Considering *APOE* Testing for Leqembi

What is Leqembi (lecanemab)?
Leqembi is a drug developed by BioArctic AB, Biogen, and Eisai Co., Ltd. Leqembi has been found to slow cognitive decline (memory loss) in people living with early-stage Alzheimer's disease. Lecanemab is the scientific name of the drug. It is marketed as Leqembi.

What is *APOE*?
APOE is a gene. Everyone has two copies of *APOE* because they inherit one from their mother and one from their father. There are three different types of *APOE*. We refer to them as the e2, e3, and e4 types of *APOE*.

Knowing what types of the *APOE* gene someone has can provide important risk information. *APOE* can impact the risk for developing Alzheimer's disease, and also the risk for certain side effects associated with some treatments, like Leqembi.

Why is *APOE* testing recommended if you are considering Leqembi?
Some people taking Leqembi can develop small spots of bleeding or temporary swelling of the brain. This is also called ARIA (Amyloid-Related Imaging Abnormalities). These types of changes can be seen on a brain scan called an MRI.

People with MRIs that show temporary brain swelling or small spots of bleeding often do not experience symptoms. But, symptoms such as headache, vision changes, confusion, and problems with walking are possible.

People with one or two copies of the e4 type of *APOE* have an increased risk for this side effect (ARIA).

If I have one or two copies of e4, can I still be prescribed Leqembi?
There are increased risks of side effects for people with one or two copies of *APOE* e4. The risks are higher in people with two copies of APOE e4. You and your physician should discuss all possible risks and benefits before making your decision about taking Leqembi.

What is the relationship between the *APOE* gene and Alzheimer's disease?
Everyone has two copies of the *APOE* gene. One copy is inherited from your mother and one copy from your father. These genes do not change with age. Each *APOE* gene is one of three types: *APOE* e2, *APOE* e3 or *APOE* e4.

This means that a person's *APOE* gene test result will be some combination of the three types. For example, someone could have an e3 and an e4 as their *APOE* result and another person may have two copies of the e3 type.

The e4 type of APOE is associated with an increased risk of developing dementia due to Alzheimer's disease. Approximately one of every four people in the general population have at least one copy of this type of *APOE* gene.
Someone who has one copy of the *APOE* e4 gene is at higher risk for developing dementia due to Alzheimer's disease than someone who has no copies of e4. If a person has two copies of *APOE* e4, their risk is further increased.

The e4 type of the *APOE* gene is only one of many possible risk factors for dementia due to Alzheimer's disease. Not everyone with the e4 type of the *APOE* gene will develop dementia due to Alzheimer's disease. In fact, there are people with dementia due to Alzheimer's disease who have no copies of *APOE* e4.

The e2 and e3 types of *APOE* are not considered to be risk factors for developing dementia related to Alzheimer's disease.

What can my *APOE* result tell me about my family members?
Learning your *APOE* results could also have implications for family members. Some people may have feelings of worry or guilt when thinking about children or siblings who may have also inherited one or two copies of *APOE* e4.

If someone has two copies of *APOE* e4, this means that all of their children must have at least one copy of the *APOE* e4 gene type. For someone with an *APOE* e3/e4 result, this would mean that there was a 50% chance of passing the e4 copy to any children, and an equal 50% chance of passing the e3 copy. Their children would also inherit one type of *APOE* from their other parent, which could be the e2, e3, or e4 type.

Keep in mind that you got one copy from your mother and one from your father. Your results could also show a possible risk for *APOE* e4 for your parents and siblings. For these reasons, you may want to consider discussing your decision to learn your *APOE* results with family members.

Should my family members get *APOE* genetic testing*?*
APOE testing is currently recommended only for patients with cognitive decline considering Leqembi.

APOE testing is NOT currently recommended for people without cognitive decline. Family members who do not have cognitive decline who are interested in more information about *APOE* testing should speak with a genetic counselor. A genetic counselor can address the limitations and potential impact of *APOE* testing for people without symptoms.

What does my *APOE* result tell me about my diagnosis of Alzheimer's disease?
Your *APOE* results do not impact your clinical diagnosis of mild cognitive impairment or Alzheimer's disease. APOE e4 cannot confirm or predict an Alzheimer's disease diagnosis. It is important to remember that there are other factors, besides *APOE*, that could increase or decrease a person's risk for Alzheimer's disease.

Are there other risk factors in addition to the *APOE* e4 gene that can lead to dementia caused by Alzheimer's disease?
Yes. The greatest risk factor for developing Alzheimer's disease is older age, especially for those who are over 70 years old. However, Alzheimer's disease is not a normal part of aging.

Other factors that might increase the risk for Alzheimer's disease:

- Having a family history of dementia
- Certain health conditions, such as cardiovascular disease, diabetes and high blood pressure

If you have any questions regarding these risk factors, please consult with your doctor.

What if I have multiple family members with dementia? Is the *APOE* gene the only possible genetic link?
APOE is not the only gene that has been associated with dementia. *APOE* is a genetic risk factor for the most common type of Alzheimer's disease. There is a less common type of Alzheimer's disease that affects people at a younger age (before age 65).

This young-onset type of Alzheimer's disease can be caused by genes other than *APOE*. There are also other types of dementia that are not Alzheimer's disease. Examples of these other types include frontotemporal dementia (FTD) and Lewy body dementia (DLB). These different types of dementia are associated with different genes.

If you have concerns about your family history of dementia, ask your doctor to refer you to a genetic counselor. A genetic counselor can help make sure that the most appropriate genetic test is offered to you.

Is the APOE gene associated with risk for any conditions besides Alzheimer's disease?
The *APOE* gene is also known to play a role in the cardiovascular system. Some people with different versions of the *APOE* gene can have increased risk for conditions related to the heart.

For example, people with one or two copies of e4 can have higher risk for buildup of plaque in the heart's arteries that could lead to coronary artery disease (CAD) and heart attack, also known as myocardial infarction (MI). *APOE* can also influence a person's risk for stroke and vascular dementia.

People with two copies of the *APOE* e2 gene have risk for a condition called type III hyperlipoproteinemia. There have also been associations between *APOE* and age-related hearing loss and age-related macular degeneration.

Does my ancestry matter when thinking about *APOE* and Alzheimer's disease risk?
We still have a lot to learn about how genes impact health risks in different racial and ethnic groups. From what we know today, the e4 type of *APOE* has the strongest impact on risk of Alzheimer's disease in people of White, European ancestry. *APOE* e4 has less of an impact on Alzheimer's risk in those who are of Latin American, Hispanic or African descent. More research needs to be done to better understand how the e4 type of *APOE* impacts risk for Alzheimer's disease in diverse populations.

How can I access genetic counseling?

If you have additional questions and would like to speak with a genetic counselor, please contact Penn Telegenetics at 215-614-0262 or telegenetics@pennmedicine.upenn.edu.

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