

An Executive Summary

On the Brink of Change: How Academic Data and Machine Learning Can Revolutionize Alzheimer's Drug Development



Bruno Dubois, MD, PhD
President
French Society of Neurology

Professor of Neurology
Dementia Institute of the
University Salpêtrière Hospital
Sorbonne University



Olga Uspenskaya-Cadoz, MD, PhD
Senior Medical Director
CNS Center of Excellence
IQVIA



Yuliya Nigmatullina, PhD
Manager
Next Generation of Clinical
Development Solutions
IQVIA

Introduction

Alzheimer's disease is both a devastating degenerative brain disorder and the most common type of dementia. About 5.7 million Americans live with Alzheimer's today and a new person is diagnosed with the disease every 65 seconds (1, 2). Elderly Americans are more afraid of developing Alzheimer's or dementia (35%) than cancer (34%) and for good reason.

The prognosis is not good, but the future is hopeful when human science meets data science. When scientific expertise and advances in data analytics and innovative technologies—like predictive analytics and machine learning—come together, we can ask better questions and extract more meaningful insights about Alzheimer's disease, while proactively creating a more accurate and predictable picture of the patient pipeline, identifying patients earlier in the diagnosis, optimizing study planning and speeding time to market.

In this white paper, you will:

- Hear about current industry challenges in Alzheimer's drug development and glean insights as to why we must explore new clinical approaches
- Understand the importance of machine learning and predictive analytics for identifying non-diagnosed prodromal Alzheimer's disease patients—and why we must tap into this unexplored general population to bring about real advancement
- Learn why innovative approaches to Alzheimer's drug development are not only necessary, but how they will positively impact the future of Alzheimer's disease for patients and the medical community alike

Challenges and Considerations of Clinical Development in Alzheimer's Disease

More than 100 Alzheimer's agents have failed clinical trials since 1998, and early Alzheimer's trials have a high screen failure rate of about 75%. Only five agents have ever been approved: tacrine (later withdrawn for safety), donepezil, rivastigmine, galantamine, and memantine. Unfortunately, they are only able to provide a moderate symptomatic relief with no impact of disease progression.

Dozens of unsuccessful trials have provided some lessons, which are important to understand since at least 112 potential agents to treat Alzheimer's and its symptoms are currently in clinical trials.

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First, for drug development efforts, it is critical to target Alzheimer's pathology as early as possible before the onset of dementia to lessen the disease's effects. Amyloid deposits and other brain changes associated with Alzheimer's appear more than 20 years before the onset of clinical symptoms. As per Alzheimer's Association, earlier diagnosis (even with no disease-modification treatment yet available) may also save \$7.9 trillion in healthcare costs in the US alone (1, 2).

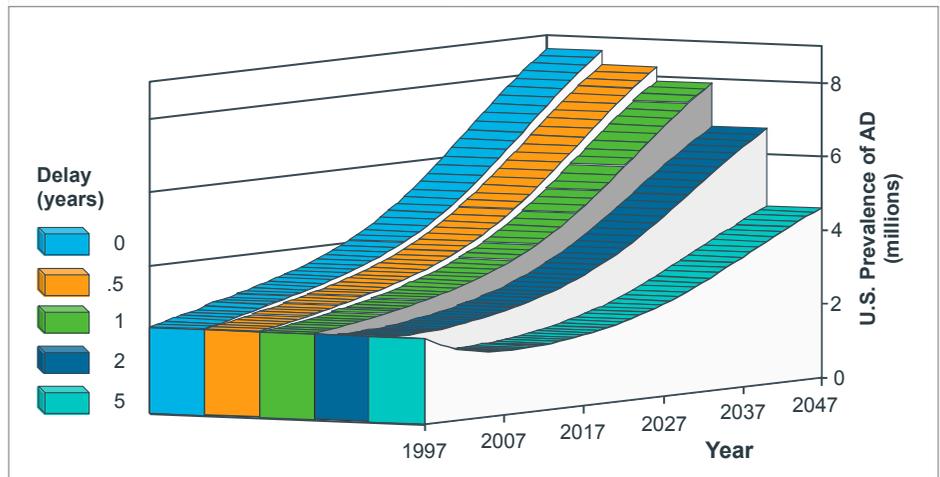
Second, it is critical to enroll a well-defined patient population using biomarker confirmation of diagnosis.

In addition, because most agents currently under trial are monoclonal antibodies (mAbs), the blood-brain barrier poses a substantial challenge. These challenges translate into four concerns:

- The generally low penetration of mAbs into the brain requires elevated dosing, which raises safety issues.
- Trial participants must be stratified by apolipoprotein E (APOE4) for safety management. Between 10% and 15% of the population is APOE4+, which increases the risk for developing Alzheimer's and lowers the age of onset.
- Dose titration to mitigate amyloid-related imaging abnormalities is a particular concern for APOE4+ individuals.
- The primary outcome measure, the clinical dementia rating (CDR) scale, must be protected by using blinded raters.

Novel biomarkers are easing some of those concerns. Prodromal research criteria proposed in 2007 by the International Working Group (Dubois et al., 2007) established the concept of Alzheimer's as a clinico-biological entity rather than a clinico-pathological entity. It is no longer necessary to wait for full-blown dementia to diagnose the disease or wait for autopsy for confirmation. Research criteria from the International Working Group for New Research Criteria for the Diagnosis of Alzheimer's Disease and the National Institute of Aging and Alzheimer's

Figure 1: Effects of delay of onset of disease on prevalence of dementia (estimates for U.S.)



Association encourage early inclusion of individuals into clinical trials focusing on prodromal and preclinical disease using biomarkers as diagnosis confirmation.

Pathophysiological biomarkers reflect the *in vivo* pathology of both amyloid and tau changes. These diagnostic markers are present at all stages of Alzheimer's and can be observed even when patients are asymptomatic.

Topographic markers have poorer disease specificity, but they indicate clinical severity. These progression markers may not be present in the earliest stages, but they can quantify time-to-disease milestones and indicate disease progression.

Moving trials into preclinical disease adds complexity. Screening failure rates jump to around 90%, underlining the need for enrichment strategies to increase the proportion of amyloid-positive participants. Larger sample sizes are needed and trials of four to five years might not be long enough to show treatment effect.

There are also important patient population questions. At what point should preclinical disease be targeted? Which participants are at higher risk of rapid progression to clinically manifest disease? Is the preclinical Alzheimer cognitive composite (PACC) the most appropriate outcome measure?

And which is more productive: adaptive trials or pivotal Phase 2b/3 designs? Separate Phase 2 and Phase 3 trials are not realistic due to the large populations and long duration needed to show separation.

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The State of Alzheimer's Disease Trial Design

Most recent Alzheimer's trials with amyloid targeting antibodies and secretase inhibitors have been negative. However, trials with bapineuzumab, gantenerumab, and aducanumab all show reductions in amyloid load or deposition. The observed effects on brain lesions shifted the conceptual base to treating cerebral lesions well before clinical symptoms arise to have a better chance of seeing an effect on clinical symptoms.

The reasoning behind the shift is clear: Delaying the onset of Alzheimer's by five years decreases the prevalence of clinical disease by 50% over the next 50 years (see **Figure 1**).

The latest evidence suggests that while brain lesions are nearly always present in those who develop Alzheimer's, lesions alone are not sufficient to trigger clinical symptoms onset. The INSIGHT-pre AD study, a single center observational study of 318 individuals with known amyloid status and normal cognition at baseline, supports a model of Alzheimer's as a continuum of disease. It begins with a preclinical state in which the brain can compensate for lesions with no loss of mental function. Decompensation begins in the prodromal phase in which the patients show amnesic syndrome and mild executive dysfunction and progresses to dementia that impacts the activities of daily living (see **Figure 2**).

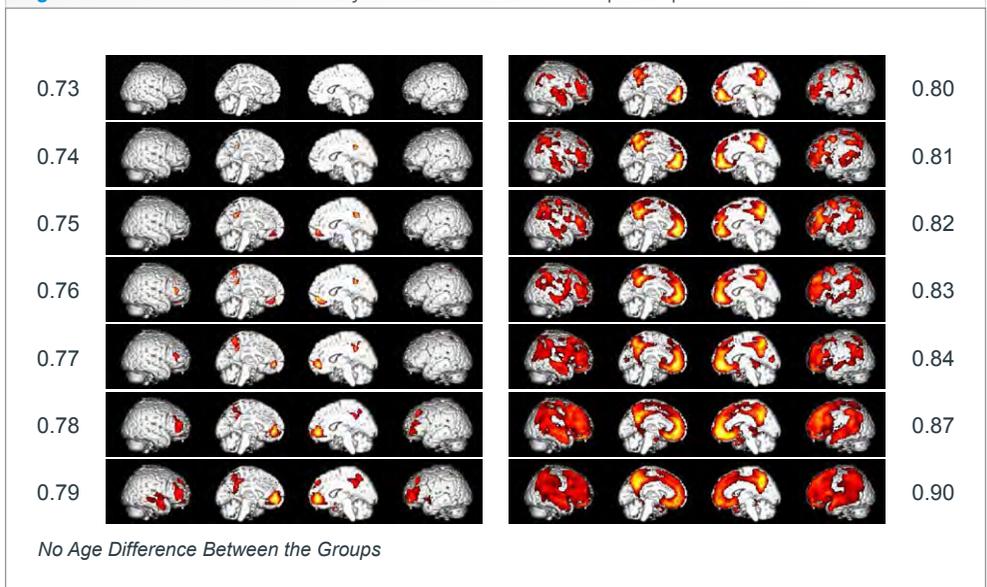
APOE4 status, family history, aging, vascular changes, smaller hippocampal volume, higher standardized uptake value ratio (SUVR), and other factors may increase the risk of progression. Neuroplasticity, genetics, higher levels of education, cognitive reserve, and hyperactivity of remaining neurons may decrease the risk of progression.

Advancing age being the major risk of amyloid positivity is an important enrichment strategy for trial population, and because higher educational level appears to delay progression to clinical disease, trial design should anticipate a low number of outcome events, which means a larger trial population and/or longer duration trials.

When selecting trial participants, it is important to distinguish between three subsets of individuals with normal cognition.

- One group is biomarker negative, no risk of progression.
- A second group is biomarker positive who compensate well. These individuals are at low risk of progression and may be candidates for secondary prevention trials.

Figure 2: Brain distribution of amyloid lesions in INSIGHT participants.



- The third group is biomarker positive and close to progression. These individuals are older, ApoE4+ and have much greater SUVR, lower hippocampal volume and mild executive dysfunction at baseline. This subpopulation is ideal for therapeutic intervention and is best suited for trial inclusion. The question is *how* and *where* to find those individuals.

Predictive Algorithms to Enrich Trial Populations

The *how* is predictive analytics and the *where* is community primary care. Predictive analytics is a collection of statistical techniques that analyze current and historical facts to gain deeper insight into the drivers of current events and to make predictions about future events.

IQVIA is building on its global data portfolios and growing experience with predictive analytics to more effectively identify patient pools that are likely to be appropriate for early-stage Alzheimer's trials. The key is developing a machine learning predictive model that can extract features and patterns from real-world databases to identify prodromal disease. And because learning is part of the algorithm, the model improves accuracy with experience and as more data become available.

The typical Alzheimer's patient journey begins with a diagnosis of mild cognitive impairment or age-related cognitive decline. However, these diagnoses can only serve as a proxy for the prodromal Alzheimer's disease as not all patients will develop Alzheimer's disease in the future. Furthermore, these patients are already seeing a specialist, at which stage it may already be too late to qualify for relevant clinical trials. Machine learning predictive model can be used in the following two application areas:

1. Hone in on patient's hotspots by identifying undiagnosed prodromal Alzheimer's disease patients associated with

healthcare providers. This can provide a more precise targeting of providers and patients for clinical trial recruitment

2. Support pre-screening of patients by embedding a screening tool at the provider site to allow early diagnosis and assessment of their eligibility for clinical trial participation

For the first application area, a machine-learning predictive model was developed and applied on more than 72 million US residents to identify about 223,000 prodromal Alzheimer's patients, 76% of whom were in primary care settings. Additional analysis was conducted to assess the potential of the primary care physician to refer patients based on patient density, physician prior clinical and referral experience and distance to the investigator site, in order to prioritize physicians with the maximum patient referral potential. These physicians must then invest time and resources to identify and select at-risk patients for referral to nearby investigator sites.

For the second application areas, a tool with the predictive model can be used at the point of care with providers to help them with real-time patient screening by the physicians for clinical trial eligibility. Such a screening tool uses different sources of real world data to make a prediction of the disease risk score as well as provide clinical trial inclusion score for patient's eligibility to enrol into a clinical trial. The physician can then decide to refer the patient to a nearby screening centre or to a specialist for diagnosis confirmation and clinical trial enrollment.

Over time, there is a potential to use additional data sources to improve the predictive accuracy, such as family health history, genetic data, or information from sensor-based wearable digital devices. The accuracy of the screening tool could be further strengthened and validated using a feedback loop involving additional screening and diagnostic testing of the identified patients.

Summary

The time has come for academic institutions, the biopharmaceutical industry and CROs to collaborate to enhance the development of effective Alzheimer's treatments. Rapid technology advances in imaging and omics as well as more powerful predictive disease models are on the verge of transforming the clinical trial universe.

It is clear that human data science—the integration of human science and human data science, coupled with predictive analytics, can significantly transform the way we diagnose and treat prodromal Alzheimer's earlier. The next step is to leverage emerging medical technologies like machine learning and predictive algorithms, to build more effective clinical trial designs, decrease trial burdens and allow better understanding of the long-term outcomes of disease-modifying treatments.

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References

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