

**Accelerate Cures/Treatments for All Dementias (ACT-AD)
16th Annual FDA/ACT-AD Allies Meeting 2023
*Dementia Research Inroads: Where Are We Now?***

1. Introduction

The 2023 FDA Accelerate Cures/Treatments for All Dementias (ACT-AD) Allies meeting convened experts from academia, pharmaceutical companies, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), as well as members of the Alzheimer's disease (AD) community. The goal of the meeting was to foster connection and meaningful dialogue around emerging issues and effective treatments for AD and Alzheimer's Disease-Related Dementias (ADRD) that may drastically improve patient and caregiver quality of life. The discussions highlighted precision medicine, research equity, emerging themes in treatment and prevention, and lessons learned in the regulatory review process.

2. Advancing AD/ADRD Research Toward Precision Medicine Strategies

The NIH and the National Institute on Aging (NIA) are continuing to support AD and ADRD research spanning from population studies, genetics and basic biology to drug development and clinical trials for pharmacologic and non-pharmacologic interventions, with a strong emphasis on heterogeneity, biomarkers, and diversity. The NIA supports a robust pipeline of programs to generate the extensive scientific knowledge needed to enable a precision medicine approach to therapy development. Many of these research initiatives have emerged from the NIH Alzheimer's Research Summits, which are key strategic planning meetings held every 3 years starting in 2012.

2.1 A growing pipeline of therapeutic agents

NIA's Alzheimer's Drug Development (ADDP)¹ funding initiative, established in 2006, focuses on building a robust portfolio of drug candidates targeting multiple aspects of the complex pathophysiology of AD/ADRD. The ADDP supports the development of small molecules and biologics for the treatment and/or prevention of AD/ADRD; over 50 projects have been funded to date. Twelve new investigational drugs developed through this program have advanced to Phase I or Phase II trials. The ADDP and other NIA/NIH drug development initiatives have in total, NIA funding through the ADDP and other NIA/NIH funding initiatives have resulted in the development of 18 new investigational drugs for AD/ADRD (see table 1). The clinical development for most of these new therapeutic agents is supported by NIA's AD/ADRD clinical trials programs. It is of note that non-profit organizations have contributed to the development of many of these therapeutic agents.

In addition to de novo drug development, NIA has made major investment in drug repositioning and drug repurposing, i.e., identifying which drugs currently approved for other conditions may be beneficial for the treatment of AD/ADRD. Since 2018, NIA's ACTDRx² program (Advancing Combination Therapy and Drug Repurposing for AD) (ACTDRx AD) has supported over 40 research grants that leverage

¹ ADDP NOFO – PAR-22-047 <https://grants.nih.gov/grants/guide/pa-files/PAR-22-047.html>

² ACTDRx-AD NOFO -PAR-20-156 - <https://grants.nih.gov/grants/guide/pa-files/PAR-20-156.html>

multimodal big data, and identified dozens of repurposable drug candidates through data-driven predictions.

Table 1. Drug Candidates Developed with NIA Support That Have Advanced to Human Trials

Drug Candidate/ Therapy Type	Targeted Biology (IADRP/CADRO Theme)	Current Development Stage
Allopregnanolone	Multi-target	Phase 2
PU-AD/PU-HZ151/Icapamespib	Proteostasis/Proteinopathies	Phase 2
MW150	Inflammation	Phase 2
MW189	Inflammation	Phase 2
LM11A-31	Growth Factors and Hormones	Phase 2
CT1812	Amyloid-beta	Phase 2
BPN14770/Zatolmilast	Neuroprotection/Resilience	Phase 2
AV-1959D (DNA vaccine)	Amyloid-beta	Phase 1
AAV2-BDNF (Gene Therapy)	Growth Factors and Hormones	Phase 1
ACU193 (Immunotherapy-Monoclonal Antibody)	Amyloid-beta	Phase 1
BMS-984923	Neurotransmitter Receptors	Phase 1
MW151	Inflammation	Phase 1
Posiphen	Proteostasis/Proteinopathies	Phase 1
OLX-07010	Tau	Phase 1
CS6253	ApoE, Lipids and Lipoprotein Receptors	Phase 1
NNI-362	Neurogenesis	Phase 1
J147	Metabolism and Bioenergetics	Phase 1
CMS121	Multi-target	Phase 1

A new NIA Notice of Funding Opportunity (NOFO) will accelerate early-stage clinical drug development by inviting applications that seamlessly combine Phase I first-in-human studies through Phase Ib/Phase IIa studies and eliminate the significant delays between the two phases.³ Candidate interventions (e.g., small molecules, biologics) must engage non-amyloid/non-tau mechanisms and meet specific safety and tolerability milestones to advance with funding from Phase I studies. 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 the Collaboration for Alzheimer's Prevention (CAP) data and sample sharing principles.

³ <https://grants.nih.gov/grants/guide/pa-files/PAR-23-274.html>

2.2 An expanding portfolio with a commitment to diversity

NIA's significant investment in early- and late-stage AD/ADRD clinical trials continues to grow. NIA is committed to inclusion and is prioritizing funding requests with proposed planned enrollments that are representative of the population affected by the disease, condition, or health experience and/or are appropriately inclusive of racial and ethnic groups across the lifespan as well as other populations experiencing health disparities, sexual and gender minorities, persons with disabilities, socioeconomically disadvantaged and geographically underrepresented populations.

2.3 Discussion

An in-depth discussion was had with substantive questions addressing multiple facets of the NIH/NIA programs.

- Question: Is NIA exploring having real world evidence (RWE) studies done on the combination of brexipiprazole (Rixulti®) for agitation and mAbs?

Answer: We would be interested in a grant application for this type of study.

- Question: Can repurposing grant applications be investigator initiated or do they need to come through NOFOs?

Answer: While NIA has targeted funding initiative for drug repurposing, investigators can also submit an investigator-initiated application.

- Question: In terms of inclusion criteria, are there any standards for AAPI, native Alaskan and American Indian populations, and will Down syndrome continue to be used as an exclusion criteria or will there be more rigor in that?

Answer: There are no standards for specific under-represented groups. Down syndrome is a special population, where we have specific funding initiatives to accelerate research on AD in Down syndrome. ABC-DS (Alzheimer's Biomarker Consortium-Down Syndrome) is one such program. Question: Are there any programs attempting to harmonize animal and human data in a meta-organized way, e.g. mouse proteomics, human proteomics? For people who are not data scientists are their approaches that make this easier to do?

Answer: The NIA funded MODEL-AD Translational centers are developing new mouse models of Late-Onset AD (LOAD) and aligning their multi-modal phenotypes to the molecular and clinic-pathologic features of the human. This cross-species, mouse to human exploration is also a component of multiple NIA systems biology consortia. The mouse model data generated by the MODEL-AD Centers and data from other cell-based and animal models are being shared via the AD Knowledge Portal, an NIA-supported FAIR data repository and the Model AD web-based knowledgebase. This allows researchers with bioinformatics expertise as well as biologists and clinicians to explore and reuse the data and build on it.

- Question: African Americans have lower levels of amyloid and tau with the same level of cognitive impairment as white populations in the global Alzheimer's platform and clinical trials, where blood-based biomarkers have set cut-off points, leading to the need to process four African Americans for every one white to get the same level of randomization. In Latinos, it is two to three to every one white to get the same level of randomization. So it is confounding something in the whole blood-based biomarker world as well. You mentioned metabolic features and social determinants of health as well, are we thinking Alzheimer's disease could be a blend of a variety of mixed dementia's - do we have a definition problem? What are we doing wrong – setting cut-off points, defining cognitive measures, are definitions of disease incorrect?

Answer: As to cut-off points, Dolores Molina Henry presented data at CTAD from ACT-C/ATRI on plasma screening from the AHEAD trial. Amyloid in the plasma screening meant the PET scan was more likely to show amyloid. The cut-offs were not an issue for this study. That said we do not fully understand which factors are affecting biomarkers and disease heterogeneity.

- Question: Are the biosamples and data from the NIA funded longitudinal studies (such as LEAD, CLEAR AD) available? Do we have to wait until the study is complete to get access to samples and is the clinical data also available?

Answer: No, you do not have to wait. For most of our studies data is curated and put up in batches. Clinical data and biosamples are available. We expect data to be accessible and reusable by the research community.

3. Evaluating the A/T/N Framework Across Diverse Populations: Path to Precision Medicine

In 2018, NIA and the Alzheimer's Association (NIA-AA) proposed a framework for AD diagnosis called A/T/N, for amyloid, tau, and neurodegeneration.⁴ This framework evaluates the presence of β -amyloid, hyperphosphorylated tau, and neurodegeneration in individuals using cerebrospinal fluid and neuroimaging measures. While these measures serve as useful biological markers for AD; there are also ongoing efforts to develop and validate A/T/N blood-based biomarkers. In 2023, the Alzheimer's Association work group proposed a revised framework that better reflects the current scientific knowledge on the biological markers of AD and acknowledges the need for diversity and more representative cohorts in observational studies and clinical trials.⁵ NIA staff is serving in an advisory capacity to the work group.

Interactions between biomarkers and genetic markers of dementia may differ by race or ethnicity as well as by social determinants of health. Addressing heterogeneity across clinical phenotypes is a major challenge but is enabling researchers to move toward a precision medicine approach by collecting multi-modal data including health records, biomarkers, data, genetics, and more. The long-term goal is to establish population-specific precision medicine approaches for discovering novel treatment and prevention strategies. Several large-scale NIA-supported clinical studies are

⁴ Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14(4):535-562.

⁵ Alzheimer Association International Conference. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. 2023.

currently evaluating disease heterogeneity and potential biomarkers in diverse cohorts and special populations. These studies emphasize not only the rigorous evaluation of A/T/N but also participant engagement, longitudinal data collection, and rapid sharing of data. The Health & Aging Brain Study – Health Disparities (HABS-HD), one of the signature programs in this effort, is currently enrolling Mexican Americans, African Americans, and non-Hispanic Whites and evaluating emerging A/T/N biomarkers using imaging and blood samples.⁶ The first project is examining the impact of vascular, metabolic, and inflammatory factors on the timing sequence and trajectories of the A/T/N biomarkers, and the impact on the exposome of sociocultural factors. The investigators previously demonstrated that metabolic factors (e.g., glucose, HbA1c, duration of diabetes) were significantly associated with amyloid burden among Mexican American adults.⁷ Mexican Americans develop cognitive loss and neurodegeneration at significantly younger ages when compared to non-Hispanic Whites. A new funding initiative, “Analytical and Clinical Validation of Biomarkers for Alzheimer’s Disease (AD) and AD-Related Dementias (ADRD)” [PAR-23-258](#), was recently issued to accelerate the establishment of effective and reliable biomarkers of AD/ADRD for use in human studies, medical product development, clinical trials, and/or clinical practice. It supports applications to conduct analytical and/or clinical validation of AD/ADRD biomarkers, or biomarker signatures within a specified context of use.⁸

NIH’s Accelerating Medicines Partnership AD Program (AMP AD 2.0) is enabling a precision medicine approach to the discovery of targets and biomarkers. The second iteration of this program is making a pivot to true precision medicine by bringing, for the first time, data sets from diverse populations, in particular African American and Hispanic American, that are disproportionately affected with risk of AD. One aim is to identify the molecular subtypes of the disease, which will have important precision medicine implications. The partnership has generated massive amounts of high-quality proteomics data across both brain and fluid compartments, as well as metabolomics and lipidomics data. These data sets are a rich substrate for discovery and validation of new biomarkers and molecular signatures specific for disease subtypes.

3.1 Translating genes, omics, and biomarkers into precision medicine

A multi-institutional NIA-funded consortium, called the Centrally-linked Longitudinal pEripheral biomARKers of AD (**CLEAR-AD**) Program, is identifying biomarkers of AD in multi-ethnic cohorts.⁹ Saykin and colleagues are among CLEAR-AD’s more than 80 investigators across 13 institutions aiming to identify the next generation of precision medicine biomarkers and potential novel therapeutic targets in AD and related dementias. Investigators will generate more than 20,000 multi-omics measures in brain and blood to harmonize and process all omics and more than 48,000 endophenotype measures from existing NIH-supported multi-ethnic datasets. The overall goal is to translate the information learned into a personalized clinical strategy for an individual, which may address amyloid, tau, immune, lifestyle factors, diet, exercise, cognitive stimulation, or other factors not yet fully identified. Data to date are showing relationships with inflammation, immune dysregulation, vascular impairment, and

⁶ <https://reporter.nih.gov/search/SLCPkzy1o0umXa2JsO8B0Q/project-details/10493844>

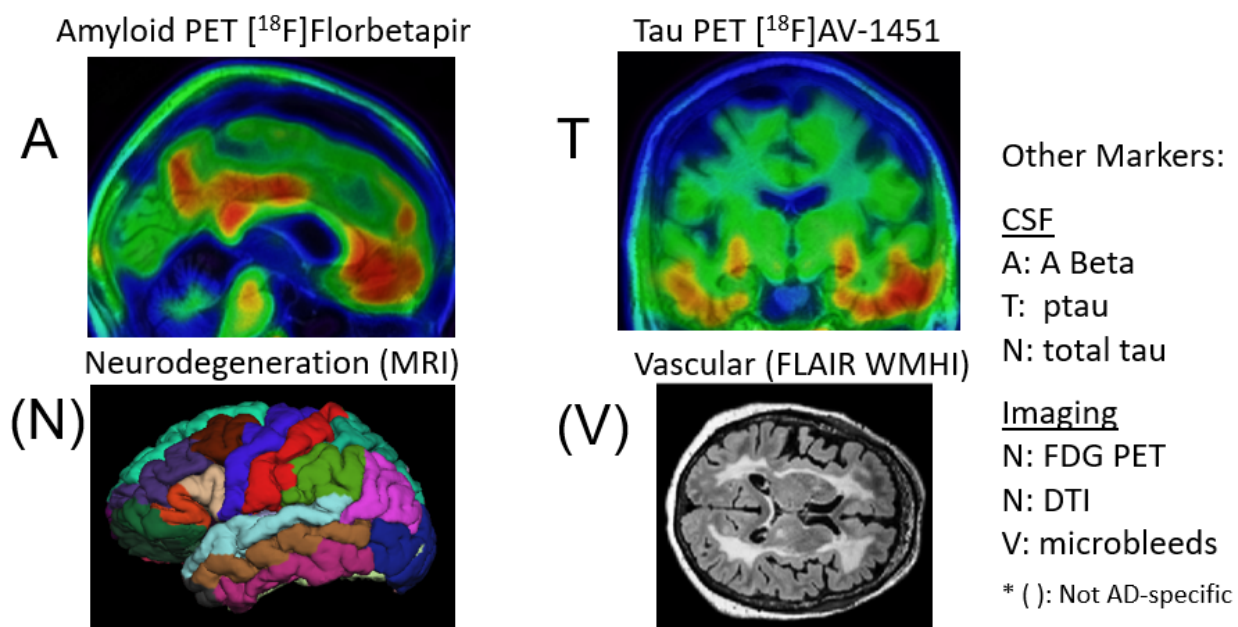
⁷ O’Bryant SE, Petersen M, Hall J, Johnson L, Team H-HS. Metabolic Factors Are Related to Brain Amyloid Among Mexican Americans: A HABS-HD Study. *J Alzheimers Dis.* 2022;86(4):1745-1750.

⁸ <https://grants.nih.gov/grants/guide/pa-files/PAR-23-258.html>

⁹ <https://clear-ad.org>

neurodegenerative disorders, indicating that other more nonspecific biomarkers may be needed in the A/T/N framework, potentially adding an “I,” “V,” and “S” to the A/T/N framework, as shown in **Figure 1**.¹⁰ The resulting data and insights from CLEAR-AD are part of an open science universe that will be extended to the community at large. CLEAR-AD also hosts a Diversity Scholar Program to train the next generation of scientists, with a focus on groups underrepresented in biomedical research.

Figure 1. A/T (N) (V) Biomarkers: Brain, CSF, Blood & Beyond



Source: Risacher & Saykin 2019, Chapter 12 in *Handbook of Clinical Neurology*, Vol. 167, *Geriatric Neurology*, <https://doi.org/10.1016/B978-0-12-804766-8.00012-1>⁸

3.2 The link between Down syndrome and AD

Adults with Down syndrome (DS) are at high risk for developing AD. In DS, the overexpression of the gene for the amyloid precursor protein on chromosome 21 leads to elevated levels of amyloid-beta (Aβ) peptides.¹¹ People with DS make large amounts of Aβ even before birth. By the age of 40, almost all people with DS have neuropathological changes consistent with a diagnosis of AD. The age of onset of dementia can vary widely, suggesting that additional genetic, biological, and environmental factors may modify the rate and degree of Aβ deposition or clearance, and that these factors may be important modifiers of risk and disease progression. The Alzheimer Biomarker Consortium – Down Syndrome (ABC-DS), a 5-year longitudinal study, is following a cohort of adults with DS over time to identify early

¹⁰ Risacher SL, Saykin AJ. Neuroimaging in aging and neurologic diseases. *Handb Clin Neurol*. 2019;167:191-227.

¹¹ Lott IT, Head E. Dementia in Down syndrome: unique insights for Alzheimer disease research. *Nat Rev Neurol*. 2019;15(3):135-147.

biomarkers that may herald the onset of AD and inform clinical trials.¹² Head and other ABC-DS investigators have found that people with DS who are symptomatic have the same amount of A β in their brains as symptomatic people with autosomal-dominant AD. Also, as soon as a person with DS is positive for A β , they will have evidence of tau within 5 years.¹³ Therefore, clinical trials that target only A β may not be enough. To date, ABC-DS data are already filling some of the gaps in the A/T/N framework, including those related to the vascular system and inflammation.¹⁴ People with DS develop A β pathology, not only in plaques, but also in blood vessels, and have more cerebral amyloid angiopathy than people with late onset AD. ABC-DS data and specimens are available for use by qualified researchers who may request access with the ABC-DS Data or Biosample Request form.¹⁵

3.3 Leveraging genetics, genomic and real-world patient data from ethnically diverse populations fuels first-in-human trials in AD

Drug discovery for AD is experiencing a paradigm shift from the symptom-based therapeutics of the past to today's disease-modifying therapy and tomorrow's data-driven personalized medicine. To identify candidate targets for therapeutics, researchers are employing computational approaches using human genetic and multi-omics data as well as real-world data (e.g., insurance claims data), as shown in **Figure 2**. Cheng and colleagues are investigators in NIA's Alzheimer's Disease Sequencing Project (ADSP) Artificial Intelligence and Machine Learning (AI/ML) Consortium, whose mission is to rapidly translate genetics and multi-omics findings from diverse populations into target identification and drug discovery.¹⁶ The team has found that diversity can play an important role in drug targeting. For example, the antihypertensive drug telmisartan was associated with a reduced risk of AD in African Americans compared with non-Hispanic Whites, suggesting that the drug had protective effects for AD in African Americans.¹⁷ This finding could prove useful when designing future clinical trials of this drug class for AD. The team is continuing to identify AD drug targets associated with AD genomic variants. They recently identified a druggable inflammation target, EPHX2, and an agent, EC5026, that inhibits it. After showing efficacy in AD preclinical models, EC5026 will be evaluated in a Phase Ib clinical trial in early AD patients, offering a potential first-in-class molecule for treating AD. Using AI/ML technologies to combine genetic/multi-omics and electronic health record data from ethnically diverse populations can fuel target and drug discovery for AD and other complex diseases.

¹² <https://www.nia.nih.gov/research/abc-ds>

¹³ Zammit MD, Betthausen TJ, McVea AK, et al. Characterizing the emergence of amyloid and tau burden in Down syndrome. *Alzheimers Dement*. 2023.

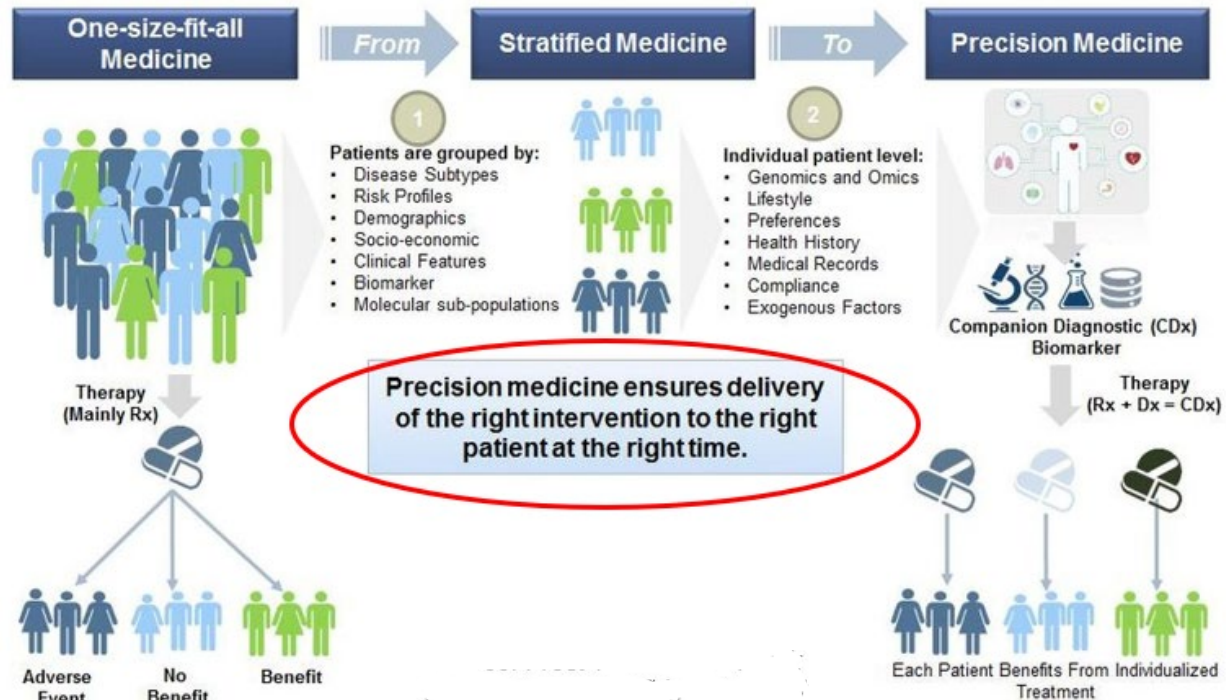
¹⁴ Boerwinkle AH, Gordon BA, Wisch J, et al. Comparison of amyloid burden in individuals with Down syndrome versus autosomal dominant Alzheimer's disease: a cross-sectional study. *Lancet Neurol*. 2023;22(1):55-65.

¹⁵ https://pitt.co1.qualtrics.com/jfe/form/SV_cu0pNCZZlrdSxUN

¹⁶ Alzheimer's Disease Sequencing Project. Artificial Intelligence and Machine Learning Consortium. <https://adsp.niagads.org/funded-programs/artificial-intelligence-and-machine-learning/>.

¹⁷ Zhang P, Hou Y, Tu W, et al. Population-based discovery and Mendelian randomization analysis identify telmisartan as a candidate medicine for Alzheimer's disease in African Americans. *Alzheimers Dement*. 2023;19(5):1876-1887.

Figure 2. From Heterogeneity to Precision Medicine in Complex Disease



Source: Frost & Sullivan - Figure 1: New Paradigm Shift in Treatment

3.4 Discussion

There was a rich discussion with multiple questions for each presenter encompassing a range of topics:

- Question: What can be done in Alzheimer's disease research to mitigate risk for Down syndrome individuals to encourage researchers to include them in clinical trials for therapeutics?

Answer: In a perfect world there would be clinical trials dedicated to this population because outcome measures need to be different as adverse events may be different for people with Down syndrome.

- Question: Would a platform study be appropriate?

Answer: A separate cohort running in parallel to a Down syndrome cohort would be ideal. It is unknown if current FDA interventions are safe for the Down syndrome population so that needs to be ascertained first.

Amyloid PET recognizes fibrillar amyloid and we know especially in Down syndrome that there is a lot of diffuse beta amyloid accruing very early. So the window of opportunity is bigger than the four to five years before tau deposition after amyloid PET. And so that then means that if you are going to go with an anti-amyloid therapy, you need to go earlier for this population which may make platform trials less viable.

- Question: What are the thoughts on treatments such as lecanemab for the Down syndrome population?

Answer: The amyloid that we see by PET is the much more mature deposits. People with Down syndrome have the diffuse plaques by their 30s. So there is a much bigger opportunity for intervention as a prevention study, which is exciting. And I like the thought of going younger because we are going to dodge the cerebral amyloid angiopathy (CAA) bullet which could lead to ARIA and people with Down syndrome do develop micro hemorrhages with age. The downside of that is the clinical readouts to show efficacy will not be there, but perhaps biomarkers will develop to the point they can be used.

- Question: Could you use AI to predict what anti-inflammatory drug used for another condition might work for Alzheimer's disease, and to predict combination therapies?

Answer: This is what we are trying to do in microglial targeted therapy as microglia are very dynamic across AD progression; early and mid-stage are completely different. Currently we do not have a good pre-clinical or human clinical model for validation of the drug combination.

- Question: What is the earliest age you would include for in a trial designed for the Down syndrome community, and are there fast progressors and slow progressors in this population?

Answer: The data does show fast and slow progressors. Some are not showing any big changes in cognitive outcomes, and we are trying to figure out what makes them different. Due to their unique age, we should be able to utilize precision medicine approaches. Different ages have different pathologies, so in people in their 20s and 30s we would target beta amyloid, vs someone in their 40s to 50s where combination treatments might make the most sense. Also, is the APP overexpression in Down syndrome an Abeta production and part of that intellectual disability? That would mean a whole different kind of clinical trial. By mapping out all this vascular inflammation, oxidative stress, all these effects with age, at each age, these are the kinds of things we need to target. After 50, all bets are off, because then you are in the multi-target range. We have DG, PET amyloid tau, and MRI data available on all participants.

- Question: How can clinical trial design incorporate the small ends of the precision medicine space, particularly in relation to go-no go decisions?

Answer: We should be able to use multimodal data integration utilizing ideas from other disease areas like cancer. We are not yet to the level of taking cells and analyzing them in a dish, but we have an iPS cell approach that is actually working, but it takes months to get it from iPS to neural.

It is extremely exciting to have the potential theoretical notion of running the trial in a dish on an individualized basis. One of the challenges, of course, is that the immortalization

requires an epigenetic reset. So you are setting the clock back to zero; others are trying derived neuronal strategies that would preserve some of the epigenetic information to have the age-related factors preserved, so maybe comparing the two would be informative. It will be very slow and inefficient because of the current state of the technology but I think we all share the vision that this is possible in the future, and we are likely to get there and be able to individualize therapy using these molecular strategies.

- Question: In Down syndrome and Alzheimer's disease the microbiome and infectious agents can play a big role. Differences in microbiome from early and mid-age could be tracked. Is the microbiome being studied in Alzheimer's disease generally and for the Down syndrome population?

Answer: That is being done in Rima Khaddura-Daouk's study Alzheimer's Gut Microbiome. It should have results in the next 6 months. Everything in the body is connected. There are also studies in antivirals for covid being associated with a reduced risk of Alzheimer's disease.

A group in Europe is creating a microbiome connectome program and there is interest in ABC-S in participating. There are co-occurring illnesses that people with Down syndrome are very vulnerable to so we need to explore this connection to the microbiome and their baseline immune system function.

- Question: Are there any Down syndrome studies looking at biomarkers in this population? Are you doing subgroup analyses for race and ethnicity, socioeconomic factors?

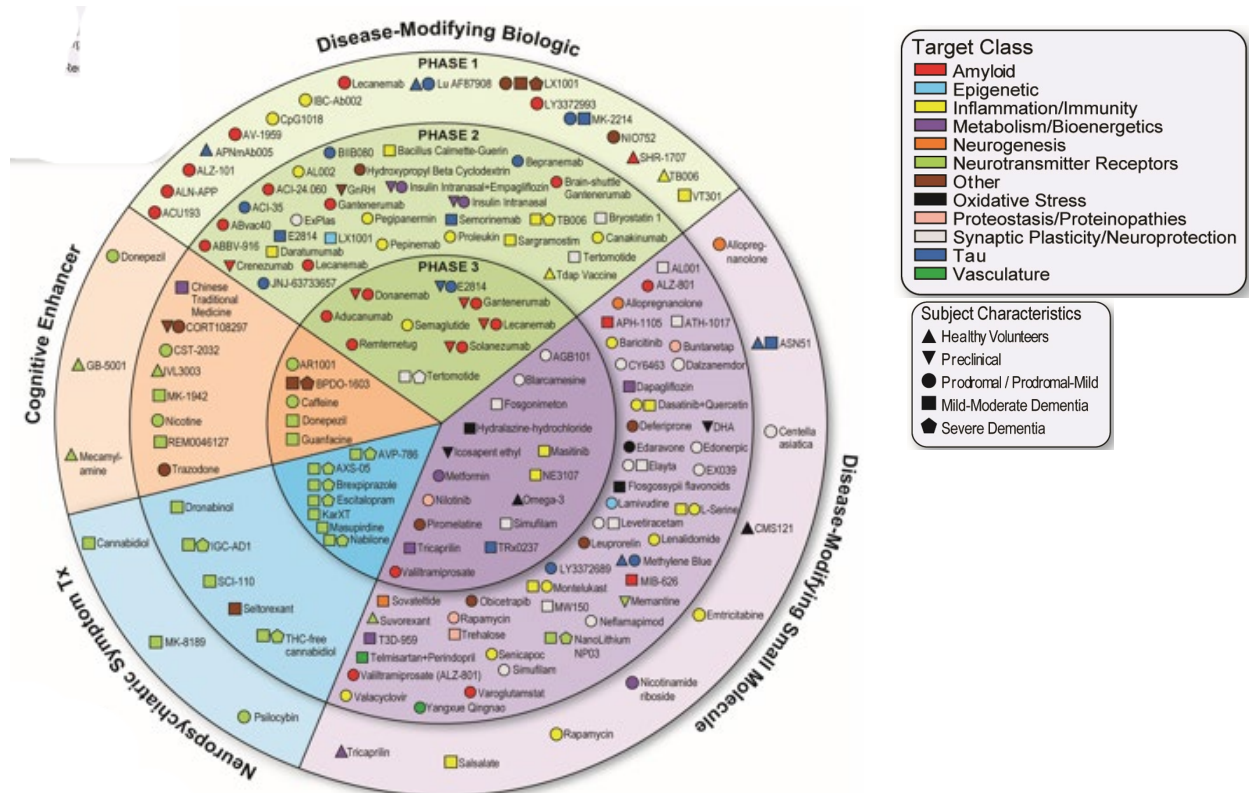
Answer: We are trying to, but we do face challenges. We are bringing on a site in Kansas to address the rural communities there. We struggle with diversity. One issue is that Hispanics and blacks with Down syndrome do not live as long, most likely due to health disparities. We have moved the lower age to 25 years to try and reach these populations. Our diversity is approximately 13% currently.

4. Emerging Therapeutics for the Treatment and Prevention of AD/ABRD: Preclinical and Clinical Development

Over the past two decades, drug development for AD has been particularly challenging. Many AD trials have failed to show efficacy in clinical trials. With the exception of the recently approved monoclonal antibodies for AD, new treatments have not yet reached the market. However, despite the challenges, researchers have not lost their confidence in drug discovery and are seeking new therapeutic targets and employing novel drug development strategies, some of which involve artificial intelligence.

Figure 3 illustrates the many compounds currently in clinical trials, including additional disease-modifying biologics, cognitive enhancers, treatments for neuropsychiatric symptoms, and disease-modifying small molecules.

Figure 3. 2023 Drug Development Pipeline



Source: Cummings, ..., Cheng, *Alzheimer's & Dementia* 2023

4.1 Targeting synaptic resilience

Synaptic degeneration is a powerful correlate of cognitive loss in AD.¹⁸ Synaptic density has been found to correlate better with cognition than tau or amyloid. Some patients who have amyloid and tau in their brains but no decreases in synaptic connections do not have dementia. Persistent spine density in the brains of patients with AD has been associated with preserved cognition and resilience to amyloid and tau, suggesting that such resilience could be created with targeted therapy. One of the challenges in identifying a potential therapeutic target is that many pathways are involved in synaptic failure. Longo and colleagues are focusing on accommodating several of these processes together to achieve synaptic resilience. They are targeting the p75 receptor, a key regulator of the RhoA/cofilin module, which becomes dysregulated in AD. In mouse models, small-molecule modulation of p75 reversed spinal loss,

¹⁸ Taddei RN, Perbet R, Mate de Gerando A, et al. Tau Oligomer-Containing Synapse Elimination by Microglia and Astrocytes in Alzheimer Disease. *JAMA Neurol.* 2023;80(11):1209-1221.

making the spines resilient.¹⁹ A Phase IIa exploratory trial of the small molecule LM11A-31 in mild-to-moderate AD has been completed at 18 sites in five countries in Europe.²⁰ Compared with placebo, the drug significantly decreased degenerative synapse markers, both pre- and post-synaptic, as well as inflammation. The clinical studies have found statistically significant effects in four different biomarker areas and a favorable safety outcome, encouraging advancement to larger and more definitive studies. Five mechanisms of action (MOAs) have been identified, which makes LM11A-31 an agent with a “combination mechanism.”

4.2 Allopregnanolone regenerative therapeutic for mild AD – ReGenBRAIN

Allopregnanolone (ALLO) is a biologic regulator with well-documented MOAs.²¹ Research in animal models of AD has demonstrated that ALLO promotes regeneration of stem cells in the subgranular and subventricular zones, targets drivers of AD pathology (such as inflammation), and collectively reduces the burden of pathology. Preclinical studies demonstrated the potential for ALLO to function as a regenerative and disease-modifying therapeutic for AD.²² Diaz Brinton and colleagues conducted a Phase Ib/IIa clinical trial of ALLO in 24 participants with early AD.²³ The primary exploratory engagement target was hippocampal volume. Findings from both the left and right hippocampi consistently indicated that positive responders to ALLO are likely APOE e4 allele carriers and that the 4-mg dose optimizes the potential for regeneration. ALLO treatment was also associated with increased white matter integrity and strengthened functional connectivity within networks critical to cognition and sensory integration. Because ALLO was shown to be safe and well-tolerated with preliminary evidence of target engagement on magnetic resonance imaging-based surrogate outcome measures, the ReGen-BRAIN Phase II safety and efficacy clinical trial is underway to study the potential of ALLO as a regenerative therapeutic for mild AD.²⁴ This multi-site, randomized, placebo-controlled trial will include 12 months of once weekly placebo or 4-mg intravenous ALLO administration in 200 APOE e4 carriers and will include a 6-month open label extension. The primary endpoint is rate of change in hippocampal volume at 12 months with secondary outcomes of cognition, function, and safety.

4.3 Levetiracetam modulates brain metabolic networks in the 5XFAD mouse model of AD

Historically, preclinical translational studies have been restricted in the application of precision medicine approaches because of animal model limitations (e.g., single sex selection), the use of behavior as a key endpoint, and arbitrary dosing that is not based on pharmacokinetic (PK)/pharmacodynamic relationships. To improve the predictive validity of preclinical studies in AD animal models, Territo and colleagues are employing a strategy of marrying drugs with a known MOA to models that share those mechanisms. Looking beyond amyloid, the researchers are exploring links between neural network

¹⁹ Yang T, Liu H, Tran KC, Leng A, Massa SM, Longo FM. Small-molecule modulation of the p75 neurotrophin receptor inhibits a wide range of tau molecular pathologies and their sequelae in P301S tauopathy mice. *Acta Neuropathol Commun*. 2020;8(1):156.

²⁰ <https://clinicaltrials.gov/study/NCT03069014>

²¹ Irwin RW, Wang JM, Chen S, Brinton RD. Neuroregenerative mechanisms of allopregnanolone in Alzheimer's disease. *Front Endocrinol (Lausanne)*. 2011;2:117.

²² Brinton RD, Wang JM. Preclinical analyses of the therapeutic potential of allopregnanolone to promote neurogenesis in vitro and in vivo in transgenic mouse model of Alzheimer's disease. *Curr Alzheimer Res*. 2006;3(1):11-17.

²³ Hernandez GD, Solinsky CM, Mack WJ, et al. Safety, tolerability, and pharmacokinetics of allopregnanolone as a regenerative therapeutic for Alzheimer's disease: A single and multiple ascending dose phase 1b/2a clinical trial. *Alzheimers Dement (N Y)*. 2020;6(1):e12107.

²⁴ <https://clinicaltrials.gov/study/NCT04838301>

dysfunction and microglia in AD. Based on earlier research that identified key brain nodes that predicted progression to mild cognitive impairment or AD, the research team established a set of validated tools²⁵ using highly sensitive positron emission tomography imaging in 5XFAD mice (a strain that rapidly develops severe amyloid pathology) and controls of both sexes. The 5XFAD mice showed differences in network node connections across age and sex compared with controls. When the model was applied to a study of the anti-epileptic drug levetiracetam in an 5XFAD mouse model,²⁶ the results showed dose-related sexual dimorphism in PK and blood and brain exposure; dose-dependent alterations in transcriptomics associated with neuronal function, cognition, and inflammation genes; gene network changes that aligned with synaptic function; and certain network “connectomics” changes in female mice only.

4.4 Harnessing amyloid and tau endophenotypes for multi-target drug repurposing in AD

The use of multi-omics data to build individualized disease network modules is showing promise for improving the success rate of AD drug discovery, guiding therapeutic evaluation during clinical trials, and optimizing new treatment for patients with AD and those at risk for AD dementia. Cheng and colleagues explored AD endophenotypes, which are inheritable biological traits that are more closely related to the root cause of the disease than the broad clinical phenotype.²⁷ Earlier research showed that synergistic interactions between amyloid and tau drove neuronal dysfunction and degeneration and predicted progression to dementia.²⁸ Using endophenotype-based medicine discovery combined with insurance record data mining, the research team identified sildenafil, a drug approved for treating erectile dysfunction, as a potential candidate drug for AD.²⁹ Sildenafil targets both tau and amyloid and is associated with a 50-70% reduced likelihood of AD in real-world patient data. Researchers then used a big data resource (i.e., a nationwide insurance database) to further explore the associations between sildenafil use and the reduced risk of AD.³⁰ In preclinical studies to date, sildenafil increased neurite growth and reduced tau hyperphosphorylation. The findings supported the use of multi-omics data for identifying drug targets, understanding disease mechanisms, and accelerating AD drug discovery. Future studies of sildenafil include a pilot trial to explore its MOA in AD and a Phase II trial to test the drug in patients with early AD or mild cognitive impairment.

4.5 Semaglutide: Pleiotropic effects to treat AD and mitigate anti-amyloid mAB-induced amyloid-related imaging abnormalities (ARIA)

²⁵ Chumin EJ, Burton CP, Silvola R, et al. Brain metabolic network covariance and aging in a mouse model of Alzheimer's disease. *Alzheimers Dement.* 2023.

²⁶ Burton CP, Chumin EJ, Collins AY, et al. Levetiracetam Modulates Brain Metabolic Networks and Transcriptomic Signatures in the 5XFAD Mouse Model of Alzheimer's disease. *bioRxiv.* 2023.

²⁷ Fang J, Pieper AA, Nussinov R, et al. Harnessing endophenotypes and network medicine for Alzheimer's drug repurposing. *Med Res Rev.* 2020;40(6):2386-2426.

²⁸ Pickett EK, Herrmann AG, McQueen J, et al. Amyloid Beta and Tau Cooperate to Cause Reversible Behavioral and Transcriptional Deficits in a Model of Alzheimer's Disease. *Cell Rep.* 2019;29(11):3592-3604 e3595.

²⁹ Fang J, Zhang P, Zhou Y, et al. Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease. *Nat Aging.* 2021;1(12):1175-1188.

³⁰ Huo X, Finkelstein J. Using Big Data to Uncover Association Between Sildenafil Use and Reduced Risk of Alzheimer's Disease. *Stud Health Technol Inform.* 2023;302:866-870.

AD encompasses a multitude of different pathologies, including the accumulation of amyloid- β oligomers, protofibrils, and plaques; tau pathology; inflammation and blood-brain barrier disruption; synapse loss; and neurodegeneration and neuron loss. Some additional aspects are insulin resistance and reduced glucose metabolism in the brain with AD. When insulin signaling goes awry, downstream effects may include mitochondrial dysfunction, oxidative stress, reduction in protein synthesis, increased inflammation, and changes in tau phosphorylation.³¹ Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist currently FDA-approved for treating type 2 diabetes, may represent a potential treatment for helping to slow the clinical progression of AD. A number of mechanisms have been proposed for how semaglutide may work in AD, including a reduction in insulin resistance and improvements in glucose metabolism, anti-inflammatory activity, and reduction of oxidative stress, which would protect neurons.³² To date, clinical trials of GLP-1 receptor agonists have shown less decline in cerebral glucose metabolism and cognitive function.³³ Real-world data from people with diabetes have shown a lower risk of all-cause dementia.³⁴ Two Phase III clinical trials of semaglutide in early AD are currently underway in patients with mild cognitive impairment due to AD or early AD.³⁵ ³⁶ Lemere and colleagues are currently exploring the possibility of mitigating risk and improving vascular health and clinical efficacy by combining semaglutide with anti-amyloid monoclonal antibodies (mAbs) in animal models.

4.6 Discussion

This session had questions focusing on the safety profiles and pertinent issues for re-purposed drugs.

- Question: Since allopregnanolone was initially approved for anxiety and postpartum depression, was it a requirement that the individuals in the study have a history of anxiety?

Answer: No, allopregnanolone has a great safety profile, safe even in women with a fetus. The treatment for postpartum depression involves a certain amount of sedation which “jump-starts” the pathway in the brain that is anti-regenerative. That is an inverted U-shaped dose response curve that translates to higher doses getting less neurogenesis. That allowed us to know that the highest maximum tolerated dose for us was the dose when they started to experience sedation. The regenerative response is very selective so changing the molecule in any way leads to a loss of regenerative function.

- Question: Since there is a strong correlation between Alzheimer’s disease and weight loss, is there any concern with using semaglutide on a population already at risk of losing weight?

³¹ De Felice FG, Goncalves RA, Ferreira ST. Impaired insulin signalling and allostatic load in Alzheimer disease. *Nat Rev Neurosci*. 2022;23(4):215-230.

³² Mahapatra MK, Karuppasamy M, Sahoo BM. Therapeutic Potential of Semaglutide, a Newer GLP-1 Receptor Agonist, in Abating Obesity, Non-Alcoholic Steatohepatitis and Neurodegenerative diseases: A Narrative Review. *Pharm Res*. 2022;39(6):1233-1248.

³³ Gejl M, Gjedde A, Egefjord L, et al. In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial. *Front Aging Neurosci*. 2016;8:108.

³⁴ Akimoto H, Negishi A, Oshima S, et al. Antidiabetic Drugs for the Risk of Alzheimer Disease in Patients With Type 2 DM Using FAERS. *Am J Alzheimers Dis Other Dement*. 2020;35:1533317519899546.

³⁵ <https://clinicaltrials.gov/study/NCT04777396>

³⁶ <https://clinicaltrials.gov/study/NCT04777409>

Answer: My understanding is that there is approximately a 7% weight loss. Many of the patients had Type-2 diabetes and/or obesity so in those populations it is not an issue. We are dosing at the early stages of disease prior to most instances of weight loss. There is also a tapering to get to the maximum dose; it does not happen immediately.

- Question: For the Evoke 1 and Evoke Plus trials, what is the representativeness of the cohorts and the exclusion criteria for the studies?

Answer: It is similar to anti-amyloid immunotherapy for micro-hemorrhages, pre-existing vascular disease, high blood pressure. Diversity is around 28% Hispanic and Latino within the US. Less than 5% are African Americans; it is still majority white.

- Question: How was the inhibitor for p-75 delivered? If it crosses the blood brain barrier does it affect all areas of the brain, or only the hippocampus, or only affected areas?

Answer: Orally in a capsule. This allows it to get through the blood brain barrier. We only image parts of the brain known to be affected by Alzheimer's disease, a voxel-based survey. Using FDG-PET we could see a slow-down in degeneration with similar results using structural MRI.

- Question: What particular cells in the brain are affected by these drugs, and is there specificity to those particular cells in the disease process? Are you affecting microglial cells in the hippocampus the same as in the parietal cortex?

Answer: Many hundreds of different kinds of cells are affected in Alzheimer's disease, as are fundamental biologic mechanisms. Many of the biomarkers for synaptic degeneration are the same whether it is a hippocampal neuron or an excitatory neuron.

- Question: Is amyloid being generated from the cells that are losing their synaptic contacts, or is the amyloid coming from other cells affecting the synapses that are important for memory and learning?

Answer: Potentially other cells but there are different theories on that. Neurons make their own amyloid as low amounts of amyloid regulate the synapses, but Alzheimer's perhaps uses too much. Amyloid oligomers have been found to bind synapses so it is likely a neuron can make and secrete beta amyloid right at the surface of the synapse. Also, keep in mind the big picture of the cells in the rest of the body, the gut, the immune system, and how they are interacting with the brain. If we can find drugs with multiple mechanisms, like magnetite in Parkinson's disease, that may address other conditions as well.

- Question: Is the change in hippocampal volume a change at the cellular level, is it a fluid change, a protein change, a white matter change?

Answer: Imaging does not help us answer that question, but from our mechanistic analyses, we find that allopregnanolone does promote regeneration, including in the sub granular zone in the hippocampus and in the sub-ventricular zones throughout the cerebral cortex and olfactory bulb. We suspect that enough neurons are being generated to change

volume, fluid is reducing because there is a reduction in inflammatory biomarkers and white matter volume is increasing, so multiple mechanisms are at play. The primary outcome is changing the rate of hippocampal atrophy.

- Question: Is the study of inflammation as a biological process of aging being connected to Alzheimer's disease at all?

Answer: Most researchers agree inflammatory mechanisms contribute to degeneration in Alzheimer's disease. We will not know for sure how much until there is a therapy that stops the inflammation, but other measures are continuing to emerge, in blood, spinal fluid, and imaging. People are researching small molecules and peripheral targets for inflammation. It is a systems biology issue with this disease. We have seen that when under stress the female brain communicates with the immune system, but when not under stress it does not.

Inflammation relates to beta amyloid in mitochondria first, before microglia. This supports the use of a combination of targets affecting multiple mechanisms, so there is also the possibility of a cocktail of mechanisms, a cocktail of therapies, but testing combinations is costly and exponentially complex, so if one drug can affect multiple targets that is perhaps the way to go. So it is the systems biology bringing it all together.

5. Industry Perspectives on Clinical Development and Regulatory Review

Discussions at the meeting focused on several topics in drug development from the perspective of industry and regulatory review. Topics addressed included the enrollment of diverse participants in clinical trials, the importance of partnering with community groups and patients advocates, and updates from the FDA on regulatory reviews and patient input.

5.1 Diversity and inclusion in drug development

During the discussion, questions were asked about recruiting people from diverse communities into clinical trials of new drugs, given that most diagnostic guidelines were based on White populations. The presenters noted that the pharmaceutical industry is recognizing the importance of integrating heterogeneity into its drug development research and having therapies be applicable across diverse populations. Researchers are gaining a better understanding of the roles of genetic and biological heterogeneity and how they contribute to disease. Although many clinical trials in dementia are becoming better in recruiting with more diversity, much work remains to be done. The CLARITY-AD trial was successful in recruiting a large Hispanic population, but less so in recruiting African Americans. Success came when investigators collaborated with community-based organizations and started community-based screening programs. Screening rates are still very much dependent on comorbidities for identifying potential participants but using blood-based biomarkers for prescreening helped to attract more people more easily. Efforts are also being made to unburden participants by including remote assessments, electronic consents, and built-in flexibility for missed visits and outcome measures. Many of these measures were driven by responses to the COVID-19 pandemic.

5.2 Importance of partnerships and education

The presenters from industry also addressed questions about the recently added indication for the drug brexipiprazole (Rixulti®) for agitation associated with dementia due to AD. They were asked to

comment on the boxed warning that this drug carries, and whether the drug will be used for other forms of dementia. The presenters said that a key learning in pursuing the new indication was recognizing the importance of working with organizations early in the drug development journey. Partnerships with patient advocates, care partners, and professional associations can help researchers navigate uncharted territory, together with early consultations with the FDA. When working with brexpiprazole's indication for agitation in AD, the first step was to roll out education around the disease for both providers and patients and address the many misconceptions about agitation and AD. Screening tools and checklists were developed to help delineate symptoms. Brexpiprazole carries a boxed warning, as do other antipsychotics, with a clarification about the new indication. Industry worked closely with the FDA to provide the appropriate risk-benefit data for the product. The presenters said that more research is needed on treating agitation in other forms of dementia.

5.3 FDA's continued support in drug and biomarker development

FDA continues to value input from patients in making regulatory decisions. Hearing about patients' individual experiences and challenges with diagnosis and treatment has been useful when considering appropriate endpoints and risk-benefit assessments for clinical trials. The FDA presenter responded to several questions about biomarkers, noting that their use is not just limited to surrogate endpoints. They are important in all stages of a drug development program. Biomarkers themselves do not require FDA approval if they were developed by a company or are not already approved but were deemed necessary for the safe and effective use of a drug. Such biomarkers may be considered "companion diagnostics," which may require involvement with the FDA's Center for Devices and Radiological Health (CDRH).

The presenter was asked to comment on the FDA's boxed warnings, the criteria for using them, and whether there are plans to reevaluate the need for them, based on accrued data. The presenter said that boxed warnings are issued when an adverse event is serious in proportion to the drug's potential benefit to ensure that prescribers are aware of the risk before prescribing, and of any monitoring and interventions available to reduce the risk. Brexpiprazole carries a boxed warning indicating that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. The drug is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to AD. The mAbs indicated for the treatment of AD (aducanumab, lecanemab) carry a class-wide boxed warning about the risk of amyloid-related imaging abnormalities (ARIA). A boxed warning must be included if the FDA requires a Risk Evaluation and Mitigation Strategy (REMS), a drug safety program that focuses on specific steps to lessen risks and which is used for only a small number of medications. The FDA continues to do safety surveillance well after a product is approved, sometimes requesting a registry, and will revisit and update the warnings as needed.

In response to questions about whether the public perceived the FDA's accelerated approvals of mAbs for treating AD as rushed, the presenter said that the Agency's accelerated approval pathway involves full regulatory approval. All of the same standards used for full approval applied.

In response to a question about how closely FDA works with regulatory agencies in other countries, the presenter said that the Agency speaks frequently with representatives from these

agencies. Although those agencies each have their own regulatory frameworks and there is no consistent framework on which to base decision-making, the agencies do share scientific opinions.

6. Conclusion

The 16th Annual FDA/ACT-AD and Allies Meeting, *Opportunities for New Interventions in Alzheimer's Disease and Related Dementias*, assembled experts from academia, industry, FDA, NIH, and the AD community to discuss current issues and emerging therapies and diagnostics in the treatment of AD/ADRD. The discussions emphasized the evolving research leading to a precision medicine approach to managing AD and ADRD. Computational models are being employed to use multi-omics and big data to identify potential drug targets and biomarkers. Biomarkers are playing an increasing role in the diagnostic guidelines for AD beyond the A/T/N framework. The importance of considering heterogeneity and the inclusion of diverse populations in research studies was stressed. Important lessons about the pathology and potential treatment of AD are being learned from research on special populations, such as those with DS. The repurposing of drugs currently approved for other indications is another area under active investigation for AD treatments. Early studies suggest that sildenafil, which is approved for erectile dysfunction, and semaglutide, which is approved for diabetes, may affect some of the biological mechanisms involved in AD.
