

# REACHING NEW FRONTIERS FOR ALZHEIMER'S THROUGH RESEARCH AND INNOVATION

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Alzheimer's is one of the most feared diseases in the world—for good reason. No other disease takes from its victims both their pasts and their futures. No other disease among the top 10 causes of death worldwide lacks a treatment to slow it down.

We see Alzheimer's both personally and professionally. One of us has a close relative with Alzheimer's disease who lives in a nursing home. One of us treats patients in a dementia clinic, where many suffer from Alzheimer's without the hope of an effective treatment. Our pharmaceutical company has been trying to develop an Alzheimer's medicine for over three decades—so far without success.

The Alzheimer's challenge is a window into the future. Aging populations will continue to strain budgets for health services—whether that's care for Alzheimer's, cancer, diabetes, heart disease, or other conditions that increase with age. The only viable solution is to stimulate innovation to produce therapies that delay disease and lessen the need for expensive services.

In this chapter, we describe the current state of Alzheimer's and the challenges of Alzheimer's drug development, which have contributed to longer development timelines for Alzheimer's and higher failure rates for clinical trials. We suggest policy solutions that could lower these barriers—helping deliver treatments that give hope to patients and the health systems that care for them.

## The state of Alzheimer's

Alzheimer's disease (AD) is a chronic, progressive illness, which mostly affects people over the age of 65. Symptoms typically begin with subjective concerns related to memory and thinking, followed by more objective deficits in cognition and behavior. Eventually, patients' daily activities become impaired. They lose the ability to care for themselves and typically spend the last years of their lives receiving care in nursing homes, which is also highly expensive (Figure 6.1).<sup>1</sup>

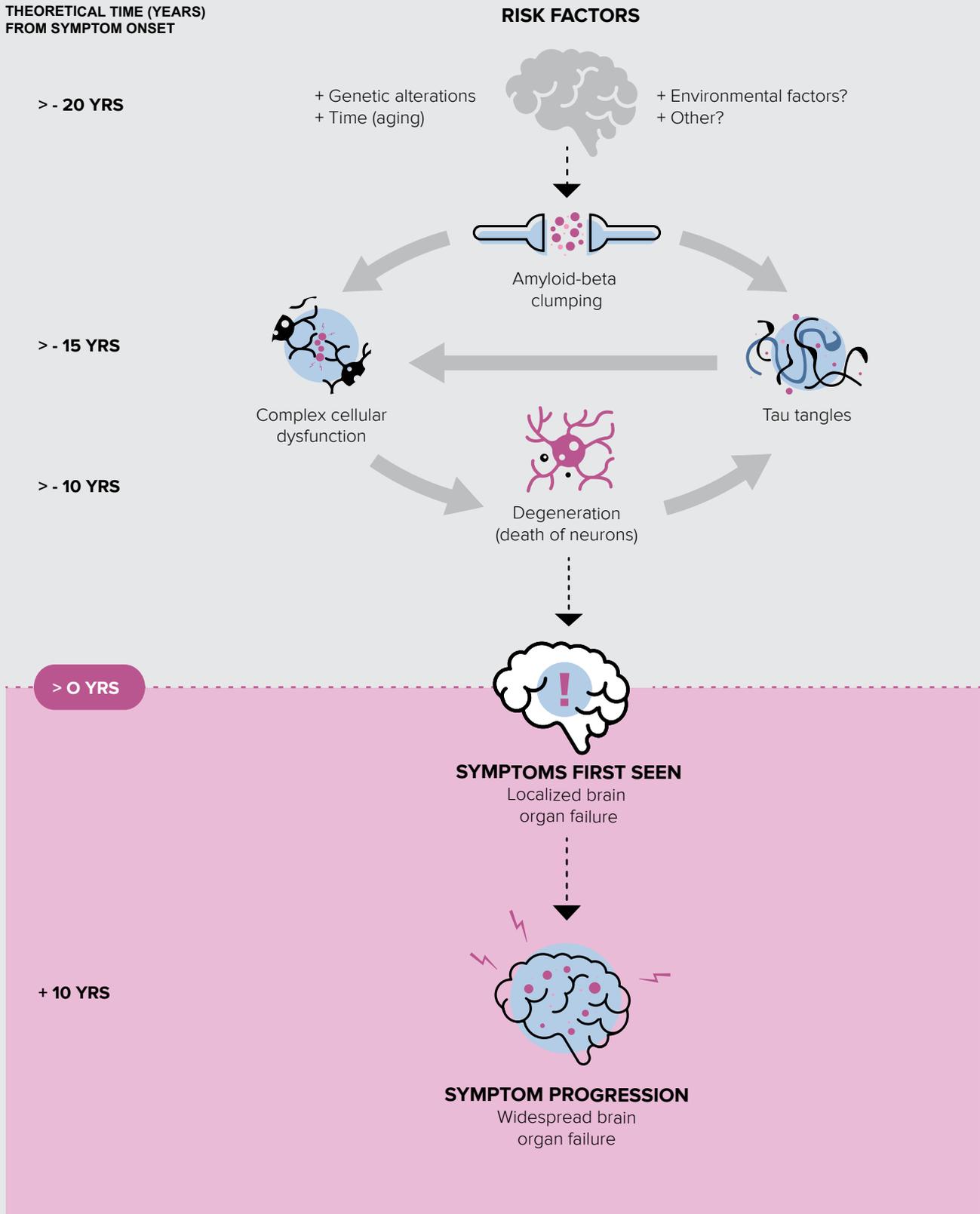
Across the globe, 50 million people are living with dementia; Alzheimer's is the most common form. The estimated yearly cost to treat and care for people with dementia is US\$1 trillion. That's equal to the total amount spent each year on all pharmaceuticals globally.<sup>2</sup> But Alzheimer's costs are expected to double in a decade as the prevalence rises to 82 million people in 2030. By 2050, as populations age significantly in numerous countries, the prevalence is expected to triple from today's levels.<sup>3</sup>

A delay in progression of only one year could reduce the total number of patients with Alzheimer's by more than 9 million by 2050.<sup>4</sup> Delaying the onset of symptoms for individuals over 70 by one year could reduce healthcare payments by 14%, with longer delays saving even more.<sup>5</sup>

Alzheimer's appears in the brain 10-20 years before patients experience any change in thinking or memory. The telltale signs under the microscope are clumps of misfolded proteins,

FIGURE 6.1

## Progression of Alzheimer's disease



Source: Golde et al., 2018.

inflammation, loss of function in the synapses between neurons, and, ultimately, the death of neurons—called neurodegeneration. One estimate suggests that eight times more people have undetected buildup of misfolded proteins or neurodegeneration than have observable Alzheimer’s symptoms.<sup>6</sup>

Targeting the following pathological proteins is a major focus of attempts to develop a disease-modifying therapy for Alzheimer’s.

### **Amyloid**

The foundation of attempts to treat Alzheimer’s is the amyloid cascade hypothesis. This hypothesis suggests that a protein called amyloid-beta slowly accumulates into clumps, which triggers a complicated cascade of events: the pathological misfolding and spread of another brain protein, tau; the activation of inflammatory pathways in the central nervous system; and eventually the death of neurons.

### **Tau**

The second hallmark of Alzheimer’s is clumps of misfolded tau protein inside neurons. These clumps, called neurofibrillary tangles, correlate with the clinical symptoms of Alzheimer’s based on autopsy studies and, more recently, based on molecular imaging of living patients’ brains. Efforts to reduce the load of tau still lag behind the anti-amyloid approaches.

### **Additional targets**

Other potentially disease-modifying approaches currently in clinical testing target inflammation, neurotransmission, and vascular and metabolic contributions to Alzheimer’s. Others attempt to promote growth of neurons and synapses, to protect neurons from damage, or to reverse brain damage via stem cell therapy (Figure 6.2).

## **Challenges of development**

Attempting to impact the trajectory of decline in a chronic and slowly progressive disease is inherently time-consuming. In Alzheimer’s, Phase 1 human testing takes about 13 months to complete; Phase 2 lasts approximately 28 months; and Phase 3 takes about 51 months, followed by an 18-month regulatory review. The process involves a commitment of nearly 10 years from bench to bedside—in addition to more than 4 years of preclinical discovery and testing. That’s about one more year than average drug development—when everything works as planned. In Alzheimer’s, it rarely does.<sup>7</sup> Development failure rates have been higher in Alzheimer’s than in almost any other disease—99.6% from 2002 to 2012, compared with 81% in cancer.<sup>8</sup> And there have been many late-stage failures in Alzheimer’s since then, including two—crenezumab and aducanumab—this year alone.

Future research will likely continue to drive disease-modifying therapeutics to earlier stages of the disease process—especially given the initial 10-20 year stage of Alzheimer’s in which

pathological proteins are active but there are no clinical symptoms. However, such trials will require an even greater investment of time and money.

The development challenges of Alzheimer’s start in the discovery phase with pre-clinical models. Although several transgenic mouse models of Alzheimer’s develop clumps of protein, or plaques, to serve as a target for amyloid-beta therapies, these mouse models differ from humans in significant ways. They do not develop the full spectrum of the human disease. They are missing tau deposition and loss of neurons, and have only a limited inflammatory response. A further challenge for Alzheimer’s is that small molecules—chemical drugs, rather than complex protein-based drugs—must penetrate the blood-brain barrier, and a molecule that does so in a mouse model does not always do the same in humans.

The challenges continue in human testing. There is a mismatch between the progression of the disease, based on the buildup of pathological proteins in the brain, and the symptoms described by patients and observed by clinicians. Clearly delineating the stages of disease progression is still imprecise and potentially inaccurate, yet has been required to define groups for standard clinical trials. This mismatch is further complicated because the rates of decline among individual patients span a wide range—due to differences in genetics, experiences, exposures, and the presence or absence of other maladies of the aging brain. Some patients present with amyloid, but then never develop the symptoms of Alzheimer’s. Others develop dementia, but not Alzheimer’s dementia. These variations among patients make it difficult to see clearly whether a treatment is having a desired effect in the right set of patients.

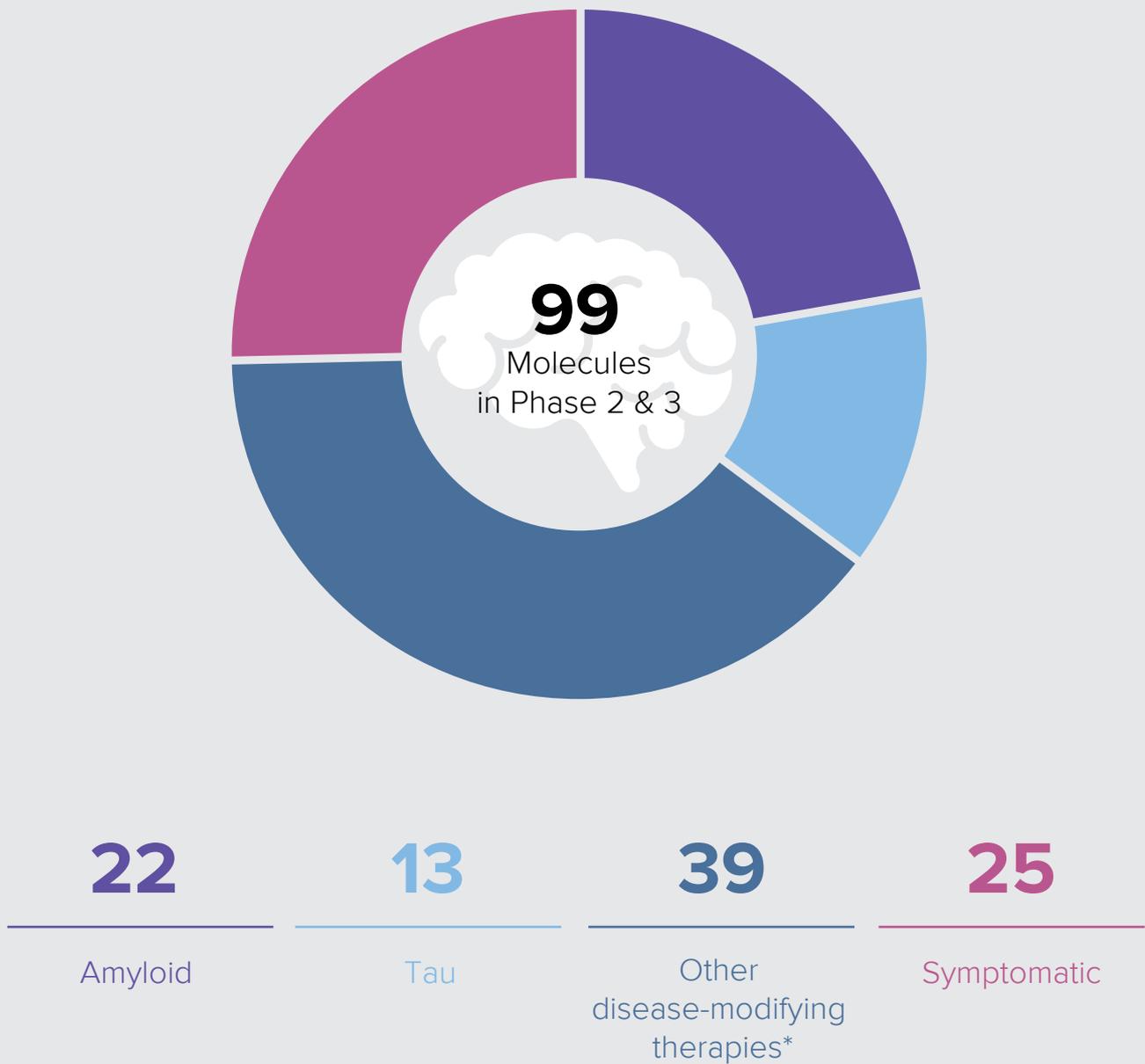
A key part of the solution to these challenges is biomarkers. They could stand in for, and even predict the progression of, Alzheimer’s—in the same way blood pressure measurement is a biomarker for hypertension and hemoglobin A1C is a biomarker for diabetes.

Potential biomarkers for Alzheimer’s are now routinely integrated into clinical trials, including brain imaging agents visible with positron emission tomography (PET) scans or measurements of cerebrospinal fluid (CSF) ratios. However, finding a biomarker that conveniently allows clinicians to track patients’ response to a treatment has proved elusive. Yet this last use may be the most critical in such a slowly progressive and individually variable disease.

Negative clinical trial findings exemplify the importance of using biomarkers to select trial participants. In some studies, approximately 25% of participants clinically diagnosed with mild Alzheimer’s and selected for clinical trial participation were later shown by amyloid imaging not to have brain amyloid consistent with Alzheimer’s.<sup>9</sup> Still, some trials that have used amyloid biomarkers have also failed, suggesting other factors may be contributing—such as lack of adequate engagement between the experimental drug and its intended target in the brain or failure to identify the maximum tolerated dose.

FIGURE 6.2

## Pipeline of experimental Alzheimer's medicines



Source: ResearchersAgainstAlzheimer's, 2018.

\*Includes therapies that target inflammation, neurotransmission, and vascular and metabolic contributions to Alzheimer's disease. Other therapies attempt to promote growth of neurons and synapses, to protect neurons from damage, or to reverse brain damage via stem cell therapy.

Until a disease-modifying therapy demonstrates a significant slowing of the decline of Alzheimer's, the interpretation of biomarkers will likely remain challenging. This presents a chicken-and-egg problem. To prove a biomarker works requires testing a drug over many years to show it successfully slows the decline of Alzheimer's. Yet the expense and practical realities of Alzheimer's testing make such a long trial difficult, if not impossible, without an accepted biomarker.

This will likely not be a one-time problem. Researchers now generally expect that successful treatment of Alzheimer's will come through a combination of therapies—as is the case with the cocktail treatment for HIV. A successful combination for Alzheimer's could pair a molecule that blocks amyloid formation with an agent that removes amyloid plaques. Or multiple molecules that function as anti-amyloid, anti-tau, and anti-inflammatory agents could be deployed simultaneously, or in series, depending on the stage of the disease. Any trials of combination therapies will be considerably more complex than trials with a single agent.

Overcoming the increasing length and complexity of Alzheimer's clinical trials requires innovative policy responses. Breakthroughs in therapy in the past have almost always been coupled with breakthroughs in regulatory standards. That was true when developing medicines for oncology, AIDS, and other diseases. It is needed now in Alzheimer's.

## The need for policy innovation

Innovation can change the math of Alzheimer's that challenges governments around the world. But to do that, governments need to change the math for innovators. Currently, the extra time and high failure rate for Alzheimer's medicines make the costs of bringing one through the regulatory process more than double the highest estimate for overall drug development.<sup>10</sup> Yet current policy offers a relatively fixed period during which an innovator can recoup those costs. Innovators are incentivized to focus their investments elsewhere—in disease areas with faster clinical trials and lower failure rates.

Pharmaceutical companies are studying more than 20 times as many drugs for cancer than for Alzheimer's, even though the global societal costs of each disease are about the same.<sup>11</sup> Empirical analysis of clinical trials has shown that private funding flows to cancers, and stages of cancer, where potential survival times are shorter—because the longer trials needed for earlier interventions or for slower-progressing cancers consume too much of a drug's patent life.<sup>12</sup>

Various solutions have been put forward to address the problematic math of Alzheimer's drug development. Below we describe five categories of policies that could make a difference.

### Research

Drug development has always operated in an ecosystem of researchers in public and private organizations, both large and small, sustained by a mix of public and private funds. Publicly

funded research often produces insights into biology that create the conditions for the development of new medicines.<sup>13</sup> So governments should maintain or even increase their funding for research for Alzheimer's.<sup>14</sup>

Start-up companies and private investors, along with large pharmaceutical companies, are also critical in this ecosystem. The vast majority of new drugs are discovered and developed by private efforts.<sup>15</sup> So governments should also take great care to create the best environment to enable private efforts to advance drug development.

One Alzheimer's drug tested by our company, Eli Lilly and Company, shows this ecosystem in action. The protein, called solanezumab, was discovered via a collaboration with Lilly scientists at a university that receives both private and public research funding. When Lilly moved solanezumab into Phase 3 testing, it helped fund those studies via a partnership with an outside hedge fund. Later studies of solanezumab relied on a brain imaging biomarker developed by a small biotech firm, which Lilly has since acquired. Solanezumab showed small effects but not enough to be clinically meaningful. We are now working with public partners to test solanezumab at four times the previous dose.

### Innovative funding

There is a need for innovative funding approaches—especially in the earliest and riskiest phases of drug discovery research. Public-private partnerships and open innovation can help in precompetitive areas, such as biomarker development, better models of Alzheimer's disease, and big data analytics to identify and stratify patients. Other possibilities include crowd-funding, patient advocacy group funding, prizes and government R&D contracting. Governments can help to integrate the disparate set of current funding sources—perhaps, as some have suggested, creating mega funds to advance research.<sup>16</sup> Some have even proposed advance market commitments, in which innovators promise to offer a new drug at a lower price while donors make a long-term contractual pledge to pay a “top-up” price. We concur with various scholars that these efforts, on a voluntary basis, are welcome additions to the search for an effective therapy.<sup>17</sup>

However, with biopharmaceutical companies sponsoring or co-sponsoring more than 70% of Alzheimer's clinical trials,<sup>18</sup> the biggest thing governments can do is change the math for these companies. The next three categories aim at that goal.

### Faster testing

In recent years, biopharmaceutical companies have worked to reduce clinical development periods through gains in operational efficiency and statistical methodologies that permit shorter and smaller trials.<sup>19</sup> But these efforts are inadequate in the face of Alzheimer's because of two major challenges.

First, a constant challenge in clinical trials of Alzheimer's therapies is getting patients enrolled. There are significant barriers—both scientific and psychosocial—to diagnosing patients. Half or more of dementia patients are not clinically diagnosed—far higher

than other diseases.<sup>20</sup> Because existing biomarkers such as PET imaging are not widely available—or widely reimbursed—diagnosis in the pre-symptomatic phase can be especially difficult. Also, doctors are reluctant to commit to a diagnosis of Alzheimer's when they can offer no effective treatment.

In response to the challenge of patient enrollment, governments and other groups could help by organizing advanced patient registries of well-characterized candidates for clinical trials. As it becomes ever clearer that Alzheimer's begins damaging people's brains years before symptoms show up, it is more critical that public and private health plans offer coverage for diagnostic tests that do exist. It may not be prudent to open coverage to everyone. But the willingness of health plans to pay for tests at the earliest signs of cognitive change would provide a significant stimulus to the makers of medical and digital technologies to push for even better and easier-to-use diagnostic tools.

The second big challenge in Alzheimer's clinical trials is the endpoints required by regulators. The ultimate goal is to find a disease-modifying therapy that changes clinical symptoms—slowing the decline in thinking and daily functioning. But to get to that point, it may be necessary for regulators to experiment with surrogate endpoints of Alzheimer's. In cancer, regulators have long accepted progression-free survival as a surrogate endpoint for new drugs—even though the ultimate goal is always overall survival for patients. Alzheimer's trials need similar flexibility from regulators. The field may not yet know what the Alzheimer's version of “progression-free survival” is. But regulators could approve a new Alzheimer's medicine that proves safe and shows progress against a surrogate endpoint—and then require a pharmaceutical company to gather the real-world evidence and long-term data necessary to see if the surrogate endpoint successfully predicted improvement in later symptoms.

In the United States of America (U.S.), the Food and Drug Administration (FDA) has this kind of accelerated approval authority—which was granted in the early 1990s to find solutions to the HIV/AIDS crisis. Former President Obama's Council of Advisors on Science and Technology recommended that the FDA use this authority broadly by approving more drugs based on surrogate endpoint results.<sup>21</sup> Such policies, if adopted by regulators worldwide, would encourage innovators to keep working on slow-progressing diseases, like Alzheimer's.

### Intellectual property

Patents provide 20 years of protection for a new medicine. But that 20-year clock starts years before a medicine is approved for sale. Patents are necessarily filed before any public disclosure, which typically is before human testing begins. The result is that every extra year of clinical testing means one less year in patent-protected sales. Over the past two decades, average post-approval patent life in the U.S. and Europe has fallen to 13 years—even including the impact of patent-term extension policies.<sup>22</sup> The combination of lengthening development timelines and fixed patent terms creates a perverse incentive for innovators to give high priority to molecules with faster development times, rather than to the medicines patients need most.

For this reason, the single best thing governments can do to incentivize development of a drug that will slow Alzheimer's is to create more uniform and sufficiently long periods of data exclusivity. There is a patchwork of terms of data exclusivity around the world—with protection running from as high as 12 years to as low as zero. Many countries also have shorter periods of data exclusivity for traditional small molecule drugs than for biologics.<sup>23</sup> These inconsistent terms mean a drug that takes a long time to develop—running out most of the years on its patent—must rely on data exclusivity in fewer countries to recoup the capital and risk expended to develop it. It also skews research arbitrarily toward biologic drugs—even though they may not be the best way to treat a disease. In short, weaker data exclusivity policies mean less money invested in fewer medicines for difficult and slow-progressing diseases like Alzheimer's.

Lilly has experienced this dynamic first hand with solanezumab, which we continue to test in Alzheimer's patients. The U.S. patent on solanezumab will expire in 2021. Yet Lilly continues to manufacture and test this molecule because the data exclusivity we have—12 years in the U.S. and 10 years in Europe—offers some potential to recoup our continued investment. Without data exclusivity, solanezumab—and many other promising compounds without adequate patent protection—would have almost no hope of reaching patients.

We recognize that extending data exclusivity is an unpopular idea to many who believe the key to pharmaceutical affordability is to reduce the duration of intellectual property (IP) protection. We believe, however, that an appropriate period of data exclusivity is essential to generate the investment necessary to create a sufficient supply of disease-modifying Alzheimer's medicines to begin with. A strong IP system, in the long run, produces more breakthroughs today and provides more bargains tomorrow. Even a disease-modifying therapy for Alzheimer's would, after about 13 years, be sold for a small fraction of its initial price and would continue delivering value to patients and health systems for decades. In our view, nothing in healthcare is more productive.

### Reimbursement

It is always healthy to ask for proof that any healthcare service is worth its cost. The evidence for pharmaceuticals is encouraging. An analysis of 15 developed countries found that those that introduced the newest medicines soonest saved the most on hospital costs—US\$2.50 saved for every US\$1.00 extra spent on the latest pharmaceuticals.<sup>24</sup> In addition, a recent analysis of the U.S. Medicare health plan for seniors found that growth in other healthcare spending slowed significantly after Medicare started paying for prescription medicines.<sup>25</sup>

The problem is that few, if any, government-funded health programs financially reward a pharmaceutical that enables reduced spending in other areas—such as, lower hospital costs or doctor fees. Funding for pharmaceuticals is typically separate from hospital and doctor care, which is separate from nursing home care. Government officials that oversee these funding streams work separately to control costs, without trying to calculate how spending in one stream might save money in

another. To prepare for the arrival of a disease-modifying therapy for Alzheimer's, governments should create mechanisms to connect these disparate funding streams.

Mechanisms could include better horizon scanning by government health programs, followed by restructuring of health systems. This is what the Government of Australia did in the 1990s and 2000s—gradually shrinking the infrastructure and workforce needed to conduct traditional Pap smear tests for cervical cancer screening, and shifting resources to simpler and cheaper polymerase chain reaction (PCR) testing.<sup>26</sup>

Mechanisms could also include outcome-based contracts. Because the clinical and economic value of a disease-modifying therapy for Alzheimer's may not be completely clear at launch, it may make sense for governments to pay a portion of a drug's cost up front, with additional payments made over time only if patients taking the drug show slower disease progression. Other innovative payment models that could work in Alzheimer's are prices that vary based on patient severity; a "Netflix" model of pricing that smooths out costs to payers; or, in the case of multiple therapies, combination pricing.<sup>27</sup>

Funding streams could even be connected via the sale of social impact bonds, which have been used to fund recidivism programs in the U.S. and the United Kingdom. In the case of a successful disease-modifying therapy for Alzheimer's, selling such bonds could raise private money to enable a government to fund payments for the new medicine. The government would repay bondholders only if, years later, savings on nursing home care materialize, freeing up the funds needed to repay bondholders.

## Conclusion

Governments face a clear choice today. Unless public policies steer private funding to difficult diseases with long development times and high failure rates—and do so strongly enough to generate multiple successful therapies—Alzheimer's will likely remain an ongoing health and budgetary challenge. If, instead, governments around the world act to change the math for innovators—by accelerating testing and strengthening incentives—they will provide the certainty that drug developers need to take on the biggest and broadest challenges society faces, including Alzheimer's.

### Notes:

- 1 Jack et al., 2018.
- 2 Aitken et al., 2019.
- 3 Patterson, 2018.
- 4 Brookmeyer et al., 2007.
- 5 Zissimopoulos et al., 2014.
- 6 Brookmeyer et al., 2018.

- 7 Cummings, Lee, Ritter et al., 2018; DiMasi et al., 2016.
- 8 Cummings et al., 2014.
- 9 Cummings, 2018.
- 10 Cummings, Reiber et al., 2018.
- 11 Long, 2017.
- 12 Budish et al., 2015.
- 13 Cleary, 2018.
- 14 Grabowski et al., 2015.
- 15 Chakravarthy et al., 2016; Kneller, 2010 (76% of new drugs approved from 1998 to 2007 were discovered inside drug companies, compared with 24% by university researchers); Sampat et al., 2011 (of drugs approved from 1988 to 2005, 9% had public-sector patents; 48% had some public-sector influence).
- 16 Cummings, Reiber et al., 2018.
- 17 Cummings, Reiber et al., 2018; Kremer, 2010.
- 18 Cummings et al., 2017.
- 19 Morgan et al., 2018.
- 20 Eichler et al., 2014.
- 21 President's Council, 2012.
- 22 Grabowski et al., 2014; Copenhagen Economics, 2018.
- 23 The U.S. offers 12 years for biologic medicines but five years for chemical, or small molecule, medicines. The EU and Canada offer 10 years for both kinds of drugs. Japan offers roughly eight years. Australia and Mexico offer five years—although Mexico recently agreed to 10 years as part of a pending trade deal with the U.S. and Canada. India offers none, and China offers practically none—although China has recently proposed adopting a policy of up to 12 years.
- 24 Lichtenberg, 2018.
- 25 Cutler et al., 2019.
- 26 Kearney, 2018; Oortwijn et al., 2018.
- 27 Multi-year payments and the "Netflix" model have been proposed by the Massachusetts Institute of Technology's New Drug Development Paradigms Initiative.

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