April 29, 2025

The Honorable Martin A. Makary, M.D., M.P.H
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903-0002

Dear Commissioner Makary:

On behalf of the ApoE4 Alzheimer's Alliance, we are pleased to congratulate you on your new role as FDA Commissioner. As a patient advocacy organization dedicated to representing the interests of ApoE4 Alzheimer's patients, we are eager to collaborate with you to ensure safe, effective, and personalized treatment strategies that reflect the unique medical needs of this population.

Recent scientific research underscores the urgent need for tailored treatment strategies for the ApoE4 high-risk population. Specifically, the study published in *Nature Medicine* by Fortea et al. (2024) provides compelling evidence that ApoE4 homozygosity constitutes a distinct genetic form of Alzheimer's disease (AD), characterized by nearly full penetrance, predictable symptom onset, and a defined sequence of biomarker progression. Given these findings, the administration of monoclonal antibody treatments without prior genetic testing poses significant risks and fails to adequately address the unmet medical needs of ApoE4 carriers.

Current anti-amyloid antibody treatments, such as lecanemab and donanemab, have shown efficacy in slowing disease progression in Alzheimer's patients. However, their use in ApoE4 carriers—particularly homozygotes—presents critical safety concerns. The *Nature Medicine* study demonstrates that nearly all ApoE4 homozygotes exhibit abnormal amyloid levels by age 65 and follow a disease progression similar to autosomal dominant AD and Down syndrome-associated Alzheimer's. Furthermore, clinical trial data for monoclonal antibodies indicate a significantly increased risk of amyloid-related imaging abnormalities (ARIA) in ApoE4 carriers, with some studies suggesting up to threefold higher risk compared to non-carriers. This raises the grave concern that administering these treatments without prior genetic screening may place patients at undue risk of serious adverse events, including brain swelling and microhemorrhages.

Adding to this concern, recent news articles have highlighted that participants in earlier trials of oflecanemab and donanemab were not given the opportunity to learn their ApoE genotypes. The reluctance to disclose ApoE status, despite its known impact on ARIA risk, means that many patients may have entered treatment without a full understanding of their potential risks. The article also underscores the broader ethical responsibility to ensure that patients are adequately informed before making treatment decisions, particularly now that the ApoE4 genotype is recognized as a key determinant of treatment risk. The failure to disclose such information undermines patient autonomy and contradicts the principles of informed consent.

Despite this heightened risk, there is currently no mandatory requirement for ApoE genotyping

prior to prescribing anti-amyloid antibody therapies. This represents a critical gap in patient safety and informed decision-making. Given the strong association between ApoE4 status and ARIA risk, it is imperative that the FDA takes proactive steps to ensure that patients and their clinicians are fully informed before initiating treatment.

To address this conundrum, we specifically urge the FDA to:

1. **Require ApoE Genotyping Prior to Treatment:** Establish a regulatory mandate that all patients considering anti-amyloid antibody treatments undergo ApoE genotyping to assess their individual risk profile whether in clinical trials or clinical practice.

2. **Mandate Full Disclosure of Genetic Risk in Clinical Trials:** Ensure that all future clinical trials involving anti-amyloid therapies provide participants with the opportunity to learn their ApoE status prior to enrollment, enabling and upholding the highest ethical standards in patient consent.

3. **Enhance Risk Communication in Practice:** Update labeling and prescribing guidelines to explicitly outline the elevated ARIA risk in ApoE-4 carriers and communicate detailed risk-benefit considerations tailored to this patient population.

4. **Support Targeted Clinical Trials:** Encourage and facilitate clinical trials that specifically address the safety and efficacy of anti-amyloid therapies and alternative modalities in ApoE-4 homozygotes, recognizing their distinct disease trajectory.

5. **Release Clinical Trial Data**: Mandate the release of study data from the sponsors of completed trials, stratified by ApoE status and sex, for all side effects (ARIA-E, ARIA-H, seizures, strokes/stroke mimics, brain shrinkage, deaths, etc.) This data is needed now by clinicians to assess and communicate safety risks to their patients

6. **Expand Patient and Provider Education:** Develop and disseminate educational materials to healthcare providers and patients regarding the implications of ApoE4 status on treatment decisions and disease progression.

The recognition of ApoE4 homozygosity, as a genetically distinct form of Alzheimer's, should prompt a shift in regulatory policy to better protect these patients. The current one-size-fits-all approach to Alzheimer's treatment does not account for the substantial genetic heterogeneity of the disease. Implementing these recommendations will help ensure that ApoE4 carriers receive safe, effective, and personalized treatment strategies that reflect their unique medical needs.

We appreciate the FDA's ongoing commitment to patient safety and innovative treatment approaches. We welcome the opportunity to discuss this matter further and provide additional data supporting the need for enhanced regulatory measures for ApoE4 carriers.

Sincerely,

Patient Advisory Board of the ApoE4 Alzheimer's Alliance

Jamie Tyrone, RN
Wendy Nelson
Kristine Shields
Jennifer Mellen
Lorraine Kristoferson
Julie McEntire
Allison Wills Brooks

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