Workgroup\(^1\) on NAPA’s Scientific Agenda for a National Initiative on Alzheimer’s Disease

Introduction:

During the last three decades remarkable progress has been made in understanding the neurobiology chronic neurodegenerative disorders such as Alzheimer’s disease [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 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 Alzheimer’.

Today, despite the remarkable advances in this formerly neglected area of medicine-science, there are growing concerns among all stakeholders with:

- The lack of effective treatments to alter the relentless progression of the disease and,
- The sluggish pace of progress in breakthrough discoveries or ideas for developing effective long-lasting interventions

Scientist in both academia and industry, along with advocacy groups and policy makers, share caregivers’ impatience with the pace of advances and appreciate their concerns regarding the inadequacies of current interventions to address the burgeoning medico-economic crisis of Alzheimer. Yet in spite of these apprehensions the scientific community is more optimistic than ever about a focused and well planned national mission to discover-develop more effective treatments; to delay the onset of symptoms, or modify the progression of the disease and/or to eventually prevent the disease. They believe that the strategic goal developing a broad spectrum of interventions to reduce the prevalence of disability is an attainable goal within a decade\(^2\). The prevailing sentiment 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.

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\(^2\) According to a survey of over 150 key opinion leaders/investigators in Alzheimer’s research, conducted as part of the Alzheimer’s Study Group’s Report to 111\(^{th}\) 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.
The full spectrum of activities in ‘therapy development’ [ranging from early phases of discovery to “translation” of fundamental knowledge about the neurobiology of the disease into practical applications of drug validation; this spectrum includes both pharmacological and nonpharmacological therapies] face 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 Alzheimer’s, inadequate resource-funding for research and development [R&D] is the single most limiting factor. This report provides an integrated, goal-directed scientific agenda for a national initiative to solve the problem of Alzheimer’s disease. The report addresses specific public policy-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.

‘Prevention’ — a National Strategic Goal:

The rationale for designating ‘Prevention’ as National Strategic Goal is to articulate a simple unifying concept for this public policy initiative. The broadly defined idea of prevention is intended to harmonize the differing interests of research, care and services towards a common objective - a national commitment to reduce the prevalence of chronic brain disorders, with Alzheimer’s as the prototype solution in light of its urgent socioeconomic implications. Such a target will allow all stakeholders in Alzheimer [e.g., services, care, basic scientist, clinicians, social and behavioral scientist] to bring their respective expertise in the effort to solve this critical public health challenge.

In this paper 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 coordinated efforts and b) commit resources towards the achievement of this goal. The rationale for a ten-year goal of prevention is to:

✓ frame the National Alzheimer initiative as an integral part of broader efforts within the Administration/DHHS seeking solution to the current national concerns about economics of healthcare
✓ reflect the urgency of the problem by specifying a ten-year clearly-defined [targeted] mission
✓ provide policy makers with tangible economic metrics [i.e., numbers of people/dollars] for an outcome; that would warrant support within Congress/Administration for massive investment of public funds

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3 ‘Prevention’ is defined broadly to include primary, secondary and tertiary prevention, thus delaying the onset of symptoms or disability will be an acceptable objective
Presently the major areas of national concern are the economics of healthcare and fiscal challenges in formulating a national budget. Thus the economics of healthcare [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 proposed in this document.

The fundamental public health problem of Alzheimer 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 healthcare 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.

**Public Policy Goal — Scientific Aims:**

Here we delineate a comprehensive Scientific Agenda for a 10-year National Initiative to accelerate the discovery-development of a broad range of interventions to alter the progression of Alzheimer 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 Alzheimer’s. 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\(^4\) of not only 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\(^5\) to preserve and/or restore health/normal neural function; aiming to maintain independent functioning for as long as possible.

The overarching [public policy] strategic goal of this 10-year enterprise is to reducing the number of people with dementia by 50% within the next 5 years, and aiming 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 five 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:

- **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 AD/Dementia.

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\(^4\) 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’ to include but not limited to: behavioral assessments, family history, genetics, biomarkers, neuroimaging and computational techniques.

\(^5\) 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 but not be limited to drugs but also to include behavioral, life-style, environmental and applications of technologies in the home or care environment.
[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 effect disease progression, d) surrogate biomarkers of the pathobiology of the disease, e) technologies/tools/algorithms for early detection of asymptomatic people at elevated risk for the disease. In addition this specific aim 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/pre-clinical dementia]

- **Objective 2:** Delay the onset of chronic disability for degenerative brain disorders such as Alzheimer’s.

  [This objective will require expansion of academia-industry joint ventures in developing-validating a broad spectrum of interventions [including pharmacological and behavioral] aimed at reducing disability [e.g., ADLs] and/or promoting independent functioning of people with the disease or at risk].

- **Objective 3:** **Lower the cost and/or burden of care**

  [This objective will require expansion of ‘health services research’ by focusing on developing new models of care-services. This effort will require a new funding mechanism and coordination of efforts between medical research programs e.g., AD Centers and service providers or agencies such as AoA/VA. This effort may also require the expansion of programs such as ETAC funded by the AA to explore the role of increased utilization of technologies in the care environment.]

**Major Opportunities & Challenges:**

The long-term implementation plan i.e., the scientific agenda, to attain the strategic goal of reducing the prevalence of chronic brain disorders within a decade, calls for 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-development of a broad spectrum of technologies related to diagnostics and therapeutics. The discussion is organized around five generic challenges a decade-long National Initiative must surmount; the major issues/hurdles under consideration include - 1- **scientific-technical**; 2- **infrastructure-resources**; 3- **administrative-organizational**; 4- **regulatory-legal**; 5- **financial-economic**.

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6 The term ‘surrogate marker’ is used to identify specific biomarkers that actual track a known pathobiology of the disease related to a clinical feature.
Scientific-Technological Challenges: The discussion in this section addresses the scientific-technical questions that must be overcome to achieve the Specific Aims of the National Initiatives on AD. The central problem has two challenges: a) discovery-validation of broad range of technologies for early identification of people with the disease or at risk to developing disease and b) discovery-validation of a number of interventions that would delay or prevent the disease; otherwise find ways to promote or maintain independent functioning for as long as possible. The discussion covers such questions as: What are the scientific and technological obstacles or problems that must be surmounted? What are some of the key scientific/technical hurdles or unanswered questions? What new programs or funding mechanisms have to be created to promote public-private partnerships in research and development?

Neurobiology of Alzheimer’s Disease: 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 systems biology that cause neuronal dysfunction and degeneration. This endeavor will expand basic knowledge about the mechanisms underlying pathophysiology, which ultimately manifests as Alzheimer’s disease (AD).

During the next decade it will be essential to provide sufficient funds to ensure funding of at least 30% of peer-reviewed/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 treatment that affect the progression of the disease. A national coordinated discovery-to-translational research program must be developed that spans both the academic, regulatory and private sectors. The program aims to identify new biological factors critical to Alzheimer’s disease development and validate agents that target and reverse these factors as potential AD therapies to be further tested in human trials. To develop mechanism based effective therapies to prevent, delay and treat Alzheimer’s, three critical components must be enabled and in some instances developed de novo. Specifically, an Alzheimer’s disease-targeted research program would include 1) discovery basic science research, 2) IND-enabling translational research and 3) national core resources [see discussion under Infrastructure].

The goals of discovery to preclinical translational research are: 1) Accelerate and diversify discovery basic science research that will provide a full understanding of AD pathobiology and will more effectively address the multi-factorial 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 multi-factorial multistage nature of Alzheimer’s disease.

Outcomes of discovery research will include (but are not limited to): 1) New and improved animal models of human populations at AD-risk, 2) A broader range of mechanism-based targets for AD-risk, 3) Expanded portfolio of targets from single targets to system-wide targets, 4) Phenotypic profile of early, mid and late stage disease in animal models of AD-risk, 5) Biomarkers of disease stage in animal models of AD-risk for therapeutic development, 6) Validated stage-based-biomarkers in human populations at risk, 7) Druggable targets for each stage of disease progression, 8) Mechanistically based candidates to hit targets in animal models of AD-risk, 9) Validation of efficacy in multiple models of AD / AD-risk, 10) Preclinical validation of combination therapies.
**Recommendation:** A sustained investment in investigator-initiated RO1 NIH funding is essential to sustain and accelerate discovery of the pathophysiology of AD, identify new targets for therapeutics and 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 Alzheimer’s field.

**Proposed Federal Funding:**
$650 million for the first year; $700 million for years 2-9; $6.95 billion over 10 years

**Genomics:** 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 disease 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 realization of these goals. Indeed in other disorders, such as diabetes such projects are already well underway. Through current AD initiatives (e.g., ADGC) a dataset of 20,000 subjects has been amassed leading to the recent identification of eight novel risk factor genes. However, a dataset of up to 100,000 individuals will be necessary, to enable a more complete characterization of AD risk genes e.g. in diabetes where such datasets already exist over 100 risk genes have been identified. Whole-genome sequencing would be performed in a subset (50,000) of higher-risk individuals from this dataset, 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 ADCs. 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 below as well as biospecimen collection in a national repository such as NCRAD. Collection of brain tissue 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/iPSCs from well-phenotyped and completely sequenced individuals 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 (see the discussion of shared computational resources below).

**Proposed Federal Funding:**
$10 million for the first year; $ 20 million per year for years 2-10; $190 million over 10 years
Disease Monitoring — Biomarkers: Biomarkers of AD measure the underlying pathophysiological processes in the brain that are responsible for observed clinical symptoms. AD biomarkers fall into two descriptive categories, imaging and biofluids, and are commonly divided into two mechanistic categories, biomarkers of brain amyloidosis/tauopathy and biomarkers of neurodegeneration/neuronal injury although the necessary further understanding of the earliest biological stages of AD will ultimately yield additional important mechanistic categories of biomarkers. Current research demonstrate 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 NIA-Alzheimer’s Association. However, 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 existing 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, diagnostic and prognostic validation in representative populations is needed. Normative values must be established. Cut points are needed for every biomarker that segregate 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.

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 MRI and PET 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 methodology for quantification of biomarkers needs to be established and harmonized across sites. Important to progress in this area will be 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 above have been initiated on a smaller scale. However, for AD biomarkers to reach full public health potential and function as biomarkers in other fields now do (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 measurement of cerebrospinal fluid (CSF) biomarkers. This initiative includes scientists from the academic, diagnostic, pharmaceutical and private sectors who work in pre-competitive space to focus on these critical needs.

**Proposed Federal Funding:**

$10 million for the first year; $20 million per year for years 2-10; $190 million over 10 years

*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 in use today were developed for assessment of patients at the more severe end of the 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 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, as well as Web-based methods.

As with biomarkers, the development, validation and standardization of the improved methods for cognitive and functional assessment 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, across the adult age range (including those who may have preclinical AD). 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 disease. This effort will provide improved tools for drug development, as well as for identifying those individuals who can benefit from treatment, once improved medications are available.

**Proposed Federal Funding:**

$2 million for the first year; $4 million per year for years 2-10; $38 million over 10 years

*A National ‘Community-Based’ Longitudinal Study of Cognitive Aging*: [Note - This initiative has two separate but related components: the first related to research in a number of areas [e.g., epidemiological studies, GWAS, biomarker/risk factor discovery-validation, prevention, clinical trials etc], the second aspect deals with 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 [culturally-genetically diverse] population based cohort is required by studies designed to determine the influence of genetic, lifestyle, and environmental factors on risk and clinical course of AD and possibly other dementias. Also a fundamental understanding of the heterogeneity in the prevalence-incidence of AD as well as the knowledge about people at greatest risk for developing AD requires such a large national epidemiological research resource. 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 designed to understand the life-course (early, middle and late life) influence of genetic, lifestyle, environmental and novel (as yet undiscovered) factors on 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 some 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. Ideally, the study would span the life-course with early adulthood, mid-adulthood and late-life composition. 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 the assembly of the cohort and conduct of the scientific aims.

The cohort may also serve as a “living repository” of individuals interested in prevention of dementia. These participants might also be willing to participate in long-term studies to validate biomarkers and to test new therapies and to 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 below 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 brain for biological and genetic studies earlier mentioned.

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 (HMO) have large stable populations receiving health care through a single system with electronic pharmacy and medical records. Additionally, partnerships could be established with the Veterans Administration (VA) health system that has life-time clients and nationally standard electronic medical records (EMRs). These HMO and VA cohorts have the advantages that: (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) EMRs and pharmacy records are available; 4) These cohorts are representative of subjects receiving medical care in the US. These cohorts will not only be a source of research on early causes and environmental factors, but also will be 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 who are currently underway related to other diseases or health outcomes.

Proposed Federal Funding:
$500,000 for the first year; $550,000 per year for years 2-10; $5.45 million over 10 years
**Prevention Therapies:** [Note- 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 - See also Infrastructure-Research Resources]:

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

- **Biomarker development**, including the discovery of new early stage AD markers preceding current later stage amyloid/tau, injury markers, is needed for prevention studies in cognitively normal individuals at the highest imminent risk of developing AD symptoms (as noted above), in order to evaluate promising investigational treatments as soon as possible, determine which biomarkers could be used to rapidly evaluate the range of treatments, and provide the evidence required by the FDA to demonstrated that a treatment’s biomarker effects are reasonably likely to predict a clinical benefit. 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 of investigational disease-modifying treatments and promising, but unproven, risk-reducing medications, dietary supplements, and lifestyle interventions, using biomarker endpoints.

- **Prevention registry** is an important shared resource necessary to maintain an ongoing database of individuals who have indicated a willingness to enroll in prevention trials. Such individuals would need to be followed longitudinally in order to assure 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 speed of enrollment in prevention trials, which is needed in order to identify effective therapies for the expanding number of individuals who will need them. (This recommendation does not address other infrastructure, treatment discovery, or preclinical 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; $100 million per year for years 2-10; $950 million over 10 years

**Translational - Research — Introduction:** To capitalize on current national research capabilities, resources, infrastructures and ongoing programs the scientific agenda outlined in this paper has described a number of proposed initiatives. Here we describe some of the infrastructure, shared-resources and new ways of 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/involve 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 inter-related 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 also accelerate the translation of findings from selected groups of subjects to community populations. To facilitate this community-based research, the AD Centers 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 serve to complement those critically needed to accelerate the development of novel treatments aimed at delaying or preventing the onset of AD.

**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. This spectrum of activities in this initiative to foster the development of ‘Investigational New Drug [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 and adherence to clinical trial requirements), 5) Pharmacogenomic profiling of lead compounds in animal models of AD-risk with genetic mutations of human SNPs for adverse events, 6) Formulation development and testing, 7) Clinical GMP (cGMP) manufacture of lead molecules, medical foods and nutraceutical formulations, 8) Toxicology of cGMP material in two species under chronic administration, 9) PK/PD and ADME of cGMP material s (PK / PD: Pharmacokinetic / pharmacodynamics, ADME: absorption, distribution, metabolism and excretion), 10) Generation of clinical trial design in well defined target population, 11) Generation and filing of regulatory documents for clinical trials in well defined target populations.

**Outcomes of translational research will include (but not limited to):** 1) Expanded portfolio of therapeutics from disease modifying to regenerative to preventative from medical foods to nutraceuticals to behavioral 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 AD in populations at risk, 6) mechanism-based new therapeutic entities (molecules, biologics, stem cell) for disease modification of AD, 7) Decreased attrition of discovered therapeutic entities tested in Phase I, II and III clinical trials, 8) Validation of mechanism-based multi-target / agent therapies that are disease-stage specific.

**Translational IND-Enabling Research Recommendation:** Based on current attrition rates for molecular entities, to achieve 20 mechanism-based new therapeutic entities will require pre-clinical testing of ~1000 or more compounds, biologics or stem cell leads. Development and commercialization of two nutraceutical and two medical food interventions for prevention or delay of AD progression
within the 10 year time frame will require refinement of ~ 250 or more combinations / formulations. These endeavors are anticipated to have public / private funding, which may include UO1, ADRC pilot projects, SBIR or STRR mechanisms of support.

**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 2-10; $230 million over 10 years

**Component 2 - Toxicology and IND Enabling Studies:** Once the field of chemical possibilities has been narrowed down 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 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 2-10; $230 million over 10 years

**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 Alzheimer’s Disease. More representative proportions of ethnic and racial minorities than is usually seen in traditional industry-sponsored studies are needed. Also needed are more sensitive measures of cognitive function and other possible early symptoms of Alzheimer’s 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 flow from Components 1 & 2 while incorporating potentially more sensitive measures of change.

**Proposed Federal Funding:**
$100 million for the first year; $200 million per year for years 2-10; $1.9 billion over 10 years

**Translation - Clinical Research Findings into Care & Community Services:** The goal of this initiative is to support a framework for efficiently testing, over the next decade, the most promising hypotheses on both biochemical and psychosocial - processes which can be targeted to treat AD and assessing their broader social and societal impact. Such a comprehensive framework requires multiple components to fund and align early drug development and psychosocial development processes with the patient populations needed to test both new agents and new non-pharmacologic interventions that will be effective for both the patient with AD and his/her primary family caregiver. Additional 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 [1 - Preclinical Development, 2 - Toxicology and IND Enabling Studies and 3 - Pharmacologic Clinical Studies] were discussed in the above section under the heading of Translation – ‘Basic Biological Mechanisms into Therapeutics’. Here we consider the fourth and, fifth components using non-pharmacologic approaches to study the economic, quality-of-care and quality of life consequences of differing levels and types of interventions.

Component 4 – Non-Pharmacologic Trials Relevant to Care and Support: A 10 year initiative is needed to study all aspects of care-support of patients with Alzheimer’s and their family caregivers (CGs) is needed. 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). Specifically the agenda for this psychosocial program development, should include the plans for randomized clinical trials, to assess carefully the impact of novel intervention programs designed to address BOTH the patients 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);
- Establish a National Coordinating Center for this type of research, which 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 to promote inter-collaborative and inter-disciplinary 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 upon the existing ADCS infrastructure.
- Initiate appropriate longitudinal psychosocial studies. Most existing studies followed either CGs (who were the primary focus: not the dyad) on a short-term basis: 3–6 months; 1 year at the most. But that is not a long enough time frame to see how well interventions “last” over time. Since it is clear that, as AD progresses and new challenges occur, new interventions are needed – 10 year studies are required to understand these patterns, phase in new interventions at the right time, and study cumulative effects.
- Commit to research on how best to disseminate findings in “real world” situations, including social services agencies and healthcare settings. This is a chronically under-appreciated issue which, 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 “as is” 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 1–2 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 really “pay off” in clinical practice.

The specific goals of this new initiative include:

1. Reduction in 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.
2. Reduction in rates of nursing home placement and/or intensity of home assistance for AD patients.
3. Less time lost from work for CGs (a major current issue resulting, often, in quitting the work force entirely in order to care for the demented parent or spouse)

4. Improved Quality of Life for both AD patients and their CGs

(Longitudinal population health economics and services studies: $1 million for the first year; $5 per year for years 2-10; $46 million over 10 years) (Health economics analysis: $1.5 million for the first year; $1.5 million per year for years 2-10; $15 million over 10 years)

Proposed Federal Funding:
$2.5 million for the first year; $6.5 million per year for years 2-10; $61 million over 10 years

_Component 5 - Health Service Research re: 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 co-morbid 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 its efficiency and cost-effectiveness through improvements and innovation in community based health services for people with Alzheimer’s disease and their caregivers. Studies are needed (such as pragmatic trials and cost-effectiveness studies of newly approved disease modifying treatments, as well as clinical trials of new health interventions, in order to demonstrate their health economic value.

Healthcare costs and quality of care are two important issues that require vigorous studies and viable solutions. This area of health services research is critical to improve the quality of care, better managing unnecessary costs.

The health services research initiative will plan a broad spectrum of intervention to determine the efficacy/cost-effectiveness of putative psychosocial and/or pharmacological/medical intercessions vis-a-vis improving ‘the system’ and/or ‘the quality of care’ for people with Alzheimer’s. Non-pharmacologic “Clinical” and "care and support" demonstrations must be linked to sophisticated health economics input and evaluation, both in the planning and in the evaluation of studies.

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

(Cost-effectiveness studies of new therapeutics: $1 million for the first year; $5 million per year for years 2-10; $46 million over 10 years)

(System-of-care and quality-of-care studies: $1 million for the first year; $30 million for years 2-10; $270 million over 10 years)

Proposed Federal Funding:
$2 million for the first year; $35 million per year for years 2-10; $317 million over 10 years
**Infrastructure and Research Resources Needs:** 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 pre-clinical stages of the disease? What are the capacity building needs for long-term, multi-site, multi-national prevention trials?

**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 Alzheimer’s disease (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 towards prevention studies, i.e., 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 very slowly, possibly over a period of decades, therefore very 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. This type of a shared-core facility for ‘longitudinal community based study’ will foster the launch of several specific projects such as a) expansion of GWAS studies, b) prevention studies, c) state of the art “Framingham” type study for cognitive aging, 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 risk and clinical course of AD and possibly other dementias. [See further details under longitudinal community-based studies].

The cohort may also serve as a “living repository” of individuals interested in prevention of dementia. These participants might also be willing to participate in long-term studies to validate biomarkers and to test new therapies and to 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 in the context of Prevention Therapies re: Biomarkers, Trials and Registries).

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) Organizational, administrative, and management structure for multi-site research resource/infrastructure, b) The mechanics of a ‘registry’ e.g., inclusion criteria, measurement domains, and a minimal data set; c) Instruments for gathering data, e.g., 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 2-10; $750 million per year over 10 years
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 multi-modeling 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, or the use of commercial cloud computing. The system, which will be capable of storing large datasets 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 (genetics, imaging, patient records, etc). They would also be an important resource for genomic studies, as described above.

Proposed Federal Funding:
$30 million for the first year; $30 million per year for years 2-10; $300 million over 10 years

National Core Resource Support for Discovery / Pre-clinical 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 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.

**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 IPS cells, repository of biospecimens from persons at AD-risk
- Expansion of brain collection/banking and its standardization to reflect urgent needs for controls across the lifespan, early stage AD brains and additional needs for 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, 6) cGMP laboratories for generation of lead compounds, biologics and stem cells
- Regulatory IND Resources - Dedicated regulatory services for Alzheimer’s disease including but not limited to, generation of preIND meeting and response documents for 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; $30 million per year for years 2-10; $300 million over 10 years

**Consortia and Public-Private Partnerships:** 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 Alzheimer’s, 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 Alzheimer’s Disease Neuroimaging Initiative, a partnership between government, industry, foundations and associations coordinated in “pre-competitive” space through the Foundation of the National Institutes of Health has provided an open data base of findings that have greatly influenced both academia, industry, the FDA and international regulatory bodies in terms of the diagnosing pre-symptomatic Alzheimer’s and providing a path for testing preventive treatments. A similar public-private partnership is being put in place for prevention trials in dominantly inherited families 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 Alzheimer’s. 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 requires 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. 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 which emerge from the consortia efforts over the next decade.

**Proposed Federal Funding:**
$50 million for the first year; $51 million per year for years 2-10; $509 million over 10 years

**Expand-Restructure Current Programs as National Resources:**

**ADCs** - The Alzheimer’s Disease Research Centers 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 Centers program should be modified and expanded to meet the new challenges of the field. The number of Alzheimer’s Disease Research Centers (ADRC) should be increased to 30 and funded at $5.0 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 (NACC), the National Cell Repository for Alzheimer’s Disease (NCRAD), the Alzheimer’s Genetics Consortium (ADGC), and the Alzheimer’s Disease Cooperative Study (ADCS), and any new national efforts that might be initiated (such as the Prevention Registry described below). In addition, the coordinating activities represented by the programs listed above 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 which already have contributed greatly to our understanding 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 data-bases be exploited to the full with additional secondary analyses and meta-analyses. The capabilities of NACC could be expanded to accomplish this goal.

**Proposed Federal Funding:**
$300 million for the first year; $3000 million per year for years 2-10; $3 billion over 10 years
ADCS - The NIA funding for the Alzheimer’s Disease Cooperative Study, an extremely vital resource for the field of therapy development, been capped at the FY’06 level through the end of the next cycle [FY’17] 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 the entire participating site. For example now the sites rely solely on the current inadequate per-subject payments, which is well below industry level. The estimate is that an adequate funding of the ADCS cores and projects would require $20M per year.

**Proposed Federal Funding:**
$20 million for the first year; $ 20 million per year for years 2-10; $200million over 10 years

ADNI - The original budget estimates [grant request] for the Alzheimer’s Disease Neuroimaging Initiative was $69 million, but the award was for $60 million, thus there was at the onset a $9 mil shortfall. In addition this $60 million award “assumes” that FNIH will receive $20 million from pharmaceutical partners. Given the economy, it is not clear how many funds industry will finally contribute towards ADNI. Assuming $10 million, ADNI will have an additional shortfall of $10 million. Third, because of slow enrollment the project was extended from a 5-year period to a 7-year project, which essentially causes the loss of another $5 million. This brings the ADNI project to a total shortfall of $24 million. Adding a 3rd amyloid imaging timepoint to the ADNI will bring the total budget for ADNI to $25.5 million. The projections for an add-on DOD ADNI study with 630 subjects will require an additional $72 million. ‘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 2-10; $1.7 billion over 10 years

- **Administrative-Organizational Solutions:** What type of project management team, organizational or administrative structure will be needed to facilitate or harmonize multinational collaborative R & D? 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 below [this is work in progress could be expanded]. 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 DHHS or the NIH Director [or may require legislative action e.g., authorization]

**Leverage ongoing programs:** The proposed initiative is intended to take into account all of the ongoing programs/initiative/funding mechanism at NIH, Alzheimer’s Association and industry and build upon, leverage and/or expand these efforts rather than abolish or replace these activities. Some example, include but not limited, are: AD Centers, ADCS, ADNI, NCRAD, ADGC, ETAC, Drug Discovery, Translational Research, academe-industry partnerships etc.
Collaborative multi-site research and development: During the last three decades some of the most successful scientific programs have emerged from collaborative multi-institutional efforts. Given the scientific complexities of the strategic goals of the 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 ADC/ADCS/ADNI, ‘Cooperative Research & Development Agreements [CRADA] etc.

National Shared Resources: Several of the programs outlined in the proposed scientific agenda for a national initiative calls 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. For example diversity and very large sample sizes required by such projects as GWAS/genomics/prevention trials/epidemiological studies seeking risk factors or efforts to identify-validate surrogate markers.

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 below). In additional we recommend that six additional centers should be established, with the designation of Comprehensive Centers (similar to the NIH-designated Comprehensive Cancer Centers).

Integrated Network for Discovery -Translation of Interventions: ADRCs serve as the initiating hub for convening discovery, translational and clinical scientists and enabling development of innovative therapies, biomarkers and interventions for Alzheimer’s disease. ADRCs partner with institutional CTSA to enable access to translational expertise, technologies, regulatory expertise and management of IND-enabling therapeutic development and Phase I clinical trials. ADRCs/CTSAs transition therapeutics for Phase II proof of concept clinical trials to ADCS. In turn therapeutics with demonstrated Phase II efficacy transition to public / private partnerships to conduct Phase III clinical trials. Nesting of each the resources enabling entities represents the integration across domains of development. Key to the success of this network is shared vision and commitment along with strategic and tactical integration across all entities.

Public/Private Partnerships (PPPs): 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 potential 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 insure all promising mechanisms are moved into the clinic in a timely manner. Although funding is required to initiate and maintain partnership model the long term net result should be an overall savings which would be captured by the investments of industry in late phase studies of the most promising compounds. New
PPPs focused 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 realistically implemented within 10 years; 2) Developing comprehensive detailed budgets with accountability; and 3) Providing professional project management to deliver results on schedule.
### Proposed Federal Funding
(in millions)

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