Lecanemab and APOE genotyping in clinical practice: navigating uncharted terrain

Madhav Thambisetty[1*] MD, PhD and Robert Howard[2] MRCPsych MD

[1]Clinical and Translational Neuroscience Section, Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, USA.

[2]Division of Psychiatry, University College London, London, UK

*Corresponding author: Dr Madhav Thambisetty

Email: thambisettym@mail.nih.gov

Phone: 410-454-8678

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Publication of results from the phase-3 CLARITY-AD trial of lecanemab, with demonstration that the drug provided a small clinical benefit and may have slowed disease progression, has brought hope to millions of Alzheimer's patients and their families around the world [1]. The US Food and Drug Administration (FDA) recently approved lecanemab for treating patients in early stages of Alzheimer's disease (AD). Analyses of CLARITY-AD results have already spurred passionate debate about the meaningfulness of clinical benefits observed and whether after consideration of associated risk of adverse events, the drug represents a truly effective and safe treatment.

In addition to these issues, a largely overlooked question has been the importance of APOE genotyping in clinical decision-making by physicians who are considering the drug for eligible AD patients. As with other amyloid-targeting antibodies, such as aducanumab and donanemab, designated "breakthrough therapies" by the FDA, lecanemab is associated with increased risk of amyloid related imaging abnormalities (ARIA), particularly in APOE ε4 carriers. In CLARITY-AD, APOE ε4 homozygous patients were more than six times likely to experience symptomatic ARIA-E (i.e., ARIA with edema or effusions) and more than three times likely to experience ARIA-H (i.e., ARIA with cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis) than APOE ε4 non-carriers [1]. Given three currently reported deaths related to intracerebral hemorrhage associated with lecanemab, including two patients receiving concomitant anticoagulants or thrombolytics [2], there is an urgent need to identify patients at higher risk of life-threatening adverse events prior to treatment initiation.

The CEO of Eisai, lecanemab's manufacturer and sponsor of CLARITY-AD, recently advised that APOE ε4 homozygous patients should only receive the drug if they and their physicians agreed to "close monitoring" because of increased risk of brain hemorrhage [3]. However, while the FDA has not mandated APOE genotyping or provided specific guidance on additional safety monitoring in high-risk patients, the 'warnings and precautions' section of the prescribing label for lecanemab, advises physicians should *"consider testing for* APOE ε4 *status to inform the risk of developing ARIA when deciding to initiate treatment"*. Taken together with subgroup analyses of

CLARITY-AD suggesting that APOE Ɛ4 homozygous patients may derive relatively little clinical benefit from the drug [1], the role of routine APOE genotyping in guiding assessment of risk versus benefit of treatment remains a crucial unresolved question.

The fourth Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study compared the impact of communicating AD risk, with and without APOE genotype status, to patients with a diagnosis of mild cognitive impairment (MCI) and their clinic visit companions. The study showed that patients presented with risk estimates of progression to AD based on their APOE Ɛ4 status were not at higher risk for subsequent depression or anxiety than those who did not receive such test results [4]. The study also underscored the active role that family members of patients can play in conveying complex genetic test results from physicians to cognitively impaired patients. A key implication for clinical practice was the importance of communication skills training for clinicians, MCI patients, as well as their visit companions, to improve effective and safe disclosure of genetic test results. However, the profile of patients who will receive APOE genotyping to guide risk-benefit considerations of lecanemab differs from participants in REVEAL as it would include both people with MCI and mild dementia due to AD who have previously undergone PET imaging or cerebrospinal fluid assays to establish the presence of brain amyloid pathology. This will present unprecedented challenges to clinicians, their patients, and families, as well as to healthcare and insurance providers. The implications of large-scale APOE genotyping as a routine part of treatment and disclosure of the results to patients and their family caregivers poses difficult ethical, legal, and financial concerns that will require urgent attention by lawmakers and policy framers.

For physicians who have determined that a patient meets prescribing label criteria for lecanemab, any consideration of APOE genotyping to assess risk of adverse events or potential treatment benefits should include pre- and post-test counseling as well as an assessment of associated patient and/or caregiver distress, especially if a determination is likely to be made not to provide treatment for APOE Ɛ4 carriers. If the physician decides that close monitoring is feasible and may be effective in avoidance of treatment-associated intracerebral hemorrhage with additional clinical evaluations and more frequent MRI scans in APOE Ɛ4 homozygous patients, the burden of these additional

measures both on caregivers and patients must be determined and clearly presented prior to initiating treatment. Physicians will also need to be aware of existing legal protections against genetic discrimination for their patients and their asymptomatic children as well as their limitations.

While the Genetic Information Non-discrimination Act (GINA) of 2008 protects pre-symptomatic individuals at risk of a disease based on their genetic profiles from discrimination by health insurance providers and employers, it may be of limited relevance to patients with an established clinical diagnosis of AD who are already cognitively impaired [5]. However, APOE Ɛ4 carriers are also at greater risk of other diseases that may manifest subsequent to disclosure of their test results, including ischemic stroke, lobar intracerebral hemorrhage, depression, epilepsy, and coronary artery disease [6]. Important exceptions to protection by GINA include discrimination for life, disability and long-term care insurance based on a patient's genetic information. Further, disclosure of a cognitively impaired parent's APOE Ɛ4 carrier status would allow their biological children to infer their risk of being an Ɛ4 carrier. Might APOE results in a patient's clinical record be accessible to providers of these specific insurance products who could refuse to extend coverage to Ɛ4 carriers, including their asymptomatic children, or underwrite their policies at higher rates? In this context, it is important to remember that when asymptomatic individuals are presented with APOE genetic testing results, APOE Ɛ4 carriers are more than twice as likely to change their long-term insurance coverage than Ɛ4 non-carriers [7]. If higher numbers of APOE Ɛ4 carriers, whether they are patients with clinically diagnosed AD or asymptomatic children who have become aware of their parent's APOE Ɛ4 status, seek long-term insurance coverage, this would raise concerns about the financial viability of the long-term care market.

The availability of direct-to-consumer APOE genetic testing services also means that practicing physicians may encounter patients seeking newer Alzheimer's treatments such as lecanemab who have already determined their APOE Ɛ4 status as part of their own preparation for and consideration of treatment. Such patients would also benefit from post-test counseling to address concerns both about their risk for AD and other medical conditions, legal protections against genetic discrimination as well as implications of

disclosing the results to their asymptomatic family members. The protections under GINA notwithstanding, an insurer can request genetic information to make coverage determinations for specific claims. For example, the disclosure of a patient's BRCA status may be used to assess coverage for prophylactic mastectomy. In the case of APOE ε4 carriers who elect to receive lecanemab treatment, their ε4 carrier status might adversely influence coverage determination for treatment-related complications such as ARIA compared to non-carriers. These considerations are also relevant to clinical practice settings outside the United States, including Europe and Asia where legal protections against genetic discrimination range from robust to non-existent.

While the potential of lecanemab as an effective and accessible treatment for Alzheimer's remains to be established within clinical practice, the requirement to obtain APOE genetic testing in eligible patients poses a societal challenge that will require physicians, patients, caregivers, advocacy groups, healthcare organizations, insurance providers and lawmakers to come together to ensure that we first do no harm to patients with Alzheimer's disease as well as the families and healthcare systems that support them.

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Competing interests

The authors declare no competing interests.