WHITEPAPER

New Paradigms in Alzheimer's Research:

Reviving the treatment landscape

5,000,000+
Americans living with the disease

6th leading cause of death in the US

15,500,000
caregivers in the US

Every
66 seconds
someone develops Alzheimer's in the US

Alzheimer's Association
http://www.alz.org/facts/overview.asp

Table of Contents

There is scientific knowledge. And there is public perception. But often, the two collide.

Nowhere is this reality more explicit than with the current state of Alzheimer's (AD) disease research. Scientists hypothesize, but cannot definitively prove, that tangles of tau protein and build-ups of beta-amyloid plaque contribute to the hallmark cognitive decline of Alzheimer's disease. There is no specific test for the disease, no defining treatment, and no reliable yardstick to measure its progression.

Without a definitive cause or diagnosis – and with no cure in sight – many aging adults see no reason to assess their risk, or determine their cognitive status, if little can be done to stave off the disease.

Perceptions such as these present a growing challenge to Alzheimer's research. While mounting evidence validates the benefits of early identification in keeping symptoms at bay, patients and their families often feel they have nothing to gain by seeking treatment or joining a clinical trial. Still others deny they have symptoms, due to fear of social reprisal or loss of independence. Lastly, many people with AD do not even realize there is a problem; they simply "forget they forget" (clinically referred to as anosognosia).

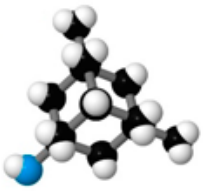
Understanding these clinical research barriers is critical to developing strategies to overcome them.

Research failures and their impact on patient perceptions

Both patients and the public have reason to be skeptical. No new Alzheimer's drugs entered the market between 2004 and 2019, and 244 unique compounds failed to show benefit in clinical trials between 2002 and 2012. [1,2]

Moreover, the small number of approved Alzheimer's drugs – only five on the global market – do nothing to prevent or slow the disease. Rather, they attempt to alleviate symptoms by inhibiting one of two brain chemical messengers, either acetylcholinesterase or glutamate. Excessive amounts or dysregulation of either chemical can contribute to memory and movement disorders.

244 unique compounds
Failed in trials from 2002 – 2012



1379 clinical trials
Since 2003 have not shown benefit

In recent years, a multitude of new drug candidates have entered various phases of clinical testing, but none has conclusively shown an appreciable or sustained impact on improving memory or cognition across large populations of Alzheimer's patients. (However, more sensitive outcome scales are being developed to perhaps better detect a signal of efficacy.)

In short, the cumulative failure of Alzheimer's research to produce innovative drugs with definitive benefits creates yet another obstacle to clinical trial enrollment in a field where engaging participants is already fraught with complications.

New drugs on the horizon

Two new drugs on the horizon are creating both hope and skepticism.

Aducanumab has generated the most buzz with its rapid ascent, dramatic plunge, and recent resurrection as leading contender among investigational drugs for Alzheimer's disease. The drug is designed to target and clear the build-up of toxic beta-amyloid protein plaques in the brain, long thought to be a contributing factor to the diffuse cell death and signature memory loss of Alzheimer's disease.

Yet many elderly patients with no signs of dementia show extensive build-up of beta amyloid plaque, a dichotomy that has created ongoing debate about the root causes of Alzheimer's brain changes.

The second drug, Oligomannate, was conditionally approved in China in November of 2019, after trials in China showed improved cognitive function in patients with mild to moderate Alzheimer's disease. Derived from brown seaweed, the drug was developed after noting that elderly individuals who consumed large amounts of seaweed had lower rates of Alzheimer's disease. But details from Chinese trials of Oligomannate are not yet available, and global trials in Europe, the U.S. and Asia are just preparing to launch.

A third class of drugs is garnering greater support as studies increasingly show that the tau protein, which gives rise to tangled filaments inside the brain, is a viable target for slowing Alzheimer's disease progression and memory loss.

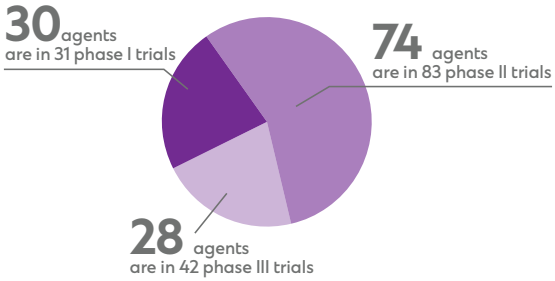
Expanding potential targets

Recognizing the need for fresh ideas, researchers are exploring alternate theories for Alzheimer's brain degradation beyond the traditional "beta-amyloid plaque" and tau tangles paradigms, which hold these rogue proteins primarily responsible for the disease.

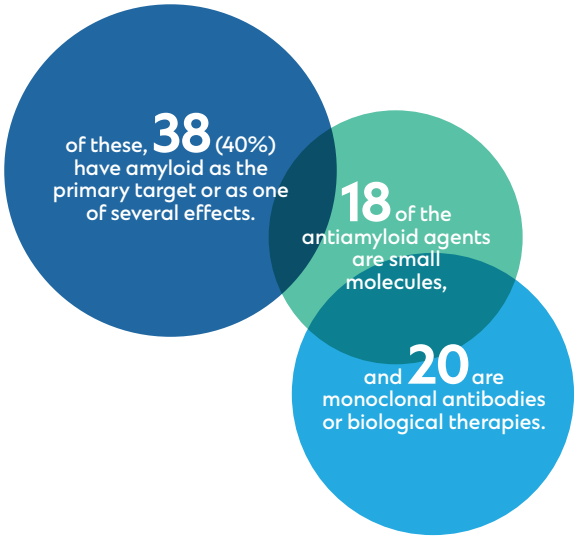
Recent studies have implicated a wide range of previously unexplored processes in the progression of Alzheimer's, from leakiness in the blood-brain barrier membrane [3,4] to an inflammatory response involving the brain's microglial immune cells.[5] Each of these mechanisms presents a potential target for treating symptoms or slowing disease progression, and drug companies are seizing upon these opportunities with significant resources.

Currently, there are 132 Alzheimer's drug candidates in various stages of clinical testing [6,7] with an estimated 50,000+ Alzheimer's patients and healthy volunteers needed to test their safety and efficacy. [8]

132 agents in clinical trials for the treatment of AD



There are 96 agents in disease modification trials;



Companies are increasingly broadening their targets beyond beta-amyloid and tau to identify proteins and pathways that may alter the course of Alzheimer's through unexplored mechanisms. Developing drugs that will slow the progression of the disease is one of the most pressing needs in medicine today, as 76 million baby boomers continue to age.

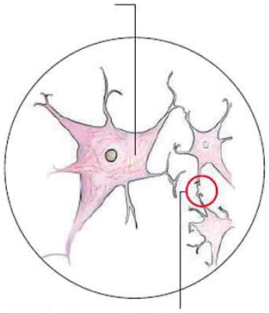
Among the new targets are 5-HT6 receptors, which are abundantly located throughout the brain's learning and memory regions such as the hippocampus, nucleus accumbens and striatum.[9] Drugs that target these receptors, known as 5-HT6 antagonists, work by promoting the release of acetylcholine as well as other neurotransmitters known to affect cognition and memory. While recent results from 5-HT6 clinical trials have been disappointing, this class of drugs could ultimately improve symptoms in subsets of patients, and several phase II and III trials are progressing as planned.

Yet another mechanistically different class of drugs targets the brain's alpha-7 nicotinic acetylcholine receptors, which may influence brain function by acting directly on neuronal pathways and by reducing inflammation in the central and peripheral nervous systems. Compounds in this class of drugs have not yet shown clinical benefit, but research continues to move forward. [10]

Alzheimer's Brain Changes

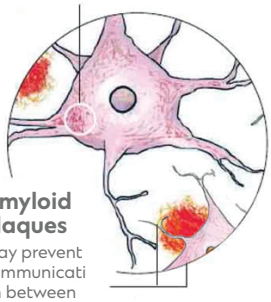
In a healthy brain
Protein fragments known as amyloid peptide develop between the neurons. A healthy brain can dissolve them.

A normal neuron
Normal transmission of nutrients within brain cell



Normal transmission of signals between two neurons

In an Alzheimer's brain
Neurofibrillary (TAU) Tangles
Stunt the transmission of nutrients and/or other substances within the neuron.



Amyloid Plaques
May prevent communicati on between neurons

In a brain with Alzheimer's brain disease
Beta-amyloid proteins build up and form hard plaques in the spaces between neurons. Tau proteins malfunction and form twisted threads or "tangles" inside the neurons.

Improving detection

On the diagnostic front, the Alzheimer's community is making great strides toward earlier and less invasive methods for detecting the disease and its precursors. According to *Datamonitor Healthcare's* Alzheimer's disease report, "A substantial opportunity thus exists for pharmaceutical companies to drive an increase in the wider Alzheimer's disease market by improving diagnostic capabilities, dispelling the notion that cognitive decline is a normal fact of aging, and increasing awareness of the benefits of obtaining an early diagnosis." [11]

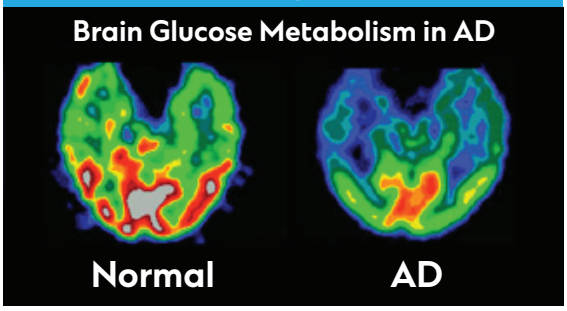
In fact, researchers have linked nearly 20 biological markers in blood plasma or cerebrospinal fluid – including T-tau, P-tau, Aβ42, and NFL – to the presence or eventual onset of Alzheimer's disease.[12,13]

In addition, sophisticated imaging techniques are illuminating structural and functional brain changes caused by Alzheimer's, from shrinkage of the hippocampus, the brain's central memory repository; to the slowing of glucose metabolism, which serves as brain fuel for nerve cells.

Protein imaging PET scans (in addition to already available amyloid PET imaging) will include tau PET imaging as well as a PET scan to document neuroinflammation. The latter is now considered the third necessary component to pathologically confirm Alzheimer's disease, and could also gauge efficacy of new neuroinflammation targeting treatments. Likewise, the development of a PET imaging tracer of neuronal synaptic density, which correlates strongly with the clinical picture, has potential to be a useful tool to measure disease progression as well as measure treatment response. Pinpointing these hallmark changes will help scientists find new ways to thwart them.

Even more exciting, researchers at several institutions have developed experimental blood tests that do not require a lumbar puncture to detect proteins that signal the onset of Alzheimer's brain changes. In a proof-of-concept study published in the journal *Alzheimer's and Dementia*, researchers identified a set of 50 antibodies in blood samples that predicted with 100 percent accuracy whether a patient with mild cognitive impairment would eventually develop Alzheimer's disease. The test, while experimental, was so sensitive that it was able to distinguish between mild cognitive impairment caused by Alzheimer's versus Parkinson's or multiple sclerosis.[14,15] Researchers expect an Alzheimer's blood test to be available within the next few years.

Glucose Utilization
PET scans showing much reduced glucose utilization in the AD brain compared to controls



New Jersey Institute for Successful Aging, Rowan University.
Robert Nagele, PhD; Anita Chopra, MD.

Rapid drug screening

Behind the scenes, researchers are fervently working toward expediting the screening of promising compounds that could block, activate or otherwise influence Alzheimer's pathways to alter the disease trajectory. While animal research models have long been the mainstay for testing a drug's potential, a staggering number of Alzheimer's drugs – 99.6 percent between 2002 and 2012 – have failed once they enter human trials.[16] The current mouse models of Alzheimer's can't fully reproduce the genetic, cellular, or behavioral complexity of Alzheimer's disease.

Researchers around the world are in the midst of testing intriguing new models of the human brain that are more robust and predictive of how investigational drugs will behave in humans. From a "mini-brain" organoid model of Alzheimer's disease[17] to a 3-D human neural culture model that produces beta-amyloid plaques and tau tangles,[18] these brain models are designed to provide faster, cheaper, and more reliable screening platforms to test new Alzheimer's agents.

2002 - 2012: 413 AD trials conducted in US
(78 percent sponsored by pharma)

124 phase 1
206 phase 2
83 phase 3

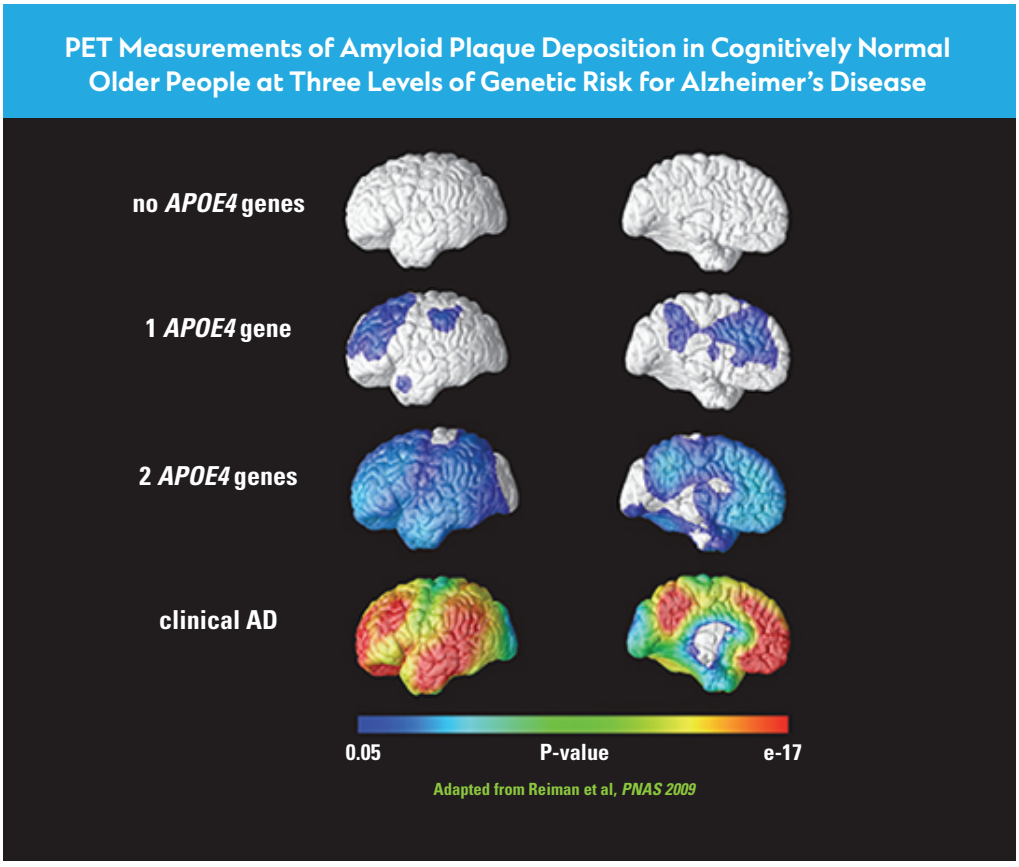
99.6%
Failure rate

A new research paradigm

To energize the field, a significant shift in Alzheimer's clinical practice is underway worldwide, where providers are increasingly treating patients with mild cognitive impairment or assessing at-risk individuals with no symptoms at all. In part, this shift is dictated by practical matters. Medicines that have failed in moderate or severe Alzheimer's disease have performed better in its earlier or preclinical stages. But from a macro level, halting the disease before it inflicts major damage is a more viable approach than trying to reverse damage once it has occurred.

Evidence supports this change in approach. A range of new studies has identified subtle brain changes as early as four years old in children with the APOE4 version of the gene, along with corresponding deficits in tests of executive function and working memory.[19] A similar study found that young adults who scored high on a test measuring all the high-risk Alzheimer's gene variants were more likely to have a smaller hippocampus – a brain structure critical for learning and memory.[20]

Yet early treatment requires early identification of high-risk patients, a challenge that has plagued the clinical research community for decades. Currently, 80 percent of Alzheimer's studies are delayed because of insufficient patient enrollment,[21] and this delay significantly impedes the testing and approval of new drugs. To speed the clinical trial enrollment process, collaborative programs such as GENEMATCH are building huge databases of high-risk older adults in order to pre-screen subjects who can then be matched to Alzheimer's clinical trials that best fit their qualifications. And clinical trials worldwide are enrolling at-risk, asymptomatic patients to test investigational drugs designed to arrest brain changes before they cause irreparable damage.



People with two copies of the APOE4 gene are at greatest risk for developing Alzheimer's disease.

Barriers to clinical trial recruitment

Despite these advances, substantial barriers are slowing the clinical testing of new drugs on the horizon. Among them is the unpredictability of human behavior. People with few or no symptoms may perceive a low risk of Alzheimer's or attribute their forgetfulness to normal aging, thereby ignoring clinical trials. Those with substantial cognitive decline are unreliable witnesses to their symptoms, and caregivers may not be fully aware of, or agree upon, their loved one's deficits.

In addition, symptoms progress along a continuum, not in the distinct phases that clinical trials delineate for inclusion. Each of these factors could dictate whether patients meet study trial criteria and whether the right patient with the correct symptoms is placed in the appropriate trial. Experts in the field acknowledge that recruiting and retaining clinical trials participants is "currently the greatest obstacle to developing new Alzheimer's treatments." [22]

Patient barriers to participation include:

- **Stigma.** Social exclusion is a major theme for people with dementia, with 40 percent of survey respondents reporting they were avoided or treated differently because of their dementia.[23]
- **Concomitant health factors.** Patients may rank acute conditions such as cancer, diabetes or hypertension as more pressing issues.
- **Treatment risks.** Invasive testing of cerebrospinal fluid or imaging modalities such as PET or MRI may deter healthy patients from enrolling in trials.
- **Perceived benefit.** In the absence of clear benefit to early diagnosis or treatment, patients may choose to forgo a clinical trial.
- **Logistics.** Trials require frequent and often lengthy visits. Some patients lack a caregiver to transport them to clinical visits, and not all patients are healthy enough to attend regularly.
- **Lack of awareness.** Mild symptoms may be attributed to normal aging, thus deterring people from seeking a medical evaluation.
- **Placebo.** Patients may worry about the potential for receiving a placebo and not active drug.

Clinician barriers include:

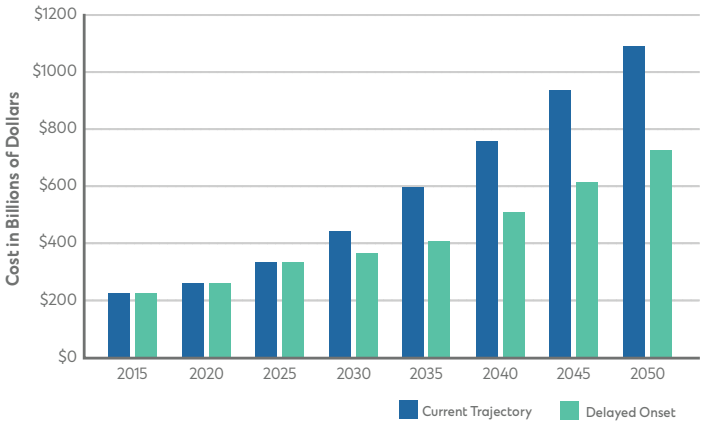
- **Lack of standard AD test.** The number and variety of tests makes it difficult to uniformly assess symptoms. Some tests measure cognitive abilities while others measure functional decline.
- **Primary Care Physician (PCP) vs. Specialist.** Specialists have access to more precise and sophisticated screenings and computerized tests than PCPs, which could affect the patient's diagnosis and/or clinical stage.[24]
- **Interpretation.** AD occurs along a continuum rather than distinct stages. Without clear consensus on the staging of Alzheimer's progression, clinical diagnoses vary.
- **Disease variability.** Not all patients with mild cognitive impairment will progress to Alzheimer's. There are no set parameters for distinguishing the two groups.
- **Repetitive testing.** Patients frequently repeat the same test and may recall the answers, thereby skewing the results.
- **Unknown population.** Defining a population by the absence of disease is a difficult endeavor. At-risk patients may not see themselves at risk and thus may not come forward to participate.

From a psychological perspective, physicians are often reluctant to refer asymptomatic or mildly impaired patients to clinical trials because they fear that current investigational drugs are no different mechanistically than previous Alzheimer's drugs that have failed. They also worry that genetic testing for high-risk individuals may provoke fear and anxiety without any viable options for preventing or treating the disease.

Patients do not necessarily share physician concerns. A study published in the *New England Journal of Medicine* found that healthy, asymptomatic adults in their 50s did not suffer more anxiety or depression upon finding out they had the APOE4 gene than the individuals who found out they did not have the gene variant. Those who tested positive for APOE4 were slightly more distressed, but they quickly rebounded, the study found. With proper genetic counseling, patients understood and accepted the results of the genetic test.[25]

However, a growing body of evidence reinforces the benefits of early intervention as a means of potentially slowing pathological processes that lead to neurodegeneration and eventual cognitive decline.[26] New compounds in development are likely to have greater efficacy in modifying the disease course when used before extensive and irreversible damage has occurred. The reduction in societal burden would be massive, according to the National Center for Biotechnology Information. A hypothetical intervention that delays the onset of Alzheimer's dementia by five years would reduce the number of patients with this symptom by 57 percent and thus reduce the projected Medicare costs of treating AD from $627 billion to $344 billion.[27]

Projected Impact of a Medicine that Delays Alzheimer's Disease Onset by 5 Years, 2015-2050



Source: Alzheimer's Association. "Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2015 Saves Lives and Dollars." May 2015, http//www.alz.org/documents_custom/trajectory.pdf

The critical role of a study partner

Overcoming obstacles to clinical trial participation requires a much greater degree of sophistication in recruitment strategies and more in-depth screening and retention practices than is typically the case with a less complex condition. Working with an experienced patient recruitment partner can relieve the burden of attending to exhaustive recruitment strategies, which have exponentially increased in number and complexity as Alzheimer's trials have grown longer and more involved. An experienced patient recruitment partner has access to trial-ready patients and/or caregivers; a thorough understanding of patient motivations; keen awareness of the nuances and subtleties of effective messaging to reach the target audiences; proven methodology of screening and qualifying participants; on-the-ground site collaboration and site support; and partnerships with experts and patient groups in the field.

Expansive database

Relevant data and strategic insight are critical, but they won't connect you to actual individuals who can enroll in an Alzheimer's trial. A patient recruitment partner with an expansive database of trial-ready patients provides a ready-made source of potential participants that can be easily tapped via email, phone, mail, or digital media without having to rent or purchase an outside database. Using this proprietary database enables the study partner to conduct surveys in a matter of hours or days, not weeks or months, to obtain valuable feedback on patient motivations, barriers to participation, and attitudes toward Alzheimer's research. The input obtained from patients and caregivers enables the study partner to identify unique subgroups of patients within each therapeutic area. The study partner can then develop and refine high-impact messages that speak directly to the concerns and motivations of each respective subgroup.

Patient perceptions

To better understand the target audiences for Alzheimer's-related clinical trials, Accelerated Enrollment Solutions (AES) identified and surveyed at-risk patients and family members from its database of households with memory loss or Alzheimer's disease. Responses from 1,886 asymptomatic individuals revealed four distinct patient segments.

Avoiders who are afraid to assess their risk

Unaware individuals who presume they are not at risk in the absence of a family history of Alzheimer's

Cautiously aware individuals who are worried about their risks and would consider taking action

Active seekers who are looking for ways to reduce their risk or prevent the onset of symptoms

More than 78 percent of patients said they were interested in learning whether they are at risk for Alzheimer's, although self-reporting does not always correspond to patient behaviors. The feedback obtained from the survey provides valuable insights that shape AES messaging and recruitment strategies. Ultimately, the goal of a successful Alzheimer's messaging strategy is to shift the mindset of individuals from the first three categories into the seeker mode, where they understand the benefits of early testing and treatment, embrace the opportunity to assess their risk, and are willing to participate in trials that may reduce their risk or alleviate symptoms.

The role of caregivers

Caregivers are one of the most important audiences for clinical trials. This population knows the realities of the disease, and they are motivated to advance research on behalf of their loved ones and their own future risk. In the AES survey, nearly 67 percent of caregivers have shared their family member's status with others, indicating they feel it is important to openly discuss the topic. They are interested in genetic testing, and they understand the benefits of early treatment. However, caregivers indicated they are stressed and overburdened, and they have little time for anything other than caregiving, much less a clinical trial. Offering transportation to and from study visits and reimbursement for time and travel could help alleviate their barriers to trial participation.

Protocol matching

Alzheimer's disease progresses along a continuum rather than in distinct stages, making it extraordinarily difficult to match patients to specific protocols. Understanding relevant milestones along the Alzheimer's continuum allows an experienced study partner to build nuanced screeners and train qualified phone support to match patients with the protocols that best fit their symptoms. The AES team of 200 protocol-trained call center professionals, located in seven strategically placed call centers, manages 3,000 to 4,000 calls per day.

Ground force support

Knowledge breeds empowerment. Educating the local community provides a mechanism for dispelling myths and breaking down barriers. In-person meetings engender goodwill by demonstrating a level of commitment and accountability to local needs that paper flyers and phone calls cannot achieve. Successful outreach strategies focus on giving, not asking for, information. In return, community members are more likely to volunteer their contact information for future engagements or clinical trials.

Examples of outreach events include meeting with chapters of patient advocacy groups; hosting awareness events at community centers, libraries, churches, synagogues and senior centers; memory screenings at health fairs; and presentations to local civic groups.

Data-driven and technology-enabled pre-screening and enrollment

Screening technologies must be built to handle not only volume, but complex protocol logic, especially as it relates to Alzheimer's-related studies. Measures of mood and memory are notoriously fickle and given to individual interpretation, so the study enrollment partner must have extensive experience in screening vast numbers of people to successfully pinpoint qualified patients.

AES globally pre-screens an average of 10,000 study candidates per day for dozens of trials and has pre-screened up to 50,000 study candidates for its largest trials. Our combination of technology, data assets, site infrastructure and employee headcount is engineered to handle tens of thousands of randomized patients per year.

To navigate the complexity of Alzheimer's disease, AES employs phone- and web-based cognitive testing at the pre-screening level to more precisely segment study candidates into the cognitive ranges required for randomization in a given study protocol.

Patient-centric tactics

Clinical trials are designed to answer very specific questions that must satisfy medicine's need for clarity and specificity, and regulatory agencies' need for compliance and safety. The patient perspective is typically not part of the clinical trial design. However, this model has created a less-than-ideal scenario for recruiting patients. Minimizing the patient burden will create a more favorable climate for attracting greater numbers of patients to enroll in Alzheimer's clinical trials.

- **Reduce bureaucracy:** Work with the sponsor to shorten lengthy paperwork and consent forms that might deter physician clinics from becoming study sites and/or patients from enrolling.
- **Listen and learn:** Understand the attitudes, beliefs and motivations of potential patients through interviews, surveys, patient panels, and advisory boards. Closely follow social media to gauge patient and caregiver sentiments about Alzheimer's disease and its impact on the family, and clinical trials. Social media listening and interaction requires daily monitoring and nearly instantaneous responsiveness.
- **Be nimble and responsive:** When strategies fail, quickly shift messaging to a new approach or an untapped population of patients. Social media allows for instant output, input, and the ability to rapidly tweak messages accordingly.

The silver lining: Nowhere to go but up

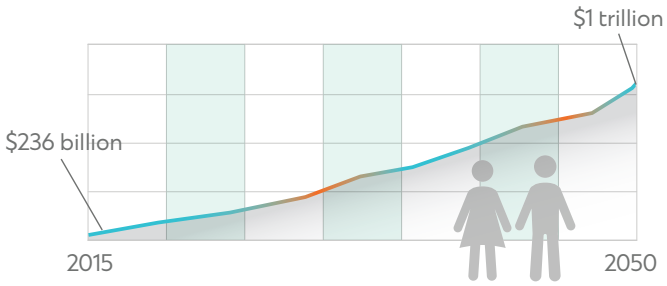
Given today's challenging landscape, the playing field for new Alzheimer's drugs is wide open and primed to embrace even small, but measurable, gains in delaying the disease or effectively reducing its symptoms.

The burden is collectively placed on the pharmaceutical industry to dramatically change its approach to brain research, and then communicate successes in ways that the public can embrace and understand Public perception about Alzheimer's research is understandably negative, and this perception must change before patients decide it is worthwhile to join clinical trials.

Appealing to people in ways that speak to their fears, desires and motivations will move them toward a clearer understanding of the benefits of early intervention.

The biggest winners will be families and society at large, both of which are suffering under the massive weight of mental anguish and financial debt. Alzheimer's currently effects 5.2 million Americans, and that number is expected to triple by 2050 as the population increases. The global economic cost of caring for patients with Alzheimer's and other dementias is estimated to be $1 trillion annually, including direct, indirect and intangible costs.[28]

Cost of caring for AD patients



Despite these numbers, the Alzheimer's community at large has been frustratingly slow to abandon strategies and classes of drugs that have failed to show benefit or efficacy. In the race to reverse this paradigm, the first company to succeed with a new drug that delays, treats, or halts the ravages of Alzheimer's stands to reap inestimable gains. When this happens, everybody wins.

References:

[1] Jeffrey L Cummings, Travis Morstorf and Kate Zhong. "Alzheimer's disease drug-development pipeline: few candidates, frequent failures." Alzheimer's Research and Therapy, July 3, 2014. https://alzres.biomedcentral.com/articles/10.1186/alzrt269

[2] https://www.sciencedirect.com/science/article/pii/S2352873719300290

[3] Walter H. Backes, PhD, et al. "Blood-Brain Barrier Leakage in Patients with Early Alzheimer Disease." Radiology. Nov. 2016, Volume 281, Issue 2. http://pubs.rsna.org/doi/abs/10.1148/radiol.2016152244

[4] https://stm.sciencemag.org/content/11/521/eaaw8283

[5] Brent Cameron and Gary E. Landreth. "Inflammation, Microglia and Alzheimer's Disease." Neurobiology of Disease. 2010 Mar; 37(3): 503–509. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823849/

[6] Pharmaprojects. Alzheimer's Drug Report. June 2016. https://citeline.com/wp-content/uploads/Alzheimer-Drug-Report.pdf

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6617248/

[8] https://www.alz.org/images/northcentraltexas/clinical_trials.pdf

[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533589/

[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943903/

[11] Maha Elsayed, Sabada Dube, and Charlotte Huntley. Datamonitor Healthcare. Alzheimer's disease, Disease coverage, July 2016.

[12] Bob Olsson, et al. Lancet Neurology. "CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis." June 2016. https://www.ncbi.nlm.nih.gov/pubmed/27068280

[13] https://www.alzforum.org/news/conference-coverage/fluid-ad-biomarkers-link-p-tau-synapses-inflammation

[14] Robert G. Nagele, PhD, et al. "Detection of Alzheimer's disease at mild cognitive impairment and disease progression using autoantibodies as blood-based biomarkers." Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. Volume 3, 2016, pages 51 – 62 http://www.dadm.alzdem.com/ article/S2352-8729(16)30015-X/abstract

[15] https://n.neurology.org/content/93/17/737

[16] Jeffrey L Cummings, Travis Morstorf and Kate Zhong. "Alzheimer's disease drug-development pipeline: few candidates, frequent failures." Alzheimer's Research and Therapy. July 3, 2014, https://alzres.biomedcentral.com/articles/10.1186/alzrt269

[17] Rene Anand, PhD and Susan McKay, MS. Human Brain Organoids Derived from Induced Pluripotent Stem Cells. Dept of Biological Chemistry and Pharmacology & Dept of Neuroscience. The Ohio State University College of Medicine & Wexner Medical Center. https://news.osu.edu/news/2015/08/18/human-brain-model/

[18] Rudolph E. Tanzi and Doo Yeon Kim. "A three-dimensional human neural cell culture model of Alzheimer's disease." Nature. Nov. 13, 2014. 274–278. http://www.nature.com/nature/journal/v515/n7526/full/nature13800.html

[19] Linda Chang, MD, et al. "Gray matter maturation and cognition in children with different APOE ε Genotype." Neurology. July 13, 2016. http://www.neurology.org/content/early/2016/07/13/WNL.0000000000002939.short

continued

[20] Elizabeth C. Mormino, PhD, et al. "Polygenic risk of Alzheimer's disease is associated with early- and late-life processes." Neurology. July 6 2016. (http://www.neurology.org/content/early/2016/07/06/WNL.0000000000002922.short)

[21] Galaxybraintrust.org. http://www.prweb.com/releases/2016/10/prweb13780013.htm

[22] Phrma. 2016. http://www.phrma.org/report/medicines-in-development-for-alzheimer-s-disease-2016-report

[23] World Alzheimer Report. 2012. http://www.alz.org/news_and_events_negative_perceptions.asp

[24] https://content.iospress.com/articles/journal-of-alzheimers-disease/jad190146

[25] Cinnamon S. Bloss, Ph.D., Nicholas J. Schork, Ph.D., and Eric J. Topol, M.D. "Effect of Direct-to-Consumer Genomewide Profiling to Assess Disease Risk." New England Journal of Medicine. Feb. 10, 2011; 364:524-534

[26] Reisa A. Sperling, et al. "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimer's & Dementia. May, 2011. 280–292. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3220946/

[27] Reisa A Sperling, et al. Criteria for Preclinical Alzheimer's Disease. http://www.alz.org/research/diagnostic_criteria/preclinical_recommendations.pdf

[28] https://www.sciencedaily.com/releases/2019/07/190730092616.htm