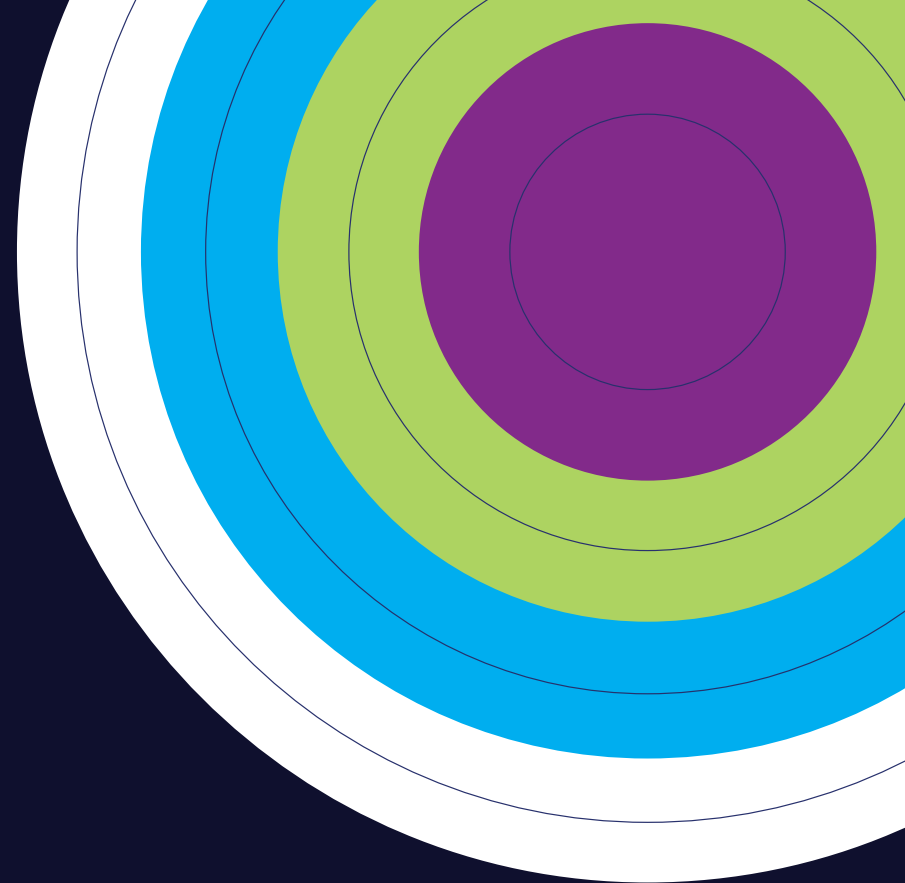




Alzheimer's
Drug Discovery
Foundation

2018 ALZHEIMER'S CLINICAL TRIALS REPORT



"The time is now to strengthen our commitment to conquer this disease"

Dear Friends,

Alzheimer's disease is a progressive neurodegenerative disease that affects 5.5 million people in the United States and at least 50 million globally. With a growing aging population, these staggering statistics could triple by 2050. New therapies that prevent, slow, or stop the disease are urgently needed.

As a neuroscientist and geriatrician, I have been involved in Alzheimer's research and care for almost 40 years. With the publication of this report, I have never been more optimistic than I am today about finding a cure. We see a diverse pipeline with over 100 drugs in clinical trials; the Alzheimer's Drug Discovery Foundation (ADDF) has provided support for nearly 20% of these.

Our understanding of Alzheimer's is stronger than ever before. We have entered an exciting era as researchers have begun to focus on a wide range of therapeutic avenues and approaches that go beyond the traditional amyloid and tau targets. Many are focused on targets associated with aging biology. Given that aging is the leading risk factor for Alzheimer's disease, the ADDF has long focused its attention to better understand why the aging brain is vulnerable to Alzheimer's disease, and is driving the translation of the biology of aging into new drugs.

This report highlights the potential treatments currently being tested in clinical trials for Alzheimer's, with more than half in phase 2. As we move forward, it is critical to have the right diagnostic tools in place to increase the success of these clinical trials.

The time is now to strengthen our commitment to conquer this disease. It will take the continued collaborative efforts of philanthropists, investors, government, academia, and the biopharma industry to get there. We have developed safe and effective therapeutics for other chronic diseases of aging, like cancer and heart disease. We can do it for Alzheimer's. We could be just one idea away.

Sincerely,



HOWARD FILLIT, MD

Founding Executive Director and Chief Science Officer
Alzheimer's Drug Discovery Foundation

TABLE OF CONTENTS

1

Executive Summary

2-3

Terms & Definitions

4

Clinical Trials Pipeline

5

2018 Clinical Trials
by the Numbers

6-7

Phase 1 Clinical Trials

8-9

Phase 2 Clinical Trials

10-11

Phase 3 Clinical Trials

12

Drugs for Behavioral
Symptoms in Clinical Trials

13

Prevention Treatments
in Clinical Trials

14-17

The State of the Field,
and Looking Ahead

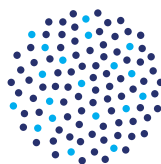
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Our Methods

EXECUTIVE SUMMARY

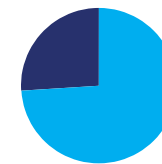
The past 20 years have seen tremendous progress in understanding the biological changes that can lead to Alzheimer's disease. Despite this progress, and notwithstanding the hundreds of drugs that have been tested in clinical studies, we still lack treatments that can slow or prevent the disease. Alzheimer's drug development is complicated by the fact that Alzheimer's is a complex disease that can be caused by multiple factors. Patients can have varying brain pathologies that may require different and individualized therapies. The development of drugs that combat different underlying causes may one day provide patients with targeted and personalized treatment options.

In this report, the Alzheimer's Drug Discovery Foundation (ADDF) surveys the landscape of clinical trials for Alzheimer's. As of the writing of this report, there were over 220 active clinical studies. These include studies of drugs and interventions like diet and exercise, and the testing of new PET tracers for disease detection. The data presented here focus on: **disease-modifying agents** that slow, stop, or possibly even reverse the disease course once cognitive symptoms are present; **symptomatic agents** that treat behavioral symptoms like agitation; and **drugs for prevention** that avert cognitive decline in at-risk subjects before a diagnosis. The following is a summary of key highlights:



102 Potential Treatments for Alzheimer's Disease are in Clinical Development

The ADDF has supported nearly 20% of these clinical-stage drugs.



74% of Potential Treatments Focus on Novel Targets

Researchers are now moving beyond traditional amyloid and tau approaches and are developing drugs for a multitude of targets associated with aging biology in the effort to combat Alzheimer's. All of the therapies supported by the ADDF use novel approaches.



63% of Potential Treatments are in Phase 2 Trials

There are 20 drugs in phase 1, 65 in phase 2, and 17 in phase 3.

15 Drugs to Address Symptoms and 14 Prevention Drugs

Beyond the 102 potential treatments, other clinical trials are underway for agents designed to prevent the onset of the disease, or to address symptoms experienced by Alzheimer's patients, such as agitation, depression, and insomnia.

Biomarkers Are Strengthening Clinical Trials

Biomarkers, or objective measurements of biological processes, are helping to increase the success of clinical trials and have been used to measure successful target engagement. More than half of ADDF-funded trials use target engagement biomarkers.

TERMS & DEFINITIONS

The ADDF's scientific staff carefully reviewed information about each drug listed. This section defines the terms used in this publication.

Path to the Clinic



Novel

These drug programs were wholly developed by researchers and generate intellectual property considered "novel composition of matter."



Repurposed

This refers to existing drugs that are FDA-approved for other diseases or conditions and are now being tested for Alzheimer's.



Repositioned

These are drugs in development that entered clinical trials for other indications, have not yet been approved by the FDA, and are now being tested for Alzheimer's.



Combination

This refers to a combination of more than one of the above.

Type of Therapy



Small Molecule

These are small chemical compounds that can regulate biological processes. Most drugs are small molecules.



Biologic

These include antibodies, hormones (e.g., insulin, allopregnanolone), oligonucleotides (e.g., DNA or RNA), and peptides. Immunotherapies are biologics.



Cell Therapy

These are exclusively stem cell approaches.



Natural Product

This refers to supplements such as vitamins and amino acids, as well as plant extracts.

Type of Research Organization

This refers to the institution that conducts the trial. This is separate from financial support, which can come from a variety of funders, including foundations like the ADDF, federal agencies like the NIH, venture capital, and pharma.



Academic & Non-Profit: Medical centers, universities, or non-profits.



Small-to-Mid-Sized Biotech: Early stage startups and biotechs with an annual revenue of <\$1 billion.



Large Biotech/Pharma: Companies with an annual revenue of >\$1 billion, and a network of production and distribution.



Government Agency: Federal agencies like the National Institutes of Health (NIH) and the VA.

Type of Target

This is the primary biological process the drug is attempting to affect. (We labeled a target as “unknown” when the mechanism of the drug remains unclear or has not been disclosed).

Neuroprotection: As Alzheimer’s disease progresses, neurons lose their connections and begin to die, causing the loss of memory and other essential cognitive functions. Neuroprotective strategies attempt to shield brain cells from multiple causes of damage and death.

Inflammation: Chronic inflammation in the brain can accelerate Alzheimer’s disease and may be a trigger of the disease. But normal inflammatory responses can also protect the brain from damage.

Synaptic Activity & Neurotransmitters: Synapses are spaces between our neurons and are important for communication between these cells. Neurotransmitters carry signals across these spaces, which is critical for memory and cognition. In Alzheimer’s, these synapses can become damaged and their ability to send or receive neurotransmitters is often impaired.

Genetics & Epigenetics: Inheriting certain genes such as APOE4 can affect our risk for Alzheimer’s disease. Epigenetic processes regulate how much our genes are expressed. They act like a dimmer switch, turning genes on and off.

Misfolded Proteins: In Alzheimer’s, proteins like amyloid, tau, and TDP-43 can misfold and become toxic. These misfolded proteins accumulate into plaques, tangles, and other forms in the brain if not cleared by the brain’s self-repair mechanisms.

Mitochondria & Metabolic Function: All cells need energy to maintain healthy function, and neurons (i.e., brain cells) are among the highest energy users. As we age, mitochondria—the energy centers of our cells—can become impaired as can other aspects of cellular metabolism.

Vascular: Healthy blood flow is required for optimal brain function. Vascular damage can affect how misfolded proteins and toxins are removed from the brain and can limit the ability of neurons to get sufficient oxygen and vital nutrients.

THE CLINICAL TRIALS PIPELINE

Clinical trials are the final stops along the drug discovery pipeline before a drug can be approved by the FDA and made available to the public. The active Alzheimer's clinical trials in this report are organized by phase. The objectives of each phase are as follows:

PHASE 1

Testing for Safety

This is generally the first point at which a drug is tested in humans. The drug is evaluated for safety and possible side effects, and its optimal dose is determined.

PHASE 2

Testing for Efficacy

Successful trials then move to the "proof-of-concept" stage in patients. Researchers further evaluate safety and test a drug's efficacy for the first time. They may also use biomarkers to test whether or not the drug interacts with its target. This is known as target engagement.

PHASE 3

Proof of Efficacy in Larger Trials

Drugs that succeed in phase 2 are then tested in large groups of patients over a longer time. These trials can include thousands of patients at multiple sites. If successful, the drug can be submitted for FDA approval.

Overview:

2018 CLINICAL TRIALS BY THE NUMBERS

TYPE OF TARGET

- Neuroprotection 25
- Inflammation 10
- Synaptic Activity & Neurotransmitters 18
- Genetics & Epigenetics 2
- Misfolded Proteins 29
- Mitochondria & Metabolic Function 11
- Vascular 5
- Unknown 2



* Including Alzheimer's dementia and mild cognitive impairment

PHASE 1

By Type of Target



NEUROPROTECTION

Longeveron Mesenchymal Stem Cells

NDX-1017 ●

INFLAMMATION

AL002

COR388

NP001

Salsalate

SYNAPTIC ACTIVITY & NEUROTRANSMITTERS

Bisnorcymserine (BNC)

GENETICS & EPIGENETICS

AAVrh.10hPOE2 (AAV delivery of APOE2) ●

Vorinostat

MISFOLDED PROTEINS

BIIB076

JNJ-63733657

Lu AF20513

NPT088

TPI-287

MITOCHONDRIA & METABOLIC FUNCTION

Insulin aspart ●

Medium chain triglyceride drink (MCT drink)

Oxaloacetate (OAA)

Resveratrol and grape seed polyphenolic extract

Tricaprilin (oral formulation of caprylic triglyceride)

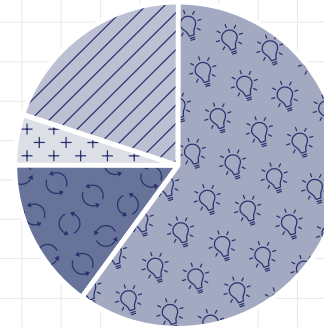
VASCULAR

—

UNKNOWN

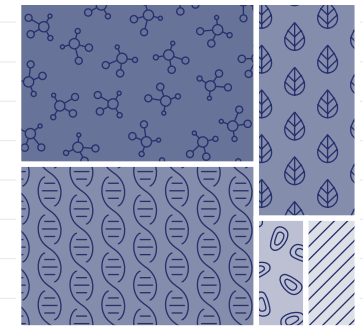
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PATH TO CLINIC



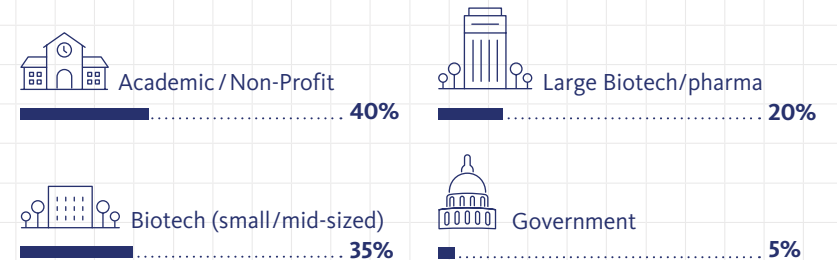
- Novel (60%)
- ↻ Repurposed (15%)
- ↔ Repositioned (0%)
- + Combination (5%)
- /// Other/Unknown (20%)

TYPE OF THERAPY



- Small Molecule (35%)
- ⌚ Biologic (35%)
- 🧬 Cell Therapy (5%)
- 🌿 Natural Product (20%)
- /// Unknown (5%)

RESEARCH ORGANIZATION CONDUCTING THE TRIAL



● Funded by the ADDF

PHASE 2

By Type of Target



NEUROPROTECTION

AMX0035 (sodium phenylbutyrate and TUDACA) ●

ANAVEX2-73

AstroStem (autologous fat stem cells)*

Bryostatin ●

CB-AC-02 (Placental mesenchymal stem cells)*

CERE-110 (AAV Delivery of NGF)

Curcumin and aerobic yoga

Deferiprone (delayed release tablets)

GRF6019 (plasma derived product)

GV1001

Human Mesenchymal Stem Cells and Lactated Ringer's Solution

Human umbilical cord blood derived mesenchymal stem cells*

ID1201

LM11A-31-BHS* ●

Lupron Depot

MLC901

N-831 (Traneurocin)

Omega-3 (PUFA)

RPh201

S-equal*

STA-1

UCMSCs (umbilical cord mesenchymal stem cells)*

INFLAMMATION

Montelukast buccal film

Neflamapimod (VX-745)

Sagramostim (GM-CSF) ●

Valaciclovir

Xanamem

SYNAPTIC ACTIVITY & NEUROTRANSMITTERS

AD-35

BI 425809

CT1812 ●

DHP 1401

Formoterol

Levetiracetam

MMFS-205-SR (L-Threonic Acid Magnesium Salt)

Nicotine Transdermal Patch ●

Piromelatine

Rasagiline ●

Riluzole ●

Rotigotine transdermal patch ●
SUVN-502

GENETICS & EPIGENETICS

—

MISFOLDED PROTEINS

AADvac1
ABBV-8E12
ABvac4o
BIIB092
IONIS MAPTRx*
LY3002813
LY3303560
Meganatural-Az Grapeseed Extract
Methylene Blue
NewGam 10% IVIG
Nilotinib ●
Octagam 10%
Posiphen*
RO7105705
Thiethylperazine (TEP)
UB-311

MITOCHONDRIA & METABOLIC FUNCTION

Benfotiamine (Vitamin B1) ●
Insulin glulisine
Liraglutide ●
Nicotinamide

VASCULAR

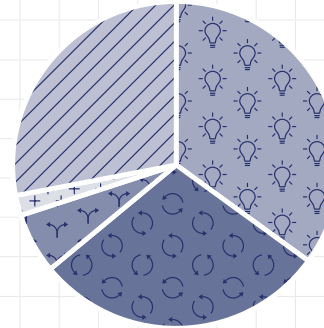
AR1001
Candesartan ●
Cilostazol
Perindopril and telmisartan (comparative effectiveness) ●

UNKNOWN

BAC

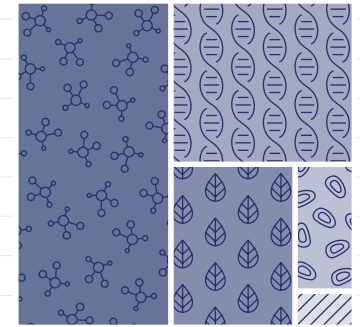
● *Funded by the ADDF* **Designated as phase 1 | phase 2*

PATH TO CLINIC



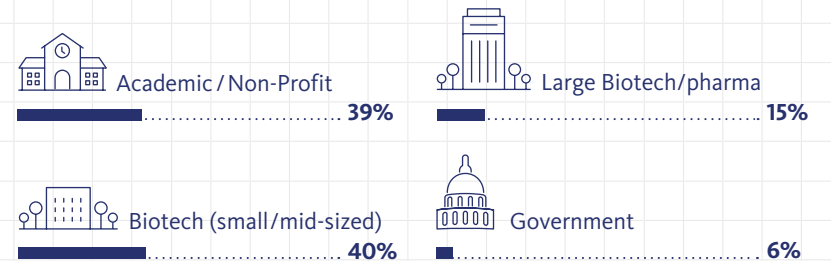
- 💡 Novel (35%)
- ↻ Repurposed (29%)
- ↔ Repositioned (6%)
- ⊕ Combination (2%)
- ⚡ Other/Unknown (28%)

TYPE OF THERAPY



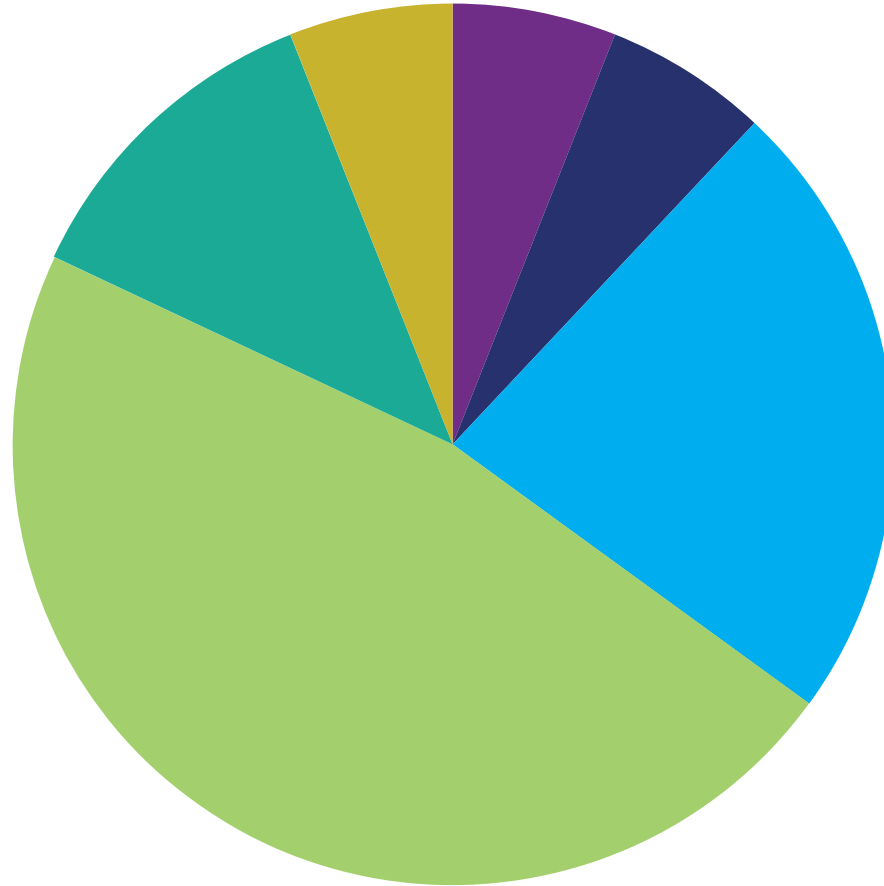
- 🧪 Small Molecule (46%)
- 🧬 Biologic (27%)
- 👤 Cell Therapy (7%)
- 🌿 Natural Product (18%)
- ⚡ Unknown (2%)

RESEARCH ORGANIZATION CONDUCTING THE TRIAL



PHASE 3

By Type of Target



NEUROPROTECTION

Omega-3 (DHA/EPA) ●

INFLAMMATION

ALZT-OP1a (NSAID and cromylyn)

SYNAPTIC ACTIVITY & NEUROTRANSMITTERS

AGB101 (low dose levetiracetam) ●

Guanfacine

Octohydroaminoacridine Succinate

Trigriluzole*

GENETICS & EPIGENETICS

—

MISFOLDED PROTEINS

Aducanumab*

Albumin/Immune globulin

Crenezumab

Elenbecestat

Gantenerumab

Lanabecestat

Sodium oligo-mannurate

TRxo237*

MITOCHONDRIA & METABOLIC FUNCTION

Ginkgo biloba dispersible tablets
+/- Donepezil*

Insulin (Humulin R U-100)*

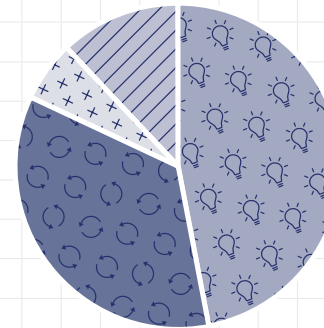
VASCULAR

Isosorbide Mononitrate XL (ISMN)
and Cilostazol*

UNKNOWN

—

PATH TO CLINIC



💡 Novel (47%)

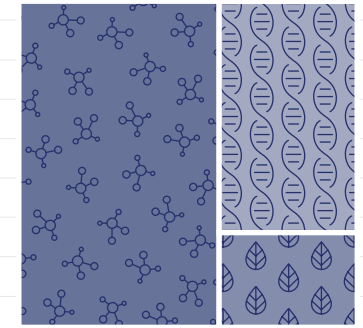
🔄 Repurposed (35%)

↔️ Repositioned (0%)

⊕ Combination (6%)

🌀 Other/Unknown (12%)

TYPE OF THERAPY



🧪 Small Molecule (59%)

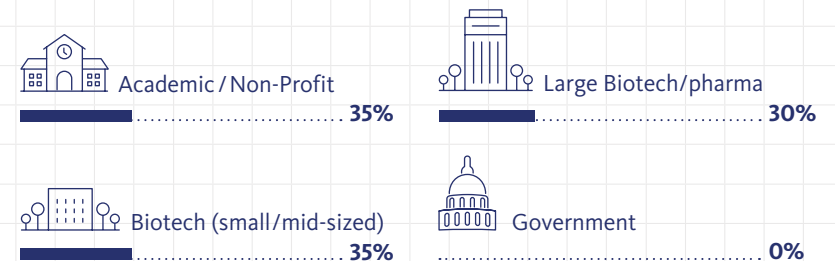
🕒 Biologic (29%)

👤 Cell Therapy (0%)

🌿 Natural Product (12%)

🌀 Unknown (0%)

RESEARCH ORGANIZATION CONDUCTING THE TRIAL



● Funded by the ADDF

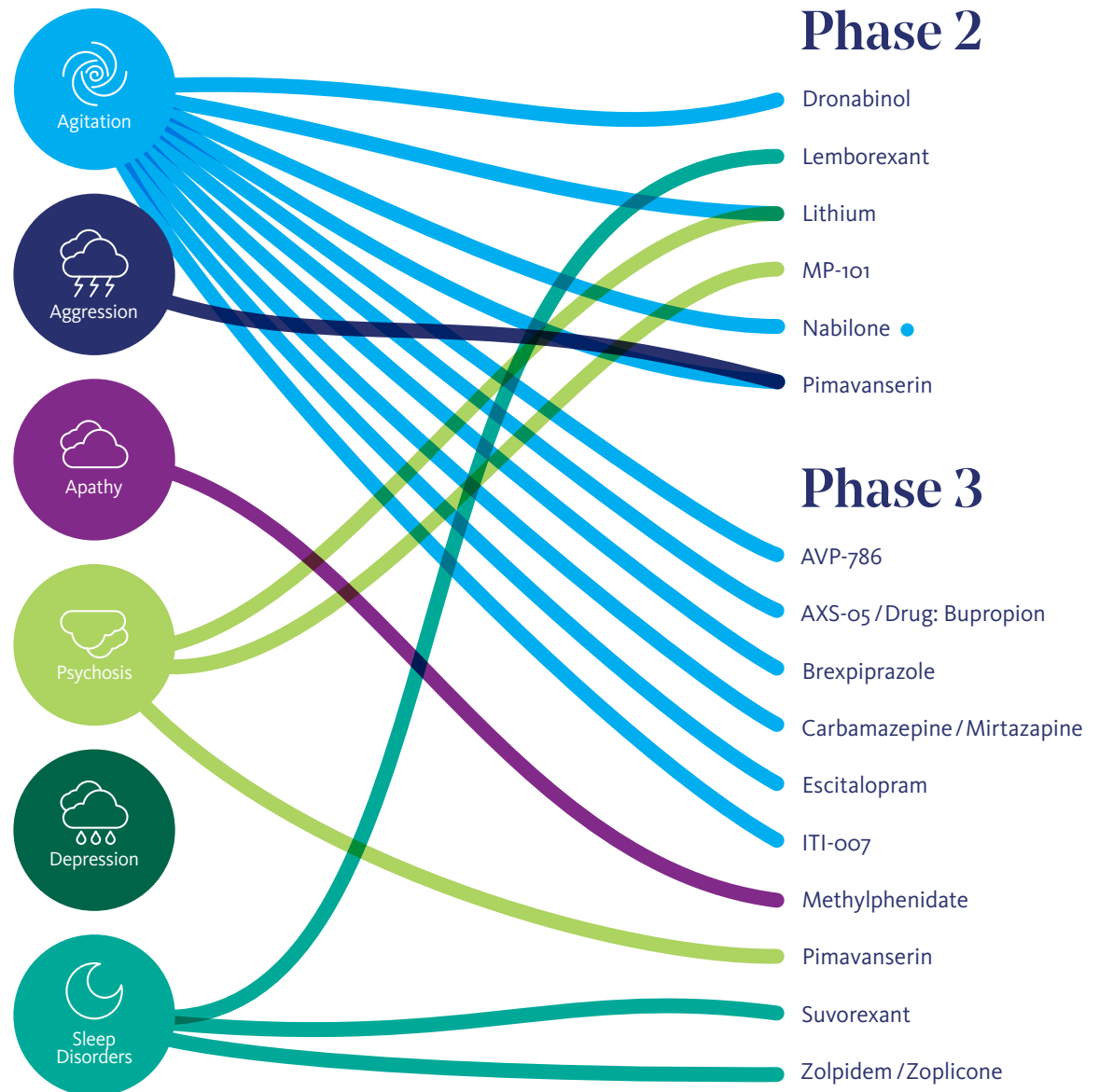
*Designated as phase 2 / phase 3

DRUGS FOR BEHAVIORAL SYMPTOMS

In Clinical Trials

Drugs in this category target behavioral symptoms associated with Alzheimer's. Although these drugs are not disease-modifying, they have the potential to improve quality of life for Alzheimer's patients and their caregivers.

● Funded by the ADDF



PREVENTION TREATMENTS

In Clinical Trials

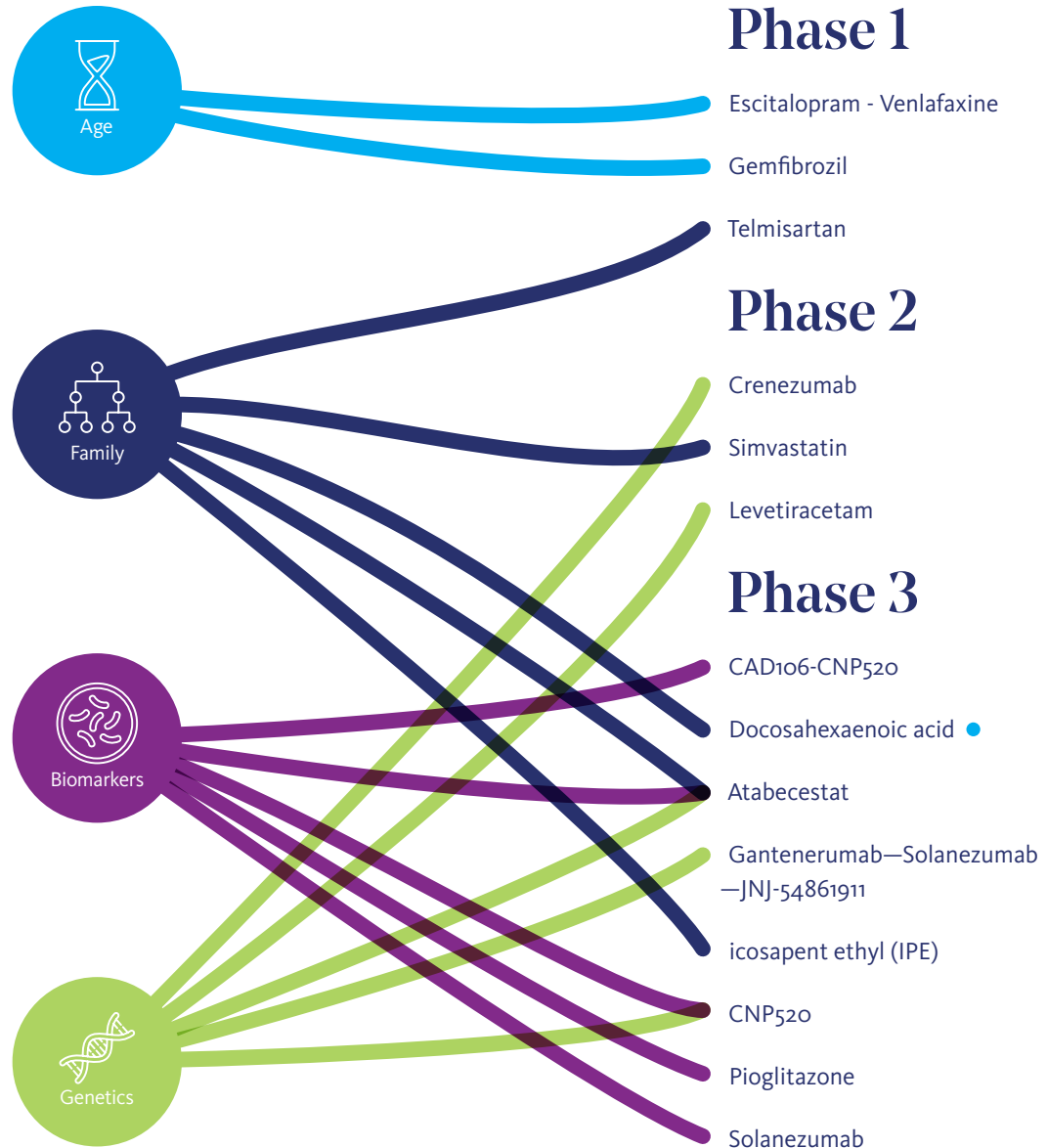
These drugs have the potential to prevent cognitive decline in people who have not developed symptoms or been diagnosed with Alzheimer's disease. The trials are designed to include people with one or more of the following **risk factors**:

Age: Older individuals without symptoms or with reported subjective memory complaints.

Family History: Healthy individuals with relatives who have had dementia.

Early Biomarker Indications: Pre-symptomatic individuals identified as at-risk based on biomarker measures, such as amyloid in the brain.

Genetics: Carriers of genes associated with risk for Alzheimer's (like APOE or rare familial early-onset genes).



THE STATE OF THE FIELD, AND LOOKING AHEAD

Taking Aim at the Right Targets: Aging Biology

Scientists first discovered over 100 years ago that changes occur in the brains of Alzheimer's patients. They observed two distinct features—plaques, which are sticky clumps containing beta-amyloid protein, and tangles, which consist of a protein called tau. Based on these discoveries, much of the focus in the last two decades has been on developing drugs that reduce the abnormal build-up of amyloid and, more recently, tau. Unfortunately, the majority of anti-amyloid drugs have not been successful, leading to uncertainties about the effectiveness of targeting amyloid as a stand-alone therapy. As the field shifts towards new approaches, aging biology may hold promise in developing Alzheimer's treatments.

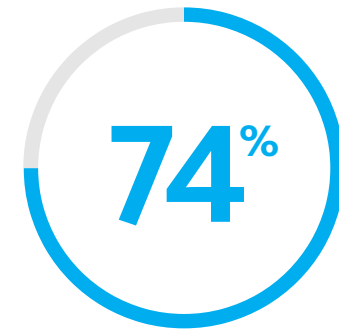
Aging is the leading risk factor for Alzheimer's disease. As we age, many biological processes start

to change in our bodies. Aging and chronic disease can lead to increased inflammation, vascular problems, and changes to our metabolism—all of which can place stress on our brain cells and increase vulnerability to Alzheimer's. These changes can lead to the protein misfolding and dysfunction of our synapses (connections between brain cells), ultimately resulting in the cell death associated with Alzheimer's disease. As was highlighted in a recent review from the ADDF¹ and in the **ADDF's 2017 Alzheimer's Clinical Trials Report**, researchers are now developing drugs for a multitude of targets associated with aging biology, moving beyond traditional amyloid and tau approaches. These novel approaches now make up 74% of the 102 potential treatments in clinical trials listed in this report.

Foundations like the ADDF are contributing to this change by supporting a far-reaching, diversified portfolio that includes drugs targeted toward multiple aging pathways, along with repurposed drugs. In fact, 100% of the therapies supported by the ADDF do not directly target amyloid or tau.

The Importance of Biomarkers

As the field develops more non-amyloid and non-tau drugs, the need has never been greater to expand our arsenal of biomarkers used to



of the 102 potential treatments in clinical trials focus on targets other than amyloid and tau

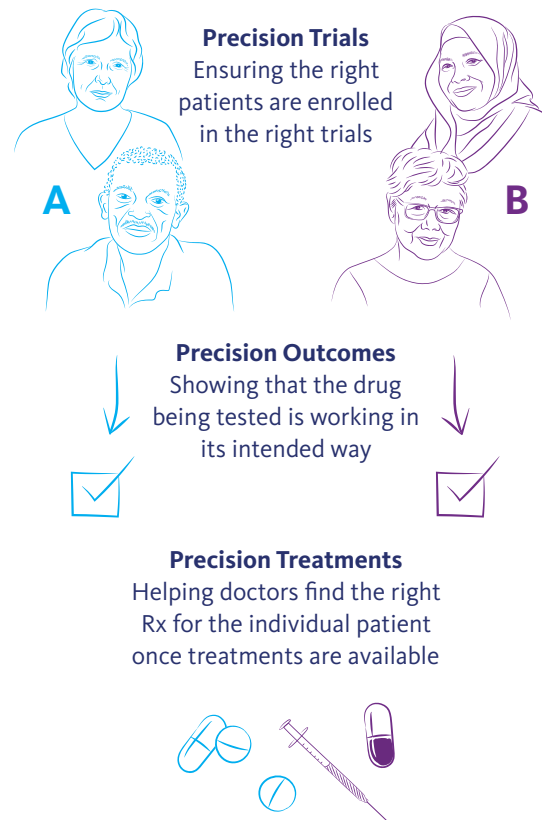
evaluate these novel drugs. As objective, accurate, and reproducible measurements of biological processes, biomarkers provide a window into what's happening inside our bodies and are invaluable tools in drug development. For other diseases, examples of biomarkers include

established technologies like mammograms, tumor biopsies, and blood tests, in addition to emerging technologies such as wearables that can measure heart rate. For cardiovascular disease, one of the most common biomarkers is a blood test for serum cholesterol levels, which can identify at-risk patients and guide treatment recommendations, including lifestyle changes or the prescription of statins. The low cost, ease, and accessibility of the test has revolutionized the treatment of cardiovascular disease.

Currently Available Biomarkers for Alzheimer's
Alzheimer's disease is most commonly diagnosed using basic cognitive tests administered in a doctor's office. These tests may also be used in clinical trials to help enroll patients and to assess the effectiveness of drugs. However, these tests cannot give a definitive Alzheimer's diagnosis. The cognitive symptoms being tested are not specific to Alzheimer's, and results can be highly variable within the same individual depending on the test administrator, and the patient's anxiety level or sleep quality the night before the test, among other factors.

Fortunately, we now have tools that, together with cognitive tests, can help to increase diagnostic

Biomarkers Can Help Advance New Drugs and Get Them to the Right Patients



accuracy and rule out other forms of dementia.² These include PET imaging tests that detect amyloid in the brains of living patients, and spinal taps that test for amyloid and tau in cerebrospinal fluid (CSF), the fluid that bathes the brain and spinal cord.

How Current Biomarkers Improve Clinical Trials

The success of a clinical trial often hinges on how the study is designed. In order to assess whether a drug will be effective in patients, clinical researchers need to be able to show that the drug is acting in the way it was intended (or "hitting its target"), and that it is being tested in people who are likely to benefit from the drug.³ This is where biomarkers can play an essential role.

Showing drug effects

In earlier-stage trials, aside from establishing that the treatment is safe, researchers want to learn the answers to key questions to determine how a drug is working in patients. How does the body respond to a treatment and which dose is the most effective? Does the drug reach the brain and does it interact with its intended target? This is known as target engagement.

In smaller phase 2 trials, for example, if a drug is designed to reduce tau tangles, CSF biomarkers can indicate whether the drug is reducing tau in the brain

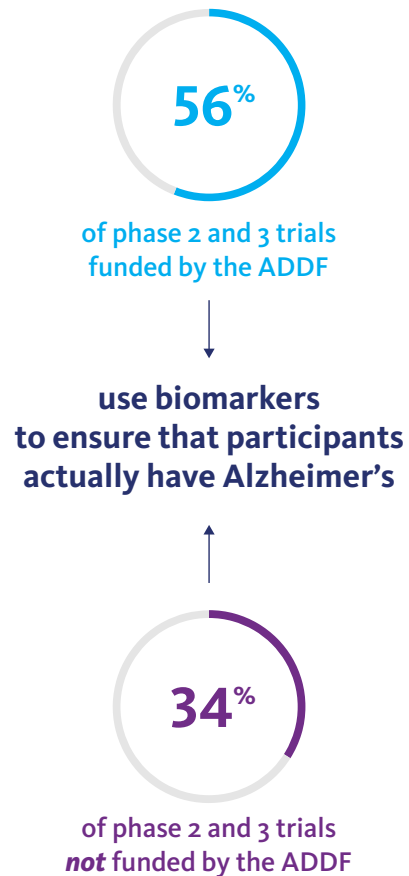
and how many patients are responding to the drug. This information can prevent ineffective drugs from moving forward into long and expensive phase 3 trials that involve thousands of patients. If a drug is eventually approved, physicians can use these biomarkers to determine whether a patient should receive the treatment.

Selecting the right patients

A critical component of clinical trial design is selecting participants who are most likely to benefit from a particular treatment. Existing amyloid and tau biomarkers can provide more confidence that participants enrolled in Alzheimer's trials actually have the disease,⁴ or can identify symptom-free people at risk for developing Alzheimer's, allowing researchers to test drugs designed to thwart the onset of the disease.

The advent of amyloid PET scans has transformed anti-amyloid drug trials, which have historically had a high failure rate. These scans revealed that nearly one third of patients enrolled in previous anti-amyloid trials may not have had amyloid in their brains.⁵ Recent anti-amyloid trials have required that enrolled patients have a positive amyloid PET signal. Ensuring that enrolled participants in these trials have amyloid plaques has increased the odds of success.

The ADDF is a Leader in Funding Better Clinical Trials



Developing More—and Better—Biomarkers

While existing biomarkers have revolutionized the way we conduct clinical trials and will ultimately accelerate the development of drugs for Alzheimer's disease, their use in practice remains limited due to their expense and/or invasiveness of the procedures.

As more therapies with targets other than amyloid and tau are developed—including metabolic problems or increased inflammation—we will need more novel biomarkers that can measure changes in these processes. There are many biomarkers already in development, but they need further research to confirm that they work in patients or to refine methodologies for more widespread use.

The ADDF has long supported the development of biomarkers; we were one of the early funders of Amyvid™, the first approved amyloid PET scan, and we have supported programs developing novel PET agents and tests in CSF and blood. To address the need for more biomarkers, the ADDF partnered with Bill Gates and others to launch the Diagnostics Accelerator in 2018, which aims to advance the development of simple and inexpensive biomarkers for Alzheimer's and related dementias. These include blood tests and digital

With the right tools in place, we can deliver better-designed clinical trials and get treatments to patients faster.

technologies like app-based cognitive testing. These tools will help make clinical trials more rigorous, affordable, and efficient, thus accelerating the development of new drugs and ensuring that they are tested in the right populations.

Where We Go Next:

The Right Therapy for the Right Patient

Oncologists often tailor treatments for a patient's specific type of cancer based on their genetic

background or biomarker information from their tumor.⁶ Ultimately, this is the goal for treating Alzheimer's. Given the different underlying causes of the disease, presentation of symptoms, and genetic backgrounds of patients (with or at risk for the disease), a single treatment may not work in all patients. A personalized medicine approach to Alzheimer's will allow physicians to treat the various contributors to each individual patient's disease. For instance, Alzheimer's patients with elevated inflammatory markers may be more likely to benefit from a drug designed to reduce brain inflammation compared with patients that have plaques and tangles but no signs of abnormal inflammation. Biomarkers that accurately measure inflammation in Alzheimer's patients are needed to get to this more personalized therapeutic approach.

With the right tools in place, we can deliver better-designed clinical trials and get treatments to patients faster. With more treatments and biomarkers on the horizon, we may soon be able to use a personalized medicine approach to treat each Alzheimer's patient.

1. Hara Y, McKeegan N, Fillit HM (2019) **Translating the biology of aging into novel therapeutics for Alzheimer disease. *Neurology* 92, 94-93.**
2. Hampel H, Frank R, Broich K, Teipel SJ, et al. (2010) **Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nat Rev Drug Discov.* 9, 560-574.**
3. Cummings, J (2018) **Lessons Learned from Alzheimer Disease: Clinical Trials with Negative Outcomes. *Clin Transl Sci.* (2018) 11, 147-152.**
4. Ritter A, Cummings J (2015) **Fluid Biomarkers in Clinical Trials of Alzheimer's Disease Therapeutics. *Front Neurol.* 6, 186.**
5. Dolgin E (2018) **Alzheimer's disease is getting easier to spot. *Nature* 559, S10-S12.**
6. Ludwig JA, Weinstein JN (2005) **Biomarkers in Cancer Staging, Prognosis and Treatment Selection. *Nat Rev Cancer* 5, 845-856.**

OUR METHODS

On October 3, 2018, we accessed trial data from **ClinicalTrials.gov** using the following criteria:

Condition / Disease	Status
Alzheimer	Not yet recruiting, Recruiting, Enrolling by invitation, or Active not recruiting
Study Type	Phase*
Interventional studies	Early phase 1, phase 1, phase 2, phase 3

On the date above, there were over 220 active clinical studies, including pharmacological (e.g., drugs, natural products, stem cells) and non-pharmacological (e.g., dietary) interventions, as well as PET imaging agents. Here we report on the pharmacological agents, which were characterized as disease-modifying (aimed at slowing, stopping, or possibly reversing the disease once cognitive symptoms are present), symptomatic (treating behavioral symptoms like agitation), or prevention (preventing cognitive decline in at-risk subjects before a diagnosis). When more than one trial was listed for a single drug, we only listed that drug once. Our analysis centers on the 102 disease-modifying drugs (Pages 6–11).

**For therapies tested in more than one trial, we listed the most advanced trial they have entered or completed. For example, a drug that is being tested in both phase 2 and 3 trials would be listed in phase 3.*



Alzheimer's
Drug Discovery
Foundation

Accelerating the Discovery of Drugs to
Prevent, Treat, and Cure Alzheimer's Disease
[AlzDiscovery.org](https://www.alzdiscovery.org)

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