Accelerate Cures/Treatments for All Dementias (ACT-AD)
15th Annual FDA/ACT-AD Allies Meeting 2022
Opportunities for New Interventions in Alzheimer's Disease and Related Dementias

1. Introduction

The 2022 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, to robustly discuss emerging issues and innovative therapies for AD, and Alzheimer's Disease-Related Dementias (ADRD).

In 2011, the National Alzheimer's Project Act (NAPA) established the NAPA Council and the National Plan, which aims to effectively treat AD/ADRD by 2025. In 2017, the 10th Annual ACT-AD Allies meeting examined the behavioral and neuropsychiatric symptoms (NPS) of AD/ADRD; the 15th Annual meeting continued these discussions. NPS affect approximately 98% of individuals with AD/ADRD and have been demonstrated to exacerbate the progression of the disease while increasing caregiver burden.[1] NIH-funded research is evaluating the therapeutic benefits of tetrahydrocannabinol (THC) and cannabidiol (CBD), investigating the role of the gut microbiome in neurological health, and utilizing advanced genomic and proteomic approaches to identify novel therapeutic targets and biomarkers for NPS in AD/ADRD.

2.1. Advancing precision medicine approaches for AD/ADRD treatment and prevention

The National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS) have established robust translational programs such as the AD Drug Development Program (ADDP) and the Blueprint Neurotherapeutics Program—that provide funding and expertise to researchers in academia and biotech communities to more effectively execute preclinical and early clinical drug development for AD/ADRD. NIA's ADDP program has delivered 13 new clinical drug candidates that are currently being tested in Phase I and Phase II clinical trials. The clinical development for most of these new drug candidates is supported by NIA's AD/ADRD Clinical Trials funding initiatives and clinical trials infrastructure for AD/ADRD. In addition to providing funding opportunities for all stages of AD/ADRD drug discovery and drug development, NIA has established a series of large precision medicine consortia, translational centers and clinical infrastructure programs that provide critical data and research resources to overcome major barriers in drug discovery and drug development for AD/ADRD. These programs target discovery to clinical trials and bring open science practices in translational research.

One of the signature programs through which NIA supports AD/ADRD research is the Accelerating Medicines Partnership for Alzheimer's Disease (AMP AD), a public-private partnership between NIH, pharmaceutical companies, and non-profit organizations. In February 2021, AMP AD expanded its target discovery and validation projects portfolio by pivoting to implement a precision medicine approach to identifying candidate targets and biomarkers. The resulting AMP AD 2.0 strives to gather data from diverse populations, including African Americans and Hispanic Americans, who are

[1] Phan SV, Osae S, Morgan JC, Inyang M, Fagan SC. Neuropsychiatric Symptoms in Dementia: Considerations for Pharmacotherapy in the USA. Drugs R D. 2019 Jun;19(2):93-115. doi: 10.1007/s40268-019-0272-1. PMID: 31098864; PMCID: PMC6544588.

disproportionately affected by AD. The NIA AD/ADRD research portfolio also supports research on all aspects of the exposome, including research aimed at understanding how the gut microbiome impacts AD/ADRD risk and resilience.

2.2. Expanding the therapeutic pipeline for AD/ADRD

NIA funds a large and growing portfolio of early- and late-stage AD/ADRD clinical trials evaluating the safety and efficacy of a diverse set of new and repurposed drug candidates for AD/ADRD targeting various aspects of disease biology beyond amyloid and tau. A key component of NIA's translational and clinical research portfolio is focused on understanding the heterogeneity of disease and differential responsiveness to treatment across diverse populations. Thanks to NIA's data and resource sharing requirements that are being implemented in discovery research as well as in NIA-supported clinical trials, the research community has learned that cognitively healthy, older, non-Hispanic Blacks show comparatively less amyloid positivity compared to non-Hispanic Whites when matched for age, sex, and geographic location.[2] NIA's policy requires that data and biosamples from non-pivotal trials are shared at the time of publication or within nine months of the data lock. For pivotal trials, the expectation is that data and biosamples from the pre-randomization screening are made available within 12 months of completing patient enrollment; post-randomization data and biosamples must be available after regulatory approval, or within 18 months of trial completion/trial termination, whichever comes first.

Other studies comparing non-Hispanic Whites to the Mexican Americans have shown that Mexican Americans develop mild cognitive impairments at younger ages, have lower levels of APOE4, and present with biomarkers of neurodegeneration earlier in the disease process.[3] These findings emphasize the need to evaluate the ATN biomarkers across diverse populations.

NIA has placed major emphasis on improving the inclusion and retention of under-represented groups including racial and ethnic minorities in clinical research and clinical trials. To this end, NIA established the Clinical Research Operations and Management System (CROMS). CROMS tracks, reports, and manages enrollment data, in real time, across all NIA clinical research projects. CROMS will serve as a key tool for addressing issues and gaps related to recruitment and retention of diverse populations. Complementing NIA's existing data and resource sharing policies, the NIH is expanding data sharing expectations for all NIH-funded projects.

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[2] Deters KD, Napolioni V, Sperling RA, Greicius MD, Mayeux R, Hohman T, Mormino EC. Amyloid PET Imaging in Self-Identified Non-Hispanic Black Participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) Study. Neurology. 2021 Mar 16;96(11):e1491-e1500. doi: 10.1212/WNL.0000000000011599. Epub 2021 Feb 10. PMID: 33568538; PMCID: PMC8032379.

[3] O'Bryant SE, Johnson LA, Barber RC, Braskie MN, Christian B, Hall JR, Hazra N, King K, Kothapalli D, Large S, Mason D, Matsiyevskiy E, McColl R, Nandy R, Palmer R, Petersen M, Philips N, Rissman RA, Shi Y, Toga AW, Vintimilla R, Vig R, Zhang F, Yaffe K; HABLE Study Team. The Health & Aging Brain among Latino Elders (HABLE) study methods and participant characteristics. Alzheimers Dement (Amst). 2021 Jun 21;13(1):e12202. doi: 10.1002/dad2.12202. PMID: 34189247; PMCID: PMC8215806.[4] Schrantee A, Tamminga HGH, Bouziane C, et al. Age-Dependent Effects of Methylphenidate on the Human Dopaminergic System in Young vs Adult Patients With Attention-Deficit/Hyperactivity Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2016;73(9):955–962. doi:10.1001/jamapsychiatry.2016.1572

3. Moving Forward: Exploring Behavioral and Neuropsychiatric Symptoms

NPS are a common feature of AD/ADRD but are poorly understood. NPS are associated with higher rates of caregiver burden and accelerated disease progression. Additionally, pharmacological treatments for NPS in AD/ADRD may produce unwanted side effects, such as insomnia, movement disorders, and increased risk of suicide. Thus, elucidating the underlying mechanisms of NPS and identifying novel therapeutic targets are essential to improving quality of life for individuals suffering from AD/ADRD.

3.1. Exploring use of cannabinol and tetrahydrocannabinol in HAAD

Approximately 50% of people diagnosed with AD/ADRD will receive end-of-life hospice care, and 70% of that population will receive psychiatric medication for agitation. Approved guidelines for the treatment of hospice care-eligible, agitated people with AD (HAAD) currently do not exist; clinicians thus often use commonly prescribed medications like benzodiazepines and antipsychotics that produce unwanted side effects such as confusion, sedation, and increased risk of falling. Alternatively, emerging research studies have explored the therapeutic benefits of tetrahydrocannabinol (THC) and cannabidiol (CBD) to reduce agitation in dementia. Many clinical trials have administered synthetic THC analogues, such as Dronabinol or Nabilone, and a significant portion of participants in those trials have used or are currently using psychoactive medications. Jacobo Mintzer and Brigid Reynolds, supported by the Alzheimer's Clinical Trials Consortium (ACTC), aim to assess the efficacy of an oral combination of THC and CBD on agitation in HAAD patients. In addition, they explore commonly prescribed medications, such as opioids, benzodiazepines, and antipsychotics, and their impact on caregiver burden and quality of death. Their team is committed to maximizing the recruitment of people from underrepresented populations by working with each recruitment site to understand its unique challenges and to develop a tailored recruitment plan.

3.2. Effects of methylphenidate on apathy

Apathy in dementia is characterized by a lack of initiative, interest, and emotion. Approximately 49% of people with AD will develop apathy, which often goes untreated despite its correlation with increased mortality and caregiver burden. Physiologically, apathy is generally associated with disruption of the dorsal anterior cingulate cortex and ventral striatum, and imaging studies utilizing single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) suggest that altered frontal subcortical neural circuitry underlies the occurrence of apathy in AD. Furthermore, tau-related pathologies in the orbitofrontal cortex are also linked to the presence of apathy in AD.

Methylphenidate, also known as Ritalin, is a well-studied dopaminergic treatment to increase motivation and attention.[4] Two preliminary studies by Mintzer and colleagues assessed the benefits of methylphenidate as a treatment for apathy in older populations and revealed a potential therapeutic

[4] Schrantee A, Tamminga HGH, Bouziane C, et al. Age-Dependent Effects of Methylphenidate on the Human Dopaminergic System in Young vs Adult Patients With Attention-Deficit/Hyperactivity Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2016;73(9):955–962. doi:10.1001/jamapsychiatry.2016.1572

benefit when used in conjunction with a psychosocial intervention.[5,6] Subsequently, Mintzer and colleagues conducted a third study (ADMET 2) on the efficacy of methylphenidate, which followed 200 participants for 6 months. Compared to placebo control, participants who received methylphenidate exhibited decreased apathy—measured by the Neuropsychiatric Inventory subscale—after two months of treatment; the diminished apathy persisted for four months without affecting other NPS, except for increased motor behavior.[7] Notably, 79% of participants were simultaneously being treated with current dementia medications, such as cholinesterase inhibitors and memantine. Although no drug cross-interactions were observed, participants who benefited from methylphenidate were more likely to be on cholinesterase inhibitors and less likely to have NPS other than apathy. To follow up on the ADMET 2 study, Mintzer and colleagues are developing the ADMET 3 study which will utilize predictive biomarkers identified from ADMET 2 to select participants likely to respond to methylphenidate.

3.3. NPS in ADRD and FTD

Different neurodegenerative disorders are often characterized by distinct changes in neuroanatomical structures or biological markers. Intriguingly, AD and frontotemporal dementia (FTD) can have overlapping cognitive and non-cognitive (including NPS) symptoms. This potential overlap in therapeutic targets presents an exciting opportunity for drug discovery research. Recent work by Huey and colleagues determined that behavioral symptoms and NPS, such as apathy, disinhibition, and agitation, were among the earliest identifying markers of FTD, even prior to detectable cognitive decline.[8] Additionally, neuropsychiatric tests have utility as measures for trial outcomes and to detect the earliest cases to enroll in clinical trials for both AD and FTD. Currently, Dr. Huey is utilizing a factor analysis approach to determine the most significant forms of NPS in ADRD and corresponding involvement of neuroanatomical structures. Preliminary data have identified hypersomnolence, insomnia, irritability, and apathy as significant distinct factors in ADRD which can be assessed with novel psychometric evaluations in the future.

3.4. Tyrosine kinase inhibitor therapy in Parkinson's disease dementia

Parkinson's disease dementia (PDD) is characterized by an accumulation of alpha-synuclein proteins, which inhibit synaptic transmission and induce the activation of glia as an immune response. Furthermore, PDD is characterized by disruption of lysosomal and proteasomal autophagy, suggesting that mechanisms to enhance autophagy may provide therapeutic benefits. In rodent models of PD,

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[5] https://clinicaltrials.gov/ct2/show/NCT01117181

[6] Rosenberg PB, Lanctôt KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, Mintzer JE, ADMET Investigators. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. J Clin Psychiatry. 2013 Aug;74(8):810-6. doi: 10.4088/JCP.12m08099. PMID: 24021498; PMCID: PMC3902018.

[7] Mintzer J, Lanctôt KL, Scherer RW, et al. Effect of Methylphenidate on Apathy in Patients With Alzheimer Disease: The ADMET 2 Randomized Clinical Trial. JAMA Neurol. 2021;78(11):1324–1332. doi:10.1001/jamaneurol.2021.3356.

[8] Megan S Barker, Reena T Gottesman, Masood Manoochehri, Silvia Chapman, Brian S Appleby, Danielle Brushaber, Katrina L Devick, Bradford C Dickerson, Kimiko Domoto-Reilly, Julie A Fields, Leah K Forsberg, Douglas R Galasko, Nupur Ghoshal, Jill Goldman, Neill R Graff-Radford, Murray Grossman, Hilary W Heuer, Ging-Yuek Hsiung, David S Knopman, John Kornak, Irene Litvan, Ian R Mackenzie, Joseph C Masdeu, Mario F Mendez, Belen Pascual, Adam M Staffaroni, Maria Carmela Tartaglia, Bradley F Boeve, Adam L Boxer, Howard J Rosen, Katherine P Rankin, Stephanie Cosentino, Katya Rascovsky, Edward D Huey, ALLFTD Consortium, Proposed research criteria for prodromal behavioural variant frontotemporal dementia, Brain, Volume 145, Issue 3, March 2022, Pages 1079–1097, https://doi.org/10.1093/brain/awab365

animals reared on Nilotinib, a tyrosine kinase inhibitor that enhances autophagy in the central nervous system (CNS), recover cognitive and motor functioning and display decreased phosphorylated alpha-synuclein. In addition, Pagan and colleagues assessed the potential therapeutic benefits of Nilotinib in 12 patients with PDD or dementia with Lewy bodies.[9] Participants showed improved cognition and motor function that correlated with reduced alpha-synuclein and phosphorylated tau levels; participants did not experience edema, stroke, or seizures. Nilotinib putatively inhibits the Discoidin Domain Receptor Tyrosine Kinase 1 (DDR1 receptor), decreasing inflammation while enhancing autophagy; Nilotinib reverses deterioration of the blood-brain barrier as well. [10, 11] Future studies will explore the effects of combining Nilotinib treatment with traditional standards of care, and will assess the role of kinase inhibitor Bosutinib in reducing PDD; exploratory trials currently demonstrate that Bosutinib reduces levels of alpha-synuclein in the cerebrospinal fluid (CSF)[12].

3.5. Genetic and proteomic landscape of NPS

Insights into the genetic architecture of NPS are limited. Individuals diagnosed with schizophrenia during early adulthood have 6 times greater risk for developing dementia,[13] individuals that experience major depression before 45 years of age have 4 times higher risk of developing dementia,[14] and up to 90% of individuals with ADRD develop NPS.[15] Wingo and colleagues interrogated the shared genetic underpinnings between major depressive disorder and ADRD by analyzing data from over 1.2 million individuals who participated in genome-wide association studies (GWAS) using the linkage disequilibrium score regression.[16] They found that there is indeed some shared genetic basis between major depression and AD. Furthermore, using results from a large GWAS of depression, Wingo and team estimated a depression polygenic risk score (PRS), or an estimate of the genetic risk for depression, in 1,288 participants and found that high depression PRS was associated with faster episodic memory decline. In a follow up study, they found that high AD PRS was also associated with higher risk

[9] https://content.iospress.com/articles/journal-of-parkinsons-disease/jpd160867

[10] Fowler AJ, Hebron M, Balaraman K, Shi W, Missner AA, Greenzaid JD, Chiu TL, Ullman C, Weatherdon E, Duka V, Torres-Yaghi Y, Pagan FL, Liu X, Ressom H, Ahn J, Wolf C, Moussa C. Discoidin Domain Receptor 1 is a therapeutic target for neurodegenerative diseases. Hum Mol Genet. 2020 Oct 10;29(17):2882-2898. doi: 10.1093/hmg/ddaa177. Erratum in: Hum Mol Genet. 2021 Jun 17;30(13):1271-1272. PMID: 32776088; PMCID: PMC7566445./

[11] Fowler AJ, Ahn J, Hebron M, Chiu T, Ayoub R, Mulki S, Ressom H, Torres-Yaghi Y, Wilmarth B, Pagan FL, Moussa C. CSF MicroRNAs Reveal Impairment of Angiogenesis and Autophagy in Parkinson Disease. Neurol Genet. 2021 Nov 12;7(6):e633. doi: 10.1212/NXG.0000000000000633. PMID: 34786477; PMCID: PMC8589263.

[12] Pagan, FL, Torres-Yaghi, Y, Hebron, ML, et al. Safety, target engagement, and biomarker effects of bosutinib in dementia with Lewy bodies. Alzheimer's Dement. 2022; 8:e12296. https://doi.org/10.1002/trc2.12296

[13] Richmond-Rakerd LS, D'Souza S, Milne BJ, Caspi A, Moffitt TE. Longitudinal Associations of Mental Disorders With Dementia: 30-Year Analysis of 1.7 Million New Zealand Citizens. JAMA Psychiatry. 2022 Apr 1;79(4):333-340. doi: 10.1001/jamapsychiatry.2021.4377. PMID: 35171209; PMCID: PMC8851362.

[14] Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol. 2011 May 3;7(6):323-31. doi: 10.1038/nrneurol.2011.60. PMID: 21537355; PMCID: PMC3327554.

[15] van der Linde RM, Dening T, Stephan BC, Prina AM, Evans E, Brayne C. Longitudinal course of behavioural and psychological symptoms of dementia: systematic review. Br J Psychiatry. 2016 Nov;209(5):366-377. doi: 10.1192/bjp.bp.114.148403. Epub 2016 Aug 4. PMID: 27491532; PMCID: PMC5100633.

[16] Harerimana NV, Liu Y, Gerasimov ES, Duong D, Beach TG, Reiman EM, Schneider JA, Boyle P, Lori A, Bennett DA, Lah JJ, Levey AI, Seyfried NT, Wingo TS, Wingo AP. Genetic Evidence Supporting a Causal Role of Depression in Alzheimer's Disease. Biol Psychiatry. 2022 Jul 1;92(1):25-33. doi: 10.1016/j.biopsych.2021.11.025. Epub 2021 Dec 16. PMID: 35177243; PMCID: PMC9200901.

for experiencing depression before any manifestation of cognitive impairment.[17] Further analysis identified transcripts and proteins that are associated with both major depression and AD.[18] Lastly, Wingo and colleagues found 13 shared causal proteins among ADRD and psychiatric conditions (major depression, schizophrenia, anxiety, etc.) that likely underlie the manifestation of NPS in ADRD.[19]

3.6. Gut microbiome and dementia

Individuals with AD have an altered gut microbiome compared to healthy, non-AD individuals, and these alterations are correlated with beta-amyloid and tau levels in the CSF.[20] In animal models, germ free mice and antibiotic-treated mice both show decreased beta amyloid plaques,[21] but these changes appear to be male specific.[22] Additional work found that only female mice on a calorie restricted diet had reduced plaques,[23] a finding attributed to the diet blocking an age-related increase in the bacteria Bacteroides;[24] delivering Bacteroides to mice led to elevated plaques by suppressing immune responses to amyloid-beta. Microglia, in particular, are one mechanism by which the gut may affect the brain, but effects may be different depending on the disease In AD and PD, antibiotics decrease microglial inflammation and improve the disease, whereas the depletion of microbiota with antibiotics is shown to activate microglia and stimulate neurodegeneration in an animal model of amyotrophic lateral sclerosis (ALS, Lou Gherig's disease).[25] In the future, it may be possible to treat neurologic diseases with beneficial microbes, but more work is needed to identify disease-specific bacteria. Cox and colleagues were able to identify a unique bacterium called Akkermansia associated with progressive multiple sclerosis and found that increase in this bacterium may play a protective

[17] Wingo TS, Gerasimov ES, Canon SM, Lah JJ, Levey AI, Wingo AP. Alzheimer's disease genetic burden is associated with mid-life depression among persons with normal cognition. Alzheimers Dement. 2022 Jun 21. doi: 10.1002/alz.12716. Epub ahead of print. PMID: 35727298.

[18] Harerimana NV, Liu Y, Gerasimov ES, Duong D, Beach TG, Reiman EM, Schneider JA, Boyle P, Lori A, Bennett DA, Lah JJ, Levey AI, Seyfried NT, Wingo TS, Wingo AP. Genetic Evidence Supporting a Causal Role of Depression in Alzheimer's Disease. Biol Psychiatry. 2022 Jul 1;92(1):25-33. doi: 10.1016/j.biopsych.2021.11.025. Epub 2021 Dec 16. PMID: 35177243; PMCID: PMC9200901.

[19] Wingo TS, Liu Y, Gerasimov ES, Vattathil SM, Wynne ME, Liu J, Lori A, Faundez V, Bennett DA, Seyfried NT, Levey AI, Wingo AP. Shared mechanisms across the major psychiatric and neurodegenerative diseases. Nat Commun. 2022 Jul 26;13(1):4314. doi: 10.1038/s41467-022-31873-5. PMID: 35882878; PMCID: PMC9325708.

[20] Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A. et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep 7, 13537 (2017). https://doi.org/10.1038/s41598-017-13601-y

[21] Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang X, Oyler-Castrillo P, Zhang X, Musch MW, Shen X, Jabri B, Chang EB, Tanzi RE, Sisodia SS. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APPSWE/PS1ΔE9 murine model of Alzheimer's disease. Sci Rep. 2017 Sep 5;7(1):10411. doi: 10.1038/s41598-017-11047-w. PMID: 28874832; PMCID: PMC5585265.

[22] Dodiya HB, Kuntz T, Shaik SM, Baufeld C, Leibowitz J, Zhang X, Gottel N, Zhang X, Butovsky O, Gilbert JA, Sisodia SS. Sex-specific effects of microbiome perturbations on cerebral Aβ amyloidosis and microglia phenotypes. J Exp Med. 2019 Jul 1;216(7):1542-1560. doi: 10.1084/jem.20182386. Epub 2019 May 16. PMID: 31097468; PMCID: PMC6605759./

[23] Schafer MJ, Alldred MJ, Lee SH, Calhoun ME, Petkova E, Mathews PM, Ginsberg SD. Reduction of β-amyloid and γ-secretase by calorie restriction in female Tg2576 mice. Neurobiol Aging. 2015 Mar;36(3):1293-302. doi: 10.1016/j.neurobiolaging.2014.10.043. Epub 2014 Dec 4. PMID: 25556162; PMCID: PMC4346433.

[24] Cox LM, Schafer MJ, Sohn J, Vincentini J, Weiner HL, Ginsberg SD, Blaser MJ. Calorie restriction slows age-related microbiota changes in an Alzheimer's disease model in female mice. Sci Rep. 2019 Nov 29;9(1):17904. doi: 10.1038/s41598-019-54187-x. PMID: 31784610; PMCID: PMC6884494.

[25] https://microbiomejournal.biomedcentral.com/articles/10.1 186/s40168-022-01232-z

role.[26] Cox and colleagues aim to assess the protective effects of Akkermansia across multiple neurodegenerative diseases including AD.

4. Perspectives on Clinical Development

Discussion at the meeting highlighted the importance of (1) listening to patients and amplifying their voices within the regulatory environment, (2) leveraging research opportunities in disease prevention and early treatment, (3) understanding the role of regulatory flexibility during drug development and approval, and (4) addressing the spread of misinformation.

4.1. Challenges in drug development during COVID-19

During the COVID-19 pandemic, pharmaceutical companies faced challenges in drug development because many sites and staff were reassigned to COVID-19 research and trials. Although trials in neurological diseases, such as AD and PD, did not experience site closures, many trial participants were hesitant about in-person site visits. This participant hesitation forced many sites to begin conducting at-home trials, and in turn develop novel assessments and endpoints. At-home trials have provided a substantial benefit for clinical trial infrastructure by increasing the number of participants and easing their travel burden. Because of these benefits, at-home trials have become a permanent fixture for clinical trials that involve participants who struggle to travel, highlighting a patient-centered aspect of care that arose from the COVID-19 pandemic.

4.2. Patient voice and advocacy groups

The patient's voice is critical for informing drug and therapeutic development, as opposed to the notion that the expertise of physicians and researchers alone should determine patient treatments. FDA and patient advocacy organizations host patient-focused drug development (PFDD) meetings, which help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation processes. During these meetings, patients have expressed that they do not expect complete cures for diseases, but rather desire more therapeutic options.. In recent years, patients have also expressed frustration that their participation in a clinical trial often contributes little data to other research outside of the trial itself. This frustration has led to revised informed trial consents that now outline broader contributions per participant, including sample banking for future third party research.

Patient advisory meetings face unresolved communication barriers that arose during the COVID-19 pandemic, when these meetings moved to a teleconferencing model that created a more impersonal atmosphere and thus hindered the exchange and impact of patient opinions. In addition to this relatively new barrier, researchers and clinicians have often assumed that patients are desperate for treatment and that this desperation invalidates their therapeutic risk assessments. Focusing on measuring and mapping biomarkers can reduce the impression of patient desperation by including delayed-onset and at-risk patients in advocacy groups. Patient advocacy organizations can help combat the spread of misinformation by relaying public misconceptions to federal agencies and pressing social

[26] Cox, L.M., Maghzi, A.H., Liu, S., Tankou, S.K., Dhang, F.H., Willocq, V., Song, A., Wasén, C., Tauhid, S., Chu, R., Anderson, M.C., De Jager, P.L., Polgar-Turcsanyi, M., Healy, B.C., Glanz, B.I., Bakshi, R., Chitnis, T. and Weiner, H.L. (2021), Gut Microbiome in Progressive Multiple Sclerosis. Ann Neurol, 89: 1195-1211. https://doi.org/10.1002/ana.26084

media companies to screen posts for misinformation. The Alliance for Aging Research also hosts a Talk NERDY to Me program, which brings older adults, caregivers, clinicians, and researchers together to discuss aspects of disease research and treatment that are most important to patients.

4.3. Advancing biomarker studies

In the era of biomarker cartography, listening to patients can help guide research on biological mechanisms of action for targeted therapy. Progressive diseases provide researchers with the opportunity to identify biomarkers before the emergence of symptoms, which justifies research into early treatments that can prevent symptom onset. In addition, identifying biomarkers can help define diseases based on biological mechanisms rather than clinical phenotypes alone, which will help further characterize complex disease populations for more targeted therapeutics.

The research community can also address misperceptions of terminology—for example, by defining "early-onset" to include sporadic emergence of disease based on disease-indicative biomarkers,. Identifying such biomarkers can assist in designing trials, as well as aid in early clinical decisions about treatment. However, the complex interplay of different biomarkers calls for an increase in biomarker measures in trials, as exemplified by the recognition that anti-amyloid treatments for AD have been associated with an effect on tau and other downstream biomarkers. In addition to biomarker measures, a national registry, such as the recently launched Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) platform, can aid in collaborative efforts and sample banking to provide ongoing information about the effects of new agents.

4.4. FDA's support and role in drug development

Although all international regulatory agencies may not review primary clinical trial data, FDA rigorously reviews clinical trial data in-house to determine whether they are suitable to support development programs and approval. FDA also offers guidance to clinical developers during the drug development process, which can be especially relevant in the context of severe and life-threatening diseases. For example, when a sponsor is conducting investigational new drug (IND) development, it can hold a pre-submission IND meeting (i.e., a type B meeting) with FDA. Under circumstances of novel treatment areas or rare disease treatment, FDA may grant additional pre-submission IND meetings (i.e., type C meetings) to help address the development needs of sponsors.

Although sponsors are often familiar with pre-submission IND meetings, sponsors may be less familiar with other aspects of flexibility that may be relevant during development FDA frequently considers the complexity of diseases, and specifically considers patient input, novel outcome measures, and other innovative approaches to help advance development for serious and life-threatening diseases with unmet medical needs.

As part of the drug approval process, FDA emphasizes the importance of communicating its decisions in a clear manner, for instance by the provision of approval documents, drug labeling, and other information. FDA works to develop clear language in drug labels to convey accurate information to prescribers and patients. This clear and accurate portrayal of information can provide context for the general public to make well-informed decisions about treatments, as well as combat the spread of scientific misinformation.

5. Conclusion

The 15th 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 learn about emerging issues and therapies in the treatment of AD/ADRD. The meeting centered on advancing research underlying NPS in AD/ADRD, with discussions encompassing the use of THC, CBD, and Ritalin, investigating the gut microbiome in neurological health, and utilizing advanced genomic and proteomic analysis to identify novel therapeutic targets. The novel research approaches discussed during this meeting simultaneously repurpose currently existing drugs, which may help streamline the path to potential approval by regulators. Furthermore, the meeting emphasized the differences with which biological markers express across categories of race and sex, highlighting the importance of including diverse populations in research studies. Collectively, these breakthroughs provide an entrée into deep research discoveries to unravel the genetic-molecular-behavioral interplay that characterizes AD/ADRD, and ultimately to generate impactful and inclusive treatment for all individuals affected.