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VIEWPOINT

Uninformed consent in nutrigenomic research

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Genetic testing for personalizing diet and wellness programs is performed without extensive counseling that informs about the potential implications of knowing one's genotype status. Genetic counseling seems redundant for genes that impact the effect of diet on biomarkers such as cholesterol and blood pressure, but the same genes may have pleiotropic effects that cannot be ignored. A well-known example is the *APOE* gene, which is implicated in cholesterol regulation and is a major risk factor for Alzheimer's disease. Not fully informing participants about the major pleiotropic effects of genes has ethical implications and invalidates informed consent.

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Imagine you are invited to participate in a nutrigenomic study that investigates whether genetic testing can enhance nutrition recommendations. You decide to join the study, sign the informed consent, and undergo genetic testing. A few weeks later, you learn that you carry one or two copies of the *APOE**4 allele. On the basis of this result, you are recommended to reduce saturated fat intake to maintain healthy cholesterol levels and improve your cardiovascular health. You try to comply with this recommendation. Then one evening, sitting on the couch, watching television, you hear a doctor say that *APOE* is a major risk factor for Alzheimer's disease and that having two copies of the *APOE**4 allele increases the risk of Alzheimer's disease by >10-fold. You were not informed about this risk. What would you think? How would you feel?

This story may be fictional, but the problem, unfortunately, is not. The European Food4me project investigated whether personalized nutrition advice could be improved by genetic testing of five genes, one of which was *APOE*.[1] Participants were informed that *APOE* plays a role in determining cholesterol levels and the development of cardiovascular disease, but not that the gene is a major risk factor for Alzheimer's disease (AD). Carriers of the *APOE* risk variant were recommended to reduce saturated fat intake to improve cholesterol levels and other factors related to cardiovascular health.[1] While the researchers may not have intended to disclose the risk variant—they did not specify the risk variants for the four other genes—the participant feedback did reveal that the targeted *APOE* variant was E4 (see Supplementary Figure 7 in Celis-Morales *et al.*[2]). Consequently, participants were informed whether they carry an E4 variant, but not how many copies. Another nutrigenomic study investigated the impact of learning about *APOE* genotype on adherence to genotype-based dietary and physical activity advice. The researchers informed participants in the invitation letter that the AD risk of *APOE*4 carriers is increased by 3–4 or 10–15 fold depending on the number of risk alleles, and that 'carrying the E4 variant does not automatically mean the person is invariably going to have Alzheimer's disease, and that the pathogenic effects of *APOE* can, at least to some extent, be counteracted by adopting a healthy diet and increasing physical exercise.'[3] In this study, the question is whether the brief written information about relative risks was sufficient for participants to understand the potential serious implications of knowing their AD risk. Participants gave informed consent in the baseline interview with a nutritionist and they did have the opportunity to decline the blood test and gene results but this option was not preceded by adequate information about reasons to decline the disclosure of genetic test results. Genetic counseling was offered only after learning about the genetic test results, not before.

There are no guidelines or protocols that specify how people should be informed about their *APOE* genotype in nutrigenomic testing, but clinical guidelines exist for genetic testing related to AD risk. The American College of Medical Genetics and the National Society of Genetic Counselors recommend against the use of *APOE* testing for predicting AD risk because of its poor predictive value and limited clinical utility.[4] While the *APOE**4 allele substantially increases the risk of AD, the exact risk estimates vary widely between populations and there are no options for preventing or postponing the disease that can be adopted upon early knowledge of increased risk. It is therefore not clear that the eventual benefits of testing might outweigh the burden and risks. American College of Medical Genetics and National Society of Genetic Counselors also state that when testing is done for genetic conditions involving a high risk, it should occur only within the context of pre-and post-test counseling and with support of someone with expertise in the genetics of AD.[4] It would seem self-evident that these guidelines should also inform research studies that involve such testing.

Testing and disclosing *APOE* genotypes without providing full information about the gene's impact on the risk of AD should be considered as serious neglect for several reasons. First, in research involving human subjects, potential harms must be minimized.[5] When participants are not informed about the full meaning and implications of learning about their *APOE* status, they may be confronted with these implications later on, unexpectedly and involuntarily. We know from the REVEAL I study that children of AD patients seem to handle the disclosure of genetic test results relatively well, but these people opted for testing after being informed about its implications, and were already aware of being at increased risk based on family history.[6] The findings from the REVEAL study cannot be extrapolated to unsuspecting research participants in the context of nutrigenomics studies, hence the impact of AD risk disclosure in the latter population is unknown. In the absence of the safeguards commonly provided by professional counseling

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and clinical advice, the risk of psychological harm might be substantial.

Second, withholding full information about the association between *APOE* status and AD risk violates participants' right to information, as well as their right not to know. In the REVEAL I study, 50% of the invited people declined participation before randomization;[6] rates of refusal were similarly high in the REVEAL II study.[7] Such high degree of non-participation suggests that many participants did not want to be informed about their *APOE* status, which underlines the importance of informing participants about the disclosure of AD risk even when AD is not the focus of the study. Research participants should be given the opportunity to opt out of receiving their test results or to withdraw from the study to prevent disclosure of AD risk. Although participants could withdraw from the two nutrigenomics studies, they were not informed that the AD risk could be a reason to do so. The ethical requirement of informed consent formally presupposes that prospective participants are educated about the risks and implications of a study before they decide whether or not to participate. Learning about the risk of AD is a serious implication of *APOE* testing that should be disclosed as part of the informed consent process.[8] Testing individuals without proper information about potential serious implications is a major omission that invalidates the informed consent.

In a research field with no tradition of genetic counseling, no risk communication and no focus on diseases as endpoints, it is understandable that the testing of the *APOE* gene did not raise the question about the need for genetic counseling. Nutrigenomic testing generally focuses on single nucleotide polymorphisms that each only have a minimal impact on the risk of disease. This minimal impact conveys no real potential for harm for participants and therefore genetic counseling about disease risks is simply not standard practice for nutrigenomic tests. Also, nutrigenomic test reports typically mention whether a variant is present or absent, instead of communicating genetic risks—the impact of the variants on disease risk is generally so small that a motivational influence on diet, lifestyle and health behavior should not be expected from communicating genetic risk information.[9] This small impact might also be the reason why nutrigenomic tests focus on changing intermediate phenotypes, such as cholesterol, folic acid and waist circumference, rather than reducing the risk of disease.

These studies illustrate the disconnect between nutrigenomics and clinical genetics. The name might suggest a multidisciplinary research field, but nutrigenomics is predominantly a sub-discipline of nutrition sciences, not of genomics, and apparently not informed by clinical genetics. Nutrigenomic research teams are primarily affiliated at nutrition departments, institutions and the industry, and when genomic researchers are involved, their expertise is mostly in the basic sciences such as molecular biology and population genetics, not in clinical genetics. Nonetheless, the Nutrigenomics (NuGO) BioEthics Guidelines state that 'genotyping that will allow predicting high disease susceptibility is only acceptable to be disclosed in a research context if it is subjected to appropriate genetic counseling.'[10] With these self-imposed guidelines in place since 2007, it is surprising that pre-test genetic counseling was not part of the protocol for *APOE* testing in the two studies.

The need for genetic counseling was apparently also not considered during the ethical evaluation. Both studies were approved by institutional review boards, which for the European project were review boards at each of the participating institutions. The question is whether the researchers provided the review boards with the information that was essential to decide about ethical approval. Review boards cannot be expected to possess detailed knowledge about the pleiotropic effects of polymorphisms and the potential harms of genetic testing, when these are not explicitly mentioned by the researchers in the protocol. The responsibility for assessing the risks and benefits associated with the research protocol and for presenting these to the review board, falls first on the investigators themselves.[8]

The responsibility to accurately inform people about genetic risks is not limited to researchers, it also holds for companies.[11] *APOE* genotyping is also used for recommending diet, lifestyle, and nutritional supplements by companies who offer their products directly to consumers.[12] And, until recently, several companies were offering *APOE* testing to predict concussion risk, including one that offered *APOE* testing for children.[13] Some companies would recommend that people with E4 variations avoid high impact sports because of their increased concussion risk, without disclosing the AD risk.

Researchers have an obligation to fully inform participants about the benefits and potential harms of research participation as part of the informed consent process. They also have an obligation to minimize potential risks and to help maintain trust in scientific research. Not informing participants about AD risk before testing *APOE* genotype is a major omission. While *APOE* may be an exception in terms of the magnitude of the pleiotropic effect, there are other genes whose effects on disease risk may be stronger than their impact on diet, exercise, sports performance and other wellness outcomes, such as *F5* (thrombophilia), *HFE* (hemochromatosis), and *HLA* (autoimmune diseases), and pharmacogenetics markers such as *CYP1A2*.[14] Evaluation by multidisciplinary institutional review boards is needed to decide whether and which pleiotropic effects need to be communicated. This evaluation should require the involvement of clinical genetics experts to prevent undisclosed harms of participation in genetic research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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