Economic analysis of opportunities to accelerate Alzheimer’s disease research and development

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The development of disease-modifying treatments for Alzheimer’s disease (AD) faces a number of barriers. Among these are the lack of surrogate biomarkers, the exceptional size and duration of clinical trials, difficulties in identifying appropriate populations for clinical trials, and the limitations of monotherapies in addressing such a complex multifactorial disease. This study sets out to first estimate the consequent impact on the expected cost of developing disease-modifying treatments for AD and then to estimate the potential benefits of bringing together industry, academic, and government stakeholders to co-invest in, for example, developing better biomarkers and cognitive assessment tools, building out advanced registries and clinical trial-readiness cohorts, and establishing clinical trial platforms to investigate combinations of candidate drugs and biomarkers from the portfolios of multiple companies. Estimates based on interviews with experts on AD research and development suggest that the cost of one new drug is now $5.7 billion (95% confidence interval (CI) $3.7–9.5 billion) and could be reduced to $2.0 billion (95% CI $1.5–2.9 billion). The associated acceleration in the arrival of disease-modifying treatments could reduce the number of case years of dementia by 7.0 million (95% CI 4.4–9.4 million) in the United States from 2025 through 2040.

Keywords: Alzheimer’s disease; dementia; biomarkers; drug development; R&D; efficiency; infrastructure; public–private partnership

Introduction

Alzheimer’s disease (AD) is the most common form of dementia, accounting for over half of all diagnosed cases. Dementia, a degenerative condition that impairs memory, thinking, and independent functioning, is estimated to afflict between 3 and 5 million people in the United States and 35 million people worldwide. Without effective treatments to prevent or slow the course of AD and other dementias, the number of people living with dementia is projected to roughly double by 2035 and triple by 2060 as the world population ages.1–3

To stem the tide of this worsening public health burden, significant advances in therapeutic discovery and development are needed. To date, five drugs have been approved for the treatment of AD, all of which were approved before 2004. These drugs treat only the symptoms of AD, and the medical community considers their clinical effects to be modest in that regard.4,5

Over the past decade, the focus of drug discovery and development efforts has shifted toward disease-modifying therapeutics for AD—treatments that could slow the progression of the disease as opposed to only controlling its symptoms.6,7 Less encouraging is that over the same time period all drug candidates that advanced to the final phase of clinical trials failed, without any new drugs being approved for marketing.8,9

These efforts are being hindered by a number of barriers to the discovery and development of AD therapeutics.a

aSee also Greenberg et al. for a discussion of barriers addressed to a technical audience.9

[Correction added on May 15, 2014, after publication: copyright line and license statement updated.]
Without surrogate markers, drug development is risky and inefficient

There is a critical infrastructure need for a surrogate biomarker (or surrogate biomarkers) that would provide an early indication that a drug is having an effect that will ultimately lead to improvements in cognition and function. Without surrogate markers, ineffective drug candidates advance to the largest, the longest, and the most expensive (Phase III) clinical trials when they otherwise would not. More insidiously, the lack of a surrogate marker results in the misguided use of resources on nonviable compounds or inappropriate dosages. A compound may fail in Phase III where it or a closely related one could have succeeded if it had been tested at the ideal dose.

Demonstrating a treatment effect requires long trials with many participants

A slowing in the rate of cognitive decline, which is a minimum requirement to show a disease-modifying effect, takes a comparatively long time and large sample size to establish because of the variability across patients and measurement variability in cognitive and functional assessments. Patients in more advanced stages of the disease decline faster, meaning that a treatment effect obtained in these populations might be more readily observed. However, patients in more advanced stages of the disease may also be more resistant to disease-modifying treatments.

Difficulties in identifying appropriate populations for clinical trials increase the risks and costs of drug development

AD remains difficult to diagnose with the degree of specificity needed for testing therapeutics that target a single disease mechanism. Similar cognitive symptoms may be caused by different underlying mechanisms. Without tools to stratify patients by disease mechanism, the effect of drug candidates may be limited to only a subset of patients enrolled in a clinical trial, making it more difficult to demonstrate a statistically significant slowing in the rate of cognitive decline. More daunting is that it may be necessary to begin treating patients before symptoms appear, which brings up the need to identify cognitively normal individuals who are likely to progress and to measure that progression. Again, the problem in enrolling too many of the wrong patients is that any treatment effect obtained in a subset of patients is diluted. Costs are higher because statistical significance requires larger studies, and the risk is higher that a treatment effect will go undetected.

Significant treatment effects may require combinations of drugs

Learning about optimal combinations of drugs, which may reside at different companies, is impossible without a means of effective collaboration in drug development.

Overcoming barriers

These AD-specific barriers are related to recognized barriers to technology development and innovation (Table 1). A rich economic literature analyzes the factors contributing to these barriers and potential policy remedies. This literature highlights the potential for collaboration among public- and private-sector stakeholders to improve the productivity and efficiency of research and development (R&D) investments.

In recognition that overcoming these barriers will require collaborative technology development and investigation, leaders from industry, government, and academia have co-invested in multiple initiatives to make the most effective and efficient use of their resources. Initiatives include, for example, the Leon Thal Symposia, the National Institutes of Health Alzheimer’s Disease Research Summit, the Ware Invitational Summit, the New York Academy of Sciences’ Alzheimer’s Disease and

Table 1. General barriers to technology and innovation

| Barriers                                                                 |
|-------------------------------------------------------------------------|
| 1. High technical risk associated with the underlying R&D               |
| 2. High capital costs to undertake the underlying R&D with high market risk |
| 3. Long time to complete the R&D and commercialize the resulting technology |
| 4. Underlying R&D spills over to multiple markets and is not appropriable |
| 5. Market success of the technology depends on technologies in different industries |
| 6. Property rights cannot be assigned to the underlying R&D             |
| 7. Resulting technology must be compatible and interoperable with other technologies |
| 8. High risk of opportunistic behavior when sharing information about the technology |

Note: See Ref. 13 for a detailed discussion of these barriers.
Dementia Initiative (ADDI), and the Global CEO Initiative on Alzheimer’s Disease.

The following five broad recommendations were distilled from these initiatives’ individual assessments of infrastructure needs to overcome barriers to the discovery and development of AD therapeutics.\(^b\)

**Invest in biomarkers and cognitive assessment tools.** Better detection and monitoring of AD, especially from its earliest clinical manifestations, and better prediction of treatment response (thereby decreasing the risk of clinical development) will be made possible by developing, validating, and standardizing a robust hierarchy of biomarkers and sensitive cognitive and functional assessment tools and by elucidating relationships among biological and cognitive markers.

**Streamline enrollment in clinical trials with an advanced registry.** The time and cost of enrolling participants for research studies and clinical trials could be reduced by establishing a registry of well-characterized candidates, containing standardized demographic, genetic, biologic, cognitive, and environmental information on each potential participant.

**Establish clinical trial platforms to investigate biomarker and drug combinations.** Efficient learning about AD biomarker and drug combinations—testing, analytically validating, and qualifying biomarkers as new drugs are tested—could be enabled by incorporating promising biomarkers into Phase III and adaptive Phase II–III trials of potentially disease-modifying therapeutics.\(^c\)

**Keep the preclinical pipeline full of novel therapeutic approaches and targets.** Conducting translational research in a precompetitive commons, advancing a greater diversity of novel therapeutic approaches and validated targets into clinical trials, could increase the likelihood that success in preclinical development will translate to success in clinical development (thereby de-risking clinical development).\(^d\)

**Realize economies of scope between research and drug development.** Establishing a network of comprehensive Alzheimer’s disease centers, integrated with existing resources, would promote understanding of the mechanisms of AD and speed the translation of this knowledge into the clinic.\(^f\)

These recommendations call for improvements in the technical research infrastructure—broadly defined as the technologies, tools, knowledge, methods, and standards—that support AD drug discovery and development. These recommendations will work most effectively when they are openly available for all to use, and implementing them will require combining the capabilities of industry, government, and academia. As stated by the U.S. Department of Health and Human Services in the 2013 update of the National plan to address Alzheimer’s disease:\(^f\)

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\(^b\)The list of five broad recommendations offered here is not exhaustive. For more, see the Alzheimer’s Association Expert Advisory Workgroup on the National Alzheimer’s Project Act,\(^14\) Greenberg et al.,\(^8\) Khachaturian et al.,\(^15,16\) Khachaturian,\(^17\) Naylor et al.,\(^18\) Trojanowski et al.,\(^19\) and the U.S. Department of Health and Human Services.\(^20–22\)

\(^c\)‘I-SPY 2 breast cancer trials could, for example, serve as a model for clinical trials of this nature in AD. I-SPY 2 is a public–private partnership of university scientists, the National Cancer Institute, the U.S. Food and Drug Administration (FDA), and pharmaceutical and biotech companies under the auspices of the Biomarkers Consortium, which is managed by the Foundation for the National Institutes of Health. For more on I-SPY 2, see Ref. 23.

\(^d\)Examples of partnerships for translational research include the National Heart, Lung, and Blood Institute’s SMARTT Program (www.nhlbismartt.org), the National Institute of Allergy and Infectious Diseases’ Preclinical and Clinical Research Resources (www.niaid.nih.gov), and Pfizer’s Centers for Therapeutic Innovation.

\(^e\)For more details of this proposal, see Trojanowski et al.\(^19\) The centers envisioned could be integrated with, for example, the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and National Institute on Aging–funded Alzheimer’s disease research centers.

\(^f\)For the most recent update of the National Plan, see the U.S. Department of Health and Human Services.\(^24\) The National Plan was called for by the National Alzheimer’s Project Act (NAPA), Public Law 111–375 (42 U.S.C. 11225), signed into law by President Obama on January 4, 2011. The origins of the National Plan and many of the recommendations being advanced today may be traced to the first Leon Thal Symposium. See Khachaturian et al.\(^15\) and Khachaturian.\(^17\)
The scope of the problem of Alzheimer’s disease is so great that partnerships with a multitude of stakeholders will be essential to making progress. This National Plan begins the partnership process by identifying areas of need and opportunity. The National Plan represents a first step in an undertaking that will require large-scale, coordinated efforts across the public and private sectors.

The New York Academy of Sciences and its Alzheimer’s Disease and Dementia Leadership Council contracted with RTI International, a not-for-profit research institute, to conduct an independent economic analysis of overcoming critical technical barriers in AD research. Specifically, the Council requested RTI to quantify (1) the capitalized cost of developing a new disease-modifying therapeutic in the current environment with existing technical infrastructure and in an improved environment with the recommended technical infrastructure, (2) the likely increase in private-sector drug development funding if technical barriers were overcome, and (3) the potential reduction in the future burden of AD.

This report provides an assessment of the potential economic impact of improving the infrastructure supporting AD drug discovery and development. The assessment was informed by detailed interviews with experts in AD research and drug development both in the pharmaceutical industry and in academia.

The remainder of this report is organized as follows. The next section describes the analysis procedures used to develop economic impact estimates, including those for eliciting data from experts in AD research and senior executives in the pharmaceutical industry. The Results section provides a discussion of the recommendations and their intended impacts. This discussion incorporates qualitative insights from the interviews and serves to link the recommendations to the barriers, explaining how they are expected to help, from the point of view of the experts interviewed. We further characterize the landscape for developing disease-modifying AD drugs in terms of drug development risk, time, and cost. Two estimates of the cost of drug development are presented: (1) if the current environment with the existing infrastructure were to prevail and (2) if a new environment with improved infrastructure were to take its place. This is followed by discussion of the effects on private investment in AD drug discovery and development of the changes in risk, time, and cost that could be expected with improved infrastructure. Interviewees generally predicted that the total private investment would be higher in the environment with improved infrastructure. Further, we provide quantitative estimates of the reduction in the expected burden of AD that could result from accelerating the arrival of disease-modifying treatments. The burden of AD is considered in two ways: as the expected number of case years of dementia over time and as the cost of care associated with those case years (a case year is 1 year in which one person has dementia). In the environment with improved infrastructure, the probability of being able to attain three benchmark treatment effects is estimated to be higher over a span of years, and the estimated burden of AD is estimated to be correspondingly lower. Finally, the report concludes with a discussion of the implications of our findings subject to the limited scope of the study.

Analysis approach

RTI employed a mixed-methods approach to this prospective economic analysis. These methods included (1) logic modeling of how the recommendations to improve AD research infrastructure would have impacts on AD research and drug development; (2) economic modeling of AD drug development cost, time, and risk; (3) economic modeling of potential changes in the future financial burden of AD; and (4) interview data collection with leaders in the field of AD research and drug development at the level of vice president (or equivalent) and above.

Logic modeling of recommended infrastructure improvements

RTI developed a logic model of the recommendations to improve AD research and drug development and their points of influence in the therapeutic development pipeline and refined the model based on discussions with 11 members of the New York Academy of Science’s Alzheimer’s Disease and Dementia Initiative working groups and Leadership Council.

These discussions confirmed that (1) the most direct impact of the successful achievement of the recommendations would be to reduce the time and risk involved in conducting clinical trials and thus
reduce the expected capitalized cost of developing new drugs to treat AD and increase the expected value of any new drug approved for marketing by increasing income-generating patent life; (2) these effects would lead to increased investment in AD research and drug development; and (3) the combination of shorter development times, greater probability of success, lower costs, and the increased investment that these effects would generate would mean that new treatments for AD could be expected to arrive sooner than they otherwise would.

Based on this background information, RTI developed spreadsheet models that could be calibrated to quantify these impacts and an interview guide to elicit the opinions and perspectives of experts in AD research and drug development to inform the calibration of these spreadsheet models. The interview guide is provided in the online appendix.

Estimating the impact on AD drug development time, cost, and risk

We developed an economic model of the expected capitalized cost of drug development, taking as inputs the cost per month and duration of the phases of clinical development and the transition probabilities from one phase to the next and from the final phase (III) to drug approval.\(^8\)

The expected cost of developing a new drug is calculated by summing the risk-adjusted, capitalized cost of each phase of development, which is calculated using the following formula:

\[
\left( c \int_{t_{\text{start}}}^{t_{\text{end}}} e^{rt_{\text{start}}/12} dt \right)/p = \left( \frac{c}{p} \right) \left( \frac{12}{r} \right) \left( e^{rt_{\text{start}}/12} - e^{rt_{\text{end}}/12} \right).
\]

Parameters in the formula are defined in Table 2. The inputs that populated the model were collected from more than 32 experts in AD research, with the exception of the real cost of capital, which was set at 11%. This value was chosen to be consistent with prominent recent studies of the cost of drug development in other disease areas, which estimate the average cost of a new drug to be between $1.5 and $2 billion in current dollars, including the expected cost of failures.\(^{25,26}\) Thus the difference between these estimates, which are for a range of diseases, can be compared with the AD-specific estimates presented here and the differences in cost attributed to differences in the duration and risk of drug development phases. It is these fundamental differences, which improved infrastructure can directly address, that are the focus of this study. To the extent that higher-risk drug development efforts incur a higher cost of capital (because of a higher-risk premium), our estimates, which fix the cost of capital at 11%, are conservative. For more on estimating the cost of capital for pharmaceutical and biotechnology companies, see Ref. 27.

**Table 2. Parameters characterizing each phase of drug development**

| Parameter | Description |
|-----------|-------------|
| \(t_{\text{start}}\) | Time in months from start of phase to date of new drug approval |
| \(t_{\text{end}}\) | Time in months from end of phase to date of new drug approval |
| \(c\) | Cost, per month, per compound in phase |
| \(p\) | Probability that a compound undergoing this phase of development is ultimately approved for marketing |
| \(r\) | Cost of capital, as an annual interest rate |

Estimating the impact on the future burden of AD

We developed a second economic model that linked the probability of having effective treatments by 2025 with expected AD caseloads in the United States to quantify the economic potential of the recommendations to lower future expected costs of care for patients. The model takes as inputs (1) U.S. population projections by single year of age; (2) current estimates of the probability of dementia by age and the cost of care per case year of dementia,\(^2\) and (3) expert assessment of alternative treatment scenarios based on the probability of the recommendations’ ability to modify AD.

The treatment scenarios reflect that the probability of having effective treatments for AD is not zero for the foreseeable future: it is lower over the
next year than over the next 10 years, lower over the next 10 years than over the next 20 years, and so on. Thus, in contrast to other studies that forecast the burden of dementia (1) without treatments and (2) with the certainty of treatments being available immediately,\textsuperscript{28,29} we forecast the burden of dementia for probability-weighted averages of those two scenarios.

Our model asserts that the impact of improving infrastructure supporting AD research and drug development is to increase the probability of having effective treatments by any given year, so that the probability of having achieved some level of effectiveness in treatment rises more quickly over time with better infrastructure and that the benefit of this is to reduce the expected number of cases of dementia in future years.

**Interview data collection**

Models of the cost of drug development and expected caseloads were calibrated based on information collected through interviews with 32 individuals from pharmaceutical companies and universities. Of these, 27 individuals represented 11 companies currently pursuing AD drug discovery and development.

The majority of these industry interviewees were at the level of vice president (or equivalent) and above and were responsible for aspects of AD drug development or for diseases of the central nervous system more broadly. Interviewees participated under confidentiality agreements that specified no individual responses would be attributed to any individual person or firm.

The five non-industry interviewees held positions of distinction in university settings, and each had more than 20 years of experience in AD-related research. Table 3 provides a representative listing of interviewees’ titles.

Data were collected by e-mails and telephone and conference calls between May and August 2013. Additionally, Troy Scott of RTI attended the annual Alzheimer’s Association International Conference held in Boston in July 2013, where he interviewed multiple AD experts in person.

RTI initially contacted AD experts from pharma and academia via e-mail to introduce the study and to schedule in-depth interviews. Some interviewees’ contact information was provided by the New York Academy of Sciences. Others were identified by RTI through independent searches of ClinicalTrials.gov and LexisNexis Academic’s company information database or were provided to RTI as referrals by other interviewees. Once scheduled, the interviews ranged from 30 to 90 minutes and were facilitated by an interview guide (provided in the online appendix). We also engaged in unstructured discussion of AD, including interviewees’ thoughts on the current barriers, proposed recommendations, and other talking points related to clinical design.

The interview guide was designed to capture quantitative inputs for the spreadsheet models and consisted of three sections. In the first section, transition probabilities and cycle times were developed for AD research and drug development based on interviewees’ knowledge and experience for both the current infrastructure and the recommended infrastructure. The second section asked interviewees to characterize potential outcomes of AD investment assuming that the infrastructure recommendations have been fully implemented. The last section asked interviewees to estimate the probabilities of having a disease-modifying drug for AD on the market by 2025 under both the existing and recommended infrastructures.

**Results**

This section presents our study findings, beginning with a qualitative discussion of how experts in AD drug discovery and research expect the infrastructure recommendations to accelerate and reduce the cost of AD research and drug development.

| Chief Executive Officer | Chief Scientific Officer | Executive Associate Dean |
|-------------------------|--------------------------|--------------------------|
| Senior Vice President, R&D | General Manager, Research |
| Executive Vice President | Senior Medical Director |
| Vice President, Research | Director |
| Senior Director | Co-director, Neurology |
| Professor of Neurology |
| Research Fellow |
| Department Head |
| Principal Investigator |
The study then reviews how the proposed solutions could lower the expected capitalized cost of a disease-modifying AD therapeutic from $5.7 billion to $2.0 billion, increase private-sector investment in AD drug discovery and research by 23%, and save between $74 billion and $100 billion at a 7% discount rate or $158 billion to $214 billion at a 3% discount rate in the future cost of caring for AD patients by accelerating the introduction of disease-modifying therapeutics.

**Intended impacts of the recommendations**

In explaining their quantitative estimates, the experts participating in this analysis offered insights on how the recommended improvements to the technical and research infrastructure would make a difference. In distilling their insights, we focused on their assessment of how these recommendations may be expected to affect the risk and time associated with the development of disease-modifying AD drugs.

**Investing in biomarkers and cognitive assessment tools.** Better detection and monitoring of AD, especially from its earliest clinical manifestations, and better prediction of treatment response (thereby reducing risk clinical development) could be promoted by developing, validating, and standardizing a robust hierarchy of biomarkers and sensitive cognitive and functional assessment tools and by elucidating relationships among biological and cognitive markers.

**Impacts on risk.** Enrolling the wrong participants in clinical trials increases the risk that a potentially efficacious drug will fail to meet its clinical endpoints. Participants who are not progressing and patients who are progressing because of a mechanism other than that targeted by the drug candidate mask differences between treatment and control groups. Biomarkers that indicate whether a cognitively normal person is progressing and allow stratification by disease mechanism would reduce the risk that a clinical trial fails to identify a drug that works.\(^h\)

Tools for cognitive assessment are not sensitive enough to discern treatment effects among participants with milder cognitive impairments.\(^i\) For drug candidates that may be most effective when delivered in earlier stages of the disease, being able to detect a treatment effect in milder participants is crucial to reducing the risk of failure.

A surrogate biomarker—a marker that could in the short term predict whether a drug is having an effect that would lead to cognitive and functional improvements in the longer term—would reduce risk in a number of ways. First, ineffective drug candidates could be identified sooner so that failures are less costly. Second, surrogate markers could enable better decisions about which compounds (from a number of closely related candidates) to advance and at what dosage. This would reduce the overall risk of failure for a family of compounds entering first-in-human clinical trials.

A further way that surrogate markers could reduce overall risk is as follows. Companies often repeat the failures of other companies, advancing their own compounds after similar compounds (similar in the sense of targeting the same disease mechanism with a similar chemical entity) of other companies have failed. In an environment where one company’s failure can be attributed to imperfect

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\(^h\)As it has focused more attention on developing disease-modifying drugs, the pharmaceutical industry has realized the importance of using biomarkers to identify patients who are most likely to benefit from a specific intervention: patients who, for example, are accumulating plaque in addition to having clinical symptoms of AD (e.g., memory and cognitive deficits). Trials of symptomatic AD drugs relied successfully on clinical diagnosis of dementia following McKhann *et al.*\(^30\) to enroll patients. For trials of disease-modifying drugs, it is more important that enrollment be limited to patients who at least exhibit the physiological process with which the drug is designed to interact. Recognizing the heterogeneity of dementia, new diagnostic guidelines incorporate biomarkers (see Refs. 31 and 32). These new diagnostic guidelines are informed by the work of the Alzheimer’s Disease Neuroimaging Initiative (ADNI). See Ref. 33 for a review of the research that the ADNI has influenced. Cummings\(^34\) discusses how the knowledge generated by the ADNI can be further integrated into clinical trials.

\(^i\)Greenberg and colleagues\(^9\) describe the limitations of ADAS-cog and discuss alternatives. Adopting alternative assessment tools is not a simple matter of each company choosing for itself. Ideally, companies and regulatory agencies with drug approval authority (the FDA in the United States) would work together toward a new industry standard that would benefit everyone.
candidate and dosage selection (the lack of surrogate markers making optimal selection difficult or impossible), other companies behave rationally by not inferring that they will necessarily have the same bad result with their own candidates—they may simply have better luck in choosing the best candidate and the most efficacious dose. With surrogate biomarkers enabling proper candidate and dosage selection, one company’s failure is more informative about other companies’ chances for success with similar compounds. Accordingly, companies could be expected to make better decisions about which drug candidates to take into human trials, leading to lower overall risk (i.e., higher probability, on average, that a compound will advance from Phase I to approval).

Impacts on development time. Surrogate biomarkers could reduce the duration of Phase II trials by providing a reliable signal of efficacy in less time than would be required for cognitive assessments. With surrogate markers, companies could run shorter, smaller Phase II trials in the conventional way—establishing proof of concept (a high probability that the drug will meet prespecified clinical endpoints in a Phase III trial) and determining the ideal dosage before scaling up for a full Phase III trial.

Incorporating less expensive and less invasive biomarkers into a hierarchy could streamline enrollment in clinical trials. Even if these biomarkers are less sensitive, when used as an initial screening step they could reduce the number of potential participants who must undergo the more invasive and time- and cost-intensive procedures used to determine eligibility for a clinical trial.

Streamlining enrollment in clinical trials with an advanced registry. The time and cost of enrolling participants for research studies and clinical trials could be reduced by establishing a registry of well-characterized candidates, containing standardized demographic, genetic, biologic, cognitive, and environmental information on each potential participant.

Impacts on development time. Enrolling the necessary number of participants for a Phase III trial typically takes approximately 2 years from the first person to the last person enrolled. Each potential participant must undergo cognitive assessments and biomarker tests to determine his or her eligibility. Each clinical trial begins from scratch and collects information only for its own use. Consider instead a platform for characterizing large numbers of potential clinical trial participants and making these data available to companies and other organizations enrolling participants for clinical trials. The information available in such an advanced registry (which is not to be confused with a list of names and contact information) would reduce the number of additional screening steps that must be undertaken for each trial, and it would reduce the number of individuals who must undergo additional screening to fill a particular trial. Those who fail the screening for one trial will remain available for other trials.

Impacts on risk. There is a trade-off between the higher risk associated with enrolling a suboptimal set of participants in a clinical trial and the cost of identifying exactly the right participants. By lowering the cost of enrolling the appropriate participants in clinical trials, advanced registries should lead companies to purposefully reduce risk by enrolling more uniformly appropriate sets of participants.

Establishing clinical trial platforms to investigate biomarker and drug combinations. Efficient learning about AD biomarker and drug combinations—testing, analytically validating, and qualifying biomarkers as new drugs are tested—can be enabled by incorporating promising biomarkers into Phase III and adaptive Phase II–III trials of potentially disease-modifying therapeutics.

Impacts on risk. Data from failed trials can be nested among multiple sponsors, enabling a selection of more likely-to-succeed follow-on drug candidates.

Toward a surrogate biomarker. The more clinical trials that incorporate potential surrogates, the sooner the discovery and qualification of a surrogate marker can be expected. Implementing this recommendation would thus move the field closer to realizing the impacts of a surrogate biomarker on risk and development time that are discussed above.1

1Three public–private partnerships are currently conducting AD trials that will generate valuable information for the field, possibly including progress toward a surrogate biomarker. They are the Anti-Amyloid Treatment in Asymptomatic AD (A4) trial, the Dominantly Inherited Alzheimer’s Network–Therapeutic Trials Unit (DIAN-TTU), and the Alzheimer’s Prevention Initiative.
Toward an advanced registry. Running an ongoing series of clinical trials and testing biomarkers and drugs from multiple sponsors will require a large number of well-characterized potential participants. Establishing an advanced registry and establishing a clinical trials platform can therefore be seen as complementary investments, and a cohesive group of stakeholders committed to establishing a clinical trial platform could also take steps toward establishing a registry. A further complementarity, albeit a subtle one, is that participants might be more motivated to enroll in a trial with the broader objective to advance knowledge in the field.

Broader impacts. Improvements in study designs, especially statistical frameworks for adaptive designs; protocols for data sharing, standardization, and harmonization across multiple sites; and approaches to intellectual property, will be modeled for others to emulate, moving the field forward.

Keeping the preclinical pipeline full of novel therapeutic approaches and targets. We can increase the likelihood that success in preclinical development will translate to success in clinical development (thereby reducing risk in clinical development) by conducting translational research in a precompetitive commons, advancing a greater diversity of novel therapeutic approaches and validated targets into clinical trials.

Impacts on risk. Greater collaboration between academic researchers and industry could increase the probability that companies will be able to replicate the results of academic research. This could lead to more novel therapeutic approaches and targets entering the clinical development pipeline. Greater diversity in the pipeline does not necessarily imply less risk for any one drug candidate, on average. Rather, to the extent that greater diversity implies less correlation among the outcomes of different candidates, it does imply that the probability of all candidates failing should be lower. Holding constant the probability of any one drug candidate succeeding, greater diversity in the pipeline implies a higher probability that at least one candidate will succeed.

Realizing economies of scope between research and drug development. Establishing a network of comprehensive AD centers, integrated with existing resources, can enhance understanding of the mechanisms of AD and speed the translation of this knowledge into the clinic.

Impacts on development time and risk

Comprehensive disease centers as described by Trojanowski and colleagues could provide care to patients, conduct natural history studies, and provide well-characterized participants for clinical trials, delivering the same impacts as the advanced registry described above.

Broader impacts

Data standardization and harmonization across centers would promote wider dissemination and more efficient utilization of information. An improved understanding of the pathology of AD will lead to better therapeutic approaches and targets, better tools such as biomarkers and cognitive assessments, better selection of participants for clinical trials, better clinical trial designs, and ultimately a greater likelihood of finding effective treatments.

Impacts on the cost of AD drug development

The expected capitalized cost of developing a disease-modifying drug for AD is estimated to be $5.693 million (95% CI, $3,691–9,541 million) in the current environment with the existing infrastructure and $2,027 million (95% CI, $1,453–2,935 million) in an environment with the improved infrastructure (Fig. 1). Thus, an improved technical approach...

Figure 1. Expected capitalized cost to develop a disease-modifying drug for AD
### Table 4. Average durations of drug development phases for an AD-modifying therapeutic

| Phase          | Existing infrastructure mean (95% CI) (months) | Recommended infrastructure mean (95% CI) (months) |
|----------------|-----------------------------------------------|-----------------------------------------------|
| Preclinical    | 50.1 (46.5–53.8)                              | 49.9 (46.2–53.5)                              |
| Phase I        | 12.8 (11.7–13.9)                              | 12.6 (11.7–13.5)                              |
| Phase II       | 27.7 (24.6–30.9)                              | 25.2 (23.0–27.4)                              |
| Phase III      | 50.9 (48.7–53.2)                              | 39.4 (36.2–42.7)                              |
| Regulatory review | 18.0 (16.9–19.1)                          | 16.9 (15.0–18.8)                              |
| **Total**      | 159.6 (148.4–170.8)                           | 144.0 (132.1–155.9)                           |

Note: Based on interviews with experts in AD research. Confidence intervals (CIs) are ±1.96 times the standard error (estimated standard deviation of the mean).

and research infrastructure supporting AD research and drug development is expected to reduce the cost of the first disease-modifying AD therapeutic by $3,667 million (95% CI, $1,340–5,994 million).

The majority of the overall cost reduction depicted in Figure 1 results from (1) shortening the overall development time by 16 months (Table 4), (2) increasing the probability that a compound entering Phase II progresses to marketing approval from 11% to 24% (Table 5), and (3) shifting failures from Phase III to Phase II (so that, of all compounds entering Phase II that are ultimately abandoned, 77% instead of 60% fail in Phase II).

Table 6 offers a comparison of the capitalized cost of drug development under the existing and improved infrastructure, breaking out the costs by development Phase. The remainder of the section explores the cost reduction in greater depth.

**Relative contributions of reducing risk and time in Phases II and III to cost reductions with and without better infrastructure.** Significant differences between the cost characterizations with the existing and the recommended infrastructure were found in four aspects of the development environment: the durations of Phases II and III, the transition probability from Phase II to approval, and the ratio of Phase II failures to the total failures in Phases II and III combined.

Shortening Phases II and III could by itself reduce the expected cost of a new drug by 18%. Reducing the risk of failure in clinical trials and shifting failures from Phase III to Phase II could reduce the expected cost of a new drug by 55%. Specifically, in comparison to the baseline capitalized cost estimate of $5,693 million to develop one new disease-modifying drug, shortening Phases II and III by 2.5 and 11.5 months, respectively, reduces the expected cost to $4,667 million, while increasing the probability of transitioning from Phase II to approval from 11% to 24%, and increasing the ratio of Phase II failures to the total failures in Phases II and III from 60% to 77% reduces the expected cost to $2,544 million.

Reducing the overall risk of failure has a relatively larger impact on expected cost compared with shifting failures from Phase III to Phase II. Again, compared to the baseline estimate of $5,693 million, if the probability of transitioning from Phase II to approval is increased from 11% to 24%, while the ratio of Phase II failures to the total failures in Phases II and III holds constant at 60%, the expected cost is reduced to $2,768 million. This represents a 51% reduction.

Although the confidence intervals for the average durations of Phase II with existing and recommended infrastructure overlap in Table 4, the difference between Phase II durations (the duration of Phase II with existing infrastructure minus the duration with the recommended infrastructure) had a mean of 2.5 months with a standard error of 1.2 months.
cost reduction that is spread over all stages of development. If, instead, the probability of transitioning from Phase II to approval is held constant at 11%, while the ratio of Phase II failures to the total failures in Phases II and III is increased from 60% to 77%, the expected cost falls by only 10%, with all of the reduction concentrated in Phase III (a 32% reduction in the capitalized cost incurred in Phase III for each new drug approved).

### Inclusion of the costs of failures in cost estimates.

The estimated costs of developing a disease-modifying drug for AD ($5.7 billion with the current infrastructure and $2.0 billion with improved infrastructure) are estimates for the industry as a whole, including the cost of all failures by all companies that would be expected before one drug is approved for marketing. The relationship between the perspective of industry and that of an individual company can be better understood by considering the cost of drug development from the perspective of a single drug candidate entering Phase I trials.

Tables 7 and 8 develop the estimates by first deriving the expected cost associated with entering a drug candidate into Phase I trials, based on the different possible outcomes and the respective probability of each. For example, when a company enters a drug candidate into Phase I, it faces a 33 percent chance

### Table 6. Average costs of drug development for an AD-modifying therapeutic

| Phase     | Monthly out-of-pocket cost ($ millions per molecule in development) | Existing infrastructure mean (95% CI) | Recommended infrastructure mean (95% CI) |
|-----------|---------------------------------------------------------------|------------------------------------|----------------------------------------|
| Preclinical | 0.72                                                                                  | 1,658 (1,041–2,872)                  | 642 (440–969)                           |
| Phase I    | 2.73                                                                                   | 1,193 (757–2,039)                   | 458 (323–673)                           |
| Phase II   | 2.00                                                                                   | 1,048 (690–1,714)                   | 387 (279–555)                           |
| Phase III  | 5.64                                                                                   | 1,794 (1,203–2,916)                 | 539 (410–738)                           |
| Total      | 5.693 (3,691–9,541)                                                                   | 2,027 (1,453–2,935)                 |

**Note:** All costs were calculated using the average durations and transition probabilities from Tables 4 and 5. CI refers to confidence interval. Cost lower bounds were calculated using lower-bound durations and upper-bound transition probabilities. Cost upper bounds were calculated using upper-bound durations and lower-bound transition probabilities. An alternative method, based on cost estimates derived from a subset of individual respondents who gave complete sets of answers, yielded similar confidence intervals. The cost of capital was fixed at 11% to facilitate comparison with recent prominent studies of the cost of drug development in other disease areas.25,26 Monthly out-of-pocket costs per compound are based on Refs. 25 and 35 and adjusted for inflation using the GDP Implicit Price Deflator (U.S. Department of Commerce, Bureau of Economic Analysis, Series ID: GDPDEF).
### Table 7. Cost of AD-modifying drug development with existing infrastructure

| Eventual outcome for a compound entering Phase I | Out-of-pocket cost ($ millions) | Cost ($ millions) capitalized to date that development stops or drug is approved | Present-value cost ($ millions) at date of Phase I start (11% discount rate) | Probability |
|-------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------|
| Development stops after Phase I                  | 71                              | 89                                                                              | 79                                                                       | 0.33        |
| Development stops after Phase II                  | 126                             | 177                                                                             | 122                                                                      | 0.35        |
| Development stops after Phase III                 | 413                             | 648                                                                             | 280                                                                      | 0.24        |
| Drug is approved                                  | 413                             | 765                                                                             | 280                                                                      | 0.07        |

Expected present-value cost = (79 × 0.33) + (122 × 0.35) + (280 × 0.24) + (280 × 0.07) = $157 million
Cost per new drug approval = $157 million ÷ 0.07 = $2,087 million
Capitalized to date of drug approval = $2,087 million × e^{109.4}(0.11/12) = $5,693 million
(Phase I starts an average of 109.4 months before approval)

Note: Numbers may not exactly replicate because of rounding. For example, $2,087 million comes from dividing approximately $156.5 million by approximately 0.075. Confidence intervals (provided in Tables 4 through 6) are omitted here, where the purpose is to explain the relationship between the perspective of the industry and that of an individual company.

Of incurring costs of $89 million and then advancing no further than Phase I, and it faces a 35% chance of incurring costs of $177 million over Phases I and II and then advancing no further (Table 7).

The total capitalized cost per new drug approved is then derived by first dividing the expected present-value cost by the probability that a compound entering Phase I will eventually be approved for

### Table 8. Cost of AD-modifying drug development with recommended infrastructure

| Eventual outcome for a compound entering Phase I | Out-of-pocket cost ($ millions) | Cost ($ millions) capitalized to date that development stops or drug is approved | Present-value cost ($ millions) at date of Phase I start (11% discount rate) | Probability |
|-------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------|
| Development stops after Phase I                  | 70                              | 87                                                                              | 78                                                                       | 0.31        |
| Development stops after Phase II                  | 121                             | 167                                                                             | 118                                                                      | 0.40        |
| Development stops after Phase III                 | 343                             | 507                                                                             | 250                                                                      | 0.12        |
| Drug is approved                                  | 343                             | 592                                                                             | 250                                                                      | 0.17        |

Expected present-value cost = (78 × 0.31) + (118 × 0.40) + (250 × 0.12) + (250 × 0.17) = $144 million
Cost per new drug approval = $144 million ÷ 0.17 = $855 million
Capitalized to date of drug approval = $855 million × e^{94.1}(0.11/12) = $2,027 million
(Phase I starts an average of 94.1 months before approval)

Note: Numbers may not exactly replicate because of rounding. For example, $855 million comes from dividing approximately $143.5 million by approximately 0.168. Confidence intervals (provided in Tables 4 through 6) are omitted here, where the purpose is to explain the relationship between the perspective of the industry and that of an individual company.
marketing (equivalent to multiplying by the number of times a new compound must enter Phase I for every new drug approved, on average) and then capitalizing costs to the date that a drug is approved.

In the present environment with the existing infrastructure (Table 7), the expected cost associated with a Phase I compound is $157 million. There is estimated to be a roughly 7% chance that the compound will eventually be approved for marketing. A compound that is eventually approved will have accumulated a capitalized cost of $765 million by the date of its approval. The difference between that amount and $5,693 million is the cost of developing (to various stages) the other roughly 93% of Phase I compounds that will never win approval.

In the improved environment with the recommended infrastructure (Table 8), the expected cost associated with a Phase I compound is $144 million (only 8% less), and a compound that is eventually approved will have accumulated a capitalized cost of $592 million by the date of its approval (23% less). However, a Phase I compound will be more than twice as likely to eventually be approved for marketing: the probability of approval is estimated at 17%. It is this reduction in risk that is responsible for most of the reduction in the expected cost of developing a single new drug: from $5,693 to $2,027 million.

**Increasing private investment in Alzheimer’s drug development**

In the improved environment with the recommended infrastructure, it is expected that total planned private-sector investment in AD R&D would increase by 23% (95% CI, 12–34%), based on quantitative estimates provided by 10 interviewees. Overcoming barriers would have the effect of crowding in investment by increasing firms’ expected rates of return on their R&D investments.

Although the majority of interviewees believed that there would be greater private investment in the new environment, two alternative views were offered. One alternative view was that the same level of planned investment would be maintained, but that this investment would yield greater results in the new environment with the improved infrastructure.

A second alternative view was that the impact of the improved infrastructure would depend on whether clinical trials currently underway succeeded in launching new drugs. Interviewees reasoned that the first approval of a disease-modifying drug would spur greater private investment, and the additive impact of an improved infrastructure would be less in this case. However, if current efforts failed to launch new drugs and infrastructure improvements were not made, then planned investment in the field could drop — and some companies could drop out altogether. The additive impact of an improved infrastructure would be critical in this case to keeping companies invested in AD.

**Reducing the burden of Alzheimer’s disease**

Increasing R&D efforts and bringing disease-modifying drugs to market sooner would have a significant impact on the future social burden of AD.

To quantify this impact, interviewees were asked to estimate the probability of having the capability to slow the progression of AD by 2025 so that onset of dementia (conversion from mild cognitive impairment to dementia) would be delayed (1) by at least 2 years in at least 50% of cases, (2) by at least 5 years in 50% of cases, and (3) by at least 5 years in 75% of cases.

For all three treatment scenarios, the estimated probabilities became significantly greater in the new infrastructure environment with improved infrastructure (Table 9).

**Reduction in case years of AD.** To translate these mean probabilities into estimates of the impact on the burden of AD, the number of cases of dementia in each year (case years) was first projected under each treatment scenario. The expected number of case years of dementia was then calculated as the probability-weighted average of the caseloads under these treatment scenarios.

Estimating caseloads required two sets of information: (1) population projections for different ages and (2) the likelihood of dementia at different ages. Population projections by single year of age are from the U.S. Census Bureau. Estimates of the probability of dementia were 0.028 for 71–74 years of age, 0.049 for 75–79, 0.130 for 80–84, 0.203 for 85–89,

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“The time until each scenario is achieved is assumed to follow a Weibull distribution. The probability of having achieved a given scenario by a given time is therefore given by the cumulative Weibull distribution function. A detailed description of the methodology is provided in the online Appendix.
Table 9. Probability of delaying onset of dementia by 2025

| Treatment scenario                                      | Probability with existing infrastructure mean (95% CI) | Probability with recommended infrastructure mean (95% CI) | Difference in probability mean (95% CI) |
|--------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------|----------------------------------------|
| At least a 2-year delay for 50% of cases                | 0.32 (0.22–0.42)                                       | 0.49 (0.39–0.59)                                         | 0.17 (0.11–0.23)                       |
| At least a 5-year delay for 50% of cases                | 0.16 (0.09–0.23)                                       | 0.31 (0.22–0.40)                                         | 0.15 (0.10–0.20)                       |
| At least a 5-year delay for 75% of cases                | 0.05 (0.02–0.07)                                       | 0.12 (0.07–0.17)                                         | 0.07 (0.04–0.11)                       |

Note: CI refers to confidence interval. Probability estimates were obtained from interviews with experts in Alzheimer’s research. Answers for 2–year and 5–year delays in 50% of cases were provided by 17 interviewees. Answers for a 5–year delay in 75% of cases were provided by 12 interviewees. Confidence intervals are ± 1.96 times the standard error (estimated standard deviation of the mean).

and 0.385 for 90 or older.\(^2\) For example, the probability that a person between the ages of 85 and 89 would have dementia is 20.3%.

Holding the probabilities of dementia constant over time, the number of cases of dementia is projected to grow from 3.0 million in 2013 to 4.1 million in 2025, 6.9 million in 2040, and 8.5 million in 2055.

To project dementia cases under each treatment scenario, a percentage of the population (50% or 75%) was assigned the probability of dementia for the cohort 2 or 5 years younger, according to the treatment scenario.

Earlier expected realization of each of the three treatment scenarios under the infrastructure recommendations is estimated to avoid 7.0 million (95% CI 4.4–9.4 million) case years of dementia between 2025 and 2040. Figure 2 shows these 7 million avoided case years as the shaded area between the heavy dashed and solid lines.

**2025–2040 time frame of analysis.** An appropriate interval for thinking about disease burden impact estimates is 2025 to 2040. Recommendations to improve infrastructure may take some years to fully implement, and clinical trials that benefit from the new infrastructure will then take time to read out. Beginning to think about impacts in 2025 allows 12 years for the effects of the new infrastructure to be reflected in pivotal trials reaching completion. Note that the predicted impacts focus mostly on clinical trials, and especially Phases II and III. Thus, looking at impacts beginning in 2025 allows roughly 4–5 years for infrastructure improvements to be put in place before trials are undertaken with improved transition probabilities and shorter timelines. Beyond 2040, impact estimates become more sensitive to assumptions about the rapidity with which probabilities of having realized the treatment scenarios increase after 2025. If the probabilities increase more gradually, there is room for greater impact between 2040 and 2055. If instead the probabilities increase more rapidly between 2025 and 2040, there is less room for improvement after 2040. The upshot is that results are fairly robust to different assumptions between 2025 and 2040 but diverge in later years.\(^2\) Excluding impacts after 2040 altogether naturally leads to more conservative estimates.

**Avoided cost of care for AD sufferers.** Restricting attention to the estimated 7.0 million (95% CI, 4.4–9.4 million) case years of dementia avoided from 2025 to 2040, it is possible to offer a cautious estimate of the monetary value of this impact, based on cost-of-care estimates from Hurd and colleagues.\(^2\)

Using a value of $41,689 per case year (which uses the valuation of forgone wages to estimate the cost of informal care) and applying a 7% discount rate, the present value of avoided cases is $74.0 billion (95% CI, $46.1–100.1 billion).

Using a value of $56,290 per case year (which uses the valuation of replacement cost to estimate the cost of informal care), the present value of avoided cases is $100.0 billion (95% CI, $62.3–135.2 billion). For comparison, Table 10 provides estimates using both 7% and 3% discount rates.

\(^a\) Additional details are provided in the online appendix.
Annual cost-of-care estimates from Hurd and colleagues do not reflect the full burden of the disease, both to the person with dementia and to that person’s family, friends, and community. The cost incurred to care for a condition is rightly seen as a lower bound on the value of avoiding the condition altogether. For this reason, our approach may tend to underestimate the value of accelerating the development of disease-modifying treatments.

We have not attempted to account for longer life expectancy resulting from delay of the onset of dementia. Recognizing that a portion of avoided case years may be only postponed, our approach may tend to overestimate the impact on cost of care. Still, each year that the onset of dementia is postponed is a year of relatively independent function reclaimed, and—for reasons discussed above—the value to society of one such year reclaimed can reasonably be expected to exceed the monetary cost of caring for someone who has lost the ability to function independently. We are of the opinion that our approach is more likely to lead to an underestimation of the full social value of accelerating the development of disease-modifying treatments.

### Conclusions

The barriers to developing disease-modifying treatments for Alzheimer’s today still mirror those discussed by Fillit and colleagues over a decade ago. The field still lacks validated therapeutic targets, animal models that adequately model all of the features of AD, robust surrogate markers for therapeutic endpoints, and more efficient designs for AD clinical trials. Underfunding remains a problem. Alzheimer’s drug development efforts would almost certainly also benefit from improved technical infrastructure in areas such as bioinformatics and gene expression, where needs have been identified for the biopharmaceutical industry more broadly.

These barriers will not be overcome by any single company. While large pharmaceutical companies realize economies of scale and scope and internalize to some extent the positive externalities associated with R&D, even the largest companies are limited in their ability to develop treatments for such a complex multifactorial disease as AD. Co-investment by public- and private-sector stakeholders is needed to overcome these barriers, and the consensus among the experts in industry and academia who provided input for this study was that the benefits to society

### Table 10. Present value of 7 million avoided case years of dementia from 2025 to 2040

| Annual cost of care ($ billions) | 7% discount rate (95% CI) mean | 3% discount rate (95% CI) mean |
|----------------------------------|---------------------------------|--------------------------------|
| $41,689                          | 74.0 (46.1–100.1)               | 158.4 (98.8–213.3)             |
| $56,290                          | 100.0 (62.3–135.2)              | 213.8 (133.5–288.0)            |

Note: CI refers to confidence interval. Annual cost-of-care estimates come from Ref. 2. The lower estimate uses the valuation of family members’ forgone wages to estimate the contribution of informal care to total cost; the higher estimate uses the replacement cost, meaning the cost of hiring a caregiver to provide the services performed by family members. The number of avoided case years of dementia from 2025 to 2040 is as shown in Figure 2. Details are provided in the online appendix.
of successfully meeting these common needs would be significant.

This study has sought to quantify these potential benefits to the extent possible given the many uncertainties around the exact form that collaborative initiatives will take and the amount of public and private resources that will be invested, and given that the outcomes of these efforts—like the outcomes of the drug discovery and development efforts they seek to support—are themselves uncertain. Given these issues and the relatively small sample size on which the quantitative estimates were based, these estimates should be viewed as an initial indication of the potential impacts that can reasonably be expected if coordinated efforts by public and private stakeholders are successful.

The methodology presented here can be used to evaluate future initiatives based on their expected impacts on the timeline and transition probabilities of the drug development cycle, thus helping to select projects that are likely to have the greatest impact. Recent initiatives—such as the Innovative Medicines Initiative European Platform for Proof-of-Concept for Prevention in Alzheimer’s Disease (EPOC-AD) and the National Institutes of Health Accelerating Medicines Partnership (AMP)—align closely with the recommendations from the AD community. The broad conclusion of this study is that these and similar initiatives hold great promise for advancement toward the effective treatment and prevention of AD and dementia.

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Conflicts of interest

The authors declare no conflicts of interest.

Supporting Information

Additional supporting information may be found in the online version of this article.

Table 1. Development costs per approved new drug ($ millions).

Table 2. Transition probabilities

Table 3. Cycle times (months from start of phase to start of next phase)

Table B1. Parameters characterizing each phase of drug development

Table B2. Durations of drug development phases (months)

Table B3. Average transition probabilities

Table B4. Average costs of drug development

Table B5. Cost of AD disease-modifying drug development with existing infrastructure

Table B6. Cost of AD disease-modifying drug development with recommended infrastructure

Table C1. Cases of dementia by age group, 2012

Table C2. Cases of dementia by single year of age, 2012

Table C3. Probability of delaying onset of dementia by 2025

Table C4. Sensitivity of estimates to Weibull α

Table C5. Avoided cases of dementia and present discounted value

Figure C1. Projected cases of dementia in the United States

Figure C2. Weibull distributions

Figure C3. Expected number of cases of dementia in the United States

Figure C4. Avoided case years of dementia attributable to improved infrastructure
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