The hidden harm behind the return of results from personal genome services: a need for rigorous and responsible evaluation

A. Cecile J.W. Janssens, PhD^{1,2}

Whether the delivery of genetic test results directly to consumers has harmful effects has been the subject of scientific debate since the first personal genome services became available. Many researchers and professional societies have expressed concerns about the unclear predictive ability and clinical utility of the tests;^{1–3} others showed no evidence of adverse psychological or behavioral consequences.^{4–10} Although the scientific studies conducted so far have indeed shown no evidence of adverse effects, they all had serious limitations that hampered the proper interpretation and generalizability of the findings.

Many studies were conducted among “early adopters” of personal genome services, who were most often white, better educated, and in better physical and mental health.^{4–7} The largest study of its kind ($n > 2,000$) concluded that these early adopters may better understand the minor impact that genes have on the development of common diseases.^{4,5} However, regarding the generalizability of their findings, the authors wrote that “given that [our sample] is quite homogenous (e.g., highly educated, high income), our conclusions may not be applicable to other groups of individuals should the market expand, or to the general population.”⁵

In a study reported in this issue of *Genetics in Medicine*, Hartz et al.⁸ investigate a population that is virtually the opposite of the early adopters. Of their population, 66% had levels of depression above clinical thresholds, all were nicotine-dependent smokers, and more than half were African American, did not have a college education, were unemployed, and had no health insurance. So far, so good. However, although the authors concluded that “even in an underserved population ... subjects responded positively to personalized genetic results,” upon close analysis their results suggest that participants may not have understood the tests: The observed increase in smoking cessation attempts was unrelated to receiving test results of increased risk, and 95% of the participants considered their test results useful while they all received risks that were predicted for Caucasians, also the African-American customers.

A major and unavoidable limitation of studies of consumer experiences with personal genome services is that tests for

common diseases still have limited predictive ability.² Most people have probably received risk estimates that were only slightly higher (or lower) than the average risk for a disease, and these were not sufficiently alarming to increase anxiety and distress. The findings of such studies can be generalized to other personal genome tests with limited predictive ability but not to tests that yield very informative test results.

That even the return of results from highly predictive tests may not increase harm is often evidenced by citing the REVEAL study,¹¹ which investigated responses to receiving *APOE* results for the risk of Alzheimer disease. The study was conducted in children of patients with Alzheimer disease, who were well aware of their risks. The authors cautioned that “if *APOE* genotyping had been provided without genetic counseling or to subjects who had no family history of Alzheimer’s disease, the results might have been different.”¹¹ Furthermore, of the 301 people who initially consented, 139 (46%) declined participation before randomization in the study; the people who did participate may have been those who thought themselves able to deal with the results.

Similar limitations were observed in a recent interview study of 23andMe customers who tested positive for *BRCA1/2* mutations.⁶ Although the title of the article suggests that the results were “unexpected,” most did know about their possible genetic predisposition: 81% self-identified as Ashkenazi Jewish, two-thirds had a first- or second-degree relative with breast or ovarian cancer, and 22% even knew already that they were carriers. This study also had a low participation rate (24%), which the authors acknowledged by stating that they “relied on volunteers willing to share their experiences. The emotional responses reported by the 16 men and 16 women ... may differ from those experienced by the 61 male and 43 female mutation-positive individuals who did not reply to our invitation.” Moreover, one-third of all customers had not accessed their *BRCA* test results at the time of the study, which further suggests that not everyone was ready to receive these results.

Reviewing these and other studies^{7,9} in light of their methodological shortcomings makes it less surprising that they found

¹Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA; ²Department of Clinical Genetics/EMGO Institute for Health and Care Research, Section Community Genetics, VU University Medical Center, Amsterdam, The Netherlands. Correspondence: A. Cecile J.W. Janssens (cecile.janssens@emory.edu)

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no evidence of adverse psychological responses. When people are aware that they may be at increased risk, a transient impact is expected to be observed. When tests have limited utility and no demonstrated utility, no harmful effects are expected, especially not among more highly educated early adopters. And when the participation rate is low, it is more likely that the population consists of people who anticipate that they will be able to handle possible adverse results.

What these studies do show is that early adopters can handle noninformative test results, that relatives of patients who choose to receive the test results can handle highly predictive results as well, and that genetic testing might be confusing for people from underserved populations. But their generalizability is otherwise limited. None of the study populations were representative of the general population at large, and other groups may still experience adverse psychological or behavioral effects, for example, late adopters of personal genome testing for low-risk genes and those without a family history who undergo testing for highly predictive variants.

Findings such as these are also not generalizable to future scenarios in which genetic tests for common diseases have higher predictive ability. Discoveries in genomics research are being made so quickly that applied psychological and behavioral studies are virtually outdated by the time their scientific articles are published. For example, at the time of participant recruitment for the study by Hartz et al.,⁸ published genetic risk models already included twice as many single-nucleotide polymorphisms (SNPs) as were included in the test that was studied, namely, 40 SNPs (instead of 16) for type 2 diabetes and 33 SNPs (instead of 17) for prostate cancer.^{12,13}

Yet, apart from the potential of harm in populations that were not investigated in previous studies, there is also evidence suggesting hidden harm among people who were invited to participate in the study but declined or did not finish the study. The *nonparticipation* rates of the four mentioned studies ranged from 39 to 76%. The potential for harm in these groups is not merely theoretical; (anticipated) feelings of anxiety and distress might have been an important reason for nonparticipation. That the low participation rates were not considered in the conclusions of these studies is a concerning omission. Qualitative studies are needed to examine the concerns and worries of those who declined participation.

The 2010 Cochrane Review of risk-reducing behaviors following communication of predictive genetic test results concluded that the methodological quality of most early studies

was poor.⁹ In addition, more recent studies had methodological limitations that hampered the interpretation and generalizability of the findings, such as small sample size, short follow-up, self-reported behavioral change, and a focus on intentions and not actual behavior change.^{4-8,11} Although these studies may have been the most feasible at the time, we now need a more rigorous effort for better-quality studies with appreciable participation rates and responsible interpretation of the findings. With regard to the return of results to consumers regarding their risk of common diseases, an absence of harm has not been demonstrated. Well-designed studies that investigate both benefits and harms are desperately needed if we are to ultimately realize the promise of genomic medicine.

DISCLOSURE

The author declares no conflict of interest.

REFERENCES

1. Caulfield T, McGuire AL. Direct-to-consumer genetic testing: perceptions, problems, and policy responses. *Annu Rev Med* 2012;63:23-33.
2. Kalf RR, Mihaescu R, Kundu S, de Knijff P, Green RC, Janssens AC. Variations in predicted risks in personal genome testing for common complex diseases. *Genet Med* 2014;16:85-91.
3. Baudhuin LM. The FDA and 23andMe: violating the First Amendment or protecting the rights of consumers? *Clin Chem* 2014;60:835-837.
4. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N Engl J Med* 2011;364:524-534.
5. Bloss CS, Wineinger NE, Darst BF, Schork NJ, Topol EJ. Impact of direct-to-consumer genomic testing at long term follow-up. *J Med Genet* 2013;50:393-400.
6. Francke U, Dijamco C, Kiefer AK, et al. Dealing with the unexpected: consumer responses to direct-access BRCA mutation testing. *PeerJ* 2013;1:e8.
7. Kaphingst KA, McBride CM, Wade C, et al. Patients' understanding of and responses to multiplex genetic susceptibility test results. *Genet Med* 2012;14:681-687.
8. Hartz SM, Olsson E, Culverhouse R, et al. Return of individual genetic results in a high-risk sample: enthusiasm and positive behavioral change. *Genet Med* 2014;xx:xxx-xxx.
9. Marteau TM, French DP, Griffin SJ, et al. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. *Cochrane Database Syst Rev* 2010;10:CD007275.
10. Green RC, Farahany NA. Regulation: The FDA is overcautious on consumer genomics. *Nature* 2014;505:286-287.
11. Green RC, Roberts JS, Cupples LA, et al.; REVEAL Study Group. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med* 2009;361:245-254.
12. de Miguel-Yanes JM, Shrader P, Pencina MJ, et al.; MAGIC Investigators; DIAGRAM+ Investigators. Genetic risk reclassification for type 2 diabetes by age below or above 50 years using 40 type 2 diabetes risk single nucleotide polymorphisms. *Diabetes Care* 2011;34:121-125.
13. Johansson M, Holmström B, Hinchliffe SR, et al. Combining 33 genetic variants with prostate-specific antigen for prediction of prostate cancer: longitudinal study. *Int J Cancer* 2012;130:129-137.