Research Subcommittee Draft Recommendations

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January 14, 2013

1. **We support and applaud the goal of the National Plan -- to prevent and effectively treat Alzheimer's Disease by 2025, and recommend that interim milestones be explicitly stated, through development of a clear roadmap of research and treatment discovery priorities and timelines, to assure continuing and successful progress toward achievement of this goal.**
    - The text of the next version of the National Plan should include the outcome of the process currently underway to specify and prioritize interim milestones. Data from the International Alzheimer's Disease Research Portfolio (IADRP), and recommendations from the May 2012 Alzheimer's Disease Research Summit, private public working groups, and other scientific meetings and collaborations is being used in the first instance to set immediate (2013 - 2015), mid-term (2016 - 2020), and longer term (2021 - 2025) milestones to achieve the goal. Interim milestones should also include information about federal roles and responsibilities and the roles of other sectors in achieving such milestones.
    - A model of a grid with interim milestones is attached to these recommendations (Appendix A). These milestones rely on and relate to the final recommendations from the May 2012 Alzheimer's Disease Research Summit and thus represent a focused subset of potential milestones for achieving the 2025 goal. This grid is intended to be a dynamic document that will be continuously improved and refined based on the process outlined above, including input from nationally and internationally- based public and private sources.
    - While the goal of making new remedies for AD available within the next 10-12 years is ambitious, it should not be interpreted as favoring translational drug development over basic discovery. New investment in basic research and drug discovery must reflect a critical balance between long-term investment and the urgency of immediate progress to our nation's public and fiscal health.

2. **There is an urgent need for annual federal research funding to be increased to the level needed to fund a strategic research plan and to achieve the breakthroughs required to meet the 2025 goal. Initial estimates of that level are $2 billion per year but may be more. That investment would be applied to Alzheimer's research initiatives spanning basic, translational and clinical research.**
    - The Administration, working with the research and business communities, should develop an overall budget needed to achieve the 2025 goal, and should propose to Congress and support a rapid ramp up to a minimum $2 billion in Alzheimer's research at NIH. The optimum levels of annual funding

needed to achieve the 2025 goal should be determined in connection with the preparation of the President's budget, and should be reviewed and adjusted each year based on progress and new developments.

- As part of the strategic research plan mentioned in the National Alzheimer's Plan, we recommend that NIH develop a system of accountability to monitor progress toward the 2025 goal.
- We recommend that NIH coordinate with other federal agencies to ensure that overall federal Alzheimer's funding complements the NIH's investments and enhances progress towards the goal of preventing and effectively treating Alzheimer's by 2025. We also recommend that the strategic research plan identify and monitor not only existing resources within the Federal government, but also new resources outside the Federal government, including new private-public partnerships, incentives for increased private investment, State-based research funding, and mobilization of global investments.

3. **We recommend that HHS continue to develop, execute and regularly update a strategic research plan and priorities to accelerate breakthroughs in AD research.**
    - The process of developing that scientific research plan and accompanying priorities should be viewed as shared project of NIH, FDA, and other relevant government agencies; the academic and corporate research community; industry; and NGO's.
    - Given the global scope of the Alzheimer's challenge and the international character of the research enterprise, we recommend that the strategic research plan continue to be coordinated with the research efforts of other nations and that stakeholders from other countries with Alzheimer's plans in place or in process be included in the planning process.
    - The structure of the scientific research plan should be framed with the National Alzheimer's Plan updating process in mind so that issues can be addressed not only annually, but also in synch with the plan updates so that progress can be tracked using potential convening partners for different action or convening 'streams'.
    - The Director of NIH should monitor the Alzheimer's research portfolio across all Institutes and Centers of the NIH.

4. **To address disparities, we recommend that clinical research studies and activities aimed at translation of research findings into medical practice and to the public include specific targets for outreach to specific populations by racial/ethnic group, sex, and socioeconomic status, as well as to populations at high risk for AD (e.g., people with Down Syndrome).**
    - Specific recommendations for recruitment and outreach goals for diverse populations should, in our view, be integrated into planned AD research meetings/summits.
    - Resources and "formulas for success" of NIH-funded RCMARs, ADRCs, and R01 awards that have successfully recruited large numbers of ethnic

minorities and socioeconomically diverse people for clinical aging research can, in our judgment, be leveraged to inform any future recruitment efforts taken via NAPA initiatives.

- In our view, private and public entities can collaborate to increase diversity within clinical trial participation through open-architected prevention registries such as the Alzheimer's Prevention Initiative, Alzheimer's Association TrialMatch, and NIA-funded RCMARs, producing increased identification of ethnically and socioeconomically diverse people for participation in clinical studies of AD.

5. **We recommend that HHS, in partnership with experts from the research community and industry, take steps to accelerate public access to new therapeutic interventions by compressing the current average time in the process of identification of therapeutic targets, validation of those targets, development of behavioral and pharmacologic interventions, testing of efficacy and safety, and regulatory review, by:**
    - Convening expert advisory panels/conferences to identify genetic, family history, medical co-morbidities, biomarkers, and clinical features in asymptomatic persons that are risk or protective factors for AD neuro-pathological physiology and ultimately AD clinical symptoms.
    - Continuing to catalogue existing Alzheimer's biological and behavioral marker initiatives including their current development and review, and identify gaps and a plan for addressing them.
    - Issuing, upon endpoint approval, of unambiguous guidance on the use of behavioral and biological markers to industry on their usage.
    - Examining and reporting how the HHS uses existing authorities to reduce drug development barriers and accelerate development of new therapies
    - Reporting immediate steps the HHS will take to address any identified drug development barriers, including regulatory hurdles; patent, intellectual property, regulatory science, or clinical trial infrastructure weaknesses; and plans to advance regulatory science, guidance, and other initiatives under existing authorities;
    - Describing additional authorities or other legislative action that may be needed to accelerate development of therapies and diagnostics; and
    - Taking immediate steps to shorten time from market approval to coverage decision for innovative therapies and diagnostics.
    - We recommend that the FDA continue to review and periodically report to the Advisory Council recommendations to further accelerate FDA review processes without compromising current standards of safety and efficacy.

6. **We recommend that the HHS Secretary develop and describe a continuing process by which research priorities aimed at accelerating the delivery of effective treatments would be set, including input from scientific experts.**
    - There are now existing models of joint academic and Industry Working Groups, which can serve as opportunities to create true partnerships between government and industry to inform research priorities.

- In order to accelerate the process of discovery, we recommend that Working Groups identify strategies for increasing the increased standardization, disclosure, pooling and analysis of pre-clinical, clinical and electronic health data.

7. **We recommend that HHS develop accurate and relevant metrics for assessing the impact of Alzheimer's on the U.S. economy.**
   - We believe it important to develop a system of accountability for the achievement of the 2025 goal including estimates of the impact of prevention and effective treatment of Alzheimer's Disease on the US economy, families and costs to Federal health care programs.
   - Identify and rectify the shortcomings of the data needed to assess the prevalence, costs (financial, fiscal and economic), and deaths relevant to Alzheimer's disease.

8. **We recommend that HHS commit to an effort to maximize private investment in the development of treatments and improvements in disease monitoring technology by identifying policies that would encourage private industry to invest aggressively in disease-modifying interventions, to support technologies that improve our ability to detect the disease as early as possible, monitor the disease accurately so that the effectiveness of interventions can be tested, and identify and prioritize the action steps needed to reduce the time for moving therapies from target identification and validation through clinical development, regulatory review, market approval, and reimbursement determinations**
   - The Secretary, in conjunction with NIH and FDA, should increase targeted public-private partnerships that bolster innovation and regulatory science progress.
   - As part of the larger NAPA agenda, we recommend that a process or mechanism for securing sustained industry input on topics such as measures to spur discovery and streamline regulatory review, tax, and Intellectual Property be established, with a particular emphasis on diminishing the barriers to sharing both basic scientific and clinical data), and other incentives.
   - We believe a strategic use of SBIR, STTR and other co-investment initiatives can be used to promote advanced research and support from small businesses engaged in this work.
   - Through a joint public-private process, we believe that we can advance other related actions included under other recommendations (e.g., the industry engagement with NIH, research prioritization, behavioral and biomarker and endpoint validation, etc.) that are already known to be of importance to industry.

9. **We recommend that the Administration continue to expand and enhance meaningful coordination with global partners and move forward to establish a Global Alzheimer's Action Plan to respond to the global scope of the problem.**
    - Continue to meet with nations or regions with National/Regional Alzheimer's Plans in place or under development by 2013 in order to compare approaches and identify mechanisms to foster global coordination and progressively address the global problem.
    - The responsibility for such an initiative would require the identification of a single high-level U.S. official as the point person for the National Alzheimer's Plan and appointment of that person to represent the nation as part of an ongoing dialogue with global counterparts.
    - Any Global Alzheimer's Action Plan should foster ongoing international dialogue and potential coordination on Alzheimer's regulatory review and related issues.

10. **We recommend that the Administration designate specific Offices and officials within the White House and the Office of the Secretary of Health and Human Services with responsibility and accountability for effective implementation of, and timely, transparent reporting on, all aspects of the implementation of this National Alzheimer's Plan, including responsibility for issuing statutorily required reports to Congress on behalf of the Secretary, reports to the Advisory Council, and other reports as warranted.**
    - The designated Office within the White House should be responsible for adequate monitoring across agencies and the designated Office within the Office of the Secretary of HHS should be responsible for monitoring within the departments of HHS.
    - These officials will develop a system of accountability for the achievement of the 2025 goal based on quantifiable metrics and milestones with respect to the action steps and strategies in the national plan.
    - We recommend that the Secretary, as part of her annual report to Congress and the Advisory Council, report on progress over the prior year in meeting the annual objectives, strategies and actions enumerated in the National Alzheimer's Plan, as well as providing a comprehensive, multi-year perspective, and mid-course corrective action steps, that are needed in order to meet the 2025 goal of this Plan.

APPENDIX A

INTERIM MILESTONES TO COMPLETE THE FIRST GOAL OF THE NATIONAL ALZHEIMER'S PLAN BY 2025 (includes cross references with *Alzheimer's Disease Research Summit 2012* recommendations)		
Years	**Milestones in Research**	**Milestones in Regulatory Review**
2013-2015	• Adoption of National IRB (S3B8[i];S6B7[ii]) • Develop mechanism for sharing of new data via web-based resource S1B8 • International Infrastructure for academic/industry interface and data sharing accelerates research (S1B8[iii];S6B4[iv]) • Initiate standardization and validation studies in biomarkers for MCI due to AD (S1B6[v];S3B5[vi]) • Investigate cognitive and behavioral measures for earliest detection of AD that are sensitive to change and predict long-term clinical and functional outcomes. (S3B4[vii]) • Large-scale registry of early midlife to late-life individuals, oversampling ethnic minorities and those with lower education speeds trial enrollment. (S3B3[viii]) • Secondary prevention trials launched, including behavioral interventions such as physical exercise and cognitive training (S3B1[ix]) • International research collaborations initiated	• FDA adaptive trial model for AD is adopted in industry trials (S2B10[x]) • Biomarkers for MCI due to AD are incorporated into industry trials[xi] • Clinical endpoints for MCI due to AD incorporated into industry trials[xi]
2016-2020	• Established pathological pathway for AD including genomics for accurate target identification in clinical trials (S1B1[xii];S1B2[xiii]) • Validated biomarker for asymptomatic AD and disease progression (S3B5[xiv]) • Validated cognitive marker for asymptomatic AD (S4B3[xv];S5B3[xvi]) • Active implementation of secondary prevention into clinical communities in asymptomatic AD (S5B7[xvii])	• New FDA approved treatment to ameliorate symptoms of AD dementia[xi] • Surrogate biomarker for preclinical AD • FDA approved treatment for MCI due to AD[xi] • FDA approved treatment to delay Alzheimer's dementia in people with MCI due to AD[xi]
2021-2025	• Active implementation of secondary prevention into clinical communities in asymptomatic AD (S5B7[xviii]) • Delay onset of MCI in people with preclinical AD	• FDA guidance on cognitive endpoint for asymptomatic AD[xi] • FDA approved treatments for asymptomatic AD[xi] • FDA approved treatment to delay MCI due to AD in people with preclinical AD[xi]

NOTE: Each endnote cites a recommendation from *Alzheimer's Disease Research Summit (ADRS) 2012* (http://www.nia.nih.gov/announcements/2012/05/alzheimers-research-summit-may-14-15-2012). Citations are made using the format S#B#, where S# refers to the Session number, and B# refers to a particular bulleted recommendation from that session. For instance, S3B4 would refer to the fourth bulleted recommendation from Session 3. These recommendations are available directly at: http://www.nia.nih.gov/newsroom/announcements/2012/05/alzheimers-disease-research-summit-offers-research-recommendations.

i. S3B8: "Support broad infrastructure changes that will accelerate and improve the efficiency of prevention initiatives, including the formation of a national centralized Institutional Review Board for multi-center Alzheimer's disease trials and the development of agreements for data sharing of de-identified data from both placebo and treatment arms via public databases."

ii. S6B7: "Develop a National Institutional Review Board for Alzheimer's disease studies accessible to both public and private funding research organizations."

iii. S1B8: "Enable rapid sharing of new data via web-based resources with the capacity to store large and diverse datasets (such as data about clinical phenotypes, genetics, epigenetics, proteomics, and metabolomics) that can be used for testing different models or hypotheses at the computational level."

iv. S6B4: "Data sharing (with standardized ontologies and metadata)."

v. S1B6: "Develop robust biomarkers that can feasibly be obtained in large cohorts of volunteers, including metabolic signatures to develop and validate diagnostic, prognostic, and surrogate biomarkers for Alzheimer's disease and biomarkers for disease subtypes."

vi. S3B5: "Optimize biomarkers for detecting and monitoring the progression of Alzheimer's disease, and focus particularly on standardization. These biomarkers will be used to elucidate the temporal trajectories over the course of preclinical and prodromal Alzheimer's disease, to assess the proximity to onset of clinical symptoms, and to predict long-term clinical response to treatment."

vii. S3B4: “Develop, validate, and standardize sensitive neuropsychological and other clinical and behavioral measures to detect and track the earliest clinical manifestations of Alzheimer’s disease and to predict long-term clinical and functional outcomes. These measures should be sensitive to change and capture the variability in cognitive function that may be an important predictor of treatment response.”

viii. S3B3: “Expand large-scale registries and natural history cohorts of healthy individuals from early midlife to late-life, as well as individuals with subjective and/or objective cognitive impairment and use the data generated to inform clinical trial design. These cohorts should be population-based and should oversample underrepresented ethnic minorities and groups with lower education.”

ix. S3B1: “Initiate treatment trials in asymptomatic, at-risk individuals (e.g., individuals at risk genetically, older adults positive for biomarkers for Alzheimer’s disease) using uniform biomarkers and cognitive outcomes, informed by data from Alzheimer’s disease trials using patients with more advanced disease.”

x. S2B10: “Provide an expedited review track for applications focused on drug discovery, preclinical, and clinical drug development for Alzheimer’s disease to mitigate difficulties with intellectual property and commercialization issues that are imposed by the current lengthy review/grant cycle at the NIH. Establish multi-disciplinary review panels with adequate expertise to evaluate all aspects of translational research.”

xi. While not directly referenced in ADRS 2012 recommendations, this milestone is a straightforward and critical milestone in the translation of research advances to full the purposes of PL 111-375 (http://www.gpo.gov/fdsys/pkg/PLAW-111publ375/pdf/PLAW-111publ375.pdf) and Goal 1 and corresponding strategies in the National Plan to Address Alzheimer’s Disease (http://aspe.hhs.gov/daltcp/napa/NatlPlan.shtml).

xii. S1B1: “Intensify scientific efforts to deepen the understanding of the complex pathobiology of Alzheimer’s disease, and diversify target identification to better address the multifactorial nature of the disease. These efforts should include the use of systems biology approaches and tools, as well as cutting-edge stem cell technology.”

xiii. S1B2: “Develop a better systems-level understanding of how the many discoveries that have already been made (e.g., genetic, pathological, biochemical, radiological, neuropsychological) and the contributory factors that have already been identified (e.g., Ab, tau, apoE4, a-synuclein, TDP-43, aging, proteostasis failure, mediators of inflammation, comorbidities) are related mechanistically.”

xiv. S3B5: “Optimize biomarkers for detecting and monitoring the progression of Alzheimer’s disease, and focus particularly on standardization. These biomarkers will be used to elucidate the temporal trajectories over the course of preclinical and prodromal Alzheimer’s disease, to assess the proximity to onset of clinical symptoms, and to predict long-term clinical response to treatment.”

xv. S4B3; “The optimal therapy for Alzheimer’s disease may involve the use of drug combination cocktails and require different composition of these cocktails at different stages of the illness. To facilitate the development of effective combination therapies, develop translational workgroups that include experts in network biology and network pharmacology.”

xvi. S5B3: “Initiate rigorously designed clinical trials in asymptomatic and cognitively impaired older adults to establish the effectiveness of physical exercise, cognitive training, and the combination of these interventions for Alzheimer’s disease treatment and prevention.”

xvii. S5B7: “Invest in research to develop technologies that promote prevention and treatment trials, clinical care, caregiver support, and in-home monitoring.”

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