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PERSPECTIVE

Pathways to personalized medicine—Embracing heterogeneity for progress in clinical therapeutics research in Alzheimer's disease

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Abstract

Biological and clinical heterogeneity is a major challenge in research for developing new treatments for Alzheimer's disease (AD). AD may be defined by its amyloid beta and tau pathologies, but we recognize that mixed pathologies are common, and that diverse genetics, central nervous system (CNS) and systemic pathophysiological processes, and environmental/experiential factors contribute to AD's diverse clinical and neuropathological features. All these factors are rational targets for therapeutic development; indeed, there are hundreds of candidate pharmacological, dietary, neurostimulation, and lifestyle interventions that show benefits in homogeneous laboratory models. Conventional clinical trial designs accommodate heterogeneity poorly, and this may be one reason that progress in translating candidate interventions has been so difficult. We review the challenges of AD's heterogeneity for the clinical trials enterprise. We then discuss how advances in repeatable biomarkers and digital phenotyping enable novel "single-case" and adaptive trial designs to accelerate therapeutics development, moving us closer to personalized research and medicine for AD.

KEYWORDS
Alzheimer's disease, amyloid, biomarkers, clinical trials, combination therapy, co-morbidities, dementia, digital health, heterogeneity, inflammation, personalized medicine, risk factors, tau

Highlights

- Alzheimer's disease is diverse in its clinical features, course, risks, and biology.
- Typical randomized controlled trials are exclusive and necessarily large to attain arm comparability with broad outcomes.
- Repeated blood biomarkers and digital tracking can improve outcome measure precision and sensitivity.
- This enables the use of novel "single-case" and adaptive trial designs for inclusivity, rigor, and efficiency.

"… practitioners of wide experience have frequently re-echoed the old saw: 'It is more important to know what sort of a patient has the disease than what sort of a disease the patient has.'"[1]

1 | HETEROGENEITY IN ALZHEIMER'S DISEASE AND ITS CONSEQUENCES FOR CLINICAL THERAPEUTICS DEVELOPMENT

1.1 | Biological and clinical heterogeneity in Alzheimer's disease

Alzheimer's disease (AD) may be defined by the presence of amyloid beta (Aβ) and tau protein pathologies in the brain,[2] but we know that myriad genetics, central nervous system (CNS) and systemic pathophysiological processes, and environmental-experiential factors contribute to both AD's essential pathologies and to the protean characteristics and course of its clinical dementia syndrome (Table 1). This heterogeneity presents challenges for researchers and clinicians alike.

Biologically, genetics are an important ground for heterogeneity in AD, from rare deterministic mutations (amyloid precursor protein/presenilin 1/presenilin 2 (*APP/PS1/PS2*)) to strong variants that increase or decrease risk (apolipoprotein E [*APOE*] ε4, *APOE* ε2) and many gene variants of small effect.[3] Neuropathologically, large-scale autopsy studies find that mixed pathologies, especially AD plus cerebrovascular disease, but also TDP-43, other tau, and/or α-synuclein proteinopathies are far more common than pure AD.[4,5] The relative contributions of each of these to AD and its dementia syndrome are difficult to ascertain. In addition, we increasingly recognize many associated pathophysiological processes among people with AD. Underlying the plaque and tangle lesions and gliosis visible under the microscope are a host of invisible molecular abnormalities spanning proteostasis, inflammation, metabolism, neurovascular functioning, and many other homeostatic and repair responses.[6,7] Varying degrees of these exist in vicious cycles—both cause and consequence—further exacerbating amyloid and tau pathologies and promoting neurodegeneration.

Clinically, AD varies widely in its cognitive and behavioral profiles. Diagnosing and tracking progression from pre-clinical stages to mild cognitive impairment (MCI) or dementia can be hard. An amnesia predominant decline is most common, but it is not unusual to see atypical presentations such as aphasia syndromes or apathetic/disinhibited behaviors reminiscent of frontotemporal dementias, or visual processing syndromes with relative sparing of memory. Furthermore, although the degrees of cognitive impairment correlates with the density and extent of AD pathology, the correlation is modest and some people have high levels of AD pathology with minimal cognitive impairment or vice versa.[8] Indeed, adjusted for age, sex, and education, plaque and tangle pathology account for no more than 30%–40% of the variance of cognitive functioning in older adults.[9] This attests to the importance of the many varied or unknown residual factors conferring resistance, reserve, resilience, or vulnerability to the clinical expression of AD pathology. Ages at onset vary widely. AD disease duration until end-stage or death is 6–10 years for most,[10,11] but may be 20 or more years for others, with varying rates of progression at different stages. Cognitive functioning varies within the individual, with good days and bad days.[12] A wide variety of ethnoracial, educational, socioeconomic, sociocultural, dietary, lifestyle, and environmental factors may either increase or decrease vulnerability to the disease, its clinical expression, or the sensitivity of clinical measurements.[13,14]

Finally, most older adults have medical co-morbidities and concurrent medications that impact AD pathology, biology, symptoms, and functioning. This confounds our ability to measure and interpret the response to an AD treatment.[15,16] Eighty percent to 90% of older adults are taking at least one prescription drug, 70%–80% are taking two, and 30%–40% are taking at least five.[17] To further complicate matters for clinical trials, some of the most common medications are themselves of interest for re-purposing in AD, including angiotensin receptor blockers, anti-diabetes drugs, anti-inflammatories, and psychotropics.[18]

1.2 | Consequences for clinical therapeutics research and development

1.2.1 | Targeting single biology in multifactorial disease

Focusing on only one biological feature (e.g., Aβ) in a complicated disease without accounting for others may lead to disappointing results in outcomes. For example, the new anti-amyloid immunotherapies can lower AD's Aβ biomarkers down to normal or near-normal levels with secondary effects of lowering tau biomarkers too.[19–21] However, this appears to only modestly slow the progression of dementia, not stop it. Demonstration of any clinical benefits of amyloid reduction is an important and hard-won scientific advance, but it also underscores that AD's dementia progression is due to more than Aβ, and there is also heterogeneity in treatment responses.[22] Multipronged approaches will be necessary.

1.2.2 | Limitations in the translational value of common non-clinical experimental findings

Hundreds of small molecules, biologicals, gene therapies, biophysical treatments, lifestyle and dietary interventions, supplements, and other approved pharmaceuticals have shown benefit for AD-related phenomena in transgenic mice or other laboratory models of AD. Non-clinical in vivo research commonly compares experimental and control treatments between "groups" of genetically and experientially identical cells or animals. In essence, this is an n-of-1 experiment, with treatment repeated multiple times in virtually the same mouse. Almost all heterogeneity is controlled for, allowing sensitive detection of signal above random confounds' noise (and yet there is still variability in response). Much is learned about the pharmacological, biological, or

TABLE 1 Heterogeneities affecting clinical research and personalized medicine in AD.

Signs, Symptoms, Syndromes	**Demographic and Life History**
Cognitive deficits: memory, executive, language, visual	Age at onset
Neurobehavioral features: mood, anxiety, psychosis, apathy, disinhibition	Sex
Major variants: amnestic, posterior cortical atrophy, logopenic primary progressive aphasia, behavioral	Gender
Clinical Stages	Sexual orientation
Asymptomatic/pre-symptomatic/resilient	Race
Mild cognitive impairment/prodromal	Ethnicity
Dementia, mild/moderate/severe/agonal	Education
Neuropathology	Socioeconomic status
Mixed pathologies	Cultural factors
Thal phases of amyloid plaques	Nutrition and diet
Braak stages of tau neurofibrillary tangles	Environmental exposures
Tau strains	Habits and other lifestyle
Cerebral amyloid angiopathy	Health care access
TDP-43	Stress
α-Synuclein	**Health**
Gliosis	Co-morbidities: systemic, neurologic and psychiatric
Cerebrovascular	Concurrent medications and dietary supplements
Course	**Pathophysiology**
Age at onset	Protein synthesis, folding, post-translational modification
Progression stable, slow – > rapid	Proteolysis, autophagy, proteasome
Genetics	Inflammation and immune dysregulation
APOE	Oxidative stress
Familial PS1/PS2/APP	Metabolism
Polygenic risk and small effect variants	Mitochondrial/bioenergetic
	Vascular
	Neuroprotection
	Neuroplasticity

Abbreviations: AD, Alzhemer's disease; *APOE*, *apolipoprotein E*; PS1, presenilin 1; PS2, presenilin 2; APP, amyloid precursor protein.

behavioral effects, but no animal or cell culture models encompass the plethora of neuropathology, heterogeneous backgrounds, lived experiences, and uniquely human features of dementia in people with AD. The generalizability of findings to mice of other genetic backgrounds, ages, or environmental exposures is rarely explored. When diverse genetic strains of mice have been compared for the effects of the 5XFAD APP or p301L tau transgenes, for example, *multifold differences* have been observed in amyloid pathology, tau propagation, gliosis, and behavior.[23,24] Perhaps if such research included more genetic, age, and environmental diversity, fewer but more robust treatment candidates would emerge with greater likelihood of benefit in human AD. Another strategy for non-clinical evaluation of treatment effects amid heterogeneity might be to sequentially test in animal or cell models of increasing complexity with mixed pathologies. There are informative conditional transgenic and other models for Aβ, tau, α-synuclein, TDP-43, cerebrovascular, metabolic, and other disease processes in AD and related dementias. This is already done to limited degrees. Examples include the 3xTg amyloid and tau transgenic mouse,[25] and various Aβ and tau transgenic mice plus viral-mediated overexpression of α-synuclein or atherosclerosis.[26,27] Investigated systematically, much can be learned about how these different pathologies interact, and how well candidate treatments for proteostasis, vascular injury, metabolism, or inflammation, for example, prevent neurodegeneration in heterogeneous, complex disease.

1.2.3 | Limitations of conventional parallel group experimental designs in clinical research

Candidate drugs enter Phase 2 clinical trials seeking signals of efficacy based on compelling biological mechanisms of action, promising pharmacological activity in non-clinical models, and favorable safety data from non-clinical toxicology studies and Phase 1 trials. In terms of study design, the parallel-group, randomized, placebo-controlled trial is considered the gold standard trial design for drug development[28] and is used in the overwhelming majority of Phase 2 clinical trials in AD and all Phase 3 trials for common diseases. In this design, participants are randomly allocated to placebo or one or more active treatment arms run in parallel and then the average effects of the treatment in each group are compared. Treatment arm groups are necessarily large to achieve average comparability of demographics and clinical and disease severity amidst the heterogeneity of disease pathology, clinical symptoms, rates of progression, and diversity of people. They are complex to manage and paralyzingly expensive, with Phase 2 trials costing tens of millions of dollars, or more.[29,30]

Participants in the parallel arms need to be as comparable as possible to interpret efficacy signal above heterogeneity's noise. The three main design strategies used to achieve this are to narrow eligibility for purer samples, balance who is in each arm for known potential confounds using stratified randomization, and enlarge sample size to

enable the randomization to effectively achieve this goal. Each comes with drawbacks—scientific, practical, and ethical.

Restrictive eligibility reduces heterogeneity by selecting the people for whom the drug may be hypothesized to work best or in whom one can most reliably measure an effect. Common exclusion criteria include age, language proficiency, education, standardized cognitive test scores (too high, too low), biomarkers of AD pathology (too much, too little), atypical AD syndromes, medical and psychiatric comorbidities, concurrent medications, and more. However, overly restrictive eligbility criteria create rarefied samples that lack representativeness of the majority of people with AD and are vulnerable to missing those persons or those forms of AD for which the drug may be helpful. Practically, screen failure rates may approach 90%,[31] increasing the time and expense for full enrollment. Such exclusionary criteria also are systematically discriminatory. In the United States and Europe at least, typical eligibility criteria favor White, educated, affluent people who have had good health care and are culturally comfortable with the medical research enterprise over people of color, ethnicities, socioeconomics, lifestyles, and health issues that themselves are risk factors for the diseases we investigate. Eligibility criteria do not accommodate the well-known ethnoracial differences in performances on tests used in eligibility screening and for possible differences in normative values for AD biomarkers.[32–34]

Balancing parallel groups for known or presumed confounds through stratified randomization attenuates the effects of heterogeneity at the time of randomization. Common factors for balancing include age, sex, education, cognitive impairment, *APOE* genotype, and more recently, amyloid and tau pathology measured with positron emission tomography (PET). But many other known contributors to progression are not included such as common co-morbidities (e.g., diabetes, hypertension, and depression) and common medications, some of which are themselves under investigation for dementia. Better balancing for other biomarkers, such as inflammatory, vascular, metabolic, renal, or even cerebral atrophy could be important in parallel designs, but given our still limited knowledge about their roles in AD, they are rarely measured or considered. With all this complexity, Phase 3 trials typically do not utilize more than a few strata, if any.

The remaining solution is to increase sample size to dilute or average out the effects of uncertain, unknown, or random confounds. For 382 *Phase 2* drug, biological, dietary supplement, or neurostimulation treatment trials for AD or MCI listed in clinicaltrials.gov since 2000, a total of 337 were parallel-group randomized controlled trials with an average enrollment of 170 (median 120, data accessed January 1, 2024). This requires many sites and/or lengthy enrollment periods, introducing yet other kinds of assessment and sociodemographic heterogeneities, as well as the complexity and expense of site training and monitoring. Special efforts may be expended to increase participation by under-represented groups, but this is in tension with the need for comparability of participants and enrollment pace. It is scientifically and ethically imperative to do so but requires further expansion of sample size, recruitment effort, time, and expense.

1.2.4 | Universal outcome measures

Parallel designs strive for comparable groups that are then assessed for outcomes that are suitably broad for all participants. The administration of commonly used standardized cognitive tests and test batteries favored by regulatory agencies like the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) is variable[35] and may lack sensitivity to the changes in cognition and function that might be most meaningful to one or another participant in a heterogeneous group and may be especially unsuitable for members of minoritized groups poorly represented in the development of these tests.[36] Variable or uncommon manifestations of AD are ignored if not excluded (e.g., visual, language, or frontal variants). While looking for average outcomes, true responses at the individual level can be missed. More personalized measures like the Clinician's Interview-Based Impression of Change Plus caregiver input (CIBIC-Plus) or Goal Attainment Scaling (GAS) measures might accommodate heterogeneity better[37] but are still vulnerable to many biases. Finally, trial durations are necessarily long to detect enough change above the heterogeneous rates of progression and variable clinical performances (good and bad days) measured only a handful of times over a year or two.

1.2.5 | Reporting of clinical trial results

Just as AD is heterogeneous in its disease biology and clinical features, it is likely to be heterogeneous in its responses to any given treatment. Efficacy is typically reported as the average difference between experimental and control groups for a top-line, primary endpoint (e.g., a global measure of cognition or function) that is either statistically significant or not. If the primary outcome is not met, secondary and exploratory outcomes are discounted or ignored irrespective of what they showed, and the development of that treatment stalls. Responder analyses for efficacy, if undertaken, are rarely reported and we do not learn if anyone benefited in a negative study or who benefited in a positive study. In the example of lecanemab reporting, we appreciate that the drug slowed clinical decline by an average of 27% after 18 months of antibody treatment compared to placebo treatment.[19] In secondary analyses, we see that male patients seemed to improve more than female patients and older people more than younger. However, even in large trials like this where subgroup analyses are reported, effect size and statistical power for secondary analyses may be lacking to draw confident conclusions. This should not detract from the primary outcome, but follow-up studies or different analytical approaches that carefully identify "responders" would be very informative to fully understand for whom the treatment was effective and how much so. Some reasons for not reporting may have to do with the insensitivity and imprecision of endpoint measures for any given person, high rates of placebo response, and limitations of conventional data analytic methods to identify true responders with some degree of statistical confidence. Furthermore, there may be complex underpinnings to response related to unobserved factors and, therefore, inferences

about responders may be subject to misinterpretation. With new and emerging statistical techniques such as counterfactual prognostic models and machine learning, we can now generate more reliable individual-level predictions, for example, constructing individual treatment response (ITR) scores using multi-modal baseline information on a training set to reveal covariates-treatment interactions.[22,38]

Insufficiently informative reporting of trials also may be related to the constraints of regulatory approval pathways as well as economic interests within the health care investment community driving drug development. Regulatory agencies are responsible for protecting the *public health* by ensuring the safety and efficacy of drugs, biological products, medical devices, and so forth. This population orientation may at times be in tension with the *individual patient* orientation of health care practitioners. If a drug does not show statistical benefit in the population with the indication for which it is intended, it cannot move forward. Yet within that population there may be subgroups or individuals for whom the drug really worked. Responder analyses might elucidate these, but the consequence might be having to redefine the indication, setting development back to conduct more trials. This is inefficient and costly.

2 | APPROACHES TO EMBRACE HETEROGENEITY AND ACCELERATE THERAPEUTICS DEVELOPMENT

2.1 | Biomarker profiling

Transformational advances in biomarkers and digital health technologies now provide a host of new diagnostic and assessment tools to enrich our understanding of each person's AD and they enable more powerful trial designs to measure treatment effects. These can accommodate individual differences and evaluate treatment responses at the individual level with greater rigor.

2.1.1 | Imaging and biofluid biomarkers for AD "AT(N)"

Among the major biomarkers for aging and dementia, PET imaging for amyloid (A) and tau (T) is now generally accepted as proxy for gold standard AD histopathology. Cerebrospinal fluid (CSF) measures of Aβ1–42 and Aβ1–40, total tau (t-tau), and several phospho-isoforms of tau (p-tau) are also well established. Measurement of p-tau and Aβ in plasma is rapidly improving, now with 90+% accuracy in predicting amyloid PET or CSF AD biomarkers.[39,40] Along with amyloid and tau biomarkers, multi-sequence MRI can be used to gauge vascular contributions in the form of infarcts, small vessel ischemic disease, and cerebral amyloid angiopathy, as well as for rough staging of neurodegeneration (N) by patterns of atrophy. Measuring "AT(N)" biomarkers is now essential when considering amyloid-specific immunotherapies where amyloid pathology must be confirmed to ensure potential benefit and amyloid angiopathy must be recognized to avoid undue risk.

2.1.2 | Blood-based biomarkers

The measurement of AD-related proteins in blood[39,40] is a tremendous achievement for clinical chemistry, and the minimal risk, broad accessibility, low burden, and economy of blood collection are transforming clinical diagnosis and research for AD. Until recently, quantifying very low levels of brain-specific proteins, including Aβ and tau diluted in the vast blood pool was not possible. But new ultrasensitive reagents and microfluidic, electrochemiluminescent, aptamer, nucleic acid tagged proximity extension assay, and mass spectrometric technologies now provide unprecedented sensitivity. Different proteoforms of tau, especially p-tau^{181}, p-tau^{217}, and p-tau^{231} have shown the most benefit for diagnosis and possibly for staging AD too.[41] Aβ proteoforms measured with mass spectrometry also show good discriminatory reliability, especially in combination with other features.[42] And data for other biomarkers such as neurofilament proteins (e.g., neurofilament light [NfL]) and glial fibrillary acidic protein (GFAP) are also accruing to characterize their utility.

Blood-based biomarkers for brain disorders have limitations though. They are most useful for CNS-specific (or CNS-predominant) proteins like brain-specific p-tau, GFAP, or NfL. Other interesting proteins, especially inflammatory, metabolic, and vascular proteins produced in the brain in AD are diluted in blood amid those same proteins produced by other tissues throughout the body. Increased or decreased levels of such proteins measured in blood cannot be confidently attributed to the AD affecting the brain. This issue prompted interest in neural-derived and glial-derived exosomes for measurement of intracellular proteins and RNAs, although this promising area is still fraught with technical challenges and difficulties in replicability. Finally, blood levels of all proteins (CNS or not) are affected by systemic metabolism and excretion that may differ among people, potentially confounding interpretation of the measurements. Nonetheless, as these challenges are overcome, we will see new molecular biomarkers of neuroinflammation, cerebrovascular dysfunction, neurometabolism, and other processes yielding greater insights and person-specific targets for intervention.

2.1.3 | Biomarkers for broader profiling of multiple pathophysiological processes

As blood-based biomarkers for AD make great strides, CSF remains an important, accessible biofluid for biomarkers of neurodegenerative dementias beyond Aβ and tau. In continuity with the brain's interstitial fluid, CSF is enriched in proteins and other biochemicals secreted, excreted, or otherwise released from neurons, glia, and the cerebral vasculature. CSF biomarkers showing promise include α-synuclein seeding assays for Lewy body diseases,[43] tau seeding assays for tauopathies,[44,45] synaptic and axonal degeneration (e.g., neurogranin, post-synaptic density protein 95 [PSD95], NfL),[46,47] and gliosis (e.g., GFAP, chitinase-3-like protein 1 [YKL-40], soluble triggering receptor expressed on myeloid cells 2 [sTREM2]). There are many other assays of brain-generated proteins enriched in CSF that may be informative

for a host of other pathophysiological processes relevant to AD, including inflammation, metabolism, oxidative stress, and vascular integrity. Profiling these can be useful for identifying those pathophysiological processes most active in a given person's disease and can guide personalized treatment and monitoring.

2.1.4 | Digital health "biomarkers" for ecological, person-specific clinical profiling and tracking

Digital health technologies, including wearables, smartphone apps, and remote monitoring systems are also changing the landscape of research in AD and related dementias (ADRD), providing valuable data for early detection, tracking progression, and evaluating treatment effects.[48–50] Smartwatches or other wearable sensor devices can collect continuous physiological data, such as pulse, electrocardiograms, electrodermal response, movement, gait, falls, and geolocation. With such massive amounts of data, both a priori and artificial intelligence (AI) driven, analyses detect changes in behavior and physiology associated with AD within the individual. Tablets, online platforms, and smartphone apps enable researchers to administer standardized cognitive tests remotely. Speech can be recorded to monitor language and voice features associated with dementias, including word-finding, grammar, fluency, articulation, and acoustics.[51,52] Finally, sensors in people's homes can track daily activities, sleep patterns, medication adherence, socialization, and other behavioral changes.

Among the key advantages of these new digital health tools are the density, continuity, saturation of learning effects, and ecological authenticity of data collected in people's natural environments. This contrasts with the sparsely administered, formalized, and stressful neuropsychological assessments in office settings. Averaging densely sampled data in the wild may give a more precise and accurate measurement of neurocognitive behaviors and physiology over time. This increases sensitivity to detect change within the individual with disease progression or intervention. In clinical trials or clinical practice, it reduces the chances of missing true change in outcomes assessments conducted amid the "good days and bad days" of infrequently scheduled visits.

A historic limitation of digital health assessment in AD clinical research has been the older generations' unfamiliarity with computers, smartphones, and other digital technologies. This is rapidly changing as Baby Boomers, who are more comfortable with digital technologies, enter the vulnerable ages for AD and health technology designers increase their focus on this demographic.[53]

Biomarkers as surrogate endpoints

The biomarkers field is booming, and knowledge about how well biomarkers (biological or digital) predict or track disease and dementia is growing rapidly. Whether that knowledge is now sufficiently mature to justify biomarkers as surrogates for clinically meaningful outcomes in trials is controversial,[54] even for the best-established biomarkers like amyloid PET. At present, they can be considered only as suggestive of potential clinical effect, and thus their best role may be as endpoints in Phase 2 trials where the goal is to vet treatment effects biologically and clinically to the degree possible with smaller scale, shorter duration and lower expense studies than in Phase 3 pivotal trials. Ultimately, clinically meaningful slowing, stopping, or improvement of dementia must be determined by clinical means, such as survival, activities of daily living assessment, patient and caregiver feedback, and health care utilization. With the continued inclusion of biomarkers in all phases of treatment development, some biomarkers may advance to a point where their surrogacy for some outcomes can be established. It is important to note that this will greatly enable primary and secondary prevention studies where the only clinically meaningful outcome is the maintenance of good cognition, function, and general health.

2.2 | Experimental designs to better accommodate heterogeneity and increase efficiency

Biomarkers and digital assessment tools enable alternative, more powerful experimental designs that can better accommodate heterogeneity while more efficiently testing for efficacy in smaller numbers of participants. Some strategies that may be especially powerful in the pilot, feasibility, early and middle stages of development to de-risk subsequent pivotal trials for regulatory approval include "single-case" experimental designs and iterative, small trials, especially with Bayesian responsive adaptive designs. Findings that replicate in multiple trials in Phase 2 provide more confidence for moving the treatment into Phase 3, and trials can be woven into a seamless Phase 2/3 program with pre-specified stopping rules and futility analyses along the way, facilitated by Bayesian methods.

2.2.1 | Single-case efficacy experimental design for personalized research

"Single-case", "within-person," or "N-of-1" designs encompass a family of experimental designs in which each person is the experimental unit serving as their own control.[55,56] Investigators repeat measurements of a dependent outcome variable before and after introducing the independent intervention variable. In most AD trials, biomarker or clinical measures are administered once at baseline, once at the end of the study, and maybe a few times between. In contrast, low-burden blood and digital biomarkers allow repeated measures in lead-in or placebo conditions, yielding baseline averages with variability for more precise estimates of biological or clinical states. Repeated measurements continue as participants then receive active treatment. Person-specific distributions of outcome measures in each condition can be compared descriptively and statistically. With each person compared to themselves, most heterogeneities are controlled, and precision, sensitivity, and confidence about change are maximized with the repeated outcome measurements. Such designs have been used commonly in education, psychology, and occupational therapy research, where the heterogeneity of behaviors and bespoke intervention strategies often preclude group designs.[57] Single-case experimental designs also have

played roles in medicine, especially in chronic respiratory, dermatologic, digestive, or orthopedic pain conditions for medication initiation and discontinuation studies. They are used increasingly in precision cancer research and care. In rare or unique diseases, they are the only viable experimental design.

Single-case experimental designs have many variations. At their simplest, a control reference period "A" is followed by an experimental treatment period "B," with repeated outcomes measures throughout. A slightly more complicated design is A-B-A, where the experimental treatment is withdrawn to see if measures return to baseline. Classic crossover trials where participants are randomized to either an A-B or a B-A sequence is yet another variation. A-B-A and classic crossover trials are especially useful when little carry-over is expected, for example, for rapid symptom relief in relatively stable chronic or very slowly progressive illnesses (e.g., dopaminergic drugs for Parkinson's disease). They are less useful for disease-modifying treatments or those with long-lived effects. Finally, there are multiple crossover, randomized controlled trials, where participants pass through two or more randomized sequence crossover trials, for example, B-A > A-B > A-B … or A-B > B-A > B-A. These true "N-of-1" trials are especially robust statistically, although still vulnerable to carry over effects, natural time trends, and other random and systematic confounds.[55]

Various strategies can enhance experimental rigor in single-case designs. Repeated measurement is the essential element for precision/reliability of measurement of within-subject change between control and experimental conditions. The baseline control condition can be masked with a placebo or standard-of-care treatment. The timing of the switch to or from experimental treatment may be randomized. Duration of treatment and washout periods can be tailored to the pharmacodynamic effects and the biomarker outcomes (e.g., protein half-life).

There are also vulnerabilities with single-case designs and challenges in their implementation. Although AD progression is relatively slow, there are fast or uneven progressors, the rate of change of which may shift within the trial, making the disease states different between trial phases. Other random factors of time, cumulative practice effects in cognitive outcomes, seasonality, intercurrent illnesses, as well as other uncontrollable life circumstances all can affect a person's trial. Of course, these factors are true for conventional parallel arm designs as well.

Biomarkers may change for different reasons in different people. For example, lower NfL levels may be due to improvement in AD pathology in one person, but weight loss in another, and improved kidney function in another. Findings must be interpreted cautiously both for the individual within the context of all the data accrued and especially if making generalizations from aggregated single-case trials.

Single-case experimental trials are more than anecdotes. Reporting conventions and guidelines have been laid out.[58–60] Properly designed, these trials are interrupted time series under control and experimental conditions where outcomes are assessed repeatedly and rigorously. Data are analyzed with a variety of statistical methods that can accommodate small data samples, autocorrelation, count data, and measure effect size for each individual. Each person's trial stands on its own. However, to consider the generalizability of treatment effect beyond the individual, various analytical and meta-analytical approaches may be used to combine data. The gains in statistical power for such designs over conventional parallel groups of heterogeneous participants are large.[61]

2.2.2 | Bayesian adaptive experimental designs

Bayesian inferential and response-adaptive clinical trial designs[62–65] are now slowly making their way into AD and other neurodegenerative disease trials.[66–70] Practically speaking, all therapeutics research and development begins as "Bayesian," wherein some prior knowledge about a disease including its prevalence, etiological, pathophysiological, and/or clinical features are aligned with a drug or other intervention that addresses those features to create an experiment with a reasonable expectation of measurable efficacy. In traditional clinical trials using a frequentist approach, sample size allocations and type I error allocations are pre-defined, fixed, and followed strictly. In Bayesian adaptive design, the data are evaluated recursively and the posterior parameter distributions are updated and used to modify the trial according to a priori rules. Hypotheses about treatment effects, eligibility characteristics, and other relevant parameters can be updated as trials proceed. Specialized statistical analyses enabling these modifications often involve computationally intensive modeling, machine learning, and now AI.

A U.S. Food and Drug Administration (FDA) Guidance defined adaptive trial design as "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial."[71] Adaptive trials can allow early termination for efficacy or futility in one or another arm, more rapid ascertainment of safe and effective dose, increasing or decreasing sample size, dynamically changing selection or allocation of participants to treatment arms based on their responses, and modifying biomarkers and clinical criteria for patient stratification, treatment selection, or treatment response. The conduct of these trials is demanding, but the overall efficiency and likelihood of success with sequential trial refinements are improved.

Adaptive designs enable platform trials for AD/ADRD, including umbrella trials where different treatments can be compared between each other and a common placebo arm, and basket trials in which different AD subtypes or related dementias are compared for response to a given drug that might target some common feature (e.g., inflammation) of the different diseases. Adaptively, continuous analysis of real-time data according to pre-specified parameters allows the investigator to "play the winner," advancing effective treatments or removing agents with a low probability of success, or focusing on disease indications or subpopulations in which treatment works. Ethically, the number of participants exposed to ineffective or poorly tolerated treatment is reduced. Economically, conventional trials are long and expensive due to their large and fixed nature. Adaptive designs reduce costs associated with patient recruitment, data collection, and trial duration by optimizing these elements. Analysis and modeling of accumulating

data can enhance statistical power and allow more accurate, reliable inferences and robustness. Ultimately, it is a more efficient path to personalized medicine for AD, as it successively identifies participant-specific characteristics and responses, thereby leading to targeted therapies with the greatest benefit and least risk of harm for the individual.

One limitation of adaptive design in AD is that clinical changes take longer to manifest than outcomes in, for example, tumor size or survival in cancer. By the time we identify the arm or subgroup showing better efficacy in AD, other arms may already be fully enrolled. Therefore, this trial design is better suited for biomarker or other surrogate outcomes, which can change more rapidly and with less variability compared to clinical outcomes. That said, certain plasma biomarkers do fluctuate within individuals over short durations of time,[72] and so factoring in this variability is critical to avoid premature allocation decisions.

3 | COMBINATION THERAPY AND PERSONALIZED MEDICINE FOR MCI AND DEMENTIA DUE TO AD

Since the first description of Aβ as the chief constituent of plaques in 1984,[73] the field's consensus neuropathological definition of AD includes Aβ pathology as its *sine qua non*.[74] Decades of testing the amyloid cascade hypothesis of AD ensued,[75] with Aβ as the foremost target of therapeutics research. The success of new anti-amyloid immunotherapies in lowering Aβ with a convincing slowing of clinical dementia progression, at least for some people, is a major scientific breakthrough in support of a role for Aβ in AD. Reducing Aβ may turn out to be a necessary step in the treatment of AD, but it seems insufficient to stop AD dementia, at least in its symptomatic stages. Perhaps pre-symptomatic treatment will be preventive, or more potent anti-amyloid therapies attacking various proteoforms will be more effective. Still, with increasing appreciation of the heterogeneities of AD, it is almost certain that genetic (e.g., *APOE*), inflammatory, metabolic, and other processes and co-morbidities driving neurodegeneration and dementia will need to be addressed concurrently.

Precision medicine in oncology with biomarkers and combination therapies has led to spectacular advances in survival rates.[76,77] Our accounting of the multiple pathophysiological contributions to AD dementia is far from complete, but there is a growing array of new biomarkers, technologies, and analytics to measure them with greater precision and robustness at the individual level. With continuing improvements and validation, plasma Aβ and tau biomarkers may soon supplant CSF and imaging biomarkers for diagnosis and personalized treatment decision-making for anti-amyloid immunotherapies. *APOE* genotyping will similarly be used, as *APOE* e4 homozygosity may confer an unacceptable risk of amyloid-related imaging abnormalities (ARIA), and new *APOE*-oriented therapies are emerging for which genotyping will be needed.[78] Other emerging biomarkers will delineate key pathophysiological factors and other pressure points that might be addressed in a comprehensive combination treatment plan.

Repeatable blood biomarkers and digital assessment tools can empower personalized disease management in research and likely soon in clinical practice too. For instance, tracking an individual's response to anti-amyloid therapy with plasma biomarkers may help determine responsiveness and if or how long to continue therapy. If biomarkers find no meaningful change over a 6-month or 9-month period, then that person's treatment might be reasonably discontinued. On the other hand, if there is a response, then a return to normal range might prompt tapering or stopping treatment. Should levels rise again, treatment can be re-initiated. Similarly, objective detection of clinical benefit may be facilitated with home-based digital monitoring, which may be more informative than periodic office-based evaluations to guide treatment decisions.

In clinical research, adaptive and/or single-case experimental designs also enable efficient combination therapy trials. Treatments can be implemented sequentially, perhaps with randomization of order and start times to enhance rigor, all the while tracking with repeatable measures within the individual for convincing or meaningful change. In such a design platform, heterogeneity is both used and controlled, accelerating the process of early phase development and determining the benefits for the individual participant.

We are in an extremely exciting era in AD research. Leveraging the advances of accessible, minimally invasive, and easily repeatable blood-based and digital biomarkers for precise biological and functional measurement, along with big data and AI analytics, we advance toward personalized treatment and prevention as we also increase our understanding of this complicated and heterogeneous disease.

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CONSENT STATEMENT

Consent is not necessary.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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