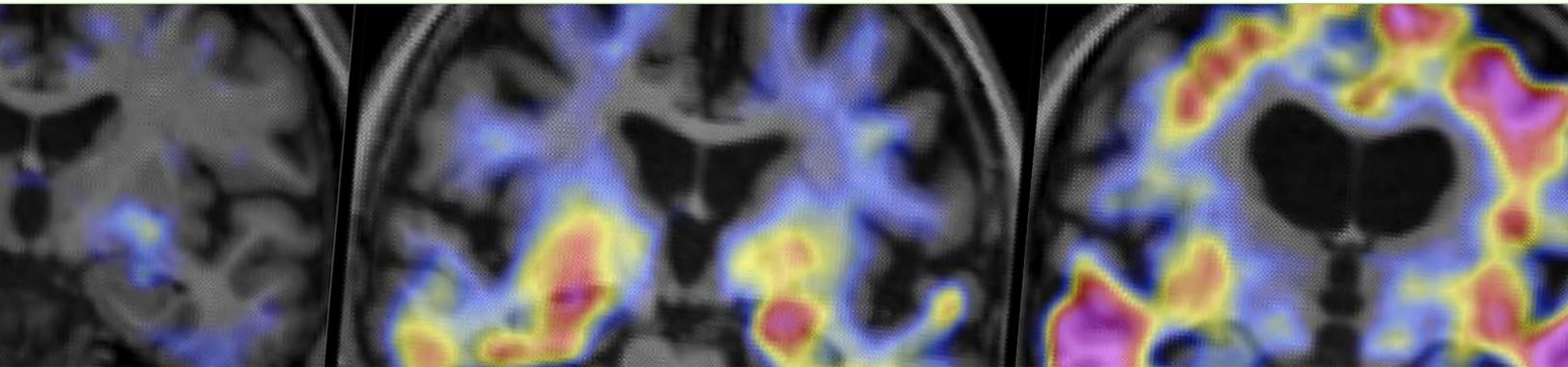


**A JOURNALIST'S GUIDE TO**

# ALZHEIMER'S DISEASE AND DRUG DEVELOPMENT



# **A JOURNALIST'S GUIDE TO COVERING ALZHEIMER'S DISEASE AND DRUG DEVELOPMENT**

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*Cover image:* Courtesy of Keith A. Johnson

## A JOURNALIST'S GUIDE TO ALZHEIMER'S DISEASE AND DRUG DEVELOPMENT

### KEY FACTS ABOUT ALZHEIMER'S

#### Alzheimer's is a disease; it's not just normal aging

Alzheimer's is the most common form of *dementia*. It is a biological disease marked by physical changes in the brain—most notably buildup of small protein clumps called *plaques* and *tangles*—that lead to the death of nerve cells. The cell death usually starts in specific regions of the brain and then spreads to others; as cells die, functions controlled by those areas fade and ultimately disappear, resulting in characteristic signs and symptoms at each stage of the disease.

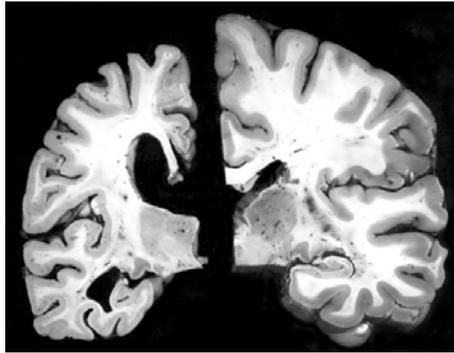
Alzheimer's stages and symptoms <sup>1</sup>	
Preclinical AD	<ul style="list-style-type: none"><li>• no obvious symptoms</li><li>• brain changes detectable by spinal fluid analysis and neuroimaging</li></ul>
Mild Cognitive Impairment (MCI) due to Alzheimer's	<ul style="list-style-type: none"><li>• slight but measurable decline in memory and thinking skills but no decline in ability to function</li></ul>
Mild AD	<ul style="list-style-type: none"><li>• problems coming up with right word or remembering names when introduced to new people</li><li>• forgetting material one has just read</li><li>• harder time performing work tasks</li><li>• misplacing valuable objects; trouble with planning or organizing</li><li>• often patient can still drive, work, and function independently</li></ul>
Moderate AD	<ul style="list-style-type: none"><li>• forgetting events or details about personal history</li><li>• moody or withdrawn</li><li>• confused about where they are or what day it is</li><li>• changes in sleep patterns</li><li>• increased risk of wandering and getting lost</li><li>• personality and behavioral changes</li><li>• patient requires greater level of care</li></ul>
Severe AD	<ul style="list-style-type: none"><li>• losing awareness of recent experiences and surroundings</li><li>• failure to recognize or even remember close family and friends</li><li>• increasing difficulty communicating to complete inability to speak</li><li>• more trouble with walking, sitting, and swallowing</li><li>• patient needs around-the-clock help with daily activities and personal care</li></ul>

At the molecular level, Alzheimer's begins years before a person would suspect something is wrong. Devoid of noticeable symptoms, this period is called "asymptomatic" or "preclinical" Alzheimer's disease and often lasts 10-20 years. During this stage telltale plaques and tangles accumulate in the brain. Plaques are mostly made of a protein called *beta-amyloid*. Tangles are formed when the protein *tau*—which normally binds to support structures important for cell function—

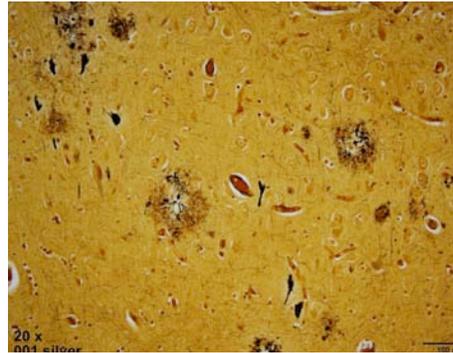
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aggregates into twisted threads. As the disease progresses, plaques and tangles grow in number and spread throughout the brain, choking nerve cell communication and leading to loss of cognitive function.

Alzheimer's is a progressive brain disease that currently has no cure.



Courtesy of Nigel Cairns



Courtesy of Shahriar Salamat

(Left) An Alzheimer's brain, left, is significantly smaller than a normal brain, due to the death of brain cells. (Right) Plaques and tangles stained in a magnified section of a brain from an Alzheimer's patient.

### How was Alzheimer's first described?

In 1901, a German railway worker admitted his wife to a psychiatric hospital in Frankfurt because she had become unmanageable. Disoriented and delusional, she had trouble sleeping, screamed for hours in the middle of the night, and couldn't remember much of anything. Asked by the examining physician to write her name, she barely got started before muttering helplessly: "I have lost myself."<sup>2</sup>

Back then memory loss and dementia were viewed as simply a consequence of old age, a misconception that persists even today.<sup>3</sup> So the medical community took notice when the German patient presented with such disabling mental illness at just 51 years of age, and then died within five years. When psychiatrist Alois Alzheimer studied her brain at autopsy, he found it littered with unusual protein clumps and twisted bundles of intracellular protein fibers<sup>4</sup>—clues that her condition was not simply a routine consequence of aging.

At the time, these deposits were considered extremely rare, but by the 1970s scientists recognized the same plaques and tangles as key pathological features of Alzheimer's disease. Alzheimer's has now replaced "senile dementia" as the most common form of dementia.<sup>5</sup>

### Alzheimer's by the numbers

Worldwide nearly 50 million have Alzheimer's or a related dementia.<sup>6</sup>

In the US, Alzheimer's afflicts one in nine people 65 years or older.<sup>7</sup>

Caring for people with Alzheimer's and other dementias cost more than \$226 billion in 2015,<sup>8</sup> making it America's most expensive disease.<sup>9</sup>

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### Alzheimer's is not the only cause of memory loss.

Loss of memory and other mental abilities could result from other dementias:<sup>10</sup>

- vascular dementia
- dementia with Lewy bodies
- mixed dementia
- Parkinson's disease
- frontotemporal dementia
- Creutzfeldt-Jakob disease
- normal pressure hydrocephalus
- Huntington's disease
- Wernicke-Korsakoff syndrome

### DIAGNOSIS

Skilled physicians can diagnose the disease in living patients with about 90 percent accuracy.<sup>11</sup> However, there's no single test that shows if a person has Alzheimer's, so reaching a diagnosis can take time.

Diagnostic Toolkit <sup>12,13</sup>	
Procedure	Purpose
medical history	provides a broad picture of cognitive and behavioral changes over time; helps doctors determine if cognitive decline is due to other factors (such as medication)
family history	note whether other family members have disease; individuals with a family history of Alzheimer's are at higher risk for developing the disease
physical and neurological exam	check hearing, vision, blood pressure, sensation, muscle strength, and reflexes; abnormal findings may indicate causes of cognitive decline other than Alzheimer's
lab tests (glucose, hormones, vitamin deficiencies, electrolytes, etc.)	rule out metabolic disorders, which can sometimes lead to cognitive symptoms
tests for psychological, functional, and cognitive status	assess mental and daily living function; rule out depression, which can sometimes cause problems with memory; assess cognitive symptoms, as other forms of dementia can manifest in different ways
<i>magnetic resonance imaging (MRI)</i> or computerized tomography (CT) scan	look for brain structural lesions and atrophy; tumors or strokes can also cause cognitive symptoms
<i>positron emission tomography (PET)</i> scan	less common than MRI, it may be used to diagnose certain dementias, including Alzheimer's, with more certainty
cerebrospinal fluid (CSF) analysis	can be used to confirm or rule out Alzheimer's disease; CSF analysis can look for free-floating proteins that make up plaques and tangles that are the hallmarks of Alzheimer's

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Perhaps due to this diagnostic complexity and the presence of other chronic diseases in older people, many cases of Alzheimer's and other dementias slip under the radar. Recent studies in high-income countries and a US study of death certificate data<sup>14</sup> indicate that more than half of dementia patients go undiagnosed.<sup>15</sup> Alzheimer's cannot be confirmed definitively until after death, when the patient's brain is examined under a microscope.

New technologies being used in research studies on Alzheimer's are shifting toward diagnosing the disease at earlier stages, when symptoms are mild or even absent. Although developing drugs for Alzheimer's has proven a formidable challenge, experts think treating at early stages—before full-blown dementia sets in—will stand the best chance of success.<sup>16</sup>

### DIFFERENT TYPES OF ALZHEIMER'S

Clinicians recognize two forms of Alzheimer's, *early-onset* and *late-onset*. Early-onset is so named because symptoms develop earlier, generally between 30 and 60 years of age.<sup>17</sup> This form of the disease represents less than 5 percent of Alzheimer's cases. Most cases of early-onset Alzheimer's are caused by *heritable* changes in one of three genes, called *APP*, *PSEN1*, and *PSEN2*. These gene mutations act in *autosomal dominant* fashion. That means inheriting just one copy of the mutation virtually guarantees disease, and parents with one of these mutations have a 50 percent chance of passing it to their children. Consequently, early-onset Alzheimer's tends to run in families.

The vast majority of Alzheimer's patients have the late-onset type, with symptoms typically beginning after age 60. Like other complex medical disorders, late-onset Alzheimer's has no single cause. Rather, a person's risk of late-onset Alzheimer's is the result of a combination of genetic and environmental influences. The greatest risk factor is one we cannot control: growing older. After 65 years of age, a person's risk of developing Alzheimer's doubles every five years.<sup>18</sup>

After 65 years of age, a person's risk of developing Alzheimer's doubles every five years

	Early-onset	Late-onset
frequency	<5% of AD cases	>95% of AD cases
onset of initial symptoms	30-60 years of age	60 years or older
cause	mostly inherited gene mutations; little or no environmental influence	risk influenced by multiple genetic and environmental factors

### Late-onset Alzheimer's risk factors: genetic

Besides advancing age, family history also seems to make a difference. People whose immediate family members have Alzheimer's face a higher risk of developing the illness.<sup>19</sup> This means there are likely genetic factors yet to be identified that contribute to the development of Alzheimer's.

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The strongest risk gene is apolipoprotein E (*APOE*), which encodes a protein involved in cholesterol metabolism. *APOE* comes in several forms, or *alleles*:

- *APOE3* (*APOE* ε3) is the most common allele. Found in 79 percent of the population,<sup>20</sup> this *APOE* variant is considered “neutral”—neither decreasing nor increasing a person’s risk for Alzheimer’s.
- *APOE2* (*APOE* ε2) is believed to be protective, but only 7 percent of people have this variant.<sup>21</sup>
- *APOE4* (*APOE* ε4), found in about 14 percent of the population,<sup>22</sup> is the strongest *genetic risk factor* for late-onset Alzheimer’s disease. On average, people with a single copy of *APOE4* are three times as likely to develop Alzheimer’s, relative to individuals with the neutral variant *APOE3*. Having two copies of *APOE* ε4 drives up one’s disease risk 12-fold.

However, the connection between Alzheimer’s and its top risk gene is murky at the level of the individual. Since only 40 to 65 percent of Alzheimer’s patients carry at least one copy of *APOE4*,<sup>23</sup> clearly this variant does not guarantee disease. And, importantly, many with Alzheimer’s do not have the *APOE4* gene variant. Other genes also contribute to disease risk,<sup>24</sup> though their influence is not as strong as that of *APOE4*. The overall amount of Alzheimer’s risk attributed to all known genetic factors is estimated to be around 70 percent<sup>25</sup>—which means lifestyle and other environmental factors play a role as well.

### Why the big ranges?

Genetic studies—even those focusing on the same gene—can report different estimates due to variations in sample population or methods. For example, one study might enroll subjects in a certain age range while another focuses on those of a particular ethnicity. Other differences could arise from the methods or statistical techniques used by researchers to analyze the data. Sometimes researchers will conduct a *meta-analysis* to pool findings from multiple studies. This was done to study how age, sex, and ethnicity can influence the effect of the *APOE4* risk allele on Alzheimer’s disease.<sup>26</sup>

### Late-onset Alzheimer’s risk factors: environmental

Studies suggest that people who suffer a head injury face higher risk of future Alzheimer’s,<sup>27</sup> and growing evidence links heart health with brain health.<sup>28</sup> Having diabetes, for instance, is associated with increased risk for Alzheimer’s.<sup>29</sup> This suggests that staying fit and eating healthy—measures to prevent cardiovascular disease and diabetes—may also help stave off future dementia.

Keeping the brain active through social engagement or intellectually stimulating activities also seems to be associated with a lower risk of Alzheimer’s. Scientists believe these activities could protect the brain by establishing “cognitive reserve,” which allows the brain to function effectively even when damaged.<sup>30</sup>

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### MANAGING DISEASE

Several medications can help manage cognitive symptoms of Alzheimer's disease by boosting communication between nerve cells.<sup>31</sup> Severe behavioral symptoms of Alzheimer's are sometimes treated with antidepressants, antipsychotics, or sleep medications.<sup>32</sup>

Drug	Brand name	Approved for	FDA approved
donepezil	Aricept	all stages	1996
galantamine	Razadyne	mild to moderate	2001
memantine	Namenda	moderate to severe	2003
rivastigmine	Exelon	all stages	2000
donepezil +memantine	Namzaric	moderate to severe	2014

That said, despite decades of research and billions of dollars in *clinical trials*, there is yet no approved therapy that targets the underlying mechanisms of Alzheimer's disease.

Nevertheless, steady small gains in federal funding in recent years—including a 60 percent boost in 2016—have rejuvenated the field.<sup>33</sup> Researchers are pursuing a wider variety of potential drug targets, and companies are aiming to test therapies in people in whom the disease hasn't progressed as far.

#### What about behavioral interventions?

On the nonpharmaceutical front, consumer interest in so-called brain training—computer-based games or exercises that claim to boost cognitive performance—is growing. However, the science on whether these interventions are effective remains unclear. One research group reported in 2010 that brain-training programs had little to no impact on cognition.<sup>34</sup> However, five years later the same group published a study in the elderly that shows online cognitive training did produce some benefits in reasoning and other cognitive skills.<sup>35</sup> And research suggests that lifestyle factors such as nutrition, exercise, stress management, and keeping the heart healthy could stave off dementia.<sup>36</sup>

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## CLINICAL TRIALS

### THE BASICS<sup>37, 38</sup>

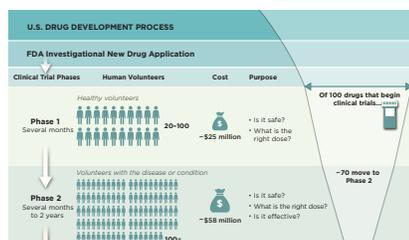
The quest for a new drug begins in the laboratory with *basic* and *preclinical research*, in which scientists conduct experiments to study a compound's effects on cells or animals. Preclinical studies may screen for compounds that have the desired effect. They also weed out compounds with dangerous and adverse effects. Most candidate drugs tested in preclinical research never make it out of the laboratory.

Promising candidates move into clinical trials, which enroll human subjects to answer important questions: Does the drug have side effects? Does it work? How does it compare to other therapies for the same disease? Clinical testing—mostly funded by the pharmaceutical industry but also by the US National Institutes of Health and other agencies—proceeds in several phases. Each has a different focus, but together they have the overarching goal of determining if a new treatment is safe and effective.

To distinguish true drug effects from beneficial physical or emotional changes that don't derive from the substance being tested, clinical trials *randomize* some participants into a *placebo* group. These individuals receive an inactive substance that looks like the drug being tested. In addition, many studies are *double-blinded*—meaning that neither investigators nor participants know who receives drug or placebo. To make sure company personnel don't influence study procedures or outcomes, some study sponsors will hire a *contract research organization* (CRO) to conduct trials and analyze data.

Compounds that succeed in phase 3 of clinical testing can be submitted for review by the Food and Drug Administration (FDA). At this point the agency decides if the evidence for a drug's safety and effectiveness is good enough to let it go to market, a process that takes at least six months for new drugs.<sup>39</sup> Some approved therapies undergo further testing (phase 4) in larger numbers of people to monitor long-term safety and effectiveness. Many studies are listed in [clinicaltrials.gov](http://clinicaltrials.gov), a public registry of the NIH with information including the trial's location, who is eligible, and what will be measured.

(See Addendum: [Clinical Trial Pipeline Graphic](#).)



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	Participants	Study length	Purpose	% of drugs that reach next phase
Phase 1	20-100 healthy volunteers or people with the condition	several months	safety and dosage	70%
Phase 2	up to several hundred people with the disease	several months to two years	efficacy and side effects	30%
Phase 3	300 to 3,000 volunteers with the disease	one to four years	efficacy and monitoring side effects	25%-30%
FDA Review and Approval				
Phase 4	several thousand volunteers with the disease	longer trials done after drug gains FDA approval	long-term safety and efficacy	N/A

**Don't take phase 1 results as a demonstration of efficacy.** Phase 1 studies are small studies that are usually done in healthy volunteers. The primary goal is to determine if the drug is safe and figure out what doses to use in subsequent studies.

On average, a drug's journey from initial lab discovery to the patient takes more than a decade and costs about \$2.6 billion.<sup>40</sup> That huge price tag factors in research and development costs for compounds that looked promising initially but ultimately failed to gain FDA approval—the fate awaiting about 90 percent of experimental therapies that enter clinical testing.<sup>41</sup>

**New Drug Application (NDA)**<sup>42</sup> If a drug succeeds in phase 3, the study sponsor completes an NDA to ask the FDA to consider approving the new therapy for marketing in the US. An NDA includes all animal and human data as well as information about how the drug behaves in the body and how it is manufactured. The FDA then has 60 days to decide if the application is complete and suitable for review. Once the FDA decides to file the NDA, the agency aims to review the evidence and make a decision in 6 to 10 months.

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### ALZHEIMER'S DISEASE CLINICAL TRIALS

Developing new drugs to address an unmet medical need such as Alzheimer's is a long, complex, and expensive process. This is in contrast to the relatively fast and less expensive process of getting approval of a drug in an existing class: for example, a slightly modified painkiller. For Alzheimer's drug candidates, the success rate has been especially low. Of 230 experimental therapies in clinical trials completed between 2002 and 2012, only one (memantine) was approved for marketing—a 99.6% failure rate.<sup>43</sup>

More than 95 percent of the therapeutic agents in Alzheimer's clinical trials during that decade (2002-2012) were classified as “symptomatic” or “disease-modifying.”<sup>44</sup>

	Symptomatic		Disease-modifying		Therapeutic device	Stem cells
	for mental function	for behavior	small molecule	immuno-therapy		
Total	151	22	145	76	16	3
Percent	37	5	35	18	4	1

Symptomatic therapies can help by reducing signs and symptoms. All existing medications for Alzheimer's, including memantine, fall under this category. Some of these drugs can boost mental function by preventing breakdown or enhancing activity of chemical messengers called neurotransmitters. However, they only work for about half the people who take them, and their benefits are temporary, lasting six to 12 months, on average.<sup>45</sup> This is because, as the disease progresses, new symptoms emerge that are caused by mechanisms not targeted by the medication.

Some medications can alleviate behavioral issues—for example, anxiety, depression, and sleep disturbances—associated with Alzheimer's.<sup>46</sup>

The holy grail for Alzheimer's drug development is a disease-modifying agent that slows the rate of cognitive decline by targeting underlying biological mechanisms. No disease-modifying drug has yet shown effectiveness in an Alzheimer's phase 3 trial. Disease-modifying therapies have predominantly targeted beta-amyloid. Other approaches have focused on neuroprotection or inflammation, and some target a brain protein called tau.<sup>47</sup>

Multiple lines of evidence point to beta-amyloid and tau playing central roles in Alzheimer's disease.

- Amyloid plaques often accumulate in the brain before tau tangles—and these brain changes are detectable with PET imaging 10 to 20 years before a person shows signs of dementia.

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- Genetic mutations associated with beta-amyloid synthesis and regulation are found in families with the hereditary, early-onset form of Alzheimer's.
- Tangles tend not to spread throughout the brain unless amyloid is present.
- Buildup of tau, compared to amyloid, seems more closely linked to neuron death.

As one Alzheimer's researcher puts it, the current thinking is that beta-amyloid pulls the trigger and tau is the bullet that eventually kills the nerve cells.<sup>48</sup>

### Challenges for Alzheimer's drug trials

While researchers *can* reliably detect brain changes that indicate high likelihood of developing Alzheimer's (the first such test gained FDA approval in 2012<sup>49</sup>), the methods are costly and invasive. Thus, the procedures are not accepted for wide clinical use, especially as there is yet no effective treatment for Alzheimer's. However, the methods are used increasingly in research. It is precisely those individuals—cognitively normal people on the verge of decline—whom researchers want to *recruit* for newer clinical trials, because they think such individuals stand the best chance of benefiting from a potential treatment.

As one Alzheimer's researcher puts it, the current thinking is that beta-amyloid pulls the trigger and tau is the bullet that eventually kills the nerve cells

**Long studies.** In order to show that a treatment “works” in people who don't show symptoms, researchers need to monitor participants for years—long enough to see a slower *rate* of cognitive decline in the group randomly selected to receive the treatment, compared to the subjects randomized to a placebo.

**Enrolling enough participants.** People with Alzheimer's—and even those on the verge of Alzheimer's—are older and often have other health issues. Some are not mobile and many have trouble traveling to the trial sites for all the required testing. And since the trials last for years—and involve multiple invasive and time-consuming procedures—some participants drop out before testing is complete, which makes it harder to analyze and interpret results.

**Methodological difficulties.** Many of the standard cognitive tests for Alzheimer's are not sensitive enough to distinguish a cognitively normal person from someone who is showing subtle hints of decline. Plus, there isn't yet a blood test or other cheap, reliable method to screen for early Alzheimer's before symptoms appear. Developing more sensitive cognitive tests and detecting beta-amyloid and tau in cerebrospinal fluid represent the cutting edge of clinical Alzheimer's research today.

**Finding the right participants.** Experts say some Alzheimer's drug trials have failed because tests were not conducted on the right people.<sup>50</sup> Often the subjects' brain damage was too advanced—by the time symptoms appear, neurons in the brain have already died, causing

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irreversible damage. Sometimes the drug did not enter the brain in sufficient quantity to make a difference. In other cases, patients who were recruited for a study might not have had Alzheimer's to begin with. In several high-profile drug trials, brain imaging revealed that about a quarter of the study's patients turned out to lack the amyloid *pathology* that the experimental therapies were designed to target.<sup>51</sup>

### ON THE HORIZON

With this in mind, researchers have initiated several large clinical trials<sup>52</sup> to see if amyloid-lowering immunotherapies can stop Alzheimer's before symptoms begin.

	DIAN-TU	API Colombian	API APOE4	A4
enrollment	210	300	1,340	1,150
phase	Phase 2/3	Phase 2	Phase 2/3	Phase 3
length for each participant	4 years	5 years	5 years	3.25 years
anticipated end date	2019	Sep 2020	Aug 2023	2020
interim results expected	2017, 2018	TBD	TBD	N/A
drug(s)	gantenerumab (Roche) and solanezumab (Eli Lilly)	crenezumab (Genentech/Roche)	CAD106 vaccine & CNP520 oral BACE inhibitor (Novartis/Amgen)	solanezumab (Eli Lilly)
mode of action	amyloid-binding antibodies	amyloid-binding <i>antibody</i>	beta-amyloid <i>immunization</i> ; small molecule designed to prevent amyloid production	amyloid-binding antibody
participants	15 years before to 10 years after family member's age of onset; have autosomal dominant AD gene mutation and/or have parent/sibling with mutation	age 30-60; no memory problems; participants come from an extended family with history of early-onset Alzheimer's	age 60-75; no memory problems; two copies of <i>APOE4</i> risk allele	age 65-85; no memory problems; brain amyloid detected with PET scan

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The Dominantly Inherited Alzheimer Network Trial Unit (DIAN-TU)<sup>53</sup> enrolled people from families with a known genetic mutation that causes autosomal-dominant Alzheimer's; participants need not find out their own genetic status but must have an affected parent or sibling with a known genetic mutation.

The Alzheimer's Prevention Initiative (API) launched a major prevention trial to test if a drug can delay or stop Alzheimer's disease. The trial has enrolled members of a large extended Colombian family destined to develop symptoms in their 40s because they carry a gene mutation.<sup>54</sup> More recently, API launched a trial in older adults who are clinically healthy but carry two copies of the *APOE4* risk allele.<sup>55</sup> The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study has enrolled over 1,000 older adults who were cognitively normal but deemed "at risk" based on PET scans that detected high levels of brain amyloid.<sup>56</sup>

Despite several decades of failed drug trials, the detection of telltale brain changes (e.g., amyloid plaques) 10-20 years before symptoms gives many Alzheimer's researchers reason for hope. In their view, the ability to measure presymptomatic disease was the way forward in other disorders such as arteriosclerosis, cancer, diabetes, and osteoporosis. For Alzheimer's, the slow buildup of amyloid plaques in the brain could be considered "a glass half-full," offering a window of time to give treatment that could prevent disease.<sup>57</sup>

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### GLOSSARY

**allele**—one of several forms of a gene. Different alleles can result in different characteristics, such as an increased or decreased risk of developing Alzheimer's.

**antibody**—a protein produced by the immune system in response to bacteria, viruses, or other foreign substances in the body. Antibodies bind to these substances and tag them for destruction.

**autosomal dominant (inheritance)**—a pattern of inheritance in which having a single copy of an allele is sufficient to cause a particular outcome or characteristic.

**basic research**—fundamental research driven by a researcher's curiosity or interest in a scientific question. (See also "applied research" and "preclinical research".)

**beta (or  $\beta$ )-amyloid**—a part of the amyloid precursor protein found in plaques, the clumps of protein characteristic of Alzheimer's disease.

**clinical trial**—a research study involving humans that tests safety, side effects, and how well a medication or behavioral treatment works.

**contract research organization (CRO)**—a person or organization (commercial, academic, or other) contracted by a trial sponsor to run and analyze data from a clinical trial.

**dementia**—a broad term referring to a decline in cognitive function to the extent that it interferes with daily life and activities.

**double-blind**—a clinical trial study design in which neither investigators nor participants know the dose of medication (or placebo) the subject is receiving.

**early-onset Alzheimer's disease**—the rarer form of Alzheimer's disease that usually affects people between ages 30 and 60. It is called familial AD (FAD) if it runs in the family.

**genetic risk factor**—a variant in a person's DNA sequence that does not determine whether that person will get a particular disease, but increases their chance of developing the disease.

**heritable**—able to be inherited; transmissible from parent to offspring.

**immunization**—process by which a person is made immune or resistant to an infectious disease, usually by administering a vaccine.

**late-onset Alzheimer's disease**—the most common form of AD. It occurs in people aged 60 and older.

**magnetic resonance imaging (MRI)**—a diagnostic and research technique that uses magnetic fields to generate a computer image of internal structures in the body. MRIs are particularly good for imaging the brain and other soft tissues.

**meta-analysis**—statistical technique for combining findings from multiple independent studies.

**pathology**—study of the nature of disease and its causes, processes, development, and consequences; the typical behavior of a disease.

**placebo**—an inactive substance delivered in an identical manner as an active drug being tested. It is used as a control to rule out psychological effects that may be associated with being in a trial.

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**plaque (amyloid)**—a sticky protein deposit that accumulates in the space between nerve cells in the brain in Alzheimer's patients. Plaques may be present years before any noticeable symptoms of disease. Plaques form when protein pieces called beta-amyloid clump together.

**positron emission tomography (PET)**—a type of imaging test that uses a radioactive substance called a tracer to observe processes in the body.

**preclinical research**—the stage of research, using animals and/or cell culture, that takes place before any testing in humans is done, primarily to assess safety and dosage.

**randomization**—assignment of study participants into groups in such a way that individuals may be assigned to each treatment or control group.

**recruitment**—process of enrolling subjects who meet the study's inclusion criteria into a clinical trial.

**tangle (neurofibrillary)**—aggregates of twisted, abnormal forms of tau protein found in the cell body of a neuron in Alzheimer's disease and other neurodegenerative diseases.

**tau**—a protein that helps to maintain the structure of microtubules in normal nerve cells. Abnormal tau is the principal component of neurofibrillary tangles associated with a variety of neurodegenerative conditions, including Alzheimer's disease.

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### RESOURCES AND CONTACTS

Alzheimer's Association

<http://www.alz.org/>

Alzheimer's Disease Education and Referral Center

<https://www.nia.nih.gov/alzheimers/>

2015 Alzheimer's Disease Facts and Figures

[https://www.alz.org/facts/downloads/facts\\_figures\\_2015.pdf](https://www.alz.org/facts/downloads/facts_figures_2015.pdf)

Alzforum

<http://www.alzforum.org/>

AlzRisk database of environmental risk factors

<http://www.alzrisk.org/>

Warning signs of Alzheimer's and how to distinguish it from normal aging

[http://www.alz.org/national/documents/aa\\_brochure\\_10warnsigns.pdf](http://www.alz.org/national/documents/aa_brochure_10warnsigns.pdf)

Database of therapies currently or previously tested as treatments  
for Alzheimer's or related disorders

<http://www.alzforum.org/therapeutics>

Worldwide trials registry and results database

<https://clinicaltrials.gov>

Alzheimer's disease genetics fact sheet

<https://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-genetics-fact-sheet>

Database of genetic association studies in Alzheimer's

<http://www.alzgene.org/>

NIH clinical trials basics

<http://www.nih.gov/health-information/nih-clinical-research-trials-you/basics>

"Addressing Alzheimer's: What Do We Know?" A conversation with  
Duke psychiatrist P. Murali Doraiswamy at 2016 World Economic Forum

<http://www.weforum.org/events/world-economic-forum-annual-meeting-2016/sessions/addressing-alzheimer-s-what-do-we-know>

*Can Alzheimer's Be Stopped?* A PBS-NOVA special

<http://www.pbs.org/wgbh/nova/body/alzheimers-be-stopped.html>

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## ADDENDUM

### The Clinical Trial Pipeline

