

Addressing Alzheimer's Disease and the Needs of APOE e4 Homozygotes

Patient-Led Listening Session with the FDA

July 22, 2025

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Overview

On July 22, 2025, members of the Alzheimer’s Disease (AD) and APOE e4 homozygotes held a Patient Listening Session with the U.S. Food and Drug Administration (FDA). Approximately 52 FDA staff attended, to listen and learn from APOE e4 homozygotes. APOE e4 homozygotes have been tremendously impacted by Alzheimer’s Disease across generations due to the increased risk for AD with the APOE gene. There are over 6 million estimated APOE e4 homozygotes in the US, and over 1 million of them are AD patients, representing about 15 - 20% of AD cases.

Despite this risk, APOE e4 homozygotes are rarely treated as a separate predefined treatment group in clinical trials. There are currently no approved treatment options specifically for APOE e4 homozygotes, and existing amyloid targeting therapies commonly cause amyloid-related imaging abnormalities (ARIA) in APOE e4

homozygotes.

The session opened with Dr. Marwan Sabbagh (the Moreno Family Chair for Alzheimer's Research, Alzheimer's and Memory Disorders Program, Barrow Neurological Institute; Professor and Vice Chair of Research, Department of Neurology, Barrow Neurological Institute) providing a clinical overview of APOE e4 homozygosity and how it relates biologically and medically to Alzheimer's Disease. Four APOE e4 homozygotes shared their stories – all of whom have confirmed their genetic status and have a 60% chance of developing AD by age 85. Three of the four patient representatives are asymptomatic, while one patient representative is living with amnesic mild cognitive impairment (aMCI) due to Alzheimer's Disease. Three of the patient representatives have familial history of Alzheimer's Disease and have been caregivers to loved ones.

Our speakers shared their personal experiences, which included the personal and familial burden of their genetic status, the lack of support for the APOE e4 homozygotes, and the need for improved treatment options, especially prevention and early intervention in the preclinical, asymptomatic phase. These deeply personal stories were bolstered by Dr. Sabbagh's presentation of research indicating that APOE e4 homozygote population is a significant subset of the overall and AD population, bears increased risk, and lacks viable treatment options. Speakers expressed their interest in advocating for their peers, for improving clinical trial inclusion and participation, their motivation for participating in clinical trials, and their willingness to take on some level of risk.

Key Highlights

In their testimony, speakers presented the following key points:

- **APOE e4 homozygote status is overwhelming, anxiety and depression-inducing.** It can feel incredibly bleak, with no clear answers, no real roadmap, and a lack of support.
- **AD symptoms arise 7-10 years earlier and disease progresses more rapidly in APOE e4 homozygotes than in non-carriers.** Earlier monitoring, diagnosis, and support is necessary.
- **Current treatments are limited; available amyloid-targeting monoclonal antibody therapies have adverse side effects for APOE e4 homozygotes that deter APOE e4 homozygotes from such treatment.** Asymptomatic and presymptomatic APOE e4 homozygotes may be more limited to focus on prevention through lifestyle changes (e.g., diet, sleep, exercise, etc.)
- **APOE e4 homozygotes feel that new treatment options should have less risk than the existing monoclonal antibodies (mAbs).**
- **APOE e4 homozygotes are interested in participating in clinical trials and studies, though are not usually specified as a treatment group in clinical trials.** APOE e4 homozygotes want to be included in clinical trials and made strong statements regarding the potential benefits for research and for this subpopulation.
- **APOE e4 homozygotes urge the FDA to incentivize AD prevention/early intervention trials beyond amyloid-targeting antibodies, consider earlier stage, preclinical biomarkers in such trials, and mandate trial sponsors' inclusion of APOE genotype,** along with sex and ethnicity, in trial design and data analysis.

Session Objectives

UsAgainstAlzheimer's coordinated with APOE e4 Homozygote individuals and organized this Patient Listening Session to educate and increase the FDA's awareness of the scale of the APOE e4 population, their increased risk for Alzheimer's Disease, and their lack of viable treatment options. This session sought to achieve these goals through both a scientific overview of APOE e4 homozygosity and the lived experience of APOE e4 homozygotes. Additionally, carriers provided insight into the APOE e4 homozygotes' perspectives on trial involvement, risk willingness, and preferred treatment options.

Attendees

52 staff members attended this session, from a total of 21 different offices/divisions across 4 different FDA Centers, the Reagan-Udall Foundation for the FDA, and the National Institutes of Health.

Requesting Organization

- Chantez Bailey, UsAgainstAlzheimer's; Listening Attendee
- Catherine Patterson, UsAgainstAlzheimer's; Listening Attendee
- Russ Paulsen, UsAgainstAlzheimer's; Host Speaker

APOE e4 Homozygote Speakers

- Wendy Nelson; Speaker/Asymptomatic APOE e4 Homozygote
- Michael Payne; Speaker/Asymptomatic APOE e4 Homozygote
- J; Speaker/Asymptomatic APOE e4 Homozygote
- Rev. Dr. Cynthia Huling Hummel; Speaker/Symptomatic APOE e4 Homozygote and Person Living with aMCI due to Alzheimer's Disease

Partner Organization Attendees

- Jim Taylor, Voices of Alzheimer's; Listening Attendee

FDA Attendees:

- Office of the Commissioner (OC) – 2 offices
 - OC/OEA/PES – Office of External Affairs/Public Engagement Staff (organizer)
 - OC/OCMO/OPT – Office of the Chief Medical Officer/Office of Pediatric Therapeutics
- Center for Biologics Evaluation and Research (CBER) – 4 offices
 - CBER/OCBQ/DIS/PSB – Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Program Surveillance Branch
 - CBER/OCD – Office of the Center Director
 - CBER/OTP/OCE/DCEGM/GMB2 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 2
 - CBER/OTP/PSPS – Office of Therapeutic Products/Policy and Special Projects Staff

- Center for Drug Evaluation and Research (CDER) – 6 offices
 - CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Sciences/Division of Clinical Outcome Assessment
 - CDER/OND/ON – Office of New Drugs/Office of Neuroscience
 - CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neuroscience I
 - CDER/OND/ON/DNP – Office of New Drugs/Office of Neuroscience/Division of Psychiatry
 - CDER/OND/ORDPRUM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
 - CDER/OTS/OCP/DTPM – Office of Translational Sciences/Office of Clinical Pharmacology/Division of Translational and Precision Medicine
- Center for Devices and Radiological Health (CDRH) – 9 offices
 - CDRH/OCD – Office of the Center Director
 - CDRH/OPEQ/OHTI - Office of Product Evaluation and Quality/Office of Health Technology I
 - CDRH/OPEQ/OHTI/DHT1A – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IA
 - CDRH/OPEQ/OHTI/DHT1C – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IC
 - CDRH/OPEQ/OHTIII - Office of Product Evaluation and Quality/Office of Health Technology III
 - CDRH/OPEQ/OHTIII/DHT3B - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology 3B
 - CDRH/OPEQ/OHTIII/DHT3C - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology 3C
 - CDRH/OPEQ/OHTVIII/DHT8C - Office of Product Evaluation and Quality/Office of Health Technology VIII/Division of Health Technology 8C
 - CDRH/OSPTI/OEID/DCPD – Office of Strategic Partnerships and Technology Innovation/Office of Equity and Innovative Development/Division of Patient-Centered Development

Non-FDA Attendees

- Reagan Udall Foundation
- National Institutes of Health (NIH)
 - NIH/NCATS – National Center for Advancing Translational Sciences

Financial Disclosures

UsAgainstAlzheimer's receives funding from a variety of sources, including sponsors. However, none of these funds were used for the purposes of organizing or participating in this session. None of the participants in this meeting are receiving compensation for attendance or participation. Other than Dr. Marwan Sabbagh and Dr. Wendy Nelson, none of the participants have any financial interests to disclose.

Dr. Marwan Sabbagh has consulting relationships with Eisai, Lilly, Synaptogenix, NeuroTherapia, Signant Health, Novo Nordisk, Anavex, Cognito Therapeutics, GSK, Abbvie, Alzheon, and Athira. He serves on the Board

of Directors of EIP Pharma/CervoMed.

Dr. Wendy Nelson has a consulting relationship with New Amsterdam Pharma.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the UsAgainstAlzheimer's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of APOE e4 homozygosity and Alzheimer's Disease health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire APOE e4 Homozygote and Alzheimer's Disease patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Session Outline

Physician Remarks and Disease Overview

Dr. Marwan Sabbagh, a behavioral neurologist at the Barrow Neurological Institute (the Moreno Family Chair for Alzheimer's Research, Alzheimer's and Memory Disorders Program, Barrow Neurological Institute; Professor and Vice Chair of Research, Department of Neurology, Barrow Neurological Institute), thanked the FDA for this listening session and presented an overview of apolipoprotein E (APOE) e4 homozygosity.

APOE e4 is the strongest genetic association risk factor for late-onset Alzheimer's Disease. APOE e4 homozygotes carry two copies of the APOE e4 allele, which conveys a high risk for developing Alzheimer's Disease. It is not autosomal dominant but a susceptibility gene.

Overall, APOE e4 homozygotes are 2-5% of the population and 15-20% of AD patients in research studies. Two percent of the United States population (330 million as of the 2020 US Census) translates to more than 6.6 million people who are APOE e4 homozygotes. 60% of these APOE e4 homozygotes (approximately 4 million) will develop symptomatic AD in their lifetime. Currently, an estimated 1.05 million people who have symptomatic AD are APOE e4 homozygotes. APOE e4 carriers (homozygotes and heterozygotes) are about 24% of the healthy population but make up 55-75% of AD dementia cases.

There is a predictable journey for APOE e4 carriers. There is a preclinical phase, where amyloid starts to accumulate 20-30 years before symptoms. The next phase is the symptomatic, or prodromal phase, where carriers are amyloid PET positive, are clinically independent but mildly symptomatic. When advancing to dementia, carriers lose their functional independence and have functional decline.

Almost all APOE e4 homozygotes exhibit AD pathology and have higher mortality rates compared to

heterozygotes and non-carriers. Furthermore, AD progresses more rapidly for APOE e4 homozygotes. On average, APOE e4 homozygotes began experiencing AD symptoms estimated at age 65, about 7 to 10 years earlier than non-homozygotes. On average, mild cognitive impairment diagnosis occurred estimated at age 72, dementia diagnosis estimated at age 74, and death estimated at age 77. APOE e4 homozygotes have a 60% chance of developing symptomatic AD by age 85. Kaplan-Meier survival curves started to diverge from the age of 72 years, with an acceleration beginning at 76 years for APOE e4 homozygotes relative to non-homozygotes. The probability of living past 90 is very low.

Dr. Sabbagh emphasized that more treatment options are needed, and that prevention does not equal treatment. APOE e4 homozygotes are rarely treated as a separate predefined treatment group in clinical trials. There are no approved treatments specifically for APOE e4 homozygotes and there are continued unmet needs for treatments in APOE e4 homozygotes given risk benefit analysis of the monoclonal antibodies. These approved amyloid targeting therapies have increased risk for APOE e4 homozygotes, including Amyloid-Related Imaging Abnormalities (ARIA) edema (ARIA-E) and hemorrhage (ARIA-H). These ARIA were more commonly found among APOE e4 homozygotes in clinical trials for amyloid targeting therapies. Physicians are thus more reluctant to prescribe these drugs and patients are more reluctant to take them. There are more opportunities for developing and approving treatments focused on symptomatic and prevention.

Dr. Sabbagh concluded by thanking the FDA for this discussion and expressed his interest in working with the FDA, advocates, and caregivers for meaningful solutions.

Wendy Nelson, PhD: Asymptomatic APOE e4 Homozygote, Alzheimer's caregiver

Dr. Nelson's life is one ravaged by Alzheimer's Disease. Both her maternal grandfather and great aunt had AD, and her mother lived in fear of developing the disease. Her mother was then diagnosed at age 63 and passed away at age 76.

Her father was also diagnosed with Alzheimer's five years ago. Dr. Nelson has been the caregiver to both her parents. She watched her mother's body forget how to swallow, suffocating on her own saliva for seven agonizing days before her death. Now, her father requires eyes on him nearly every minute of the day. Dr. Nelson is faced with being the bad guy, taking away his driver's license, coordinating caregiver shifts, managing finances, supervising daily activities, and so much more. Caregiving is a tremendous burden.

After her mom's death, Dr. Nelson decided to test her DNA to hopefully rid herself of the fear of inheriting an APOE variant, but then in 2020 received confirmation that she carried two copies of the APOE e4 allele. The floor dropped out from beneath her. Most people don't know what the results mean or where to turn to for help. Unlike receiving a cancer diagnosis, where an oncologist leads your treatment plan, you might receive chemotherapy and/or radiation, or they might find a clinical trial for you, an APOE e4 designation is not a diagnosis. No one picks up your case. You are left to figure it out on your own. There is no roadmap – just silence and fear.

Since her genetic confirmation, Dr. Nelson has adjusted her life to live well and take preventative measures, exercising her brain and body even more than she already did, abstaining from drinking alcohol and she never smoked, etc. Despite these lifestyle adjustments, her genetic predisposition means she is still very likely to develop Alzheimer's Disease.

Unfortunately, the complicated biology behind the disease remains unsolved. Much of the damage to your brain is done long before one is ever diagnosed. Amyloid plaques build up, tau tangles form, and your brain mass begins to decrease 15-20 years before one becomes symptomatic. Therefore, we NEED more preclinical research to solve this puzzle, and we need to improve early detection of this disease.

Many people do not want to know if they are a carrier of the APOE variant because there are currently no treatment options for asymptomatic carriers. There are only two anti-amyloid drugs currently commercially available and this very population that is most likely to get this horrid disease are the most likely to suffer from ARIA as a side effect of these anti-amyloid drugs.

Dr. Nelson has three daughters, all of whom carry a single copy of APOE e4. She has explained to them that she does not want to be a burden on them or for them to see her suffer in the same way she has seen her own parents suffer. The likelihood of disease progression, lack of treatment options, and associated feelings of helplessness and hopelessness have prompted Dr. Nelson to explore physician-assisted euthanasia. She sees this as a more humane way to exit the earth, but due to stipulations that you must execute euthanasia when you are still mentally aware, it is something that she might be required to do when she is still able to contribute to society, when she still knows who her children are, and maybe when her daughters are engaged to be married or when she is expecting a grandchild. This haunts her and keeps her up at night.

Dr. Nelson made several key points calling for more action, which are especially important to her as funding for research and innovation is cut.

- We need more preclinical research to solve this puzzle and we need to improve early detection of this disease.
- More funding for companies that have achieved only fair results with potential therapies in patients with mild cognitive impairment and mild Alzheimer's to expand their clinical trials into an earlier population of asymptomatic APOE e4 homozygotes.
- We need to conduct far more clinical trials in asymptomatic carriers who are at super high risk of getting this disease and see if we can halt progression before the beginning of cognitive decline.

Michael Payne: Asymptomatic APOE e4 Homozygote, former Alzheimer's caregiver

Michael's relationship with Alzheimer's Disease is very personal. Michael was his father's primary caregiver after his dementia diagnosis. His dad passed away after five years of a painful journey with the disease, after

which Michael drifted away from the world of AD. Years later, his curiosity about his own genetics prompted a 23andMe test where he then discovered his own APOE e4 homozygosity.

There was minimal counseling about what to do with this information. Given his experience with his father and the lack of good treatments, he buried his head in the sand. Years later, a friend with similar familial experience got Michael involved in the Alzheimer's Clinical Trials Consortium. The ACTC seeks to push clinical trial managers to remain inclusive and include the widest population possible to ensure that any treatments developed are effective for all members of the community. Michael has been on the ACTC board since 2023.

He is also a participant in the ADNI neuroimaging study which involves MRI and PET imaging and bloodwork to track early markers of Alzheimer's disease progression. He will be going into his second round of MRI and PET scans soon. He is interested in finding even more ways to contribute meaningfully to research, given the challenges that APOE e4 homozygotes like him have.

As he learns more, he sees that clinical trials are not as inclusive of people in the APOE e4 community as he would hope. He knows that some of this hesitancy is because there have been complications in treating APOE e4 homozygotes with the current monoclonal antibody therapies. While he understands the caution, he believes exclusion is not the answer. APOE e4 homozygotes need to be part of the solution. He fears that APOE e4 homozygotes may continue to be excluded in the short term because they are seen as a complication to the current progress of the therapies, given some side effects experienced such as ARIA.

Michael posits that there is another side to the exclusion, where there is hesitancy within the APOE e4 homozygote community because they have not been meaningfully brought into the treatment conversation. After distancing himself from the Alzheimer's community, he is motivated as an advocate and research participant and wants to ensure that that clinical trials and treatment development include people like him from the beginning – not as an afterthought.

When considering his own likelihood of developing Alzheimer's Disease, he is most focused on treatments that can slow down how quickly the disease progresses. Given advances in early diagnosis, he believes this combined approach would provide the best opportunity to add more years of manageable MCI once the disease has been diagnosed, even if the early treatments do not cure or address all symptoms. Continued progress is the most important motivation for him. Michael believes that a large proportion of the APOE e4/4 (homozygote) community would be very interested in taking such a treatment once made fully aware of any potential side effects. As long as the side effects are relatively minor and do not affect daily activities, he sees no reason that he would not take it.

Michael closed his testimony by calling for action:

- For the FDA to continue to support inclusive trial designs and therapeutics development that encourages research participation by underrepresented genetic subgroups.

- For regulators, researchers, and pharmaceutical companies to work together to ensure that all, including the APOE e4 community, are seen, heard, and served.
- For himself to continue to be an ambassador for his community and to raise their level of awareness and engagement.

J: Asymptomatic APOE e4 Homozygote

J is a cognitively normal Asian female in her late 50s, a former senior biotech executive with a PhD in biochemistry. Over 10 years ago, J's husband died of cancer, leaving her as a single mother and sole caretaker of their young son.

J discovered her own APOE e4 homozygosity in 2023 through a genetic testing kit, which reported East Asians with this genotype have a risk of AD 25 times that of non-carriers. Without any family history of AD and with her father still mentally sharp, the threat of Alzheimer's felt distant. That changed when the Nature Medicine paper ([Fortea et al., 2024](#)) came out, claiming APOE e4 homozygosity was not just a risk factor but a genetic cause of Alzheimer's, and that the average age of symptom onset for people with her genotype was about 65.

After this news, J began to experience symptoms of crippling anxiety and could not eat or sleep. To her, losing her mind, identity, and autonomy in as little as seven years was a fate worse than death. And as a single mother without a partner to help care for her, she did not want to burden her only son with the duties of dementia caregiving. She even began looking into physician-assisted suicide and eventually started seeing a therapist. Eventually, J found comfort and community support in groups including APOE4.info forums, Facebook, and her local Alzheimer's Association chapter.

With her ethnicity, gender, genotype, and age a perfect storm of Alzheimer's risk factors, J chose to volunteer for local AD prevention clinical trials. In 2024, she enrolled in a UCSD phase 2 brain health study, where she saw significant memory improvement in post-trial cognitive tests and began applying learned strategies in her daily life.

APOE e4 carriers are the most vulnerable population for late onset Alzheimer's; they account for 2% of the overall population yet make up 15% of AD cases. Women like J account for two-thirds of AD patients and are guaranteed to pass their high-risk APOE e4 gene down to their children. This is why it is crucial for the FDA to prioritize research that targets the APOE e4 genotype.

J is interested in AD prevention in various modalities if shown compelling clinical trial data in cognitive function improvement or delaying AD onset with minimum side effects, especially in APOE e4 homozygotes. She is interested in future AD prevention (targets beyond Amyloid) and early diagnostic trials provided there is guaranteed data transparency from trial sponsors. She is not interested in trials involving Amyloid-targeting antibodies due to the elevated risk of detrimental side-effects in APOE e4 homozygotes. She may be interested in AD prevention trials if given a placebo, depending on the likelihood of post-trial open label extensions and how promising initial study results/mechanism might be in AD prevention.

J closed her testimony by advocating for a continuation and expansion of research into prevention, early detection, and effective combination therapies for Alzheimer's disease, especially in APOE e4 homozygotes. J made the following points and recommendations to the FDA:

- Grant priority review vouchers to companies developing drugs for prevention and early intervention of Alzheimer's in APOE e4 carriers.
- The APOE e4 genotype also confers significantly higher risks of detrimental side effects like ARIA-E (brain edema) and ARIA-H (brain bleeding) when taking certain FDA-approved amyloid-targeting antibodies. The risks for 4/4 women are even higher because of minimal efficacy seen in newer antibody drugs, 31% less than men.
- Expand FDA guidance on Diversity Action Plans in clinical trials by requiring trial sponsors to list APOE e4 carrier status as an essential demographic factor.
- Require AD trial design with sufficient statistical power to show treatment efficacy & side effect differences in subgroups and to release all findings of such data based on all demographics, especially sex and genotype.
- Develop policies to enforce full trial sponsor compliance.

Rev. Dr. Cynthia Huling Hummel: Symptomatic APOE e4 Homozygote, living with aMCI due to Alzheimer's Disease

Pastor Cynthia is a symptomatic APOE e4 homozygote, currently living with amnesic mild cognitive impairment due to Alzheimer's Disease. Her cognitive problems began in 2003 at 49 years old. At that time, she was pastoring a busy church in upstate New York and realized that she was having problems recognizing her parishioners and remembering what they had shared with her. Pastor Cynthia asked a member of the church about her mother, not remembering that she had buried the parishioner's mother months before. It was painful and embarrassing for Pastor Cynthia and confusing and upsetting to the parishioner.

This instance and other gaffes prompted Pastor Cynthia to figure out what was wrong with her brain. She saw many specialists, and each had their own theories about her cognitive problems, from menopause, to stress, to a head injury she sustained, to the radiation treatments she received as an infant for hemangioma. One neurologist ordered a PET scan, but insurance denied it with the rationale that if it was indeed Alzheimer's, then there was no point because there were no treatment options at that time.

Pastor Cynthia continued to experience forgetfulness and memory problems after moving to a new parish in 2007, getting lost while on church business. Most upsetting was getting lost on the way to the town cemetery to bury a church member. Pastor Cynthia's new primary care doctor sent her for neuro-psych exams which showed severe deficits and recommended leaving parish ministry because things would only get worse. She got the official diagnosis of amnesic MCI due to AD. This was not so much a surprise but was a great sadness. It meant that Pastor Cynthia had to leave her life's work of being a pastor. She was depressed, sad, and angry.

She decided to enroll in the ADNI study and will start her 16th year in ADNI soon. Around 2010, Pastor Cynthia used a genetic testing kit which confirmed that she was an APOE e4 homozygote. It explained a lot, as her mother and her uncle (mother's brother) were diagnosed with Alzheimer's, and their mother (Pastor Cynthia's grandmother) had some sort of dementia.

Pastor Cynthia is grateful to have access to her APOE e4 risk information, especially as new treatments become available. People ask her if she will take one of the new Alzheimer's drugs, but she has to explain that she cannot due to the brain bleeds and swelling APOE e4 homozygotes. She is better able to weigh the dangers against the benefits of such treatments. Pastor Cynthia needs to be extra cautious with regard to side effects, as she lives alone. She hopes to join another study soon which is said to have fewer side effects. She is eager to get started because APOE e4 homozygotes have such few options. The clock is ticking for Pastor Cynthia and other APOE e4 homozygotes and they need more treatment options.

Since her diagnosis, Alzheimer's Disease has become her mission and ministry. She has served as National Early Stage Advisor for the Alzheimer's Association in 2015 and served two years on the National Advisory Council on Research Care and Services. She currently sits on the NIH's National Advisory Council on Aging (NACA), where her term was extended beyond 4 years. She served as an advisor to two Alzheimer's decadal studies at the National Academies of Science, Engineering, and Medicine and has spoken at five NIH Research Summits and will be heading to Toronto to speak at AAIC2025. She was one of the authors of the Research Participants Bill of Rights and is an advocate for the disclosure of personal results. She was recently honored with the 2024 Global Alzheimer's Citizen Scientist Catalyst Award. Pastor Cynthia shared her background to demonstrate her commitment to Alzheimer's research and her hopes and prayers for a greater focus on treatment options for all.

Pastor Cynthia closed by thanking the FDA for their service and their commitment to learn more about pharmacological interventions, their commitment to protect and ensure the health and safety for those like her who are at greater risk. She thanked the FDA for the opportunity to speak.

Q&A

FDA Public Engagement Staff thanked everyone for their willingness to share their experiences and stories, then opened then opened the meeting to colleagues for comments and questions.

- 1) FDA CDER/OND/ON: Thank you to everyone who shared their stories. The FDA strives to make sure that clinical trials are representative of the population that bears the burden of the disease. For FDA sponsored clinical trials, we require APOE4 carriers be included in the study participants. We try our best not to exclude patients.
 - a. Russ Paulsen and Dr. Sabbagh thanked FDA CDER/OND/ON for her remarks.
 - b. Dr. Sabbagh mentioned the potential for trials designed specifically for APOE4 e4 homozygotes that really look at prevention and treatment.
- 2) FDA: What would you have liked to know in terms of early intervention that could have made an impact on managing your APOE4/4, especially after seeing your parent or taking care of a family

member with APOE4 and Alzheimer's?

- a. Dr. Nelson responded that she already knew she was at a higher risk because both of her parents developed AD. However, she noted that she's only 54 and would like to see more trials that address pre-symptomatic 4/4 carriers so that no one has to wait until they have symptoms.
 - b. J shared that she wanted to see the FDA look into the pre-clinical stage biomarkers for patient recruitment and evaluation of efficacy. Clinical trials could look beyond existing genetic markers that often show AD in more advanced stage when it's much harder to reverse symptoms once they start. She mentioned the FDA's new AI tool ELSA and shared that she saw real promise in using this tool to see if it could help identify safe treatments for 4/4s. It could also take into account different genotypes and ethnicities. She would like to see the FDA designate priority review vouchers for those trials that focus on prevention and early-stage intervention, preferably prior to AD symptoms, for preclinical stage participants.
 - c. Michael noted that this question resonated deeply with him. It became increasingly clear that his father was experiencing real issues with his cognition. He shared that his dad was having difficulty following plots of tv shows. Then his father had a stroke and that made it harder to realize that he had dementia. The ability to determine if he had Alzheimer's earlier would have been really helpful so that family members could have been aware of what is going on.
- 3) FDA: What about the risk of ARIA and brain bleeds? What risks are you willing to take when it comes to treatment options?
- a. Michael noted that he is pretty open to risk, but if they are debilitating, he'd opt out.
 - b. Pastor Cynthia shared that she hopes to be in a clinical trial this summer but needs to consider the fact that she lives alone. The possibility of having adverse side effects is risky for her because she does not have someone in her home who could alert her to those potential side effects.
 - c. Dr. Nelson shared that she had made comments about ARIA and brain bleeds and is not comfortable with that level of risk. She shared that she would like to see the FDA utilize the new AI tool ELSA to evaluate risk for 4/4s. Given that damage in the brain occurs years before you ever show symptoms, having early intervention options are critical.
 - d. J shared that she is not interested in trials for amyloid-targeting antibodies but interested in looking for more treatment options beyond the anti-amyloid drugs. Different modalities should be explored, including small molecule drugs, as well as digital, remote cognitive assessments like [BRANCH](#), and hippocampal volume as an important indicator of brain function and cognitive abilities.

Appendix: Physician Remarks and Selected APOE e4 Homozygote Testimony

The appendix contains the entire transcripts of physician remarks and selected APOE e4 homozygote testimony. Highlights from these full remarks are also captured in earlier sections.

Marwan Sabbagh, MD, FAAN: Behavioral neurologist

I want to take this moment to thank the FDA officials who are participating in this patient listening session on Alzheimer's disease and APOE4 homozygosity. I am Marwan Noel Sabbagh. I hold the Moreno Chair for

Alzheimer's research in the Alzheimer's and Memory Disorders Division at the Barrow Neurological Institute, where I also serve as Vice Chairman and Professor in the Department of Neurology at the Barrow Neurological Institute.

So, why are we discussing APOE4 homozygotes? It's because it turns out to be the strongest genetic association risk factor for late-onset Alzheimer's disease, not autosomal dominant but a susceptibility gene, and that APOE4 homozygotes represents 2 to 5 percent of the general population and 15 to potentially 20 percent of patients with Alzheimer's disease in research studies.

So, if we do the numbers, 2 percent of 330 million is about 6.6 million, of which 60 percent will develop symptomatic Alzheimer dementia, so approximately 4 million APOE4 homozygotes alone will develop Alzheimer's disease dementia in their lifetime, and the current estimates, when we look at the 15 to 20 percent rubric of symptomatic Alzheimer dementia, we're talking about 1.05 million people who are APOE4 homozygotes.

Almost all of them have more Alzheimer pathology, have more mortality, have earlier onset of symptoms compared to heterozygotes and non-carriers. When we look at the statistical probability, of course, APOE4 carriers represents 24 percent of the general population and up to 75 percent of Alzheimer cases. This has been reproduced in every single epidemiological study that's performed in the United States, every case control study, every clinical trial performed in the United States.

It is very, very rare for the APOE4 to be significantly less than half, usually around 2/3rds, and we know that if we follow the prescribed journey, there's a pre-clinical phase where amylose starts to accumulate, 20 to 30 percent before onset of symptoms, and then you go into the early symptomatic phase, which we now call the prodromal phase, where they are amyloid PET positive, but they're clinically independent, but mildly symptomatic, and when they advance to dementia, they've lost their functional independence and have functional decline.

So, the numbers are represented here. The worldwide estimates also are represented here. When we look at the fact that APOE4 not only represent an increased lifetime risk, that it also represents an earlier age of onset and an increased risk of progression to dementia. So, on average, APOE4 homozygotes experience symptoms earlier than non-carriers, about 7 to 10 years before onset of non-carriers.

It occurs, MCI, at around 72, dementia at 74, and death at 77. We also know that by age 85, more than 60 percent of APOE4 homozygotes will have developed symptomatic Alzheimer's disease dementia. So, when you look at the Kaplan-Meier survival curve that you see here, the green line tells you everything you need to know, is that the all-cause mortality just gets bigger and bigger, the older you get, and you see that the curves really quickly diverge, starting in the early-to-mid 70s, and the probability of being alive past 90 is very, very low.

So, we know that it is an increased risk for developing lifetime dementia. You tend to develop symptoms earlier, at age 72. You tend to become dementia in mid-70s, and you tend to have death, all-cause mortality, earlier. So, we've framed the argument that the risk is higher, the need is there, and I think you're going to hear a lot of discussions on treatments and prevention. So, we understand that their lifetime risk is higher.

We understand that we need to address both new treatments, symptomatic treatments for Alzheimer's, and increased risk...because of increase of developing Alzheimer's in your lifetime, we should be targeting the therapies that are focused on prevention. As a group, APOE4 homozygotes are usually lumped in as a subcategory. They're not usually targeted or specifically called out as their own pre-specified, pre-defined group.

There are no approved treatments specifically for APOE4 homozygotes, and we know that this is an area of unmet need. Why, because the improved anti-amyloid targeted therapies have been known to have higher risks of developing complications like ARIA, amyloid-related imaging abnormalities, more so than heterozygotes or non-carriers. So, that makes reluctance to be using this class of drugs by physicians and by patients, and we have to take extra care to do so, but this leaves an area of unmet need.

And so, I think there are more opportunities for developing and approving treatments focused on symptomatic and prevention. So, with that, I want to thank the FDA for this opening discussion, and I look forward to working with both the caregivers, advocates, and the FDA on meaningful solutions.

Rev. Dr. Cynthia Huling Hummel: Symptomatic APOE e4 Homozygote, living with aMCI due to Alzheimer's Disease

I am the Rev. Dr. Cynthia Huling Hummel from Owego, NY and I am homozygous APOE4. I started experiencing cognitive problems back in 2003 when I was just 49 years old. At that time, I was pastoring a busy church in upstate NY and realized that I was having problems recognizing my parishioners and remembering what they had shared with me. I remember asking a member of the church about her mom, not remembering that I had buried her mother several months before. It was painful and embarrassing to me and confusing and upsetting to the woman. But that instance and other gaffes set me on a quest to figure out what was wrong with my brain. I went from doctor to doctor seeking answers. I visited all sorts of specialists and each had a theory about my cognitive problems, from menopause, to stress, to a head injury I had sustained, to the radiation treatments I received on my face as an infant for a hemangioma. One neurologist ordered a PET scan, but my insurance denied it with the rationale that if it was indeed Alzheimer's there was no point because there were no options for treatment at that time. So that was that.

When I moved to a new parish in 2007, my Alzheimer's moved with me. I continued to have trouble remembering conversations and faces and frequently got lost on my way to visit parishioners or on other church business. One of the most upsetting of those was when I got lost on the way to the town cemetery to bury a church member. I ended up calling a local florist to help me get there. Everyone was upset with me when I finally arrived, late and shaken.

My new primary care doctor sent me for neuro-psych exams which showed severe deficits and recommended that I leave parish ministry because it would only get worse. There was nothing he could prescribe that would help. My diagnosis was amnesic mild cognitive impairment due to Alzheimer's disease. It wasn't a surprise, but it was a sadness. I loved being a pastor, but I couldn't do it any longer. When I asked my doctor about my prognosis, he said "Seven years. Maybe longer. I had to move out of the church's housing to make room for the pastor who would follow me. I was depressed, sad and angry. It just felt so unfair. In any case, I decided to enroll in an Alzheimer's study and called the Alzheimer's Associations Trial Match 800# and was matched with the ADNI study ("Alzheimer's Disease Neuroimaging Initiative)" at the University of Rochester, NY and I will be starting my 16th year in ADNI next month.

It was somewhere around 2010 that I heard about 23 & me and sent away for my kit. I remember looking up information on APOE and learned there were 3 types of alleles that provided risk information: the APOE2 (a protective allele), APOE3 (a neutral allele) and APOE4 (a risk factor.) I can remember nervously awaiting the results because I suspected that they would reveal an APOE4 allele, and my fears were confirmed. It explained a lot. My mother Claire and her only brother Austin had been diagnosed with Alzheimer's disease and their mother, my "Grandma Mimi" had some sort of dementia. So I wasn't shocked, I felt a deep sadness. A few months ago, I read that 23 and me might be selling their data so I printed out my report and deleted my account.

I am grateful to have had access to my APOE risk information, especially as new treatments have become available. People will sometimes ask if I am going to take one of the "new Alzheimer's drugs" and I explain to them that I can't, because the "new Alzheimer's drugs" have been known to cause brain bleeds and swelling in some, like me who are homozygous e4. Having more information regarding my increased risk for potentially fatal reactions, I am better able to weigh the dangers over and against the benefits- including my costs and time versus the modest benefits of the drugs now available. Moreover, I live alone and need to be extra cautious with regard to the side effects of some of the medications that are now on the market. I hope to join the study later this summer out of the University of Rochester. I have heard that there are fewer side effects, including brain swelling and bleeding for those who are APOE4 positive with this particular drug. Time will tell. I am anxious to get started and hopeful that this new medication will help others like me because right now, those of us with APOE4 have so few options. The clock is ticking for me- and we APOE4 carriers want and need more treatment options.

Since being diagnosed, Alzheimer's has become my mission and my ministry. I was honored to serve as National Early Stage Advisor for the Alzheimer's Association in 2015, as well as serving a two-year term on the National Advisory Council on Research Care and Service. Currently, I am sitting on the NIH's National Advisory Council on Aging. I have served as an advisor to two Alzheimer's decadal studies at National Academies of Science, Engineering and Medicine and have spoken at five NIH Research Summits and will be heading to Toronto to speak at AAIC2025. I was one of the authors of the Research Participants Bill of Rights and I am an



advocate for the disclosure of personal results. I was recently honored with the 2024 Global Alzheimer's Citizen Scientist Award. I share my background so you have a sense of my commitment to Alzheimer's research and my hopes and my prayers for a greater focus on treatment options for all of us. I also want to thank YOU today for your service to the FDA and your commitment to learn more about the pharmacological interventions that are in the treatment pipeline.

Thank you for the opportunity to speak to you today and for your commitment to protect and ensure the health and safety for those like me who are at greater risk.