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Patients asking about *APOE* gene test results? Here's what to tell them

This guidance can help shape the conversations you have with patients who want to understand the results of their gene and biomarker testing for Alzheimer disease.

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Advances in Alzheimer disease (AD) genes and biomarkers now allow older adults to undergo testing and learn about their risk for AD.[1] Current routes for doing so include testing in cardiology, screening for enrollment in secondary prevention trials (which use these tests to determine trial eligibility),[2] and direct-to-consumer (DTC) services that provide these results as part of large panels.[3] Patients may also obtain apolipoprotein (*APOE*) genotype information as part of an assessment of the risks and benefits of treatment with aducanumab (Aduhelm) or other anti-amyloid therapies that have been developed to stop or slow the progression of AD pathologies.

Expanded access to testing, in combination with limited guidance from DTC companies, suggests more older adults may consult their primary care physicians about this testing. In this narrative review, we use a vignette-driven approach to summarize the current scientific knowledge of the topic and to offer guidance on provider-patient discussions and follow-up.

First, a look at *APOE* genotyping

In cognitively unimpaired older adults, the *APOE* gene is a known risk factor for mild cognitive impairment (MCI) or AD.[3] A person has 2 alleles of the *APOE* gene, which has 3 variants: ε2, ε3, and ε4. The combination of alleles conveys varying levels of risk for developing clinical symptoms (**TABLE 1**[4]), with ε4 increasing risk and ε2 decreasing risk compared to the more common ε3; thus the ε4/ε4 genotype conveys the most risk and the ε2/ε2 the least.

The *APOE* gene differs from other genes that have been identified in early-onset familial AD. These other genes, which include *APP*, *PSEN1*, and *PSEN2,* are deterministic genes that are fully penetrant. The *APOE* gene is not deterministic, meaning there is no combination of *APOE* alleles that are necessary or sufficient to cause late-onset AD dementia.

In clinical trials of amyloid-modifying therapies, the *APOE* gene has been shown to convey a risk of amyloid-related imaging abnormalities (ARIA).[5] That is, in addition to conveying a risk for AD, the gene also conveys a risk for adverse effects of emerging treatments that can result in serious injury or death. This includes the drug aducanumab that was recently approved by the US Food and Drug Administration (FDA).[6] In this review, we focus primarily on common clinical scenarios related to *APOE*. However, in light of the recent controversy over aducanumab and whether the drug should be offered to patients,[7-9] we also describe how a patient's *APOE* genotype may factor into drug candidacy decisions.

Testing, in clinic and "at home." To date, practice guidelines have consistently

TABLE 1

Risk for MCI or dementia due to AD based on *APOE* genotype[4]

APOE genotype[a]	Lifetime risk estimate[b]
ε4/ε4	30%-55%
ε3/ε4	20%-25%
ε3/ε3	10%-15%

AD, Alzheimer disease; *APOE*, apolipoprotein; MCI, mild cognitive impairment.
[a] For the remaining genotypes (ε2/ε2, ε2/ε3, ε2/ε4), insufficient data exist to calculate reliable estimates.
[b] Through age 85.

recommended against *APOE* genetic testing in routine clinical practice. This is primarily due to low clinical prognostic utility and the lack of actionable results. Furthermore, no lifestyle or pharmaceutical interventions based on *APOE* genotype currently exist (although trials are underway[10]).

In 2017, the FDA approved marketing of DTC testing for the *APOE* gene.[11] While DTC companies tend to issue standardized test result reports, the content and quality can vary widely. In fact, some provide risk estimates that are too high and too definitive and may not reflect the most recent science.[12]

7 clinical scenarios and how to approach them

Six of the following vignettes describe common clinical scenarios in which patients seek medical advice regarding *APOE* test results. The seventh vignette describes a patient whose *APOE* genotype may play a role in possible disease-modifying treatments down the road. Each vignette is designed to guide your approach to patient discussions and follow-up. Recommendations and considerations are also summarized in **TABLE 2**[13-16].

Vignette 1

Janet W, age 65, comes to the clinic for a new patient visit. She has no concerns about her memory but recently purchased DTC genetic testing to learn about her genetic health risks. Her results showed an *APOE* ε4/ε4 genotype. She is now concerned about developing AD. Her mother was diagnosed with AD in her 70s.

Several important pieces of information can be conveyed by the primary care physician. First, patients such as Ms. W should be told that the *APOE* gene is not deterministic; many people, even those with 2 ε4 alleles, never develop dementia. Second, no specific preventive measures or treatments exist based on an individual's *APOE* genotype (see Vignette 5 for additional discussion).

In this scenario, patients may ask for numeric quantification of their risk for dementia (see **TABLE 1**[4] for estimates). When conveying probabilistic risk, consider using simple percentages or pictographs (eg, out of 100 individuals with an ε4/ε4 genotype, 30 to 55 develop MCI or AD). Additionally, because people tend to exhibit confirmatory bias in thinking about probabilistic risk, providing opposing interpretations of an estimate may help them to consider alternative possibilities.[17] For example, ε4/ε4 individuals have a 30% to 55% risk for MCI or AD. Alternatively, they have a 45% to 70% risk of *not* developing MCI or AD.

There are important caveats to the interpretation of *APOE* risk estimates. Because *APOE* risk estimates are probabilistic and averaged across a broader spectrum of people in large population cohorts,[4] estimates may not accurately reflect a given individual's risk. The ranges reflect the uncertainty in the estimates. The uncertainty arises from relatively small samples, the rareness of some genotypes (notably ε4/ε4) even in large samples, and variations in methods and sampling that can lead to differences in estimates beyond statistical variation.

Vignette 2

Eric J, age 85, presents for a new patient visit accompanied by his daughter. He lives independently, volunteers at a senior center several times a week, and exercises regularly, and neither he nor his daughter has any concerns about his memory. As a gift, he recently underwent DTC genetic testing and unexpectedly learned his *APOE* result, which is ε4/ε4. He wants to know about his chances of developing AD.

Risk conveyed by *APOE* genotype can be modified by a patient's age. At age 85, Mr. J is healthy, highly functional, and cognitively unimpaired. Given his age, Mr. J has likely

TABLE 2

How to address *APOE* genetic test results with older adults in primary care[13-16]

Approaches	Action steps	Examples
Counsel about *APOE*	Provide education and discuss expectations. Help individuals avoid predatory advertising of products that are, without scientific evidence, suggested to modify personal risk or cognitive function and often marketed as "memory boosters." Refer to a genetic counselor to provide patients with access to added expertise and guidance, as appropriate.	"Out of 100 individuals with an ε3/ε4 genotype, 20-25 develop MCI or AD." Offer opposing interpretations of an estimate, such as: "ε3/ε4 individuals have a 20%-25% risk of developing MCI or AD. Alternatively, they have a 75%-80% risk of *not* developing MCI or AD." "Many people, even those with 2 ε4 alleles, never develop dementia, and there are no specific preventive measures or treatments based on an individual's *APOE* genotype." "Estimates may not reflect your specific risk, as they're based on generalizations about groups of people."
Assess and reassess psychological well-being	Use a behavior scale to aid assessing and monitoring an individual's well-being. Reassess at a 2 to 4–week follow-up visit. Reinforce routines and encourage healthy and mindful practices to help alleviate patient distress from unexpected genetic test results. Consider referring the patient to a psychologist or psychiatrist.	Administer measures such as The Impact of Genetic Testing for Alzheimer's Disease (IGT-AD) scale and Patient Health Questionnaire-9 (PHQ-9). Ask, "How does this test result compare to other pieces of health information that you've learned?" "For individuals who learn this result unexpectedly, it can be particularly upsetting. Was this how it was for you?"
Complete baseline cognitive assessment	For patients > 60 years, assess subjective memory concerns and perform a brief cognitive exam to serve as a baseline for future evaluations.	Complete a brief cognitive assessment, such as the Mini-Mental Status Exam, and a self-report questionnaire of cognitive symptoms.
Address stigma	Personalize and validate an individual's experience to help address internalized stigma. Correct misinformation and adjust expectations to be more accurate.	"Tell me what you know about *APOE*? … about AD?" Use answers to these questions to correct beliefs that are false or exaggerated.
Make recommendations to reduce dementia risk	Address 9 modifiable risk factors—education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact—and their potential effect in reducing individuals' risk of dementia.[15,16]	Recommend 150 min/wk of aerobic exercise and diets that support brain health, such as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet.[13,14] Manage depression and chronic illness. Prevent social isolation. Support smoking cessation.
Document with discretion	Be cautious about documenting discussions in the medical record because the results can have unforeseen consequences, such as later limiting an individual's ability to obtain long-term care insurance.	In the chart, you might say, "Discussed questions about direct-to-consumer testing" rather than, "Discussed patient's *APOE* test result."

AD, Alzheimer disease; *APOE*, apolipoprotein; MCI, mild cognitive impairment.

"outlived" much of the risk for dementia attributable to the ε4/ε4 genotype. His risk for dementia remains high, but this risk is likely driven more by age than by his *APOE* genotype. Data for individuals older than age 80 are limited, and thus risk estimates lack precision. Given Mr. J's good health and functional status, his physician may want to perform a brief cognitive screening test to serve as a baseline for future evaluations.

Vignette 3

Audrey S is a 60-year-old African American woman who comes to the clinic for her annual

visit. Because her father had AD, she recently purchased DTC genetic testing to learn about her *APOE* genotype and risk for AD. Her results are ε3/ε4. She is wondering what this may mean for her future.

Lack of diversity in research cohorts often limits the generalizability of estimates. For example, both the frequency and impact of *APOE* ε4 differ across racial groups.[18] But most of the data on *APOE* lifetime risk estimates are from largely White patient samples. While *APOE* ε4 seems to confer increased risk for AD across sociocultural groups, these effects may be attenuated in African American and Hispanic populations.[19,20] If Ms. S is interested in numeric risk estimates, the physician can provide the estimate for ε3/ε4 (20%-25% lifetime risk), with the important caveat that this estimate may not be reflective of her individual risk.

It may be prudent to determine whether Ms. S, at age 60, has subjective memory concerns and if she does, to perform a brief cognitive exam to serve as a baseline for future evaluations. Additionally, while the Genetic Information Nondiscrimination Act (GINA, 2008) prohibits health insurers and employers from discriminating based on genetic testing results, no legal provisions exist regarding long-term care, disability, or life insurance. Documented conversations about *APOE* test results in the medical record may become part of patients' applications for these insurance products, and physicians should be cautious before documenting such discussions in the medical record.

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Vignette 4

Tina L, age 60, comes to the clinic for a routine wellness visit. She recently developed an interest in genealogy and purchased a DNA testing kit to learn more about her family tree. As part of this testing, she unexpectedly learned that she has an *APOE* ε4/ε4 genotype. She describes feeling distraught and anxious about what the result means for her future.

Ms. L's reaction to receiving unexpected genetic results highlights a concern of DTC *APOE* testing. Her experience is quite different from individuals undergoing medically recommended genetic testing or those who are participating in research studies. They receive comprehensive pre-test counseling by licensed genetic counselors. The counseling includes psychological assessment, education, and discussion of expectations.[2]

In Ms. L's case, it may be helpful to explain the limits of *APOE* lifetime risk estimates (see Vignettes 1-3). But it's also important to address her concerns. There are behavior scales that can aid the assessment and monitoring of an individual's well-being. The Impact of Genetic Testing for Alzheimer's Disease (IGT-AD) scale is a tool that assesses psychological impact. It can help physicians to identify, monitor, and address concerns.[21] Other useful tools include the Patient Health Questionnaire-9 (PHQ-9) and the Geriatric Depression Scale (GDS) for depression, and a suicide or self-harm assessment.[2,22,23] Finally, a follow-up visit at 2 to 4 weeks may be useful to reassess psychological well-being.

Vignette 4 (cont'd)

Ms. L returns to the clinic 2 weeks later, reporting continued anxiety about her *APOE* test result and feelings of hopelessness and despair.

Some patients struggle with knowing their *APOE* test result. Test result–related distress is often a combination of depression (as with Ms. L), anger, confusion, and grief.[24] Cognitions often include worries about uncertainty, stereotyped threat, and internalized stigma.[25,26] These issues can spill over to patient concerns about sharing an *APOE* test result with others.[27]

Intolerance of uncertainty is a transdiagnostic risk factor that can influence psychological suffering.[28] Brief cognitive behavioral interventions that reinforce routines and encourage healthy and mindful practices may help alleviate patient distress from unexpected genetic test results.[29] Interventions that personalize and validate an individual's experience can help address internalized stigma.[30] Referral to a psychologist or psychiatrist could be warranted. Additionally, referral to a genetic counselor may help provide patients with access to added expertise and guidance; useful web-based resources for identifying an appropriate referral include https://medlineplus.gov/genetics/

understanding/consult/findingprofessional/ and https://findageneticcounselor.nsgc.org/.

Vignette 5

Bob K, age 65, comes to the clinic for his annual exam. He is a current smoker and says he's hoping to be more physically active now that he is retired. He says that his mother and grandmother both had AD. He recently purchased DTC genetic testing to learn more about his risk for AD. His learned his *APOE* genotype is ε3/ε4 and is wondering what he can do to decrease his chances of developing AD.

Mr. K likely would have benefited from pretest counseling regarding the lack of current therapies to modify one's genetic risk for AD. A pre-test counseling session often includes education about *APOE* testing and a brief evaluation to assess psychological readiness to undergo testing. Posttest educational information may help Mr. K avoid predatory advertising of products claiming—without scientific evidence—to modify risk for cognitive decline or to improve cognitive function.

There are several important pieces of information that should be communicated to Mr. K. Emerging evidence from randomized controlled trials suggests that healthy lifestyle modifications may benefit cognition in individuals with *APOE* ε4 alleles.[31] It would be prudent to address proper blood pressure control[32] and counsel Mr. K on how he may be able to avoid diabetes through exercise and weight maintenance. Lifestyle recommendations for Mr. K could include: smoking cessation, regular aerobic exercise (eg, 150 min/wk), and a brain-healthy diet (eg, the Mediterranean-DASH Intervention for Neurodegenerative Delay [MIND] diet).[13,14] Moreover, dementia prevention also includes appropriately managing depression and chronic illnesses and preventing social isolation and hearing loss.[15,16] This information should be thoughtfully conveyed, as these interventions can improve overall (especially cardiovascular) health, as well as mitigating one's personal risk for AD.

Vignette 6

Juan L, age 45, comes in for his annual physical exam. He has a strong family history of heart disease. His cardiologist recently ordered lipid disorder genetic testing for familial hypercholesterolemia. This panel included *APOE* testing and showed Mr. L's genotype is ε2/ε4. He read that the *APOE* gene can be associated with an increased AD risk and asks for information about his genotype.

Mr. L received genetic testing results that were ordered by a physician for another health purpose. Current recommendations for genetic testing in cardiology advise pretest genetic counseling.[33] But this counseling may not include discussion of the relationship of *APOE* and risk for MCI or AD. This additional information may be unexpected for Mr. L. Moreover, its significance in the context of his present concerns about cardiovascular disease may influence his reaction.

The ε2/ε4 genotype is rare. One study showed that in healthy adults, the frequency was 7 in 210 (0.02 [0.01-0.04]).[34] Given the rarity of the ε2/ε4 genotype, data about it are sparse. However, since the ε4 allele increases risk but the ε2 allele decreases risk, it is likely that any increase in risk is more modest than with ε3/ε4. In addition, it would help Mr. L to know that AD occurs infrequently before age 60.[35] Given his relatively young age, he is unlikely to develop AD any time in the near future. In addition, particularly if he starts early, he might be able to mitigate any increased risk through some of the advice provided to Mr. K in Vignette 5.

Vignette 7

Joe J, age 65, comes to the clinic for a new patient visit. He has no concerns about his memory but has a family history of dementia and recently purchased DTC genetic testing to learn about his genetic health risks. His results showed an *APOE* ε4/ε4 genotype. He is concerned about developing AD. He heard on the news that there is a drug that can treat AD and wants to know if he is a candidate for this treatment.

Mr. J would benefit from the education provided to Ms. W in Vignette 1. Patients such as Mr. J should be advised that while an *APOE* ε4/ε4 genotype conveys an increased risk for AD, it is not deterministic of the dis-

Emerging evidence from RCTs suggests that healthy lifestyle modifications may benefit cognition in individuals with *APOE* ε4 alleles.

ease. While there are no specific preventive measures or treatments based on *APOE* genotype, careful medical care and lifestyle factors can offset some of the risk (see Vignette 5 for discussion).

Recently (and controversially), the FDA approved aducanumab, a drug that targets amyloid.[6,36] Of note, brain amyloid is more common in individuals with the *APOE* ε4/ε4 genotype, such as Mr. J. However, there would be no point in testing Mr. J for brain amyloid because at present the drug is only indicated in symptomatic individuals—and, even in this setting, it is controversial. One reason for the controversy is that aducanumab has potentially severe adverse effects. Patients with the ε4/ε4 genotype should know that this genotype carries increased risk for the most serious adverse event, ARIA—which can include brain edema and microhemorrhages.

One reason for the aducanumab controversy is that the drug has potenially severe adverse effects.

What lies ahead?

More research is needed to explore the impact that greater AD gene and biomarker testing will have on the health system and workforce development. In addition, graduate schools and training programs will need to prepare clinicians to address probabilistic risk estimates for common diseases, such as AD. Finally, health systems and medical groups that employ clinicians may want to offer simulated training—similar to the vignettes in this article—as a practice requirement or as continuing medical education. This may also allow health systems or medical groups to put in place frameworks that support clinicians in proactively answering questions for patients and families about *APOE* and other emerging markers of disease risk. JFP

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