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Lecanemab Therapy and *APOE* Genotype

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Introduction

Lecanemab, brand name Leqembi, is a monoclonal antibody that targets amyloid beta (Aβ) aggregates for the treatment of Alzheimer disease (AD) (1). It is approved by the US Food and Drug Administration (FDA) for individuals with mild cognitive impairment (MCI) or mild dementia stage AD with confirmed amyloid pathology (1). Tests to confirm Aβ pathology in the clinical trials included positron emission tomography (PET) or cerebrospinal fluid (CSF) measurement of the Aβ42/Total Tau ratio (2). This disease-modifying medication is based on the amyloid cascade hypothesis, which suggests Aβ aggregates are a key driver in AD pathogenesis and that the removal of Aβ aggregates should slow cognitive decline.

Lecanemab is associated with amyloid-related imaging abnormalities (ARIA) due to edema (ARIA-E) or hemorrhage (ARIA-H) from blood vessels in the brain (3, 4). Individuals who have one or 2 copies of the AD risk-associated apolipoprotein E (*APOE)* ε4 (NM_000041.4:c.388T>C) allele have an increased risk of ARIA-E or -H (1) (Table 1). These individuals require additional monitoring during the first year of treatment (5). The FDA-approved label reports that concomitant antithrombotic medication (aspirin, antiplatelet, or anticoagulant) with lecanemab therapy resulted in intracerebral hemorrhage in 2.5% of individuals during clinical trials (1).

The appropriate use recommendations from the Alzheimer's Disease and Related Disorders Therapeutics Work Group state that individuals requiring anticoagulants should not be treated with lecanemab until additional data regarding this interaction are available (5). Both the FDA-approved label and Alzheimer's Disease and Related Disorders Therapeutics Work group encourage clinicians to consider participation in a registry for AD treatment to gather additional real-world data on lecanemab therapy (1, 5).

Table 1: Amyloid Related Imaging Abnormalities (ARIA) Risk Based on *APOE* Genotype

APOE ε4 status	Frequency of symptomatic ARIA-E[a]	Frequency of any ARIA[b]
Homozygous (ε4/ ε4)	9%	45%
Heterozygous (ε4/ εx)	2%	19%

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Table 1 continued from previous page.

APOE ε4 status	Frequency of symptomatic ARIA-E[a]	Frequency of any ARIA[b]
No ε4 allele detected	1%	13%

ARIA-E Amyloid-related imaging abnormalities, edema; εx any other *APOE* ε allele other than 4.
APOE – Apolipoprotein E
[a] Percent of individuals within the CLARITY-AD (study 2) who experienced a symptomatic ARIA-E.
[b] Percent of individuals within the CLARITY-AD (study 2) who experienced any ARIA event.
Adapted from (1).

Drug: Lecanemab

Lecanemab is a humanized monoclonal antibody that targets Aβ protein in the soluble protofibril form and is indicated for the treatment of AD (1). Administered by infusion once every 2 weeks at a dose of 10 mg/kg body weight, it is approved by the FDA for individuals with MCI or mild dementia stage AD who have confirmed amyloid pathology (1). Tests to confirm Aβ pathology used in the clinical trials included PET or CSF measurement of the Aβ42/Total Tau ratio (2). Appropriate use criteria for amyloid PET imaging, CSF collection, and testing for biomarkers to diagnose AD have been issued by the Alzheimer's Association (6, 7, 8). Appropriate use recommendations for lecanemab have been provided by Alzheimer's Disease and Related Disorders Therapeutics Work Group (5).

The leading definition for AD diagnosis from a radiologic perspective relies on evidence of amyloid, tau, and neurodegeneration (ATN) biomarkers (9), though neurologic functional impairment is an included criterion in other definitions (10). Diagnosis and staging of AD have been covered in numerous guidelines, all include the utilization of both biomarkers and clinical assessment (11, 12, 13). Mild cognitive impairment clinical criteria include expressed concerns on changes in the individual's cognition, impairment in one or more cognitive domains (as measured by established cognitive assessments), and maintenance of independence in functional abilities (11). Determination of cognitive impairment in the lecanemab clinical trials was obtained via the Mini-Mental State Examination, and individuals qualified based on scores between 22 and 30 (5). Diagnosis based on a combination of cognitive assessment and fluid biomarkers or radiologic findings–or both–represents a significant advancement in the understanding of AD.

One of the leading hypotheses for AD pathology is that Aβ aggregates initiate and drive AD pathogenesis. The amyloid precursor protein (APP) normally undergoes proteolytic processing, but in AD, there is a cleavage into an abnormal length peptide (42 amino acid Aβ form). This protein assembles into toxic, soluble oligomers and protofibrils (14). The abnormal amyloid oligomers cause cell stress and damage, leading to the secretion of more abnormal Aβ proteins and aggregates, which in turn trigger other diseases processes; this model of AD pathology is named the amyloid cascade hypothesis (15). Protofibrils of Aβ can also be sequestered into insoluble amyloid fibrils and plaques. While plaque density has long been correlated with AD severity, some have proposed that the aggregates may protect neuronal cells (14). Notably, individuals homozygous for the "Osaka" variant (NM_000041.4: c.527G>C (p.R176P)) of *APP* present with typical Aβ and tau levels in CSF but no detectable plaques even after AD onset (16), supporting the role of soluble Aβ aggregates in disease pathogenesis.

Other pathological hallmarks of AD include higher levels of tau protein phosphorylation, the formation of insoluble tau aggregates and fibrils (neurofibrillary tangles), and neuroinflammation, which increase with disease severity (14, 17). Elevated levels of phosphorylated tau are associated with an increased risk of progression from MCI to AD dementia (18), and post-mortem studies have found a direct correlation between tau neurofibrillary tangles and the severity and progression of AD (17). Current neuropathological and PET findings also highlight that tau pathology is a strong correlate of neurodegeneration and symptoms (19, 20), and is an indicator of clinical prognosis in cognitively unimpaired individuals (21). Numerous additional hypotheses

for AD pathology have also been proposed. One hypothesis includes cholesterol and lipid metabolic dysregulation as a contributing factor for AD pathogenesis, providing a potential mechanism to explain the role of variation in the *APOE* gene in AD risk (22). In this model, abnormal cholesterol levels and metabolism, as well as abnormal Aβ, contribute to other AD pathologies such as tau phosphorylation and loss of blood-brain-barrier integrity (22, 23). The *APOE4* variant is a risk-conferring allele for developing late-onset AD (22). Additional genetic risk factors include *SORL1*, *ABCA7*, and *TREM2* (24, 25, 26, 27). These genetic associations suggest that changes in immune response, endocytosis, and vascular factors may also contribute to AD pathogenesis (28). Dominantly inherited AD (also called early onset AD) has been associated with rare variants in *PSEN1*, *PSEN2*, and *APP*, all of which impact Aβ metabolism (29, 30).

Based on the predominant amyloid cascade hypothesis, anti-amyloid therapies target aggregated forms of Aβ with the goal to modify the course of AD (2, 4, 31, 32). After crossing the blood-brain barrier, lecanemab binds preferentially to Aβ soluble aggregates (oligomers and protofibrils) to facilitate immune clearance, leading to decreases in Aβ plaques (2, 3, 14, 33). The safe and effective dose for lecanemab was studied in a phase 2b trial, BAN2401-G000-201 (Study 201), and found to be 10 mg/kg body weight every 2 weeks (33). The phase 3 CLARITY trial reported a smaller decrease in cognitive function in the study population taking lecanemab (1.21 point change from baseline on the Clinical Dementia Rating-Sum of Boxes [CDR-SB] score, maximum possible score of 18) than the placebo group (1.66 point change) (2). Additionally, the CLARITY study results indicated a significant reduction in brain amyloid levels over 18 months with lecanemab treatment, as well as a decrease in CSF levels of phosphorylated tau and neuroinflammatory markers (2). Despite these findings, there has been ongoing debate within the scientific community regarding the clinical significance of the cognitive outcomes from this trial (discussed below). However, these data supported the FDA decision to grant full approval of lecanemab in July 2023 (34) with a black box warning for ARIA (1).

Similar to other anti-amyloid therapies, lecanemab treatment can trigger ARIA-E, defined as "the extravasation of fluid resulting in interstitial vasogenic edema or sulcal effusion in the leptomeningeal/subpial space" (35), or hemosiderin deposits (ARIA-H), characterized as cerebral microhemorrhages and/or hemosiderosis (35), more frequently than placebo (2, 5, 31, 33). It is thought that Aβ plaques contribute to the loss of cerebral vascular integrity and are a prime target of anti-amyloid therapy, which may further disrupt vascular integrity in response to therapy (35). Clinically, ARIA can be asymptomatic but can sometimes lead to serious or fatal intracerebral hemorrhage (1, 36, 37, 38) or, in the case of ARIA-E, fatal inflammatory arteritis (39).

Sub-study analyses from the phase 2b clinical trial and post-hoc analysis of the phase 3 trial found that individuals with the *APOE* ε4 variant (*APOE4*) were significantly more likely to experience ARIA than individuals with other *APOE* alleles (2, 33, 40). Additional analysis in the phase 3 CLARITY trial found that the population with 2 *APOE4* alleles experienced ARIA more frequently than the study subpopulation with only one allele (2). The FDA-approved label for lecanemab advises testing for ApoE ε4 status "prior to initiation of treatment to inform the risk of developing ARIA" (41). Cummings and colleagues also recommend genotyping *APOE* before initiating lecanemab therapy (5).

Other factors contributing to the risk of ARIA include prior cerebral microhemorrhage, advanced age, antithrombotic medication use, and history of prior strokes (38, 42). Despite the exclusion of individuals with clinical findings suggesting cerebral amyloid angiopathy (CAA) (more than 4 microbleeds) from clinical trials with lecanemab (CLARITY, "study 2"), this is not an explicit contraindication in the FDA-approved drug label (1). However, the Appropriate Use Recommendations advise against using anticoagulants or acute thrombolytics while taking lecanemab due to the increased risk of hemorrhage (5). Preliminary results suggest that increasing the rate of antibody passage through the blood-brain barrier, thus bypassing vascular amyloid, may reduce ARIA incidence and increase the rate of amyloid clearance from the CSF (43).

It is recommended to perform a baseline MRI and then periodic monitoring for ARIA, particularly during the first 14 weeks of lecanemab therapy (1, 5). A baseline MRI is required to identify cerebral pathologies that

indicate an increased risk of ARIA (5). It is recommended to obtain additional MRIs after the 5th, 7th, and 14th infusions (1, 5). An additional scan at 52 weeks of therapy is also recommended, especially for individuals with an *APOE4*-positive genotype (5). If an ARIA occurs, the appropriate use recommendations are to suspend or discontinue dosing in nearly all cases, except for mild ARIA-E or -H with no symptoms (5).

Additional warnings for lecanemab include hypersensitivity reactions and infusion-related reactions. Hypersensitivity reactions can include angioedema, bronchospasm, and anaphylaxis and should result in prompt discontinuation of the infusion (1). Infusion reactions such as fever and flu-like symptoms, nausea, vomiting, and hyper- or hypotension led to medication discontinuation in 1% of participants in a clinical trial. Management to avoid discontinuation may include reducing the infusion rate or prophylactic treatment with antihistamines and other medications (see drug label for full details) (1).

Lecanemab has not been adequately evaluated in pregnant or nursing mothers to determine the risk of birth defects, miscarriage, or adverse effects on a breastfed infant. Additionally, the safety and efficacy of lecanemab in a pediatric population have not been established. The age range of clinical study participants was between 50 and 90 years, and no overall differences in safety or efficacy were observed in individuals aged more than 65 years compared to younger individuals. (1) The clinical trials also did not include individuals with comedications or comorbidities that may increase bleeding risk or interfere with MRI (such as a pacemaker), which may be common in the Alzheimer population in real-world use (2). Conditions that require acute thrombolytics, such as ischemic stroke or myocardial infarction, present a unique challenge for clinicians and will require advance directives and planning (44).

The reported benefit of lecanemab therapy considering the risks of ARIA, intracranial hemorrhage, and other side effects, has led to significant debate in the medical community regarding the use of lecanemab. Many authors have been critical of the clinical significance reported by the CLARITY trial, including the small CDR-SB score differences in treatment versus placebo, calculation of the actual scores, or the limited benefit to subgroups (women or *APOE4* positive individuals) (45, 46, 47, 48, 49, 50, 51, 52, 53). Other concerns over the conclusions from CLARITY have been raised regarding the risk of bias due to functional unblinding of study participants based on ARIA occurrence (51, 54, 55, 56). Additionally, the increased risk of ARIA, intracranial hemorrhage, or vascular central nervous system (CNS) changes has been argued to be too great relative to the reported benefit of lecanemab, and some authors have suggested that real-world use could result in higher rates of these adverse events (47, 57). Planche and Villain have questioned the notion that these treatments, which were designed to modify the course of AD, have yet to produce convincing evidence of disease modification given the limited time on the medication relative to the 7–17 years observed for disease progression and lack of observed impact on all implicated biomarkers(58).

The authors of the CLARITY trial and others defend the conclusions and assessment of the trial results, citing differences in the definition of clinically meaningful CDR-SB values, the lack of power in the study to accurately perform subgroup analysis (such as those based on gender or *APOE* status), significant impact on amyloid pathology across multiple clinical trials (phases 2b and 3), and the predicted long-term benefit in slowing cognitive or functional decline on both health outcomes and quality of life (59, 60, 61). Other authors not affiliated with the study or sponsoring pharmaceutical company also expressed optimism for the benefits of anti-amyloid therapy, including lecanemab, while acknowledging the risk of ARIA (31, 62, 63, 64, 65, 66, 67). It is also noteworthy that most of the ARIA-E events (71%) were detected early in the course of therapy (5), and if appropriately managed, an individual may be able to resume therapy without experiencing future ARIA events (42). A correlation between amyloid clearance and clinical benefit has been made across the various anti-amyloid therapies trialed over the years, with more significant amyloid clearance associated with slowed cognitive decline (4). In line with the ATN definition of AD, CLARITY reported more reduction in biomarkers for all 3 categories with lecanemab therapy compared to placebo (2). Ongoing trials will assess the impact of lecanemab therapy before the onset of cognitive impairment in populations with intermediate (20–40

Centiloids) or elevated (>40 Centiloids) amyloid burden via PET (68). Additional questions remain regarding the appropriate duration of lecanemab therapy and whether there is a benefit to lecanemab co-medication with symptomatic therapies like cholinesterase inhibitor or memantine (69).

The appropriate use recommendations for lecanemab from the Alzheimer's Disease and Related Disorders Therapeutics Work Group state that before initiating lecanemab therapy, there must be established amyloid positivity, a baseline MRI, evaluation for vascular disease or other ARIA risk factors like anticoagulant therapy, as well as the recommended *APOE* testing and genetic counseling (5). Treatment itself is an hour-long infusion plus additional time for monitoring for infusion reactions, which must be performed in an appropriate clinical setting with the necessary training and equipment to manage infusion reactions. Monitoring MRIs must be performed 3 or 4 times during the first year of treatment, requiring clinical expertise in detecting ARIA (1, 5). Care teams are advised to develop a plan for responding to serious and severe ARIA and have sufficiently trained staff to manage seizures or other complications resulting from ARIA (5). There has been speculation that these aspects of clinical implementation may result in the use of lecanemab mostly in specialized care centers (69). All these care components carry an expense, in addition to the estimated cost of the medication itself ($26,500 per individual annually) (70). The United States Veteran Health Authority announced in March 2023 that it would cover lecanemab costs when medically indicated for veterans (71). Medicare coverage was also extended beyond the scope of use in clinical trials when traditional FDA approval was granted (72). Lecanemab has been approved for use in Japan (73) and China (74). The Japanese Pharmaceutical and Medical Devices Agency review report states that "the safety data showed that the risk of lecanemab including ARIA can be managed irrespective of *APOE* genotype… and it is considered that lecanemab has a favorable risk-benefit balance" (75). Lecanemab review with the European Medicines Agency for marketing authorization was delayed in March 2024, and other country-specific applications are also pending at the time of writing (41).

Determination of real-world safety and benefits of lecanemab therapy will require additional time and research. Clinicians are encouraged to participate in a registry to collect information on AD treatment, including lecanemab, such as the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET, www.alz-net.org). These data will, ideally, include a broader population than those eligible in the existing published studies with strict eligibility criteria. Based on the eligibility criteria from the lecanemab and aducanumab studies, researchers at the Mayo Clinic found that approximately 5–8% of the Mayo Clinic Study of Aging cohort with MCI or mild dementia and brain amyloid burden would have qualified for either medication (76). The specific amyloid burden requirement from anti-amyloid trials may also have resulted in the exclusion of some racial and ethnic groups, such as Hispanic and non-Hispanic Blacks, Hispanic Whites, and non-Hispanic Asians (terms utilized by the study authors) (77). Considering this, along with the limited data from individuals of Asian descent with AD (78), highlights the need for additional research in these underrepresented populations to understand disease mechanism, clinical presentation, and potential benefits and risks of anti-amyloid therapy.

Gene: *APOE*

The *APOE* gene encodes apolipoprotein E, which functions in lipid transport between cells and organs, binding to a variety of lipid-containing complexes including very low-density, intermediate-density, and a few subclasses of high-density lipoproteins, as well as chylomicron remnants (79, 80). It is expressed in various tissues, but it is one of the primary apolipoproteins in the CNS (79). The APOE protein facilitates the clearance of lipoproteins from the plasma or CSF by binding to both lipids and receptors in the LDL family or heparan sulfate proteoglycans (80). This is mediated by 2 functional domains in the APOE protein: the N-terminal portion of the protein interacts with receptor proteins, and the C-terminal portion interacts with lipids (80).

Variation in the *APOE* gene has been associated with AD, age-related macular degeneration, type III hyperlipoproteinemia, lipoprotein glomerulopathy, sea-blue histiocyte disease, and CAA (81, 82, 83, 84, 85, 86). Emerging evidence suggests that *APOE* variants or altered expression may also confer an increased risk for

Parkinson disease dementia and dementia with Lewy bodies (23, 87). However, the specific association for an allele can vary among these diseases, with an allele conferring risk for one disorder but protecting against another. There are 3 common alleles of *APOE*: ε*2,* ε*3*, and ε*4*, with *APOE* ε*3* (also written as *APOE3*) representing the reference, normal function allele (78, 79, 80). The APOE4 protein (from *APOE* ε*4* or *APOE4* allele) is a well-established risk factor for AD. The *APOE2* allele appears to be a protective variant for AD development but is a causative allele for type III hyperlipoproteinemia (78, 80). Initially identified by differences in isoelectric focusing, subsequent studies have identified the underlying genomic changes. The *APOE2* allele has an additional cysteine residue (rs7412, NM_000041.4:c.526C>T, p.R176C) and *APOE4* has one less cysteine residue (rs429358, NM_000041.1:c.388T>C, p.C112R) (Table 2). These changes can impact dimerization, protein processing, and binding to other proteins (79).

Table 2: Common *APOE* Allele Minimum Variant Definitions and Associations

APOE allele	rs429358 genotype (cDNA and protein change)[a]	rs7412 genotype (cDNA and protein change)[a]	Protein function[b] and disease association
ε2	T (c.388T; p.Cys130=)	T (c.562C>T; p.Arg176Cys)	Decreased receptor binding, protective for AD; risk allele for ARMD and type III hyperlipoproteinemia
ε3	T (c.388T; p.Cys130=)	C (c.562C; p.Arg176=)	Normal receptor binding and reference disease risk
ε4	C (c.388T>C; p.Cys130Arg)	C (c.562C; p.Arg176=)	Normal receptor binding, likely toxic gain of function; risk for AD

AD - Alzheimer disease, ARMD - Age-related macular degeneration
[a] cDNA coordinates given for NM_000041.4; protein change in NP_000032.1
[b] Function relative to lipid receptor binding, adapted from (80).

The frequency of *APOE* alleles varies across populations; overall *APOE3* is the most common, followed by *APOE4* and then *APOE2* (88). The global minor allele frequency for the *APOE4* (rs429358) allele reported in the Allele Frequency Aggregation (ALFA) project is 0.074, though the 1000 Genomes data estimates it to be 0.15; in both data sets, the minor allele is more common in African ancestry than other groups (89). The global minor allele frequency reported in ALFA for *APOE2* (rs7412) allele is 0.083, though it is reported as high as 0.11 in some African descent populations and as low as 0.02 in South Asian populations (90). The frequency of the *APOE4*-defining allele (rs429358) has been reported to be 0.11 in a study population from India; a frequency that the authors note is lower than the European, African, and non-Finnish European population data reported in gnomAD (91). The frequency of *APOE4* in Hispanic ancestry is reported to be 0.12, though the frequency is 0.24 in Hispanic individuals with AD (92).

Despite the higher prevalence of the *APOE4* allele in populations of African descent, the surrounding genomic context may also have a significant impact on the expression of the allele. Studies suggest that the genomic context from a European ancestral background promotes higher expression of *APOE4* than an African ancestral background (78). This may be due to non-coding genetic variation at *APOE* enhancers, changes in chromatin accessibility, or both, resulting in a decreased risk of *APOE4*-assocated disorders for individuals with African ancestry (78). An *APOE4* genotype was associated with elevated Aβ levels in non-Hispanic White individuals, but not in individuals of African American descent (93). The association between *APOE4* and AD is also weaker in individuals of Hispanic ancestry compared to Caucasian ancestry (94, 95). Variation in the *APOE* region does seem to contribute to AD risk in Hispanic populations, but the *APOE4* allele alone showed a weaker association than polygenic risk scores that included other *APOE*-linked variants (96).

Whether *APOE4* is a toxic gain-of-function or loss-of-function allele has been studied using various approaches and could influence the utility of APOE4 as a disease target for future therapeutic efforts (78). Increased *APOE4* expression in African or European ancestry populations is associated with a higher frequency of AD or CAA and some studies have suggested that non-coding variants in a European ancestry haplotype may further

contribute to increased *APOE4* expression and AD risk (78). Genetic analysis of the Alzheimer's Disease Sequencing Project identified putative loss-of-function variants as being associated with reduced risk of AD or later onset of AD (97). Mouse studies further support a model where increased *APOE* expression (either ε3 or ε4 variant forms) exacerbated Aβ accumulation and that downregulating *APOE4* expression could reduce amyloid deposits in the brain (98). The APOE4 variant protein is more susceptible to abnormal proteolytic cleavage, creating a C-terminal fragment that is neurotoxic in transgenic mouse models (80). Thus, the overall conclusion of the National Institute on Aging/Alzheimer's Disease Sequencing Project consortium is that reducing the levels of APOE4 in individuals of European or African ancestry would be an appropriate therapeutic target; additional studies are needed to confirm if this approach would also be beneficial to individuals of Asian ancestry (78).

Linking *APOE* Genetic Variation with Treatment Response

Clinical trial data from the lecanemab studies showed a clear, gene dose-dependent risk for ARIA in individuals with the *APOE* ε4 (*APOE4*) variant allele (2, 33). The frequency of symptomatic ARIA-E during the phase 3 CLARITY trial for individuals with 2 *APOE4* alleles was 9.2%, versus 1.7% in individuals with only one *APOE4* allele and 1.4% in individuals without an *APOE4* allele (2). The frequency of ARIA-H was 39% in *APOE4* homozygotes, 14% in heterozygotes and 11.9% in individuals without an *APOE4* allele (2). This increased frequency of ARIA in *APOE4* is the rationale behind Cummings et al's recommendation that *APOE4*-positive individuals receive an additional monitoring MRI scan during the first year of lecanemab therapy (5).

Given *APOE4*'s role as a genetic risk factor for sporadic AD, it is useful to test whether this variation may also impact the cognitive benefits from anti-amyloid therapies like lecanemab. A pooled analysis of published studies of the anti-amyloid medications lecanemab, aducanumab, solanezumab, and donanemab suggests that *APOE4*-positive individuals have the same or better response to amyloid-targeting therapies compared to individuals without an *APOE4* allele (99). However, *APOE4* is also associated with increased risk of ARIA for aducanumab and donanemab (37, 100). Specifically reviewing data from the lecanemab studies, some reports have suggested that *APOE4*-positive individuals experienced a reduced clinical benefit of lecanemab therapy (48, 54), though study authors state there is insufficient statistical power to perform this subgroup analysis from the CLARITY trial data (59). Additional data are needed to comprehensively assess the connection between *APOE4* status and anti-amyloid efficacy.

The proposed mechanisms underlying APOE4's contribution to AD and subsequent ARIA risk with anti-amyloid therapy are complex, with proposed Aβ-dependent and -independent mechanisms (78, 80, 101). Within the CNS, astrocytes are the primary producers of APOE protein and roughly 60% of the protein is secreted into the extracellular space (101). In a transgenic mouse model, abnormal APOE4 protein altered lipid metabolism in astrocytes and led to decreased astrocyte-blood vessel contacts, triggering increased leakiness in the blood-brain barrier (101). If this holds true in humans, it may explain, at least in part, the increased risk of ARIA observed in *APOE4*-positive individuals during from anti-amyloid trials. Other hypotheses for this observed ARIA association include the increased amyloid oligomer burden in *APOE4*-positive individuals, which leads to a higher level of disruption of blood vessel integrity during amyloid clearance (3). Finally, the potential link between ARIA and CAA-related inflammation suggests a shared pathophysiology between the 2 conditions (102). It known that *APOE4* increases the likelihood of CAA (49), suggesting that the APOE4 effect may be mediated by the increased presence of CAA among *APOE4*-positive individuals, even in the absence of radiological evidence.

Genetic Testing

The NIH Genetic Testing Registry (GTR) includes tests for *APOE* genotype. The appropriate use recommendations as well as the FDA-approved drug label recommend testing individuals for *APOE4* before initiating therapy (1, 5). While an *APOE4*-positive genetic result is not a contraindication for lecanemab therapy,

it should prompt additional discussion regarding the risk of ARIA and the potential for related individuals to also have an *APOE4* allele (5). One suggested course of clinical care is to initiate *APOE* genetic testing only after AD biomarker (namely, amyloid levels) testing is complete and interest in anti-amyloid therapy is confirmed with the individual to be treated, since *APOE* genotype results are unlikely to impact clinical care with other therapeutic approaches (103).

Genetic testing for *APOE* comes with challenges. In the context of testing before initiating anti-amyloid therapy, both pretest and posttest counseling are recommended to ensure the individual with AD and their caregiver are informed of the risks and benefits of testing and treatment; this can be particularly challenging if the individual has MCI (104). In addition to the risks associated with *APOE4* genotype and ARIA, there are additional disease risks for the individual, such as ischemic stroke, lobar intracerebral hemorrhage, and others, as well as the possibility of additional family members also having an *APOE4* allele (104). Diagnosis of an *APOE4* allele may also impact medical insurance decisions, potentially from the individual subscriber, the payer, or both, particularly with regard to life, disability, and long-term care insurance plans (104). Within the United States, federal laws are in place to protect from discriminatory practices based on genetic data (the Genetic Information and Nondiscrimination Act and Affordable Care Act), however, there are state-to-state differences in regulations for life, disability, or long-term care insurance (105). Legal or regulatory guidelines in other countries may warrant considerations as lecanemab or other anti-amyloid therapies with an *APOE*-associated risk genotype are introduced into clinical care elsewhere.

The *APOE* Gene Interactions with Medications Used for Additional Indications

Variation in *APOE* increases the risk of ARIA not only for lecanemab but for other anti-amyloid medications like aducanumab (3, 4, 100). Weak evidence links *APOE* and 3-Hydroxy-3-Methylglutaryl-CoA reductase variation to statin response, though it was insufficient to warrant actionable guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (106).

Additional information on gene-drug interactions for *APOE* are available from PharmGKB, CPIC and the FDA (search for "APOE").

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2023 Statement from the US Food and Drug Administration (FDA):

Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including [lecanemab], have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with lecanemab; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA… Consider the benefit of lecanemab for the treatment of Alzheimer's

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes, and genetic variants may be corrected in accordance with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

disease and potential risk of serious adverse events associated with ARIA when decided to initiate treatment with lecanemab.

Please review the complete therapeutic recommendations that are located here: (1).

Nomenclature for Selected *APOE* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
APOE3	ε3	NM_000041.4: c.[388=;526=]	NP_000032.1	(none)
APOE2	ε2	NM_000041.4:c.562C>T	NP_000032.1:p.Arg176Cys	rs7412
APOE4	ε4	NM_000041.4:c.388T>C	NP_000032.1:p.Cys130Arg	rs429358

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).

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