


## REVIEW ARTICLE

# New directions for Alzheimer's disease research from the Jackson Laboratory Center for Alzheimer's and Dementia Research 2022 workshop

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## Abstract

**INTRODUCTION:** In September 2022, The Jackson Laboratory Center for Alzheimer's and Dementia Research (JAX CADR) hosted a workshop with leading researchers in the Alzheimer's disease and related dementias (ADRD) field.

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**METHODS:** During the workshop, the participants brainstormed new directions to overcome current barriers to providing patients with effective ADRD therapeutics. The participants outlined specific areas of focus. Following the workshop, each group used standard literature search methods to provide background for each topic.

**RESULTS:** The team of invited experts identified four key areas that can be collectively addressed to make a significant impact in the field: (1) Prioritize the diversification of disease targets, (2) enhance factors promoting resilience, (3) de-risk clinical pipeline, and (4) centralize data management.

**DISCUSSION:** In this report, we review these four objectives and propose innovations to expedite ADRD therapeutic pipelines.

## 1 | INTRODUCTION

Given that Alzheimer's disease (AD) is the most common underlying cause of dementia in elderly individuals, there is a need for therapeutics targeting the multitude of pathways dysregulated in the disease. Pharmacological treatments targeting acetylcholinesterase (donepezil, rivastigmine), N-methyl-D-aspartate (NMDA) receptors (memantine), and amyloid (aducanumab, lecanemab) for Alzheimer's disease and related dementias (ADRD) have failed to produce lasting cognitive benefits. The accelerated United States Food and Drug Administration (FDA) approval of aducanumab (Aduhelm)<sup>1</sup> and full FDA approval of lecanemab (Leqembi)<sup>2</sup> have generated considerable public excitement. Yet, anti-amyloid therapies are not the silver bullet AD treatment. Given the complexities of ADRD, it is clear that therapeutic strategies to prevent neurodegeneration and cognitive decline must go beyond targeting the characteristic pathological molecules of AD, namely, amyloid and tau. At the same time, it is imperative to improve clinical translation of novel experimental approaches. Below, we discuss promising targets and outline a paradigm for the implementation of clinical pipelines.

## 2 | TARGETING AD: GOING BEYOND AMYLOID AND TAU

Given the partial success of anti-amyloid therapies, additional focus on other components of ADRD – individually or in combination – is critical to drive continued progress in the field. Here, we highlight seven promising avenues of investigation that could lead to the identification of novel druggable targets for this family of diseases.

### 2.1 | Neuroinflammation

Neuroinflammation (e.g., activation of microglia and astrocytes, infiltration of peripheral immune cells), a potential driver of ADRD pathogenesis, is currently the most active area of investigation after amyloid and tau. Several studies have recently explored the role of microglia in modifying ADRD susceptibility.<sup>3</sup> Neurotoxic cytokines released by microglia have been hypothesized to contribute to neurodegeneration.<sup>4</sup> Cytokines, or the mechanisms driving their release by neuroinflammatory cells, are potential druggable targets for ADRD, and may serve as peripheral biomarkers for increased risk of ADRD development (reviewed here<sup>5</sup>). For example, targeting p38 $\alpha$  MAPK was shown to suppress cytokine upregulation, lessen synaptic loss, and ameliorate cognitive deficits in mouse models of ADRD.<sup>6</sup> Furthermore, several genetic variants associated with AD risk lie within genes that are highly expressed by immune cells (reviewed here<sup>7</sup>). Some of these proteins, such as TREM2, CD33, and INPP5D, are actively being explored as potential druggable targets for ADRD. Much effort is currently focused on determining the potential for targeting neuroinflammatory processes and future studies should broaden the search to identify additional druggable targets based on the products of these microglial genes to ameliorate ADRD pathogenesis. Finally, genetic testing for a panel of neuroinflammation-related genes may be a viable strategy to indicate a patient's increased risk.

### 2.2 | Synaptic and intrinsic neuronal factors

Loss of neurons and their synapses is a hallmark of ADRD and ultimately results in cognitive deficits. Therefore, targeting neuronal

health, particularly synaptic health, offers promise in treating ADRD. Dissecting genetic differences underlying susceptibility or resilience to neuron loss in mice, and validating these findings in humans, is essential to identifying neuronal-intrinsic druggable targets that might sustain or prevent disease progression. In addition to neurons, glial cells also play a critical role in synaptic health and function. Complement-mediated synaptic pruning (i.e., the elimination of weak synapses by microglial cells) has been shown to damage neuronal connectivity in ADRD,<sup>8</sup> indicating the importance of neuronal-glial interactions in the context of these diseases.

### 2.3 | Vascular abnormalities

It is now widely accepted that cerebrovascular deficits, commonly referred to as vascular contributions to cognitive impairment and dementia, are early pathological events in ADRD.<sup>9,10</sup> Blood–brain barrier (BBB) breakdown is thought to impair the clearance of amyloid, allowing parenchymal plaque deposition and its consequent pathological cascade.<sup>11</sup> Loss of BBB integrity also contributes to cerebral amyloid angiopathy (CAA), the deposition of amyloid peptide within the walls of cerebral vessels.<sup>11</sup> Microhemorrhages, ischemia, and loss of white matter induced by BBB disruption all potentially contribute to ADRD-related neurodegeneration and the worsening of cognitive outcome measures. Therefore, therapeutically targeting mechanisms driving BBB breakdown may slow or prevent CAA and ADRD-relevant pathologies. Potential therapeutic approaches involve: (i) pharmacologically strengthening tight junctions between cerebral endothelial cells, (ii) preventing pericyte or endothelial cell apoptosis, and (iii) bolstering astrocytic endfeet-endothelial cell contacts. Recently reported side effects of Aduhelm and Leqembi, including amyloid-related imaging abnormalities (ARIAs)<sup>2,12</sup> that may be a result of damaged vessels,<sup>13</sup> underscore the importance of testing combinatorial treatments that simultaneously clear amyloid and improve vascular integrity. ARIA is reviewed elsewhere,<sup>14</sup> but it is important to note that apolipoprotein E (APOE) status appears critical in determining risk for ARIA, and should be taken into account when considering combinatorial therapies.

### 2.4 | Bioenergetics

Physiologically, fuel substrate utilization successfully shifts between carbohydrate and lipid metabolism. During aging, this process is shifted toward increased lipid utilization, reflecting the inability to adapt fuel oxidation to fuel availability.<sup>15</sup> With respect to mitochondria, a general decline of mitochondrial fitness during the lifespan of an individual is signaled by the accumulation of oversized, abnormal mitochondria.<sup>16</sup> These mitochondria undergo remodeling, which results in the reduced capacity to exclude calcium, generate adenosine triphosphate (ATP), and protect against reactive oxygen species. In the context of ADRD, multiple interrelated alterations can lead to bioenergetic dysfunctions such as imbalances in mitochondrial respiration versus glycolysis, a

#### RESEARCH IN CONTEXT

1. **Systematic review:** During the workshop, the authors were divided among groups to discuss the major limitations and advances necessary in their respective fields. During the workshop, participants decided on the topics for the review, and thereafter, literature was reviewed using standard methods (e.g., PubMed, Google Scholar, etc).
2. **Interpretation:** Through in-person discussion with leaders in the field during the workshop and subsequent writing of the review, we propose new directions to pursue for the advancement of treatments for Alzheimer's disease and related dementias (ADRD).
3. **Future directions:** We call for a focused approach to tackle creating disease-modifying ADRD drugs from multiple directions. First, we highlight new research opportunities to focus on, second, we propose unifying definition for cognitive resilience in ADRD, third, we outline how to de-risk proposed treatments, and, fourth, we discuss data management for ADRD research.

reduction in the levels of nicotinamide adenine dinucleotide and hydrogen (NAD/NADH), a diminished glucose uptake, and decreases in both insulin receptor and glucose transporter densities.<sup>17,18</sup> This bioenergetic dysfunction can directly impact inflammation, blood flow, and cell survival, exacerbating the phenomenon of aging in the brain. Thus, targeting the mechanisms that drive a decline in bioenergetics may be a suitable strategy to prevent or delay ADRD. Furthermore, these same mechanisms may serve as early biomarkers to identify patients at risk.

### 2.5 | Metabolic and lifestyle risk factors for ADRD

Metabolic syndrome, including obesity, diabetes, high cholesterol, and hypertension, is a growing worldwide concern<sup>19</sup> and patients with metabolic risk factors are significantly more likely to develop ADRD and/or vascular dementia. Thus, tracking and targeting these risk factors in tandem with other ADRD therapeutics continues to be an important area of investigation. Obesity, lack of exercise, and poor diet are among the few actionable risk factors for the development of dementia and ADRD. For example, the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet was shown to slow cognitive decline and, with other healthy lifestyle habits, lengthen the health span of individuals in the study with and without AD.<sup>20</sup> The impact of diet on AD pathogenesis is inconsistent across studies, which may be explained by differences in the start and duration of the treatments and in the composition of the diets.<sup>21</sup> To achieve higher rigor and reproducibility, metabolic dietary effects should be assessed by measuring multiple parameters, such as blood glucose, blood pressure,

low-density and high-density lipoprotein levels, triglyceride levels, and body weight. A potential strategy would be to leverage AD mouse models that display one or more aspects of metabolic syndrome (e.g., obesity). Successfully unveiling the molecular underpinnings of these aspects of the metabolic syndrome, individually and in combination, will be critical to targeting one or more mechanisms to alleviate risk or slow ADRD.

## 2.6 | Targeting aging to treat ADRD

Although there is a strong genetic component to determining an individual's risk for developing ADRD, age remains the greatest risk factor, with prevalence doubling every 5 years after the age of 65.<sup>22</sup> While chronological aging cannot be altered, the rate of biological aging is believed to be a modifiable factor that, much like ADRD risk, is strongly influenced by individual genetic variation.<sup>23</sup> Thus, interventions that target conserved pathways associated with longevity and healthy aging may yield new, effective therapeutics for ADRD. For example, treatments with rapamycin and metformin have been reported to extend the lifespan and health-span in mice.<sup>24</sup> Of note, rapamycin was shown to be effective in altering the progression of AD-like symptoms in mouse models of AD.<sup>25</sup> Resources such as the Alzheimer's disease - C57BL/6J crossed with DBA/2J (AD-BXD) panel and other genetically diverse AD-relevant mouse strains are powerful tools to investigate how factors such as genetic background, aging, and AD determine an individual's responsiveness to anti-aging therapeutics.

## 3 | HARNESSING RESILIENCE TO TARGET COGNITIVE DECLINE

It is known that some individuals do not exhibit characteristic ADRD-associated cognitive decline despite harboring pathological hallmarks. This phenomenon is called resilience and provides a powerful new framework to study and nominate personalized therapeutic targets for ADRD. Recently, a new framework was proposed to define resilience and its mechanisms.<sup>26</sup> Here, we build off this framework to show a more generalizable and operational definition of resilience, and propose new methods for investigating and translating findings on the biology of resilience to expand potential treatments for ADRD.

### 3.1 | Operational definition of resilience for molecular and clinical settings

The concept of resilience has offered exciting insights into potential biomarkers and therapeutic targets for ADRD. However, its clinical translation and cross-species comparison have been hampered by the plethora of definitions and the confusion between resilience and the mechanism leading to it, causing ambiguity in its meaning. In an attempt to standardize these definitions, the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia has

defined resilience as "a general term that subsumes any concept that relates to the capacity of the brain to maintain cognition and function with aging and disease" and clearly connects brain maintenance, cognitive reserve, and brain reserve as different mechanisms underlying resilience (reserveandresilience.com).<sup>26</sup> Under this framework, brain reserve is defined as the preservation of brain structure in the face of aging or disease, cognitive reserve as an active process geared to preserve brain function upon aging or disease, and brain maintenance as a mechanism preventing cognitive decline in the absence of risk factors. In all three cases, the context (disease or aging) and the outcome (cognition or brain structure) are predefined. However, resilience can arise in contexts other than aging or disease and can manifest in properties other than cognition or brain function. For example, contexts involving non-clinical risk factors, like diet or socioeconomics, and/or stressors (i.e., acute events that challenge homeostasis), like stroke or traumatic brain injuries, and outcomes like neuropathology<sup>27</sup> or highly penetrant genetic mutations.<sup>28</sup> Additionally, the current framework could account for risk factors or stressors also being outcomes. For instance, pathology can be both a risk factor or an outcome.

To account for these aspects, we propose defining resilience by identifying a measurable outcome and a risk factor/stressor modifying that outcome, on a context-by-context basis (Figure 1). Under this framework, all three of brain maintenance, brain reserve and cognitive reserve are seen as cases of resilience to different outcomes in the face of different contexts. Specifically, cognitive reserve can be framed as resilience to cognitive decline given the presence of ADRD pathology, brain reserve as resilience to cognitive decline given neurodegeneration, and brain maintenance as resilience to ADRD pathology given genetic risk factors. Many variables can be used as outcomes, risk factors/stressors, or both when defining resilience (Figure 1). For example, two individuals with familial AD harboring increased amyloid pathology show resilience to cognitive decline and tau pathology mediated by APOE3<sup>28</sup> and reelin (RELN)<sup>29</sup> – AD pathology as both a risk factor and an outcome. Importantly, by operationalizing resilience as we propose here, these variables need not be constrained to cognition only, as resilience arises in psychosocial and physical domains as well.<sup>30</sup> For instance, in the physical domain, an aspect of frailty can be conceptualized in our framework as resilience to age-associated sarcopenia and so on for other frailty components. Regardless of the outcomes and risk factors selected, this new, more parsimonious framework – (1) allows for unambiguous and operational use of the term "resilience", (2) recognizes the multiplicity of interacting factors that comprise it, (3) can be used across clinical domains, and (4) leaves the door open to include potential novel resilience mechanisms that lie outside the three existing concepts (Figure 1).

#### 3.1.1 | Defining resilient populations using continuous metrics

Besides the ontological definition of resilience in ADRD, there is also substantial heterogeneity in the measurements used to define it operationally. For instance, the categorization of cognition as a binary





executive function reserve).<sup>35</sup> Other studies have relied on positron emission tomography (PET) imaging to understand resilience. One study used <sup>18</sup>F-fluorodeoxyglucose (FDG)-PET in a cohort of cognitively resilient individuals and found that higher cognition was associated with enhanced FDG uptake in the bilateral anterior cingulate and temporal pole. These regions were then used as a reserve signature in an independent cohort, and higher uptake in these regions was associated with slower longitudinal cognitive decline.<sup>35</sup> Other studies have taken multimodal approaches incorporating multiple neuroimaging types. For instance, a recent study using data from the UK Biobank (n = ~19,038) built age-prediction models and found that these residuals were most associated with a variety of traits previously linked to AD (e.g., blood pressure, cardiac output, smoking).<sup>36</sup> Despite the progress in this area, additional studies are necessary to better characterize the biological mechanisms that drive brain resilience. For example, diffusion tensor imaging allows for the quantification of whole-brain white matter changes, which may contribute to measuring resilience. Additionally, advanced harmonization techniques have made it easier to leverage multi-site neuroimaging data to conduct large-scale statistical analysis. Using large-scale, harmonized data in tandem with genetic, biomarker, and cognitive data will drastically enhance our understanding of resilience.

### 3.1.3 | Using cohort characteristics to study resilience

Cohort characteristics must be considered to identify resilience factors and develop therapeutic interventions. Since no resilience biomarkers have been identified and the phenomenon of resilience may unfold over a long period of time, continuing to use already existing human cohorts to identify resilience factors (and biomarkers) is warranted. Two opportunities are particularly promising to aid the identification of resilience factors in ongoing studies. First, given the advancements in neuroimaging harmonization, there is an unprecedented opportunity to merge well-established longitudinal cohorts that follow cognition and evaluate aging and ADRD individuals to conduct large-scale analyses of resilient populations that may comprise small proportions in each of their cohorts (Table 1). While merging these cohorts is appealing, this process must be conducted carefully. For most existing studies, diversity must be improved in categories including, but not limited to, geographic location, educational attainment, race, ethnicity, socioeconomic status, biological sex, and gender and sexual identity. Including and exploring variation across these important categories is critical for the improved applicability of findings related to resilience across the general population.

Second, other resources can be used for resilience studies. For example, linking multiple brain banks, that are currently underutilized, can boost the power and diversity with the caveat that some have sparse *ante mortem*/longitudinal data. A uniform procedure to sample, process, analyze, and post data would allow resilience studies (and others) to access more information. Another idea is to study cognitive resilience in cohorts created for other purposes. For instance,

future research can draw on data from events that lead to cognitive decline, perhaps in a shorter time frame than cognitive decline due to AD. Namely, delirium occurs very quickly (within hours) with rapid cognitive decline, attention deficits, and high risk of later development of dementia. Elective surgery could be a suitable model in which behavioral testing can be performed pre- and post-procedure, as done in the SAGES study at Harvard.<sup>37</sup> Another possibility is to study chemotherapy patients, as chemotherapy accelerates cellular senescence – especially in those treated as children – and the onset of disease/conditions associated with aging.

When studying resilience, one must keep in mind that there is no uniform presentation. Therefore, studying larger and more diverse resilience cohorts will be essential in subtyping resilience using biomarkers or different mechanisms of action. After resilience pathways and biomarkers are identified, and drugs are nominated, therapeutics must be tested in clinical trials. For these studies, it can be beneficial to identify individuals with high AD risk and separate them into groups with low or high resilience scores. Although resilience timeline is unknown, it may be necessary to follow individuals for a prolonged amount of time to effectively assess cognitive performance and measure pathology. Resilience biomarkers would allow us to shed some light on pathway engagement. Importantly, a biomarker cannot be related to pathology per se, as it would confound the assessment of efficacy (outcome). Additionally, accounting for environmental and societal factors is important in resilience studies, as is determining whether to factor these variables out or to stratify populations based on them.

Data from identified resilient individuals can also be used to test nominated resilience targets from other studies, for example, using human data to cross-reference resilience targets from a model system.<sup>38</sup>

### 3.2 | Using model systems to nominate, identify, and investigate cognitive resilience factors to AD pathology

Some limitations of studying resilience in humans are the inaccessibility of brain tissue during lifetime, the inability to study the causes and mechanisms underlying nominated resilience factors, and the inability to perform preclinical validations. Therefore, it is necessary to complement human cohort studies with model systems that represent controlled environments where it is possible to refine potential resilience factors acquired in longitudinal studies. This subsection addresses the appropriate resilience models and the cognitive metrics and biological readouts that are necessary to enable translation.

Transgenic mouse models used for nomination and validation of resilience targets currently include familial ADRD models of either amyloid (5XFAD, Tg2576, J20) or tau (P301L, P301S) expression.<sup>38</sup> In the future, research will benefit from studying resilience in models of late-onset AD (LOAD), such as next-generation AD models in development by the Model Organism Development and Evaluation for Late-onset Alzheimer's Disease (MODEL-AD) Consortium (see Section 5.1 for more details on MODEL-AD).<sup>39</sup> Another factor to consider

**TABLE 1** Longitudinal cohorts with outcomes and risk factors/stressors that can be used to identify therapeutic targets and elucidate disease mechanisms.

Cohort	Acronym	Distinguishing feature	Available genetic and omics data	Imaging	Study website	Selected publications
Religious Order's Study and Memory Aging Project and Minority Aging Research Study	ROS/MAP/ MARS	Ethnically diverse	SNP, WGS, WES, methylation, acetylation, RNA-seq, proteomics, metabolomics	MRI/DTI	<a href="https://www.rad.ccrush.edu/">https://www.rad.ccrush.edu/</a>	ROS/MAP: PMID:29865057; MARS: PMID:22471868
National Alzheimer's Coordinating Center	NACC	Centralized data repository		MRI/DTI/PET	<a href="http://naccdata.org">naccdata.org</a>	PMID: 15592144
Alzheimer's Disease Neuroimaging Initiative	ADNI	Longitudinal imaging, ethnically diverse	GWAS, WGS	MRI/DTI/PET	<a href="https://adni.loni.usc.edu/">https://adni.loni.usc.edu/</a>	PMID: 18302232
Framingham Heart Study	FHS	Multigenerational, ethnically diverse	Microarray, Exome, WGS, targeted sequencing, methylation, RNA-seq, miRNA-seq, proteomics, lipidomics		<a href="http://framinghamheartstudy.org">framinghamheartstudy.org</a>	PMID: 26705418, PMID: 33568140
UK Biobank		Dataset for half a million people in UK	WGS, WES, Telomeres	MRI/DTI	<a href="https://www.ukbiobank.ac.uk/">https://www.ukbiobank.ac.uk/</a>	PMID: 30305743
University of Washington Open Access Series of Imaging Studies	OASIS	Open-access imaging datasets		MRI/DTI/PET	<a href="https://www.oasis-brains.org/">https://www.oasis-brains.org/</a>	<a href="https://doi.org/10.1101/2019.12.13.19014902">https://doi.org/10.1101/2019.12.13.19014902</a>
National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site	NIAGADS	Open-access datasets, national data repository for NIH-funded research	GWAS, WGS, DNA microarray, RNA-seq, methylation, proteomics, lipidomics		<a href="https://www.niagads.org/">https://www.niagads.org/</a>	<a href="https://doi.org/10.1002/alz.062285">https://doi.org/10.1002/alz.062285</a>
Biomarkers of Cognitive Decline Among Normal Individuals	BIOCARD	Identifies factors associated with development of cognitive impairment		MRI/DTI/PET	<a href="https://biocard-se.org/">https://biocard-se.org/</a>	PMID: 25444602
Baltimore Longitudinal Study on Aging	BLSA	95% cognitively unimpaired		MRI/DTI/PET	<a href="http://www.blsa.nih.gov">www.blsa.nih.gov</a>	PMID: 19126858
Wisconsin Registry for Alzheimer's Prevention	WRAP	Longitudinal observational cohort, ethnically diverse	GWAS, WGS	MRI/DTI/PET	<a href="http://www.wrap.wisc.edu">www.wrap.wisc.edu</a>	PMID: 29322089
Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease	A4	Studies anti-amyloid treatments		MRI/PET	<a href="http://www.a4study.org">www.a4study.org</a>	PMID: 24648338
Vanderbilt Memory and Aging Project	VMAP	Includes vascular health		MRI/DTI/PET	<a href="https://www.vmacdata.org/">https://www.vmacdata.org/</a>	PMID: 26967211

(Continues)

TABLE 1 (Continued)

Cohort	Acronym	Distinguishing feature	Available genetic and omics data	Imaging	Study website	Selected publications
Dominantly Inherited Alzheimer Network	DIAN	Mutations in PSEN1, PSEN2, or APP		MRI/PET	<a href="https://dian.wustl.edu/our-research/observational-study/">https://dian.wustl.edu/our-research/observational-study/</a>	PMID: 37550416
Alzheimer Biomarkers Consortium—Down Syndrome	ABC-DS	Down Syndrome	GWAS, karyotyping	MRI/PET	<a href="https://www.nia.nih.gov/research/abc-ds">https://www.nia.nih.gov/research/abc-ds</a>	PMID: 37641577
MindCrowd	MC	Online assessments of cognitive performance	SNP, WGS	Low-field MRI	<a href="https://mindcrowd.org/">https://mindcrowd.org/</a>	PMID: 31210642
Harvard Aging Brain Study	HABS	Ethnically diverse		MRI/PET	<a href="https://habs.mgh.harvard.edu/">https://habs.mgh.harvard.edu/</a>	PMID: 29799986
Washington Heights/Inwood Columbia Aging Project	WHICAP	Multi-ethnic cohort	WES	MRI/DTI	<a href="https://www.columbianeuroresearch.org/taub/res-normal.html">https://www.columbianeuroresearch.org/taub/res-normal.html</a>	<a href="https://doi.org/10.31234/osf.io/rtbkj">https://doi.org/10.31234/osf.io/rtbkj</a>
Atherosclerosis Risk in Communities	ARIC	Largest heart health study in African Americans		MRI/PET	<a href="https://aric.csc.unc.edu/aric9/">https://aric.csc.unc.edu/aric9/</a>	PMID: 34786837
Australian Imaging Biomarkers & Lifestyle Flagship Study of Aging	AIBL	Longitudinal data collection	SNP, exome, methylation	MRI/PET	<a href="https://aibl.org.au/">https://aibl.org.au/</a>	PMID: 35445885
ADNI Worldwide	WW-ADNI	World-wide collaborative effort	Study-dependent	MRI/PET	<a href="https://adni.loni.usc.edu/study-design/collaborative-studies/worldwide-adni/">https://adni.loni.usc.edu/study-design/collaborative-studies/worldwide-adni/</a>	PMID: 35005206
PResymptomatic EValuation of Experimental or Novel Treatments for AD	Prevent-AD	Presymptomatic AD, open science datasets	SNP, RNA-seq, targeted Proteomics	MRI/PET/Retinal	<a href="https://prevent-alzheimer.net/">https://prevent-alzheimer.net/</a>	PMID: 34192666
Retirement Study	HRS	In-depth interviews, ethnically diverse	SNP, exome, telomere length		<a href="https://hrs.isr.umich.edu/about">https://hrs.isr.umich.edu/about</a>	PMID: 35727298

Note: By mining individuals harboring a risk factor or stressor who have control-like outcome values, we can investigate such targets and mechanisms in the context of resilience.



is genetic diversity, as most studies use mice from a single or mixed genetic background. Recently, genetically diverse mouse models of AD (AD-BXDs) have been used to nominate resilience genes.<sup>40</sup> The next frontier for mouse models of resilience will be combining LOAD models with genetically diverse mouse panels, such as BXD, HET3, Collaborative Cross, and Diversity Outbred, to yield novel, more translationally relevant AD resilience models.

Another advantage of using transgenic and CRISPR edited mouse models with mutations that cause early-onset AD is the possibility of studying the effect of the pathology versus aging within the same genetic background (i.e., assessing cognition across ages in noncarriers versus carriers allows discernment of the effects of aging versus amyloid, as some strains cognitively decline with age even in the absence of pathology). These next-generation, genetically diverse mouse models that present a wide range of behavior should be followed in large-cohort studies to map the origin and progression of resilience in the brain. Applying new neuroimaging-omics, machine learning, and computational tools to create spatial brain-wide profiles of integrated -omics and imaging data<sup>41</sup> would enable us to determine in which brain areas neuronal function is maintained, the signatures of resilience, and how they propagate through animals' lifetime. Since the genetics of resilience differ from the genetics of AD,<sup>42</sup> resilience pathways may take separate trajectories from AD pathways. Discovering the brain regions involved in resilience and whether individuals utilize different regions or combinations thereof to achieve resilience would guide the choice of the appropriate behavioral tests to characterize the resilience phenotype. For example, contextual fear conditioning may be appropriate for hippocampus-dependent tasks, while active avoidance may be most appropriate for tasks that rely on cortical areas.

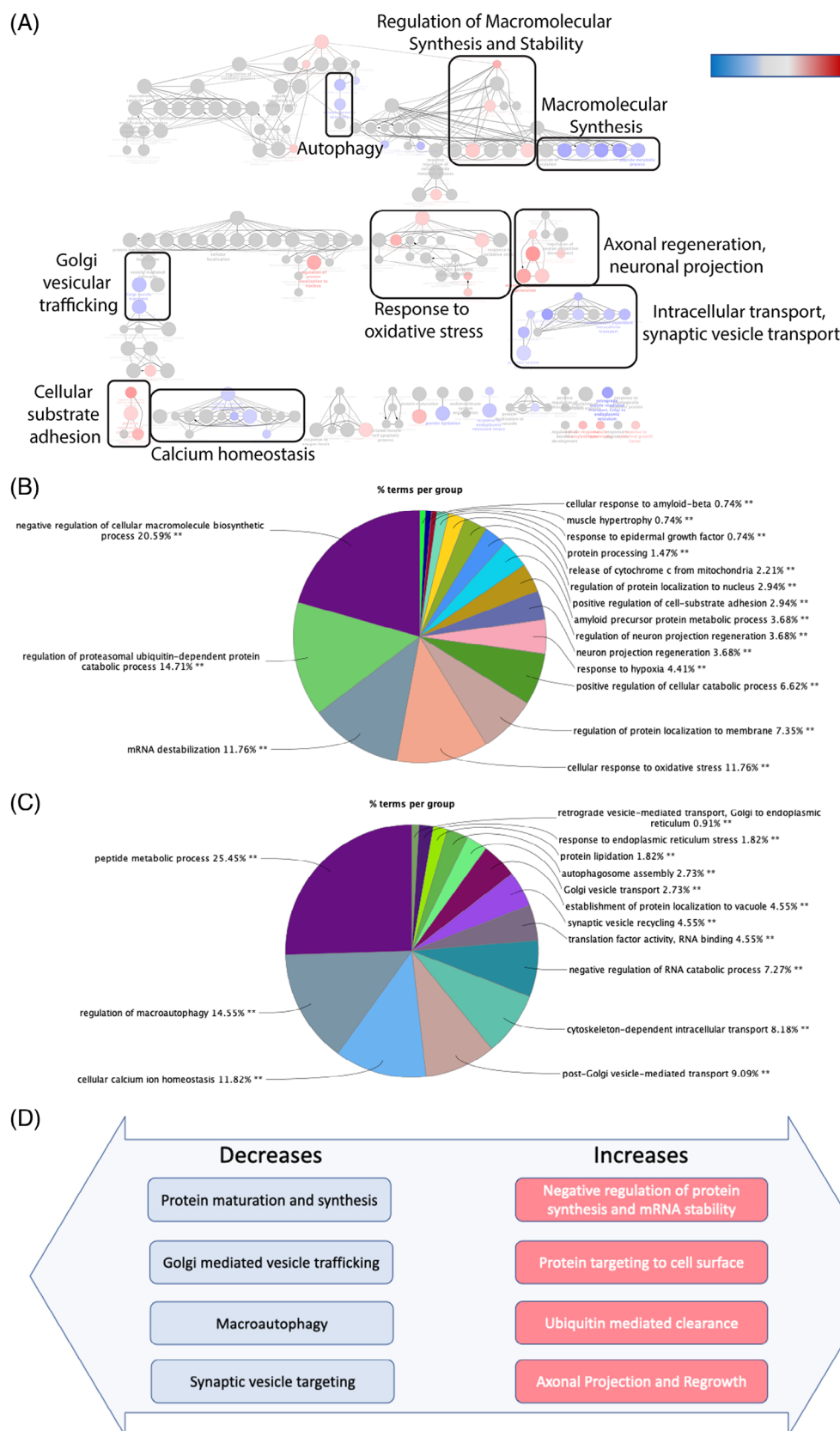
Primate models of AD are being established in marmosets, which develop AD pathologies naturally,<sup>43</sup> and in rhesus monkeys.<sup>44</sup> Future studies are needed to establish whether these models exhibit cognitive resilience and how they may be leveraged in testing resilience therapeutics. Finally, to ensure the translatability of results, it is important to establish which resilience phenotypes are replicated in human cell lines and which tools are available to compare mouse and human data. For example, induced pluripotent stem cell (iPSC)-derived neurons from 53 religious orders study and memory aging project (ROSMAP) participants for whom deep cognitive phenotyping and brain-tissue data are available were developed and characterized<sup>45</sup> including individuals cognitively resilient and susceptible to AD pathology. This effort provided a cellular platform needed to nominate and test neuron-specific resilience factors and targets. Another example is to use an integrated mouse-human data space to discover resilience factors.<sup>40</sup>

### 3.3 | Harnessing nominated and validated signatures of resilience for further therapeutic development

Known resilience factors include structural, genetic, and molecular factors from human to mouse studies (recently reviewed here<sup>39</sup>). Efforts are ongoing to validate the mechanism/cause of resilience versus

biomarker, and prioritize potential therapeutic targets. One important consideration is whether the resilience factors or molecular signatures emerge in response to pathology or if they are correlated with better cognition in individuals without ADRD pathology. Through discussion, we concluded that, in the end, it may not matter as long as the therapeutic strategy is proven successful in clinical trials. From this perspective, no matter what the means, improving neuronal function is the goal. In fact, neuronal dendritic spine density is a better correlate of cognition than amyloid and tau levels, and several different strategies have been demonstrated to make synapses resilient to AD pathology.<sup>46</sup> These considerations and findings also highlight the importance of recognizing gene candidates and processes that promote neuronal survival that are converging between labs. However, it must be kept in mind that the directionality of gene signatures may not be indicative of resilience or susceptibility to AD pathology, and that up- or downregulation of a gene due to pathology may not have a pernicious effect on biological function. Furthermore, from directionality alone, it may be difficult to distinguish cells with mechanisms that suppress neuronal damage from cells with mechanisms that actively activate survival. Thus, when gene expression is elevated in resilient individuals, it may not be a true candidate for resilience intervention. All four possibilities are important to consider: (1) upregulated genes in resilient individuals compared to susceptible individuals with negative effects on cognition, (2) upregulated and positive, (3) downregulated and negative, and (4) downregulated and positive. Thus, testing mechanisms is necessary to establish resilience factors definitively.

One method to address how altered regulation of specific genes impacts disease etiology is to capture the gene in the context of the larger biological process. We have designed biological domains (or endophenotypes) of AD that are constructed from extensive Gene Ontology (GO) term collection, leveraging the gene to GO-term annotation relationships, to place that gene in a broader biological context.<sup>47</sup> The up- and downregulated genes within any one biological domain can be used to "heat-map" the subordinate processes relative to the disease state. The GO terms assembled in clusters will either have mixed directionality (both up- and downregulated genes) or will collect genes that have an altered expression consistently in the upward or downward direction. Here, we have carried out this heat mapping process for "proteostasis" (see Figure 2), revealing that most terms are mixed in direction, while some show a consistent directionality. This approach facilitates the examination of dysregulated biological processes in relation to one another, and makes the compensatory nature of the opposing regulation more clear in the context of AD. For example, we observe a downregulation of translation-related anabolic processes and a parallel upregulation of translation and mRNA destabilization (Figure 2). The point-counterpoint biological process regulation observed in the proteostasis domain may suggest that some processes may benefit from moderate stress to facilitate a compensatory response. This concept of moderate stress being beneficial (i.e., hormesis) is observed in numerous biological contexts. The underlying mechanism may be that limited gating of stress confers a resilient phenotype, while an unbalanced hormetic process renders a system more vulnerable to disease pathology.



**FIGURE 2** Proteostasis regulation in LOAD patients. This figure shows changes in families of related biological processes associated with the AD endophenotypic area "proteostasis". We developed computational models for 19 endophenotypes associated with LOAD for large scale data integration. All the graphs in this figure are taken from analysis done utilizing the genes associated with proteostasis. In (A)–(C), we employ the cytoscape java/R application ClueGO to map genes that are AD risk associated and either up- or down-regulated. In this manner, we can identify biological processes that are specifically associated with a unidirectional shift in AD. In (A), the network of linked terms are used to heatmap the

### 3.4 | Creating a neurocentric Connectivity Map for resilience drug repurposing

Another area that has the potential to expedite resilience therapy development is the repurposing of approved and in-development drugs to the field of resilience. The Connectivity Map (CMap) is a minable resource<sup>48</sup> of gene-expression profiles of human cells treated with small molecules. This resource has been recently used to nominate drugs for resilience.<sup>40</sup> However, one limitation is that most cell lines are cancer cell lines, with no non-cancer neuronal lines present. Nevertheless, CMap reported identifying compounds using AD-related signatures,<sup>48</sup> as noted by the authors: “[...] the neuronal lines are more different from the cancer lines than the cancer lines are from each other, at least in the space of these 189 compounds. Therefore, expanding the cell line set into neuronal cell types may be beneficial.”<sup>49</sup> To improve the identification of resilience drugs, neuronal cells should be included in drug screens. For this purpose, we propose the implementation of the aforementioned iPSC-derived neurons<sup>45</sup> or three-dimensional models (i.e., organoids) in secondary screens to evaluate neuronal activity in already validated assays.<sup>45</sup> These models can be used to define a signature of resilience and mine an established “neuro-CMap” database to determine which drugs shift the molecular profile towards those observed in resilient individuals. Central nervous system (CNS)-penetrant drugs and closely related compounds with known effects on neuronal function should be prioritized. Importantly, to move forward with resilience drug candidates, mechanisms of action would not be needed at this stage.

Finally, during the workshop, modeling aging in *in vitro* models was discussed, as aging is the biggest risk factor for AD. It was noted that studying the impact of rapid aging on cellular processes under pathological conditions can help determine resilience mechanisms that lead to cell survival versus death.

## 4 | DE-RISKING CLINICAL TRANSLATION

Preclinical and clinical studies must be integrated to validate therapeutic targets and biomarkers of ADRD, ultimately enabling translation. Doing so requires collaboration between academic laboratories and pharmaceutical companies, as both settings offer unique and essential resources and insights into drug and biomarker development. Unfortunately, standardized approaches for collaboration between academia and pharma are limited; however, the Accelerated Medicines Partnerships for AD (AMP-AD) is a good example of how academia and pharma can work together. Therefore, we propose suggestions for biomarker identification in the context of a standardized pipeline for collabora-

tion between academia and pharma that will expedite the development of new diagnostic and therapeutic tools for ADRD and “de-risk” ADRD clinical trials.

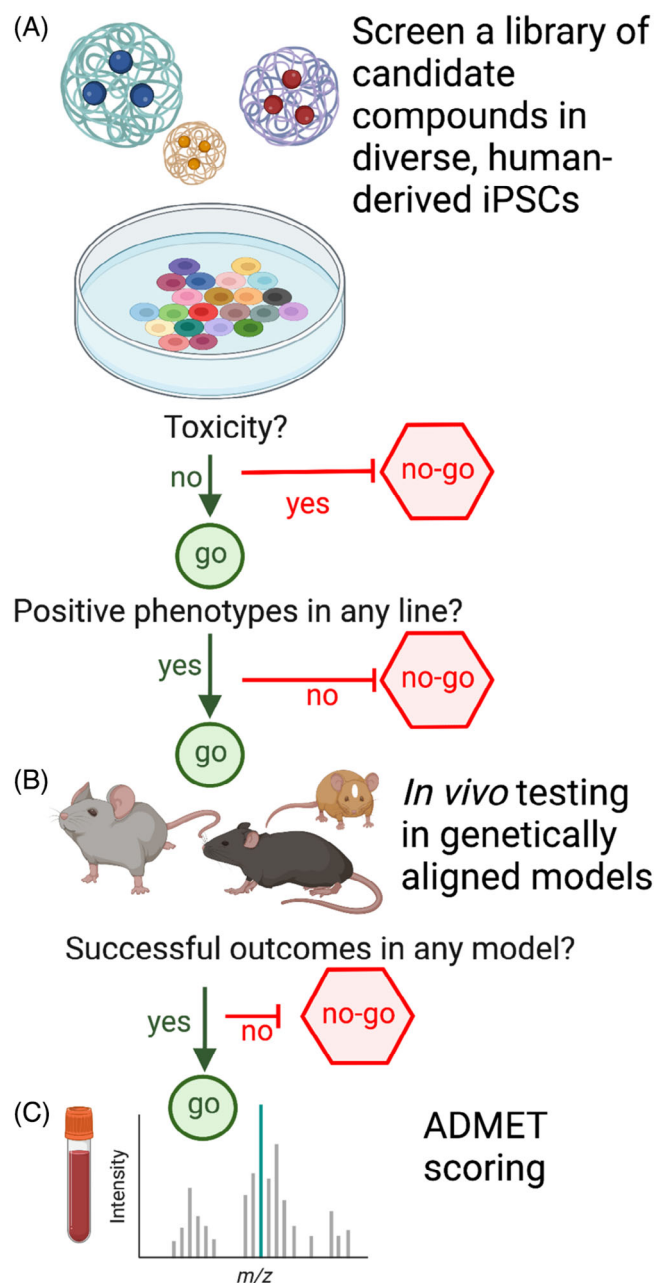
### 4.1 | Biomarkers

Hand-in-hand with novel targets and therapeutic compounds is the identification of valid biomarkers. These are critical for the early identification of patients at higher risk for ADRD, as treatments are likely to be most effective at this stage. Several articles have recently reviewed current biomarkers and ADRD therapeutics – particularly fluid-based biomarkers that include amyloid and tau species; neurofilament light chain; and synaptic, neuroinflammatory, and vascular proteins.<sup>50</sup> However, more effort should be invested toward a unified or standardized panel of ADRD-relevant biomarkers that are non-invasive and inexpensive to obtain – ideally through the primary care physician, home-testing, or other medical appointments – to provide the widest reach that includes the socio-economically and other disadvantaged populations. The standardized panel could include memory assessment, blood-based biomarkers, eye examination, testing of urine or stool, and genetic testing that collectively could indicate increased risk for dementias and provide more granularity regarding the type and stage of dementia. Individuals identified as “at risk” would then be subjected to more invasive and expensive tests to strengthen or confirm the diagnosis, including medical imaging (e.g., PET and MRI) and cerebrospinal fluid biomarkers. The recent success of at-home diagnostic testing kits during the coronavirus disease 2019 (COVID-19) pandemic and at-home genealogical (e.g., 23andMe) testing kits suggests there is strong potential for wider-reaching ADRD diagnostic panels.

### 4.2 | Bridging basic science and pharma

With the large increase in the array of potential therapeutic strategies for ADRD, the validation process becomes ever more important. Identifying the most promising therapies and letting go of those not likely to succeed (fast-fail) is critical. The “fast-fail” ideology is centered around the fact that most clinical trials will fail and that it is of the utmost importance to eliminate them earlier in development to reduce costs.<sup>51</sup> Currently, therapeutic development for AD-related and other drugs is envisioned very differently in the academic versus the biotech/pharma setting. Academic labs use public funds (i.e., National Institutes of Health [NIH] or foundation grants) to focus on basic science and often do not move beyond the discovery stages. Large pharmaceutical companies and smaller biotechs, while focused on all the stages of

network of processes that are either upregulated (red) or down-regulated (blue). (B) The metrics associated with global patterns of up-regulated biological processes are grouped together into related terms and represented by lead term in the pie chart. (C) The down-regulated processes are aggregated and shown by lead term. In (D), a conceptual representation of opposing directions of linked processes are demonstrated within macromolecular synthesis, vesicle trafficking associated with protein maturation, protein homeostasis, and synaptic function. The regulation of processes suggests a direct and oppositional response within proteostatic subdomains indicative of counter-regulation, potentially suggestive of hormesis. AD, Alzheimer's disease; LOAD, late-onset AD.



**FIGURE 3** Go/No Go pipeline to de-risk preclinical trials. An example of a testing pipeline for prioritized targets. (A) Ideally, prioritized drug candidates would first be tested in vitro in a panel of genetically diverse, patient-derived iPSCs. If toxicity were to consistently occur in any such stem cell population, further testing would not continue in relevant genetic contexts (no-go). Similarly, lack of positive response in any stem cell line would end testing for this compound. (B) If any iPSC population exhibited promising responses, follow-up in vivo experiments would be conducted using mice with appropriate genetic alignment. Lack of successful outcome measures in these mice would end further testing. (C) Successful treatment in at least one mouse model would warrant the establishment of an ADMET score. As an example, if we consider a screen for compounds to increase synaptic density (phenotype) in neurons (cells), any indication that the compound was toxic to neurons, or did not show an increase in synaptic density would not pass the go/no-go gates. (A) If successful, however, the compound would go on to be tested in diverse mouse strains to represent the likely diverse responses that would be

drug discovery, encompass more of the latter part of the drug-testing pipeline, such as in vivo efficacy, pharmacokinetic/pharmacodynamic, and lead optimization. They have large capitals (e.g., investor dollars) and must make quick decisions – too often not dependent on efficacy – about whether a drug is worth further development. This knowledge is filed away in case a particular molecule becomes a viable candidate later. Unfortunately, due to a magnitude of factors such as intellectual ownership, regulatory and privacy issues, as well as speed of development, crosstalk and partnerships between academia and pharma are rare. All the data behind these “abandoned” compounds is lost and may lead to a significant waste of resources across pharma and academia to repeat the same studies. This results in what is known as the “Valley of Death” between academia and pharma.<sup>52</sup> While some NIH-funded programs aim to bridge this gap by facilitating partnerships between academic institutions and small biotechs (i.e., Small Business Innovation Research and Small Business Technology Transfer), these are small awards (\$50K–\$200K) and are underutilized.

What can be done to overcome this “Valley of Death” apart from establishing multiple small biotechs associated with individual academic labs? It is agreed upon that collaboration generally yields better results than individuals alone, that centralized resources (especially financial) lead to more productivity, and that, once a target has been prioritized, target-engagement studies should be conducted in order to decrease expensiveness. To build upon these concepts, it would be helpful to have a standard pipeline defining how academic scientists should collaborate with pharma and when studies should be transferred between these settings to de-risk partnerships.

One possible pipeline is outlined in Figure 3. First, as more is learned about AD/ADRD and the multitude of different risk or resilience factors that define the aging population, the group agreed that accounting for genetic diversity during testing is critical at all stages: from in vitro to in vivo target engagement and efficacy assessments. While academic scientists have started to embrace this approach, it is less prevalent in industry. After adopting a target-based approach to scout for implicated pathways or mechanisms, an ideal testing pipeline would use tool compound libraries in a panel of genetically diverse, patient-derived iPSCs. If a compound is successful in at least one of these cell lines it could be moved forward to in vivo testing in an animal model that matches the defining genetics of that cell line alongside other selected, genetically diverse models. Similarly, if a compound induces a negative effect, such as toxicity in one of the iPSC lines, further development would be halted (a “no-go”). This approach aligns with “fast-fail” in order to save money, time, and effort and allow for development of other promising candidates. Successful in vivo testing in one or multiple models would then lead to the establishment of an ADMET (chemical Absorption, Distribution, Metabolism, Excretion, and Toxicity) score<sup>53</sup> as well as the “right time to drug” or begin treatment. While this

observed in the human population. If a compound showed increase in synaptic densities in vivo in at least one mouse model, (B) that compound would go on to ADMET scoring (C). ADMET, chemical absorption, distribution, metabolism, excretion, and toxicity; iPSC, induced pluripotent stem cells.



pipeline represents a powerful preclinical testing strategy, it remains to be determined who should shoulder the financial burden of the pipeline and at what time a compound would be “de-risked” enough to be adopted by pharma.

In clinical trials, it is essential to establish drug-specific outcomes based on the chosen biomarkers to enable mechanism-based studies that precede large monetary investments into costly clinical phases.<sup>51</sup> PET imaging and cerebrospinal fluid analysis have been used as clinical diagnostics with an accuracy of nearly 90%.<sup>54</sup> However, these methods are expensive, invasive, and not widely available, especially in rural areas, presenting an obstacle to best match the timing of treatment with the patients most likely to benefit. A growing number of studies are investigating less invasive ocular and blood biomarkers. However, these biomarkers have not yet been studied in controlled longitudinal studies. Once established biomarkers for AD-relevant biological processes are identified, ADRD research will be better poised to test therapeutics with greater efficiency and enable the implementation of the “fast-fail” strategy.

### 4.3 | Changing inclusion/exclusion criteria in clinical trials toward precision medicine

Given the heterogeneity of ADRD clinical presentation and patient genetics, subjects in intervention trials and observational/biomarker studies must reflect the patient population. Limited representativeness in sample populations is an active area of concern for the National Institute of Aging (NIA) and the Alzheimer's Association. In fact, the NIA recently outlined the National Strategy for Recruitment and Participation in ADRD Clinical Research.<sup>55</sup> The Alzheimer's Association, the largest private AD research-funding and lobbying organization, has also outlined strategies for improving the recruitment of diverse populations for clinical trials. These include devising strategies to address the historically low participation of underserved populations (e.g., people are more likely to participate in clinical studies if someone of their same race invites them; more participants can be recruited by extending clinical study opportunities in rural areas) and reconsidering limiting exclusion criteria that disproportionately affect underrepresented groups. Importantly, exclusion criteria that include common comorbidities are inadvisable, as these comorbidities may be closely linked to the clinical features and progression of AD. Strikingly, the clinical trial population for the phase III study for aducanumab was non-representative of race/ethnicity (e.g., <1% of participants were Black individuals), comorbidities, and disease features<sup>56</sup>; the trial also excluded patients with a history of cardiovascular, kidney, liver, blood disease, among others. According to a recent study of Medicare recipients >90% of patients with AD/ADRD/mild cognitive impairment do not meet inclusion criteria and could be expected to respond poorly to the drug.<sup>56</sup> Moreover, the aducanumab trials indicated that APOE $\epsilon$ 4 carriers are also more susceptible to adverse outcomes, further highlighting the importance of considering gene-by-intervention (GxI) interactions for both efficacy and adverse outcomes. Thus, to develop therapies that cater to a wider range of individuals, we must

study disease mechanisms and therapies within patient populations that are more inclusive and representative.

Genetic differences across diverse populations may lead to different disease presentations and therapy responses. There are several subtypes of AD, defined molecularly, pathophysiologically, and symptomatically (e.g., tau-dominant, amyloid-dominant, synapse dysfunction-dominant, immune-dominant, etc.; behavioral variant versus memory variant, minimal atrophy, limbic-predominant, hippocampal-sparing, AD with vascular or CAA components, etc.). Rather than a “one-size-fits-all” approach targeting one feature of the disease (e.g., amyloid deposits), treatment strategies for AD should be tailored to target-specific disease mechanisms that vary across subtypes/individuals. Genetic context may also affect how individuals respond to drug or behavioral interventions, a concept demonstrated in oncology. In oncology, it is relatively common to genotype patients for particular mutations (e.g., BRCA1/2 mutations) in order to characterize the disease and predict treatment response and thus tailor treatment strategies to the individual. In many cases, molecularly phenotyping tumors using companion diagnostics is used in the same way. For example, breast/gastric/adeno tissues may be tested for overexpression of the human epidermal growth factor receptor 2 (HER2) gene/protein in order to assess the feasibility of trastuzumab treatment.

Other highly individualized approaches are being tested and are likely to reach clinical practice soon. For instance, the patient-derived xenograft, also known as Cancer Avatar, programs at JAX and other institutions across the globe allow researchers and clinicians to test therapies in tissue derived from patient tumors (or humanized animal models) to measure responses to therapies and thus choose the best therapeutic strategies for each person or cancer subtype.<sup>57</sup> Besides cancer, preclinical studies of alcohol/substance abuse and certain psychiatric conditions show clear GxI interactions, even for behavioral interventions.<sup>58</sup> Thus, the future may hold promise for the routine implementation of genotyping to predict who will respond better to therapy, even in the case of highly complex disorders. For example, if we have tested a particular pathway in the applicable preclinical model that is relevant to a person's genotype, inclusion criteria would be based on the presence of a biomarker that correlates with that pathway.

## 5 | UNITING AND HARMONIZING DATA

The proliferation of large-scale genetic and genome-scale molecular assays (e.g., transcriptomics, proteomics, metabolomics) has substantially expanded the characterization of dementias and broadened the landscape of potential therapeutics. The structured nature of molecular phenotypes, which can commonly be defined by their molecular features (e.g., genes) with abundant functional annotations (e.g., kyoto encyclopedia of genes and genomes (KEGG) pathways), enables reliable data integration across species, assays, and biological contexts. As these systems biology approaches to studying dementia mature, we advocate for improved communication between data repositories and



analytical tools. Additionally, with the expanded use of cellular models, we envision a federated data ecosystem in which researchers can build on prior experiments to accelerate the next steps in their research programs.

## 5.1 | Status today

AD research already benefits from a set of centralized systems created for broad data dissemination. These resources commonly aim to provide data access following findable, accessible, interoperable, and reusable (FAIR) principles. Such standards require significant investments in data management infrastructure, expert curation, and intuitive user interfaces. Notably, the AD research field has benefitted from strong supporters of FAIR resources, with the NIA being a key leader in their creation. The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) has become the preeminent national repository for AD genetics data, while the AD Knowledge Portal collects multi-omics studies of AD in the AMP-AD. Both platforms provide access to raw data with appropriate deidentification for human subjects as well as interactive tools to obtain summary-level outcomes from multiple studies (GenomicsDB and Agora). This ability to utilize AD data at multiple levels maximizes community engagement by allowing both detailed reanalysis of full data sets and rapid data-driven assessment of individual molecules for disease relevance. These advanced data platforms will greatly improve the power of studies in experimental systems. The use of model systems, from cells to rodents to non-human primates, remains the primary strategy for understanding the origins and progression of AD. Molecular and physiological assays have become increasingly translatable through genetic homology, shared metabolites, and cross-species anatomical maps. These advances often enable the direct alignment of experimental outcomes with human-study data informing the design of further mechanistic studies in model systems.

One notable example is the ROSMAP-IN study, which leveraged the expansive ROSMAP data resource to create and analyze iPSC lines in the context of known donor outcomes (see Section 2.2 also). By repeating the same transcriptomic and proteomic assays that were previously used to characterize postmortem brain tissues on differentiated iPSC neural lineages, researchers were able to confirm broad agreement of molecular phenotypes at the individual level.<sup>45</sup> Such analyses can guide functional studies in multiple cell types to investigate genetic risk for AD. Furthermore, the concurrent curation and release of these data through the AD Knowledge Portal allowed immediate sharing of the data with the scientific community. A similar strategy is being used by the MODEL-AD consortium, which was established in 2016 to create new mouse models based on late-onset genetics. This project edits candidate genetic variants into mouse strains and follows AMP-AD molecular phenotyping to characterize the disease relevance of each introduced variant. Mouse models can then be matched with targeted mechanisms of action in preclinical studies of new therapeutic candidates. In addition to the unrestricted distribution of all mouse strains, all MODEL-AD data are distributed through the AD Knowledge Portal

and supported by an interactive data explorer (modeladexplorer.org). While data from experimental platforms are often readily organized and disseminated once appropriate resources are allotted, managing human-study data presents ongoing challenges. Although genetic studies often collect rich biomarker and subject-health data, the necessity of large sample sizes for sufficient statistical power reduces the outcomes to binary case-control status that can be easily standardized across multiple study cohorts. The result is a mix of very large, superficially phenotyped datasets, such as in the Alzheimer's Disease Sequencing Project (ADSP), and relatively small, well-characterized datasets, such as in ADNI and AMP-AD. Greater curation of existing and future data into datasets that scale from richly phenotyped small-to-medium data up to very large case-control designs would enable users to maximize the utility of public data.

## 5.2 | Uniting data in the short term

Efforts are now in place to begin the process of cross-cohort data harmonization. Heterogeneity in clinical measures of cognition has limited joint analyses, and new workflows have been designed to harmonize and co-calibrate these data across multiple studies (see Section 3.1.3).<sup>59</sup> This approach, which has merged data for over 76,000 subjects across 10 studies, is designed to include additional studies as data are released. Such efforts can improve the power of association studies and potentially enable robust disease stratification into stages or subtypes. Cross-study data comparison is the focus of the Alzheimer's Disease Preclinical Efficacy Database, which uniformly documents published studies of preclinical efficacy for candidate AD treatments. Data and biospecimen resources of potential importance also reside outside of the existing AD community. For example, the Framingham Heart Study documents health data from multiple generations of individuals. As genetic and other biomarkers become more robustly associated with ADRD, these outside data sources provide a deeper understanding of how dementias intersect with lifelong health and disease metrics (see Section 3.1.3).

Moving forward, the potential for cross-study data integration and cross-species validation will be improved with the increased use of standard reporting and sample collection criteria. FAIR data principles set baselines for accessibility and potential reuse, applicable to all published studies. The TRUST principles have been developed for best practices in transparency, responsibility, user focus, sustainability, and technology for centralized data repositories.<sup>60</sup> Animal research has historically suffered from uneven reporting to lack of standards; the ARRIVE 2.0 Guidelines now provide a contemporary set of practices.<sup>61</sup> Finally, we encourage researchers to use standard experimental techniques and assays when possible, as documented for studies in the AD Knowledge Portal.

Guidance on data reporting and experimental design is especially important for studies of diagnostic and prognostic biomarkers of AD, an active area of research. Progress in this field is reminiscent of the candidate-gene era of AD genetics, in which multiple small-scale studies were pursued independently without having a broader con-

text for the interpretation of target loci. The result was a proliferation of false positives due to the unavoidable combination of low sample numbers and publication bias. Genome-wide association studies and the creation of consortium-level genetics ultimately addressed these issues. With greater data availability and pooling of results, false positives would likely have been recognized from the onset. Therefore, we encourage disseminating of the full results of biomarker studies, ideally using standardized measures for cross-study analysis or direct data harmonization.

Adoption of standard data management and reporting practices by the broader community would ideally be paired with advanced integration of data platforms. Such integrative efforts are already underway in many cases, such as AMP-AD and MODEL-AD, and shared analyses in ADNI and ADSP. Standard data formats, molecular identifiers, and application programming interfaces (APIs) can facilitate federation of existing resources without their redesign or reconstruction. For example, stronger links between the molecular data housed in the AD Knowledge Portal and the genetic-association data in NIAGADS could be based on genomic identifiers and phenotype mappings. The recent creation of the ADSP Functional Genomics Consortium (FunGen-AD), along with the continued funding of AMP-AD provides a natural pathway of increased integration, given the similarities in genome-based analysis present in both programs. Increased integration with other resources such as the Brain Research Through Advancing Innovative Neurotechnologies Initiative, the CRISPRBrain project, and the Allen Brain Atlas might then proceed based on the interfaces developed.

### 5.3 | Uniting data in the long term

In the long term, a fully integrated research ecosystem for ADRD would enable the next generation of researchers to take advantage of a more complete knowledge base than currently provided by curation of scientific literature. Complete data sharing inherently reports both positive and negative results, which is instrumental to overcome the selection biases of current publishing models. New findings could then be assessed in a less biased context of broader work, rather than only buttressed by supportive findings mined from decades of literature. Furthermore, rapid access to experimental data could potentially mitigate the need for validation experiments or, more constructively, immediately refine validation strategies.

We note that this vision to accelerate discovery in ADRD studies will require substantial efforts in data infrastructure, curation, governance, and management. The necessary expertise is only recently becoming recognized and rewarded in academic science, and competition for talent is substantial. Data teams must therefore be well-funded, sustained, and deeply integrated with ongoing research. Such investments are further motivated by the current NIH Data Management and Sharing Policy, which strives toward many of the goals in this section.

## 6 | CONCLUSIONS

The 2022 New Directions for AD Research Workshop at the JAX's Center for Alzheimer's and Dementia Research identified several opportunities to improve the odds of getting successful medication to ADRD patients. Among other considerations, we highlight the need to diversify targets, create a neuro-centric drug screening database, and improve resources utilization. We also concluded that building the best team with the right amount of expertise and experience is essential to the success of both academic and industrial approaches to drug development. We conclude there is still a need to continue to close the gap between academia and pharma through a variety of initiatives including Open Science, recognizing the challenge of evolving metrics by which particularly junior faculty are evaluated in academic institutions. As increasingly larger datasets are being created collecting multiple measurements for each individual (neuropathology, biomarker measures, etc.), more and more data are available to mine for critical risk and resilience factors for ADRD. A key approach is to use this data in a way that allows investigators to "fast-fail" and focus resources on targets/compounds that might be missed with a one-size-fits-all approach to treating ADRD.

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## CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest. G.W.C. has consulted for Astex Therapeutics Ltd. Author disclosures are available in the [Supporting Information](#).

## CONSENT STATEMENT

Consent was not necessary.

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## APPENDIX

### Collaborators

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