



Generation Program

ALZHEIMER'S PREVENTION INITIATIVE

Getting to Know the Generation Program's Approach to Disclosing Information about Your Risk for Alzheimer's disease

The Generation Program is made up of two clinical trials: Generation Study 1 and Generation Study 2. The trials will enroll people with a specific gene that may increase the risk of developing Alzheimer's disease. It is your genes, along with other information about you, which will determine whether you are eligible to take part in either of these studies.

Overview of the Generation Program

The Generation Program focuses on people ages 60-75 who do not have symptoms of Alzheimer's disease but who have one or both of two factors that are known to increase a person's risk of developing dementia caused by Alzheimer's disease. Those factors include:

- **The APOE e4 Gene** – People who have one or two copies of the gene APOE e4 are more likely to develop dementia due to Alzheimer's disease. It is important to note that not every person who has the APOE e4 gene will develop dementia caused by Alzheimer's disease.
- **Elevated Amyloid Plaques** – Amyloid is a protein produced normally in the brain. Recent research studies suggest that people over the age of 65 who have evidence of higher than normal levels of amyloid plaques in their brains are at higher risk for dementia due to Alzheimer's disease. However, not every person who has higher than normal levels of amyloid plaques will develop dementia due to Alzheimer's disease.

The Relationship between the APOE e4 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.

Langlois CM, Bradbury A, Wood EM, Roberts JS, Kim SYH, Riviere ME, Liu F, Reiman EM, Tariot PN, Karlawish J, Langbaum JB. Alzheimer's Prevention Initiative Generation Program: Development of an APOE genetic counseling and disclosure process in the context of clinical trials. *Alzheimer's Dement* (N Y). 2019 Nov 6;5:705-716. doi: 10.1016/j.trci.2019.09.013.

The Generation Program was funded by Novartis and Amgen, in collaboration with the Banner Alzheimer's Institute. Generation Study 1 was supported by funding from the National Institute on Aging (1UF1AG046150), part of the National Institutes of Health, as well as the Alzheimer's Association, FBRI, GHR Foundation and Banner Alzheimer's Foundation.

This means that a person's individual 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 gene (which is the most common APOE result).

The APOE e4 gene 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 an individual has two copies of APOE e4, their risk is further increased.

The e4 type of APOE gene is only one of many possible risk factors for dementia due to Alzheimer's disease. Not everyone with the e4 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 the APOE e4 gene.

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

You will be required to learn your APOE result if you decide to participate in the study.

What to Consider Before Learning Your APOE Result

The decision whether to learn your APOE result is very personal. There are many factors to consider and there is no right or wrong answer. To help you with your decision, we encourage you to think about the different possible APOE results and how you might feel about each. You may also want to consider how learning this information might impact your family members.

Protection from Genetic Discrimination

Learning your APOE result may have implications for decisions you make about your employment as well as life and long-term care insurance. For example, in the United States, the Genetic Information Nondiscrimination Act (GINA) is a federal law that protects against genetic discrimination for health insurance and employment, but does not cover life insurance, long-term care/disability policies or small workplaces.

GINA sets a minimum standard for protection against discrimination based on a genetic test result. Some states also have laws that provide additional protections. Information on state laws in the United States may be found through the National Conference of State Legislatures (www.ncsl.org).

Your Unique Emotional Response

Each person will have a unique emotional response to learning they are at increased genetic risk for dementia due to Alzheimer's disease. Some people may experience anxiety, depression or worry when thinking about their risk.

Others may feel an urgent need to take action to reduce their risk. While some of these actions could be healthy and appropriate, for example, making positive dietary changes and committing to an exercise program. Other actions may prove to be very expensive with little or no benefit.

Still other people may feel empowered by learning this information and use it to inform their future decisions, like improving healthy behaviors or getting more involved in research.

Your Family Members

Learning APOE results could also have implications for family members. Some individuals may have feelings of worry or guilt when thinking about children or siblings who may have inherited the APOE e4 gene.

If someone has two copies of APOE e4, this means that all of their biological children must have at least one copy of the APOE e4 gene. For someone with an APOE e3/e4 result, this would mean that there was a 50 percent chance of passing the e4 copy to any children, and an equal 50 percent chance of passing the e3 copy.

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

Our Support

If you decide to learn your APOE result in order to participate in the Generation Program, an experienced study team member will be available to discuss your result with you. A study team member will also follow up with you a few days after learning your APOE result. That person will be available for questions throughout the study.

The Relationship between Amyloid and Alzheimer's disease

Amyloid is a protein produced normally in the brain. In Alzheimer's disease, amyloid forms plaques, which are dense areas of the protein. These are not normal. Amyloid plaques are always found in the brains of patients with dementia due to Alzheimer's disease. Although

having an elevated level of amyloid plaques in the brain is associated with thinking and memory problems, doctors don't yet know whether amyloid plaques cause dementia due to Alzheimer's disease. Amyloid plaques can build up in the brain over many years, sometimes more than a decade, before a person has memory problems.

It is important to remember that elevated levels of amyloid plaques do not necessarily mean a person will develop dementia due to Alzheimer's disease. Some studies suggest that about 30 percent of older people with normal memory and thinking abilities also have elevated levels of amyloid plaques in their brains.

Amyloid Result Disclosure in the Generation Program

Which Generation Program trial you are enrolled in will determine whether or not you will need to learn your amyloid test results:

- **Generation Study 1 participants** will not learn their amyloid status as it is not a requirement for eligibility for that study.
- **Generation Study 2 participants** who have **one** copy of the APOE e4 gene will be required to learn their amyloid status. This is because potential participants with only **one** copy of the APOE e4 gene must also have enough amyloid plaques in their brain to be eligible for Generation Study 2.
- **Generation Study 2 participants** who have **two** copies of the APOE e4 gene will have the choice to learn their amyloid status. Elevated amyloid is not required for study eligibility for participants with **two** copies of the APOE e4 gene.

Considerations for Learning Your Amyloid Status

Just like with learning APOE test results, each person will have a unique emotional response to learning their amyloid status. The emotions associated with learning amyloid status are as varied as the people receiving the information. Some people may become anxious or upset after learning they have an "elevated amyloid" result.

On the other hand, some study participants feel empowered by learning about their risk factor for developing Alzheimer's disease. They use this information to inform their future decisions about living arrangements and finances.

And, some people may also use this information as an opportunity to increase their healthy behaviors or get more involved in research. We encourage anyone considering learning their

Alzheimer's risk information to think about the different possible results and how they might feel about them.

As with your APOE result, an experienced study team member will discuss your amyloid result with you. A study team member will also follow up and check in with you a few days after you learn your amyloid status and will be available for follow-up questions throughout the course of the study.

Frequently Asked Questions

How do doctors determine whether someone has high levels of brain amyloid?

In one of two ways. A PET scan test for brain amyloid (also referred to "brain amyloid scan" or "amyloid PET scan") allows physicians to detect amyloid plaques in the brain. Amyloid may also be detected in spinal fluid collected from a lumbar puncture.

Participants in Generation Study 2 will learn whether the level of amyloid in their brain is either "elevated" or "not elevated." Please note that amyloid tests do not measure whether you have dementia due to Alzheimer's disease nor can they predict whether you will develop dementia due to Alzheimer's disease in the future.

How is an amyloid PET scan performed?

The test takes about two hours to complete. First, the person is given an injection of a dye (called a "radiotracer"). About an hour later, the person undergoes a 20-minute CAT exam.

During the exam, the radiotracer dye "lights up" where amyloid plaques are located and the PET scan turns this information into images. A qualified expert will then assess the images to determine whether the level of amyloid is "elevated" or "not elevated."

How is a lumbar puncture performed?

During this procedure, a thin needle is inserted into the lower part of the person's spinal column to collect spinal fluid. The amount of amyloid in the spinal fluid is then measured to determine whether the level of brain amyloid is "elevated" or "not elevated."

What does an "elevated" level of brain amyloid mean?

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An “elevated” amyloid result means that you have enough amyloid plaques in your brain to meet the criteria that make you eligible to participate in the study. While an “elevated” amyloid result is associated with an increased risk of developing dementia due to Alzheimer’s disease, it does not mean definitively that you will develop dementia due to Alzheimer’s disease.

Studies suggest that the increased risk of developing dementia due to Alzheimer’s disease associated with an “elevated” amyloid level is spread out over years or even decades. Scientists do not yet know which people with normal memory and thinking ability as well as elevated brain amyloid will develop dementia due to Alzheimer’s disease. Some people with elevated levels of amyloid plaques in their brain may never develop dementia in their lifetimes.

Frequently Asked Questions, continued

Is an “elevated” level of amyloid similar to other risk factors?

Having an “elevated” level of amyloid plaques may increase the risk of developing memory problems and dementia due to Alzheimer’s disease but it does not mean a person will definitely develop dementia due to Alzheimer’s disease.

Studies suggest the relationship between elevated amyloid plaques and Alzheimer’s disease dementia may be similar to the relationship between cholesterol and heart disease. Having high cholesterol increases the risk of having heart disease, but having high cholesterol does not mean that person will definitely have a heart attack. Years of research involving thousands of people enabled us to calculate a person’s risk of heart disease. There are not yet enough amyloid test research results available to calculate an individual’s risk of developing Alzheimer’s disease-related memory decline.

There are some factors that may protect a person from developing memory or thinking problems, even if they do have elevated levels of amyloid plaques. For example, some protection may come from a person’s genes, but good general health and a healthy lifestyle may also lower the risk of Alzheimer’s disease-related memory decline.

What does a “not elevated” level of brain amyloid mean?

A “not elevated” amyloid result means you do not have enough amyloid plaques in your brain to be eligible to participate in the study. It does not mean that you will never develop dementia due to Alzheimer’s disease. A person who has a “not elevated” amyloid level at the time of

testing could in the future develop an “elevated” level of amyloid or dementia due to Alzheimer’s disease.

Are there other risk factors in addition to the APOE e4 gene and amyloid plaques that can lead to dementia caused by Alzheimer’s disease?

Yes. The greatest risk factor for developing dementia caused by Alzheimer’s disease is advancing age, especially for those who are over 70 years old. However, dementia caused by Alzheimer’s disease is not a normal part of aging.

Another risk factor is having a family history of dementia or Alzheimer’s disease. Some studies also indicate that cardiovascular disease and conditions such as diabetes and high blood pressure are associated with a higher risk of developing dementia due to Alzheimer’s disease as well as other types of dementias. If you have any questions regarding these risk factors, please consult with your study team.