Reply to Stephan et al.

To the Editor: Stephan et al. advocate for a responsible approach to the use of personal genomic profiles in disease prevention, early detection, and treatment. They stress that companies should use only results of high-quality association studies to bring customers accurate genetic risk predictions, as well as effective strategies for reducing risk for those conditions to which they are predisposed. We agree fully.

Our review of genomic profiles currently offered by seven different companies found that all of the profiles were based in part on genetic associations that are not well established.[1] On average, statistically significant associations were found for 58% of the genes included in the profiles listed in Table 1 of our article, which specifies the results per company. This percentage varied among profiles offered by each company: 38% to 83% for the profiles offered by Company 1, 38% to 60% for Company 2, and 40% to 80% for Company 3. Companies 4, 5, 6, and 7 each offered a single profile; for these profiles, the proportions of included gene variants with statistically significant associations were 42%, 80%, 47%, and 47%, respectively. All of these proportions can be calculated directly from Table 1 in our article.[1]

Stephan et al. note that genome-wide association studies have provided strong evidence for disease associations with several genes in multiple studies, including *TCF7L2* (MIM 602228) and *NOD2* (MIM 605956), and that customers can benefit from a personalized report of these associations. On the whole, our review found that even statistically significant associations had fairly small effects on disease risk. The associations with the largest effects were of *APOE* (MIM 107740) and *IL-6* (MIM 147620) with Alzheimer's disease (MIM 104300) (odds ratios [ORs] 3.2 and 0.54, respectively) and *TNF-α* (MIM 191160) with systemic lupus erythematosus (MIM 152700) (OR 2.1) and psoriasis (MIM 177900) (OR 0.57). These effects are larger than the effect of *TCF7L2* on the risk of type 2 diabetes (MIM 125853)[2] and are comparable to the per-allele effect of *NOD2* on the risk of Crohn's disease (MIM 266600) in most populations.[3] Most genetic variants identified in genome-wide association studies have even smaller effects in the range of OR 1.15–1.35.

Although establishing robust, consistent genetic associations is a necessary first step to developing any genetic test, robust association is insufficient to establish utility. Genetic variants with small effects—and even genetic variants with apparently large effects—tend to have low predictive value, because the difference in absolute risks between carriers and noncarriers of the risk variants tends to be small.[4,5] Determining whether combining tests for multiple variants in genomic profiles will yield higher predictive value still requires empirical evidence. Furthermore, evidence is lacking to argue that knowledge of risk is sufficient to motivate healthy behavior in carriers without promoting complacency in noncarriers. Controlled clinical trials are needed to assess the impact of such information on behavior change in people with positive and negative tests.

At this stage, given our incomplete knowledge in the genetics of common diseases, there is no evidence that health benefits can be meaningfully personalized on the basis of genomic profiles. Therefore, a responsible approach to personal genomics requires conducting additional research to adequately translate genomic research findings into useful tools for disease prevention. At the same time, it is important to continue to educate the public that healthy behavior—such as physical activity and eating a balanced diet—is good for all, regardless of genetic susceptibility.

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Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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DOI 10.1016/j.ajhg.2008.06.012.