controls in the genomic regions we presented, on the SNP level as evidenced by the basic allele test, and on the allele level as evidenced by the haplotype association test (Fig. 2 of our article). Imputation of classic HLA alleles, which in general are determined by appreciation of known variants only, may lead to rare alleles being missed or imputed with low confidence because of the limited size of the reference database given the highly polymorphic HLA locus.[2] Since ultimately even the presence of statistically independent signals does not prove their causality, only sequence-based methods with accompanying cell and molecular biologic analyses will be able to confirm causative variants within genomic regions recognized by a genomewide association study.[3]

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Since publication of their article, the authors report no further potential conflict of interest.

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Direct-to-Consumer Genomewide Profiling

TO THE EDITOR: Before we conclude that genomewide profiling does not cause psychological harm, we need to use the correct measures. Bloss and colleagues (Feb. 10 issue)[1] assessed whether profiling triggered situational anxiety and symptoms of post-traumatic stress. It is not surprising that the authors found no increase in adverse outcomes: the scales they used measured whether participants felt jittery or blue at the time of the survey or whether knowledge of the test results caused participants to have trouble breathing or sleeping. Such generic measures of well-being may not detect the stresses that medical testing exerts on some people.[2,3] For example, news of having a high risk of diabetes would probably not cause symptoms that are global or severe, but it might result in a meaningful increase in anxiety about diabetes.

We do not know whether participants felt heightened distress about their newly discovered health risks. Querying consumers about their distress in relation to these risks is crucial. Until we understand whether knowledge of the results of genomewide profiling has disease-related adverse affects on well-being, policy decisions made about access to these tests are premature.

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TO THE EDITOR: The expansion of direct-to-consumer marketing of individual genetic profiles for risk assessment and disease prevention is symptomatic of a larger problem concerning the relationship between clinicians and diagnostic testing. Although the direct-to-consumer genomewide test is designed to provide an estimate of risk rather than diagnostic information, it is similar to many diagnostic tests in that it may be prematurely deployed without appropriate evidence to support its use.[1] Several limitations and the lack of valuable requirements in the process of evaluating and adopting new diagnostic tests are being increasingly emphasized. Issues that need to be addressed include not only the lack of measurable short-term outcomes[2] but also the appropriateness of testing, interpretation, and

use of results and the lack of demonstration of positive long-term clinical outcomes. The evidence indicating that there are no direct effects is a sign that the request for diagnostic tests unrelated to a true clinical question does not translate into medical actions and health care benefits. Finally, the easy availability of these tests brings with it a financial burden, both for patients and for health care systems, especially when the tests requested by the patient do not have a pertinent medical indication.[3]

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THE AUTHORS REPLY: Salz and Brewer point out that disease-specific distress was not evaluated in our study on direct-to-consumer genomewide profiling. Although we agree that this is an important question, we did not address it because of the need to keep our assessments brief (completion of a separate instrument for each of 23 conditions would have been prohibitively time-consuming) and because of our interest in assessing the overall effect of disclosing the risk associated with multiple conditions simultaneously. Nevertheless, we did examine statistical associations between condition-specific risk estimates and scores from the psychological measures used. In addition, the instruments we selected are the same as or similar to those used in previous single-gene, single-condition studies of psychological response to genetic testing,[2] and our finding of lack of psychological harm after testing is highly consistent with the findings in these studies (most of which evaluate the effect of estimates of risk that have a much higher degree of association with a particular condition — e.g., testing for mutations in *BRCA1* and *BRCA2*). Finally, to delay policy-making decisions until all possible questions have been answered with respect to direct-to-consumer genomewide testing is unrealistic[2] given the state of the field.

Plebani and Lippi state that several important issues related to direct-to-consumer genomewide testing remain unaddressed. We agree that there are several outstanding research questions. However, Plebani and Lippi also suggest that our findings of lack of effect at short-term follow-up, coupled with what they cite as the "financial burden" of direct-to-consumer genomewide testing, imply that such tests should not be readily available to consumers. We observed no increases in actual health screening after testing, and so we question the assertion that these tests constitute a significant financial burden for the health care system. Until evidence of detrimental effect emerges, we suggest erring on the side of allowing patients access to the genetic information made available by direct-to-consumer genomewide tests.

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Point-of-Care Ultrasonography

TO THE EDITOR: With respect to the review article by Moore and Copel (Feb. 24 issue)[1] on point-of-care ultrasonography, we have several concerns that we hope will be carefully considered by anyone who is thinking about embarking on the use of such technology. The study by the U.S. Preventive Services Task Force (USPSTF) that is cited by the authors pertained to "ultrasonography performed in a setting with adequate quality assurance (that is, in an accredited facility with cre-