National Alzheimer's Project Act (NAPA)

The information that follows was included as an attachment to an email submitted by the public.

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http://aspe.hhs.gov/national-alzheimers-project-act

Alzheimer's & Dementia 10 (2014) S265–S268

Editorial

Perspective on the "2014 Report on the Milestones for the US National Plan to Address Alzheimer's Disease"

The "*Report on National Alzheimer's Plan Milestones—FY' 2014*" [1], which appears in the current issue of *Alzheimer's & Dementia*, provides an overview of progress in Alzheimer's research and "professional judgment" recommendations for specific "new milestones," as a road map, for implementing the legislative intent of the National Alzheimer's Project Act (NAPA). This report reflects the collective thinking of the Alzheimer's Association's Workgroup on Milestones (ALZ-WG), which included key leaders in dementia/Alzheimer's disease research.

Public Law (PL 111-375), a.k.a., NAPA—enacted by Congress in 2011, mandated the formulation of a "national strategic plan" to mobilize research and development (R&D) resources, which would alter the catastrophic trajectory of an imminent public health crisis due to the exponential increases of people with the disease and explosive costs of health care. The overall strategic goal of the "national plan" is to promote the discovery and validation of wide arrays of new scientific knowledge and associated novel technologies, which would ameliorate the progression of not only Alzheimer's disease but also other chronic brain disorders due to degenerative processes. The ultimate aim of the "national plan" is to expand or develop the national scientific-technical capabilities, which would eventually enable the prevention of the onset of disabling symptoms within a decade. The strategic public health objective of the national plan is based on the premise that a modest delay of 5 years in the onset of symptoms will reduce the prevalence and health care cost of the disease by 50% [2].

A national strategic goal to prevent Alzheimer's disease and other chronic brain disorders within a decade is indeed a difficult challenge; however, such an ambitious mission is no less daunting than the start up of other great "big science" enterprises such as the Human Genome Project. This grand vision accelerating the discovery of interventions is not framed as a promise for disease eradication, but rather, as a national commitment for a decade-long sustained support to mobilize coordinated efforts to focus allocation of funds and resources toward such achievement.

1. What are some of the decisive challenges for a grand "national plan?"

The ALZ-WG was convened by the Alzheimer's Association not only to review and evaluate the progress in attaining the objectives of various "milestones" of the national plan but also to recommend "new milestones." The ALZ-WG was organized as an open forum for key leaders in the worldwide scientific community to participate in the planning process by sharing their ideas regarding crucial scientific needs and questions that must be addressed by a prospective national strategic plan. The ALZ-WG deliberations have identified the major challenges that the prospective national plan must surmount to attain its ultimate grand vision of the scientific capability to "prevent Alzheimer's disease within a decade."

Among the major challenges facing the prospective national plan, the gross inadequacy of funds allocated to Alzheimer's research is the most critical rate-limiting factor, which is hindering the progress toward a cure. The strategic mission to prevent the disease is in jeopardy because of the dwindling resources applied to support the necessary work. Neuroscience research is extremely costly and highly technical. The cost of conducting research continues to rise with technological advances. Thus, the national strategic plan urgently requires a compelling, scientific, rational, and a persuasive business justification for a strategy for sustained (10-year) systematic investment in research.

That investment plan should be incremental – with goal of $2.0 billion additional new funds per year for next 10 years [2]. This professional judgment budget estimate, essential for accomplishing the ultimate mission of the National Plan, is formulated on the basis my administrative experiences in planning, developing, and coordinating large national research programs on brain aging and Alzheimer's disease; as the former Director, Office of Alzheimer's Disease, National Institutes of Health (NIH) and Associate Director, Neuroscience Program, National Institute on Aging/NIH, 1978–1995. These projected needs for research

This "Report" reflects the recommendations of the Alzheimer's Association Expert Advisory Workgroup II.

1552-5260/$ - see front matter
http://dx.doi.org/10.1016/j.jalz.2014.08.102

funding are independently corroborated by the recommendations of other research planning workgroups and prominent leaders in neurology-neuroscience [2,3].

Here, we summarize the main ideas and rationale behind the ALZ-WG recommendations for new milestones by highlighting an array of strategic R&D targets for a decade-long investment that are deemed essential to the overall mission of the national plan. To facilitate the discussion in this perspective article, we have grouped the recommendations of the ALZ-WG into five general categories of challenges facing the national R&D enterprise. The five broad areas, which will need significant expansion of resource and sustained funding to accelerate innovations, include the domains of (1) science-technical, (2) infrastructure/research resources, (3) financial, (4) administrative, and (5) regulatory [1,2,4–6].

1.1. Science-technical

The three major battlefronts in the arena of scientific-technical challenges for the national plan include the discovery and validation of

1. Interventions, both behavioral and pharmacological to delay the onset of symptoms by slowing or halting the progression of the disease,
2. Technologies for early diagnosis of the disease and algorithms for accurate detection of people at elevated risk in asymptomatic populations or preclinical stages of the disease, and
3. Novel research strategies to study the biology of the disease based on the paradigm of systems theory and exploiting knowledge derived from computational biology.

1.1.1. Interventions

In the area of therapy development, the most crucial projected milestone is the need for substantially expanded national R&D programs in academia, as well as industry, to focus on discovery and validation of broad spectrum of novel intervention therapies based on compelling basic scientific knowledge about the complete biology of neurodegeneration. Typically, the available fundamental knowledge base on the biological underpinning of the disease based on prevailing theories about pathogenesis is the essential scientific engines that drive the overall therapy development enterprise. Thus far, current notions about Alzheimer's disease, along with therapy development paradigms derived from these theories, have not yielded the positive outcomes anticipated. A number of variables could account for the failures in productivity of therapy development; however, one important contributing factor that needs further consideration is the validity of ideas about pathobiology of the disease. One of crucial scientific challenge for the field is the necessity for a rigorous reassessment of existing theories through a formal process of dispassionate examination of the shortcomings of current ideas along with their derivative paradigms that have guided therapy development.

Such are examination of assumptions about the disease is a prerequisite for the need to widen the field of exploration for new and novel therapeutic targets by considering different alternative conceptual models of dementia-neurodegeneration. The prospective national plan should outline a program for systematic investment of resources to expand substantially the spectrum of potential therapeutic targets based on (1) alternative conceptual models of the pathobiology of dementia and (2) more accurate knowledge about the neurobiology of complex polygenic syndromes, such as Alzheimer's/dementia.

1.1.2. Technologies for Dx

During the last decade, emerging knowledge about Alzheimer's disease/dementia/neurodegenerative chronic brain disorders indicates that these conditions (1) are characterized as being heterogeneous, polygenic, and complex; (2) have decades-long "silent stages" or prolonged preclinical and asymptomatic phases; and (3) are unresponsive to interventions or less likely to benefit from disease-modifying treatments and are the apparent failure in some clinical trials. Thus, the national plan should expand resources for R&D activities regarding the discovery and validation of a broad spectrum of putative risk factors, including genetic, biomarkers, behavioral indices, and other technologies that will accurately identify people at risk for the disease in asymptomatic populations. The prognostic capabilities and values of these technologies for early and accurate detection need to be validated in longitudinal prospective studies with very large numbers of well-diversified populations (see discussion on research resources).

1.1.3. Novel research paradigms

The emerging knowledge regarding the heterogeneity, polygenic etiologies, and the prolonged degenerative process of the condition will require the adoption of new and different research paradigms that will require allocation or significant expansion of resources for the field to shift toward the framework of systems biology. The complexity of the disease due to the polygenic nature of its etiology will also require the infusion of concepts from computational biology and the development of computational capabilities for simulation or *in silico* modeling.

1.2. Infrastructure/research resources

The second major category of challenge for the national plan is the requirement for expansion of R&D capabilities in planning and building new shared research resources. Such national "core facilities" can be readily built on existing infrastructure within academia/industry/government and/or by expanding ongoing research networks that already

have well-established data-sharing and data-harmonization programs.

The National Institutes of Health (NIH) has used the concept of core facility as a shared research resource for some time as an inherent part of various funding mechanism to support collaborative multi-investigator or multicenter research programs. The utility of these resources in facilitating research in cost-effective manner has been well vetted. Now, the strategic goals of the national plan to accelerate therapy development will require systematic expansion of national R&D infrastructure, as part of research capacity building initiative, by funding the creation or construction of a series of national core facilities for shared research resources. High-priority core facilities include

1. National Database for Longitudinal Studies of Healthy Aging and Dementia
2. Assays, analytical methods, and instrumentation
3. Models of the disease and modeling systems, including In Silico simulation
4. Computational biology—data analysis
5. Drug design validation testing

1.3. Financial

The implementation proposed under "milestones," that is, the strategic goal of the national plan, would require an unprecedented level of financial commitment from both the public and private sectors. There is an urgent need to explore new or alternative models for financing the new initiatives/milestones outlined in this document, for example, public-private R&D investment partnerships.

Scarcity of funds to promote the exploration of new and potentially good ideas is a major limiting factor for the prospects of discovering disease-modifying therapies. Research funds are not available to begin new initiatives; often "high-risk, high-reward projects" are at greater risk of being passed over. This is particularly important when it is essential to attract new investigators or expertise from other fields to explore new therapeutic targets. Today, even the very small number of proposals with exceptional scientific merit fortunate enough to be funded routinely experience sever budgets. In the end, scientifically meritorious projects often are forced to limit the scope of the work or abandon valuable avenues of exploration because of the lack of dollars. Thus, many investigators are seriously constrained by the lack of easy access to essential resources.

The success of a prevention initiative hinges on an unwavering national commitment to allocate appropriate levels of funding during the next decade. The national plan should target significant and systematic increases in funds to be allocated for capacity building and/or expansion of national R&D enterprises devoted toward the goal of prevention. A sustained investment of $2.0 billion per year in new funds over current expenditures for the next 10 years will be required. This recommendation is based on the premise that substantially increased funding and investment in brain research is the only cost-effective means to address a pending health care crisis brought on by the exponential increase in the prevalence of neurodegenerative disorders and the ever-increasing life span.

1.4. Administrative

Presently, no single entity possesses all the necessary resources, including scientific-technical knowledge or administrative capabilities to implement fully the decade-long strategic objective of the national plan—the prevention of Alzheimer's disease. Thus, it is imperative for the national plan, through administrative or regulatory actions, to create an environment that will facilitate forging strategic alliances to expand the role of industry. There is a need for exploration of alternative options/models through government-industry-academia collaborations, building on or expansion of some current successful paradigms (e.g., Alzheimer's Disease Neuroimaging Initiative or others) for such collaborative R&D endeavors. The proposed model should adopt novel grants/contracts management policies and procedures (re: administrative-financial aspects of agreements) that encourage the establishment of multiple "collaborative R&D agreements (CRDA)" by creating incentives for all stakeholders (e.g., government, academia, industry, nongovernmental organizations) to form such public-private partnerships. The new paradigm for such collaborative public-private R&D initiatives must focus on eliminating organizational, administrative, and legal barriers by reengineering the structures and the processes for R&D across the full spectrum of activities from early discovery to clinical validation of interventions. The ideal model for such "agreements" must offer reasonable and fair financial incentives to industry partners both to expand their

1. Internal R&D on new treatments that focus on the national plan's 10-year objective of developing interventions to delay or prevent the onset of disease and
2. Collaborations with academic and government research on these projects.

Along with new models of CRDA, another important challenge for advancing the strategic mission of the national plan is the need to reengineer current administrative structures for funding R&D projects. The present "research support systems" needs to be modernized and streamlined to function more effectively. Often, the most important breakthrough ideas in science come from unconventional thinkers, yet the present prevailing model of research support systems cannot meet the needs of rapidly evolving dynamic fields of research. The traditional peer-review processes, that is, procedures for identifying cutting edge ideas, creative investigators, and new scientific opportunities, are inadequate, and present decision-making systems frequently fail to

accommodate risk taking on truly imaginative ideas. There is a need to replace the current traditional approaches for merit evaluations with a streamlined system which can (1) provide rapid decision making, (2) be flexible to handle unexpected opportunities or potential breakthrough ideas, and (3) allow greater risk taking on projects with longer-term public health goals.

1.5. Regulatory

As the field of therapy development moves from conventional paradigms of testing symptomatic treatments toward disease modification in earlier preclinical stages of the disease, there will be a need to reevaluate our regulatory requirements for assessing efficacy of putative interventions for prevention. Current criteria or definitions of clinical outcomes in asymptomatic people may need to be revised. The development and validation of new interventions for prevention requires different paradigms for determining efficacy of treatment. These approaches may involve not only the traditional clinical trial strategies of developing symptomatic treatments but also other approaches such as those of public health and prevention strategies.

Systematic research on the neurobiology of aging and Alzheimer's disease, as distinct areas of investigations within the much broader fields of neuroscience, neurology, and psychiatry, began as national programs to promote the development of scientific knowledge on brain aging and dementia in 1978 at the National Institute on Aging (NIA)/NIH. In a relatively short span of three decades, remarkable progress was made in advancing the understanding of the neurobiological underpinnings of these brain phenomena, moving these areas of brain research from near obscurity to the forefront of neuroscience as "hot topics" [7].

An objective scrutiny of total national expenditures (i.e., analysis of "cost vs. return on investment") during the last three decades for brain aging research will indicate a very profitable payoff, thus, the credible justification for a substantial expansion of sustained investment of national resources. The first "call to arms" to mobilize national resources and capabilities to address the looming public health crisis was made in 1992 by NIA [8]. Now, after nearly a quarter of a century since the plea for action, the scientific community is well poised to make a quantum advance toward the strategic objectives of the National Plan To Address Alzheimer's Disease.

Two decades ago in a Congressional Testimony on the "Prospects of Prevention" [9], Alzheimer's Association argued for a radical shift in therapy development toward a strategy of "prevention." Now, it is widely recognized that current symptomatic treatments are woefully inadequate. Earlier calls for adoption of alternative paradigms to focus for therapies toward prevention were considered untenable goals; today, there is an overwhelming optimism in the field for prospects of developing disease-modifying intervention to delay the onset of disabling symptoms and eventually to prevent [2,10].

The consensus view is that disease-modifying interventions are technically feasible; however, this optimism is conditional to surmounting the challenges outlined in this document regarding the array of barriers to progress in the domains of science resources/infrastructure, regulatory, administrative, and financial. Thus, the present ALZ-WG recommendations for action via the National Plan To Address Alzheimer's Disease and parallel efforts by OECD/G-8 Dementia Summit reflect the global concerns and international efforts to formulate strategies to surmount these challenges [2,4,6,10,11].

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