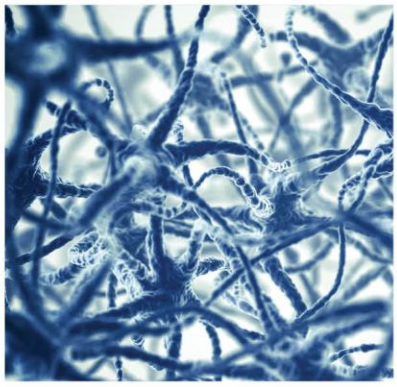
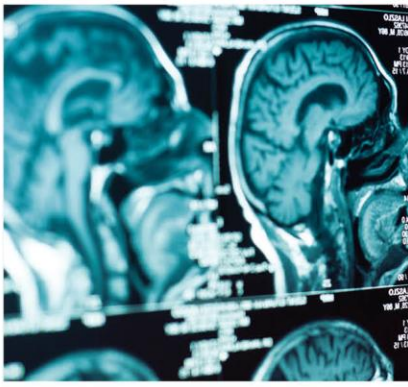
Economic Analysis of Opportunities to Accelerate Alzheimer's Research and Development



The New York Academy of Sciences
Alzheimer's Disease & Dementia Initiative

GLOBAL CEOINITIATIVE
ON ALZHEIMER'S DISEASE

Economic Analysis of Opportunities to Accelerate Alzheimer's R&D

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Founded in 1817, **the New York Academy of Sciences** is one of the oldest scientific institutions in the U.S. with more than 24,000 members in 140 countries. The Academy fosters new collaborations among experts in academia, industry, and government to drive advances in science, medicine, technology, and sustainability. In 2011, the Academy expanded its portfolio of interdisciplinary scientific programs to launch the **Alzheimer's Disease and Dementia Initiative (ADDI)** that seeks to accelerate the transfer of basic research into the development of new methods to address Alzheimer's disease and dementia. The ADDI has assembled an advisory council of multi-sector stakeholders to define priorities and develop actionable plans around four key areas: the basic research landscape, early drug development/translation, prevention trials, and the public-private interface. Please visit **www.nyas.org/ADDI**.

The **Global CEO Initiative on Alzheimer's Disease** represents an acceptance of the invitation from public authorities, domestically and internationally, to the private sector to forge robust public-private partnerships to stop Alzheimer's disease and dementia. Our vision is that the CEO Initiative becomes a leading business voice on this seminal public health issue of our time, which will have profound impact in fiscal, social and political matters as we "change the game" on Alzheimer's. By working together and in partnership with leading non-governmental organizations and governments, the CEO Initiative will identify and pursue research, therapy development, financing, and public awareness projects of the highest priority that, when achieved, can transform the global fight to stop Alzheimer's disease. Please visit **http://www.ceoalzheimersinitiative.org/**.

RTI INTERNATIONAL

RTI International is a trade name of Research Triangle Institute

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Executive Summary

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

Only symptomatic treatments for AD are currently available; the most recent of these, memantine, was approved in 2003. Since then, numerous candidate agents have failed after reaching the final Phase of clinical development.[1]

In response to the challenges faced by the drug industry, industry leaders and academics have come together in joint initiatives to work toward overcoming common barriers to the discovery and development of AD therapeutics, especially those therapeutics that could prevent or slow disease progression (Table ES-1). Example initiatives include the National Institutes of Health Alzheimer's Disease Research Summit, Ware Invitational Summit, The New York Academy of Sciences' Alzheimer's Disease and Dementia Initiative (ADDI), and the Global CEO Initiative on Alzheimer's Disease.

[1] Cummings (2013) provides a recent listing of 22 agents that completed Phase III trials for AD and showed no drug-placebo difference on prespecified primary outcomes.

Table ES-1. Barriers to the Discovery and Development of AD Therapeutics

▪ Without surrogate markers (biomarkers correlated with disease progression and predictive of treatment effect), drug development is risky and inefficient.
▪ Demonstrating a treatment effect requires long trials with many participants; the time and cost involved in both recruitment and treatment in clinical trials is higher for AD than for other diseases.
▪ Difficulties in identifying appropriate populations for clinical trials increase the risks and costs of drug development.
▪ Significant treatment effects may require combinations of drugs, making it difficult for any single company to independently develop an effective treatment.

These initiatives have made recommendations to overcome barriers through co-investment by private- and public-sector stakeholders in the technical and research infrastructure supporting research and drug development.

Their recommendations include the following:

- ***Invest in biomarkers and cognitive assessment tools***—Better detect and monitor AD, especially from its earliest clinical manifestations, and better predict treatment response (thereby de-risking clinical development by targeting therapeutics to subpopulations of patients) by developing, validating, and standardizing a robust hierarchy of biomarkers and sensitive cognitive and functional assessment tools, elucidating relationships among biological and cognitive markers.
- ***Streamline enrollment in clinical trials with an advanced registry***—Reduce the time and cost of enrolling participants for research studies and clinical trials 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***—Enable efficient learning about AD biomarker and drug combinations—testing, analytically validating, and qualifying biomarkers as new drugs are tested—by incorporating promising biomarkers into Phase III and adaptive Phase II-III trials of potentially disease-modifying therapeutics.
- ***Keep the preclinical pipeline full of novel therapeutic approaches and targets***—Increase the likelihood that success in preclinical development will translate to success in clinical development (thereby de-risking clinical development) by conducting translational research in a precompetitive commons, advancing a

greater diversity of novel therapeutic approaches and validated targets into clinical trials.

- ***Realize economies of scope between research and drug development***—Better understand the mechanisms of Alzheimer's and speed the translation of this knowledge into the clinic by establishing a network of comprehensive Alzheimer's disease centers, integrated with existing resources.

On behalf of The New York Academy of Sciences, RTI International conducted an economic analysis of meeting these infrastructure recommendations. Specifically, RTI estimated

- the capitalized cost of AD drug development in the current R&D environment with the current infrastructure *and* in an improved environment with the recommended infrastructure,
- the timeframe for developing disease-modifying therapeutics,
- the extent to which improved infrastructure for AD research and drug development could increase private investment in drug research, and
- how improved infrastructure could translate into a lower future burden of AD.

ES.1 ANALYSIS APPROACH

In consultation with a team of senior industry researchers and executives, university researchers, and ADDI working group leaders, RTI analyzed the recommendations' points of influence within the therapeutic development pipeline.

Next, we interviewed in-depth senior pharmaceutical executives and experts in Alzheimer's research and drug development to ascertain how fulfilling infrastructure needs would affect

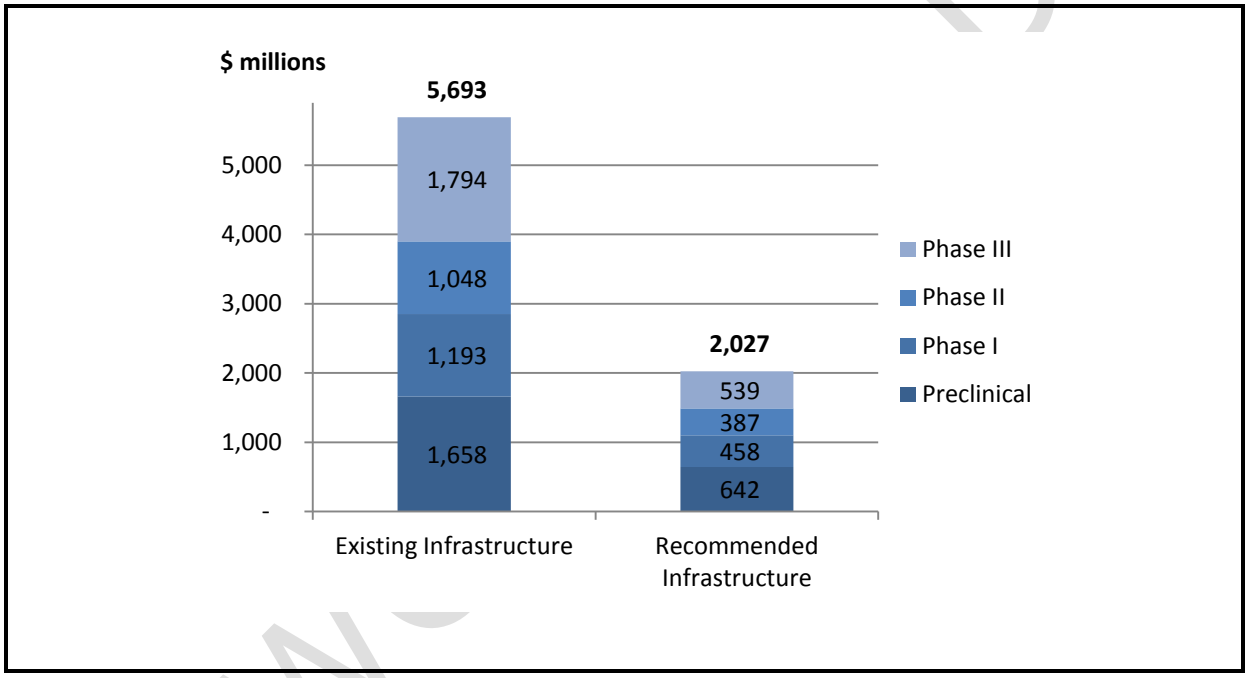
- AD drug discovery and development constraints, including the duration and cost of preclinical and clinical development Phases and the expected number of failures in each Phase;
- the amount of private investment in AD drug discovery and development from an industry-wide perspective; and
- the probability of having effective treatments for AD by 2025.

Responses to interview questions were used to estimate both the reduction in the expected capitalized costs of new AD drugs and the reduction in the number of case-years of dementia in the United States that could be expected if infrastructure needs were met.

ES.2 ANALYSIS FINDINGS

The average capitalized cost—the cost of a successful drug, including the cost of failures—of developing a disease-modifying drug was estimated at $5.7 billion in the current environment with the current or existing infrastructure, falling to $2.0 billion in the new environment with the recommended infrastructure. This is lower than what is expected in the current environment, but still $500 million more than the expected cost of $1.5 billion for other diseases (Figure ES-1).

Figure ES-1. Expected Capitalized Cost to Develop a Disease-Modifying Drug for AD



The majority of the estimated $3.7 billion in cost reduction results from a combination of shortening the overall development time by an estimated 16 months, increasing the probability that a compound entering Phase II will progress to marketing approval (launch) from 11% to 24%, and shifting failures from Phase III to Phase II.

Table ES-2. Cost of Developing a Disease-Modifying Drug for AD

Scenario	Capitalized Cost of Developing a Disease-Modifying Drug for AD, *Assuming No Failures in Clinical Trials*	Probability That a Compound Entering Phase I Trials Will Eventually Be Approved for Marketing	Capitalized Cost of Developing a Disease-Modifying Drug for AD, *Taking Into Account the Cost of Failures*
Present environment with existing infrastructure	$765 million	7%	$5.7 billion
Improved environment with recommended infrastructure	$592 million	17%	$2.0 billion

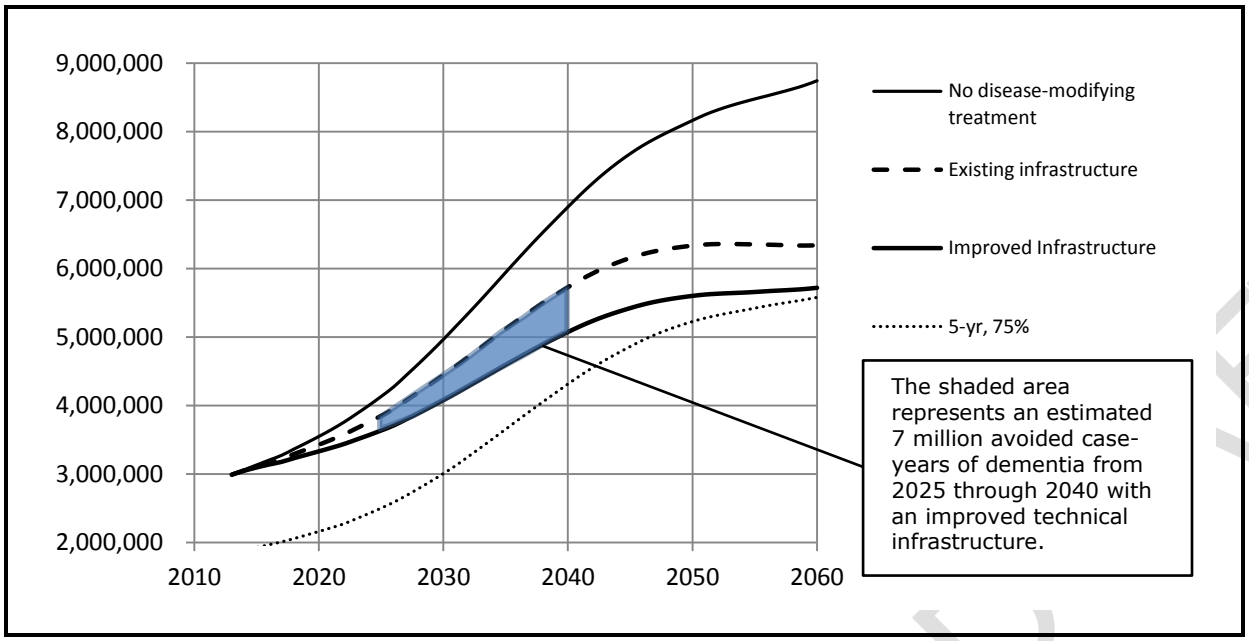
Note: These results are presented in Section 3.2. Additional details are provided in Appendix B.

It was estimated that in an improved environment with the recommended infrastructure total private investment in Alzheimer's R&D would increase by 23%.

Shorter development times, reduced risk, and the additional private investment in the improved environment are expected to result in disease-modifying drugs being brought to market sooner than would be the case in the current environment with the existing technical infrastructure.

The impact of bringing effective treatment to market sooner is estimated to be on the order of 7 million fewer case-years of dementia over the period 2025 to 2040, where 1 case-year is defined as one person living with AD for 1 year. Figure ES-2 shows these 7 million avoided case-years as the shaded area between the heavy dashed and solid lines.

Figure ES-2. Potential Reduction in the Number of Cases of Dementia in the United States with an Improved Technical and Research Infrastructure



Based on two recent estimates of the cost of care (see Table ES-3), the present discounted value of avoiding those 7 million cases is $74 billion or $100 billion using a 7% discount rate, and it is $158 billion or $214 billion using a 3% discount rate.

Table ES-3. Present Value of 7 Million Avoided Case-Years of Dementia, from 2025 to 2040

Basis for Annual Cost of Care—Method of Estimating the Contribution of Informal Care to Overall Cost	Annual Cost of Care	7% Discount Rate ($ billions) Mean (95% CI)	3% Discount Rate ($ billions) Mean (95% CI)
Cost of family members' forgone wages	$41,689	74.0 (46.1, 100.1)	158.4 (98.8, 213.3)
Replacement cost, meaning the cost of hiring a caregiver to provide the services performed by family members	$56,290	100.0 (62.3, 135.2)	213.8 (133.5, 288.0)

Note: Annual cost-of-care estimates come from Hurd et al. (2013). One case-year is defined as 1 person living with AD for 1 year. These results are presented in Section 3.4. Additional details are provided in Appendix C.

1 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 million 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.[2]

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 prior to 2004. These drugs treat only the symptoms of AD, and the medical community considers their clinical effect to be modest in that regard.[3]

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.[4] Less encouraging is that over the same time period all drug candidates that advanced to the final Phase of clinical

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[2] For estimates of worldwide prevalence and a detailed overview of dementia, see the World Alzheimer Report 2009, available from www.alz.co.uk/worldreport. For recent estimates of the prevalence of dementia in the United States, see Hebert et al. (2013) and Hurd et al. (2013).

[3] See for example Qaseem et al. (2008) and Raina et al. (2008).

[4] For more on the distinction between disease-modifying and symptomatic agents, see Cummings (2008). For a discussion of how disease modification could be established in a clinical trial, see the Center for Drug Evaluation and Research (2013).

trials failed, without any new drugs being approved for marketing.[5]

These efforts are being hindered by a number of barriers to the discovery and development of AD therapeutics. These include the following:[6]

- ***Without surrogate markers, drug development is risky and inefficient***—A critical infrastructure need is a surrogate biomarker, meaning an early indicator that a drug is having an effect that will ultimately lead to improvements in cognition and function. Without a surrogate marker, ineffective drug candidates advance to the largest, longest, and 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 were 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 any treatment effect that could be 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

[5] Cummings (2013) provides a recent listing of 22 agents that completed Phase III trials for AD and showed no drug-placebo difference on prespecified primary outcomes. Greenberg et al. (2013) provide 12 brief case studies of drug development efforts, a discussion of lessons learned, and six specific recommendations for improving Phase II clinical trials.

[6] See also Greenberg et al. (2013) for a discussion of barriers addressed to a technical audience.

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.

These AD-specific barriers are related to recognized barriers to technology development and innovation generally (Table 1-1). A rich economic literature analyzes the factors contributing to these barriers and potential policy remedies.[7] 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.

Table 1-1. General Barriers to Technology and Innovation

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 Link and Scott (2011) for a detailed discussion of these barriers.

[7] For reviews of this literature, see Combs and Link (2003), Link and Link (2009), and Tassey (2005).

In recognition that these barriers will take collaborative technology development and investigation to be overcome, 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, National Institutes of Health Alzheimer's Disease Research Summit, Ware Invitational Summit, The New York Academy of Sciences' Alzheimer's Disease and 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:[8]

- ***Invest in biomarkers and cognitive assessment tools***—Better detect and monitor AD, especially from its earliest clinical manifestations, and better predict treatment response (thereby de-risking clinical development) by developing, validating, and standardizing a robust hierarchy of biomarkers and sensitive cognitive and functional assessment tools, elucidating relationships among biological and cognitive markers.
- ***Streamline enrollment in clinical trials with an advanced registry***—Reduce the time and cost of enrolling participants for research studies and clinical trials 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***—Enable efficient learning about AD biomarker and drug combinations—testing, analytically validating, and qualifying biomarkers as new drugs are tested—by incorporating promising biomarkers into Phase III and adaptive Phase

[8] The list of five broad recommendations offered here is not exhaustive. For more, see Alzheimer's Association Expert Advisory Workgroup on the National Alzheimer's Project Act (NAPA, 2012), Greenberg et al. (2013), Khachaturian et al. (2008, 2012), Khachaturian (2009), Naylor et al. (2012), Trojanowski et al. (2010), and U.S. Department of Health and Human Services (2012, 2013b, 2013c).

II–III trials of potentially disease-modifying therapeutics.[9]

- ***Keep the preclinical pipeline full of novel therapeutic approaches and targets***—Increase the likelihood that success in preclinical development will translate to success in clinical development (thereby de-risking clinical development) by conducting translational research in a precompetitive commons, advancing a greater diversity of novel therapeutic approaches and validated targets into clinical trials.[10]
- ***Realize economies of scope between research and drug development***—Better understand the mechanisms of Alzheimer's and speed the translation of this knowledge into the clinic by establishing a network of comprehensive Alzheimer's disease centers, integrated with existing resources.[11]

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.

This need for co-investment by public- and private-sector stakeholders is also recognized by the National Plan to Address Alzheimer's Disease, which includes support for such collaborative efforts as a guiding principle:[12]

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[9] 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 Barker et al. (2009).

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

[11] For more details of this proposal, see Trojanowski et al. (2010). 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.

[12] For the most recent update of the National Plan, see U.S. Department of Health and Human Services (2013a). The National

> *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.* U.S. Department of Health & Human Services (2013a, p. 9).

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

- 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,
- the likely increase in private-sector drug development funding if technical barriers were overcome, and
- 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:

- **Section 2** and accompanying technical appendices describe the analysis procedures used to develop economic impact estimates, including those for eliciting

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. (2008) and Khachaturian (2009).

data from experts in AD research and senior executives in the pharmaceutical industry.

- **Section 3.1** 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.
- **Section 3.2** characterizes 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.
- **Section 3.3** discusses the effects on private investment in AD drug discovery and development of the changes in risk, time, and cost described in Section 3.2. Interviewees generally predicted that the total private investment would be higher in the environment with improved infrastructure.
- **Section 3.4** provides 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: first as the expected number of case-years of dementia over time and second 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.
- **Section 4** concludes the report with a discussion of the implications of our findings subject to the limited scope of the study.

2 Analysis Approach

RTI employed a mixed-methods approach to this prospective economic analysis. Methods included

- logic modeling of how the recommendations to improve AD research infrastructure would have impacts on AD research and drug development;
- economic modeling of AD drug development cost, time, and risk;
- economic modeling of potential changes in the future financial burden of AD; and
- interview data collection with leaders in the field of AD research and drug development at the level of vice president (or equivalent) and above.

2.1 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

- 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 (1) reduce the expected capitalized cost of developing new drugs to treat AD and (2) increase the expected value of any new drug approved for marketing by sparing valuable patent life;
- these effects would lead to increased investment in AD research and drug development; and

- 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 (1) spreadsheet models that could be calibrated to quantify these impacts and (2) 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 Appendix A.

2.2 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.[13]

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:

$$\left(c\int_{t_{end}}^{t_{start}} e^{rt/12}\,dt\right)/p = \left(\frac{c}{p}\right)\left(\frac{12}{r}\right)\left(e^{rt_{start}/12} - e^{rt_{end}/12}\right)$$

Parameters in the formula are defined in Table 2-1. The inputs that populated the model were collected from more than 32 experts in AD research, as described in Section 2.4, with the exception of the real cost of capital, *r*, which was set at 11% (Harrington, 2012). The results based on this spreadsheet model are presented in Section 3.2 and with greater detail in Appendix B.

[13] The model followed an analysis framework developed by DiMasi and Grabowski (2007), who calculated a $1.2 billion capitalized cost ($1.5 billion in 2013$) to develop a new approved biopharmaceutical product. The model was also able to replicate the conceptually similar model used by Paul et al. (2010).

Table 2-1. Parameters Characterizing Each Phase of Drug Development

Parameter	Description
t_{start}	Time in months from start of Phase to date of new drug approval
t_{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

2.3 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 the expected burden of Alzheimer's 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:

- U.S. population projections by single year of age,
- current estimates of (1) the probability of dementia by age and (2) the cost of care per case-year of dementia from Hurd et al. (2013), and
- expert assessment of alternative treatment scenarios based on the probability of the recommendations' ability to modify AD.

The treatment scenarios reflect the fact 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,[14] 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

[14] See Brookmeyer et al. (1998, 2007).

effectiveness in treatment rises more quickly over time with better infrastructure and that the benefit of this is to reduce the expected burden of dementia in the future.

The results based on this spreadsheet model are presented in Section 3.4 and with greater detail in Appendix C.

2.4 INTERVIEW DATA COLLECTION

These models 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 2-2 provides a representative listing of interviewees' titles.

Table 2-2. Representative Titles of AD Experts Interviewed

Chief Executive Officer	Chief Scientific Officer	Executive Associate Dean
Senior Vice President, R&D	General Manager, Research	Professor of Neurology
Executive Vice President	Senior Medical Director	Research Fellow
Vice President, Research	Director	Department Head
Senior Director	Co-Director, Neurology	Principal Investigator

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 the interview guide (Appendix A). 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.

Interviews were conducted under confidentiality agreements that specified that only aggregated interview responses would be available in any format outside of the RTI project team. Notes were taken during all interviews; most interviews were audio-recorded, when we were provided approval, to resolve any discrepancies in the compared notes of RTI interviewers. Recordings were destroyed upon project completion.

3 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 reduce the cost of and accelerate AD research and drug development. 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 bringing forward in time the introduction of disease-modifying therapeutics.

3.1 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.

3.1.1 Invest in Biomarkers and Cognitive Assessment Tools

Better detect and monitor AD, especially from its earliest clinical manifestations, and better predict treatment response (thereby de-risking clinical development) by developing, validating, and standardizing a robust hierarchy of biomarkers and sensitive cognitive and functional assessment tools,

elucidating relationships among biological and cognitive markers.

Impacts on Risk

(1) 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 different from 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.[15]

(2) Tools for cognitive assessment are not sensitive enough to discern treatment effects among participants with milder cognitive impairments.[16] 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.

(3) 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

[15] As it has focused more attention on developing disease-modifying drugs, the pharma 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. (1984) 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 Dubois et al. (2010) and McKhann et al. (2011). These new diagnostic guidelines are informed by the work of the Alzheimer's Disease Neuroimaging Initiative (ADNI). See Weiner et al. (2012) for a review of the research that ADNI has influenced. Cummings (2010) discusses how the knowledge generated by ADNI can be further integrated into clinical trials.

[16] Greenberg et al. (2013, §3.5) 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.

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.

(4) Relatedly, 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 the 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 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

(1) 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.

(2) Incorporating less expensive and less invasive biomarkers into a hierarchy could streamline enrollment in clinical trials. Even if these biomarkers are less sensitive, 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.

3.1.2 Streamline Enrollment in Clinical Trials with an Advanced Registry

Reduce the time and cost of enrolling participants for research studies and clinical trials 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.

3.1.3 Establish Clinical Trial Platforms to Investigate Biomarker and Drug Combinations

Enable efficient learning about AD biomarker and drug combinations—testing, analytically validating, and qualifying biomarkers as new drugs are tested—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 shared 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.[17]

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.

[17] Three 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.

3.1.4 Keep the Preclinical Pipeline Full of Novel Therapeutic Approaches and Targets

Increase the likelihood that success in preclinical development will translate to success in clinical development (thereby de-risking 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.

3.1.5 Realize Economies of Scope between Research and Drug Development

Better understand the mechanisms of Alzheimer's and speed the translation of this knowledge into the clinic by establishing a network of comprehensive Alzheimer's disease centers, integrated with existing resources.

Impacts on Development Time and Risk

Comprehensive disease centers as described by Trojanowski et al. (2010) 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

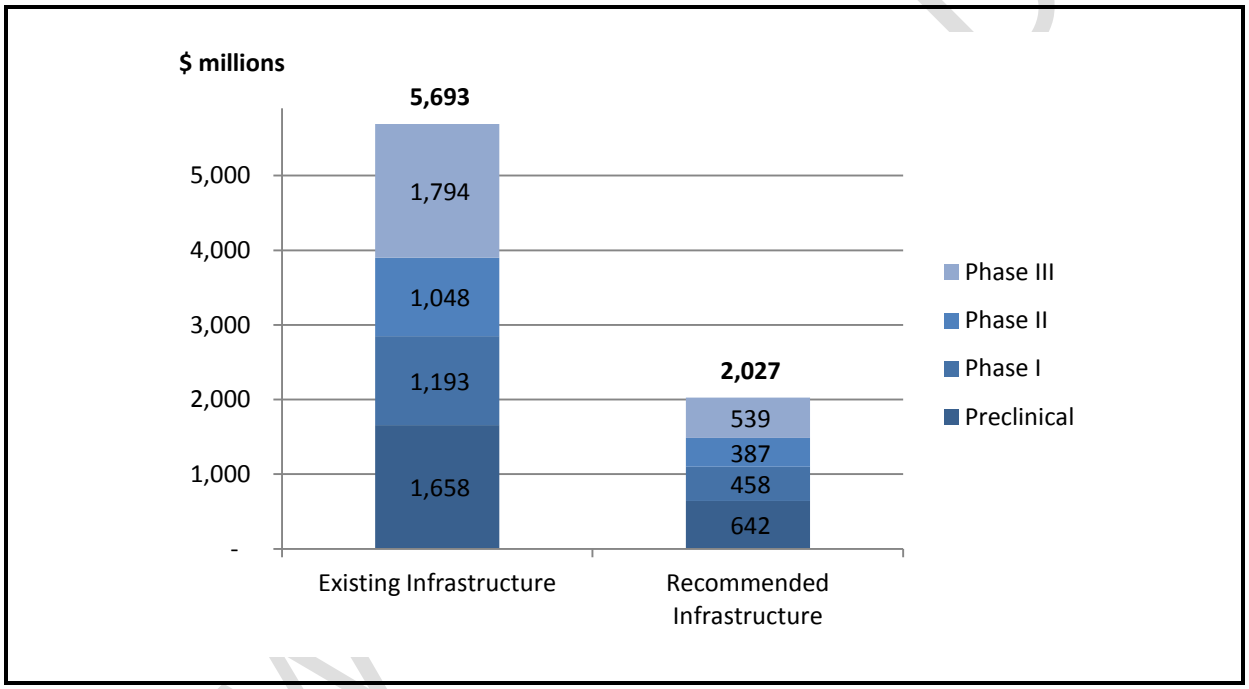
Data standardization and harmonization across centers would promote wider dissemination and more efficient utilization of information. An improved understanding of the pathology of AD will lead to better therapeutic approaches and targets, better tools such as biomarkers and cognitive assessments, better

selection of participants for clinical trials, better clinical trial designs, and ultimately a greater likelihood of finding effective treatments.

3.2 IMPACTS ON THE COST OF AD DRUG DEVELOPMENT

The expected capitalized cost of developing a disease-modifying drug for AD is estimated to be $5.7 billion in the current environment with the existing infrastructure and $2.0 billion in an environment with the improved infrastructure (Figure 3-1).[18] Thus, an improved technical and research infrastructure supporting AD research and drug development is expected to reduce the cost of the first disease-modifying AD therapeutic by $3.7 billion.

Figure 3-1. Expected Capitalized Cost to Develop a Disease-Modifying Drug for Alzheimer's



[18] In comparison, recent studies estimate the average capitalized cost of developing a typical new drug, including the cost of failures, at between $1.5 billion and $2 billion. The executives participating in this analysis unanimously agreed that the expected cost of developing a disease-modifying drug for AD would assuredly be higher than the average because of the longer duration of clinical trials and greater risk, particularly in Phase III where failures are most expensive.

The majority of the cost reduction depicted in Figure 3-1 results from

- shortening the overall development time by 16 months (Table 3-1),
- increasing the probability that a compound entering Phase II progresses to marketing approval from 11% to 24% (Table 3-2), and
- 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 3-3 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 Section 3.2 explores the cost reduction in greater depth.

Table 3-1. 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 Alzheimer's research. Confidence intervals (CIs) are plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

Table 3-2. Average Transition Probabilities for an AD-Modifying Therapeutic

Transition	Existing Infrastructure Mean (95% CI)	Recommended Infrastructure Mean (95% CI)
Phase I to II (1)	0.67 (0.63, 0.70)	0.69 (0.67, 0.71)
Phase II to III (2)	0.47 (0.43, 0.51)	0.42 (0.41, 0.43)
Phase III to Approval (3)	0.24 (0.16, 0.34)	0.58 (0.47, 0.68)
Phase II to Approval (2)×(3)	0.11 (0.08, 0.15)	0.24 (0.20, 0.29)
Phase I to Approval (1)×(2)×(3)	0.07 (0.05, 0.09)	0.16 (0.14, 0.19)
Ratio of Phase II failures to total failures in Phase II and III combined	0.60 (0.53, 0.66)	0.77 (0.73, 0.80)

Note: Based on interviews with experts in Alzheimer's research. Confidence intervals (CIs) are plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

Table 3-3. Average Costs of Drug Development for an AD-Modifying Therapeutic

Phase	Monthly Out-of-Pocket Cost ($ millions per molecule in development)	Existing Infrastructure Capitalized at 11% ($ millions per new drug approved) Mean (95% CI)	Recommended Infrastructure Capitalized at 11% ($ millions per new drug approved) 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 3-1 and 3-2. 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. The use of an 11% cost of capital was per Harrington (2012). CI refers to confidence interval. Monthly out-of-pocket costs per compound are based on DiMasi and Grabowski (2007) and DiMasi, Hansen, and Grabowski (2003) and adjusted for inflation using the GDP Implicit Price Deflator (U.S. Department of Commerce, Bureau of Economic Analysis, Series ID: GDPDEF).

3.2.1 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.[19]

[19] Although the confidence intervals for the average durations of Phase II with existing and recommended infrastructure overlap in Table 1, the difference between Phase II durations (the duration of

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%, while 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 with the baseline estimate of $5,693 million, if the probability of transitioning from Phase II to approval is increased from 11% to 24%, while holding constant at 60% the ratio of Phase II failures to the total failures in Phases II and III, the expected cost is reduced to $2,768 million. This represents a 51% 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).

3.2.2 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

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.

the cost of drug development from the perspective of a single drug candidate entering Phase I trials.

Tables 3-4 and 3-5 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. 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 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.

Table 3-4. 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 = $(79 \times 0.33) + (122 \times 0.35) + (280 \times 0.24) + (280 \times 0.07)$	$157 million
			Cost per new drug approval = $157 million divided by 0.07	$2,087 million
			Capitalized to date of drug approval = $2,087 million $\times e^{(109.4)(0.11/12)}$ (Phase I starts an average of 109.4 months prior to approval)	$5,693 million

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. See also Appendix B.

Table 3-5. 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 = $(78 \times 0.31) + (118 \times 0.40) + (250 \times 0.12) + (250 \times 0.17)$	$144 million
			Cost per new drug approval = $144 million divided by 0.17	$855 million
			Capitalized to date of drug approval = $855 million $\times e^{(94.1)(0.11/12)}$ (Phase I starts an average of 94.1 months prior to approval)	$2,027 million

Note: Numbers may not exactly replicate because of rounding. For example, $855 million comes from dividing approximately $143.5 million by approximately 0.168. See also Appendix B.

In the *present environment with the existing infrastructure* (Table 3-4), 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 3-5), 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.

3.3 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 Alzheimer's R&D would increase by 23% (95% CI 12% to 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.

3.4 REDUCING THE BURDEN OF ALZHEIMER'S DISEASE

Accelerating 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 Alzheimer's by 2025 so that onset of dementia (conversion from mild cognitive impairment to dementia) would be delayed

- by at least 2 years in at least 50% of cases,
- by at least 5 years in 50% of cases, and
- 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 3-6).

Table 3-6. 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.

Source: 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 plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

3.3.1 Reduction in Case-Years of AD

To translate these mean probabilities into estimates of the impact on the burden of Alzheimer's, 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 case loads under these treatment scenarios.[20]

Estimating caseloads required two set 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, and 0.385 for 90 or older (Hurd et al., 2013). For example, the probability that a person between the ages of 85 and 89 would have dementia is 20.3%.

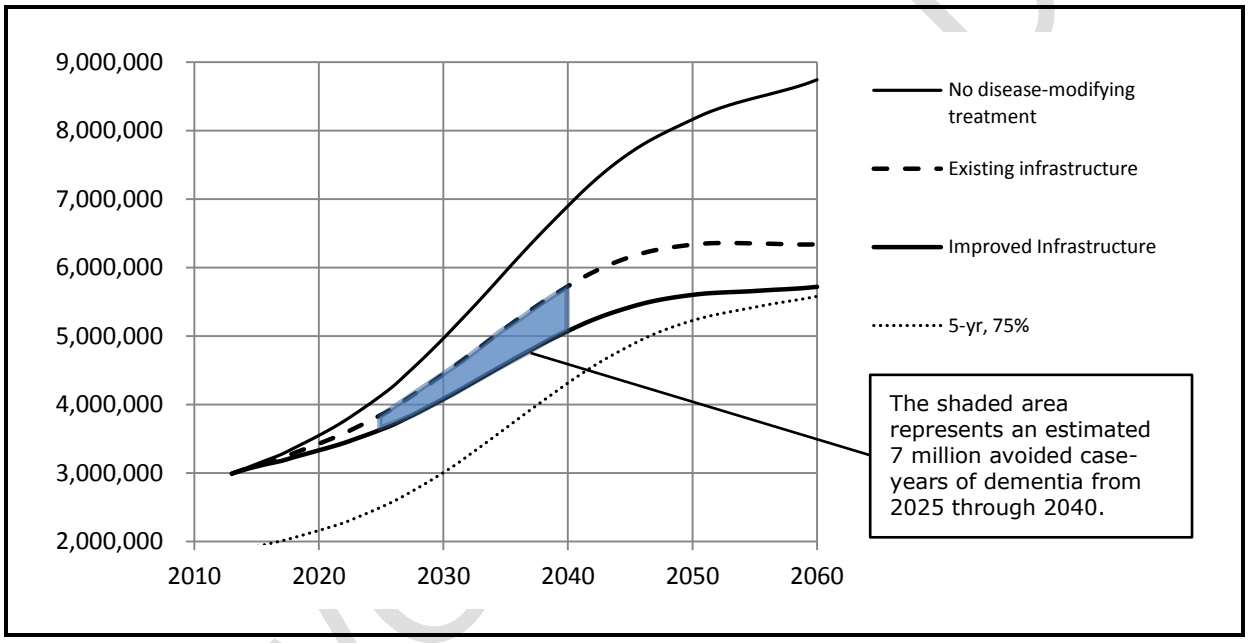
[20] The time until each scenario is achieved is assumed to follow a Weibull distribution. The probability of having achieved a given scenario by a given time is therefore given by the cumulative Weibull distribution function. A detailed description of the methodology is provided in Appendix C.

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.[21]

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 million to 9.4 million) case-years of dementia between 2025 and 2040. Figure 3-2 shows these 7 million avoided case-years as the shaded area between the heavy dashed and solid lines.

Figure 3-2. Expected Number of Cases of Dementia in the United States



[21] Hurd et al. (2013) provide the more conservative of available estimates for the United States. Hebert et al. (2013) estimate that there were 4.7 million cases of Alzheimer's dementia in 2010.

3.3.2 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. 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.[22]

3.3.3 Avoided Cost of Care for AD Sufferers

Restricting attention to the estimated 7.0 million (95% CI 4.4 million to 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 et al. (2013).

Valued at $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 billion to $100.1 billion).

Valued at $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 billion to $135.2 billion). For comparison, Table 3-7 provides estimates using both 7% and 3% discount rates.

[22] Additional details are provided in Appendix C.

Table 3-7. Present Value of 7 Million Avoided Case-Years of Dementia from 2025 to 2040

Annual Cost of Care	7% Discount Rate ($ billions) Mean (95% CI)	3% Discount Rate ($ billions) Mean (95% CI)
$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.

Source: Annual cost-of-care estimates come from Hurd et al. (2013). 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 3-2. Details are provided in Appendix C.

Annual cost-of-care estimates from Hurd et al. (2013) 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.

4 Concluding Remarks

The barriers to developing disease-modifying treatments for Alzheimer's today still mirror those discussed by Fillit et al. (2002) 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.

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 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 the fact 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.

References

Alzheimer's Association Expert Advisory Workgroup on NAPA. (2012). Workgroup on NAPA's scientific agenda for a national initiative on Alzheimer's disease. *Alzheimer's & Dementia*, *8*, 357–371.

Barker, A. D., Sigman, C. C., Kelloff, G. J., Hylton, N. M., Berry, D. A., & Esserman, L. J. (2009). I-SPY 2: An adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clinical Pharmacology & Therapeutics*, *86*(1), 97–100.

Brookmeyer, R., Gray, S., & Kawas, C. (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *American Journal of Public Health*, *88*(9), 1337–1342.

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia*, *3*(3), 186–191.

Center for Drug Evaluation and Research (CDER), Food and Drug Administration, U.S. Department of Health & Human Services. (2013). Guidance for industry. Alzheimer's disease: Developing drugs for the treatment of early stage disease. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf

Combs, K. L. & N. Link, A. N. (2003). Innovation policy in search of an economic foundation: The case of research partnerships in the United States. *Technology Analysis & Strategic Management*, *15*, 177–187.

Cummings, J. L. (2008). Controversies in Alzheimer's disease drug development. *International Review of Psychiatry*, *20*(4), 389–395.

Cummings, J. L. (2010). Integrating ADNI results into Alzheimer's disease drug development programs. *Neurobiology of Aging*, *31*, 1481–1492.

Cummings, J. L. (2013). Alzheimer's disease drug development: Translational neuroscience strategies. *CNS Spectrum*, *18*, 128–138.

DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics*, *22*, 151–185.

DiMasi, J. A., & Grabowski, H. G. (2007). The cost of biopharmaceutical R&D: Is biotech different? *Managerial and Decision Economics*, *28*(4-5), 469–479.

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau, P., … Scheltens, P. (2010). Revising the definition of Alzheimer's disease: A new lexicon. *The Lancet Neurology*, *9*(11), 1118–1127.

Fillit, H. M., O'Connell, A. W., Brown, W. M., Altstiel, L. D., Anand, R., Collins, K., … Dewey, C. F. (2002). Barriers to drug discovery and development for Alzheimer disease. *Alzheimer Disease & Associated Disorders*, *16*, S1–S8.

Greenberg, B. D., Carrillo, M. C., Ryan, J. M., Gold, M., Gallagher, K., Grundman, M., … Siemers, E. R. (2013). Improving Alzheimer's disease Phase II clinical trials. *Alzheimer's & Dementia*, *9*(1), 39–49.

Harrington, S. E. (2012). Cost of capital for pharmaceutical, biotechnology, and medical device firms. In P. M. Danzon & S. Nicholson (Eds.), *The Oxford handbook of the economics of the biopharmaceuticals industry* (pp. 75–99). New York: Oxford University Press.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 Census. *Neurology*, *80*(19), 1778–1783.

Hurd, M. D., Martorell, P., Delavande, A., Mullen, K. J., & Langa, K. M. (2013). Monetary costs of dementia in the United States. *New England Journal of Medicine*, *368*(14), 1326–1334.

Khachaturian, Z. S., Petersen, R. C., Gauthier, S., Buckholtz, N., Corey-Bloom, J. P., Evans, B., … Bain, L. J. (2008). A roadmap for the prevention of dementia: The inaugural Leon Thal symposium. *Alzheimer's & Dementia*, *4*(3), 156–163.

Khachaturian, Z. S. (2009). A roadmap for the prevention of dementia II: Leon Thal symposium 2008. *Alzheimer's & Dementia*, *5*(2), 85–92.

Khachaturian, Z. S., Khachaturian, A. S., & Thies, W. (2012). The draft 'national plan' to address Alzheimer's disease-National Alzheimer's Project Act (NAPA). *Alzheimer's & Dementia*, *8*(3), 234–236.

Link, A. N. & Link, J. R. (2009). *Government as entrepreneur*. New York: Oxford University Press.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. *Neurology*, *34*(7), 939–939.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 263–269.

Naylor, M. D., Karlawish, J. H., Arnold, S. E., Khachaturian, A. S., Khachaturian, Z. S., Lee, V. M. Y., … Trojanowski, J. Q. (2012). Advancing Alzheimer's disease diagnosis, treatment, and care: Recommendations from the Ware invitational summit. *Alzheimer's & Dementia*, 8(5), 445–452.

Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., & Schacht, A. L. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*, *9*(3), 203–214.

Qaseem, A., Snow, V., Cross, J. T., Forciea, M. A., Hopkins, R., Shekelle, P., … American College of Physicians/American Academy of Family Physicians Panel on Dementia. (2008). Current pharmacologic treatment of dementia: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Annals of Internal Medicine*, *148*(5), 370–378.

Raina, P., Santaguida, P., Ismaila, A., Patterson, C., Cowan, D., Levine, M., … Oremus, M. (2008). Effectiveness of cholinesterase inhibitors and memantine for treating dementia: Evidence review for a clinical practice guideline. *Annals of Internal Medicine*, *148*(5), 379–397.

Tassey, G. (2005). Underinvestment in public good technologies. *Journal of Technology Transfer*, *30*(1), 89–113.

Trojanowski, J. Q., Arnold, S. E., Karlawish, J. H., Brunden, K., Cary, M., Davatzikos, C., … Lee, V. M. (2010). Design of comprehensive Alzheimer's disease centers to address unmet national needs. *Alzheimer's and Dementia*, *6*(2), 150–155.

U.S. Census Bureau. (2012). National population projections: Downloadable files. Table 1: Middle Series. Retrieved from http://www.census.gov/population/projections/data/national/2012/downloadablefiles.html

U.S. Department of Health and Human Services. (2012). *Alzheimer's disease research summit offers research recommendations*. Retrieved from http://www.nia.nih.gov/newsroom/announcements/2012/05/alzheimers-disease-research- summit-offers-research-recommendations

U.S. Department of Health and Human Services. (2013a). *National plan to address Alzheimer's disease: 2013 update*. Retrieved from http://aspe.hhs.gov/daltcp/napa/NatlPlan2013.pdf

U.S. Department of Health and Human Services. (2013b). *2013 recommendations of the public members of the Advisory Council on Alzheimer's Research, Care, and Services*. Retrieved from http://aspe.hhs.gov/daltcp/napa/2013AdvCounRec.pdf

U.S. Department of Health and Human Services. (2013c). *Interim milestones to complete the first goal of the National Alzheimer's Plan by 2025*. Retrieved from http://aspe.hhs.gov/daltcp/napa/ 2013AdvCounRec-A.pdf

Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., … Alzheimer's Disease Neuroimaging Initiative. (2012). The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception. *Alzheimer's & Dementia*, *8*(1), S1–S68.

Appendix A: Interview Guide

The New York Academy of Sciences (The Academy) has commissioned RTI International[23] to conduct an economic study of the potential impact of recommendations from the (1) NIH Alzheimer's Disease Research Summit, (2) Ware Invitational Summit, (3) National Alzheimer's Project Act (NAPA) Advisory Council, (4) Global CEO Initiative on Alzheimer's Disease, and (5) The Academy's Alzheimer's Disease and Dementia Initiative (ADDI) to improve the national infrastructure supporting therapeutic research and development (R&D) on Alzheimer's disease and dementia (hereafter Alzheimer's). The study will estimate the value of stakeholders co-investing in precompetitive public-private partnerships to overcome common roadblocks.

As a starting point for our discussion, some of the recommendations from these organizations are:

- Better detect and monitor Alzheimer's disease, especially from its earliest clinical manifestations, and better predict treatment response (thus de-risking clinical development) by developing, validating, and standardizing a robust hierarchy of **biomarkers** and sensitive cognitive and functional assessment tools, elucidating relationships among biological and **cognitive markers**.
- Enable efficient learning about Alzheimer's drug and biomarker combinations – testing, analytically validating, and qualifying biomarkers as new drugs are tested – by implementing **adaptive clinical trial designs** modeled on I-SPY 2.
- Reduce the time and cost of enrolling volunteers for research studies and clinical trials by expanding longitudinal databases, or **registries,** with standardized demographic, genetic, biologic, cognitive, and environmental information on likely volunteers.
- Increase the likelihood that success in preclinical development will translate to success in clinical development (i.e., **de-risk clinical development**) by conducting translational research in a precompetitive commons through public-private partnerships (modeled on, e.g., the Structural Genomics Consortium and Arch2POCM, NHLBI's SMARTT Program, or NIAID's clinical and preclinical resources for researchers), advancing a greater diversity of novel therapeutic approaches and validated targets into clinical trials.
- Better understand the etiology and mechanisms of Alzheimer's and speed the translation of this knowledge into the clinic by establishing a network of comprehensive **Alzheimer's disease centers**, integrated with existing infrastructure and resources such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and NIA-funded Alzheimer's disease research centers.

The purpose of these interviews is to learn the opinions of scientists and managers involved in Alzheimer's R&D about the potential of these recommendations to reduce the time, cost, and risk associated with therapeutic development and speed the arrival of disease-modifying therapies for Alzheimer's. In advance, we appreciate you sharing your thoughts and opinions with us.

The information from this interview will be kept confidential; individual responses will not be shared. Only aggregated responses will be summarized and included in our final report to The Academy on August 31, 2013. Our findings will be published in *Annals of the New York Academy of Sciences* around the end of the year.

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[23] RTI International is a not-for-profit research institute located in Research Triangle Park, NC. Please see: www.rti.org

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Organization of the Interview Guide

A. Respondents' backgrounds
B. Baseline and counterfactual costs of Alzheimer's R&D
C. Changes in Alzheimer's R&D performance
D. Acceleration of disease-modifying therapies for Alzheimer's

A. Respondents' backgrounds

With a short discussion, we would like to get a sense of

1. who is speaking more from a research science perspective and who is speaking more from a marketing perspective (both are important to hear from, as some questions are geared more to the science and some more toward the marketing side)
2. whether experience is in Alzheimer's research, CNS, or other disease area
3. and how familiar respondents are with the recommendations (from the five organizations noted on p. 1) to improve Alzheimer's R&D infrastructure.

B. Baseline and counterfactual costs of Alzheimer's R&D

Average development costs per approved new drug (for all diseases, not Alzheimer's specifically) are estimated to be as follows:[24]

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

	Biotech out-of-pocket ($millions)	Biotech capitalized ($millions)	Pharma out-of-pocket ($millions)	Pharma capitalized ($millions)
Preclinical	230	720	174	510
Phase 1	124	278	156	338
Phase 2	121	217	171	312
Phase 3	173	235	279	385
Total	**648**	**1,450**	**780**	**1,545**

[24] Joseph A. DiMasi and Henry G. Grabowski. 2007. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 27: 1–11. Note: costs have been adjusted for inflation using the GDP implicit price deflator.

The cost estimates in Table 1 are based on the estimates of transition probabilities in Table 2 and cycle times in Table 3.

In this section, we would like to

1. customize these cost estimates for Alzheimer's by adjusting the transition probabilities in Table 2 and the cycle times in Table 3 to reflect the **current environment with existing infrastructure** (Question 1) and then

2. estimate the potential impact of improved infrastructure on development costs by re-estimating the transition probabilities in Table 2 and the cycle times in Table 3 **as they might be in a new environment with better infrastructure as would exist if the recommendations above were fully implemented** 3 to 5 years from now (Question 2).

Question 1 In the **current environment with existing infrastructure**, what are the transition probabilities (Table 2) and cycle times (Table 3) for Alzheimer's disease-modifying drug candidates?

Question 2 In the **new environment with the recommended infrastructure**, what would be the transition probabilities and cycle times for Alzheimer's disease-modifying drug candidates? (A likely range of possibilities is fine.)

Numbers **[in brackets]** are based on preliminary interviews.

From your perspective, do these numbers seem reasonable? too high? too low?

(Please provide AD-specific numbers)

Table 2. Transition Probabilities

	Biotech	Pharma	**Question 1** Alzheimer's Existing Infrastructure	**Question 2** Alzheimer's Improved Infrastructure
Phase 1 to 2	0.84	0.71	**[.70]**	**[.70]**
Phase 2 to 3	0.56	0.44	**[.50]**	**[.40]**
Phase 3 to approval	0.64	0.69	**[.20]**	**[.50]**
Phase 2 to approval	**0.36**	**0.30**	**[.10]**	**[.20]**
Phase 1 to approval	**0.30**	**0.21**	**[.07]**	**[.14]**

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

	Biotech	Pharma	**Question 1** Alzheimer's Existing Infrastructure	**Question 2** Alzheimer's Improved Infrastructure
Preclinical	52.0	52.0	**[52]**	**[52]**
Phase 1	19.5	12.3	**[12]**	**[12]**
Phase 2	29.3	26.0	**[26]**	**[26]**
Phase 3	32.9	33.8	**[48]**	**[40]**
Regulatory Review	16.0	18.2	**[18]**	**[18]**
Total	**149.7**	**142.3**	**[156]**	**[144]**

Question 3 If in Table 3 you indicated a change in cycle time for preclinical, Phase 1, Phase 2, or Phase 3, would this imply a change in the average cost of taking a drug candidate through the Phase? Y/N If yes, would that change be proportional to the change in cycle time (e.g. half the time implies half the cost), or more/less than proportional? Please explain. [ ]

C. Changes in Alzheimer's R&D performance

What would happen to private investment in Alzheimer's R&D in the new environment with the recommended infrastructure?

Question 4 Would companies that are currently pursuing Alzheimer's R&D plan to invest

[ ] less OR [ ] more OR [ ] about the same

in the new environment with the recommended infrastructure?

If less or more, roughly what percent? **[ ]**

Question 5 Taking into account how companies that are NOT currently pursuing Alzheimer's R&D might respond, would TOTAL planned investment in Alzheimer's R&D be

[ ] less OR [ ] more OR [ ] about the same

in the new environment with the recommended infrastructure?

If less or more, roughly what percent? **[ ]**

D. Acceleration of disease-modifying therapies for Alzheimer's

In this section, we ask about the likelihood of having – by 2025 – therapies approved that slow the progression of Alzheimer's so that onset of dementia (conversion from mild cognitive impairment to dementia) is delayed

- by **at least two years** and by **at least 5 years** and
- in **at least 50% of cases** and in **at least 75% of cases**.

Note: We are asking about your perception of the probability of achieving these targets based on the effectiveness of **any** drug or combination of drugs making it to market—not necessarily drugs developed by your company.

Question 8 Please provide estimates of the probabilities in the table below:

By 2025, delay onset of dementia	Probability with existing infrastructure	Probability with the recommended infrastructure
by at least **2 years** in at least **50%** of cases	[ ]	[ ]
by at least **5 years** in at least **50%** of cases	[ ]	[ ]
by at least **5 years** in at least **75%** of cases	[ ]	[ ]

Thank you again for the time and thought you have put into answering our questions. We look forward to sharing the results of our study with you.

Appendix B: Reducing the Cost of Alzheimer's Disease Drug Development

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. Parameters in the formula are defined in Table B-1. Capitalization assumes continuous compounding at the annual interest rate r, which is set at the 11% real cost of capital for the biopharmaceutical industry (Harrington, 2012).

$$\left(c\int_{t_{end}}^{t_{start}} e^{rt/12}\,dt\right)/p = \left(\frac{c}{p}\right)\left(\frac{12}{r}\right)\left(e^{rt_{start}/12} - e^{rt_{end}/12}\right)$$

Table B-1. Parameters Characterizing Each Phase of Drug Development

Parameter	Description
t_{start}	Time in months from start of Phase to date of new drug approval
t_{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

Tables B-2, B-3, and B-4 illustrate the calculation of the capitalized cost of an Alzheimer's disease (AD) disease-modifying drug, under the existing infrastructure and recommended infrastructure scenarios. The duration, cost, and probability estimates were provided by experts in AD research and drug development. Taking the means of the data they provided for each development Phase, we found the capitalized cost of an AD-modifying therapeutic would be $5,693 million under the current infrastructure and $2,027 million under the recommended infrastructure.

Table B-2. Durations of Drug Development Phases (Months)

Phase	Typical New Drug Mean	Alzheimer's Disease-Modifying: Existing Infrastructure Mean (95% CI)	Alzheimer's Disease-Modifying: Recommended Infrastructure Mean (95% CI)
Preclinical	52.0	50.1 (46.5, 53.8)	49.9 (46.2, 53.5)
Phase I	12.3	12.8 (11.7, 13.9)	12.6 (11.7, 13.5)
Phase II	26.0	27.7 (24.6, 30.9)	25.2 (23.0, 27.4)
Phase III	33.8	50.9 (48.7, 53.2)	39.4 (36.2, 42.7)
Regulatory Review	18.2	18.0 (16.9, 19.1)	16.9 (15.0, 18.8)
Total	142.3	159.6 (148.4, 170.8)	144.0 (132.1, 155.9)

Source: The mean for a typical new drug is from DiMasi and Grabowski (2007). Alzheimer's figures are based on interviews with experts in Alzheimer's research. Quantitative answers to these questions were provided by 15 interviewees. Confidence intervals are plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

Table B-3. Average Transition Probabilities

Transition	Typical New Drug	Alzheimer's Disease-Modifying: Existing Infrastructure Mean (95% CI)	Alzheimer's Disease-Modifying: Recommended Infrastructure Mean (95% CI)
Phase I to II (1)	0.71	0.67 (0.63, 0.70)	0.69 (0.67, 0.71)
Phase II to III (2)	0.44	0.47 (0.43, 0.51)	0.42 (0.41, 0.43)
Phase III to Approval (3)	0.68	0.24 (0.16, 0.34)	0.58 (0.47, 0.68)
Phase II to Approval (2)×(3)	0.30	0.11 (0.08, 0.15)	0.24 (0.20, 0.29)
Phase I to Approval (1)×(2)×(3)	0.21	0.07 (0.05, 0.09)	0.16 (0.14, 0.19)
Ratio of Phase II failures to total failures in Phase II and III combined	0.80	0.60 (0.53, 0.66)	0.77 (0.73, 0.80)

Source: The mean for a typical new drug is from DiMasi and Grabowski (2007). Alzheimer's figures are based on interviews with experts in Alzheimer's research. Confidence intervals are plus or minus 1.96 times the standard error (estimated standard deviation of the mean). A full complement of quantitative answers (first three rows, from which the last three rows can be calculated) under both scenarios (existing infrastructure and recommended infrastructure) was provided by 19 interviewees; another 2 interviewees provided only Phase I to II and Phase II to approval estimates for both scenarios; another 2 interviewees provided only Phase I to II and Phase II to approval estimates for existing infrastructure. To obtain a set of averages consistent with one another, the reported average transition probabilities for Phase II to III and Phase III to approval were calculated by using the Phase I to II and Phase II to approval means (based on the greatest number of interviews in each scenario, 23 for existing and 21 for recommended infrastructure) and the mean ratio of Phase II failures to total failures in Phase II and III combined (which is calculated from a subset of 19 interviews).

Table B-4. Average Costs of Drug Development

Phase	Monthly Out-of-Pocket Cost ($ millions per molecule in development)	Typical New Drug Capitalized at 11% ($ millions per new drug approved)	Alzheimer's Disease-Modifying: Existing Infrastructure Capitalized at 11% ($ millions per new drug approved) Mean (95% CI)	Alzheimer's Disease-Modifying: Recommended Infrastructure Capitalized at 11% ($ millions per new drug approved) Mean (95% CI)
Preclinical	0.72	510	1,658 (1,041, 2,872)	642 (440, 969)
Phase I	2.73	338	1,193 (757, 2,039)	458 (323, 673)
Phase II	2.00	312	1,048 (690, 1,714)	387 (279, 555)
Phase III	5.64	385	1,794 (1,203, 2,916)	539 (410, 738)
Total		1,545	5,693 (3,691, 9,541)	2,027 (1,453, 2,935)

Source: Monthly out-of-pocket costs per compound are based on DiMasi and Grabowski (2007) and DiMasi, Hansen, and Grabowski (2003) and adjusted for inflation using the GDP Implicit Price Deflator (U.S. Department of Commerce: Bureau of Economic Analysis, Series ID: GDPDEF). All costs were calculated using the average durations and transition probabilities from Tables B-2 and B-3. 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. The 11% cost is from Harrington (2012).

The estimated costs of developing a disease-modifying drug for AD ($5,693 million with the current infrastructure and $2,027 million with improved infrastructure) are estimates for the industry as a whole, including the cost of all failures by multiple 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 B-5 and B-6 develop the $5,693 million and $2,027 million estimates in a different way. The steps are mathematically identical to using the formula illustrated at the beginning of Appendix B, but they are arranged to highlight the expected cost of entering a drug candidate in Phase I trials and then develop the total capitalized cost of one new drug approval.

Table B-5. Cost of AD Disease-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 = $(79 \times 0.33) + (122 \times 0.35) + (280 \times 0.24) + (280 \times 0.07)$	$157 million
			Cost per new drug approval = $157 million divided by 0.07	$2,087 million
			Capitalized to date of drug approval = $2,087 million $\times e^{(109.4)(0.11/12)}$ (Phase I starts an average of 109.4 months prior to approval)	$5,693 million

Notes: (1) Numbers may not exactly replicate because of rounding. For example, $2,087 million comes from dividing approximately $156.5 million by approximately 0.075.

(2) Out-of-pocket cost is the monthly cost for each Phase (Table B-3) times the number of months spent in that Phase (Table B-2):

$$71 = (0.72)(50.1) + (2.73)(12.8)$$

$$126 = 71 + (2.00)(27.7)$$

$$413 = 126 + (5.64)(50.9)$$

(3) Present-value cost is value of costs incurred at the date the drug candidate enters Phase I:

$$79 = \int_{-50.1}^{0} 0.72e^{t(0.11/12)}dt + \int_{0}^{12.8} 2.73e^{t(0.11/12)}dt$$

$$122 = 79 + \int_{12.8}^{12.8+27.7=40.5} 2.00e^{t(0.11/12)}dt$$

$$280 = 122 + \int_{40.5}^{40.5+50.9=91.5} 5.64e^{t(0.11/12)}dt$$

(4) Probabilities are derived from Table B-3 as follows (note that probabilities do not sum to 1 due to rounding): $0.33 = 1 - 0.67$, $0.35 = (0.67)(1 - 0.47)$, $0.24 = (0.67)(0.47)(1 - 0.24)$.

Table B-6. Cost of AD Disease-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 = $(78 \times 0.31) + (118 \times 0.40) + (250 \times 0.12) + (250 \times 0.17)$	$144 million
			Cost per new drug approval = $144 million divided by 0.17	$855 million
			Capitalized to date of drug approval = $855 million $\times e^{(94.1)(0.11/12)}$ (Phase I starts an average of 94.1 months prior to approval)	$2,027 million

Notes: (1) Numbers may not exactly replicate because of rounding. For example, $855 million comes from dividing approximately $143.5 million by approximately 0.168.

(2) Out-of-pocket cost is the monthly cost for each Phase (Table B-3) times the number of months spent in that Phase (Table B-2):

$$70 = (0.72)(49.9) + (2.73)(12.6)$$

$$121 = 70 + (2.00)(25.2)$$

$$343 = 121 + (5.64)(39.4)$$

(2) Present-value cost is value of costs incurred at the date the drug candidate enters Phase I:

$$78 = \int_{-49.9}^{0} 0.72e^{t(0.11/12)}dt + \int_{0}^{12.6} 2.73e^{t(0.11/12)}dt$$

$$118 = 78 + \int_{12.6}^{12.6+25.2=37.8} 2.00e^{t(0.11/12)}dt$$

$$250 = 118 + \int_{37.8}^{37.8+39.4=77.2} 5.64e^{t(0.11/12)}dt$$

(3) Probabilities are derived from Table B-3 as follows: $0.31 = 1 - 0.69$, $0.40 = (0.69)(1 - 0.42)$, $0.12 = (0.69)(0.42)(1 - 0.58)$.

Appendix C: Reducing Burden of Alzheimer's Disease

Estimates of the future burden of Alzheimer's disease (AD) are based on U.S. population projections by single year of age from the U.S. Census and on the estimated probabilities of having dementia at different ages from Hurd et al. (2013). The future burden of AD is characterized in two ways: first as the number of people with dementia on an annual basis and second as the cost of providing care for those people. The expected near tripling of the number of cases of dementia—from 2.9 million in 2012 to 8.7 million in 2060—is driven by a predicted 140% increase in the U.S. population over the age of 70, with a disproportionate increase in the number of people in the oldest age groups.

Assuming no change in the age-specific probability of dementia, the probability that a typical person over the age of 70 will have dementia increases from 10.9% to 13.5%. Note that the number of cases refers to the total number of people living with dementia in a given year, not the number of newly diagnosed people in a given year.

For this study, estimates of the probability of dementia from Hurd et al. (2013) were converted from 5-year age group estimates to single-year-of-age estimates by an interpolation procedure. Using a functional form suggested by Brookmeyer et al. (2007), we assumed the probability of dementia depends on age according to $\alpha e^{\beta \cdot \mathrm{AGE}}$, where e is the base to the natural logarithms and α and β are constants chosen to be consistent with Hurd et al. (2013) age group probability estimates. These probabilities were applied to U.S. Census population estimates by single year of age for 2012 through 2060 (U.S. Census, 2012).

Table C-1 presents the estimated number of cases of dementia by age group for 2012 after applying Hurd et al.'s (2013) estimated probabilities to U.S. Census data. Table C-2 presents the results of the interpolation procedure for estimating dementia cases by single year of age. (The rightmost columns of Tables C-1 and C-2 can be compared to see that single-year probability estimates generate results that are consistent with Hurd et al. [2013].)

Table C-1. Cases of Dementia by Age Group, 2012

Age Group	2012 Population	Probability of Dementia, Hurd (2013)	Estimated Population with Dementia
71–74 yr	7,728,716	0.028	216,404
75–79 yr	7,487,387	0.049	366,882
80–84 yr	5,781,364	0.130	751,577
85–89 yr	3,760,561	0.203	763,394
≥90 yr	2,144,224	0.385	825,526
Total	26,902,252	0.109	2,923,783

Source: Population estimates come from the U.S. Census. The estimated probability of dementia for each age group comes from Hurd et al. (2013, Table 1).

Table C-2. Cases of Dementia by Single Year of Age, 2012

Age	2012 Population	Probability of Dementia	Estimated Population with Dementia	Total for Age Group for Comparison
71	2,088,697	0.0232	48,446	
72	1,979,907	0.0263	52,008	216,405
73	1,867,500	0.0297	55,556	
74	1,792,612	0.0337	60,395	
75	1,657,546	0.0382	63,245	
76	1,587,866	0.0432	68,615	
77	1,527,381	0.0489	74,748	366,882
78	1,377,410	0.0554	76,341	
79	1,337,184	0.0628	83,933	
80	1,282,942	0.1067	136,842	
81	1,228,215	0.1179	144,783	
82	1,183,624	0.1303	154,200	751,577
83	1,074,395	0.1440	154,691	
84	1,012,188	0.1591	161,061	
85	930,150	0.1678	156,098	
86	834,342	0.1859	155,070	
87	758,772	0.2058	156,182	763,393
88	666,314	0.2280	151,892	
89	570,983	0.2525	144,151	
90	490,779	0.2796	137,220	
91	409,098	0.3096	126,677	
92	325,568	0.3429	111,647	
93	241,442	0.3798	91,697	
94	194,638	0.4206	81,867	
95	141,801	0.4658	66,054	825,526
96	105,998	0.5159	54,683	
97	77,755	0.5713	44,424	
98	55,076	0.6327	34,849	
99	37,251	0.7008	26,104	
100	64,818	0.7761	50,304	

Source: Population estimates come from the U.S. Census. The estimated probability of dementia for each year is given by $\alpha e^{\beta \cdot \mathrm{AGE}}$, where α equals 3.374×10^{-6} for ages 71–79, 3.578×10^{-5} for ages 80–84, and 2.859×10^{-5} for ages 85–100, and β equals 0.1244 for ages 71–79, 0.1000 for ages 80–84, and 0.1021 for ages 85–100.

Having estimates of the number of cases of dementia by single year of age allows us to simulate the effect of delaying the onset of dementia. To simulate the effect of delaying the onset of dementia by 2 years for 50% of cases, we applied to 50% of the population the probability of dementia for people 2 years younger. For example, half of all 78-year-olds would face the probability of dementia faced by 76-year-olds.

Figure C-1 projects the number of cases of dementia in the United States under four scenarios:

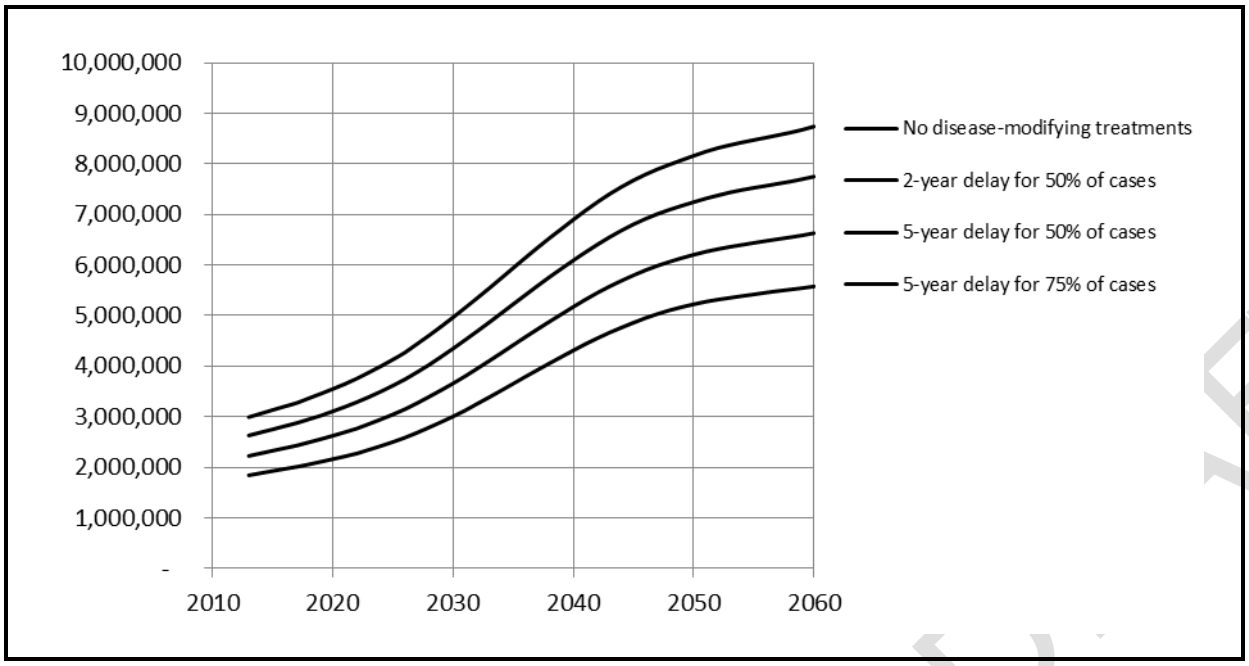
Scenario 1—No disease-modifying treatments. The probabilities in Table C-2 were applied to U.S. Census population projections, showing the number of cases increasing from 2.9 million in 2012 to 8.7 million in 2060 as discussed above.

Scenario 2—Two-year delay for 50% of cases. For half of the population, the probabilities in Table C-2 were shifted by 2 years: 71- and 72-year-olds face no probability of dementia, 73-year-olds face a 0.0232 probability of dementia instead of 0.0297, etc. Under this scenario, the number of cases of dementia is 11% lower in 2060.

Scenario 3—Five-year delay for 50% of cases. For half of the population, the probabilities in Table C-2 were shifted by 5 years: 71- to 75-year-olds face no probability of dementia, 76-year-olds face a 0.0232 probability of dementia instead of 0.0432, etc. Under this scenario, the number of cases of dementia is 24% lower in 2060.

Scenario 4—Five-year delay for 75% of cases. For 75% of the population, the probabilities in Table C-2 are shifted by 5 years: 71- to 75-year-olds face no probability of dementia, 76-year-olds face a 0.0232 probability of dementia instead of 0.0432, etc. Under this scenario, the number of cases of dementia is 36% lower in 2060.

Figure C-1. Projected Cases of Dementia in the United States



Note: The rising number of cases is driven by the increasing population over 70 years of age in the United States. Age-specific probabilities of dementia are held constant over time.

The expected number of cases of dementia in a future year depends on the probability of developing disease-modifying treatments. Take the year 2030 in Figure C-1 as an example. Only if one believes that there is zero probability of being able to delay—by any amount—the onset of dementia by 2030 would one expect there to be 5 million cases of dementia in the United States in 2030. If instead one believed that we would be able to delay the onset of dementia by 5 years in 75% of cases by 2030, then one would expect there to be 3 million cases of dementia in 2030.

Under uncertainty about our ability to alter the course of AD by any future year, it is appropriate to view the expected number of cases of dementia in a given year as a probability-weighted average of all possible treatment scenarios. To have a tractable problem, we have focused on just three treatment scenarios: those discussed above and illustrated in Figure C-1.

The three scenarios are ordered: Achieving *at least* a 5-year delay for 75% of cases (where *at least* applies to both the delay and the percent of cases) implies *at least* a 5-year delay for 50% of cases, which in turn implies *at least* a 2-year delay for 50% of cases. Trivially, any treatment scenario implies *at least*

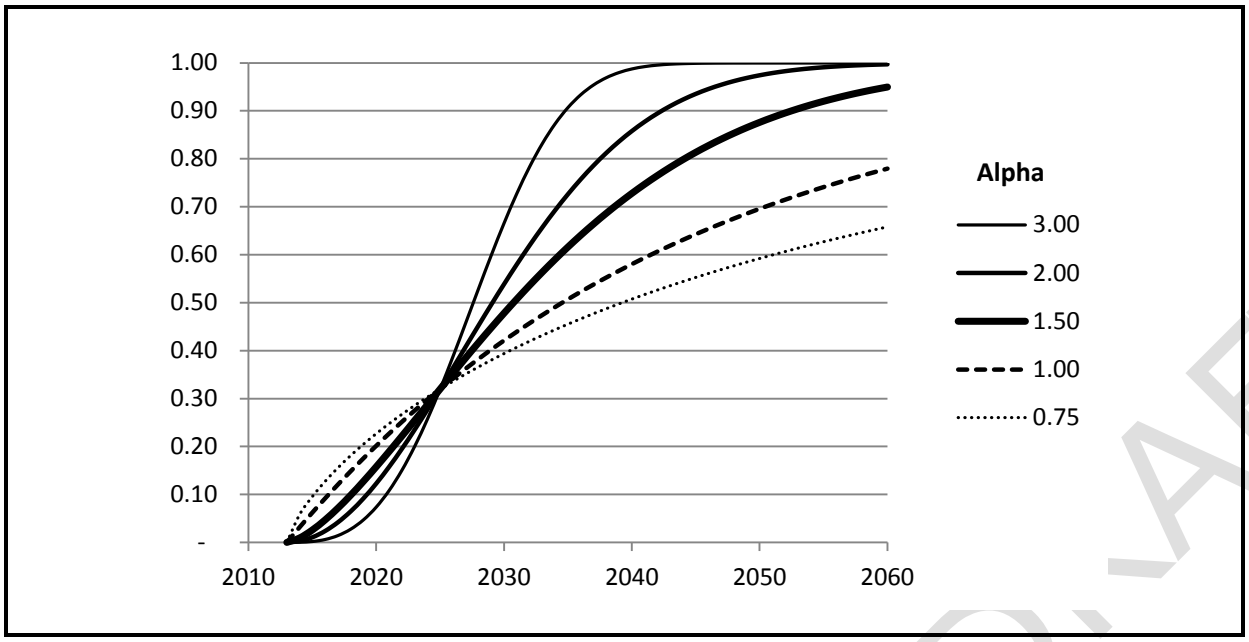
a delay by zero years for 0% of cases. The probabilities of these events are ordered as follows:

$$1 = \Pr(\geq 0 \text{ yr delay for } 0\%) > \Pr(\geq 2 \text{ yr delay for } 50\%) > \Pr(\geq 5 \text{ yr delay for } 50\%) > \Pr(\geq 5 \text{ yr delay for } 75\%)$$

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 t is therefore given by the cumulative Weibull distribution function $1 - e^{-(t/\beta)^{\alpha}}$, where β determines how quickly the probability accumulates (the larger is β the more slowly the probability accumulates) and α determines the shape of the distribution. For values of α less than 1 (equal to 1; greater than 1), the distribution describes a process where the probability of the scenario being achieved in a given interval of time is decreasing (constant; increasing) as time goes on.

For describing the time until a treatment scenario is achieved, it seems appropriate to consider values for $\alpha \geq 1$, because the knowledge accumulated through ongoing research and drug development efforts can be applied to improve tools and methods. Values for $\alpha < 1$ could describe a situation in which, if a treatment is not developed within a certain timeframe, it is less likely to be pursued going forward. This situation might be appropriate to describe the development of a compound from a particular class, but it is less likely to describe the development of *any* compound that achieves a given treatment scenario. Figure C-2 illustrates a number of cumulative Weibull distributions passing through probability 0.32 in the year 2025.

Figure C-2. Weibull Distributions



For any given choice of α, the value of β is chosen to reflect experts' predictions, summarized in Table C-3. For example, to parameterize the Weibull distribution for "at least a 2-year delay for 50% of cases," with existing infrastructure, β is chosen such that $1 - e^{-((2025-2013)/\beta)^{\alpha}} = 0.32$. The metric we are interested in—the number of avoided case-years of dementia attributable to improved infrastructure—turns out to be relatively insensitive to the choice of α. (We will return to this point later in the appendix.)

Table C-3. Probability of Delaying Onset of Dementia by 2025 (Reproduces Table 3-4)

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.

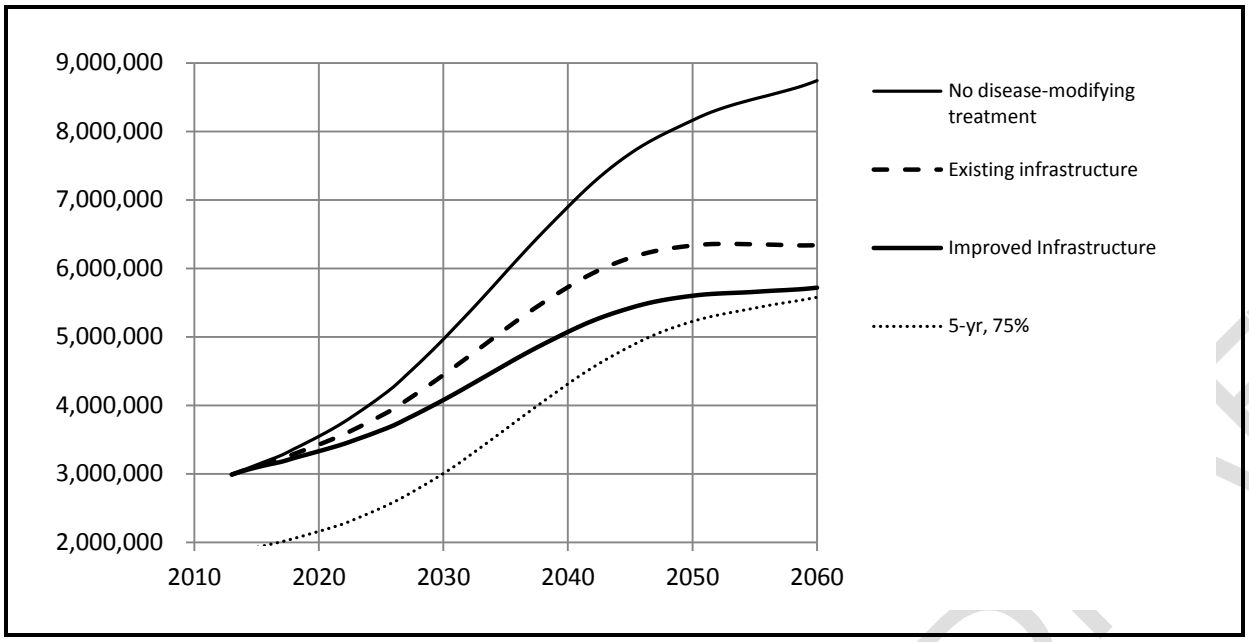
Source: Probability estimates were obtained from interviews with experts in Alzheimer's research. Answers for 2-year and 5-year delay in 50% of cases were provided by 17 interviewees. Answers for 5-year delay in 75% of cases were provided by 12 interviewees. Confidence intervals are plus or minus 1.96 times the standard error (estimated standard deviation of the mean).

Having parameterized a Weibull distribution for each treatment scenario for a given situation (e.g., existing or improved infrastructure, upper or lower bound estimate), the probability-weighted average of the treatment scenarios is constructed for each year as follows. We will use the probabilities in the first column of Table C-3 to illustrate.

Taking 0.32 as the probability of at least a 2-year delay for 50% of cases, we assigned the complementary probability 0.68 to the scenario with no disease-modifying treatment. Then taking 0.16 as the probability of at least a 5-year delay for 50% of cases, we assigned the probability (0.32 – 0.16 equals) 0.16 to the scenario with exactly a 2-year delay in exactly 50% of cases. Likewise (referring to the probabilities 0.16 and 0.05 in the first column of Table C-3), we assigned the probability (0.16 – 0.05 equals) 0.11 to the scenario with exactly a 5-year delay in exactly 50% of cases. Finally, we assigned the probability 0.05 to the scenario with exactly a 5-year delay in exactly 75% of cases.

Recall that Figure C-1 projected the number of cases of dementia in the United States under each of the treatment scenarios. Figure C-3 projects the expected number of cases with the existing infrastructure and with improved infrastructure. Projections are based on probability-weighted averages of the treatment scenarios, constructed as described above. The Weibull distributions use $\alpha = 1.25$ for the 2-year/50% scenario, $\alpha = 1.58$ for the 5-year/50% scenario, and $\alpha = 2.23$ for the 5-year/75% scenario.

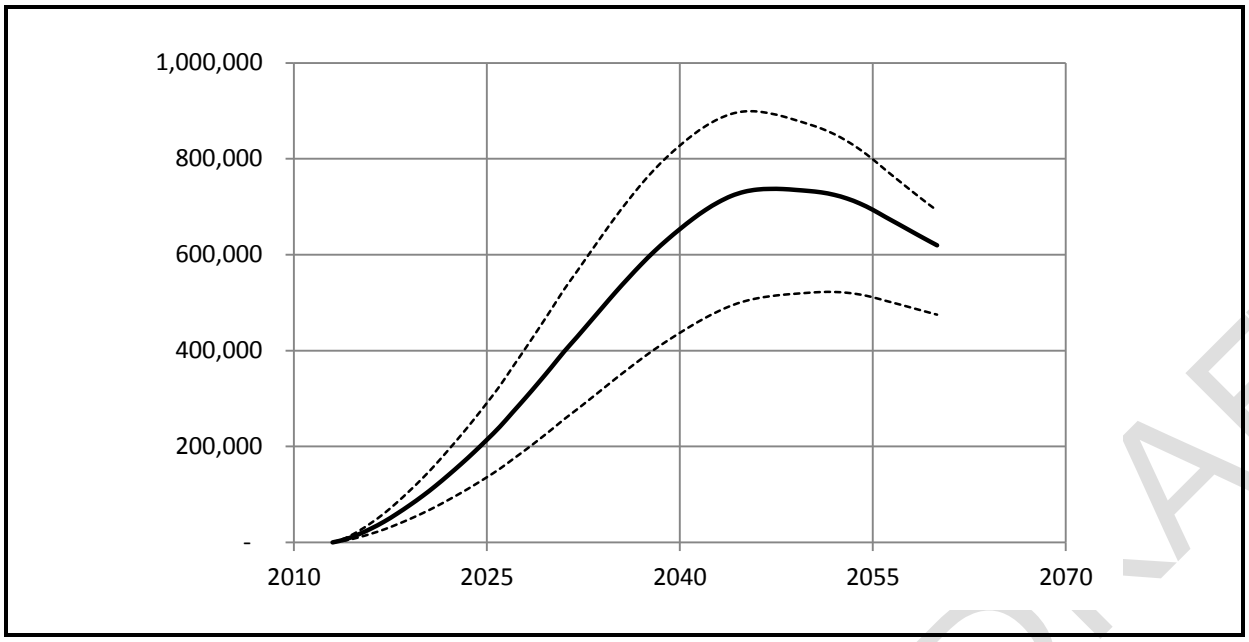
Figure C-3. Expected Number of Cases of Dementia in the United States



Note: The Weibull distributions underlying these projections use $\alpha = 1.25$ for the 2-year/50% scenario, $\alpha = 1.58$ for the 5-year/50% scenario, and $\alpha = 2.23$ for the 5-year/75% scenario.

Figure C-4 shows the number of avoided cases of dementia corresponding to the projections in Figure C-3—the difference between the projection with existing infrastructure and that with improved infrastructure. Note that these are the numbers of avoided cases on an annual basis, or avoided case-years. Dashed lines indicate confidence intervals based on the rightmost column of Table C-3. The total number of avoided cases from 2025 to 2040 is 7.0 million cases with a confidence interval of 4.6 million to 9.2 million cases.

Figure C-4. Avoided Case-Years of Dementia Attributable to Improved Infrastructure



Note: The Weibull distributions underlying these projections use $\alpha = 1.25$ for the 2-year/50% scenario, $\alpha = 1.58$ for the 5-year/50% scenario, and $\alpha = 2.23$ for the 5-year/75% scenario.

The estimates in Section 3 combined two parameterizations of the Weibull distributions. The first used $\alpha = 1.00$ for the 2-year/50% scenario, $\alpha = 1.35$ for the 5-year/50% scenario, and $\alpha = 1.95$ for the 5-year/75% scenario. The second used $\alpha = 1.50$ for the 2-year/50% scenario, $\alpha = 1.80$ for the 5-year/50% scenario, and $\alpha = 2.50$ for the 5-year/75% scenario. These alternative parameterizations were combined by averaging the point estimates and taking the widest of their respective upper and lower bounds, year by year. This resulted in a point estimate of total avoided cases from 2025 to 2040 of 7.0 million cases and a confidence interval of 4.4 million to 9.4 million cases. The confidence intervals shown in Figure 3-2 are wider than those in Figure C-4 although the point estimates are very similar.

Table C-4 makes the point that as long as we restrict attention to the number of cases avoided from 2025 to 2040, estimates are relatively insensitive to the choice of α. The variation resulting from the choice of α is small in comparison to the variation in experts' opinions as reflected in the confidence intervals.

Table C-4. Sensitivity of Estimates to Weibull α

Weibull α			Avoided Cases (millions), Mean (95% CI)	
2-yr/50%	5-yr/50%	5-yr/75%	2025–2040	2025–2060
0.75	1.13	1.68	6.37 (4.11, 8.48)	21.48 (14.23, 27.60)
1.00	1.35	1.95	6.74 (4.37, 8.89)	21.86 (14.81, 27.47)
1.25	1.58	2.23	7.04 (4.60, 9.21)	21.07 (14.63, 25.88)
1.50	1.80	2.50	7.28 (4.80, 9.42)	19.2 (13.66, 23.14)
1.75	2.03	2.78	7.42 (4.94, 9.50)	16.68 (12.10, 19.86)
2.00	2.25	3.05	7.45 (5.02, 9.44)	14.08 (10.32, 16.69)
2.25	2.48	3.33	7.38 (5.02, 9.24)	11.8 (8.66, 13.99)
2.50	2.70	3.60	7.19 (4.95, 8.91)	9.98 (7.31, 11.86)

Note: CI refers to confidence interval.

Table C-5 shows the number of avoided cases of dementia from 2025 to 2040 corresponding to the projections in Figure 3-2. Recall that these are similar to what is shown in Figure C-4, but with wider confidence intervals to account for uncertain α. Table C-5 then shows the present discounted value of these avoided cases, using 3% and 7% discount rates and valuing an avoided case-year at $41,689 and $56,290, following Hurd et al. (2013). The lower estimate of cost of care 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.

Limitations

The values suggested by Hurd et al. (2013) are costs of care and do not reflect the full disutility 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 a lower bound on the value of avoiding the condition. Therefore, 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 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 the

utility 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. On balance, 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.

Table C-5. Avoided Cases of Dementia and Present Discounted Value

		Present Discounted Value of Avoided Cases ($ billions)			
Year	**Avoided Cases (thousands), Mean (95% CI)**	**$41,689 per Case-Year, Discounted at 7%**	**$56,290 per Case-Year, Discounted at 7%**	**$41,689 per Case-Year, Discounted at 3%**	**$56,290 per Case-Year, Discounted at 3%**
2025	216 (135, 297)	3.99 (2.50, 5.50)	5.39 (3.37, 7.43)	6.30 (3.94, 8.69)	8.51 (5.33, 11.73)
2026	243 (152, 334)	4.21 (2.63, 5.78)	5.68 (3.55, 7.81)	6.90 (4.32, 9.49)	9.32 (5.83, 12.81)
2027	272 (170, 374)	4.4 (2.74, 6.05)	5.94 (3.70, 8.17)	7.50 (4.68, 10.32)	10.12 (6.31, 13.93)
2028	302 (187, 417)	4.57 (2.83, 6.30)	6.16 (3.82, 8.51)	8.08 (5.01, 11.16)	10.92 (6.76, 15.06)
2029	333 (206, 461)	4.71 (2.90, 6.50)	6.36 (3.92, 8.78)	8.66 (5.34, 11.97)	11.69 (7.21, 16.16)
2030	365 (224, 504)	4.81 (2.96, 6.65)	6.50 (4.00, 8.97)	9.20 (5.66, 12.70)	12.42 (7.64, 17.15)
2031	396 (243, 546)	4.88 (3.00, 6.73)	6.59 (4.05, 9.09)	9.70 (5.96, 13.36)	13.09 (8.04, 18.04)
2032	427 (262, 587)	4.92 (3.02, 6.76)	6.65 (4.08, 9.13)	10.16 (6.24, 13.95)	13.71 (8.42, 18.84)
2033	458 (282, 626)	4.94 (3.04, 6.75)	6.66 (4.10, 9.11)	10.58 (6.50, 14.45)	14.28 (8.78, 19.51)
2034	488 (301, 663)	4.92 (3.03, 6.68)	6.64 (4.09, 9.01)	10.94 (6.75, 14.86)	14.78 (9.11, 20.06)
2035	517 (321, 695)	4.86 (3.02, 6.54)	6.57 (4.07, 8.83)	11.24 (6.98, 15.12)	15.18 (9.42, 20.42)
2036	545 (340, 726)	4.79 (2.99, 6.39)	6.47 (4.04, 8.62)	11.51 (7.18, 15.34)	15.54 (9.69, 20.71)
2037	571 (359, 754)	4.70 (2.95, 6.20)	6.34 (3.98, 8.37)	11.72 (7.36, 15.46)	15.82 (9.94, 20.88)
2038	596 (378, 778)	4.58 (2.90, 5.98)	6.19 (3.92, 8.07)	11.88 (7.52, 15.50)	16.03 (10.15, 20.93)
2039	619 (396, 801)	4.45 (2.84, 5.75)	6.00 (3.84, 7.77)	11.98 (7.65, 15.49)	16.17 (10.33, 20.92)
2040	640 (413, 823)	4.30 (2.77, 5.52)	5.80 (3.74, 7.46)	12.02 (7.76, 15.45)	16.23 (10.48, 20.86)
Total	6,990 (4,369, 9,386)	74.02 (46.13, 100.08)	99.96 (62.28, 135.16)	158.36 (98.84, 213.30)	213.83 (133.46, 288.01)

Note: CI refers to confidence interval. Present discounted value for a given year y is $V \cdot N \cdot (1+r)^{2013-y}$, where V is the monetary value associated with an avoided case ($41,689 or $56,290), N is the number of avoided cases, and r is the discount rate (0.07 or 0.03).