

Implementation Plan to Prevent Alzheimer’s Disease by 2020

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Summary

This document outlines the key planning parameters to implement a ***National Strategic Goal to Prevent Alzheimer’s Disease by 2020***. The enterprise, referred herein as **PAD 2020** or “Prevent Alzheimer’s Disease by 2020”, will rally broad national support to increase research and to build capacity to eventually prevent AD. The goal of PAD 2020 is to articulate a simple and direct statement that outlines a compelling vision powerful enough to motivate all stakeholders. The statement is not a promise to prevent AD, but rather the acceptance and commitment of a national goal to *focus* resources and *mobilize* coordinated efforts towards such achievement.

PAD 2020 seeks to:

- Expand investment for research
- Eliminate administrative and organizational impediments
- Streamline the grants review and award processes
- Optimize inter-operability and forging alliances with allied organizations and
- Increase competency and efficiency in the selection and use of research resources
- Support rapid advances in science necessary to AD prevention

Background and Rationale

The final report of the ***Alzheimer’s Study Group (ASG)***, “*A National Alzheimer’s Strategic Plan: The Report of the Alzheimer’s Study Group*”, and sent to the 111th Congress and the Obama Administration, recommended the launch of the ***Alzheimer’s Solutions Project (ASP)***, which identified prevention as a key priority.

PAD 2020 operationalizes this key ASG goal. PAD2020 regards increased investment in brain research as the only cost-effective means to address pending health care crisis due to the graying of America and the exponential increase in the prevalence of neurodegenerative disorders.

Recent advances in understanding the neurobiology of neurodegeneration simplify this challenge. The question no longer exists of whether there is a scientific knowledge base to ensure the success of such a bold initiative, but rather if there is a national commitment to move forward.

THE FIRST STEP HAS BEEN TAKEN BY ASG WITH THE PROPOSAL TO LAUNCH THE ASP. NOW, THE SCIENTIFIC COMMUNITY MUST RALLY AROUND A COMMON CAUSE AND DEVELOP AN IMPLEMENTATION PLAN FOR MOVING FORWARD.

The ASG report provides an important impetus to the scientific community to reevaluate the national research agenda. Consequently, scientists must develop priorities and credible plans for significantly expanding research on disorders of the aging brain.

A national strategic goal to prevent Alzheimer's disease within a decade will be difficult and costly. However, the challenges confronting the PAD 2020 mission are no less daunting than other *great human endeavors* of the past such as:

- Transcontinental Railroad 1862-1860; championed by Abraham Lincoln – completed in 7 years,
- Panama Canal 1904-1914; championed by Theodore Roosevelt – completed in 10 years,
- Manhattan Project 1939-1945; championed by Franklin D. Roosevelt- completed in 6 years,
- Apollo Program 1961-1969; championed by John F. Kennedy- completed in 8 years,
- Human Genome Project 1990-2000; championed by William J. Clinton – completed in 10 years and
- ***PAD 2020 2010-2020; championed by Barack Obama – projected to be completed in 10 years***

Former Speaker Newt Gingrich, co-chair of the ASG, said in his testimony to the 111th Congress:

“The human pain and financial burden of Alzheimer's is so great and the potential breakthroughs in science are so encouraging that a “Manhattan Project,” “Apollo Project,” or “Human Genome Project” approach to ending Alzheimer's is more than justified. The Alzheimer's Solutions Project is in the best American tradition of solving a big problem with a big vision and a big effort. A public-private partnership is the best collaborative approach to achieve that vision as rapidly as possible. It is the combination of, first, the scale of the crisis and, second, the breadth of the new science which makes this focused, intense investment and project management approach worth implementing.”

Prevent Alzheimer's Disease by 2020

PAD2020 is a *call to arms* not only to the leaders of Alzheimer's research but also other decision makers in neurology and neuroscience. PAD 2020 advocates a national strategic goal to increase research investment in resources that will accelerate the discovery of cures for dementia and other neurodegenerative disorders.

PAD2020 ***is not a guarantee for disease eradication***. The effort does not seek, and will not ask for an assurance of success by the scientific community within the decade. Rather, the enterprise provides a framework for encouraging stretch goals from Alzheimer's researchers.

The Alzheimer's Solution Project envisions the launch of PAD 2020 as a benchmark for addressing other late-life brain-behavior disorders. These include disorders with common clinical features such as memory, movement and mood (affect). The problem of Alzheimer's is prototypical of other chronic disorders that require long-term, labor-intensive, and expensive care. AD is destined to become a significant cost component facing the aging cohort of 78 million baby boomers. An exponentially increasing segment of this group, perhaps as high as 90 percent, is already at risk for some form of dementia or other neurological disorder.

The urgency of a national goal to mitigate and forestall the ***problem of dementia*** is mandated by the looming financial catastrophe facing the U.S. national health care system. The Congressional Budget Office (CBO) estimates

that total national spending on health care has more than doubled as a share of gross domestic product (GDP) over the past 30 years. The CBO further expects that this share will double again to 30 percent of GDP by 2035, 40 percent of GDP by 2060, and almost 50 percent by 2082². Federal spending on Medicare and Medicaid, which accounts for 4 percent of GDP today, is projected to rise to 9 percent by 2035 and 19 percent by 2082 under current law.

Planning Process

The collective thinking of over 200 worldwide leaders in dementia research concur that a ***mission to prevent Alzheimer's disease within a decade is an attainable scientific objective***. Scientists understand that PAD 2020 faces several scientific, administrative and financial challenges. Yet, the scientific community is also convinced that this is not any more difficult, ambitious, or premature than the other great defining national efforts previously mentioned.

The successful initiation and execution of PAD 2020 requires bold and decisive actions by the scientific community and public policy formulators. These efforts must promote radical changes in the governance and organization of research such as:

1. Innovative and flexible mechanisms of research funding,
2. Rapid deployment of resources and infrastructure,
3. New paradigms for therapy developing, and
4. Accelerated decision-making processes to identify and support novel ideas.
5. Public-private collaborations using the best of public and entrepreneurial models to enhance research progress

As was the case with all other past grand projects, the success of this mission requires:

- Defining clear and specific scientific objectives
- Establishing an efficient organizational and management system – a single centralized administration and coordination center

- Developing realistic research and implementation plans with timelines and deliverables
- Adoption of a ***systems approach*** to the planning and execution of the effort
 - A collaborative research model that integrates knowledge, methods and perspectives from different disciplines and
 - Promotes rapid exchange and dissemination of information among virtual networks of worldwide collaborators
- Decisive leadership that yields changes in the governance and organization of research, including
 - Mechanisms of research funding,
 - Deployment of resources and infrastructure, and
 - Paradigms for developing therapies
- Sustained investment of resources and funds to support the mission
 - Ten year commitment
 - \$1 billion per year
- Unwavering national commitment to support this mission until completion

The present draft implementation plan will provide greater justification for the claim that sustained investment in research will produce results within a decade. This document provides a general framework for a strategic research plan, which includes sections devoted to discussions on:

- a) Goals and scientific objectives
- b) Potential barriers and challenges
- c) New or additional research resource/infrastructure needs
- d) Proposals for new mechanisms of funding
- e) Administrative structure and management team
- f) Research plan with timelines and deliverables
- g) Budget structure and justification

The initial draft plans for PAD 2020 will be circulated among key stakeholders for comment. The document will re-incorporate comments, with successive revisions to follow.

The most important (and perhaps the most contentious) constituency that needs to accept the plan is the scientific community. It should be noted,

that among those nearly 200 scientists who have endorsed the PAD 2020 initiative, they have done so *in principle*. Now the challenge is to fully engage this constituency in the planning process so that they will have pride of ownership of the final plan.

A tentative research plan for review and comment will be made available by the end of August. However, the process of engaging the scientific community in the process of planning a national scientific agenda will require time. However, this need not hinder parallel efforts to develop the justification and political support for this initiative.

The planning process of a national scientific agenda will consist of several phases:

Phase I. Small group led by Stan Prusiner and Zaven Khachaturian will prepare and initially draft the agenda for the scientific community.

Phase II. Convene several small **PAD 2020 Work Groups** not to exceed 10-15 people per group. The task of each Work Group [WG] is to identify:

- 1) Special scientific opportunities that are ready to be deployed and translated into practical applications,
- 2) Critical problems in developing treatments to prevent neurodegenerative disorders: where future progress will require scientific and technological innovation,
- 3) Barriers to progress: fundamental problems in basic or translational research that are difficult to initiate in academia or industry, because they require:
 - i. Expertise from disparate areas,
 - ii. Long-term support beyond standard NIH funding mechanisms and
 - iii. Major shifts in current priorities of funding agencies.

Phase III. WGs will evaluate the national resources (including human) and infrastructures that are available for the PAD 2020 initiative within academia, industry and government. Given the necessity to have a critical mass of investigators for studying each particular research problem, WGs will help establish a series of **Integrated Scientific Teams (IST)**. These are virtual

networks of collaborating investigators, who seek to break through existing barriers. Each IST will select a problem, and then will address the approach and the tools necessary to devise a solution.

Phase IV. Each IST will prepare a ***Project Plan*** that will include: a) scientific/technical objectives, b) strategy to address the problem/action plan, c) deliverables and timelines, d) resource needs and e) budget.

Phase V. Develop a governance structure for PAD 2020 initiative, which will include an external advisory council, management team and project leader/administrator.

Phase VI. Prepare a ten-year business plan, which will include legislative initiatives and a development/fund raising plan

THE PROCESS WILL BE REITERATIVE. AN IMPORTANT AIM WILL BE THE INCLUSION OF A BROAD SPECTRUM OF THE SCIENTIFIC COMMUNITY AND OTHER KEY STAKEHOLDERS. THE EFFORT'S END-STATE IS TO GAIN UNIVERSAL SUPPORT AND CONSENSUS.

Critical Challenges: for PAD 2020 Initiative

During the last three decades, Alzheimer research has not only made remarkable progress in understanding the disease but also has recruited some of the best scientists in the world. The prospect of delaying or preventing the onset of symptoms is feasible and within our grasp. However, this mission must surmount a number of barriers which include: inadequate funding of research, high cost of clinical studies, lack of appropriate infrastructure, better models, antiquated administrative structure of discovery programs, and arcane decision-making systems for selecting and funding innovative ideas.

Only a sustained commitment to overcome those hurdles will accelerate the pace of translating newly emerging or promising knowledge (e.g., stem cells, gene therapy, and neural repair/regeneration) into practical

applications. The success of PAD 2020 requires significant changes in the current philosophy and approach to:

- **ADMINISTRATIVE STRUCTURE AND MECHANISMS OF FUNDING RESEARCH:** NIH's historic and familiar system for peer-review, funding mechanisms and grant management system simply cannot meet the needs of the rapidly evolving scientific world. There is a need for a new and flexible system that supports rapid decision-making especially in circumstances of unexpected opportunities and breakthroughs.
- **SELECTION OF NEW IDEAS AND RESEARCH PRIORITIES:** the prevention initiative needs to re-direct the focus of research towards the discovery and validation of: a) methods, tools or biomarkers for *early detection of the disease in the asymptomatic* stages, b) therapeutic targets *to delay or prevent the disease progression, before the onset of symptoms*, and c) optimal means of performing large scale prevention trials.
- **CONCEPTUAL MODELS OF THE UNDERLYING NEURODEGENERATIVE PROCESSES:** The AD research fields needs to adopt new thinking about the pathogenesis of the disease. Models will need to fully incorporate the temporal lag between the initiating pathological event and the first appearance of symptoms. Thus, efforts to develop interventions to modify the course of the disease will have to be planned and administered decades before the first symptoms appear. The rationale is that therapies for prevention are more likely to succeed when applied in the earlier, pre-clinical (or asymptomatic) stages of the disease, rather than after the symptoms appear.

I. Scientific:

A. A critical scientific challenge for the prevention initiative is the discovery of new knowledge for study recruitment. At the core is the validation of methods and algorithms for identifying, selecting and detecting asymptomatic people with elevated risk early in the pre-clinical stages of the disease. The mission to prevent the neurodegenerative processes will require the development of a battery of well-validated, early markers of the disease. These markers will be used not only to identify asymptomatic individuals, but also to monitor the progression of the disease and the effectiveness of treatments in changing the course of the disease.

B. Another major scientific challenge for prevention is the paucity of validated therapeutic targets that affect neural survival. Current pipelines of potential treatments need to be expanded by supporting drug discovery programs in academia and industry. New programs on drug discovery need to focus on validation of new targets for protection against synapse loss, prevention of dendrite pruning, and repair/regeneration of dying neurons.

C. The field of Alzheimer's research urgently needs new conceptual models of the disease in order to broaden the range of therapeutic targets and increase the pipeline of potential treatments. Alzheimer's research lacks a unifying theory that would integrate all current hypotheses and clinical observations to provide a more complete account of the functional relationship between the clinical/behavioral features and the molecular or biological phenotypes of the disease.

D. Presently there is a general acceptance that the most proximal neural events that explain the symptoms of the disease are due to a *systems failure*. The gradual breakdown of the neural network reflects a degenerative process that affects fundamental cellular functions, signaling, communication, proteins (e.g., synthesis, degradation, aggregation folding synthesis) massive loss of synaptic functions and dendrite pruning. There is a growing implicit recognition that these degenerative processes involve several alternate paths and cascade of events leading to a systems failure. However, presently there is no consensus on such questions as: What factor(s) initiate the synapse loss and dendrite pruning? What can be done to slow, prevent or reverse this process? Why some neurons (neural nets) are affected while others are intact? What factors determine or modulate the age of onset?

E. Clinical studies to validate the efficacy of potential disease modifying or preventative drugs need to address an important methodological issue concerning study design. The prevention initiative needs to contend with conceptual differences in the design and conduct of clinical trials for prevention in contrast to treatment. Treatment trials are undertaken to *cure* or ameliorate disease. Prevention trials are undertaken in the hope of preventing or delaying disease onset. The differences between the two approaches relate to the choice of treatments (or interventions), outcome measures, volunteer (subject) recruitment methods, inclusion/exclusion criteria (such as age), follow-up period and other issues related to monitoring.

Prevention trials have several inherent challenges, which include: a) long follow-up periods and lack of cost-efficient data collection procedures that yield high-quality data, b) recruitment requirements of large numbers of volunteers (i.e., in excess of 5,000 persons), c) inadequate federal funding to support trials lasting more than five years, d) fragmentation of clinical care for research volunteers, e) high indirect cost rates, and f) numerous regulatory burdens for investigators and sponsors, posed by both the federal government and research institutions.

II. Mission Governance

A. The success of PAD 2020's mission requires the creation of a streamlined decision-making process in the selection of new ideas. A flexible and quick-response funding system is necessary to handle unexpected opportunities and support breakthrough projects.

One of the important impediments to progress in therapy development is the current administrative and decision-making apparatus in the ***management of discovery programs***. The present system used nationally is both antiquated and inadequate. Historically, the most important breakthroughs in science have often come from unconventional thinkers. Yet, the current decision-making system does not accommodate taking risks on truly imaginative ideas.

It can take up to two years for scientists to obtain research support if one includes the time from idea to receipt of a check. If an application is not funded after the first submission, the scientist can revise and resubmit it for the next round, delaying the research for another year. Additionally, most grants are limited to an average duration of three years, which is too short for a chronic, end-of-life condition like AD.

B. One of the most critical challenges for the national mission to prevent Alzheimer's disease is the need for centralized control and coordination of all Alzheimer's related activities.

In recent years, a number of programs related to various aspects of Alzheimer's disease have emerged in agencies other than NIH, as well as in industry and non-governmental organizations (NGOs). One of the important needs of the field is to reduce the fragmentation and duplication of these efforts. A related need is increased communications and coordination among all key players.

An important challenge for the field is to leverage and build upon ongoing programs, initiatives, and existing resources within government, industry, academia, and other NGOs. This aim can be achieved by a new administrative structure for coordination, planning and resource utilization among all stakeholders.

The Office of Alzheimer's Research (OADR), established in 1985 by the Director of NIH James Wyngaarden, set a precedent for such a coordinating function. The OADR served as the central locus for control and coordination for all Alzheimer's related work at the NIH AND was the home of the NIH's Alzheimer's Disease Research Coordinating Committee from 1985 to 1995. The concept of an ***Office of Alzheimer's Research*** could be revived to serve the functions of control and coordination of all Alzheimer's related programs and activities across all government agencies and NGOs.

Another option is the creation of a quasi-government entity such as the Alzheimer's Solutions Project (ASP) could serve the function of coordination by establishing and managing an interagency committee for coordination of AD Programs. The aim is to create an administrative structure for efficient decision-making for the selection of new ideas. This includes centralized, quick-response funding systems with flexibility and authority to handle unexpected opportunities and support breakthrough projects. This office also should serve as the instrument to lead interagency cooperation, and establish partnerships between academia, healthcare providers, volunteer health advocates, and the private sector.

C. Recommendations for Administrative Actions

- Expand current good clinical practices (GCP) guidelines to standardize procedures across clinical trials.
- Develop best practices for prevention trials in Alzheimer's disease

- Reauthorize administrative costs within National Institutes of Health (NIH) grants.
- Encourage the inclusion of potential biomarkers to supplement clinical efficacy within new drug applications.
- Support the collection of promising neuroimaging biomarkers within clinical care to build the needed databases to confirm their utility and extend their use in clinical trial designs.
- Concerns about tolerability and/or management of adverse events often prolong phase III studies or delay the approval of potentially useful therapies. To address this problem, one solution is to create a new category of drug approval, i.e., -Temporary Approval, contingent on aggressive phase IV post approval monitoring of data on adverse-events efficacy and safety.
- Create an AD drug-development program within the Food and Drug Administration (FDA) similar to the Office of Orphan Drug Product Development.
- Extend marketing exclusivity for a drug as an incentive for sponsors to develop drugs for the prevention of AD and other illnesses that may require lengthy, expensive trials.
- Develop incentives for sponsors of clinical pharmaceutical trials to use and validate biomarkers as part of their clinical trials; create a publically accessible database of biomarkers and biomarker-clinical correlations.
- Encourage the identification of individuals at high risk of AD and with mild dementia for clinical trials through the reimbursement of brief cognitive assessments and AD biomarkers.
- Develop novel means of involving broad segments of the population in trials such as web-based screening and assessment
- Reimburse dementia health education and social services during initial memory evaluations that encourage participation and retention in clinical trials.

III. Infrastructure and Resources

A. Establish a National Registry and Database

The lack of appropriate research infrastructure for long-term longitudinal studies is another critical barrier to the PAD2020 mission. ***A National Registry and Database on Successful Aging*** serving as a national research resource could satisfy multiple needs such as: clinical trials on prevention, epidemiological studies to discover and validate risk factors, discovery and validation of biomarkers, and other public health surveillance activities. For example, one of the urgent needs for a broad national prevention study is solid-state access to large cohorts of well-characterized asymptomatic volunteers. Prevention studies need to identify abundant samples of homogenous subgroups within the population. This includes individuals with elevated risk for the disease, no apparent symptoms, and who are willing to participate in long-term trials or studies to validate biomarkers and to test new interventions.

The primary objective of this national research resource is to identify asymptomatic people (either not at risk or at elevated risk for cognitive impairments), as well as people with mild cognitive impairment who have volunteered to participate in research. In addition to serving multiple needs of the field, the national database will also have linkages with electronic medical records and public health databases. The database will lead to a better understanding of changes in the natural progression of the disease. From a public-health perspective, the database will allow better targeting of communication to inform people regarding current knowledge about diseases of aging, prevention strategies, and clinical trials. Creation of the national database should be an integral part of restructuring NIA's centers program. This endeavor should be a joint and collaborative effort, with the Centers for Disease Control (CDC) and other power-users of bioinformatics technology (e.g., VA, DoD, and DoE).

B. Drug Discovery-Development Research Network

In close relation to the national registry and database, an allied infrastructure need is the establishment of a several discovery and validation teams. The current cross-agency programs at NIH (designed to provide resources for animal model exploration, formulation, medicinal chemistry, and toxicology) are not sufficient to advance new targets identified in academic laboratories along the drug-development pipeline. A new

administrative entity outside of NIH is necessary to address this critical gap in technology transfer.

The aim is to develop a ***Drug Discovery-Development Research Network (DDRN)***. This consortium will function as a *virtual research pharmaceutical company for Parallel Assessment of Candidate Compounds PACT; see attachment*). *This approach will obviate the need for sequential testing and provide a means of parallel simultaneous evaluation of promising therapies*. The main work product will be to bridge the gap between academia-based research on the discovery of potential therapeutic targets, and early drug-development work (i.e., target validation) typically conducted outside of academic settings. The output will be the acceleration of the drug-discovery process by enriching the pipeline of potential therapeutic options.

The effort will allow different laboratories (in academia and industry) to collaborate in various stages of drug development. This includes medicinal chemistry, drug metabolism and pharmacokinetics, toxicology, proof of concept in preclinical animal models, and ultimately trial design. Using a *virtual entity* alleviates the nearly insurmountable burden of requiring all such disciplines to exist at a single institution. Also, the PACT consortium could more easily potentiate funding of collaborative projects, leading to broader exchanges of novel ideas throughout the AD research field. Intellectual property issues that restrict progress need reform.

C. National Institutional Review Board (NIRB)

The creation of a ***National Institutional Review Board (NIRB)*** for the oversight of multicenter clinical trials involving chronic neurodegenerative diseases would be another key innovation as a research resource.

Presently, each clinical trial and each academic site participating in a trial must obtain separate institutional review board (IRB) approvals, with different and sometimes conflicting guidelines for each site. Many non-institutional (e.g., private clinics) and some academic sites already use commercial IRBs, providing a uniform regulatory approach without harming research volunteers. The redundancy and inconsistency of multiple IRBs in a multisite trial places a heavy, unnecessary administrative burden on academic

investigators, decreasing their efficiency and increasing the costs of clinical trials. This unnecessary complexity complicates the conduct of multicenter clinical trials, and interferes with minor modifications that might be warranted by developments in disease knowledge, such as (but not limited to) the handling of patient samples for novel biomarker discovery and validation.

In addition to the establishment of this office, clear guidelines should be developed for the conduct of clinical trials in AD that can be applied consistently across sites and trials. The challenges for the Department of Health and Human Services will be to promulgate new regulations, and to amend current policy and policy guidance to potentiate a NIRB.

D. Legacy NIH Programs

Since 1978, National Institute on Aging (NIA/NIH) established an extensive national network of AD research facilities at academic institutions. This effort produced such programs as: Alzheimer's Disease Research Centers (ADRC), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Drug Discovery Program, National Research Bank for Genetic Studies of Alzheimer's Disease, National Alzheimer's Coordinating Center (NACC), National Cell Repository for Alzheimer's Disease (NCRAD), and Alzheimer's Disease Neuroimaging Initiative (ADNI). However, despite the capacity of this network and their many critical contributions, today these programs are inadequate.

PAD2020 changes the needs of the field. Specifically, the efficiency and effectiveness of each program can be substantially improved consolidation and integration. For example, the ADRC program or the current *Centers* (P30s and P50s) can be modified so that some of the centers can be converted into Comprehensive Alzheimer's Center (P60s). A small number (5-10) of such regional centers could support not only research, demonstration projects on care/ treatment, clinical trials, and education but also allow for the integration of several multi-site collaborative studies such as ADCS, ADNI, and Patient Registry and Clinical Data Bank programs into a single administrative structure.

Integrating the administration of these programs through Regional Comprehensive Centers would offer greater efficiency and cost savings. Under this model a regional center could serve as the coordinating hub of several smaller centers within a region offering greater economies.

E. Comprehensive Alzheimer's Research Centers

The Alzheimer's Disease Centers (ADCs) Program of the National Institute on Aging (NIA) should be enhanced and reorganized as the ***Comprehensive Alzheimer's Research Centers (CARC)*** program. The new mandate will coordinate and support multisite studies on specific research themes. The objective would broaden the scope of activities to include research on interventions, diagnosis, imaging, prevention trials, and other longitudinal studies that require long-term support. As mentioned before, there is an urgent need to identify subjects at high risk of AD for prevention trials and very early in the course of their illness for clinical trials of disease modification. The enhanced program should allow more variability among centers by supporting collaborative linkages with other institutions, and thus draw on wider expertise from different locations.

F. Alzheimer's Disease Cooperative Study

The ***Alzheimer's Disease Cooperative Study (ADCS)*** consortium requires an augmented and broader mandate with a substantially increased level of funding. ADCS should become an integral component of the Comprehensive Alzheimer's Research Center. Some of the ADCS participating sites should be selected for designation of Clinical Centers of Excellence. These sites would provide data on biomarkers and support services that would link early diagnostic assessments with clinical researchers.

The ADCS investigators should be linked to community physicians to: 1) facilitate the recruitment of people with increased risk of developing AD, as well as mildly affected patients for clinical trials; 2) support the validation of biomarkers; 3) promote transfers of technology in therapeutic advances and development; and 4) encourage the training and recruitment of new clinical investigators.

The reorganization of ADCS would allow regionally based community physicians to participate in research and foster the integration of clinical care with research programs. These sites could also provide support for infrastructure at sites, loosely modeled on the Early Clinical Drug Evaluation Units (ECDEU), as established by National Institute of Mental Health in the late 1960s. Through this network, academic centers had readied facilities, staffs, and patient populations that enabled quick and cost-effective participation in collaborative multicenter trials implemented by the ADCS Consortium, a central component of the ECDEU infrastructure. Academic centers have traditionally had limited access to community populations.

The proposed changes should incorporate aspects of NIH Clinical and Translational Science Awards that provide infrastructure support to expand research to outpatient and community populations. These large, diverse populations are an underutilized resource that could decrease recruitment costs and serve as a subject pool for prevention studies.

IV. Financial

A. The mission to ***Prevent Alzheimer's Disease by 2020*** requires an unprecedented level of financial commitment from both the public and private sector. The success of this initiative hinges on *an unwavering national commitment to allocate appropriate levels of funding during the next decade.*

The success of this venture will require a sustained investment of \$1 billion per year in new funds over current expenditures for the next 10 years. An investment of \$10 billion dollars to solve the most urgent looming public health problem is not too high a cost. The high priority initiatives/programs that will require special attention and additional support include:

- a) Discovery and validation of new therapeutic targets focusing on neural repair and restoration and disease modifying agents
- b) Development and validation of technologies (including biomarkers and imaging) for early detection of neurodegeneration in asymptomatic people at risk for dementia. The goal is to develop stochastic (and possibly non-stochastic) models that use specific ***panels*** of markers

(combining data vectors from imaging, biochemistry, neurocognitive, and known risk factors) with high sensitivity to detection in the prodromal stages of the disease, and/or responsive to change with disease severity.

- c) A National Registry and Successful Aging Database to serve as a national resource for epidemiological and clinical studies including prevention trials
- d) Ten Comprehensive Alzheimer Research Centers (CARCs)
- e) Alzheimer's Disease Cooperative Study (ADCS)
- f) Drug Discovery-Development Research Network
- g) Alzheimer's Disease Neuroimaging Initiative (ADNI)

The major stumbling block to progress is inadequate level of financing the PAD 2020 mission. The recent 'doubling' of NIH budget did not have a commensurate impact on the budget for AD research. While remarkable progress has been made in AD the research, the prevention initiative will be in jeopardy because of inadequate resources to support the necessary work. Neuroscience research is extremely costly and highly technical. The cost of conducting research continues to rise with technological advances.

Many investigators, even at the world's leading research universities, are seriously constrained by the lack of easy access to essential resources. New instrumentation to permit measurement of biologic processes, not previously attainable, is also expensive and often requires highly trained scientists and technicians, which adds additional cost.

Research funds are not available to begin new initiatives or to attract new investigators (e.g. protein chemists, structural biologists and medicinal chemists) into the AD field. This is particularly so just at the moment when their expertise is most urgently needed. As a result, limitations on funding combined with arcane decision-making processes to create a situation where only fractions (xx-xx%) of applications are awarded. The National Institute on Aging, which supports nearly 70% of AD-related research, can fund only xx-xx% of the new applications it considers each year. Those applicants fortunate enough to attract some support routinely see their budgets reduced at various points in the nine-month long review process. In the end, scientifically meritorious projects cannot be completed, or cannot be completed well, due to lack of dollars.

The national commitment to discover a solution to the Alzheimer's problem, which now costs the country an estimated \$xx billion a year, is very modest-about \$x per person suffering from the disease, or \$ x for every \$xxx Alzheimer's disease is now costing society. The current level of annual support for Alzheimer's disease research at the National Institutes of Health is about \$xxx million, compared with \$xx.x billion for cancer, \$x.x billion for AIDS, and \$x billion for heart disease-all public health problems of comparable cost and concern to the American people.

B. One of the important barriers to the development of therapies for prevention is the long duration and the high cost of prevention trials. Therefore there is a need for developing new models for financing the high cost of prevention as well as new approaches aimed at reducing the duration and cost of trials.

Justifications

The idea for a national initiative to **prevent Alzheimer's disease** was first conceived in 1987 by the proposition that *delaying the onset of the AD symptoms by five years will reduce the prevalence by half*. This concept was published subsequently as a 1992 editorial entitled "The Five-Five, Ten-Ten Plan for Alzheimer's Disease"³. Today, after nearly twenty years of impressive progress in research, the 'problem' of Alzheimer's disease still lacks a tangible clinical solution, i.e., there are no long lasting treatments that are meaningful to the person with the disease or their families. In spite of the advances in understanding the biology of the disease, the major scientific challenge of the field remains untouched because of the lack of effective interventions that would: a) delay the onset of symptoms by slowing the progression of neurodegeneration, and b) eventually prevent the disease. Therefore, the goal of **reducing the number of people at risk for dementia by 50%, within the next five years and aiming for prevention within a decade**, should be the highest priority of the **National Strategic Plan for Alzheimer's Disease** as formulated by the **Alzheimer's Disease Study Group (ASG)**.

Fortunately, the necessary scientific leads and the technical information are at hand to launch such a bold initiative as PAD 2020. The field of Alzheimer's

research is more optimistic than ever about the prospects of discovering more effective treatments and, ultimately, strategies to prevent the disease entirely. These positive expectations, however, must be moderated with current realities; the barriers PAD 2020 initiative must overcome. These include: a) insufficient knowledge about critical therapeutic targets, b) inadequate funding and resources for research, and, c) an array of organizational and administrative impediments. These challenges all combine to make this initiative one of the most demanding goals brain research has ever faced; comparable to other ‘Great American Projects’.

However, this difficult path towards the strategic goal of preventing a major brain disease is well matched by a credible history of remarkable scientific achievements. In the span of three short decades the field of Alzheimer’s research overcame incredible hurdles to move from virtual obscurity to one of the most prominent areas of neuroscience; including the awarding of three Nobel Prizes for research related to dementia. This rapid pace of Alzheimer’s research would not have been possible without: a) strategic planning and b) systematic investment in research, capacity building, and infrastructure development. In 1978, the National Institute on Aging (NIA) began to develop the plans for a comprehensive national program of research on “Brain Aging” and “Alzheimer’s disease” at the National Institutes of Health (NIH). With its limited initial resources, NIA necessarily took a long-term strategic approach and systematically addressed numerous logistical hurdles.

The most critical challenges were to: 1) recruit the best scientific talent,2) identify promising ideas, and 3) develop critical research resources and infrastructures. The NIA’s experiences during the early formative years of program development might provide valuable guidelines for PAD 2020 Initiative. Today, just as it was the case nearly 30 years ago, the need for strategic thinking and planning is paramount.

- Only 30 years ago, conventional wisdom regarded Alzheimer’s disease as a hopeless and untreatable condition. In academia, the disease generated little interest in research except for a handful of plucky investigators. Federal expenditures on research were virtually zero.

- Twenty-five years ago, the clinical infrastructures essential for systematic longitudinal studies of well-characterized patients were not available.
- Twenty years ago, the concepts of “cure” and “prevention” were inconceivable. Crucial clinical tools such as diagnostic criteria, standardized assessment instruments, cadres of specialized professionals, memory disorder clinics, family support groups, or outreach programs—all of which are taken for granted now—did not exist.
- Fifteen years ago, information on genes and/or biologic pathways involved in the development of the disease was limited at best. Ten years ago, animal models of the disease did not exist.
- Five years ago, persons at high risk for the disease could not be identified, and the idea of clinical trials for prevention or for delaying symptoms was only a pipe dream. Hallmark lesions of the disease could not be directly visualized in patients until 2004.
- Today, in less than three decades, research has yielded significant progress and propelled the efforts against this disease from obscurity to the forefront of modern biomedical science. The indices of this remarkable transformation are the exponential increase in scholarly publications and the dramatic increases in the numbers of investigators. The genes involved in early-onset Alzheimer’s disease and a risk (susceptibility) gene have been identified. Brain amyloid can be imaged in living patients, and a few potentially disease-modifying treatments have been advanced to clinical testing.

Traditional thinking on brain aging has been reversed on its head with the discovery that healthy aging nerve cells can regenerate. We have learned a great deal about the genetics, synthesis, degradation, aggregation, toxicity, folding, and clearance of abnormal proteins involved in the pathogenesis; we have developed strategies on how to prevent their toxicity. Intensive studies are underway on multiple fronts, from basic science to genetics to drug therapy to caregiving.

Several clinical trials with promising leads for disease-modifying compounds are underway.

As the “baby-boom” generation ages and brain diseases become more prevalent, the need to confront the pending health care crisis this demographic change is more urgent now than ever. As resources become more difficult to allocate, we must reconsider our national priorities. As part of that exercise, it is now critical to significantly expand research expenditures on Alzheimer’s disease with special focus on prevention. Ultimately, investment in prevention research is the only cost-effective means to avoid the pending public health catastrophe this country faces.

The new battlefield for the mission to Prevent Alzheimer’s Disease by 2020 is much broader than the heated scientific disputes on various theories or scientific approaches. *The ultimate enemy is the problem that patients experience and families have to face every day, the loss of memory that is a common feature in a number of brain diseases.* The goal of the proposed National Strategic Plan is to create a new paradigm for planning and supporting the organization of worldwide cooperative research networks to develop new technologies for early detection and treatments for various forms of memory impairments. In order to accomplish this goal, the federal budget must be increased for research aimed at: a) developing national resources to discover new interventions for memory disorders, and b) creating a streamlined decision-making process for the selection and support of new ideas.

Professional Judgment Budget (TBD)

Office of Alzheimer’s Solutions Project (OASP)

National Registry and Database

Comprehensive Alzheimer’s Research Centers (CARC)

Alzheimer’s Disease Cooperative Study (ADCS)

National Institutional Review Board (NIRB)

Drug Discovery-Development Research Network (DDRN)