persons who did not have an interest in their own risk of Alzheimer's disease would therefore be inappropriate…" But this is beside the point: our critique does not imply that the appropriate control group should consist of individuals who lacked interest; the issue, rather, is the information to which those subjects *with* an interest were exposed.

Second, the authors argue, "a comparison group of persons who had such an interest and who received no information at all would have measured the effect of risk disclosure without reference to the genetic component." But from a public policy perspective, the critical question is whether a group of individuals (those with an interest in their own risk of Alzheimer's), in the aggregate, would be more anxious and/or depressed with or without the availability of testing. Whether individuals in that group actually have the relevant genetic marker has no bearing on

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[1] *2009 Alzheimer's Decease Facts and Figures,* Alzheimer's Association.
[2] Green RC, Roberts JS, Cupples LA, et al. Disclosure of *APOE* genotype for risk of Alzheimer's disease. N Engl J Med 2009;361: 245-54.
[3] Gordon, SC, and others, Disclosure of the genetic risk of Alzheimer's disease. N Engl J Med 2009;362: 181-2.

this question. (To illustrate the problem with the authors' argument, consider the following example: if we wanted to determine whether, on average, taking midterm exams is stressful to undergraduates, we would compare students randomly assigned to classes with or without midterms, not students in classes with midterms randomly assigned to have their grades revealed or withheld; the actual midterm grade of any individual student is irrelevant to the broader question of aggregate effect.)

Finally, the authors argue that priming was likely not an issue, because "subjects entered the study with an inflated sense of their risk of disease, and that "in-depth interviews of subjects whose scores changed the most did not reveal any priming but instead referenced stressors that were not related to the risk of Alzheimer's disease."

With respect to the first point, the claim that the subjects already had "an inflated sense of their risk of disease" before entering the study does not help the authors' case: (a) it represents another bias *in favor* of their null findings (it suggests that these subjects have already internalized some of the effect of knowing that one has the increased risk of Alzheimer's); and (b) an inflated sense of risk of Alzheimer's could quite plausibly *increase*, rather than decrease, the size of the priming effect: being tested and not told the results could heighten anxiety for those who are already psychologically affected by the possibility of the disease to a greater degree than for those who are not.

With respect to the second point, this approach to "explaining away" elevated depression levels seems contrary to the spirit of the rigorous quantitative analysis that otherwise guides the Green et al. study. Can one really disentangle the effects of Alzheimer's-related and non-Alzheimer's related stressors, given the possible existence of cross-stressor effects? To our knowledge, there is no accepted systematic methodology for doing this – simply because the entailed inferences would be ad hoc. Nor does the authors' comment here sit well with the fact that 14 subjects withdrew from the study, "citing study-related reasons" (Green et. al. 2009, p. 248). For those subjects, participation in the study, presumably, had some kind of negative effects, whether implicitly or explicitly psychological, or other.

We conclude with two additional notes. First, the differences reported in our Table 1 reflect what we believe are the "best available" estimates of the causal quantities of interest given the studies' flawed design – using as an approximation to the correct control group the pooled set of subjects at baseline. However, if we were conducting the study from scratch, we would implement a very different design – one in which the control group was not tested at all, and whose anxiety and depression were measured at baseline and subsequently.

Second, as indicated in our original comment on the Green et al. study, because of the effects of self-selection, the psychological consequences as measured against the correct control would probably be even greater than those we report in our comment. While Green et al.'s response suggests that they are not concerned about self-selection because only individuals motivated to learn about their own risk would ever submit to testing, this seems to miss a fundamental point about the consequences of research like this: the level of interest in testing is not fixed. Whether doctors recommend the test or whether patients develop an interest in it both depend on perceptions of the study itself.