Lecanemab and *APOE* Information Sheet

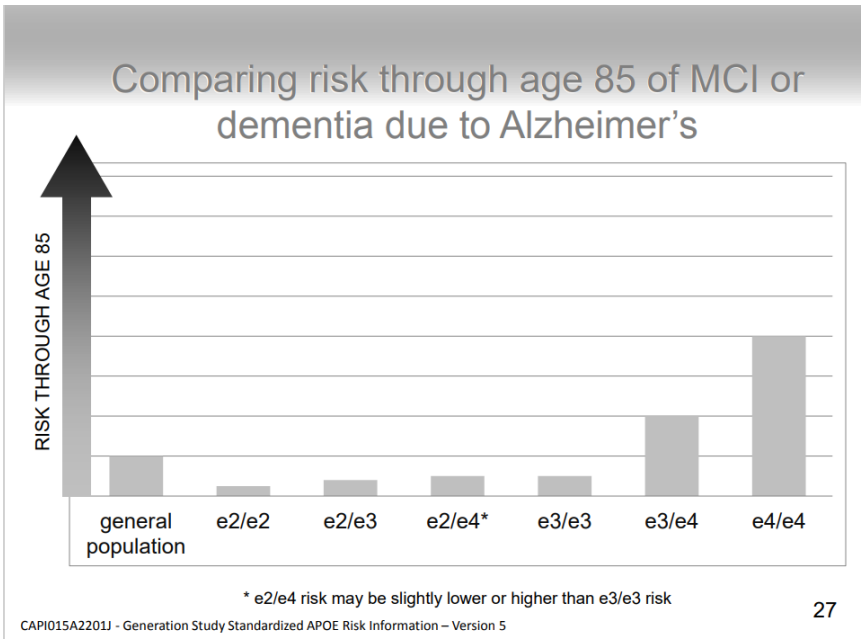
You have been given this information sheet as your doctor/health care provider is considering prescribing Lecanemab for you. Lecanemab (Leqembi) is an FDA-approved drug that targets the buildup of the amyloid-beta protein in the brain. A buildup of amyloid-beta can lead to the death of brain cells. Lecanemab has been found to slowdown cognitive decline in patients with mild cognitive impairment (MCI) or early-stage dementia caused by Alzheimer's disease (AD). Like most medications, there is a risk for certain side-effects with Lecanemab use. People with a specific variant of the *APOE* gene may have an increased risk for side effects. **Patients at MGB considering taking Lecanemab are required to have *APOE* genetic testing to assess whether they are at an increased risk for side effects**.

The *APOE* gene helps carry fats such as cholesterol in our bloodstream. While everyone has the *APOE* gene, there are different forms of this gene. The most common forms are called e2, e3, e4. Each of us has two copies of the *APOE* gene, therefore the possible *APOE* combinations individuals can have are: e2/e2, e3/e3, e2/e3, e3/e4 and e4/e4.

The *APOE* e4 allele is associated with an increased risk for potentially harmful side effect of Lecanemab called Amyloid-Related Imaging Abnormalities (ARIA). ARIA includes micro-brain bleeds and swelling, which may or may not cause symptoms. In rare instances the side effects can be life-threatening. Everyone taking Lecanemab has a risk for ARIA, however those with two copies of e4 have the greatest risk, the next highest risk is for those with one copy of e4, and those with no copies of e4 have the smallest risk for ARIA. **It is because of these potential risks while taking Lecanemab that it is required that patients at MGB have *APOE* genetic testing to assess whether they are at an increased risk for ARIA or not.**

The *APOE* e4 allele is also associated with an increased risk for MCI or dementia due to AD. Overall, the general population risk to develop AD is approximately 10-12%. AD is often described as multifactorial, which could include a complicated interaction of both environmental, lifestyle factors, and genetic factors. Some genetic risk factors such as *APOE*, are alone not sufficient to cause medical conditions. Therefore, sometimes a person can have the risk allele, but never develop the symptoms of AD themselves.

If someone has one e4 allele, they have a 20-25% chance to develop AD by age 85. If someone has two e4 alleles (e4/e4) they have a 30-55% chance to develop AD by age 85. Other factors such as biological sex or ancestry, may alter these risk estimates. *APOE* e4 is also not necessary to cause AD, which again suggests that other factors may be involved. Approximately 42% of people with AD do *not* have any e4 alleles present (Qian et al 2017). If you are not found to have an e4 allele, this does not rule out a diagnosis or risk of developing AD.



Family Members & APOE Genetic Testing

- APOE genetic testing is usually only recommended for individuals with MCI or dementia.
- There are many factors that impact our chance to develop AD, not just *APOE*. *APOE* genetic testing only tells us one part of a person's risk. For this reason, medical organizations such as the American College of Medical Genetics and National Society of Genetic Counselors do ***not*** recommend *APOE* genetic testing as part of a diagnostic work up in individuals with symptoms or in asymptomatic people.
- Family members can take steps such as exercising, eating a healthy diet, getting enough sleep, keeping one's mind active, and not smoking to maximize their health. Family members may also consider participating in research.
- If you or your family members have questions and would like to speak with a genetic counselor, please speak with your doctor about a referral or visit:
  https://www.massgeneral.org/genetics-and-genomics#counseling
  https://findageneticcounselor.nsgc.org/?reload=timezone
- For more information about *APOE*, please visit:
  https://medlineplus.gov/genetics/gene/apoe/

The above information can be confusing and overwhelming, for some individuals and their families. As there is a mildly increased risk of side effects for individuals with one copy of *APOE* e4 and there is a higher risk in individuals with two copies of e4, you and your doctor/health care professional should discuss all possible risks and benefits of Lecanemab before making your decision about whether to take it or not. Knowing your *APOE* status might help you and your physician in this decision-making process.

References

1. https://pubmed.ncbi.nlm.nih.gov/28323826/
2. https://jamanetwork.com/journals/jamaneurology/fullarticle/2802272
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10032667/pdf/07100e1.pdf
4. https://pennmemorycenter.org/legembi/