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Minding the Aging Brain: Are We Ready for Personalized Medicine?

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In this issue, Lineweaver and colleagues (1) report two remarkable findings: After cognitively normal older adults learn they have the ε4 allele of the APOE gene that increases the risk of developing Alzheimer's disease, they perform worse on measures of subjective and objective cognition compared with older adults who have this genotype but do not know their genotype. Conversely, those who learn that they do not carry an ε4 allele perform better on measures of subjective cognition compared with ε4-negative individuals who do not know they are ε4 negative.

In a nested case-control design, the APOE genotype disclosure cohort was drawn from cognitively and neurologically healthy adults whose average age was in the 70s and who were enrolled in either a study of cognitive and neuroimaging changes associated with aging or a study to assess the impact of genetic testing on mood and health behaviors. Fifteen of the 74 participants (~20%) in this cohort chose not to learn their APOE genotype and were enrolled in the nondisclosure cohort— a design that may have introduced confounding by indication, as the participants who had less desire to learn their APOE genotype may also have had less concern about their cognition. Disclosure, performed by a genetic counselor, covered the necessary topics, and notably, no participant requested additional counseling. Cognitive testing for the disclosure cohort was then performed some time after disclosure, ranging from 1 to 24 months (mean of 8 months). The control cohort of participants who did not know their APOE genotype was assembled from several memory center cohorts to match the disclosed group on age, years of education, cognition, and APOE genotype distribution.

APOE genotype alone was not associated with how participants rated their cognitive abilities, but the interactions of genotype and disclosure were associated with self-ratings of cognitive abilities. On the capacity scale of the Metamemory in Adulthood Questionnaire and on three of the five scales of the Memory Functioning Questionnaire, persons who learned that they were ε4 positive rated themselves lower than did ε4-positive individuals who did not know their genotype. In contrast, people who knew they were ε4 negative rated their memory abilities better than did ε4-negative individuals who did not know their

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genotype. These results suggest that knowledge of genotype, not the genotype itself, affects subjective cognition.

Even more provocative was the association between knowledge of ε4-positive genotype and performance on widely used measures of memory. Older adults who knew they were ε4 positive performed worse than those who were ε4 positive but did not know their genotype, although this association was seen only on the measure of verbal memory (the logical memory test) and not the measure of visual memory (the Rey-Osterrieth Complex Figure Test).

What explains these results? They do not seem to be explained by depressive symptoms. Other psychiatric features, such as anxiety and test-related distress, were not assessed in this study, so it is not possible to infer whether they may explain the findings. Given that disclosure of APOE genotype has been associated with mild, short-term test-related distress (2, 3), future work should examine the role of this and other psychiatric features. The results could potentially be explained by the content of disclosure and the affect of the researchers who told participants about their genotype risk. How we frame risk has a substantial impact on how people react to that information (the authors do not go into detail on this issue, reporting only that “disclosure was performed by an experienced genetic counselor”). The results may also reflect stereotype threat or lowered self-efficacy, in which being told that you may perform poorly on a test can in turn lead to poor performance (4). This phenomenon is well described in the educational testing literature and is often cited to explain gender, ethnic, and racial differences in test performance (5).

Regardless of the explanation, the results of this study are concerning. They come at a time when how we think about the nature of Alzheimer’s disease is radically transforming (6). Genes and biomarkers are being used to stratify cognitively normal persons who have a risk, over time, of developing clinically significant cognitive impairment. The operative word is *risk*.

Among these measures, APOE genotype is a robust predictor of a person’s lifetime risk of developing sporadic Alzheimer’s disease. In an era when hundreds of thousands of individuals have learned about their genetic risk factors for common complex disorders, including their APOE genotype (7), through consumer genomics companies, it is concerning that this knowledge alone may influence performance on cognitive tests.

Genetic tests are not the only measures that indicate risk among cognitively normal individuals. About 30% of cognitively normal older adults are amyloid positive, and the percentage is higher among persons who are ε4 positive (8). It is therefore entirely plausible that a substantial portion of the ε4-positive individuals in the Lineweaver et al. study were amyloid positive and therefore in the “preclinical” stage of Alzheimer’s disease. If severity of preclinical disease is measured by cognitive performance, then did disclosure of APOE worsen their disease? Moreover, amyloid-positive individuals are currently being recruited (with disclosure of that status) for clinical trials in which they will receive medication intended to delay the appearance of cognitive signs. If the awareness of positive amyloid

status, like awareness of APOE status, influences neuropsychological testing—the primary outcome measure in these studies—then the outcome could suffer unexpected bias.

The results from Lineweaver et al. need replication using a randomized and controlled design. Such a design has been employed by the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study to show that APOE disclosure does not adversely affect the mood and well-being of middle-aged adults with a family history of Alzheimer's dementia, but the REVEAL study did not assess effects of APOE genotype disclosure on cognition (2). If the effect is replicated, then studies would also be warranted to test whether interventions might mitigate this effect.

Alzheimer's disease is not the only neuropsychiatric disorder being transformed by biomarkers. The director of the National Institute of Mental Health has remarked that the latest edition of DSM remains overly descriptive, and he argues that disease-associated biomarkers should be the foundation for defining mental illness (9). Policy makers have been carried along. Vice President Biden recently enthused that we should "imagine when we are able to identify the biomarkers for mental illness" (10). As psychiatry and neurology leap into the era of personalized medicine, the results of studies like this one show that we must also examine how this new model of medicine and medical care will affect our patients' health and well-being. They also show how cognitive impairment in aging is not simply the result of brain lesions, but a disruption in the homeostasis between the individual, the brain, and the world the person lives in—or, in short, a disruption of the mind.

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