

Curbside Consultation

Clinical and Personal Utility of Genetic Risk Testing

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Case Scenario

A 65-year-old East Asian woman recently shared with me the results of her 23andMe test, which revealed that she had one copy of the $\epsilon 4$ genetic variant, indicating that she has a slightly increased risk of Alzheimer disease. The test instructed her to consider talking to a health care professional if she had any symptoms of Alzheimer disease or any concerns about her test results. The test results showed she was at average risk of other genetic conditions. She is otherwise healthy, takes no medications, has no known family history of Alzheimer disease, and has no chronic conditions. She works full time as a software engineer. She reports misplacing items, such as her car keys or phone, a few times per week, and she is usually able to locate them in 15 to 30 minutes. She asked me whether she should obtain long-term care insurance given her test results.

What is the evidence for *APOE* genetic predictive testing for late-onset Alzheimer disease? Should these genetic test results be included in my patient's medical record? Is she protected from health or life insurance company rate discrimination? How should I advise her about long-term care insurance?

Commentary

On April 6, 2017, the U.S. Food and Drug Administration (FDA) approved marketing of the 23andMe Personal Genome Service, the first direct-to-consumer genetic test. This test uses genomic DNA collected from mail-in saliva collection kits to provide information on a patient's genetic risk of certain medical diseases or conditions. The diseases and conditions covered by 23andMe that were originally approved by the FDA include α_1 -antitrypsin deficiency,

celiac disease, factor XI deficiency, Gaucher disease, glucose-6-phosphate dehydrogenase deficiency, hereditary thrombophilia, Parkinson disease, late-onset Alzheimer disease, primary dystonia, and hereditary hemochromatosis (Table 1). Currently, genetic testing for six of these disorders (α_1 -antitrypsin deficiency, celiac disease, hereditary hemochromatosis, hereditary thrombophilia, late-onset Alzheimer disease, and Parkinson disease) and age-related macular degeneration are offered in the 23andMe genetic health risk report. On March 6, 2018, the FDA approved testing for three mutations in the *BRCA1* and *BRCA2* genes conferring risk of hereditary breast and ovarian cancers as a separate service. Direct-to-consumer genetic testing for *BRCA1/BRCA2* is not included in this discussion because, unlike the other tests mentioned, there is evidence of clinical utility for *BRCA1/BRCA2* in patients with high-risk family histories¹ and because the complexity of the topic warrants a separate discussion.

The patient in this scenario has the $\epsilon 3/\epsilon 4$ genotype for the *APOE* gene. The *APOE* gene encodes the apolipoprotein E protein, which is a carrier for cholesterol that is found in the central nervous system and the rest of the body. The $\epsilon 4$ variant is associated with a higher risk of developing late-onset Alzheimer disease. Individuals of European ancestry with one copy of the variant have an 18% to 20% chance of developing Alzheimer disease by 85 years of age, whereas individuals with two copies of the $\epsilon 4$ variant have a higher risk—51% to 68% by 85 years of age.^{2,3}

The evidence supporting the association between the *APOE* gene and late-onset Alzheimer disease is compelling, including a genome-wide meta-analysis with a sample size of more than 70,000⁴; however, there are important caveats for this patient. First, the evidence is based mostly on studies of persons with European ancestry, although this association has also been reported in persons of East Asian descent.⁵ It is possible that the same gene influences the same phenotype (e.g., late-onset Alzheimer disease), but the clinical validity (i.e., a test's ability to identify or accurately and reliably predict the clinically defined disorder or phenotype of interest) of this genetic variant is uncertain for patients of East Asian descent.⁶

Second, there are no data from prospective trials for any racial/ethnic group establishing the clinical utility of

Case scenarios are written to express typical situations that family physicians may encounter; authors remain anonymous. Send scenarios to afpjournal@aafp.org. Materials are edited to retain confidentiality.

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genetic testing for *APOE* variants (i.e., evidence that testing leads to measurable improvement in clinical outcomes and that it adds value for management decision making compared with no genetic testing).⁶ Similar caveats apply to the other conditions covered in the 23andMe genetic health risk tests—namely, that clinical validity data are usually based on studies of European-ancestry populations and that demonstration of improved clinical outcomes has not yet been established.

The ability to use genetic health risk test results to plan for one's future may have personal utility (i.e., a test's impact on psychosocial outcomes, such as family planning, lifestyle changes, and future decision making),⁷ even if available evidence does not show clinical utility. In March 2017, the National Academies of Sciences, Engineering, and Medicine published a consensus study report that recommended consideration of the personal utility of a genetic test to individual patients when deciding whether to advise testing.¹ Therefore, although *APOE* test results may not be medically actionable for Alzheimer disease treatment or cardiovascular disease prevention,^{5,8} the results for patients may be personally valuable if it captures actual disease risk and enables future planning and risk modification. These principles also apply to the other conditions covered in the 23andMe tests.

In 2008, the Genetic Information Nondiscrimination Act was passed, prohibiting health insurance companies from discriminating based on genetic test results.⁹ However, this law does not include life insurance, long-term care insurance, disability insurance, or workplace wellness programs (which can decrease health insurance premiums), and it does not protect patients with preexisting genetic conditions from rate hikes or noninsurability.¹⁰ There is evidence that persons who learn that they have at least one *APOE* $\epsilon 4$ allele have a higher probability of increasing their long-term care insurance.^{11,12} Insurance companies can ask consumers directly to disclose if they have undergone genetic testing and can request medical records before underwriting

such policies. Including direct-to-consumer genetic testing results in medical records may have unintended consequences, so patients should be informed about the limits of the law's privacy protections and asked if they want to have these results included in their medical records.

For the patient in this scenario, after performing a neurologic examination and screening for cognitive decline, the physician should advise her that the results are not

TABLE 1

Selected Conditions from the 23andMe Personal Genome Service Genetic Health Risk Tests

Disease or condition	Effect on risk phenotype	Genetic variant
Age-related macular degeneration*	Vision loss in older adults	Y402H variant in <i>CFH</i> gene A69S variant in <i>ARMS2</i> gene
Alpha ₁ -antitrypsin deficiency*	Increased risk of lung or liver disease	PI*Z variant in <i>SERPINA1</i> gene PI*S variant in <i>SERPINA1</i> gene
Alzheimer disease*	Increased risk of late-onset Alzheimer disease	$\epsilon 4$ variant in <i>APOE</i> gene
Celiac disease*	Increased risk of celiac disease	HLA-DQ2.5 haplotype in <i>DQA1*0501</i> gene
Factor XI deficiency†‡	Increased risk of bleeding following trauma or surgery	F283L variant in <i>F11</i> gene E117X variant in <i>F11</i> gene IVS14+1G>A variant in <i>F11</i> gene
Gaucher disease†‡	Increased risk of Gaucher disease symptoms	N370S variant in <i>GBA</i> gene 84GG variant in <i>GBA</i> gene V394L variant in <i>GBA</i> gene
Glucose-6-phosphate-dehydrogenase deficiency§	Increased risk of anemia	Val68Met variant in <i>G6PD</i> gene
Hereditary hemochromatosis*	Increased risk of hereditary hemochromatosis and iron overload	C282Y variant in <i>HFE</i> gene H63D variant in <i>HFE</i> gene
Hereditary thrombophilia*	Increased risk of blood clots	Factor V Leiden in the <i>F5</i> gene Prothrombin G20210A in the <i>F2</i> gene
Parkinson disease*†	Increased risk of Parkinson disease	G2019S variant in <i>LRRK2</i> gene N370S variant in <i>GBA</i> gene
Primary dystonia†‡	Increased risk of early-onset primary dystonia (DYT1/TOR1A-related)	DeltaE302/303 variant in <i>DYT1</i> gene

*—Most relevant for persons of European descent.

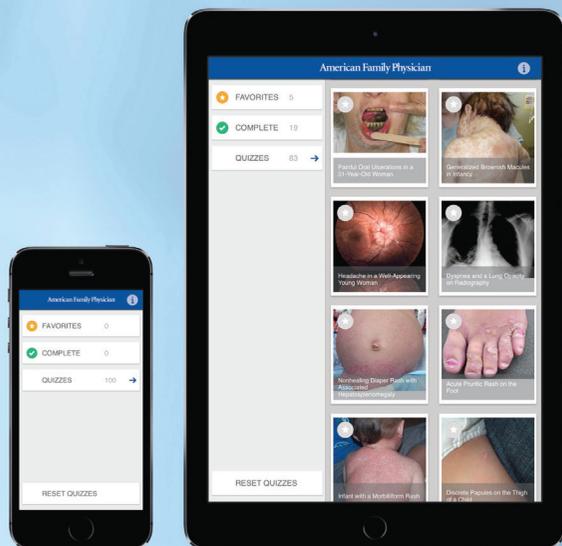
†—Most relevant for persons of Ashkenazi Jewish descent.

‡—Test cleared by the U.S. Food and Drug Administration on April 6, 2017, but not included in the 23andMe genetic health risk profile as of March 9, 2018.

§—Most relevant for persons of African descent.

||—Most relevant for persons of North African Berber descent.

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diagnostic for Alzheimer disease but that she is at increased risk because of her sex and *APOE* genotype. She should be advised that maintaining a healthy blood pressure and exercising regularly can reduce the risk of Alzheimer disease, and that it is reasonable to consider increased genetic risk as a factor in decision making regarding long-term care insurance. The physician should also advise her that at this time, the evidence has not shown improved clinical outcomes for using *APOE* genetic testing to prevent or treat Alzheimer disease. She should be asked if she wants to include the test results in her medical record, given that this information could be used by life and long-term care insurance companies to determine eligibility and insurance rates.

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