



Policy Forum

Workgroup on NAPA's Scientific Agenda for a National Initiative on Alzheimer's Disease

Alzheimer's Association Expert Advisory Workgroup on NAPA^{*,†}

Abstract

This report outlines a goal-directed scientific agenda for a national initiative to overcome the Alzheimer's disease (AD) crisis. The statement, which reflects the collective views and recommendations of leaders in AD research, is intended to aid the implementation of the National Alzheimer's Project Act (NAPA)'s National Plan to defeat AD. The primary public policy aims of this 10-year scientific agenda are to discover, validate, and develop: (1) a broad range of technologies, tools and algorithms for early detection of people with symptomatic AD, and asymptomatic individuals at elevated risk for AD and other dementias; and (2) a wide range of interventions to preserve and/or restore health and normal neural function, aiming to maintain independent functioning for as long as possible. The long-term scientific public health objectives of this comprehensive plan are to: (1) reduce the number of people with chronic disabling symptoms who will require prolonged care and, eventually, reduce the number of asymptomatic people at elevated risk for AD/dementia; (2) delay the onset of chronic disability for people with AD and other degenerative brain disorders; and (3) lower the cost and burden of care. The plan calls for significant expansion of research programs to identify and validate the cause(s) and pathogenesis of AD, genetic and epigenetic factors that contribute to AD risk, therapeutic targets that affect disease progression, surrogate biomarkers of AD pathobiology, and technologies for early detection of AD. © 2012 The Alzheimer's Association. All rights reserved.

Keywords:

National Alzheimer's Project Act (NAPA); Alzheimer's Association; Alzheimer's disease (AD); National Plan; Aging brain; Dementia; Prevention; Research infrastructure-resources; National database; Computational resources; Public-private partnerships; Funding

1. Introduction

In January 2011, the National Alzheimer's Project Act (NAPA) was signed into law requiring the creation of a national plan to overcome the Alzheimer's disease (AD) crisis. Central to NAPA is the coordination and evaluation of all national efforts in AD research, clinical care, and services. An Advisory Council was established in summer 2011 to coor-

dinate these efforts and make recommendations to the Department of Health and Human Services (HHS) on the implementation of NAPA. In January 2012, HHS presented a draft framework for the national plan to the Advisory Council.

At the same time, the Alzheimer's Association assembled a Workgroup of leading AD researchers to prepare

The "scientific agenda for a national initiative on Alzheimer's disease" reflects the collective views of not only the aforementioned Workgroup but also the participants of the Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020) Think-Tank workshops and Leon Thal Symposia (Khachaturian et al, *Alzheimers Dement* 2008; 4:156–63; Khachaturian et al, *Alzheimers Dement* 2009; 5:85–92; Khachaturian et al, *Alzheimers Dement* 2009; 5:361–6; Khachaturian et al, *Alzheimers Dement* 2010; 6:89–97; Khachaturian et al, *Alzheimers Dement* 2011; 7:127–32). This document is still a work in progress. *Alzheimer's & Dementia* invites the scientific community to participate in the NAPA planning process by submitting commentaries or alternative views.

The proposed budgets in this document reflect the collective professional judgment estimates of the Workgroup members based on their extensive experiences in managing such projects/programs. The estimates are based on projected costs to continue and/or build on ongoing programs/operations.

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a scientific agenda to inform the Advisory Council's recommendations on research. The scientific agenda prepared by the Workgroup was distributed to more than 5000 AD researchers across the United States for feedback. The scientific agenda that follows incorporates that feedback and was shared with the Advisory Council in spring 2012. The scientific agenda is a "living document," and as such, the Workgroup welcomes additional feedback.

NAPA requires annual evaluation and updating of the national plan that is ultimately implemented. As this occurs, the Workgroup will reconvene, again solicit input from the AD research community, and submit revisions of the national plan (if needed) to the Advisory Council.

2. Background

During the past 3 decades, remarkable progress has been made in understanding the neurobiology of chronic neurodegenerative disorders, such as AD. In this period, research on the aging brain and dementia has moved from relative obscurity to the forefront of neuroscience. Contributing to this is the recognition of the high prevalence and rapidly increasing incidence of AD. The magnitude of the problem, combined with the lack of effective treatments for current and future populations, has, in turn, attracted a worldwide cadre of researchers. Today, approximately 5000 investigators are working to address the grand public health challenge of our time—the problem of AD.

At present, despite the remarkable advances in this formerly neglected area of medicine and science, there are growing concerns among all stakeholders with regard to (1) the lack of effective treatments to alter the relentless progression of the disease and (2) the sluggish pace of progress in breakthrough discoveries or ideas for developing effective long-lasting interventions.

Scientists in both academia and industry, along with advocacy groups and policy makers, share the impatience shown by caregivers (CGs) with the pace of advances and appreciate their concerns regarding the inadequacies of current interventions to address the burgeoning medicoeconomic crisis of AD. Nevertheless, despite these apprehensions, the scientific community is more optimistic than ever about a focused and well-planned national mission to discover and develop more effective treatments that will delay the onset of symptoms, modify the progression of the disease, and/or prevent the disease. They believe that the strategic goal of developing a broad spectrum of interventions to reduce the prevalence of disability due to AD is an attainable goal within a decade.¹ The prevailing perspective is that such an

undertaking is within our scientific–technical reach; however, this optimism is conditional. To succeed, we must surmount several scientific, administrative, and financial impediments.

The full spectrum of activities in pharmacologic and non-pharmacologic therapy development (ranging from early phases of discovery to translation of fundamental knowledge about the neurobiology of the disease into practical applications and drug validations) faces multiple barriers that must be overcome. Among the array of critical rate-limiting factors that influence the pace of progress in discovering an effective treatment for AD, inadequate funding for research and development is the single most limiting. This report provides an integrated goal-directed scientific agenda for a national initiative to solve the problem of AD. The report addresses specific public policy and scientific objectives, scientific strategy for both discovery and translation for therapeutic development, major obstacles that must be overcome, and a 10-year budget projection to achieve the goals.

3. Prevention—a national strategic goal

The rationale for designating prevention [1] as a national strategic goal is to articulate a simple unifying concept for this public policy initiative ("Prevention" is defined broadly to include primary, secondary, and tertiary prevention; thus, delaying the onset of symptoms or disability will be an acceptable objective). The broadly defined idea of prevention is intended to harmonize the differing interests of research, care, and services toward a common objective—a national commitment to reduce the prevalence of chronic brain disorders, with AD as the prototype solution in light of its urgent socioeconomic implications. (Among the major chronic brain disorders that impair the functions of memory, movement, and mood, AD is the most prevalent. Thus, this NAPA Scientific Agenda is conceived as a prototype for addressing a wide range of scientific challenges common to a number of related dementia and/or neurodegenerative diseases. The final NAPA Strategic Plan is also intended to offer a proxy solution to the broader health care dilemma [beyond AD] associated with the increasing chronic disabilities of an aging society.) Such a target will allow all stakeholders in AD (e.g., those providing services and care, basic scientists, clinicians, and social and behavioral scientists) to contribute their respective expertise in the effort to solve this critical public health challenge.

In this document, the declaration of prevention, a decade-long national public policy mission, is simply a statement of a strategic goal rather than a pledge to eradicate the disease. The statement does not promise success within the decade. The concept of a clear public policy goal, within a well-defined timeframe, merely aims to provide a framework for strategic planning. The intent is to encourage lofty goals from researchers and persuade policy makers to accept a national mission to (a) mobilize

¹According to a survey of more than 150 key opinion leaders/investigators in AD research, conducted as part of the Alzheimer's Study Group's Report to the 111th Congress, the vision of preventing AD by 2020 is an attainable scientific objective. However, the success of this enterprise will require decisive actions by the NAPA Advisory Council. This document outlines the bold changes necessary to achieve this goal.

coordinated efforts and (b) commit resources toward the achievement of this goal. The rationale for a 10-year goal of prevention is to

- Frame the National Alzheimer's Initiative as an integral part of broader efforts within the Administration/Department of Health and Human Services that seek solutions to the current national concerns about the economics of health care,
- Reflect the urgency of the problem by specifying a 10-year clearly defined (targeted) mission, and
- Provide policy makers with tangible economic metrics (i.e., numbers of people/dollars) for an outcome that would warrant support within Congress/Administration for a massive investment of public funds.

Presently, the major areas of national concern are the economics of health care and the fiscal challenges in formulating a national budget. Thus, the economics of health care (including research) provide the central theme for framing (a) the essential public policy goals and (b) the primary thrust of the scientific agenda for a national initiative as proposed in this document.

The fundamental public health problem of AD stems from increases in life expectancy leading to the aging of the national population, and an associated nearly exponential increase in the prevalence of a number of chronic conditions that require prolonged health care and consume costly resources. Thus, the scientific agenda for a national initiative on AD presented here outlines a forward-looking roadmap for strategic solutions to the pending costly public health problem.

4. Public policy goal—Scientific aims

Here we delineate a comprehensive scientific agenda for a 10-year national initiative to accelerate the discovery and development of a broad range of interventions to alter the progression of AD and related chronic brain disorders. These interventions would have a significant impact on public health and reflect the Administration's public policy commitment to defeating AD. The primary "specific aims" of this 10-year national mission in public health and public policy are twofold:

- Specific aim 1: discover, validate, and develop a broad range of technologies, tools, and algorithms for early and accurate detection (the term "detection" is used to indicate the need for a wide all-encompassing range of research and development efforts beyond traditional interests in diagnostics, including, but not limited to, behavioral assessments, family history, genetics, biomarkers, neuroimaging, and computational techniques) of not only the people with the disease but also asymptomatic individuals at elevated risk for various forms of memory disorders.

- Specific aim 2: discover, validate, and develop a wide range of interventions to preserve and/or restore health/normal neural function, aiming to maintain independent functioning for as long as possible. (The term "intervention" is used to indicate the need for an all-inclusive range of therapies beyond traditional pharmacological treatments. The concept is intended to include not only drugs but also behavioral, lifestyle, and environmental therapies and applications of technologies in the home or care environment.)

The overarching (public policy) strategic goal of this 10-year enterprise is to reduce the number of people with dementia by 50% within the next 5 years, and aim for further substantial reductions within a decade. The rationale for the long-term public health objective of this national initiative is based on the premise that a modest delay of 5 years in the onset of disability will reduce the cost and prevalence of the disease by half. The medical–scientific–economic and public health thrust of this national effort will be organized to support the three long-term scientific objectives of this initiative:

4.1. Objective 1: Reducing the number of people with chronic disabling symptoms who will require prolonged care; eventually reducing the number of asymptomatic people at elevated risk for AD/dementia

This objective will require developing new scientific knowledge on the cause(s) of the disease and significant expansion of well-coordinated collaborative research programs to identify and validate the (a) pathogenesis of the disease, (b) genetic and epigenetic factors, (c) therapeutic targets that affect disease progression, (d) surrogate biomarkers of the pathobiology of the disease (the term "surrogate marker" is used to identify specific biomarkers that actually track a known pathobiology of the disease related to a clinical feature), and (e) technologies/tools/algorithms for early detection of asymptomatic people at elevated risk for the disease. In addition, this will require a national infrastructure for translational research and a shared database (e.g., registry for longitudinal studies of healthy aging and people at elevated risk for dementia/preclinical dementia).

4.2. Objective 2: Delay the onset of chronic disability for degenerative brain disorders, such as AD

This objective will require expansion of academia–industry joint ventures in developing and validating a broad spectrum of interventions (including pharmacological and behavioral) aimed at reducing disability (e.g., the ability to perform activities of daily living) and/or promoting independent functioning of people with the disease or who are at risk of developing the disease.

4.3. Objective 3: Lower the cost and/or burden of care

This objective will require the expansion of health service research by focusing on developing new models of care and provision of services. This effort will require a new funding mechanism and coordination of efforts between medical–research programs (e.g., Alzheimer's Disease Research Centers [ADRCs] and service providers or agencies such as the Administration on Aging/Veterans Administration [VA]). This effort may also require the expansion of programs such as the Everyday Technologies for Alzheimer Care initiative funded by the Alzheimer's Association in partnership with Intel Corporation to explore the role of increased use of technologies in the care environment.

5. Major opportunities and challenges

Attaining the strategic goal of reducing the prevalence of chronic brain disorders within a decade requires a massive mobilization of national resources. Here we consider the specific scientific objectives, rationale, and budget estimates for a significant expansion of national research efforts, capabilities, and infrastructure to promote further discovery and development of a broad spectrum of technologies related to diagnostics and therapeutics. Table 1 provides a summary of professional judgment budget estimates of the scientific community. The discussion is organized around three challenges a decade-long national initiative must surmount. The major issues/hurdles under consideration may be described as follows: (1) scientific–technical, (2) infrastructure–resources, and (3) administrative–organizational.

5.1. Scientific–Technological challenges

The discussion in this section addresses the scientific–technological questions that must be overcome to achieve the specific aims of the national initiative on AD. The central problem has two challenges: (a) discovery and validation of a broad range of technologies for early identification of people with the disease or who are at risk of developing the disease and (b) discovery and validation of interventions that would delay or prevent the disease, as well as interventions to maintain independent functioning for as long as possible. The discussion covers questions such as what are the scientific and technological obstacles that must be surmounted? What are some of the key obstacles and unanswered questions? What new programs or funding mechanisms have to be created to promote public–private partnerships (PPPs) in research and development?

5.1.1. Neurobiology of AD

The development of effective interventions to prevent, delay, and treat the disease will require a significant expansion of our basic understanding of the molecular, cellular, and system biology that cause neuronal dysfunction and degeneration. This endeavor will expand basic knowledge

about the mechanisms underlying pathophysiology, which ultimately manifests as AD.

During the next decade, it will be essential to provide sufficient funds for at least 30% of peer-reviewed and -approved research grants in this area. The availability and adequacy of fundamental knowledge about the biology of the disease is a critical rate-limiting factor in developing treatments that affect the progression of the disease. A national coordinated discovery-to-translational research program must be developed that spans the academic, regulatory, and private sectors. The program would aim to identify new biological factors critical to AD development and validate agents that target and reverse these factors as potential AD therapies to be further tested in human trials. To develop effective mechanism-based therapies to prevent, delay, and treat AD, three critical components must be enabled and, in some instances, developed *de novo*. Specifically, an AD-targeted research program would include (1) discovery/basic science research, (2) investigational new drug (IND)-enabling translational research, and (3) national core resources (refer to the discussion under the section “Infrastructure”).

The goals of discovery-to-preclinical translational research are as follows: (1) accelerate and diversify discovery/basic science research that will provide a full understanding of AD pathobiology and will more effectively address the multifactorial nature of the disease, (2) establish effective networks between basic scientists and clinical investigators and between academia and the pharmaceutical industry to expedite the discovery and validation of potential drug targets and the development of novel therapeutics, (3) leverage rapidly emerging mechanistic and technological developments in systems biology, personalized medicine, stem cell technology, and cell reprogramming to facilitate AD research and drug development, (4) generate a robust pipeline of mechanistically based efficacious lead entities (molecules, biologics, and stem cells) that address the multifactorial multistage nature of AD.

Outcomes of discovery research will include (but are not limited to) (1) new and improved experimental models of human populations at risk of AD, including integrative animal models that can predict the efficacy of novel therapeutic and behavioral strategies in humans, (2) a broader range of mechanism-based targets for AD risk, (3) an expanded portfolio of targets, from single targets to system-wide targets, (4) phenotypic profiles of early-, mid-, and late-stage disease in animal models and other experimental models of AD risk, (5) biomarkers of disease stage in animal models of AD risk that would inform therapeutic development, (6) validated stage-based biomarkers in human populations at risk, (7) drug-responsive targets for each stage of disease progression, (8) mechanistically based candidate drugs that hit the desired targets in animal models of AD risk, (9) validation of efficacy in multiple models of AD/AD risk, and (10) preclinical validation of combination therapies.

Table 1
Workgroup budget estimate*

	Year 1 funding	Per year, years 2–10	Total, years 2–10	Grand total, years 1–10
Scientific–technological challenges				
Neurobiology of Alzheimer's disease	\$650,000,000	\$700,000,000	\$6,300,000,000	\$6,950,000,000
Genomics/epigenetics	\$10,000,000	\$20,000,000	\$180,000,000	\$190,000,000
Monitoring				
Biomarkers	\$10,000,000	\$20,000,000	\$180,000,000	\$190,000,000
Cognitive assessment	\$2,000,000	\$4,000,000	\$36,000,000	\$38,000,000
National study of cognitive aging	\$750,000	\$72,140,000	\$649,250,000	\$650,000,000
Prevention therapies	\$50,000,000	\$200,000,000	\$1,800,000,000	\$1,850,000,000
Translation				
Basic biological mechanisms into therapeutics				
Preclinical development	\$5,000,000	\$25,000,000	\$225,000,000	\$230,000,000
Toxicology and IND-enabling studies	\$5,000,000	\$25,000,000	\$225,000,000	\$230,000,000
Pharmacologic clinical studies	\$100,000,000	\$200,000,000	\$1,800,000,000	\$1,900,000,000
Clinical research into care and community services				
Longitudinal population health economics and service studies	\$1,000,000	\$5,000,000	\$45,000,000	\$46,000,000
Health economics analysis	\$1,500,000	\$1,500,000	\$13,500,000	\$15,000,000
Health service research on new models of care	\$1,000,000	\$5,000,000	\$45,000,000	\$46,000,000
System and quality of care studies	\$1,000,000	\$30,000,000	\$270,000,000	\$271,000,000
Infrastructure and research resources				
Shared national database	\$75,000,000	\$75,000,000	\$675,000,000	\$750,000,000
Shared computational resources	\$30,000,000	\$30,000,000	\$270,000,000	\$300,000,000
National core resource support for discovery/preclinical translation	\$25,000,000	\$125,000,000	\$1,125,000,000	\$1,150,000,000
Consortia and partnerships	\$50,000,000	\$51,000,000	\$459,000,000	\$509,000,000
Expand–restructure current programs as national resources				
ADCs	\$300,000,000	\$300,000,000	\$2,700,000,000	\$3,000,000,000
ADCS	\$20,000,000	\$20,000,000	\$180,000,000	\$200,000,000
ADNI	\$170,000,000	\$170,000,000	\$1,530,000,000	\$1,700,000,000
	\$1,507,250,000/yr	\$2,078,640,000/yr	\$18,707,750,000	\$20,215,000,000
Administrative–organizational solutions				Included in items above

Abbreviations: IND, investigational new drug; ADCs, Alzheimer's Disease Centers; ADCS, Alzheimer's Disease Cooperative Study; ADNI, Alzheimer's Disease Neuroimaging Initiative.

*The proposed budgets for the various components reflect the collective estimates by Workgroup members based on their extensive experiences in managing such projects/programs. The estimates are based on projected costs to continue and/or build on ongoing programs/operations. For example, presently, the National Institute on Aging funds only 10% of approved grants. Raising this to 30% will still allow support for exceptionally good new ideas.

5.1.1.1. Recommendation

A sustained investment in investigator-initiated RO1 National Institutes of Health (NIH) funding is essential to accelerate discovery of the pathophysiology of AD, identify new targets for therapeutics, and conduct the early-stage tests of in vitro and in vivo efficacy of molecules that engage these novel targets. Program project (PO1) grants should be highly integrated across projects with both discovery and translational aims and with appropriate integration of expertise and innovations from beyond the AD field.

Proposed federal funding: \$650 million for the first year, \$700 million for years 2 to 9, and \$6.95 billion over 10 years.

5.1.2. Genomics/epigenetics

The time is right to launch a major new initiative to determine the complete genetic architecture of AD. This information will provide insight into the underlying pathogenic mechanisms of AD and has high potential to identify novel therapeutic targets and biomarkers as well as aid in more accurate risk prediction for the development and progression

of disease. As successful treatments are developed, it is envisaged that genetics in the form of personalized medicine will aid in the selection and dose of drugs best suited for the treatment or prevention of disease in each individual.

Recent advances in genomic and sequencing technologies make feasible large-scale genome-wide association and sequencing studies, which will enable the realization of these goals. Indeed, in other disorders, such as diabetes, such projects are already well under way. Through current AD initiatives (e.g., the Alzheimer's Disease Genetics Consortium [ADGC]), a data set of 20,000 subjects has been amassed, leading to the recent identification of eight novel risk factor genes. However, a data set of up to 100,000 individuals will be necessary to enable a more complete characterization of AD risk genes (in diabetes, where such data sets already exist, more than 100 risk genes have been identified). Whole-genome sequencing would be performed in a subset (50,000) of higher-risk individuals from this data set with a family history of AD. Recruitment of a nationally representative sample could be integrated with the longitudinally

community-based cohorts, but should also take advantage of the networks of the Alzheimer's Disease Centers (ADCs) across the country. Use of similar assessment tools across these cohorts would enable subsequent evaluation of the risk alleles in the general population and the potential to identify environmental modifiers of disease risk.

It is envisaged that a subset of individuals participating in the genetic study would undergo a more comprehensive phenotypic assessment, including detailed biomarker and cognitive assessment measures outlined later in the text, as well as biospecimen collection in a national repository, such as the National Cell Repository for Alzheimer's Disease (NCRAD). Collection of brain tissues from a subset of these subjects will provide a substrate for genomic studies, including RNA sequencing and epigenetic studies (e.g., DNA methylation and histone acetylation). Development of a cell repository for fibroblasts/induced pluripotent stem cells from well-phenotyped individuals whose genomes have been completely sequenced will provide a resource of tissue for future functional studies in relevant cell types. In addition to the investment in genomics, a major investment will be needed (1) to develop and house the data centrally in an integrated database fully accessible to the scientific community and (2) to develop computing infrastructure, statistical methods, and bioinformatics to optimize storage and analysis of the data (refer to the discussion of shared computational resources later in the text).

Proposed federal funding: \$10 million for the first year, \$20 million per year for years 2 to 10, and \$190 million over 10 years.

5.1.3. Disease monitoring—Biomarkers

Biomarkers of AD measure the underlying pathophysiological processes in the brain responsible for observed clinical symptoms. AD biomarkers fall into two descriptive categories—imaging and biofluid—and are commonly divided into two mechanistic categories—biomarkers of brain amyloidosis/tauopathy and biomarkers of neurodegeneration/neuronal injury. Further understanding of the earliest biological stages of AD is necessary and will ultimately yield additional important mechanistic categories of biomarkers. Current research demonstrates that AD biomarkers may function well as diagnostic, prognostic, and disease progression indicators. Biomarkers are employed in all three recognized stages of AD—preclinical, mild cognitive impairment (MCI), and AD dementia—in recently updated diagnostic guidelines by the National Institute on Aging (NIA)—Alzheimer's Association. However, the implementation of biomarkers in these diagnostic guidelines was outlined at a theoretical rather than a practical or operational level. This was intentional, reflecting the fact that much additional research is needed to translate biomarker research that has been successful at individual academic research centers to general clinical practice.

To realize this objective, a network is needed that is devoted to standardization and systematic validation of exist-

ing and new candidate AD biomarkers. This will require large cohorts of well-characterized subjects in all stages of the disease, including preclinical AD. Cohorts in aggregate should be representative of the general population. A multidisciplinary approach with expertise in biofluids, brain imaging, clinical care, epidemiology, public health, and other areas is needed. A uniform system-wide approach for assay validation and diagnostic and prognostic validation in representative populations is also needed. Normative values must be established. Cut points are needed for every biomarker that segregates continuous values into abnormal, normal, and indeterminate ranges based on longitudinal prognostic outcomes. Interactions among different biomarkers and appropriate use of each at different disease stages would be established. The possibility that biomarkers may operate differently depending on genetic characteristics also needs to be explored.

Practical implementation of these standards in a manner that is transferable to general clinical practice is essential. Standardized biomarker metrics developed for diagnostic and clinical prognostic purposes would be directly transferable to therapeutic trials as inclusion, predictive, and outcome metrics. In imaging, sophisticated quantitative magnetic resonance imaging and positron emission tomography methods would be standardized by this initiative across imaging vendors and distributed throughout the base of clinical scanners. Major imaging vendors have international reach; thus, an outcome of this initiative would be harmonized, fully automated, imaging-based, diagnostic metrics that are available in general community practice throughout the world. In the area of biofluids, the most accurate and reproducible methods for measuring biomarkers need to be established and harmonized across sites. Important to progress in this area will be the development of standard reference materials to enable diagnostic company vendors to implement biomarker measurement methods that harmonize their assay systems.

A central oversight board with broad representation from academia and industry is needed to ensure standardization of methods. Subject recruitment would logically be built on established networks, such as the ADCs or Alzheimer's Disease Neuroimaging Initiative (ADNI). Efforts directed toward the objectives outlined earlier in the text have been initiated on a smaller scale. However, for AD biomarkers to reach full public health potential and function as biomarkers in other fields (e.g., fasting serum glucose for diabetes or serum lipids for heart disease risk), significant additional research is needed at a much larger scale. This will necessarily require substantial investment. Accomplishment of this goal for the biofluid biomarkers can be aided by building on existing initiatives, such as the Global Consortium for Standardization of Biomarkers (sponsored by the Alzheimer's Association) efforts to establish reference materials and methods for measuring cerebrospinal fluid biomarkers. This initiative includes scientists from the academic, diagnostic, pharmaceutical, and private sectors who

work in precompetitive space to focus on these critical needs.

Proposed federal funding: \$10 million for the first year, \$20 million per year for years 2 to 10, and \$190 million over 10 years.

5.1.4. Disease monitoring—cognitive assessment

Assessment of cognitive and functional ability is central to improving early diagnosis and treatment of AD, as the primary impact of this disorder is a gradual and progressive decline in mental abilities, which ultimately results in functional incapacity. Like biomarkers, cognitive and functional assessments are currently used for monitoring disease progression in the three recognized phases of AD: the AD dementia phase, the MCI phase, and the preclinical phase. However, most tests used today were developed to assess patients at the more severe end of the AD spectrum. With the goal of striving for early intervention, novel approaches to cognitive and functional assessment are needed, particularly for the MCI and preclinical phases of the disease. Additionally, improved screening methods are essential for identifying individuals in primary care settings who can benefit from treatment at all stages of the disease. Among other things, novel approaches to assessment should be able to leverage computer technologies and Web-based methods. Practical implementation of these standards in a manner that is transferable to general clinical practice is essential.

As with biomarkers, a uniform comprehensive approach for measure validation and diagnostic and prognostic validation is needed. This will require a network of researchers devoted to this effort, with access to large cohorts of well-characterized representative subjects in all stages of the disease (including those who may have preclinical AD). Normative values for newly developed cognitive instruments must be established. It will also be important to examine the relationship between these new approaches to cognitive and functional assessment and relevant biomarkers across the spectrum of the disease. This effort will provide improved tools for drug development, as well as for identifying those individuals who can benefit from treatment, once improved treatments are available.

Proposed federal funding: \$2 million for the first year, \$4 million per year for years 2 to 10, and \$38 million over 10 years.

5.1.5. A national “community-based” longitudinal study of cognitive aging

This initiative has two separate, but related, components: the first discusses research in a number of areas (e.g., epidemiological studies, genome-wide association studies [GWASs], biomarker/risk factor discovery–validation, prevention, clinical trials) and the second discusses the need for infrastructure or shared resources required by a number of the projects proposed in this document; therefore, this topic is covered under both headings.

A very large national population-based cohort that is culturally and genetically diverse is required by studies designed to determine the influence of genetic, lifestyle, and environmental factors on the risk and clinical course of AD and possibly other dementia disorders. Such a large national epidemiological research resource is also required to understand the heterogeneity of AD prevalence and incidence as well as which populations are at greatest risk for developing AD. In the history of US public health, “The Framingham Study,” which has been one of the major success stories in cardiovascular disease, serves as a prototype for a similar national infrastructure for studies of chronic brain disorders. Research on AD would benefit greatly from the launching of a comprehensive longitudinal cohort study designed to understand the life-course (early, middle, and late life) influence of genetic, lifestyle, environmental, and novel (as yet undiscovered) factors on the risk for AD. This study would require careful integration with innovative neuroimaging and biomarker assessments (as described in this report). Such a large-scale population-based study would address important gaps in the field, including the identification of strategies to maintain cognitive function in late life and to identify factors that may delay or prevent the onset of AD.

To optimize investment, two phases for developing a prospective life-course study would be required. In the first, a pilot phase, the study sampling design, sites, measurements, uniform and standardized outcomes, and the best investigative team would be developed. The second phase would involve assembling the cohort and conducting the study to achieve the specified scientific aims.

The cohort may also serve as a “living repository” of individuals interested in the prevention of dementia. These participants might also be willing to participate in long-term studies to validate biomarkers, test new therapies, and validate the assertion that interventions are more likely to succeed when applied in the earlier stages of the disease before symptoms appear (as further discussed later in the context of Prevention Registries). An essential element of this population’s value would be brain donation to address the critical shortage of control and early-stage AD brains for biological and genetic studies mentioned earlier in the text.

Collection of data from community-based cohorts could also be augmented by establishing research relationships with existing health care–based cohorts. For example, health maintenance organizations have large stable populations receiving health care through a single system with electronic pharmacy and medical records. Additionally, partnerships could be established with the VA health system that has lifetime clients and national standard electronic medical records. These health maintenance organization and VA cohorts have the following advantages: (1) the cohorts exist, and resources do not have to be expended to assemble subjects; (2) often, complete adult care records are available that do not require resources to assemble; (3) electronic medical records and pharmacy records are available; and

(4) these cohorts are representative of subjects receiving medical care in the United States. These cohorts will not only be a resource for research on early causes of AD and environmental factors contributing to AD but also a resource for assembling well-defined clinical trial cohorts.

In addition, as the genesis of AD is likely to begin early in life, a cost-effective way of providing vital information may be to add cognitive and other AD-related risk factors, such as biomarkers, to existing large studies of younger populations that are currently under way related to other diseases or health outcomes.

Proposed federal funding: \$750,000 for the first year, \$72 million per year for years 2 to 10, and \$650 million over 10 years.

5.1.6. *Prevention therapies*

This initiative consists of three separate but related components that have overlapping elements with (a) translational research, (b) discovery–validation of biomarkers, and (c) creation of a large well-characterized cohort as a shared research resource (refer to “Infrastructure–Research Resources”)

The launch of a prevention initiative will require the investment of resources in the following four endeavors to rapidly evaluate the range of promising treatments to reduce AD risk, postpone AD onset, or completely prevent the clinical onset of AD:

- Biomarker development, including the discovery of new early-stage AD biomarkers preceding known later-stage amyloid, tau, and neuronal injury biomarkers, is needed for prevention studies in cognitively normal individuals at the highest imminent risk of developing AD symptoms to (1) evaluate promising investigational treatments as soon as possible, (2) determine which biomarkers could be used to rapidly evaluate the range of treatments, and (3) provide the evidence required by the Food and Drug Administration (FDA) to demonstrate that a treatment's biomarker effects are reasonably likely to predict a clinical benefit. This should include cognitive instruments that could be used to rapidly evaluate the range of treatments.
- Genetic risk profiles should be developed for all trials, including prevention trials, so that gene–drug interactions can be studied and evaluated.
- Prevention trials are essential for investigational disease-modifying treatments and promising, but unproven, risk-reducing medications, dietary supplements, and lifestyle interventions, using biomarker end points. The potential importance of lifestyle modification in the areas of diet, nutrition, and mental and physical activity needs to be fully explored.
- Prevention registry creation is an important step in developing the shared resource necessary to maintain an ongoing database of individuals willing to enroll in

prevention trials. Individuals would need to be followed longitudinally to ensure that their characteristics, as recorded in the registry, are as up-to-date as possible. Likewise, information about pending trials would need to be distributed in a timely manner. This will greatly accelerate the speed of enrollment in prevention trials, which are needed to identify effective therapies for the increasing number of individuals who will need them (this recommendation does not address other infrastructure, treatment discovery, or pre-clinical AD biomarker research needs, or the smaller number of more expensive and time-consuming prevention trials that may be needed to help confirm the efficacy of treatments found in this initiative). We suggest that federal funding could ramp up over 3 years and be used to leverage in-kind contributions and data sharing from industry to the fullest extent possible.

Proposed federal funding: \$50 million for the first year, \$200 million per year for years 2 to 10, and \$1.85 billion over 10 years.

5.1.7. *Translational research—introduction*

To capitalize on current national research capabilities, resources, infrastructures, and ongoing programs, the scientific agenda outlined in this article has described a number of proposed initiatives. Here we describe some of the infrastructure, shared resources, and new paradigms for organizing research and development efforts to accelerate the pace of therapy development.

A new approach is needed to more rapidly translate findings in a clinic or research setting into practical application in a residential and/or care environment. This technology transfer effort will require several shared community resources that could be leveraged to advance a range of goals, including (1) the establishment of large cohorts of well-characterized representative community-dwelling individuals, (2) shared computational resources, and (3) a registry of potential participants willing to participate in clinical trials, particularly those aimed at prevention. These shared resources would foster research in several interrelated areas, including (1) risks for disease, including those related to genetic profiles, (2) improvements in disease monitoring across the spectrum of impairment, (3) improvements in modeling disease trajectories, and (4) development of novel approaches to disease prevention. Shared resources could be used to establish and maintain these community cohorts and accelerate the translation of findings from selected groups of subjects to community populations. To facilitate this community-based research, the ADC program should be expanded to permit a larger number of centers, with community satellites specifically geared toward translating knowledge from research into community settings. These efforts would complement those critically needed to accelerate the development of novel treatments aimed at delaying or preventing the onset of AD.

5.1.7.1. Translation—basic biological mechanisms into therapeutics

The goal of translational research is to leverage the most promising molecular biological targets from discovery research, and to systematically develop these into optimized lead entities (molecules, biologics, and cell therapies). Lead therapeutic entities feed the pipeline for phase I, II, and III clinical trials. The ultimate goal is to enrich the therapy development pipeline with as many viable options as possible. The spectrum of activities in this initiative to foster the development of IND may include, but is not limited to, (1) hit to lead generation, including combination therapies, (2) single and combination therapy lead optimization, (3) *in vivo* efficacy on outcome measures predictive of outcomes in clinical trials (rigorous validation, efficacy, and engagement of target), (4) preclinical trials designed to model human clinical trial design/optimization of clinical trials and adherence to clinical trial requirements), (5) pharmacogenomic profiling of lead compounds in animal models of AD risk with genetic mutations of human single nucleotide polymorphisms for adverse events, (6) formulation development and testing, (7) clinical GMP (cGMP) manufacture of lead molecules, medical foods, and nutraceutical formulations, (8) toxicology testing of cGMP material in two species under long-term administration, (9) pharmacokinetic/pharmacodynamics and absorption, distribution, metabolism, and excretion studies of cGMP materials, (10) generation of clinical trial design in well-defined target populations, and (11) generation and filing of regulatory documents for clinical trials in well-defined target populations.

Outcomes of translational research will include (but are not limited to) (1) an expanded portfolio of therapeutics, from disease-modifying to regenerative to preventative, from medical foods to nutraceuticals, to behavioral, lifestyle, diet, and social interventions, (2) increased predictive safety of therapeutics tested in phase II and III clinical trials based on pharmacogenomic profiling of lead compounds in animal models of AD risk, (3) increased rate of therapeutic success with decreased development time, (4) commercialized mechanism-based nutraceutical interventions for prevention, (5) commercialized mechanism-based medical foods for prevention of and delay of AD progression in populations at risk, (6) mechanism-based new therapeutic entities (molecules, biologics, stem cells) for disease modification of AD, (7) decreased attrition of discovered therapeutic entities tested in phase I, II, and III clinical trials, and (8) validation of mechanism-based multitarget therapies that are disease stage specific.

5.1.7.2. Translational IND-enabling research

Based on current attrition rates for molecular entities, preclinical testing of approximately ≥ 1000 compounds, biologics, or stem cell leads is required to achieve 20 mechanism-based new therapeutic entities. Development and commercialization of two nutraceutical and two medical food interventions for prevention or delay of AD progression

within 10 years will require refinement of approximately ≥ 250 combinations/formulations. In addition, it is anticipated that a number of clinical studies investigating lifestyle variables such as diet and exercise will also be investigated. These endeavors are anticipated to have public–private funding, which could include UO1, ADRC pilot projects, or SBIR or STTR mechanisms of support.

5.1.7.2.1. Component 1—preclinical development

Basic research continues to identify a growing number of potential sites of drug action for treating AD. To test these exciting possibilities, many steps are required. These include synthesis of compounds selective for biochemical targets of interest to develop new leads. It also includes extensive *in vitro* and *in vivo* studies required before selecting compounds for full development.

Proposed federal funding: \$5 million for the first year, \$25 million per year for years 2 to 10, and \$230 million over 10 years.

5.1.7.2.2. Component 2—toxicology and IND-enabling studies

Once the field of chemical possibilities has been narrowed to those with appropriate properties to become drugs and not simply preclinical research tools, a second series of steps are required to develop something suitable for testing in humans. These tasks involve synthesis of adequate amounts of one or more compounds from preclinical development to find the one(s) that are safe in animal toxicology studies and have the right absorption and other properties for clinical administration. What is traditionally called “lead optimization” is included here.

Proposed federal funding: \$5 million for the first year, \$25 million per year for years 2 to 10, and \$230 million over 10 years.

5.1.7.2.3. Component 3—pharmacologic clinical studies

These involve both healthy volunteer and/or patient studies to establish safety and evidence of drug effects in the brain, followed by efficacy studies ranging from weeks to years depending on the type of drug and stage of AD. More representative proportions of ethnic and racial minorities than usually seen in traditional industry-sponsored studies are needed. Also needed are more sensitive measures of cognitive function and other possible early symptoms of AD to be included in future studies. Early years would use existing compounds that are ready/near ready for human use, with later years depending on the flow from components 1 and 2 while incorporating potentially more sensitive measures of change. Importantly, substantial effort will go into the development of additional measures applicable both to earlier stages of AD and assessing rates of progression for use in any type of clinical trial. Such measures will take into account whether measures need to be tailored based on cultural background or minority status. In addition, changes to the current paradigm of phase I to III clinical trials will be considered, as well as the use of novel primary end points and biomarkers.

Proposed federal funding: \$100 million for the first year, \$200 million per year for years 2 to 10, and \$1.9 billion over 10 years.

5.1.7.3. Translation—clinical research findings into care and community services

The goal of this initiative is to support a framework for efficiently testing (over the next decade) the most promising hypotheses for both biochemical and psychosocial processes that can be targeted to treat AD, as well as assessing their broader social and societal impact. Such a comprehensive framework requires multiple components that will fund and align early drug development and psychosocial development processes with the patient populations needed to test interventions. It is essential that these interventions are effective for both the patient with AD and his/her primary family CG. Efforts are also needed to demonstrate the effectiveness of these interventions in diverse populations outside research clinic settings. The first three components of the initiative (preclinical development, toxicology and IND-enabling studies, and pharmacologic clinical studies) are discussed earlier in the text. Here we consider the fourth and fifth components using nonpharmacologic approaches to study the economic, quality-of-care, and quality-of-life consequences of differing levels and types of interventions.

5.1.7.3.1. Component 4—nonpharmacologic trials relevant to care and support

A 10-year initiative is needed to study all aspects of the care and support of patients with AD and their family CGs. The proposed well-integrated program should be organized to study such problems as “excess disabilities” (neuropsychiatric/behavioral problems beyond what can be explained by AD itself). The agenda should include randomized clinical trials to carefully assess the impact of novel interventions designed to address both patients with AD and their family CGs. The current body of information has many gaps that an organized research agenda could address. The agenda of the proposed psychosocial initiative should include the following elements:

- Development of novel interventions aimed at both patients and CGs (followed by subsequent rigorous tests in controlled clinical trials in racially and ethnically diverse groups): these interventions might encompass a variety of options, including the effects of exercise, diet, and neuropsychological interventions.
- Establishment of a national coordinating center for this type of research that would coordinate efforts across multiple sites so that large-enough sample sizes can be accrued for “definitive” conclusions. This center would also have as part of its mission the promotion of intercollaborative and interdisciplinary research. Clearly, patients and their CGs are needed for the wide array of studies (e.g., genetic, pharmacologic) described elsewhere in this document. Such a center

might logically be built on the existing Alzheimer's Disease Cooperative Study (ADCS) infrastructure.

- Initiation of appropriate longitudinal psychosocial studies: most existing studies followed either CGs (who were the primary focus, not the dyad) on a short-term basis (3 to 6 months), 1 year at the most. But that is not long enough to see how well interventions “last” over time. Because it is clear that as AD progresses and new challenges occur, new interventions are needed, and 10-year studies are required to understand the patterns of progression and how to phase-in appropriate interventions at the right time to study the cumulative effects of several interventions.
- Associated challenges, phase in new interventions at the right time, and study cumulative effects.
- Commitment to research on how best to disseminate findings in “real-world” situations, including social service agencies and health care settings: this is a chronically underappreciated issue that, in the case of AD, is absolutely crucial. What works in academic medical centers (where the evidence-based programs are developed and tested) does not work necessarily once you try to apply it to community settings or with ethnically and socioeconomically diverse populations. A complex process is required to tailor evidence-based programs to the communities where they will be implemented. This process often takes 1 to 2 years in itself but must be done before the program is rolled out to community settings. This work is necessary for the research efforts to “pay off” in clinical practice. Public education will likely be necessary, especially to realize any benefits of lifestyle interventions, such as diet and exercise.

The specific goals of this new initiative include:

- Reduction in the rates of depression among the family CGs, with consequent savings in terms of the primary costs of treating that depression as well as secondary impact from depression-associated neglect of the AD patient.
- Reduction in the rates of nursing home placement and/or intensity of home assistance for AD patients.
- Reduction in the time lost from work for CGs (a major issue resulting, often, in quitting the work force entirely to care for the parent or spouse with dementia).
- Improved quality of life for both AD patients and their CGs.

(Longitudinal population health economics and service studies: \$1 million for the first year, \$5 million per year for years 2 to 10, and \$46 million over 10 years.)

(Health economics analysis: \$1.5 million for the first year, \$1.5 million per year for years 2 to 10, and \$15 million over 10 years.)

Proposed federal funding: 2.5 million for the first year, \$6.5 million per year for years 2 to 10, and \$61 million over 10 years.

5.1.7.3.2. Component 5—health service research regarding new models of care

The development of new therapies for prevention, treatment, and slowing the rate of progression can be expected to have a health economic impact by delaying the costs of long-term care (both community based and institutional), with the possible expectation that death may occur from other diseases and comorbid illnesses, and such cost for long-term care for dementia will never be incurred. In addition, a similar projection may be made for certain interventions to delay long-term care or to improve efficiency and quality through improvements and innovation in community-based health services for people with AD and their CGs. Studies are needed to better understand the impact of these changes on the health system and on individuals with AD.

Health care costs and quality of care are important issues that require vigorous studies and viable solutions. This area of health service research is critical to improve quality of care, improve health outcomes, and better manage unnecessary costs.

The health service research initiative will plan a broad spectrum of interventions to determine the efficacy of putative psychosocial and/or pharmacological/medical interventions vis-à-vis improving “the system” and/or the quality of care for people with AD. Nonpharmacologic “clinical” and “care and support” demonstrations must be linked to sophisticated health economics input and evaluation, both in the planning and evaluation of studies.

The majority of persons with AD are initially diagnosed and treated in primary care settings where they receive health care for other chronic conditions. However, research has demonstrated that the quality of care is often not optimal, with high rates of underdiagnosis and inadequate provision of information and community referrals. In addition, health care systems are not organized to provide optimal care and information for persons with AD and their families. Research to disseminate “best practices” and develop new approaches to improve the quality of care for dementia in primary care settings is needed.

(Health service research on new models of care: \$1 million for the first year, \$5 million per year for years 2 to 10, and \$46 million over 10 years.)

(System-of-care and quality-of-care studies: \$1 million for the first year, \$30 million per year for years 2 to 10, and \$271 million over 10 years.)

Proposed federal funding: \$2 million for the first year, \$35 million per year for years 2 to 10, and \$317 million over 10 years.

5.2. Infrastructure and research resource challenges

The infrastructure and research resource challenges are as follows: What types of infrastructure and resources will be needed by such an undertaking (e.g., shared research resources)? What are the additional resource needs of the field

to facilitate the discovery and validation of biomarkers or technologies for detection of the disease in asymptomatic people or subjects in preclinical stages of the disease? What are the capacity-building needs for long-term, multi-site, multinational prevention trials?

5.2.1. Shared research resource—national database

The creation of a comprehensive “National Longitudinal Database for Healthy Aging and Pre-Clinical Dementia” as a shared research resource will provide the prerequisite foundation for solving the dual challenges of developing (a) technologies for early and accurate detection of people at elevated risk for AD and (b) interventions to delay disease progression (or prevention).

One of the major stumbling blocks hindering the development of interventions for prevention is the lack of appropriate populations for long-term validation studies of such treatments. The establishment of a national shared research resource will provide the infrastructure urgently needed by the pending drive toward prevention studies, that is, access to large cohorts of well-characterized asymptomatic volunteers who are willing to participate in long-term studies to validate biomarkers and test new therapies designed to validate the assertion that interventions are more likely to succeed when applied in the earlier stages of the disease before symptoms appear.

Preclinical AD evolves slowly, possibly over a period of decades; therefore, large and diverse cohorts of highly motivated study participants are required to detect and/or validate biomarkers and genetic characteristics that predict elevated risk for AD in asymptomatic populations. The challenge of recruiting and retaining minority subjects/volunteers is an important issue not only for the proposal to establish a national database for longitudinal studies on healthy aging and dementia but also other initiatives described in this document such as GWAS research, clinical trials, health services research to develop new models of care, and the proposal to restructure the ADRCs program with satellite clinics in areas with underserved populations. Presently, knowledge about risk factors and differences in response to interventions due to genetic/epigenetic factors is limited because most of the data is derived from highly selected clinic populations; thus this information may not be applicable to the world at large. There is an urgent need to expand the cultural-genetic diversity in the pool of research subjects. The necessity for highly diverse and very large samples is a common requirement shared by many of ongoing research efforts. This type of a shared-core facility for a “longitudinal community-based study” will foster the launch of several specific projects such as (a) expansion of GWAS studies, (b) prevention studies, (c) a state-of-the-art “Framingham”-type study for cognitive aging, and (e) studies to discover and/or validate risk factors or biomarkers. For example, a large population-based cohort will be needed to study the influence of genetic, lifestyle, and environmental factors on the risk and clinical course of AD and possibly other dementia

disorders (see further details under longitudinal community-based studies).

The initiative will fund five operational components that will be required by such a national research resource (database) to be shared by multiple users: (a) an organizational, administrative, and management structure for multisite research resource/infrastructure; (b) the mechanics of a registry, for example, inclusion criteria, measurement domains, and a minimal data set; (c) instruments for gathering data, for example, assessments of behavioral/memory changes associated with aging; (d) bioinformatics and technologies for data management and mining; and (e) protocols for data sharing.

Proposed federal funding: \$75 million for the first year, \$75 million per year for years 2 to 10, and \$750 million per year over 10 years.

5.2.2. Shared computational resources and approaches

One of the most critical barriers to therapy development is the lack of modeling systems that simulate the entire spectrum of clinical phenotypes. A key limitation of current models is the inherent inability to provide insight into the precise functional relationships between the clinical (symptomatic) and biological (neurobiological marker) phenotypes. There is an urgent need to develop new modeling systems, particularly those generally referred to as multimodeling approaches, which may provide important new tools for investigators. The proposal is to build the infrastructure to support the development of computer modeling approaches (model bases) and databases. The project will create a highly integrated user-friendly tool to enable generation of new hypotheses and multidisciplinary *in silico* experiments, as well as the harmonization of different types of information (e.g., clinical, imaging, genetic, neuropsychological, and biological). The project will establish a national shared research resource, a high-performance computing research infrastructure based on “grid” and “grid cluster” technology and/or the use of commercial cloud computing. The system, which will be capable of storing large data sets and performing calculations at a high rate, is envisioned as a resource available to the entire research community.

This resource will support ongoing studies with data management and data mining and apply a systems biology approach to develop a better understanding of the physiology of disease progression and identify biomarkers that are most meaningful. Supercomputing capabilities could be especially useful in performing factor analysis in a registry of registries and in detecting small changes in continuous data gathered from home-based systems. It is unlikely that a single system design will suit all needs, and several computational models and storage centers will be needed for different types of projects (e.g., genetics, imaging, patient records). They would also be an important resource for genomic studies, as described earlier in the text.

Proposed federal funding: \$30 million for the first year, \$30 million per year for years 2 to 10, and \$300 million over 10 years.

5.2.3. National core resource support for discovery/preclinical translation

The expansion of discovery research on AD requires proportionate expansion of existing and new core support facilities, reflecting an increased need for novel animal disease models and the national distribution of these models, particularly models grown to advanced ages as greater research emphasis needs to be placed on aging mechanisms as key factors for AD risk. Discovery and characterization of novel targets based on newly identified AD risk genes will increasingly need to exploit cells derived from patients with specific genetic profiles and immortalized lines of neurons derived by stem cell technologies that are rapidly emerging. New and expanded resources are needed to rigorously develop, maintain, and distribute these lines from national cell repositories. Additional core resources would support the expanded need for medicinal chemistry for the next generation of leading molecular candidates, high throughput screening of lead compounds and biologics against mechanism-based targets, as well as bioinformatics and data sharing networks, and capabilities for standardized proteomic, genomic, lipidomic, and metabolomic screening for both biomarker development and efficacy screening of lead therapeutic entities. Support for large instrumentation and upgrading of current instrumentation resources is required in proportion to the expansion of discovery research programs. Many of these cores do not require *de novo* development and can be resourced from existing academic and commercial entities.

5.2.3.1. Core resources

- Animal models of disease: models of at-AD-risk genetic modification in aged rodent models, models of viral vector gene expression changes in aged at-AD-risk rodent models.
- Cell and specimen repositories of reprogrammed induced pluripotent stem cells and repository of biospecimens from persons at increased risk of AD.
- Expansion of brain collection/banking and its standardization to reflect urgent needs for controls across the lifespan, early-stage AD brains, and comparative analysis from cases of other related and unrelated neurodegenerative diseases.
- Technology resources: (1) proteomic target screens, (2) lipidomic target screens, (3) metabolomic target screens, (4) bioinformatics of systems biology, (5) high-throughput target screens, and (6) cGMP laboratories for generation of lead compounds, biologics, and stem cells
- Regulatory IND resources: dedicated regulatory services for AD, including, but not limited to, generation of pre-IND meeting and response documents for the FDA, generation of IND documents for the FDA, with generation of revisions, update, and CRO audit documents.
- Intellectual property management for academic/industry interface: creation of an independent entrepreneurial

resource to negotiate intellectual property issues between academic and industrial sectors to enable industrial support for target-based research within the academic sector that will lead to potential commercial development and dissemination.

Proposed federal funding: \$25 million for the first year, \$125 million per year for years 2 to 10, and \$1.15 billion over 10 years.

5.2.4. Consortia and PPPs

Aligning all stakeholders and efforts has proved the most effective way of prioritizing and dealing with major societal needs for new treatments and their means of delivery. The world of medical research into AIDS while delivering a series of evolving treatments as they emerged in real time provides a recent example of what it takes. For AD, the sense of urgency and advocacy from foundations and patient groups has already productively driven rapid sharing of focused research and development of the tools and processes necessary to advance trials of novel agents targeted to the prevailing hypotheses of the cause of the disease. Specifically, the ongoing ADNI, a partnership among government, industry, foundations, and associations coordinated in “pre-competitive” space through the Foundation for the NIH, has provided an open database of findings that have greatly influenced academia, industry, the FDA, and international regulatory bodies in terms of diagnosing presymptomatic AD and providing a path for testing preventive treatments. A similar PPP is being put in place for prevention trials in families with dominantly inherited AD through the DIAN project.

Refinement and expansion of this model will address multiple barriers to the most effective harnessing of the multiple work streams involved in addressing AD. The large investments required to identify gold standard tests for early diagnosis coupled with the risks of failure of any single agent in prospective long-term trials require rethinking how we share risks and rewards in the treatment development process.

A workgroup being organized by the Alzheimer's Association–PAD2020 (Workgroup on Public–Private Partnership) will address some of the detailed governance and financing issues in establishing such a consortia. One outcome of such deliberation would be to generate a higher level of commitment (\$15 million per year in aggregate) from industry to refining and standardizing the tools required for preventative treatment and a cost-effective means of managing those tools. An immediate application of a portion of these funds as well as those from government and foundations would be to achieve adequate support of infrastructures involved in archiving, tracking, and effectively sharing the data and processes that emerge from the consortia efforts over the next decade.

Proposed federal funding: \$50 million for the first year, \$51 million per year for years 2 to 10, and \$509 million over 10 years.

5.2.5. Expand–restructure current programs as national resources

5.2.5.1. ADCs

The ADCs program is mandated by NIA's enabling (authorizing) legislation. The program was launched in 1984 as a research resource to advance knowledge on the relationship between the biological underpinnings of the disease and the clinical characteristics. The program has played a central role in advancing knowledge about the disease, facilitating clinical studies including therapy development, training scientists and physicians, educating the public and professionals, and serving as resource in key medical centers. The needs of the field have changed. The ADCs program should be modified and expanded to meet the new challenges of the field. The number of centers should be increased to 30 and funded at \$5 million per center per year (\$150 million total). Each center should be structured to have a minimum of five satellite facilities, primarily to serve underserved populations or rural communities. The satellite facilities, as spokes to a wheel, could provide not only clinical services to the community but also serve as resources for recruitment of subjects/volunteers for research. In addition, we recommend that six additional centers should be established, with the designation of Comprehensive Centers (similar to the NIH-designated Comprehensive Cancer Centers). The clinical and research programs of all the centers should be well integrated with other ongoing national AD research efforts, including the National Alzheimer's Coordinating Center, the NCRAD, the ADGC, and the ADCS, and any new national efforts that might be initiated (such as the Prevention Registry described later in the text). In addition, the coordinating activities represented by the programs listed earlier in the text could be expanded to maximize the availability of existing data. For example, there are a number of existing population-based studies on AD and dementia that already have contributed greatly to our understanding of AD and its possible risk factors. It is recommended that as far as scientifically feasible, these studies be preserved, and in particular the information already contained in their databases be exploited to the full with additional secondary analyses and meta-analyses. The capabilities of the National Alzheimer's Coordinating Center could be expanded to accomplish this goal.

Proposed federal funding: \$300 million for the first year, \$300 million per year for years 2 to 10, and \$3 billion over 10 years.

5.2.5.2. ADCS

The NIA funding for the ADCS, an extremely vital resource for the field of therapy development, has been capped at the fiscal year 2006 level through the end of the next cycle [fiscal year 2017] of this project. This program, which has a proven record of productivity and utility to the field, is seriously underfunded. Now there is an urgent need to expand this program by enabling ADCS to provide infrastructure support to all participating sites. For example, now the sites rely solely on the inadequate per-subject payments, which

are well below industry level. The estimate is that an adequate funding of the ADCS cores and projects would require \$20 million per year.

Proposed federal funding: \$20 million for the first year, \$20 million per year for years 2 to 10, and \$200 million over 10 years.

5.2.5.3. ADNI

The original budget estimates (grant request) for the ADNI was \$69 million, but the award was for \$60 million; thus, there was at the onset a \$9 million shortfall. In addition, this \$60 million award “assumes” that Foundation for the National Institutes of Health will receive \$20 million from pharmaceutical partners. Given the economy, it is not clear how much funding industry will finally contribute toward ADNI. Assuming \$10 million, ADNI will have an additional shortfall of \$10 million. In addition, because of slow enrollment, the project was extended from 5 years to 7 years, which essentially causes the loss of another \$5 million. This brings the ADNI project to a total shortfall of \$24 million. Adding a third amyloid imaging time point to ADNI will bring the total budget for ADNI to \$25.5 million. The projections for an add-on Department of Defense ADNI study with 630 subjects will require an additional \$72 million. A “Prevent AD” project associated with ADNI will require an additional \$70.0 million.

Proposed federal funding: \$170 million for the first year, \$170 million per year for years 2 to 10, and \$1.7 billion over 10 years.

5.3. Administrative–organizational solutions

What type of project management team or organizational or administrative structure will be needed to facilitate or harmonize multinational collaborative research and development? What are some of the ideas/recommendations to streamline the selection of research priorities, identifying new approaches, organizational structures, and mechanisms of funding research?

The proposed scientific agenda for a national initiative is structured around several implicit assumptions listed later in the text. The items/topics/issues/initiatives considered in this section do not necessarily require additional funds but rather can be implemented by administrative action at the level of the Secretary of the Department of Health and Human Services or the NIH Director (or may require legislative action, e.g., authorization). Further recommendations will be developed by workgroups convened by the Alzheimer's Association and Prevent Alzheimer's Disease by 2020.

5.3.1. Leverage ongoing programs

The proposed initiative is intended to take into account all of the ongoing programs/initiatives/funding mechanisms at the NIH, Alzheimer's Association, and industry and build on, leverage, and/or expand these efforts rather than abolish or replace these activities. Some examples include, but are not limited to, ADCs, ADNI, NCRAD, ADGC,

ETAC, drug discovery, translational research, and academia–industry partnerships.

5.3.2. Collaborative multisite research and development

During the past 3 decades, some of the most successful scientific programs have emerged from collaborative multi-institutional efforts. Given the scientific complexities of the strategic goals of this initiative, this mode of planning and conducting research and development will be promoted by the proposed initiative (whenever feasible). Some examples of such programs/funding mechanism include ADCs, ADNI, and Cooperative Research and Development Agreements.

5.3.3. National shared resources

Several of the programs outlined in the proposed scientific agenda for a national initiative call for various forms of shared resources. For example, an “omnibus” national database for longitudinal studies of healthy aging and asymptomatic people at elevated risk for memory disorders will bring about efficiencies in cost and utility by serving multiple needs of the strategic goals of the mission. Other examples are the diverse populations and very large sample sizes required by such projects as GWAS/genomics/prevention trials/epidemiological studies seeking risk factors or efforts to identify and validate surrogate markers.

5.3.4. Integrate seamless links

The clinical and research programs of all the centers should be well integrated with other ongoing national AD research efforts, including ADNI, NCRAD, ADGC, ADCS, and any new national efforts that might be initiated (such as the Prevention Registry described later in the text). In addition, we recommend that six additional centers should be established, with the designation of Comprehensive Centers (similar to the NIH-designated Comprehensive Cancer Centers).

5.3.5. Integrated network for discovery—translation of interventions

ADCs serve as the initiating hub for convening discovery, translational and clinical scientists, and enabling development of innovative therapies, biomarkers, and interventions for AD. ADCs partner with institutional Clinical and Translational Science awardees to enable access to translational expertise, technologies, regulatory expertise, and management of IND-enabling therapeutic development and phase I clinical trials. ADCs/CTSAs transition therapeutics for phase II proof-of-concept clinical trials to ADCS. Consequently, therapeutics with demonstrated phase II efficacy transition to PPPs to conduct phase III clinical trials. Key to the success of this network is shared vision and commitment along with strategic and tactical integration across all entities.

5.3.6. Public–private partnerships

To achieve the greatest efficiency and speed to test multiple potential treatments with different mechanisms of action,

a new collaborative model is required. A major goal of such a model would be to share the risks of assessing the validity of any novel intervention given a potentially high failure rate and low likelihood of commercial success for any single given approach. A public “honest broker” role—a structure and process for sharing information that transcends current competitive practices in industry and academia—is required to avoid redundancy of studies and premature competition as well as provide sufficient financial support to ensure all promising mechanisms are moved into the clinic in a timely manner. Although funding is required to initiate and maintain a partnership model, the long-term net result should be an overall savings that would be captured by the investments of industry in late-phase studies of the most promising compounds. New PPPs focusing on a cure for AD will bring together advocates to drive the process, leading scientists responsible for the most advanced hypotheses, and technical and regulatory experts from government and industry who can implement the most timely and informative studies in humans. Such partnerships meld science and business practice by (1) prioritizing either the methods (e.g., ADNI) and/or hypotheses (emerging from NAPA) that can be real-

istically implemented within 10 years, (2) developing comprehensive detailed budgets with accountability, and (3) providing professional project management to deliver results on schedule.

6. Conclusion

This scientific agenda for a national initiative on AD will require further development. Details of agenda implementation, for example, are not fully described and will need input from the larger scientific community. In addition, many regulatory and legal complexities may need to be addressed after such an agenda is launched. The Alzheimer's Association is committed to engaging with scientific and other stakeholders in future discussions to ensure a scientific agenda that fully meets the aims of NAPA.

Reference

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