Accelerate Cures/Treatments for ALL neuroDEGENERATIVE DISEASES (ACT-AD)
17th Annual FDA/ACT-AD Allies Meeting 2024

November 7, 2024

1. Introduction

The 2024 Accelerate Cures/Treatments for All Dementias (ACT-AD) explored the current therapeutic and research landscape for Alzheimer's disease (AD) and AD-related dementias (ADRD). The meeting convened experts from academia, pharmaceutical companies, the Food and Drug Administration (FDA), and the National Institute on Aging (NIA), as well as members of the AD community. Discussions highlighted inclusion in research of participants with lived experience, sex and gender differences in diagnostics and disease symptoms and progression, new treatments, biological biomarkers, and emerging technologies in digital health including digital biomarkers.

2. NIH/NIA Research Update: Building a Precision Medicine Research Enterprise

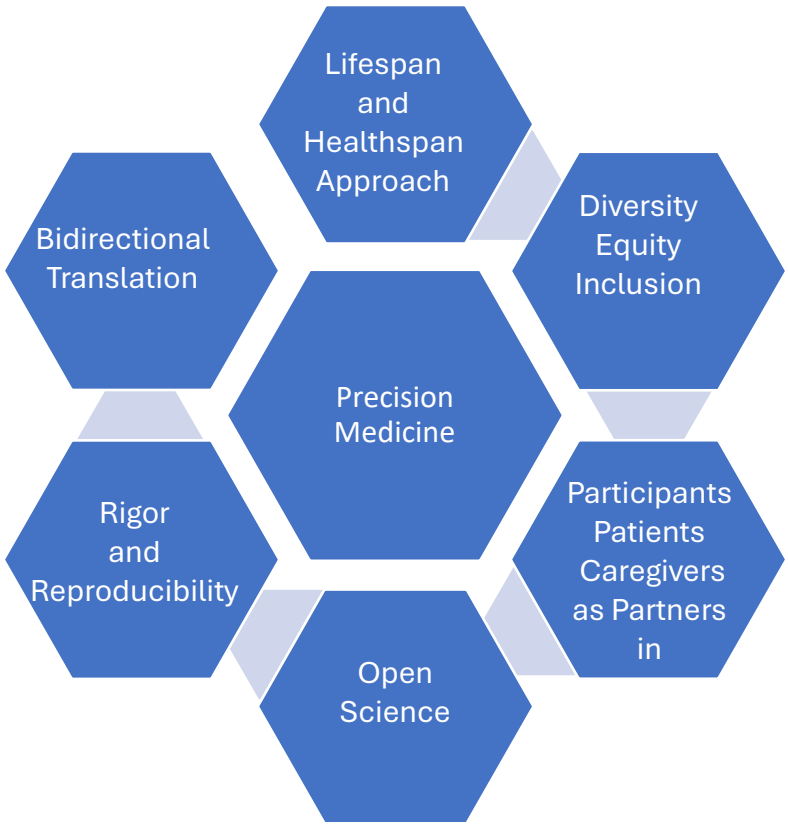
2.1 Research Summits

Since 2012, NIA has convened a research summit every 3 years. The most recent, Building a Precision Medicine Research Enterprise (September 23-25, 2024),[1] focused on ways to improve treatment and prevention. Specifically, the goal of its seven sessions was to formulate a blueprint for an integrated, translational research agenda that will enable the development of effective therapies (disease modifying and palliative) across the disease continuum for the cognitive as well as neuropsychiatric symptoms (NPS) of AD (**Figure 1**).[2] **.** After each summit, NIA hosts a post-session discussion to address gaps and opportunities.

NIA AD/ADRD research strategy builds from these summits and other external and internal input. NIH releases funding opportunities to develop comprehensive research implementation milestones, e.g., enabling access to data and associated biosamples and biomarkers from completed, ongoing, and future federally and privately funded clinical trials to clarify the biomarkers' predictive and theragnostic value, to identify surrogate endpoints, and to advance the understanding of heterogeneity of disease and treatment response.

[1] https://www.nia.nih.gov/2024-alzheimers-summit.
[2] https://www.nia.nih.gov/research/milestones.

Figure 1. Precision Medicine



Precision medicine comprises: a life-span and health-span approach; diversity, equity, and inclusion; participants, patients, and caregivers as partners in research; open science; rigor and reproducibility; and bidirectional translation. Generally, one size does not fit all, and we need to go from single-treatment to multiple-combination therapies.

2.2 Participants as research partners

The participant's voice is essential to set research priorities and address challenges, and therefore, people with lived experience should be engaged in all aspects of research, including other research related to the study topic, funding opportunities, and private and public partnerships. For this to work, it is important to integrate planning on dissemination of research outcomes and findings to the community from which participants come.

To effectively engage those with lived experience, it is not sufficient just to establish the requirement that these people be included. Investigators must develop evidence-based training to teach participants the best ways to engage with researchers so they can serve as

effective research advocates and voices with lived experience. Then investigators need to develop standardized processes for returning research results to participants with lived experience.

2.3 Data sharing

Data sharing has been required for NIA AD/ADRD clinical trial funding opportunities since 2018. Sharing of data and biosamples is expected at the time of publication of the primary results or within 9 months of data lock (whichever comes first). Pivotal trials are expected to follow Collaboration for Alzheimer's Prevention (CAP) data- and sample-sharing principles. That is, they must make screening/pre-randomization baseline data available within 12 months of enrollment completion; and make post-randomization data and biosamples available as soon as possible without compromising trial integrity, i.e., after regulatory approval or trial completion/termination or 18 months (whichever comes first).

Sharing of data and biospecimens from the Anti-Amyloid Treatment in Asymptomatic AD (A4) trial has been very successful. Screening/pre-randomization data were shared via GAAIN/LONI IDA. A data and biospecimen sharing committee was established, which resulted in 1,560 approved requests for clinical and biomarker data provided by investigators from more than 60 countries. The effort ultimately (as of September 3, 2024) enabled 68 peer-reviewed publications.

In A4, data shared were clinical and cognitive, and from lab, biomarker, neuroimaging (MRI, amyloid PET, tau PET), and genome-wide association study (GWAS) results. The A4 final study data are now available for download, and lessons learned were published in a *Journal of Prevention of Alzheimer's Disease* Special Issue.[3,4]

AD/ADRD Implementation Milestone 14.0 specified convening joint workshops and public symposia and establishing a memorandum of understanding (MOU) to promote a close collaboration between NIA/NIH and FDA for the advancement of biomarker and therapy development for AD/ADRD. An MOU that covers AD, related dementias, and other age-related diseases was established in June 2024.

2.4 Discussion

- Question: How does NIA track compliance on data-sharing?

  Answer: NIA is a funding agency, and people who do not share will be penalized in terms of future grant funding.

[3] Aisen P, Sperling R. Introduction to the Special Issue on the A4 Study. *J Prev Alzheimers Dis* 2024;11(4):801. https://doi.org/10.14283/jpad.2024.118.
[4] Deters KD, Napolioni V, Sperling RA, et al. Amyloid PET imaging in self-identified non-Hispanic Black participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study. *Neurology* 2021;96(11):e1491-e1500.

- Question: Would MOUs help?

  Answer: MOUs allow high level collaboration/discussions between NIA/NIH and FDA to align and address priorities for the advancement of biomarker and therapy development for AD/ADRD.
- Question: What about data sharing in light of inclusivity and the need for anonymity?

  Answer: Sharing involves de-identified data. We need more than the requirement that data be shared—the field of data sharing needs more innovations about how to share data and protect against participant identification. It is important to have the insights of people with lived experience in discussions of data sharing.

3. Sex and Gender Differences in ADRD

3.1 Dissecting the role of X chromosome dosage and APOE ε4 genetic risk in AD

Late-onset AD (LOAD) is a sex-biased disorder: two-thirds of those with AD are women, and the disease may progress differently in women than in men.[5,6] In addition, converging factors of age, lifestyle, hormonal status, and genetic risk may contribute.

Sex-chromosome dosage (SCD)—two X chromosomes in females or one X and one Y chromosome in males—is the main genetic difference between the sexes. X chromosome inactivation (XCI) silences most genes on one X chromosome in females; however, 15-25% of genes escape XCI and remain expressed from the inactive X (Xi), resulting in female-biased expression. SCD (XX in females and XY in males) was hypothesized to contribute to sex differences in late-onset AD, and APOE ε4 was hypothesized to exacerbate these differences.

To dissect the interaction between X chromosome dose and APOE at the cellular level, human-induced pluripotent stem cell (hiPSC)-derived models of neural cells were used as a reductionist model to directly test mechanisms that may be due to genetics. Then, post-mortem AD brain tissue was used to investigate sex and APOE-specific effects on neuroinflammation. It was discovered that X chromosome dose alters cellular phenotypes related to AD, that sex and APOE drive differential gene expression in AD microglia, and that distinct microglial subtypes also show differences with sex and APOE. Moreover, pathways that differ by APOE are enriched for proteostasis.

Sex-biased autosomal genes are differentially affected by X chromosome dose in neural progenitor cells. In microglia, X chromosome dose influences cytokine levels of APOE. Sex and APOE drive distinct microglial subtypes that also show differences with sex and APOE, and there is differential gene expression in AD microglia. X chromosome dose can regulate neuronal

[5] Zhu D, Montagne A, Zhao Z. Alzheimer's pathogenic mechanisms and underlying sex difference. *Cell Mol Life Sci.* 2021;78(11):4907-4920.

[6] Ossenkoppele R, Lyoo CH, Jester-Broms J, et al. Assessment of demographic, genetic, and imaging variables associated with brain resilience and cognitive resilience to pathological tau in patients with Alzheimer disease. *JAMA Neurol.* 2020(77):632-642.

and microglial functions. Differential gene expression in AD microglia is highly driven by sex and APOE.

3.2 Leveraging clinical data to better understand sex differences in AD

AD phenotype varies by sex, e.g., women have an increased estimated lifetime risk of AD, whereas men with AD die faster than women. Women show brain resilience to tau pathology.[7, 8, 9]

Comorbidity networks show the multimorbidity of AD. Real-world electronic health record (EHR) data provide an increasing availability of rich, longitudinal, real-world clinical data. This information was used to perform deep clinical phenotyping and network analysis of AD patients, which gave insight into its clinical characteristics and sex-specific clinical associations.[7, 10]

Differences were observed in networks of females versus those of males (**Figure 2a**). Sex-stratified analysis identifies top sex-specific–associated diagnoses as osteoporosis and urinary tract infections (UTIs) among females with AD.

Furthermore, Tang et al. showed that applying machine learning to EHR data allows prediction of AD onset up to 7 years in advance. Prediction models were interpreted using phecode categorization[11] and showed different patterns across time and by sex. While hyperlipidemia (HLD) was predictive of AD in both males and females, osteoporosis was specific to females. Both of these were validated as an AD predictor in an external EHR database across multiple medical centers. The interpretation was further enhanced by leveraging knowledge networks as well as by integrating GWAS datasets (**Figure 2b**).

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[7]Tang AS, Oskotsky T, Havaldar S, et al. Deep phenotyping of Alzheimer's disease leveraging electronic medical records identifies sex-specific clinical associations. *Nat Commun*. 2022;13(1):675-629.

[8] Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 20(5):3708-3821 Available from: https:// https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13809.

[9] Agüero-Torres H, Fratiglioni L, Winblad B. Natural history of Alzheimer's disease and other dementias: review of the literature in the light of the findings from the Kungsholmen Project. *Int J Geriatr Psychiatry.* 1998;13:755-766.

[10] Woldemariam SR, Tang AS, Oskotsky TT, et al. Similarities and differences in Alzheimer's dementia comorbidities in racialized populations identified from electronic medical records. *Commun Med (Lond).* 2023;3(1):50.

[11] Tang AS, Rankin KP, Cerono G, et al. Leveraging electronic health records and knowledge networks for Alzheimer's disease prediction and sex-specific biological insights. *Nat Aging.* 2024;4(3):379-395.

Figure 2a. Differences Observed in Networks in Females vs Males

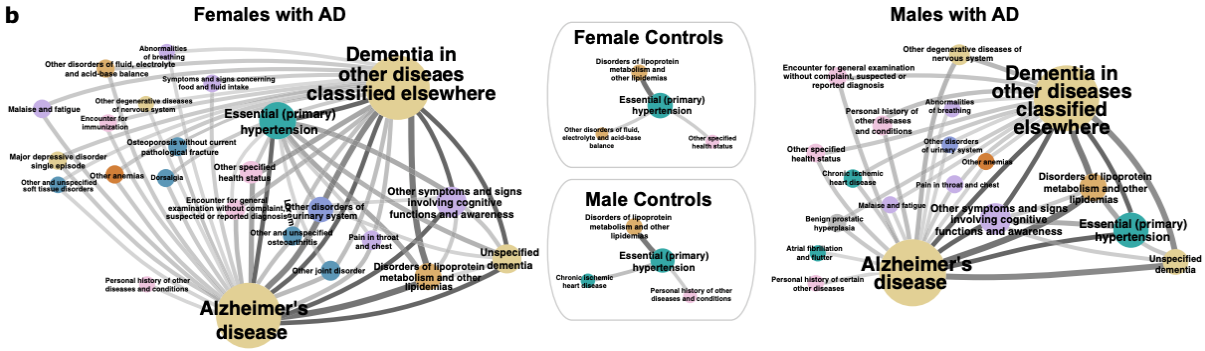
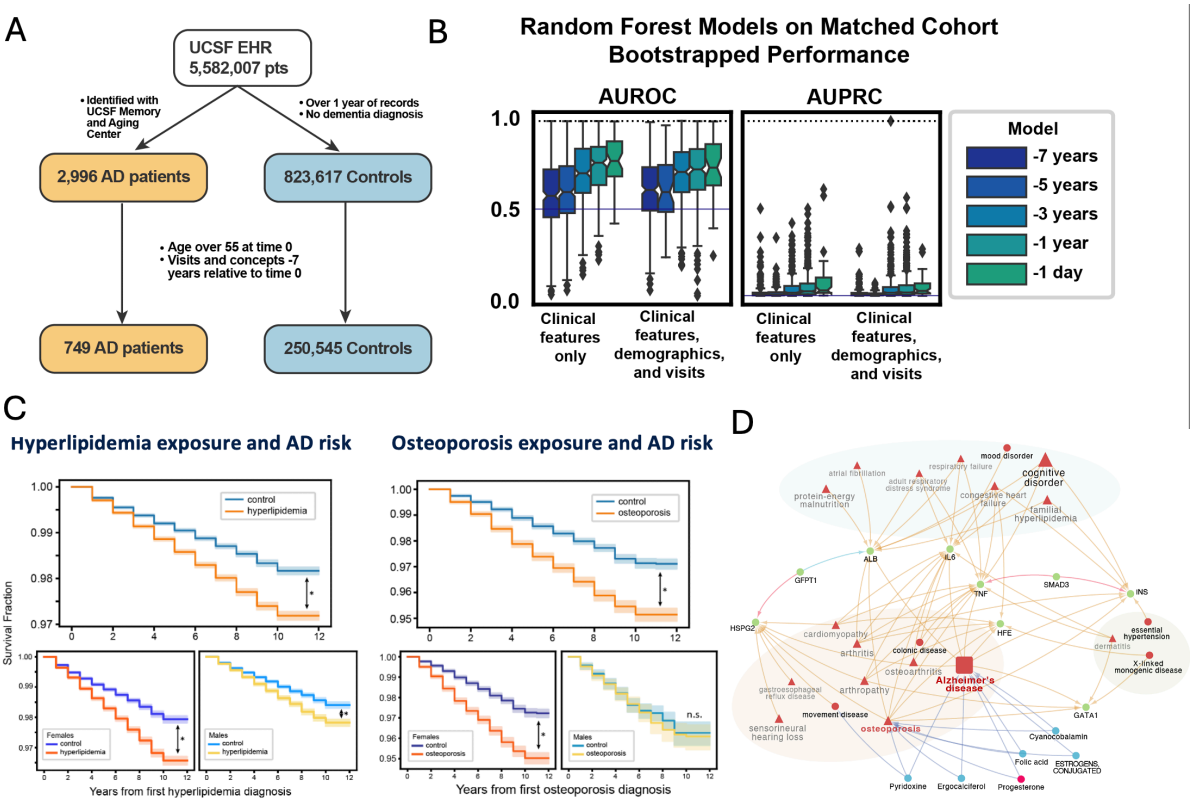


Figure 2b. Predictive Modelling of AD Diagnosis Identifies Sex-Specific Predictors Validated on an External EHR Database, and GWAS and Gene Expression Datasets



A) Identification of EHR cohorts, (B) Predictive performance of Random Forest models on EHR data for each time model (7 years, 5 years, 3 years, 1 year, and 1 day before diagnosis), (C) validation in cohorts, (D) First-degree and second-degree neighbors of HLD on the knowledge network representing all shortest paths from the top 25 features per time model

3.3 Improving predictive validity for efficacy and differential effects of sex with model systems

NIA AD/ADRD Research Summit recommendations since 2015 have aimed at increasing the predictive validity of preclinical studies in AD animal models; given that historically studies using animal models have had poor translatability, lacked key elements of rigor, and were not well-designed. With the NIA-funded resources of the Model Organism for the Development and Evaluation of Late Onset AD (MODEL-AD) these translational gaps have been improved to study the biology of LOAD, including genetic risk, aging, and environment. In addition, there are no restrictions for use of these new models by any laboratory or drug company which had previously been a hinderance. Importantly, MODEL-AD[12] uses models to study biological and drug effects applying rigorous standard operating procedures (SOPs) for model characterization that align with the pathophysiological features of AD, e.g., characterizing phenotype in alignment with clinical disease staging, and deprioritizing mouse behaviors in lieu of translationally relevant outcome measures (e.g., biomarkers, *MRI/PET*).

At the same time, resources for the research community are being established for rigorous preclinical testing of potential therapeutics with prioritization of translational outcome measures (pharmacokinetics/pharmacodynamics, *in vivo* target engagement) and powered to detect the effects of sex through the MODEL-AD Preclinical Testing Core (PTC).[13, 14, 15, 16] Data generated from these Open Science resources have the requirement of sharing all raw data including both positive and negative findings. Moreover, the PTC minimizes resourcing of rodent behavioral outcomes as a primary endpoint for drug screening, given that reversal of cognitive deficits in rodent models have failed to translate to significant cognitive improvement in AD patients. Rather, behavioral assays are used as a tertiary measure as part of the PTC drug-screening pipeline de-risk the compound for potential adverse effects and to identify the therapeutic index for efficacy relative to safety.

The PTC uses a precision medicine approach[17] that maps the mechanism of action being investigated with the most appropriate model system that recapitulates the human disease signature and biology, and that can enable and inform translational in vivo target engagement outcome measures. Compounds advancing through the pipeline that have been de-risked and demonstrate pharmacodynamic effects that may predict efficacy can be advanced to more sophisticated cognitive studies including translational touchscreen platforms in both the rodent

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[12] https://www.model-ad.org.

[13] Sasner M, Onos KD, Territo PR, Sukoff Rizzo SJ. Meeting report of the fifth annual workshop on Principles and Techniques for Improving Preclinical to Clinical Translation in Alzheimer's Disease Research. *Alzheimers Dement.* 2024;20(7):5035-5043.

[14]Quinney SK, Murugesh K, Oblak A, et al. STOP-AD portal: Selecting the optimal pharmaceutical for preclinical drug testing in Alzheimer's disease. *Alzheimer Dement.* 2023;19(11):5289-5295.

[15] Oblak AL, Cope ZA, Quinney SK, et al. Prophylactic evaluation of verubecestat on disease- and symptom-modifying effects in 5XFAD mice. *Alzheimers Dement (NY).* 2022;148(1):e12317.

[16] Sukoff Rizzo SJ, Masters A, Onos KD, et al. MODEL-AD consortium. Improving preclinical to clinical translation in Alzheimer's disease research. *Alzheimers Dement (NY).* 2020; 6(1):e12038.

[17] Cummings J, Lee G, Ritter A, et al. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (NY).* 2019;9(5):272-293.

models and that can be also employed similarly in non-human primates, as well as correlating neurophysiological outcomes using EEG.

As an extension of the model system resources funded by the NIA to improve translation through the MODEL-AD centers, a non-human primate model resource funded by the NIA, MARMO-AD[18] is studying more than 200 marmosets to bridge the translational gap between rodent models of AD and humans. Marmosets are a small non-human primate that overcomes many of the gaps between rodent models and humans including having an evolved prefrontal cortex that is critical for higher-order cognitive processes, a comparative immune system to humans, are maintained as outbred which enables the capturing of genetical and phenotypic heterogeneity, and manifest AD-related pathologies naturally with aging. The MARMO-AD consortium is studying natural aging and sporadic AD in marmosets as well as differences in marmosets genetically engineered with AD risk. The marmosets are comprehensively characterized from birth throughout their lifespan[19] using noninvasive, clinically-analogous measures. This approach will establish normative values for aging phenotypes in wild-type marmosets and in the marmosets with genetic risk for AD across the lifespan. MARMO-AD is leveraging the sophisticated cognitive, social, and affective behaviors in the marmosets to identify analogous measures that capture the spectrum of NPS comorbidities in AD patients. Aligning with the comprehensive touchscreen cognitive measures in the rodent models for MODEL-AD, MARMO-AD is also using similar translational touchscreen cognitive tests.[20] All MODEL-AD and MARMO-AD[21] resources are available to the research community. [22]

3.4 Sex-specific multi-omic predictors of Alzheimer's disease

Females have more AD pathology, i.e., levels of amyloid at autopsy, and females with AD pathology decline more rapidly than males.[23] Furthermore, cognitive decline occurs faster in females than in males.[24] Cerebrospinal fluid (CSF) biomarkers of AD neuropathology are more

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[18] Sukoff Rizzo SJ, Homanics G, Schaeffer DJ, et al. Bridging the rodent to human translational gap: Marmosets as model systems for the study of Alzheimer's disease. *Alzheimers Dement (NY)*. 2023;9(3):e12417.
[19] Homanics GE, Park JE, Bailey L, et al. Early molecular events of autosomal-dominant Alzheimer's disease in marmosets with PSEN1 mutations. *Alzheimers Dement.* 2024;20(5):3455-3471.
[20] Murai T, Bailey L, Schultz L, et al. Improving preclinical to clinical translation of cognitive function for aging-related disorders: the utility of comprehensive touchscreen testing batteries in common marmosets. *Cogn Affect Behav Neurosci.* 2024;24(2):325-348.
[21] Sukoff Rizzo SJ, Homanics G, Schaeffer DJ, et al. Bridging the rodent to human translational gap: marmosets as model systems for the study of Alzheimer's disease. *Alzheimers Dement (NY)*. 2023;9(3):e12417.
[22] https://stopadportal.synapse.org/.
[23] Koran ME, Wagener M, Hohman TJ. Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav.* 2017;11(1):205-213. https://link.springer.com/article/10.1007/s11682-016-9523-8
[24] Footnotes 7, 8 and 9 seem to contradict this. The issue of female susceptibility is very challenging; there was a debate at the Sex and Gender Differences in AD PIA on the topic of female susceptibility v. female resiliency because of the evidence on both sides. The biggest points to be made are that (1) Females have better episodic memory performance in the absence of disease, so they are starting from a higher baseline. (2) Females show higher levels of neuropathology at autopsy. You could argue this is resilience (it takes more neuropathology for a female to manifest symptoms). That said, females also show a stronger association between neuropathology and future cognitive decline, so perhaps it is better to interpret these differences as susceptibility (females decline faster in the presence of pathology).

strongly associated with atrophy in females compared to males, and APOE ε4 is associated with cognitive decline in AD more strongly in females than males.[25]

Sex-specific genetic effects studied were:

- APOE association with amyloid and tau biomarkers. Females show a stronger association between *APOE*-ε4 and tau biomarkers measures in CSF.
- Genome wide association studies (GWAS) of amyloid and tau neuropathology measured at autopsy, identifying male-specific and female-specific gene associations
- Male-specific and female-specific gene expression associations with AD neuropathology measured in human brain tissue
- Cell-specific sex differences in gene expression associations with AD neuropathology
- Tendency for female protective associations to be from neurons and female risk associations to be driven by glial cells.

Sex differences are essential when considering *APOE* in clinical trials (**Figure 3**). Sex-specific genetic effects vary by tissue, cell type, neuropathology, and clinical stage of disease. Yet, many genetic targets have not been evaluated for sex differences, which has important implications for preclinical testing for therapeutics. Sex-specific genetic associations appear to map onto sex-specific transcriptomic responses in the brain. At the single-cell level, female susceptibility can be seen in neurons, male susceptibility in endothelial cells, and numerous flipped pathways in the AD brain. These represent tremendous opportunities for sex-specific interventions in AD.

Figure 3. Sex Differences in APOE on Cognition

	Memory Performance	Executive Functioning	Language Performance
APOE-ε4	↑F M	F M	↑F M
APOE-ε2	F M	F M	F M

32,427 Participants including **4,453** non-Hispanic Black
Walters et al. *JAMA Neurology.* 2023

3.5 Discussion

- Question: Are there the same sex specificities in Down syndrome (DS)?

  Answer: There are sex specificities, but they may not be the same.

- Question: In different types of animals, much research has been done at the academic level, but not at the pharmaceutical level. What would you like to see companies do?

[25] Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. *JAMA Neurology.* 2017;74(10):1178-1189.

Answer: Pharma does a great job—better than academia—on mouse-model studies, but that could be because of funding.

- Question: Is it a good idea for NIH to encourage people to roll out this information? What makes the body deteriorate with AD symptoms?

  Answer: Findings should not remain in obscure academic journals. Clinicians can speak to patients and discuss their situations. Maybe treating comorbidities will improve AD outcomes. We need more information about finding patients earlier. SPOKE helps our understanding of biology. Then we can study the ramifications.

- Question: How can patients help with this and be better research partners?

  Answer: We make great efforts to partner with patients to get an understanding of disease effects. Patient feedback can guide research where it should go. However, there is much skepticism about research. By partnering with organizations, we can work together on these problems.

  Answer: We researchers are the biggest skeptics of our own work. Genetics affect the conditions we study, as do comorbidities, but neither may be what we intended to investigate for that particular patient.

- Question: Are we talking about time to diagnosis or time to onset of symptoms?

  Answer: That's a limitation of the clinical records we have in the system. We don't have access to the specific lab tests patients undergo.

- Question: Neuro-psychological tests are subjective. Are you hoping to be able to integrate them even so?

  Answer: Absolutely. We need to look at data in different ways to deal with AD. There is no single treatment that fits all. But we have gained insight with the data at hand.

- Question: What power do you have to do exposure analysis?

  Answer: We are continuing with University of California–San Francisco (UCSF) data about minimal cognitive impairment.

- Question: Cataracts are listed as a driving factor, but you didn't address the condition.

  Answer: That research has not been done yet. But the presenter will send Alice Tang's contact information to the questioner.

- Question: Is there speculation about the occurrence of AD in women who do not take hormone replacement therapy (HRT)? What about the inaccurate results of the Women's Health Initiative (WHI) HRT study? Recent research shows that women who were taking HRT were less at risk of getting AD.

  Answer: There is an interesting potential connection, but we need to take a closer look.

- Question: In the lecanemab study, evaluating sex differences during a Phase 3 trial proved too difficult, but are you looking at earlier data?

  Answer: Yes, it is probably unrealistic to power a Phase 3 trial for all potential stratifications. From the Donanamab results, it appears that the hints at sex differences in amyloid treatment effects (observed in lecanemab and aducanumab Phase 3 trials) evaporate when tau is used in study enrollment, suggesting the original sex differences may have been due to known sex differences in the association between amyloid positivity and tau burden.[26] The bigger issue is that we didn't know when going into the clinical trial whether we should expect a sex difference in the treatment effect. If sex is disaggregated earlier in preclinical data, it might suggest that we should expect a sex difference and should power the study for appropriate disaggregation. There are similar differences that are showing up in the Phase 3 trial data when stratifying by race or ethnicity. All this reduces the question to, is the difference across populations due to the therapeutic or context? Doing more to disaggregate preclinical results earlier in the process can help improve our Phase 3 trial designs and provide more precision around the best population for a therapeutic. Eisai noted that the study was not powered to detect potential sex differences, so we cannot make any conclusions or claims on potential sex differences as the statistics do not allow for it.

- Question: Microbes can affect the brain differently. In addition to genetics and e4, could amyloid protein be microbial?

  Answer: That's where non-human primate studies can be very useful—e.g., opportunistic pathogens could be included. We have not looked specifically at microbial differences, but we see differences in sex with GWAS.

[26] Buckley, RF, Mormino, EC, Rabin, JS, et al. Sex differences in the association of global amyloid and regional tau deposition measured by Positron Emission Tomography in clinically normal older adults. *JAMA Neurol*. 2019; 542-551. https://jamanetwork.com/journals/jamaneurology/fullarticle/2722842

4. Industry Session: Updates from the Field on Approved Therapies

4.1 Lecanemab for treatment of early Alzheimer's disease[27,28]

AD is a progressive, relentless disease caused by a continuous underlying neurotoxic process that involves both soluble and insoluble forms of Aβ.[29, 30] It is an ongoing neurotoxic process that begins before and continues after amyloid plaque deposition. Lecanemab targets both soluble and insoluble forms of Aβ species and has downstream effects on tau pathophysiology and inflammation. In the Clarity AD Phase 3 clinical trial, plaque pathology as well as tangle pathology declined after 18 months of lecanemab treatment, and cognitive and functional decline was significantly reduced on the primary endpoint. Additionally, there was slowing of patient health-related quality of life (HRQoL) and caregiver burden by 23-56% compared to placebo.

The most common adverse reactions (occurring at approximately 5% and higher incidence compared to placebo) were infusion-related reactions, amyloid-related imaging abnormalities (ARIA) with hemosiderin deposition (ARIA-H), ARIA with edema (ARIA-E), headache, superficial siderosis of the central nervous system, rash, and nausea/vomiting. There was no increase in isolated ARIA-H for lecanemab vs placebo. Symptomatic ARIA-E occurred in 3% of patients treated with lecanemab. Clinical ARIA symptoms resolved in 79% (23/29) of patients during the period of observation. Open label extension showed that patients continued to accrue benefits through 36 months of lecanemab treatment, with no known increase in adverse events over time and with open label extension still ongoing.

Lecanemab reduced biomarkers of amyloid and resulted in significantly less decline on measures of cognition and function compared to placebo at 18 months in early Alzheimer's disease, and treatment was associated with several adverse events.

4.2. Otsuka's commitment to advancing research on neuropsychiatric symptoms (NPS) in AD

Otsuka US, is a healthcare company that conducts clinical trials; its Agitation in Alzheimer's Dementia Global Medical Affairs Program has two foci—a Disease State Program intended to educate on mechanisms of disease and improving recognition of agitation in Alzheimer's dementia, and a REXULTI specific Program intended to provide data-driven solutions to important stakeholders in order to improve treatment of agitation associated with dementia due to AD.

The Disease State Program is currently focused on agitation. In addition to cognitive decline, manifestations of Alzheimer's dementia include a range of NPSs, including agitation,

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[27] van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. Poster presented at: Alzheimer's Association International Conference; July 16-20, 2017; London, UK. Poster P2-055.
[28] LEQEMBI (lecanemab-irmb). Package insert. Eisai Inc.; 2023.
[29] Hampel H, Hardy J, Blennow K, et al. The amyloid-β pathway in Alzheimer's disease. *Mol Psychiatry*. 2021;26(10):5481-5503.
[30] Pospich S, Raunser S. The molecular basis of Alzheimer's plaques. *Science*. 2017;358(6359):45-46.

which affects half of AD sufferers.[31] Agitation in Alzheimer's dementia is characterized by noradrenergic hyperactivity along with serotonergic deficits and dysregulated striatal dopamine release that contribute to agitated and aggressive behaviors. However, identifying agitation in AD is very complicated. Physicians have no clear definition of agitation; caregivers and health care professionals (HCPs) may not understand that agitation differs from cognitive impairment; and all are reluctant to talk about it. To improve recognition of agitation, the Agitation in AD Screener for Caregivers (AASC) was developed.[32] It is the first such screen based on the International Psychogeriatric Association (IPA) definition of agitation in cognitive disorders.

The goal of Otsuka's Therapeutic Program, Practice Relevant Analyses and Communication for Informed Decision Making, is to enable dissemination of relevant analyses and communication for informed decision making. The Brexpiprazole Clinical Program is a 22-year-old collaboration with health regulatory bodies dedicated to research on NPS of dementia. It provides comprehensive data analyses to inform clinicians about appropriate use of brexpiprazole in the treatment of agitation associated with dementia due to AD. The program—involving clinicians, decision-makers, caregivers, and patients—supports real-world evidence generation and independent education.

Real-world evidence enhances understanding of disease treatment to advance quality healthcare and improve the lives of patients. It also underlies independent Continuing Medical Education on the pathophysiology, burden, diagnosis, management, and monitoring of agitation in Alzheimer's dementia within the specialty and primary care settings.

4.3 Discussion

- Question: Agitation is usually observable but driven by widely different things. Medication is often used to control agitation rather than finding out what is driving the agitation. The result is that antipsychotics are over-relied on. Is this a part of your group's effort?

  Answer: Education on the IPA Definition of Agitation in Cognitive Disorders is critical to our educational outreach. The and our medical education make clear the importance of differential diagnosis.

- Question: Is agitation a syndrome of exclusion rather than a diagnosis?

  Answer: Yes, the IPA definition provides clear criteria when assessing for agitation in cognitive disorders, including criteria focused on differential diagnosis to ensure that agitation is not being driven by other medical conditions (e.g. like a UTI). That said, there is significant amounts of research supporting the underlying and distinct pathophysiology of agitation, and how development of tau pathology in certain brain regions may increase the risk of developing agitation. Additionally, our research suggests an unmet educational

[31] Cummings, JL, Brubaker, M, Selzler KJ, et al. An overview of the pathophysiology of agitation in Alzheimer's dementia with a focus on neurotransmitters and circuits. *CNS Spectrums.* 2024 Oct 23:1-10.
[32] https://www.theaasc.com

need when it comes to understanding the different forms with which agitation may present. Caregivers and physicians alike struggle with appropriately recognizing the full breadth of agitation symptoms.

- Question: How does agitation affect day-to-day living?

  Answer: Agitation compounds an already devasting Alzheimer's disease diagnosis. Further, research demonstrates that it compounds caregiver burden and that those with agitation in Alzheimer's dementia have worse outcomes than their non-agitated counterparts.

- Question: Agitation is among the key challenges that caregivers face. How do you address that?

  Answer: Recognition of agitation is first. Second is empowerment to discuss it. Otsuka has partnered with esteemed leaders in the field to develop the first quantitively validated caregiver screener focused on agitation in Alzheimer's dementia, the AASC®, which offers caregivers the opportunity to talk about agitation with a physician, giving them a voice.

- Question: Does clinician education and looking for alternative explanations include discussion about how seizures might affect diagnosis?

  Answer: Our medical education program covers the most common alternative explanations for agitation.

- Question: Nonpharmaceutical therapies that have a robust evidence base could be offered, but when those treatments are insufficient, we could move on to pharmaceutical agents. But first, we need to destigmatize this discussion. What are your thoughts on that?

  Answer: In the discussion of nonpharmaceutical vs pharmaceutical, clinical guidelines stress the importance of first using non-pharmaceutical approaches. Unfortunately, and commonly, these approaches fall short, and agitation persists. In the US, and until recently, caregivers and patients did not have any approved pharmaceutical therapies in this space and historically treatment has relied on the off-label use of several medications. Many of these options come with notable safety considerations. A focus on providing options to caregivers, patients and physicians that are based on rigorous demonstration of efficacy and safety helps when faced with these difficult decisions.

- Question: A change in setting often triggers anxiety and paranoia in patients with AD, which obfuscates what we are addressing. Is agitation secondary to dementia or is it a separate disorder?

Answer: Differential diagnosis is important when assessing for agitation, as the IPA definition for agitation in cognitive disorders makes clear.

- Question: There are techniques that work, but we must be very careful to meet patients' needs culturally in the way we express the options—thoughtless wording might even lead to suicide. Many things can be done without pharmaceutical medication, and we need to consider that dementia patients may have comorbidities. The bottom line is, what is it that makes a patient explode?

  Answer: Cultural considerations in this space are incredibly important and to be considered carefully.

5. Emerging Technologies in Digital Health

5.1 Digital phenotyping: focus on acoustics

The Global Research and Imaging Platform (GRIP) hopes to develop AD screening tools with unbiased cognitive assessments because more sensitive dementia assessment facilitates earlier diagnosis. The Precision Brain Health Initiative (Boston University) has found an association between acoustic features of AD and neuropsychological test performance. This enabled development of a method for automated prediction of progression to AD within 6 years using speech. Smart phones can be used to collect these data, and researchers are now developing a BRAIN app that includes but also goes beyond voice.[33, 34, 35]

There are many digital devices and there will only be more in the future. Current cell phones are being used for digital phenotyping, but this is not a sufficient path to digital biomarkers. According to the FDA: "Biomarkers are characteristics that are objectively measured as indicators of health, disease, or a response to an exposure or intervention, including therapeutic interventions"; whereas a "digital biomarker…[is a] characteristic or set of characteristics, collected from digital health technologies, that is measured as an indicator of normal biological processes, pathogenic processes, or a response to an exposure or intervention, including therapeutic interventions." For this, we need to build a digital support infrastructure.[36]

With digital biomarkers, we are talking about a dynamic, flowing, and ever-changing indicator, a new concept. We must generate a digital ecosystem that includes voice (acoustic, linguistic, paralinguistic), physical activity, sleep, cognition, and retinal imaging. Interoperability across platforms will lead to the creation of a precision research infrastructure. Then, filling

[33] Amini S, Hao B, Yang J, et al. Prediction of Alzheimer's disease progression within 6 years using speech: a novel approach leveraging language models. *Alzheimers Dis Demen.* 2024;20(8):5262-5270.
[34] Ding H, Mandapati A, Karjadi C, et al. Association between acoustic features and neuropsychological test performance in the Framingham Heart Study: observational study. *J Med Internet Res.* 2022;24(12):e42886..
[35] Ding H, Lister A, Karjadi C, et al. Detection of mild cognitive impairment from nonsemantic, acoustic voice features: the Framingham Heart Study. *JMIR Aging.* 2024; 7:e55126.
[36] Tavabi N, Stück D, Signorini A, et al. Cognitive digital biomarkers from automated transcription of spoken language. *J Prev Alzheimers Dis*. 2022;9(4):791-800.

research gaps will generate game-changing science. One effect will be to deliver digital brain health as a standard of care.[37]

First, we must build a digital support infrastructure that functions across the lifespan and with data that are globally attainable by and accessible to researchers. Currently, we are engaged in a "wild west search" for a digital voice indicator that has clinical utility. Digital voice is inherently identified, which has been a barrier to widespread adoption, but as with any other data, the digital voice must be de-identified (masking the person's actual voice) before the data can be shared. Through GRIP, the first version for voice alterations robust enough to use will hopefully come by next year.

In addition to collecting data, we must develop processing tools that are interoperable. The back-end infrastructure needed for this includes workspace for curation, harmonization, and interoperability. And we need to hear from people other than highly resourced investigators.

5.2 Emerging AD Biomarkers: Focus on the Lens

The ocular lens expresses age-dependent AD Aβ pathology and is optically accessible from the periphery. AD-associated Aβ accumulate in the supranuclear subregion of the lens (**Figure 4**). AD-associated Aβ supranuclear cataract (SNC) localizes to the periphery of the lens (behind the iris) and does not impair vision, even in advanced cases. The AD-linked cataract is distinct from common age-related cataracts (ARC) not only in terms of location, but also with respect to biochemistry, pathophysiology, and clinical course.[38] AD b-amyloid (Aβ) pathology in the lens is unique to Alzheimer's disease and Down syndrome (DS, trisomy 21), a common chromosomal disorder that is invariantly associated with early-onset Aβ pathology in the brain. [39] Neuropathologically-confirmed AD eye-brain donor tissue confirmed that AD SNC lens phenotype exhibits bilateral penetrance and is not detected in non-AD dementias.[40, 41, 42]

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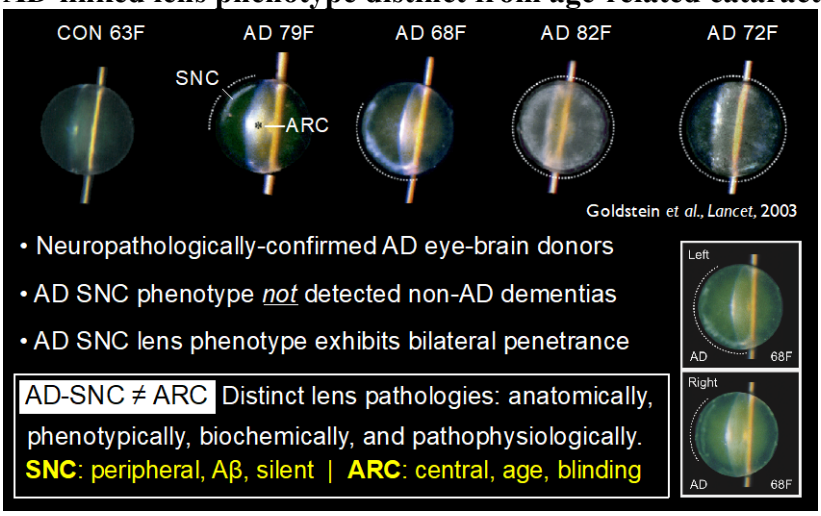
[37] Lin H, Karjadi C, Ang TFA, et al. Identification of digital voice biomarkers for cognitive health. *Explor Med.* 2020;1:406-417.
[38] Moncaster JA, Moir RD, Burton MA, et al. Alzheimer's disease amyloid-β pathology in the lens of the eye. *Exp Eye Res.* 2022;221:108974.
[39] Moncaster JA, Moir RD, Burton MA, et al. Alzheimer's disease amyloid-β pathology in the lens of the eye. *Exp Eye Res.* 2022;221:108974.
[40] Jun G, Moncaster JA, Koutras C, et al. δ-Catenin is genetically and biologically associated with cortical cataract and future Alzheimer-related structural and functional brain changes. *PloS One.* 2012;7:e43728.
[41] Kerbage C, Sadowsky CH, Jennings D, et al. Alzheimer's disease diagnosis by detecting exogenous fluorescent signal of ligand bound to beta amyloid in the lens of human eye: an exploratory study. *Front Neurol.* 2013;27(4):62.
[42] Kerbage C, Sadowsky CH, Tariot PN, et al. Detection of amyloid beta signature in the lens and its correlation in the brain to aid in the diagnosis of Alzheimer's disease. *Am J Alzheimers Dis Other Demen.* 2015;(30):738-745.

Figure 4. AD-Related Subequatorial Supranuclear Cataract (SNC)

AD-linked lens phenotype distinct from age-related cataract (ARC)



Non-congenital cataracts also occur in DS and there is a correlation between early AD and early DS cataracts that differ from ARC. DS cataract occurs as early as 18 months of age, as does Aβ. Both Aβ deposits come from the lens, not the brain. Additional evidence linking AD mouse models and lens Aβ pathology. For example, in the Tg2576 transgenic mouse model of AD, mice that express the human Swedish mutant APP gene got familial AD age-dependently express human Aβ and develop AD-related amyloid pathology not only in the brain but also the lens. Tg+ mice also develop age-dependent Aβ SNC that are similar phenotypically, pathologically, ultrastructurally, and biochemically to SNC in the lenses of people with AD.[43, 44]

These early occurrences enabled development of the Aftobetin-Sapphire II Lens Ab Scanner, which received FDA breakthrough designation in 2021. This novel drug-device enables ophthalmic detection of AD-linked Aβ lens amyloidopathy. This novel technology affords potential for early detection and noninvasive monitoring of AD at the point of care. The lens Aβ eye scanner is safe, simple, sensitive, and specific. The platform may afford additional utility to detect and monitor Aβ in the aqueous humor as a noninvasive method ("optical paracentesis") to monitor treatment-related changes in Aβ fluxes in relevant biofluids (cf. cerebrospinal fluid, CSF). An allied technique has been developed that utilizes quasi-elastic light scattering to quantitatively evaluate molecular aging. These research thrusts will enable much work to be done across NIH institutes.

5.3 Discussion

- Question: Has the eye been sequenced for microbial infections?

[43] Goldstein LE, Muffat JA, Cherny RA, et al., Cytosolic β-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. *Lancet.* 2003;361(9365):1258-1265.
[44] Moncaster JA, Pineda R, Moir RD, et al. Alzheimer's disease amyloid-beta links lens and brain pathology in Down syndrome. *PLoS One.* 2010;5(5):e10659.

Answer: No, but the investigators want to look at this. Because of the way the lens grows, you can identify when something happens. You can essentially look back in time—you can say something is there and when it happened, as with the rings of a tree.

- Question: DS patients die of infection at a young age. Is this similar with AD patients?

  Answer: Yes, and in addition, there is a huge, well-documented racial difference: Blacks with DS die at younger ages than Whites.

- Question: Do any disease-modifying therapies of AD affect animal models?

  Answer: We will be looking at the lens to potentiate it, and also at the interior chamber to do pharmacokinetics on Ab liberation. We want to see if the effect can be modulated in animals. Most of these diseases are multifactorial, e.g., there is also an inflammatory component in AD that is multifactorial. We want to identify who is at risk and intervene before irreparable damage occurs.

- Question: What about digital twinning?

  Answer: With digital twinning—which uses data to connect physical objects, processes, or assets bi-directionally—the data and the bi-directional connection provide timely insights to improve a built asset's design, construction, handover, operation, maintenance, renewal, and end-of-life processes. The infrastructure being constructed for AD brain research will address this issue but will not get to the realities until the infrastructure is built. Then, the clinical aspects must also be perfected. It's not enough just to collect data; we have to be able to use synthetic data, and we can't get to that reality until we build in the digital twinning infrastructure.

- Question: The goal with the lens research is early diagnosis and early risk-factor assessment of AD, so a digital biomarker has to be disease-specific. Is there also a causal relation between biomarker and disease event?

  Answer: We want to identify AD before there are symptoms, and to bring this knowledge to the clinic or even before the clinic. Differentiation has to be specific. Also, accessibility for patients is an important factor. Fancy scans or blood tests may not be practical for patients who live in remote areas or have complicated logistics.

- Question: What kind of changes happen to the voices of patients with AD?

  Answer: Audio features include sound quality and hesitations; linguistic markers include range of words. Unique changes and combinations take place over time. Recordings pick up the qualitative differences of sound, and

Smartphones can be used for this. They are readily accessible and can be used across languages.

- Question: Are ocular diagnostics being commercialized?

  Answer: That is the hope. These studies focused on AD-linked biomarkers where we knew there was a direct connection to the brain. Diagnostics, e.g., an AD-amyloid pathology, is a disease-linked biomarker. But investigators will collect all possible data.

6. FDA Fireside Chat

6.1 Precision medicine and Data sharing

There is interest in understanding the effects of the amyloid-directed monoclonal antibodies across AD populations to better inform benefit-risk considerations. Sex and gender differences are an active area of FDA research. FDA is conducting an analysis of sex and gender differences in efficacy using the datasets for the approved amyloid-directed monoclonal antibodies that have been submitted to the Agency. Because FDA resources are limited to conduct such analyses, having clinical trial data, including treatment arm data, more widely available through data-sharing would be helpful to allow for analyses to be conducted by other groups.

It can be challenging to interpret subgroup analyses within clinical trials as the analyses are typically not adequately powered to allow for robust conclusions. Broadening enrollment criteria for clinical trials may allow for more informative analyses across subgroups but can be challenging for sponsors to conduct. There may be concerns with diluting the ability to detect an efficacy signal with a population that is too heterogenous, and there may be feasibility and funding limitations for studies that are very large. Ultimately, data to support a personalized basis for drug use will likely come from research in the postmarketing setting and data sharing will be very important for these efforts.

6.2 Boxed warnings for antipsychotics

FDA is considering the need to update the boxed warning that has been in place since 2005 for antipsychotics and increased risk of mortality in patients with dementia-related psychosis. As a first step in the process, FDA and the Duke-Margolis Institute for Health Policy will host a joint workshop on December 10, 2024. The workshop will focus on the safety of antipsychotics for neuropsychiatric symptoms of dementia and a review of the data that led to the boxed warning. The meeting will not discuss drug development or trial designs for neuropsychiatric symptoms of dementia. This workshop is an opportunity to bring information regarding the initial data that led to the boxed warning to the table and to discuss next steps for further evaluation of the issue. It is an ongoing project.

In 2005, the results of the initial analyses were presented at public meetings, but they were never published or shared digitally. A first step will be to reassess the original data that led

to the boxed warning in the first place. The initial analyses were conducted using summary-level data, but FDA will seek individual-level data from those programs to allow more detailed analyses, such as subgroup analyses. Moreover, since 2005, FDA has approved other drugs for neuropsychiatric symptoms in dementia, e.g., for agitation in AD. FDA will also seek additional data that may have been generated in other drug development programs for neuropsychiatric symptoms to reevaluate the risk for mortality. FDA will also review the published literature on risks of antipsychotics for the treatment of neuropsychiatric symptoms of dementia, but published studies have had inconsistent findings about mortality risk.

6.3 Blood-based biomarkers

Blood-based biomarkers are very promising. At FDA, the Center for Devices and Radiological Health (CDRH) reviews the technical performance aspects of the biomarker assays, while the Center for Drug Evaluation and Research (CDER) handles the use of biomarkers in drug development programs. Some blood-based biomarkers are available commercially as lab-developed tests but are not formally cleared for use by FDA. Once blood-based biomarker assays receive formal FDA clearance and become more widely available, they will change clinical practice – the way AD is diagnosed and how patients are selected for treatment.

In drug development, biomarkers data from clinical trials can be used to support findings on clinical outcomes and bolster the overall robustness of the data package for effectiveness. Amyloid PET has been used as a reasonably likely surrogate endpoint for the accelerated approval of some drugs, but use to support efficacy for other development programs needs to be assessed in the context of the specific development program. Other biomarkers that are commonly being used in drug development for AD include microtubule binding region (MTBR) and plasma phosphorylated-tau 217 (p-tau217).

6.4 Inclusivity

FDA published a guidance document on inclusivity in clinical trials in June 2024, "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies".[45] The guidance outlines the FDA requirement for diversity action plans for drug development programs. The requirement will take effect in about a year. Sponsors will be required to develop a plan for how they will include a representative population in their drug-development programs. The diversity action plans are required to address race, ethnicity, sex, and age, but other factors may be considered based the specific disease.

FDA wants to increase underrepresented populations in clinical trials and supports methods to improve clinical trial diversity. This will require community engagement. Decentralizing clinical trials may also play an important role to improve access. Enrollment criteria may also need to be broadened. In AD, trials have been successful at enriching for trial populations that are likely to demonstrate a response to treatment, but that has resulted in excluding people who live in poorly resourced areas. It may be possible to enroll a broader

[45] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-action-plans-improve-enrollment-participants-underrepresented-populations-clinical-studies

population to characterize drug effects in the population that is likely to be treated with the drug but specify a primary analysis in the enriched population to establish efficacy.

6.5 Digital health technologies (DHTs)

FDA is open to the inclusion of DHTs in clinical trials, despite reports to the contrary. FDA has seen DHTs used in clinical trials for screening participants or monitoring treatment effects. If sponsors are considering the use of DHTs, FDA recommends including DHTs in early-stage studies because the data collected in those studies will inform their use in Phase 3 studies. FDA sees a lot of promise in DHTs. To understand regulatory consideration for use of DHTs, a good place to start is with the FDA guidance published in December 2023, "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations".[46]

6.6 Advisory committees, pharmacovigilance, and informed consent

There have been recent publications that have been critical of the FDA's approval of the amyloid monoclonal antibodies raising issues with the advisory committee process and safety. FDA screens participants invited to join advisory committees for conflicts of interest. If the expert is qualified, a waiver may be granted—after all, experts are sought by other people, too. FDA also continues to monitor safety of the amyloid antibodies after the initial approval. There are required registry studies ongoing, and FDA has a pharmacovigilance strategy in place for monitoring the safety of the amyloid antibodies in the postmarketing setting.

Whether the results of genotype analyses should have been made available to patients enrolled in the clinical trials for the approved amyloid antibodies has come to the public's notice. IRBs are responsible for reviewing informed consent documents. Decisions can only be based on the best information available at the time. For instance, at the time that those clinical trials were enrolling, the majority of cases of ARIA were asymptomatic, and the trials were conducted before genotype testing was considered standard clinical practice. What we knew at that time differs from what we know now. FDA has learned much about ARIA through the review of the marketing applications of the amyloid antibodies. Current labeling for the amyloid antibodies recommends genotype testing to inform the risk of developing ARIA, but it currently does not require genotype testing because not everyone wants to know their results.

6.7 Discussion

- Question: Among atypical and antipsychotic responses, there is high incidence of metabolic syndrome, which increases morbidity and mortality. How is FDA addressing this issue?

  Answer: FDA has some studies coming out. Glucagon-like peptide (GLP) is a real concern and something to look at in the future.

- Question: What about advisory committees in general? What do you need them to do?

[46] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations

Answer: Big teams review applications, but, it's hard to get good people who don't have conflicts of interest. FDA seeks alignment with other projects, which offers another set of eyes to help think through the particular project. Also, it is important to hear what various stakeholders are thinking.

Discussions seem to be more productive than a single vote because the experts may not also be regulatory experts. On the other hand, a vote can push committee members to make a decision. But, in the end, these committees are advising, not deciding the issues. By and large, the people FDA has found have been well qualified.

- Question: Specific, known mutations have been handled in separate trials, and risk factors may have been included in clinical trials. Yet, genetic variance may become more and more relevant. What is the recommendation for use of genetic factors as predispositions?

  Answer: APOE ε4 is challenging because the gene dose response may have an impact as well, but the data are challenged by this. It may be assessed more in a post-marketing setting. Regardless, it will have to be thought through as it becomes more characterized.

- Question: How can we make ancestry and frequency by ancestry generalizable?

  Answer: We'll have to deal with this as the facts become clearer.

- Question: Boxed warnings have produced some insights since they were first launched in 2005. What other types of data would FDA want to see?

  Answer: FDA is definitely interested in hearing more. We are looking to randomize clinical trial data as well as qualitative data, and have been discussing wording and definitions. Most of all, we need evidence-based information.

- Question: Do we have a different category for biomarkers that are digital? Will we need multimodality to get to a real level of accuracy? It doesn't seem to be either/or. What will be needed for FDA approval?

  Answer: Symptoms begin with forgetting every now and then, which a person may notice and may seek help with. An investigator focuses on cognition by asking the patient and different family members the same question. Early on, the symptoms are not constant. In fact, no one symptom is consistent, but this remains one of the most promising diagnostic tools we have. Digital tools must be able to collect this sort of information in an objective way.

> Digital biomarkers can be used in those who do not yet have neurodegenerative pathology, too. If they begin to change, they shift from an indicator of risk to a clinical outcome. We need to know when a digital biomarker becomes a clinical outcome. As changes occur in the patient as AD progresses, diagnosis ends up relying on a multimodal assessment, and when you put them all together, it makes for a robust package.

7. Conclusion

The 17th Annual FDA/ACT-AD Allies Meeting convened representatives from FDA, NIA, universities, and industry, in addition to people with lived experience. They discussed NIA and FDA updates on research on AD and other dementias, sex and gender differences, and racial/ethnic differences in ADRD, industry updates on new therapies, and emerging technologies in digital health. Specifically, research is being improved by involving people with lived experience in a reciprocal manner, and by devising ways to share data among investigators. Diagnostics is being improved with digital as well as biological biomarkers, acoustic and vocal cues, AD-specific cataracts in the eye, and molecular phenotyping.