

Policy Forum

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

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With increasing numbers of people with Alzheimer's and other dementias across the globe, many countries have developed national plans to deal with the resulting challenges. In the United States, the National Alzheimer's Project Act, signed into law in 2011, required the creation of such a plan with annual updates thereafter. Pursuant to this, the US Department of Health and Human Services (HHS) released the National Plan to Address Alzheimer's Disease in 2012, including an ambitious research goal of preventing and effectively treating Alzheimer's disease by 2025. To guide investments, activities, and the measurement of progress toward achieving this 2025 goal, in its first annual plan update (2013) HHS also incorporated into the plan a set of short, medium and long-term milestones. HHS further committed to updating these milestones on an ongoing basis to account for progress and setbacks, and emerging opportunities and obstacles. To assist HHS as it updates these milestones, the Alzheimer's Association convened a National Plan Milestone Workgroup consisting of scientific experts representing all areas of Alzheimer's and dementia research. The workgroup evaluated each milestone and made recommendations to ensure that they collectively constitute an adequate work plan for reaching the goal of preventing and effectively treating Alzheimer's by 2025. This report presents these Workgroup recommendations.

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**Keywords:**

Policy; National Plan to Address Alzheimer's Disease; Milestones

**1. Introduction**

Although significant advances have been made over the past 30 years in understanding the neurobiology of Alzheimer's disease (AD) and other chronic neurodegenerative disorders, a worldwide public health crisis continues to grow due to the aging of the world's population and the lack of effective interventions. In the United States, more than five million people currently live with Alzheimer's, including one in nine people greater than the age of 65 years [1]. The number of Americans with AD is expected to increase dramatically as the baby boom generation ages.

The cost of this crisis, both personal and societal, is enormous. In 2014, Medicare and Medicaid are projected to pay \$150 billion for the health care and long-term care of people with Alzheimer's and other dementias [1]. During the same period, out-of-pocket expenses are expected to reach \$36 billion. The total health and long-term care costs across all payers for seniors with Alzheimer's and other dementias (\$46,669 annually) are more than three times greater than for other seniors. In addition, more than 15 million Americans provide 17.7 billion hours of unpaid care giving for people with Alzheimer's and other dementias, work that is valued at \$220 billion [1]. Of course, Alzheimer's is ultimately a fatal disease. In 2014, an estimated 700,000 Americans will die with Alzheimer's [2]. The magnitude of this growing crisis demands a commensurate response.

Many countries, and international organizations, have developed national plans and analytical reports to address the problem [3–5]. In the United States, the National Alzheimer's Project Act (NAPA) was signed into law in 2011, calling for the development of a comprehensive plan to fight AD. This plan, the National Plan to Address Alzheimer's Disease (henceforth called “the National Plan”), was developed by the Department of Health and Human Services (HHS) with input from experts in aging and dementia and presented in May 2012 at the Alzheimer's Research Summit 2012: Path to Treatment and Prevention [6]. The National Plan outlined a set of initiatives to provide improved tools for clinicians, assist caregivers, and individuals with dementia, raise public awareness about the disease, and critically, to advance research. It also set an aggressive research goal to “Prevent and Effectively Treat Alzheimer's Disease by 2025.” To achieve this goal, the following strategies were set:

- Identify research priorities and milestones;
- Expand research aimed at preventing and treating AD;
- Accelerate efforts to identify early and presymptomatic stages of AD;
- Coordinate research with international public and private entities;
- Facilitate the translation of findings into medical practice and public health programs.

Table 1

Current milestones and their associated success criteria and timelines, as published by HHS and last updated in summer 2013 (available at: <http://aspe.hhs.gov/daltcp/napa/milestones/milestones-p.pdf>), along with the new milestones and changes to existing milestones recommended by the expert workgroup

Milestone	Success criteria/timeline	Suggested changes/notes
<b>A:</b> Convene an advisory meeting of experts from the pharmaceutical industry, government, academia, the FDA, and the nonprofit sector to advance rational drug repositioning and combination therapy based on translational bioinformatics and network pharmacology approaches and to explore opportunities for new public-private partnerships to facilitate drug rescue/repurposing and combination therapy.	(1) Development of recommendations for rational repositioning and combination therapy development, (2) Development, negotiation, and implementation of appropriate agreements among the stakeholders involved in repositioning and combination therapy of drugs for Alzheimer's disease (AD). These agreements should address legal issues, intellectual property rights, and liability to expedite rigorous clinical testing of repurposed drugs. <i>Timeline:</i> 1 yr; 2014	Extend the time frame and scope of the advisory committee, and expand representation of industry scientists.
<b>B:</b> Initiate research programs for translational bioinformatics and network pharmacology to support rational drug repositioning and combination therapy from discovery through clinical development.	Identification of at least 6 existing drugs suitable for repurposing and/or combination therapy for AD prevention or treatment. The drugs selected for repurposing or combination therapy will be prioritized based on: (1) Evidence that they modulate disease relevant pathways/networks gained from computational and empirical approaches. (2) Preclinical proof-of-efficacy in a relevant model system. (3) Availability of biomarkers to monitor target engagement in humans. (4) Sufficient evidence of safety for the intended target population. <i>Timeline:</i> 3–5 yrs; 2015–2019	Expand to include research on the basic science underlying combination therapy.
<b>C:</b> Initiate early clinical development for at least 6 existing drugs or drug combinations for the treatment or prevention of AD.	Completion of at least four Phase II trials with repurposed drugs and/or drug combinations. Successful trials will provide conclusive evidence of therapeutic mechanism/target engagement. <i>Timeline:</i> 2–4 yrs; 2018–2021	Note: Contingent on successful completion of Milestones A and B; therefore unable to address feasibility at this time.
<b>D:</b> Initiate at least three Phase III trials with repurposed drugs or drug combinations. Of these at least one trial will be in an asymptomatic at-risk population and at least one for individuals with advanced disease. Of the trials initiated in patients with advanced disease, at least one trial will target the neuropsychiatric symptoms of AD.	Comprehensive success/failure analyses of data from at least three Phase III trials. <i>Timeline:</i> 3–5 yrs; 2020–2024	Note: Contingent on successful completion of Milestones A and B; therefore unable to address feasibility at this time.
<b>E:</b> Initiate Phase II (proof of concept) drug trials for agents against three to six currently known therapeutic targets. Of these at least two will be for targets involved in asymptomatic stages of disease. These trials will be designed to provide or confirm proof of mechanism and/or evidence of target engagement for the therapeutic agent being tested.	Completion of three to six Phase II drug trials for agents against currently known targets, providing conclusive evidence of therapeutic mechanism/target engagement. <i>Timeline:</i> 2–4 yrs; 2015–2018	Revise the milestone to reflect a number of Phase II drug trials that will need to be initiated to achieve completion of three to six trials that show evidence of therapeutic mechanism/target engagement. Delete the requirement that trials will be for targets involved in asymptomatic disease (see note).
<b>F:</b> Initiate Phase III drug trials for agents against at least three currently known therapeutic targets. Of these at least one trial will be asymptomatic, at risk populations. These trials will incorporate a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes and include collection of DNA and other biosamples for interrogation of responsiveness.	Comprehensive success/failure analysis of data from at least three Phase III trials. <i>Timeline:</i> 3–5 yrs; 2017–2021	Revise the milestone to reflect a number of Phase III drug trials that will need to be initiated to maximize the likelihood of a successful trial. Add wording to the effect that at least one trial will be of a symptomatic therapy. Note: Public-private partnerships, similar to those created for ongoing predementia trials (e.g., DIAN-TU, API, A4) will be needed to achieve this milestone.

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Milestone	Success criteria/timeline	Suggested changes/notes
<b>G:</b> Establish a searchable, open access research database that contains all clinical, biomarker, and epidemiological data, and related genotypes and phenotypes from existing genetic studies; analyze these data to identify regions of the genome that are targets for AD therapeutics.	At least one novel target, pathway or therapeutic approach identified through use of the database. <b>Timeline:</b> 4–5 yrs; 2013–2017	Expand the analysis of data beyond identifying genomic regions (to include, for example, epigenetic data), and expand the success criteria to 12 rather than one novel target identified.
<b>H:</b> Establish a consortium of genetics and genomics experts to develop and execute a large scale sequencing project to analyze the genomes of a large number of well characterized individuals including multiethnic subjects using next generation sequencing approaches; identify a broad range of AD risk and protective gene variants in subjects with late onset AD (LOAD).	Identification of new risk and protective alleles for LOAD that lead to the identification of at least one novel therapeutic approach, drug target or pathway for prevention. <b>Timeline:</b> 5–8 yrs; 2013–2020	
<b>New:</b> Develop a uniform protocol for collecting, storing, and providing open access to biospecimens for use in genetics, proteomics, and other biomarker studies.		
<b>I:</b> Identify, characterize, and complete early validation for at least six novel therapeutic targets for AD (a minimum of three targets for presymptomatic and early stage disease and a minimum of three for advanced disease).	Validation based on availability of the following for each novel target: a systems-level understanding of the gene, protein and metabolic networks within which they operate, one or more cell based/animal models that are freely available to the research community, a quantitative assessment of the integrative response to the modulation of the target in one or more model organisms, and identification of pharmacodynamic biomarker(s) for target engagement. <b>Timeline:</b> 5–7 yrs; 2014–2020	Expand the number of novel therapeutic targets to be identified, characterized, and validated to 60 NMEs covering six new classes of targets (e.g., inflammation, tau, etc.) Note: Past history shows that only a fraction of NMEs make it from preclinical stage to Phase III trials; therefore, a much larger number of NMEs need to be identified. Moreover, novel targets need to be identified across many pathways and mechanisms.
<b>J:</b> Initiate drug discovery efforts to develop novel therapeutic agents against at least six novel therapeutic targets (a minimum of three targets for presymptomatic and early stage disease and a minimum of three for advanced disease).	Complete preclinical development, through IND filing, of therapeutics agents against at least 3 novel targets. <b>Timeline:</b> 5–7 yrs; 2017–2023	Expand the number of therapeutic agents developed to 30.
<b>K:</b> Initiate Phase II (proof of concept) drug trials for agents against three to six novel therapeutic targets. These trials will provide proof of mechanism and/or evidence of target engagement of the target being tested.	Completion of three to six Phase II drug trials for agents against novel targets, providing conclusive evidence of therapeutic mechanism/target engagement. <b>Timeline:</b> 2–4 yrs; 2020–2023	Expand the number of agents advanced to Phase II trials to at least 12.
<b>L:</b> Initiate Phase III drug trials for agents against at least three novel therapeutic targets. These trials will incorporate a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes and include the collection of DNA and other biosamples for the interrogation of responsiveness.	Comprehensive success/failure analysis of data from at least 3 Phase III trials. <b>Timeline:</b> 3–5 yrs; 2022–2026	Ensure that at least one of the agents tested in a Phase III study is for a symptomatic indication.
<b>New:</b> Enlist an unbiased, independent, nonprofit entity to conduct an annual review of clinical trial efficiencies.		
<b>New:</b> Convene a working group to consider novel trial designs including adaptive trials.		

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Milestone	Success criteria/timeline	Suggested changes/notes
<b>M:</b> Convene an advisory meeting to delineate an interdisciplinary research agenda focused on: (1) advancing nonpharmacological interventions for the cognitive and behavioral symptoms of AD by nonpharmacological treatments, (2) informing the design of therapeutic approaches combining pharmacological and nonpharmacological treatments and (3) identification of best practices for implementation of non-pharmacological interventions.	Recommendations developed for advancing non-pharmacological interventions for AD treatment and prevention to enable successful implementation of effective nonpharmacological interventions. <b>Timeline:</b> 1 yr; 2014	Revise wording to include not only cognitive and behavioral symptoms, but also functional and psychological symptoms of AD; and to develop best practices across the continuum of the disease, in different settings, and in the presence of comorbid conditions.
<b>N:</b> Convene an advisory meeting to inform the design of therapeutic approaches combining pharmacological and nonpharmacological treatments.	Recommendations developed for the design of clinical trials combining pharmacological and nonpharmacological interventions. <b>Timeline:</b> 1 yr; 2015	Revise wording to include a range of treatment targets (medical, psychosocial, behavioral, environmental, and caregiver training) for the behavioral, psychological, cognitive, and functional symptoms of AD.
<b>O:</b> Initiate interdisciplinary research programs that integrate epidemiological and mechanistic research including cutting edge systems biology approaches to gain an in depth understanding of the mechanisms by which various nonpharmacological interventions impact brain health and the course of AD.	Identification of at least three new therapeutic targets for neuroprotection based on knowledge of mechanisms mediating the impact of nonpharmacological interventions of brain health in aging and AD. Preclinical proof-of-concept for at least 3 types of nonpharmacological interventions that can inform clinical trial design. <b>Timeline:</b> 5 yrs; 2016–2020	Include clinical research and biomarker studies in the integrated interdisciplinary research programs; and in the goals of the research, add developing a theoretical rationale for mechanisms by which interventions impact brain health and the course of disease.
<b>P:</b> Initiate clinical trials for at least three nonpharmacological interventions aimed at AD prevention. Of these at least one trial will be a pivotal, Phase III trial.	Completion of at least two Phase II trials for nonpharmacological interventions aimed at AD prevention. Successful trials will provide conclusive evidence of therapeutic mechanism. Comprehensive success/failure analysis of data from at least one Phase III trial. <b>Timeline:</b> 4–5 yrs; 2017–2021	Include biomarker studies in clinical trials.
<b>Q:</b> Initiate clinical trials for at least three interventions combining pharmacological and nonpharmacological interventions for AD treatment or prevention. Of these at least one trial will be a pivotal, Phase III trial.	At least two Phase II trials completed for interventions combining pharmacological and non-pharmacological interventions for AD treatment or prevention with conclusive evidence of therapeutic mechanism. Comprehensive success/failure analysis of data from at least one Phase III trial. <b>Timeline:</b> 4–5 yrs; 2019–2023/	Include biomarker studies in clinical trials.
<b>R:</b> Review results of past and existing grants to develop technologies that promote prevention and treatment trials. Assess areas where technologies have been adopted, where there are promising results that should be followed up, and where there are remaining needs.	At least two new technologies are developed, prove useful in formal or informal care, and are widely adopted. <b>Timeline:</b> For first: 1 yr; 2015	In description of technologies to be reviewed, include those with therapeutic potential (e.g., technologies used for cognitive training, promoting or supporting physical activity, or those used as part of a reminiscence, art, or music therapy program.
<b>New:</b> Initiate research programs (R01), Small Business Innovative Research (SBIR), or Small Business Technology Transfer (STTR) focused on developing and testing new technologies or modifying and testing existing technologies to support the development of nonpharmacologic therapies (e.g., cognitive training, exercise technologies, etc.).	At least two new technologies are developed, prove useful in the development of nonpharmacologic therapies, and are widely adopted.	

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Milestone	Success criteria/timeline	Suggested changes/notes
<b>S:</b> Initiate synthesis and testing of novel PET ligands and develop and test novel CSF/blood biomarkers for assessment of disease related pathological burdens such as tau, inflammation, synaptic dysfunction.	Development and testing of three to five novel PET ligands and/or CSF/blood biomarkers for assessment of AD pathology. <b>Timeline:</b> 5 yrs; 2014–2018	
<b>T:</b> Initiate development of imaging and/or fluid biomarkers to demonstrate target engagement for 5 novel therapeutic targets for AD.	Identification of 3 imaging and/or fluid biomarkers for which there is proof of engagement of novel therapeutic targets. <b>Timeline:</b> 5 yrs; 2014–2018	
<b>U:</b> Incorporate imaging and/or fluid biomarkers into Phase II (proof of concept) drug trials to provide proof of mechanism and/or evidence of target engagement as trials for three to six existing and three to six novel therapeutic targets are initiated	Initiation and completion of 5 Phase II (proof of concept) drug trials using imaging and/or fluid biomarkers for proof of target engagement. <b>Timeline:</b> 3–5 yrs; 2017–2021	
<b>V:</b> Incorporate imaging and/or fluid biomarkers into Phase III (pivotal) drug trials to select subjects and/or provide evidence of target engagement as trials for three to six existing and three to six novel therapeutic targets are initiated.	Initiation of three Phase III (pivotal) drug trials using imaging and/or fluid biomarkers to select at risk subjects and/or for proof of target engagement. <b>Timeline:</b> 3–5 yrs; 2019–2023	
<b>W:</b> Biomarkers usable in community studies. Initiate studies to develop minimally invasive biomarkers for detection of cerebral amyloidosis and other AD pathophysiology.	Development and testing of five biomarkers that utilize biofluids or other minimally invasive imaging, electrophysiological recording, or other methodologies to assess the burden of AD pathophysiology that could be used in community based and epidemiological studies of AD. <b>Timeline:</b> 5 yrs; 2015–2019	Biomarkers should not only be minimally invasive but also portable and inexpensive to enable large studies in diverse populations.
<b>X:</b> Linking peripheral and central biomarkers Initiate studies to link peripheral blood-based biomarkers and central imaging and CSF biomarkers.	Identification of three peripheral blood-based biomarkers that have a high correlation with central imaging and/or CSF biomarkers. <b>Timeline:</b> 5 yrs; 2016–2020	Expand the success criteria to call for identifying five peripheral blood-based biomarkers that correlate with central (imaging or CSF) biomarkers. Note: Three may be insufficient to detect both cerebral amyloidosis and neurodegeneration, inflammation, and other pathologies.
<b>Y:</b> Launch research programs to develop and validate sensitive neuropsychological assessment measures to detect and track the earliest clinical manifestations of AD.	Development of at least one sensitive neuropsychological assessment measure that has been validated for the detection or tracking of the earliest clinical manifestations of AD. <b>Timeline:</b> 5 yrs; 2014–2018	Split or expand milestone and associated success criteria to differentiate neuropsychological assessment measures used for screening/enrichment vs. those used to assess treatment response.
<b>Z:</b> Biomarker standardization develop and test methods for the standardization of immunoassays and mass-spectrometry/single reaction monitoring assay or other methodologies for CSF amyloid beta (A $\beta$ ) and tau and other biomarkers as they become clinically applicable. Develop and test methods for standardization of collection and analysis of MRI and PET neuroimaging data.	CLIA laboratory qualification in US and the equivalent certification in the EU for at least one CSF biomarker of disease pathology. For neuroimaging data, qualification of at least one biomarker for use in clinical trials by the FDA and/or the EMA. <b>Timeline:</b> 5 yrs; 2014–2018	
<b>New:</b> Validate minimally invasive biomarkers in community studies.		

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Milestone	Success criteria/timeline	Suggested changes/notes
<b>New:</b> Expand existing incentives for commercialization (e.g., expanding the funding for SBIR/STTR grants by at least 100%), providing tax credits, and exploring new ways to make commercial/capital investment more accessible for companies wishing to compete in the highly regulated marketplace of medical devices.		
<b>New:</b> Establish a public-private partnership to develop mechanisms that will enable data sharing and protection or sharing of intellectual property among drug and biomarker developers.		
<b>New:</b> Convene a conference/expo that brings together researchers and companies developing technologies to capture and analyze everyday performance measures with clinical investigators. The goal of this conference would be to 1) enable cross-silo discussions that would promote collaborations across the various stakeholders groups, 2) explore challenges that need to be addressed to make best use of these new technologies, including privacy concerns, establishing validity, and aggregating and analyzing data.		
<b>New:</b> Establish criteria for publishing cognitive data to enable aggregation of data in real time to enable comparison across studies.		
<b>AA:</b> Establish an expert panel of epidemiologists and clinical trialists to make recommendations for best practices in the use of existing epidemiology of dementia databases to individualize treatments in clinical trials for AD in heterogeneous populations.	Clinical trialists and epidemiologists implement best practices and work together in the design of clinical trials for AD. <b>Timeline:</b> 1 yr; 2014	Extend the time frame of the expert panel and modify the focus to “for prevention of cognitive impairment and dementia” rather than “in clinical trials for AD...” Expand the scope of the panel’s work to include determination of the best targets for prevention and the time in the lifespan when prevention trials make the most sense.
<b>AB:</b> Initiate expansion of epidemiology of dementia cohorts to include subjects in midlife and use data generated to inform clinical trial design.	Three or more active cohorts that cover age range from midlife to late-life as a study population for investigating and reporting findings on changing risk profiles from younger to older ages. <b>Timeline:</b> 5–7 yrs; 2014–2020	Expand the cohorts to include subjects from heterogeneous populations across the life-course, beginning earlier than mid-life, and expand the research on these cohorts to include investigations of early exposures, genetics, cumulative risk exposures, epigenetics, and modifiable risk factors. Note: Timeline for these studies must extend beyond 5 yrs; therefore it will be essential to identify sustaining funding mechanisms.
<b>New:</b> Establish a working group to harmonize data collection across epidemiologic studies so that data can be combined and compared.		
<b>New:</b> Fund a multidomain prevention trial in the United States focused on modifiable risk factors.		

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Milestone	Success criteria/timeline	Suggested changes/notes
<b>AC:</b> Develop a common AD research ontology, as a unified classification system for comparative analysis of research portfolios, and strategic planning, and create a publicly available database that will house the AD research portfolios from AD funding agencies in the US and abroad.	Recruitment of all federal and nonfederal funding agencies in the US and AD funding agencies from countries that have an AD National Plan to participate in this database. <b>Timeline:</b> 2–3 yrs; 2013–2014	Extend the timeline because both CADRO and IADRP will need continuous revisions. Include the development of tools that enable funders to track and analyze their research investments.
<b>AD:</b> Convene an advisory meeting focused on facilitating public-private partnerships aimed at accelerating the development and test of effective therapies for AD treatment and prevention.	Established working groups on: (1) rapid data sharing and analysis, (2) enabling bidirectional translation in AD drug development, (3) eliminating intellectual property (IP) barriers for target validation through clinical proof of concept. <b>Timeline:</b> 1 yr; 2013	Continue support for this process to promote additional dialog and effort with the goal of developing an action plan with concrete steps.
<b>AE:</b> Convene meetings of the working groups for (1) rapid data sharing and Analysis, (2) enabling bidirectional translation in AD drug development, (3) eliminating IP barriers for target validation through clinical proof of concept. Each working group will formulate concrete steps needed to accelerate the time frame of AD drug development.	Recommendations developed on (1) the creation of an open access, web based resource that integrates complete, diverse multidimensional biological and chemical data that will be useful in advancing information on drug targets, including mechanistic information that will aid in the development of measures of target engagement (PD readouts); (2) creation of computational tools for development of biological network models of AD and normal aging; (3) creation of tools that will foster development of bio network models that provide a predictive framework for using drugs in combination or singly (4) removing legal and IP barriers surrounding data sharing. One or more partnerships established to accelerate key steps in AD drug development. <b>Timeline:</b> 1 yr; 2014	
<b>AF:</b> Create a network of translational centers that bring together expertise and technology needed for integration of multimodal data analysis, mathematical modeling and empirical testing and apply a systems biology/systems pharmacology approach to the most challenging aspects in preclinical therapy development such as: (1) therapeutic target selection and initial target validation, (2) predictive toxicology, (3) rigorous preclinical efficacy testing and development of translatable, preclinical biomarkers. The centers will provide training programs for the new generation of translational scientists.	Creation of at least three Translational Centers that will apply the principles of quantitative and systems pharmacology to AD drug development. <b>Timeline:</b> 3–5 yrs; 2014–2018	Revise the success criteria to include expansion of the ADCs program with funding for three demonstration projects to develop Comprehensive ADCs (CADCs).
<b>AG:</b> Establish an National Institutes of Health (NIH) working group to develop an expedited review track for translational AD research applications (from target identification/validation drug discovery through Phase III clinical trials).	New NIH policy in place for fast tracking of AD translational research application. <b>Timeline:</b> 1 yr; 2015	
<b>New:</b> Convene a workgroup to interact with the NIH to ensure that the NIH policy on expedited review includes and achieves specific timeline targets.		

(Continued)



Table 1

Current milestones and their associated success criteria and timelines, as published by HHS and last updated in summer 2013 (available at: <http://aspe.hhs.gov/daltcp/napa/milestones/milestones-p.pdf>), along with the new milestones and changes to existing milestones recommended by the expert workgroup (Continued)

Milestone	Success criteria/timeline	Suggested changes/notes
<b>New:</b> Mandate additional NIH funding to support five translational Alzheimer's projects per year.		
<b>AH:</b> Create a national IRB.	Initiation of at least one multicenter clinical trial that utilizes a national IRB. <b>Timeline:</b> 2 yrs; 2014–2015	
<b>New:</b> Convene a national symposium on the centralized IRB process, with representation from universities and other research institutions, government, industry, and philanthropic organizations, to 1) increase awareness and address potential concerns of research institutions, and 2) coordinate appropriate seed funding to launch the national IRB.		
<b>AI:</b> Establish a working group to identify standard outcome measures necessary for data comparisons across a variety of clinical studies.	Identification of at least two standard outcome measures for data comparison in clinical research. <b>Timeline:</b> 1 yr; 2014	Merge Milestones AI and AJ as follows: Standardize clinical trial outcome measures to facilitate comparisons across trials and thereby increase the efficiency and success of trials by (1) establishing a forum for open sharing of data, procedures, and analysis of outcome measures; (2) initiating validation studies across different stages of disease (preclinical, mild cognitive impairment, dementia) that incorporate a variety of outcome measures, with agreement to share data and data analyses; and (3) developing the infrastructure to incorporate selected outcome measures into therapeutic trials.
<b>AJ:</b> Initiate three to four clinical research studies using common standard outcome measures.	Data comparisons conducted from clinical studies using common standard outcome measures. <b>Timeline:</b> 3–5 yrs; 2014–2018	
<b>New:</b> Convene a working group that will work with global partners to develop a strategy for sharing and harmonizing data across borders.		
<b>AK:</b> Increase knowledge among research scientists of best practices for recruitment and retention of research participants.	Central resources for both references and tools, including videos and presentation materials created and available. <b>Timeline:</b> 2 yrs; 2014–2015	
<b>AL:</b> Establish a working group including clinical trial recruitment experts to dynamically evaluate and update the materials and information provided in the central resource.	Recommendations for successful recruitment methods. <b>Timeline:</b> 1 yr; 2014	
<b>AM:</b> Increase awareness of large-scale registries that encompass the spectrum of the disease from healthy to at-risk asymptomatic to symptomatic individuals from early midlife to late life willing to participate in clinical research aimed at AD prevention and treatment.	A central repository of AD related registries and cohorts created and publicized. <b>Timeline:</b> 2 yrs; 2014–2015	Success criteria should include development of tailored awareness campaigns for different population groups about the purpose of registries and the importance of participation.
<b>AN:</b> Increase the rate of enrollment for AD clinical trials and increase the participation of underrepresented populations.	Increased rates of enrollment and inclusion of underrepresented populations for AD clinical trials as evaluated using the existing NIH system for NIH funded clinical research. <b>Timeline:</b> 5 yrs; 2014–2018	Success criteria should include establishment of a national health promotion campaign, and regional campaigns to increase awareness and participation of the African American and Latino communities.
<b>New:</b> Establish and fund multiple training awards (e.g., K awards), fellowships, and R01s in the neuropathology and molecular biology of aging over the next 5 yrs.		

(Continued)

Table 1

Current milestones and their associated success criteria and timelines, as published by HHS and last updated in summer 2013 (available at: <http://aspe.hhs.gov/daltcp/napa/milestones/milestones-p.pdf>), along with the new milestones and changes to existing milestones recommended by the expert workgroup (Continued)

Milestone	Success criteria/timeline	Suggested changes/notes
<b>New:</b> Fund a substantial research program on the basic biology of aging, to include studies of vulnerabilities in the aging brain, vasculature changes and endothelial failure, neural networks, and the biological underpinnings of “superaging.”		
<b>New:</b> Dramatically increase activity and resources applied to understanding the basic cellular and molecular biology of Alzheimer’s disease, including how these processes interact with aging.		
<b>New:</b> Convene a working group/think tank to reexamine conceptual models of disease beyond amyloid.		
<b>New:</b> Define a path to validate at least one biomarker capable of predicting clinical outcome and meet conditions for an accelerated approval pathway by 2016; and define a path to achieve regulatory acceptance of this marker as a surrogate marker.		
<b>New:</b> Regulatory “qualification” of three or more markers of disease progression for application to stratification of subjects in clinical trials by 2017.		
<b>New:</b> Regulatory “white paper” or other communication, short of guidelines, giving sense of regulators to establish appropriate principles as to degree (especially duration and sample size) of safety data before allowing years of treatment of a potentially disease preventing compound.		
<b>New:</b> NIH/NIA/AA and other groups jointly convene a workshop or summit to lay the groundwork for creating a precompetitive consortium of industry partners aimed at de-risking novel targets through the proof of concept stage by sharing data and research tools. Timeline: 1 yr.		
<b>New:</b> Create a consortium of industry scientists to systematically assess, stack rank, and prioritize existing targets and conduct medicinal chemistry studies to optimize compounds that engage these targets.		
<b>New:</b> Direct HHS to convene summit of FDA, industry lawyers, and advocacy groups to devise incentives that would facilitate data and resource sharing, and find solutions to issues related to exclusivity.		

Abbreviations: DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; API, the Alzheimer’s Prevention Initiative; A4, autosomal dominant Alzheimer’s Disease trial, the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Study; NME, new medical entities.

Pursuant to the first strategy, HHS approved a set of interim milestones to provide a roadmap toward achieving the research goal of the National Plan.

NAPA established an Advisory Council, comprising both federal and nonfederal members, to help shape the National Plan and regularly review and monitor implementation of the Plan. Supplementing the work of the Council, the Alzheimer's Association established an expert workgroup to provide an independent and comprehensive analytical report on progress in the research arena and craft a scientific agenda to inform the Council's recommendations. In August, 2012, the workgroup published a goal-directed, 10-year scientific agenda intended to aid in the implementation of the National Plan [7].

Notably, neither NAPA nor the National Plan mandate the appropriation of funds to achieve the stated goals. To address the funding required to ensure the success of the research plan, the Alzheimer's Accountability Act of 2014 was introduced in Congress on April 1, 2014, and would require the Director of the National Institutes of Health (NIH) to submit an annual budget to the President and to Congress stipulating the funds that are needed to achieve the research goal of the National Plan.

In June 2014, the Alzheimer's Association convened an expert workgroup (the Alzheimer's Association National Plan Milestone Workgroup) to re-evaluate the milestones set forth in the National Plan, determine whether the field is on track to achieve these milestones, recommend changes in the parameters of the milestones, identify unaddressed gaps, and recommend additional milestones to fill these gaps. The workgroup consisted of world-renowned experts in AD research and policy. This report from the expert workgroup should inform HHS and Congress in making decisions about the activities and resources that are needed now to achieve the National Plan research goal of preventing and effectively treating AD by 2025, which is a scant decade away.

The premise of this report is that despite significant challenges associated with AD research, the scientific community remains more optimistic than ever about the potential success of a focused National Plan, if the appropriate milestones are established and if the appropriate resources are dedicated to carry out the strategies set forth therein. Many prominent investigators believe the prospect of delaying the onset of disabling symptoms within a decade is an attainable goal, provided we can surmount several scientific, administrative, and most importantly, financial impediments. Although the scientific community and the National Plan agree that major changes are needed in areas such as novel conceptual models of the disease, and new strategies for addressing scientific, administrative, regulatory, and infrastructural obstacles, the fact remains that overcoming these challenges will require a substantial financial investment. Inadequate funding remains the single most important impediment to progress in achieving the research goal of the National Plan.

**Table 1** summarizes the key milestones proposed by the Advisory Council, their success criteria, and the projected time frame for achieving each milestone. It also includes the revisions recommended by the expert workgroup, both to existing milestones and suggested new milestones. The existing milestones have been assigned identifiers (A, B, C, etc.) for the ease of reference in this document.

## 2. Targets, interventions, and biomarkers

Milestones A through Z address issues related to drug development for both currently known and new targets, repurposing and combination therapy, nonpharmacologic interventions, and biomarkers.

### 2.1. Development of targets and interventions

#### 2.1.1. Drug development: Repurposing and combinations

Milestones A through D focus on two aspects of therapy development: repurposing existing drugs for new indications, and combining two or more agents to achieve additive or synergistic effects. Both of these approaches have been used successfully to treat other disease indications but have not been applied extensively to neurological disorders.

The potential advantages of repurposing (also called repositioning) drugs for the treatment of AD include the availability of existing preclinical data on safety, tolerability, pharmacokinetics, and pharmacodynamics of compounds. For drugs that are on the market, issues related to formulation and manufacturing may also have been solved, and extensive clinical data may be available [8]. Through a systematic review of published literature and a Delphi-type consensus process with industry experts, Corbett et al. [8] identified and prioritized several classes of drugs that might be considered in repurposing studies for Alzheimer's, and the gaps in knowledge that need to be addressed.

A major roadblock to repurposing is that there may be little or no incentive for pharmaceutical companies to devote resources to drugs for which patent life has expired. The NIH has stepped into this breach through the Alzheimer's Disease Cooperative Study (ADCS) and through the work of the National Center for Advancing Translational Science (NCATS), the newest institute of the NIH. NCATS has begun to inventory, in a systematic manner, data on compounds that have been approved by international regulatory agencies or registered for clinical trials [9].

With regard to combination therapy, several recent global initiatives have suggested including drug combinations as arms in future adaptive trial designs, and at least one combination trial—combining a beta-site APP cleaving enzyme (BACE) inhibitor with an anti-amyloid antibody—has been reported [10]. In addition, the Food and Drug Administration (FDA) has signaled its interest in considering combination therapy through the issuance of a guidance on codevelopment [11,12]. However, combination therapy

faces numerous roadblocks, including the lack of a clear scientific rationale for combining certain therapies, the need for appropriate biomarkers to assess treatment effects, new trial designs, and the need for increased collaboration among industry partners. It should be noted that substantial basic science resources will need to be committed in order to understand the complex dynamics of targeting multiple molecular pathways, and how biomarkers may respond to combination therapies.

Thus, the steps outlined in Milestone A have not yet been successfully completed, and the expert workgroup recommends that more effort is needed to address industry concerns about intellectual property. The expert workgroup further calls for the expansion of Milestone B, noting that the field may not yet be ready for translational efforts given the insufficient understanding of the basic science underlying combination therapy. In addition, increased representation from industry is needed for the successful implementation of both Milestones A and B. Given that Milestones C and D are contingent on the work addressed in A and B, the expert workgroup notes that it is too soon to address conducting Phase II and III trials of combination therapies.

Recommended modifications to existing milestones:

- In Milestone A, extend the time frame and scope of the advisory committee, and expand representation of industry scientists.
- Expand Milestone B to include research on the basic science underlying combination therapy.

### 2.1.2. Drug development: Currently known targets

Milestones E and F concern the development of drugs against currently known targets. Milestone E calls for initiation of three to six Phase II drug trials against currently known targets, at least two of which should be in asymptomatic subjects. Although a number of Phase II trials have already been completed, most of them have targeted amyloid, and much more needs to be done to test nonamyloid therapeutic targets, including tau, inflammation, nicotinic agonist receptors, and others. Moreover, given the high attrition rate in Phase II trials to date [13], to achieve the success criteria (i.e., completion of three to six Phase II trials, “providing conclusive evidence of therapeutic mechanism/target engagement”) perhaps 12 or more trials will need to be initiated. The milestone also calls for trials of agents against three to six therapeutic targets, so these trials will need to involve targets beyond amyloid. Finally, because of the difficulty of conducting Phase II trials in asymptomatic subjects, it is more likely that studies to confirm proof of mechanism and/or evidence of target engagement would be embedded into Phase III trials that could be counted as registration trials by the FDA. Such trials might use an adaptive design whereby a biomarker of drug effect is included for adjusting dose and/or declaring futility.

Milestone F calls for initiation of Phase III trials against at least three known targets, with at least one of these trials in asymptomatic, at risk subjects; and for the inclusion of biomarkers and cognitive measures and the collection of biological samples. Currently four asymptomatic Phase III trials are underway (Dominantly Inherited Alzheimer Network Trials Unit [DIAN-TU], the Alzheimer’s Prevention Initiative [API] autosomal dominant Alzheimer’s Disease trial, the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Study [A4], and the TOMMORROW study). The TOMMORROW study is testing pioglitazone, whereas the three others target amyloid. All include extensive biomarker and cognitive testing and the collection of biospecimens. The expert workgroup noted that these trials have been made possible only through partnerships bringing together resources from both public and private arenas.

Drugs against several targets beyond amyloid have been explored as symptomatic therapies, including muscarinic and other cholinergic agonists and serotonin receptor ligands. Although the focus of many ongoing Alzheimer’s trials is on disease modification, symptomatic approaches may provide substantial benefits to people with AD, including maintaining function, staying active, and remaining at home longer as the disease progresses. Moreover, clinical trials of symptomatic therapies can be completed in less time and with fewer subjects, thus potentially expediting the development and approval of new therapies.

Recommended modifications to existing milestones:

- Revise Milestone E to reflect the large number of Phase II drug trials that will need to be initiated to achieve completion of three to six trials against different therapeutic targets that show evidence of therapeutic mechanism/target engagement.
- In Milestone E, delete the requirement that at least two trials will be for targets involved in asymptomatic disease.
- Revise Milestone F to reflect the large number of Phase III trials that will need to be initiated to achieve three successful trials.
- Revise Milestone F to indicate that at least one trial should be of a symptomatic therapy.

### 2.1.3. Drug development: Novel targets

Milestones G through L focus on developing novel targets into effective treatments. G and H together aim to identify genetic markers and pathways that may represent therapeutic targets by establishing and analyzing data in an open access research database containing multidomain information (clinical, biomarker, epidemiological, genetic), and developing a broad, large-scale sequencing project to identify risk and protective gene variants in late onset AD (LOAD). Progress has been made in both of these efforts. For example, the International Genomics of Alzheimer’s Project used data from four consortia in the United States and Europe to conduct a meta-analysis of the genotypes of

over 74,000 individuals, which led to the identification of 11 Alzheimer's susceptibility loci [14]. In addition, the Global Alzheimer's Association Interactive Network (GAAIN) was created in 2013 as a federated, cloud-enabled infrastructure to bring multiple data sets together and provide researchers with access to both data and analytical and computational tools [15]. However, there remain challenges to accessing and using this information. Moreover, the expert workgroup suggested expanding the databases beyond genetic studies and the goal beyond the identification of gene variants. Also needed is a uniform protocol for collecting, storing, and providing open access to biospecimens for use in genetics, proteomics, and other biomarker studies. In addition, the success criteria should be expanded from "at least one novel target... identified" to at least a dozen novel targets or pathways.

The expert workgroup supported the overall goals of Milestones I through L, but commented that history shows that only about 13% of new molecular entities (NMEs) make it from the preclinical stage to Phase III trials [16]. This suggests that to achieve the success criteria of Milestone L ("comprehensive success/failure analysis of data from at least three Phase III trials"), approximately 23 NMEs would need to be identified, characterized, and validated in Milestone I, which currently calls for only six novel therapeutic targets. Moreover, because novel targets need to be identified across many pathways and mechanisms—e.g., reducing amyloid, reducing inflammation—a much larger number of NMEs, 60, should be identified in Milestone I. Thus, the expert workgroup recommends that the numbers and projected costs in I, J, K, and L be adjusted to more accurately reflect the reality of drug development.

The expert workgroup also noted the need to dramatically increase the efficiency of Phase II and III trials to change the risk profile for drug development and spur investment. Although some of these efficiencies are addressed in other milestones—for example, implementing a National Institutional Review Board (IRB) (Milestone AH), and convening advisory meetings and working groups to address some of the barriers to drug development (Milestones AD and AE)—more activity and resources are needed in this area. Additional milestones are also recommended for developing precompetitive consortia to de-risk the early stages of drug development (see section 5.3).

Recommended modifications to existing milestones:

- In Milestone G, expand the analysis of data beyond identifying genomic regions (to include, for example, epigenetic data), and expand the success criteria to 12 rather than one novel target identified.
- In Milestone I, expand the number of novel therapeutic targets to be identified, characterized, and validated to 60 NMEs covering six new classes of targets (e.g., inflammation, tau).
- Similarly expand the number of therapeutic agents developed in Milestone J to 30; and the number of these

agents advanced to Phase II trials in K to more realistic numbers (at least 12) needed to achieve Milestone L.

- In Milestone L, ensure that at least one of the agents tested in a Phase III study is for a symptomatic indication.

Recommended new milestones:

- Develop a uniform protocol for collecting, storing, and providing open access to biospecimens for use in genetics, proteomics, and other biomarker studies.
- Enlist an unbiased, independent, nonprofit entity to conduct an annual review of clinical trial efficiencies.
- Convene a working group to consider novel trial designs, including adaptive trials.

#### 2.1.4. Development of nonpharmacologic interventions

Milestones M through R focus on advancing research and clinical studies, and developing best practices for the use of nonpharmacologic interventions, both alone and in combination with pharmacologic interventions for the prevention and treatment of AD. The expert workgroup recommends revisions to the existing milestones to address (1) the importance of treating not only cognitive and behavioral, but also the psychological and functional symptoms of AD; (2) the importance of developing best practices for the use of nonpharmacologic interventions tailored for different stages of disease, different care settings (e.g., home, hospitals, assisted living, nursing homes), and in the presence of comorbid conditions (these best practices should include nonpharmacologic medical approaches such as ruling out urinary tract infection); (3) the desirability of studying biomarkers in the context of nonpharmacologic interventions; and (4) the need to establish a theoretical rationale for using physiological outcomes for nonpharmacologic interventions—for example, how improvements in outcomes such as mood, sleep, or physical function may be reflected in imaging or other physiologic assessments.

The expert workgroup also recommends that Milestone R, which calls for a review and assessment of technologies used in prevention and treatment trials, lacks clarity and needs revised wording.

Recommended modifications to existing milestones:

- Revise wording of Milestone M to include not only cognitive and behavioral symptoms, but also functional and psychological symptoms of AD; and to develop best practices across the continuum of the disease, in different settings, and in the presence of comorbid conditions.
- Revise wording of Milestone N to include a range of treatment targets (medical, psychosocial, behavioral, environmental, and caregiver training) for the behavioral, psychological, cognitive, and functional symptoms of AD.

- Revise Milestone O to include clinical research and biomarker studies in the integrated interdisciplinary research programs; and in the goals of the research, add developing a theoretical rationale for mechanisms by which interventions impact brain health and the course of disease.
- Revise Milestones P and Q to include biomarker studies in clinical trials.
- Revise Milestone R to read: Review results of past and existing grants to develop technologies with therapeutic/preventive potential (e.g., technologies used for cognitive training, promoting or supporting physical activity interventions, or to be used as part of a reminiscence, art, or music therapy program). Assess areas where technologies have been adopted, where there are promising results that should be followed up, and where there are remaining needs.

#### Recommended new milestones:

- Initiate research programs (R01), Small Business Innovative Research (SBIR), or Small Business Technology Transfer (STTR) focused on developing and testing new technologies or modifying and testing existing technologies to support the development of nonpharmacologic therapies (e.g., cognitive training, exercise technologies).

*Success Criteria:* At least two new technologies are developed, prove useful in the development of nonpharmacologic therapies, and are widely adopted.

## 2.2. Biomarkers of disease progression

An Alzheimer's biomarker model of disease progression, proposed by Jack et al. [17] and updated with new data in 2013 [18], describes the changes in Alzheimer's biomarkers over time, beginning decades before symptoms appear. This model and supporting data provide not only clues about the mechanisms underlying the disease, including amyloidosis and neurodegeneration, but potential therapeutic targets as well. Yet, they also point to the need for the discovery of new biomarkers of other pathophysiologic processes involved across the trajectory of the disease, and less intrusive and expensive biomarkers.

Milestones addressing these concerns focus on developing, testing, validating, and standardizing novel imaging, cerebrospinal fluid (CSF), and blood-based biomarkers to assess disease burden and demonstrate target engagement; and incorporating these biomarkers into Phase II (proof of concept) and Phase III (pivotal) drug trials for study subject enrichment and/or proof of target engagement. The milestones also call for studies linking peripheral and central biomarkers, the development and testing of minimally invasive biomarkers for use in clinical studies, and the development and validation of sensitive neuropsychological assessment measures that can track early clinical manifestations of AD.

Some success has been achieved under the existing milestones. Amyloid beta (A $\beta$ ) ligands for positron emission tomography (PET) imaging are well developed—three (florbetapir, florbetaben, and flutemetamol) have been approved by the FDA and at least one other is in late-stage development [19]. The approved ligands are currently included in clinical trials, although none are yet common in clinical use. Tau ligands are also being developed for PET imaging [20]. Other imaging, biochemical, and genetic biomarkers are also widely used in research and clinical studies [21], and many novel biomarkers are in development. Standardization has also been addressed, not only in the Alzheimer's Disease Neuroimaging Initiative (ADNI), but through the Alzheimer's Associations' Global Biomarkers Standardization Consortium for Cerebrospinal Fluid [22], the Hippocampal Harmonization Project [23], and the Centiloid Project to standardize amyloid imaging measures [24,25].

The expert workgroup supports the milestones that call for development of (1) a validated tau ligand, (2) CSF biomarkers beyond existing A $\beta$  and tau biomarkers, (3) blood-based biomarkers directly associated with both amyloid and tau pathology, and (4) a biomarker of synaptic dysfunction (Milestones T, U, and V). However, given that these new biomarker milestones must be realized in parallel with new target identification and drug development (see section 2.1.3—Milestones I, J, K, and L), achieving these milestones in an efficient, step-wise manner introduces complexities related to the sharing of data, resources, and knowledge; apportioning responsibility for funding the various steps; and commercializing biomarker tests. For example, once a new target is identified, preclinical studies will be needed to establish proof of mechanism before identification of PET tracers or other biomarkers. Subsequently, these biomarkers will need to be incorporated into Phase II trials to prove mechanism and demonstrate target engagement. The cost of development before a Phase II study will thus require incentives for commercialization and/or a degree of collaboration that has to this point been difficult to bring about.

The expert workgroup endorses the milestones (W and X) that call for developing minimally invasive biomarkers for detection of AD pathophysiology in community-based studies and linking these to central imaging and CSF biomarkers, with two modifications and one addition (see later).

With regard to developing and validating neuropsychological assessment measures for use in early Alzheimer's (Milestone Y), there has been substantial initial activity in this area because the Milestones were written. The investigators from major new prospective secondary prevention trials (DIAN, API, and A4) have come together under the Collaboration for Alzheimer's Prevention (CAP) to identify common neuropsychological domains and tests to include so that results can be shared and compared across studies. These investigators are also working together to choose instrumentation, on the basis of literature published over

the last 5 to 10 years, which identifies cognitive domains affected in early stages of disease. Some of these measures are also being incorporated into other studies, including ADNI. However, these studies are just beginning, and it is as yet unknown whether the neuropsychological measures chosen will prove effective. Moreover, these markers will need to be validated both as screening/enrichment measures and as outcome assessments to demonstrate a treatment response.

Additional work is also needed to develop novel measures that will be sensitive and informative in presymptomatic Alzheimer's. Because research suggests that subtle cognitive changes may be detectable as changes in performance on everyday tasks, the expert workgroup recommends further studies to develop and validate measures of cognition based on noninvasive everyday measures that take advantage of new technologies for home monitoring, personal monitoring via smart phones, etc.

Identification and development of novel biomarkers, particularly for synaptic dysfunction and for minimally invasive markers, is likely to require significant additional efforts and resources in basic science and preclinical research. This will be particularly important with regards to finding novel biomarkers that reflect the earliest changes in the disease process, and biomarkers that do not necessarily correlate with existing biomarkers during disease progression and treatment.

Recommended modifications to existing milestones:

- Revise Milestone W to reflect that the biomarkers should not only be minimally invasive but also portable and inexpensive (e.g., blood-based or electrophysiological) to enable large studies in diverse populations.
- In Milestone X, expand the success criteria to call for identifying at least 5 (rather than 3) peripheral blood-based biomarkers that correlate with central (imaging or CSF) biomarkers because 3 may be insufficient to detect not only cerebral amyloidosis, but also neurodegeneration, inflammation, and other pathologies.
- Split or expand Milestone Y and associated success criteria to differentiate neuropsychological assessment measures used for trial screening/enrichment vs. those used to assess treatment response.

Recommended new milestones:

- Validate minimally invasive biomarkers in community studies.
- Expand existing incentives for commercialization (e.g., expanding the funding for SBIR/STTR grants by at least 100%), providing tax credits, and exploring new ways to make commercial/capital investment more accessible for companies wishing to compete in the highly regulated marketplace of medical devices.
- Establish a public-private partnership to develop mechanisms that will enable data sharing and protection or

sharing of intellectual property among drug and biomarker developers (also see section 5.3).

- Convene a conference/expo that brings together clinical investigators with researchers and companies developing technologies to capture and analyze everyday performance measures. The goals of this conference would be (1) to enable cross-silo discussions that would promote collaborations across the various stakeholder groups, and (2) to explore challenges that need to be addressed to make best use of these new technologies, including privacy concerns, establishing validity, and aggregating and analyzing data.
- Establish criteria for publishing cognitive data in a way that enables aggregation of data to facilitate comparison across studies.

### 3. Infrastructure and research resources

Milestones AA through AJ are directed toward addressing a critical lack of sufficient research infrastructure and resources to meet the research goal of the National Plan. Needs include development and maintenance of a common AD research ontology, expansion of epidemiological cohorts and databases, creation of a network of translational research centers, an NIH working group to ensure the fast-tracking of translational research applications, the creation of a national IRB, and the identification and implementation of standard outcome measures.

#### 3.1. Epidemiology

Epidemiological studies have provided important information about the natural history, incidence, prevalence, and heterogeneity of AD, and the many possible exposures that influence the risk of developing the disease [26]. Risk and protective factors for dementia and Alzheimer's identified in these studies include genetic, vascular, psychosocial, dietary, and other lifestyle factors [27]. Thus, these studies inform public health policies, prevention strategies, and the design of intervention trials. The utility and importance of epidemiologic studies have been confirmed with the recent success reported by an early analysis of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) multidomain prevention trial [28]. All the factors used as part of the intervention in this trial—diet, physical exercise, cognitive training, social activities, and control of vascular risk factors—were identified through epidemiologic studies. However, more resources must be committed to epidemiological infrastructure and studies to fully harness the power of this methodology.

Milestones AA and AB call for convening an expert panel to recommend best practices in the use of existing epidemiology of dementia databases to individualize treatments in Alzheimer's clinical trials; the expansion of existing cohorts to include subjects in mid-life; and the use of data generated

from these expanded cohorts in the design of treatment and prevention trials.

The expert workgroup called first for a reframing of these milestones to focus more broadly on prevention of cognitive impairment and dementia across the entire lifespan. Although advances have been made in identifying modifiable risk factors that influence cognition, there remains a need to determine which targets make most sense for prevention studies and the appropriate time across the life course when prevention studies should be initiated. The workgroup thus recommends that the work of the expert panel called for in these milestones be expanded both in time and scope to address these knowledge gaps and better inform future studies. In addition the workgroup recommends building upon existing cohort studies and/or initiating new cohort studies with broader research goals. These studies should be attentive to changing demographics and ethnic and racial shifts in the population, and should have harmonized data collection methods.

The expert workgroup further recommends the initiation of a large, multidomain prevention trial focused on modifiable risk factors in the United States to replicate the results of the FINGER trial in a larger, more diverse population.

Recommended modifications to existing milestones:

- In Milestone AA, extend the time frame of the expert panel and expand the scope of the panel's work to include determination of best targets for prevention and the time in the lifespan when prevention trials make the most sense. Modify the focus more broadly on prevention of cognitive impairment and dementia rather than the more specific clinical trials for AD.
- Expand Milestone AB to include subjects from heterogeneous populations across the life course, beginning earlier than mid-life, and expand the research on these cohorts to include investigations of early exposures, genetics, cumulative risk exposures, epigenetics, and modifiable risk factors.

Recommended new milestones:

- Establish a working group to harmonize data collection across epidemiologic studies so that data can be combined and compared.
- Fund a large, multidomain prevention trial focused on modifiable risk factors in the United States.

### 3.2. Research ontology

Among the additional resources and infrastructure needed to reach the goal of effectively treating and preventing Alzheimer's by 2025, eight milestones were identified (AC through AJ) that together will enable researchers across multiple stakeholder groups to collaborate, share data, translate discoveries into new interventions, and accelerate and streamline clinical trials. While progress has been made in

achieving some of these milestones, additional steps are needed to accelerate progress.

Milestone AC calls for developing a common Alzheimer's research ontology, unified classification system, and publicly available database of the research portfolios of international Alzheimer's funding agencies. Beginning in 2010, the National Institute on Aging (NIA) and Alzheimer's Association began developing CADRO, a Common Alzheimer's Disease Research Ontology [29], followed by an International Alzheimer's Disease Research Portfolio (IADRP) [30], which currently captures information from 15 organizations. The expert workgroup recommends two modifications to this milestone to extend the timeline, because both CADRO and IADRP will need continuous revisions, and to develop tools that enable funders to track and analyze their research investments.

Recommended modifications to existing milestone:

- Extend the timeline in milestone AC, because both CADRO and IADRP will need continuous revisions.
- Modify Milestone AC to include the development of tools that enable funders to track and analyze their research investments.

### 3.3. Partnerships

Milestones AD and AE address the need for public-private partnerships aimed at accelerating therapy development. An advisory meeting was convened by the NIA in 2013 (enabling partnerships for Alzheimer's Disease Drug Development), and working groups were established to address issues that have hindered progress in drug development, including data sharing and analysis, translation, and intellectual property barriers. The process led to the launching of the AD network analysis group, which has been incorporated into the Accelerating Medicines Partnership (AMP; see section 5.3). The expert workgroup recommends continuing the support for this process to promote additional dialog and effort with the goal of developing an action plan with concrete steps.

### 3.4. Translational research centers

Milestones AF and AG call for creating a network of translational research centers and expediting review of translational AD research applications. The NIH has indeed increased its focus on translational research, establishing the Clinical and Translational Science Awards (CTSAs) in 2006, which as of 2013 fund 62 institutions [31]; establishing the NCATS in 2011, which develops collaborative projects across all sectors (industry, academia, governmental agencies) and now oversees CTSA funding [32]; and creating the Network for Excellence in Neuroscience Clinical Trials (NeuroNext) to provide resources and infrastructure for Phase II clinical trials through public-private partnerships [33]. However, to achieve the goal of creating three Alzheimer's translational centers (Milestone AF), the



expert workgroup recommends leveraging these existing translational resources by modifying or expanding existing Alzheimer's Disease Centers so that they function similarly to the National Cancer Institute's Comprehensive Cancer Centers, which integrate broad transdisciplinary research programs (clinical, basic, and epidemiologic) with state-of-the-art clinical care, access to clinical trials, training of the next generation of scientists and physicians, and public outreach. A model for a Comprehensive ADC (CADC) at the University of Pennsylvania was proposed in 2010 [34]. Other ADCs also have many of the components in place to make a smooth transition to a CADC.

The expert workgroup recommends facilitating the call for an expedited review of translational Alzheimer's research applications by having a nonfederal, independent organization oversee the development and implementation of this policy. Moreover, expedited review alone, without available funding for projects positively reviewed, will not achieve the goal of accelerating translational science.

Recommended modification to existing milestone:

- For Milestone AF, the expert workgroup recommended the following revision to the success criteria: Expansion of the ADCs program with funding for three demonstration projects to develop CADCs.

Recommended new milestones:

- Convene a workgroup to interact with the NIH to ensure that the NIH policy on expedited review includes and achieves specific timeline targets.
- Mandate additional NIH funding to support five translational Alzheimer's projects per year.

### 3.5. National IRB

Milestone AH calls for creating a centralized national IRB for neurodegenerative diseases (NIRB-ND), which would address unnecessary inefficiencies in both time and costs in launching multicenter studies, for which each study site is currently required to apply individually for IRB approval. Based on the model pioneered by the National Cancer Institute, an NIRB-ND would provide a very high level of expertise in neurodegenerative diseases, drawing multidisciplinary specialist panel members from across the United States and Canada. A small workgroup, with representation from private foundations, academia, and the Alzheimer's Association, has been working on a viable plan for the preceding two years, but thus far has received only limited financial support commitments (from the Alzheimer's Association and the National Research Council of Canada). Once established, the NIRB-ND will be financially self-sufficient. However, the effort to establish the NIRB-ND has slowed due to lack of financial support required from federal and industry sources needed to establish the administrative, software, computer networking,

outreach and credentialing systems that will be required for an independent, nonprofit IRB.

Recommended new milestone:

- Convene a national symposium on the centralized IRB process, with representation from universities and other research institutions, government, industry, and philanthropic organizations, to 1) increase awareness and address potential concerns of research institutions, and 2) coordinate appropriate seed funding to launch the national IRB.

### 3.6. Standardized outcome measures

Milestones AI and AJ focus on standardizing outcome measures to be used in clinical trials, which would enable data sharing and comparison across studies. Some progress toward this goal has been made by CAP. However, optimal outcome measures need to be determined for different disease stages, followed by validation and implementation.

Recommended modifications to existing milestones:

- Combine Milestones AI and AJ to achieve standardization of clinical trial outcome measures to facilitate comparisons across trials and thereby increase the efficiency and success of trials by (1) establishing a forum for open sharing of data, procedures, and analysis of outcome measures; (2) initiating validation studies across different stages of disease (preclinical, mild cognitive impairment, dementia) that incorporate a variety of outcome measures, with agreement to share data and data analyses; and (3) developing the infrastructure to incorporate selected outcome measures into therapeutic trials.

### 3.7. Big data

Developing a comprehensive understanding of Alzheimer's and related disorders, and new targets, interventions, biomarkers, and assessment tools will require the collection, storage, and analysis of massive amounts of diverse types of data. The need for global "big data" solutions in Alzheimer's has been embraced by global organizations such as the Organisation for Economic Co-operation and Development (OECD) [4], the G8 (now G7) Health Ministers [35], and by national organizations in the United States, Europe, and Japan.

The Alzheimer's Association established the GAAIN to bring diverse data sets together via a federated, cloud-enabled infrastructure [15]. GAAIN enables researchers to access data across geographical borders and also provides computational and analytical tools. GAAIN currently connects databases of the National Alzheimer's Coordinating Center (NACC); the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site, which includes the Alzheimer's Disease Genetics Consortium; ADNI; and the Dominantly Inherited Alzheimer's Network (DIAN)

Expanded Registry. As databases and networks such as GAAIN continue to evolve, they will need to adapt to increasingly complex and diverse types of data, including data from multiple “omics” technologies, electronic medical records, payer claims, biosensors, etc.; and data from an expanded landscape of observational and clinical studies. For example, several cohort studies have collected valuable data on the normal and pathological process of aging; for example, the Cardiovascular Healthy Study, the Women’s Healthy Aging Project, the Wisconsin Registry for Alzheimer’s Prevention, and the landmark Framingham Heart Study [36]. Although lack of funding has curtailed many of these projects, GAAIN will enable capture and preservation of their data for future analysis.

The expert workgroup recommended milestones that would strongly support national and international efforts to build, expand, and maintain “big data” solutions, including integrated databases such as GAAIN and other analytic platforms that facilitate deep knowledge extraction of biomedical research data, such as the development of *in silico* modeling systems.

Recommended new milestone:

- Convene a working group that will work with global partners to develop a strategy for sharing and harmonizing data across borders.

#### 4. Study recruitment and participation

Milestones AK through AN are directed at overcoming difficulties in clinical trial recruitment and retention. Recruiting and retaining study participants in Alzheimer’s clinical trials has proved challenging and a major hindrance to the successful completion of trials [37]. Many factors contribute to sluggish recruitment, including lack of awareness on the part of both participants [38] and primary care physicians [39], stringent inclusion and exclusion criteria, and logistical issues that place unacceptable burden on patients and caregivers. Recruitment of participants from underrepresented populations has proven particularly difficult, despite the fact that studies report higher Alzheimer’s risk among both African-Americans and Hispanics [40–44]. However, African-Americans are less likely to report cognitive and functional problems in older family members until the impairments become severe [41]. This highlights the need for culturally sensitive educational programs that emphasize the differences between normal and pathological cognitive aging, and the value of research focusing on the benefits to both the individual and the whole community now and in the future [45,46].

Milestones addressing these concerns focus on providing a central resource on best practices for recruitment and retention, increasing awareness of and access to large scale Alzheimer’s-related registries and cohorts, and increasing

the enrollment of participants from underrepresented populations in clinical trials.

Creation of a central resource for best practices in recruitment and retention has been discussed by many groups including the NIA, Alzheimer’s Association, Alzheimer’s Disease Research Centers, the Alzheimer’s Disease Cooperative Study (ADCS), and ADNI; however, there is currently no consensus on best practices.

Recently, the US federal government has launched a cross-agency effort to educate older adults and encourage their participation in clinical trials. The program—named ROAR for Recruiting Older Adults into Research—involves the efforts of NIA, the Centers for Disease Control and Prevention, and the Administration for Community Living. After seeking input from a broad range of partners, the ROAR group has developed educational and recruitment materials to be used in community settings, and in conjunction with a broad range of partners, including the aging and public health networks, and the Alzheimer’s Association. These materials are currently being tested in several cities, and should be expanded to include the ADCS/ADCs and industry partners.

The expert workgroup supports the idea of a central resource for best recruitment and retention practices (such as may be developed within the ROAR infrastructure), while noting that consensus on best practices has not yet been achieved and also may differ as trials move from treating to preventing dementia. Thus, the workgroup also supports establishing a working group of clinical trial recruitment experts to develop concrete recommendations on best recruitment practices. With several large scale predementia trials (API, DIAN, A4, TOMMORROW) already beginning to enroll subjects, now is an ideal time to bring this working group together to discuss the success of various recruitment strategies (Milestones AK and AL).

With regard to increasing awareness of large-scale registries (AM and AN), tailored awareness campaigns will be needed for different population groups concerning the purpose of registries and the importance of participation. However, the expert workgroup stresses that raising awareness alone is insufficient and must be accompanied by actually increasing enrollment in registries, and enrollment and retention in trials.

A national health promotion campaign to increase awareness in African-American and Latino communities is desperately needed, and regional campaigns to address the varying needs of diverse communities. These efforts will require both public (NIH) and private (philanthropic) funds. The infrastructure provided by ROAR represents an opportunity to build such an effort, with input from multiple stakeholders. A task force comprising leaders in underrepresented communities, clinical investigators, philanthropic and health advocacy organizations, and marketing/advertising specialists should be convened to identify strategies for developing these public awareness campaigns.

Recommended modifications to existing milestones:

- For Milestone AM, the success criteria should include development of tailored awareness campaigns for different populations about the purpose of registries and the importance of participation.
- For Milestone AN, the success criteria should include a national health promotion campaign, and regional campaigns to increase awareness and participation of the African-American and Latino communities.

## 5. Additional considerations

### 5.1. *Novel paradigms on etiology-pathogenesis of AD*

Given that current approaches to treatment have not yet resulted in effective new therapies, strategies are needed to re-examine existing paradigms and consider new conceptual models of AD. The Alzheimer's Association convened a Research Roundtable in 2006 [47] and again in 2012 [48] to explore mechanisms other than the dominant amyloid hypothesis that may contribute to neurodegeneration in AD. Pathways identified that may offer additional therapeutic targets include those associated with aging, such as synaptic loss, loss of telomeres, decreased neurogenesis, autophagy, insulin resistance, and changes in lipid metabolism; and cell cycle events and other cellular processes such as inflammation, mitochondrial dysfunction, calcium homeostasis, and alterations in chaperone proteins.

Among the barriers to exploring these alternative hypotheses has been a lack of tools, infrastructure, and resources. Although some new tools, such as tau imaging and novel structural and functional imaging approaches, are in development, there remains a critical need for additional tools including additional ligands and new technologies such as nanoimaging. These new imaging technologies could be especially useful in studying a cohort of individuals who maintain cognitive function very late in life. In addition, extensive and careful autopsy studies will continue to be an extremely important aspect of future studies, including proposed large, longitudinal cohort studies. However, a rate-limiting step hindering progress in this area is the insufficient number of neuropathologists training in neurodegenerative disease.

In addition, substantial new efforts and resources are needed in the area of basic science and pre-clinical research. Clinical research depends heavily on the understanding of basic biological and disease processes that illuminated by basic science research. While much is known about Alzheimer's disease, much remains to be discovered. Basic research is needed to more fully understand cellular and molecular events associated with aging, and how these are tied to the processes that give rise to Alzheimer's disease. Areas that are ripe for study include DNA damage, mitochondrial function, and immunobiology. The potential for expanded basic research to dramatically accelerate progress in translational and clinical research is enormous, and will provide

much needed illumination in areas ranging from novel therapeutic strategies and targets to novel biomarkers.

Recommended new milestones:

- Establish and fund multiple training awards (e.g., K awards), fellowships, and R01s in the neuropathology and molecular biology of aging over the next 5 years.
- Fund a substantial research program on the basic biology of aging, to include studies of vulnerabilities in the aging brain, vasculature changes and endothelial failure, neural networks, and the biological underpinnings of "super-aging."
- Dramatically increase activity and resources applied to understanding the basic cellular and molecular biology of Alzheimer's disease, including how these processes interact with aging.
- Convene a working group/think tank to reexamine conceptual models of disease beyond amyloid.

### 5.2. *Regulatory*

The National Plan's research goal of effectively treating and preventing Alzheimer's by 2025 will be achieved not only as a result of basic and clinical research discoveries made in academic and industry labs, but in the ability to demonstrate through clinical trials that the treatments developed are safe and effective. The long, complicated, and expensive process of moving a new medical entity from the bench to the bedside has been cited as one reason for the lack of new treatments despite rising expenditures. In addition to novel trial designs, improvements in biomarkers and other outcome measures, and improvements in recruitment and retention of study participants, making clinical trials more efficient will require greater flexibility in the process of gaining regulatory approval for a new drug.

Regulatory agencies are key partners in this process and have demonstrated some willingness to adapt their requirements to the evolving science. For example, in 2013 the FDA published a draft guidance for developing drugs for early stage AD [49], which suggested a willingness to consider accelerated approval based on the demonstration of clinical efficacy in one trial (rather than the typical requirement of two pivotal trials) along with a biomarker signal of target engagement. Moreover, the agency has published guidelines for organizations to follow in seeking qualification of drug development tools including biomarkers, cognitive assessments, and modeling and simulation tools [50]. Qualification of such tools in precompetitive space through public-private partnerships could enable sponsors to avoid the costly and time consuming process of validating outcome assessments in individual trials.

Recommended new milestones:

- Define a path to validate at least one biomarker capable of predicting clinical outcome and meet conditions for an accelerated approval pathway by 2016; and define a

path to achieve regulatory acceptance of this marker as a surrogate marker.

- Regulatory “qualification” of three or more markers of disease progression for application to stratification of subjects in clinical trials by 2017.
- Regulatory “white paper” or other communication, short of guidelines, giving sense of regulators to establish appropriate principles as to degree (especially duration and sample size) of safety data before allowing years of treatment of a potentially disease preventing compound.

### 5.3. *Research financing and resource development: Forging strategic alliances to expand the role of industry*

The National Plan identifies numerous areas in which the federal government can work collaboratively with private research organizations, industry, and health care and nonprofit organizations to address AD. Yet there are no milestones that directly address how best to forge strategic alliances with the private sector on research efforts and expand the role of industry in this enterprise.

Most of the knowledge and expertise about drug development and specific drugs in the pipeline reside in industry, yet proprietary concerns make it difficult for transmission of that knowledge to the field. There have been a few notable exceptions to this; for example, industry scientists from multiple companies came together and shared data from phase I studies of phosphodiesterase 10 (PDE10) inhibitors for schizophrenia, increasing understanding of the disease and helping to clarify a path forward for drug development.

Mechanisms exist within the federal government to promote collaborations with industry, such as Comparative Research and Development Agreements. In addition, the NIH recently established the AMP, a consortium of the FDA, NIH, pharmaceutical companies and nonprofit agencies, managed by the Foundation for the NIH, which aims to jointly identify and validate disease targets for Alzheimer's and other diseases [51]. With \$67.6 million from the NIH and another \$61.9 million from industry, AMP is funding two 5-year Alzheimer's projects—one that will incorporate selected biomarkers into four NIH-funded clinical trials and the other a network analysis project of Alzheimer's brain tissue samples to validate biological targets known to be involved in disease pathogenesis and identify new targets.

From the perspective of industry, drug development for AD is a high-risk endeavor, exacerbated by the need for large and lengthy clinical trials which substantially reduce the period of marketing exclusivity. As mentioned earlier, the FDA has addressed this to some extent by publishing a draft guidance on developing drugs for early stage Alzheimer's including the use of an accelerated approval pathway [49,52]. The accelerated approval pathway was developed in the 1980s in response to the pressing need for drugs to treat AIDS, and has since been used successfully for

oncology drugs [53] but rarely for central nervous system disease.

The expert workgroup recommends that more must be done to de-risk early stage drug development and provide incentives to industry to devote the necessary resources to Alzheimer's drug development. In industry circles, extension of exclusivity is widely seen as the preferred solution. Another solution that could make it economically viable for companies to invest in Alzheimer's drugs is identifying and developing an outcome measure that provides a short-term signal early in the drug development process.

#### Recommended new milestones:

- NIH/NIA/AA and other groups jointly convene a workshop or summit to lay the groundwork for creating a precompetitive consortium of industry partners aimed at de-risking novel targets through the proof of concept stage by sharing data and research tools.
- Create a consortium of industry scientists to systematically assess, stack rank, and prioritize existing targets and conduct medicinal chemistry studies to optimize compounds that engage these targets.
- Direct HHS to convene summit of FDA, industry lawyers, and advocacy groups to devise incentives that would facilitate data and resource sharing, and find solutions to issues related to exclusivity.

## 6. Summary and conclusions

Two years after the National Plan to Address Alzheimer's Disease was presented, the Alzheimer's Association brought together a multidisciplinary group of leading researchers, clinicians, and policy makers (the expert workgroup) to evaluate progress in achieving the research goal of preventing and effectively treating AD by 2025. This document describes the deliberations and recommendations of the expert workgroup grouped into three broad areas: (1) targets, interventions, and biomarkers; (2) infrastructure and research resources; and (3) study recruitment and participation. The fourth category “additional considerations” incorporates several areas that the expert workgroup determined were insufficiently addressed in the existing milestones.

The expert workgroup did not specifically address the funding needs to achieve these milestones. However, there was broad consensus among participants in this effort that achieving these milestones will require substantial and sustained increases in support for research, combined with a comprehensive strategy for allocating those resources wisely.

### 6.1. *Targets, interventions, and biomarkers (Milestones A through Z)*

These milestones address issues related to therapy development across the entire pipeline, from discovery and validation of new therapeutic targets, the development of drugs

against currently known targets, the identification and testing of existing agents in the pharmacopeia that may be repurposed or used in combination as treatments for AD, the development of nonpharmacologic interventions, and the identification of biomarkers and cognitive markers of disease progression to enable efficient clinical trials of therapies.

With regard to repurposing existing drugs (Milestones A through D), the expert workgroup noted that despite potential advantages arising from existing preclinical data that may be available, there are few incentives to encourage pharmaceutical companies to devote resources to repurposing efforts when the patent life has long expired on a drug. Incentives are also needed to encourage pharmaceutical companies to work together toward development of combined therapies. Cross-industry collaborations are needed, for example, to establish a clear scientific rationale for combining therapies, identify appropriate outcome measures, and develop innovative trial designs to test drugs in combination. Given these pressing needs, the expert workgroup recommended extending the time frame and scope, and increasing industry representation on the repositioning and combination therapy advisory committee established in Milestone A, and expanding Milestone B to include research on the basic science underlying combination therapy.

Drug development for currently known targets (Milestones E and F) is well underway, yet the expert workgroup noted that nearly all current Phase II and III trials target amyloid, and they called for increased efforts to develop agents against nonamyloid targets and symptomatic therapies. Citing the high attrition rate in Phase II trials to date, they also recommended greatly expanding the number of trials to be initiated to achieve the success criteria indicated (three to six successful Phase II trials and three successful Phase III trials). They also recommended deleting the requirement that at least two Phase II trials will be conducted in asymptomatic individuals in favor of embedding proof of mechanism and/or target engagement studies into Phase III trials.

The expert workgroup supported Milestones G through L, which focus on developing novel targets, but called for expanding research efforts to go beyond the identification of gene variants and expanding the success criteria to 12 rather than one novel target identified. Moreover, given that only a fraction of NMEs make it from the preclinical stage to Phase III trials, the expert workgroup recommended greatly expanding the number of NMEs identified, characterized, and validated in Milestone I, covering six new classes of targets. Similar expansions of numbers are recommended for drug discovery and development efforts delineated in Milestones J, K, and L. In addition, they recommended that at least one of the agents tested in a Phase III study (Milestone L) should be for a symptomatic indication.

The expert workgroup also recommended new milestones to expedite the development of novel targets, including developing a uniform protocol for collecting, storing, and providing access to biospecimens; enlisting an unbiased and independent entity to conduct an annual review

of clinical trial efficiencies; and convening a working group to consider novel trial designs such as adaptive trials.

With regard to developing nonpharmacologic interventions (Milestones M through R), the expert workgroup suggested revisions to the existing milestones that address (1) the importance of treating not only cognitive and behavioral, but also the psychological and functional symptoms of Alzheimer's; (2) the importance of developing best practices for the use of nonpharmacologic interventions tailored for different stages of disease, different care settings, and in the presence of comorbid conditions; (3) the desirability of studying biomarkers in the context of nonpharmacologic interventions; and (4) the need to establish a theoretical rationale for using physiological outcomes for nonpharmacologic interventions—for example, how improvements in outcomes such as mood, sleep, or physical function may be reflected in imaging or other physiologic assessments. They also recommended an additional milestone to establish research and business development programs focused on developing and testing new nonpharmacologic therapies.

Citing progress that has been achieved in developing and standardizing biomarkers, the expert workgroup endorsed Milestones S through Z concerning the development of new and improved biomarkers, including minimally invasive biomarkers, and cognitive markers to assess disease progression. However, they noted that these milestones must be realized in parallel with new target identification and drug development, which will require increased sharing of resources, data, and knowledge. Thus, they recommended additional milestones to promote collaboration and expand incentives for commercialization. In addition, they suggested additional milestones to promote the development of new functional and cognitive measures—including noninvasive personal monitoring technologies, such as are found in cell phones—for use in screening, enrichment, and assessing treatment response.

## 6.2. Infrastructure and research resources (Milestones AA through AJ)

These milestones address the critical lack of sufficient research infrastructure and resources to meet the research goals of the National Plan. The expert workgroup recommended expanding both the time and scope of epidemiologic studies (Milestones AA and AB) to focus on cognitive impairment across the entire lifespan and building on existing cohort studies, or building new cohorts, to include more heterogeneous populations and investigate a broad range of risk factors. The expert workgroup further recommended initiating a large, multidomain prevention trial in the United States.

The expert workgroup recommended extending support for resources such as the Common Alzheimer's Disease Research Ontology (CADRO, Milestone AC) and the International Alzheimer's Disease Research Portfolio (IADRP), and public private partnerships aimed at accelerating therapy development (Milestones AD and AE). With regard to the creation of a network of translational research centers

(Milestones AF and AG), the expert workgroup recommended expanding the Alzheimer's Disease Centers (ADCs) program with funding for three demonstration projects to develop Comprehensive ADCs (CADCs). The expert workgroup supported the creation of a centralized national IRB for neurodegenerative disease (NIRB-ND, Milestone AH), and called for a national symposium to increase awareness and address the concerns of research institutions regarding a national IRB. Finally, with regard to standardizing outcome measures (Milestones AI and AJ), the expert workgroup recommended modifications to the milestones that would facilitate comparisons across trials and increase the efficiency and success of trials.

The expert workgroup also recommended several new milestones to address the challenges of managing the massive amounts of data generated across the range of Alzheimer's-related research studies, including developing a strategy for sharing and harmonizing data across borders.

### 6.3. Study recruitment and participation (milestones AK through AN)

The expert workgroup endorsed these milestones, which would create central resources aimed at overcoming difficulties in clinical trial recruitment and retention. Recognizing that it is especially difficult to recruit participants from under-represented populations, they suggested revisions to the milestones that would create tailored awareness campaigns for different population groups to increase awareness and participation among the African-American and Latino communities.

#### 6.3.1. Additional considerations

The expert workgroup identified two research areas not covered by the existing milestones, and recommended new milestones that would address these: (1) Novel paradigms on the etiology and pathogenesis of AD, and (2) efforts to increase the efficiency of gaining regulatory approval of new drugs. These new milestones would establish and fund training awards, fellowships, and research programs on the neuropathology and molecular biology of aging; and support the regulatory qualification of several biomarkers of disease progression.

The expert workgroup also noted the lack of milestones that directly address how best to forge strategic alliances between the federal government and the private sector, including expanding the role of industry in this enterprise. Thus, they recommended efforts toward creating a pre-competitive consortium of industry partners aimed at de-risking early stage drug development; and a summit including a broad range of stakeholders to address issues related to data sharing and patent exclusivity.

## 7. Conclusions

The expert workgroup expressed optimism that prevention of AD and the development of disease modifying inter-

ventions are realistic goals if all stakeholders can come together and work in a coordinated manner toward addressing the scientific, financial, infrastructural, administrative, and regulatory roadblocks that have hindered progress.

The recommendations of the expert workgroup complement parallel efforts by other global organizations such as the OECD, World Health Organization, and the G8 Dementia Summit. The Alzheimer's Association, and the experts who contributed to this report stand ready to work with the HHS and the NIA to ensure that the necessary resources and expertise are directed in the most effective manner possible toward achieving the goal of preventing or treating AD by 2025.

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