Research Workgroup Suggested Recommendations

Strategy	Comment	Recommendation
1A: Identify Research Priorities and Milestones	Tom Sudhof (Stanford University)	• I think we as a field need more research on the clinical and pathological definition of AD, its relation to microvascular diseases and to other types of neurodegenerative disorders, and its genetics vs. environmental factors. Large-scale genetics as done in the autism field would be particularly helpful. • It seems to me that the value of solid reproducible fundamental research should be more emphasized. At present, there are many stories coming out in the AD field in major journals almost every week, but at least some of these stories, may be the majority even, turn out to be simply wrong after closer consideration. I have the impression that we need to emphasize that at present there really are not that many 'translatable' research findings, and that obtaining a better fundamental definition of the underlying biology may be boring, but is necessary.
1B: Enhance Scientific Research Aimed at Preventing and Treating Alzheimer's Disease	David Holtzman (Washington University School of Medicine)	HHS and its Federal partners will continue to aggressively conduct clinical trials on pharmacologic and non-pharmacologic ways to prevent Alzheimer's disease and manage and treat its symptoms. HHS will build on recent advances and expand research to identify molecular underlying mechanisms in areas such as genetics, protein aggregation, neurovascular biology, and the cell and molecular biology of the nervous system to identify risk and protective factors as well as new candidate therapies. To achieve this strategy, new partnerships and outreach efforts may be needed to ensure that enough people are enrolled in clinical trials to examine the effectiveness of promising interventions.
1B: Enhance Scientific Research Aimed at Preventing and Treating Alzheimer's Disease	Charlie Glabe (University of California Davis)	To me, an important part of the initiative is "Strategy 1.B Enhance Scientific Research..." The FDA really does need to "**aggressively conduct clinical trials on pharmacologic and non-pharmacologic ways to prevent Alzheimer's disease**". Human clinical trials provide crucial information about which targets and mechanisms are most valid and currently they are a bottle neck for advancing our understanding. Basic research using transgenic models has identified a large number of potential mechanisms and targets, but we won't know which leads are most promising until they are tested in humans. There is increasing evidence that the disease process starts well before cognitive symptoms, so clinical trials designed to prevent AD could be the key to providing a therapeutic breakthrough.
1B: Enhance Scientific Research Aimed at Preventing and Treating Alzheimer's	Amy R. Borenstein, Ph.D., FAAN James A. Mortimer, Ph.D, FAAN	We and others have shown that given a level of pathology, people with more brain reserve can delay their symptoms of AD. What has not been done is to test interventions that increase brain reserve in population-based samples in the community. Most intervention studies of non-pharmacologic agents thus far have used volunteer subjects. We don't know which non-pharmacologic interventions work best in the population at large, and we don't know the relative ranking of such interventions, or if and how they interact with one another. Also, we feel strongly that interventions should be done on information

Disease	(University of South Florida (via Alz Forum))	that is personalized. In other words, someone who does not exercise and smokes should be targeted on these factors, whereas someone else who is obese and has diabetes should be targeted on those factors. Also, while biomarkers indicate that we can predict about 10 years before symptoms who is going down a malignant trajectory vs. a more normal trajectory, we know that the pathology of AD develops over decades, and that prevention must occur at a much younger age. Therefore, what is needed in the NAPA are community-based studies of young-middle aged adults. We would need to gather careful epidemiologic data, including family history, head trauma, vascular diseases, exercise habits, diet, cognitive and social stimulation, and measures such as BMI, waist and head circumference, blood pressure, HbA1c, insulin levels, DNA (APOE and others) and follow these populations over time with neuropsychologic measures and perhaps with MRI. AD is a complex disease occurring probably over the lifespan, and if we had a large enough population-based study we could design the study cleverly so that we can see what is happening at different, say, 5-year age groups over the life course (beginning perhaps as low as 20). Biomarkers are good for predicting high-risk individuals about 10 years before symptoms occur. This is occurring over a back-drop of decades of accumulating pathologies. We don't just want to predict who is at high risk - we want to take those people (and perhaps those at moderate risk) and put them into prevention programs to delay onset of the disease. If we only have the prediction part and not the prevention part, we will not be successful in Goal 1. The study does not have to be decades long, but it must have a sufficient number of people to accomplish the goal of discovering which preventions work best (by explaining the population attributable risk) and which interact. We have proposed such a study to be done in China where there is a lot of vascular brain disease and where it is easy to get thousands of people involved on a detailed research level but while we were well reviewed in study section our grant did not get funded. Dr. Mortimer and I would be happy to be involved in the design of an observational/interventional epidemiologic study in population-based subjects of primary preventions.
1C: Accelerate Efforts to Identify Early and Presymptomatic Stages of	**David Holtzman (**Washington University School of	Significant advances in the use of imaging and biomarkers in brain, blood, and spinal fluids have made it possible to detect the onset of Alzheimer's disease, track its progression and monitor the effects of treatment in people with the disease. Without these advances, these neurodegenerative processes could only be evaluated in non-living tissues. Accelerated research will improve and expand the application of biomarkers in research and practice. These advances have shown that the brain changes that lead to

Alzheimer's Disease	Medicine)	Alzheimer's disease begin up to 15 years before symptoms. Identifying imaging and other biomarkers in presymptomatic people will facilitate earlier diagnoses in clinical settings, as well as aid in the development of more efficient interventions to slow or delay progression. While additional work needs to be done on biomarkers, we have enough information now that should allow secondary prevention trials in presymptomatic people to begin immediately with the most effective therapies.
1C: Accelerate Efforts to Identify Early and Presymptomatic Stages of Alzheimer's Disease	***Charlie Glabe*** (University of California Davis)	When these trials fail, they don't tell us anything useful because the rationale for testing them was that they were harmless rather than their targets were implicated in the disease. They need to be more aggressive in testing other compounds that have a strong mechanistic rationale for prevention. If the government thinks that it will just "continue to aggressively conduct clinical trials", then they are blowing smoke because what they are doing now is not aggressive. In cancer trials, the FDA has approved trials where the treatment has killed a substantial percentage of the group because it had the potential to cure some of them and they were all going to die soon anyway. The FDA just doesn't look at AD the same way. The most significant thing to accomplish is to change the way the FDA looks at clinical trials for AD. We have lots of targets and drugs that just aren't getting tried on a reasonable time frame.
1D Coordinate Research with International Public and Private Entities	Jeff Morby (Cure Alzheimer's Fund)	• Make "third party" or "pass through" Alzheimer's organizations (such as Cure Alzheimer's Fund) eligible for federal funding. The funding should NOT be used for organizational overhead or indirect expenses, but should be used by the organization to fund breakthrough Alzheimer's research. Such organizations are excellent "aggregators" and consortia builders --- much better than the research institutions themselves which have more of an interest in funding their own institutions. Private, non-bricks-and-mortar organizations are designed to put together leading researchers for innovative research. Help from the government for these kinds of initiatives has the potential to move the field much farther much faster. • Similarly, there should be more opportunity for co-funding of projects from government and private entities. Matching funds from the government for private initiatives, or the other way around, could generate considerably more private capital for focused, high level science than is the case today.
1E Facilitate Translation of Findings into Medical Practice and Public Health Programs	David Holtzman (Washington University School of Medicine)	In regard to 1E below, there is nothing wrong with what is stated but this is not the problem! We need treatments! If there is nothing to disseminate, 1E is a waste of time. Currently, promising research and interventions are published in the research literature and presented at scientific meetings. Additional steps are needed to highlight promising findings and to facilitate dissemination and implementation of effective interventions to the general public, medical practitioners, industry, and public health systems quickly and accurately. This may require new partnerships within the Federal Government and with the private sector, and outreach through new mechanisms.

1E Facilitate Translation of Findings into Medical Practice and Public Health Programs	Sam Gandy (Mount Sinai Hospital)	Ideally, a National Institute on Dementia Research should be established as a new NIH institute with a director on par with directors of existing institutes, and supported by contributions from (and including representatives from) NIA, NINDS, NIMH, NIDDK, NIEHS, NHLBI, NCCAM, NHGRI, NCATS, NICHD, VA R&D, and DoD (and maybe others).
1E Facilitate Translation of Findings into Medical Practice and Public Health Programs	Berislav Zlokovic (University of Southern California)	I feel there is a gap there on a larger scale although there have been some good examples as well how to breach that gap. One problem when you talk with clinicians is that many of them still view Alzheimer's disease to be a very separate category from so-called 'vascular-dementia', although vascular factors and circulatory problems in brain including blood-brain barrier problems have been frequently indentified in patients diagnosed with Alzheimer's disease. In that regard the present document is not clear about whether the goal will be to cure dementias of either Alzheimer's type or so-called vascular, which to my own bias is only a different phenotypic expression of similar diseases that in some cohorts more openly shows vascular feature than in others. I feel this issue should be addressed somehow because this might impact the numbers. Another gap is between genetic studies and the biology of disease. For example, we still do not know how mutations in some genes that have been recently associated with sporadic AD relate to the biology of disease. More specific emphasis perhaps can be placed on these studies. In general it will be great to expand Strategy 1E with some more specific examples. But, perhaps that can be done after the May summit which I understand should provide some concrete guidance on the research priorities. Are we going to be represented at the May summit?
General Comments		
Bruce Lamb (Cleveland Clinic)		**1) Committing Additional Resources to Research** The planned NIA sponsored conference in May 2012 will provide invaluable insight into the goals and strategies required to achieve the goal of a treatment/prevention by the year 2025. However, while a reorganization and coordination across all research domains will increase research productivity, without additional research funds, the goals of having a treatment/prevention by 2025 is likely unattainable. There is currently no effective treatment for AD and thus additional funds are necessary to promote basic research, translational research, drug development and clinical research. Currently, funding rates at NIH and most non-profits is in the single digits (5-10% of all grant being funded), thus leaving a very large number of meritorious applications (the top 20-25%) unfunded. If we are truly

	serious about achieving the goals set forth in the Draft Framework, additional federal, non-profit and industrial investments in Alzheimer's research have to be part of the answer. While there will likely a considerable debate about the exact amount of investment required to achieve this goal, a starting point would likely be $2 billion/year as put forward in the Alzheimer's Breakthrough Act of 2010. As clearly laid out in the attached paper by myself, Dr. Todd Golde and Dr. Doug Galasko, similar types of investments in other diseases (i.e., HIV/AIDS) have proven transformative and lead to effective therapies. While I appreciate that the current funding climate is very tight and highly political, it is only with these types of investments are we likely to transform the Alzheimer's research endeavor and achieve Goal 1 of the Framework. **2) Strategies/Goals** The conference in May of 2012 will certainly help identify the key research areas that need to be addressed to achieve Goal 1 of the Framework. As part of the detailed National Plan, it will be important to both identify these targets as well as commit funding commensurate to achieve the goals identified. Funding one research domain at the expense of another with not enable us to achieve the ultimate goal laid out in the Framework. For each target, clear goals must be identified and a infrastructure/organization (see below) put in place to regularly assess progress within these areas. **3) Infrastructure/Organization** To achieve Goal 1 of the Framework, it will be absolutely critical to have an infrastructure and organization that can coordinate federal research efforts across all funding agencies, interact with non-profits and industry, promote awareness of the disease and the role that research will play in combating the disease as well as reporting to the Advisory Council directly as outlined in the Framework. In order for this organization/infrastructure to be truly successful and transformative, it will be essential that its efforts are entirely focused on combating Alzheimer's disease. This will provide a uniquely focused organization that will have the most chance of success. A similar "disease-focused" agency was created in 1988 for HIV/AIDS entitled the "Office of AIDS Research" (OAR) within the Office of the NIH Director, that played a key role in successfully coordinating the federal response to AIDS. The NIH Revitalization Act of 1993 strengthened the OAR, providing it with increased authority in the planning, coordination and evaluation of AIDS research. If we are truly serious about transforming Alzheimer's research and achieving the goals laid out in the Framework, a similar type of organizational structure (perhaps an Office of Alzheimer's Research?) is required.
Tim Armour (Cure Alzheimer's Fund)	My bias is to support Goal 1 of the Draft Framework in order to raise urgency, create more awareness and focus resources on the issue.

	However, for this to be an effective strategy, we need to be able to: 1. Set a time limit as is being suggested. 2. Define the goal as precisely as we can. Does our goal mean: " Delay onset of Alzheimer's disease, minimize its symptoms, and delay its progression" as the text goes on to say in this Goal? If so, we need objective metrics to measure these outcomes. We also need to be clear about expectations around the nature of the therapies to be developed. Almost certainly there will not be one blockbuster drug that "cures" people, but rather different interventions used at different phases of the pathology and with different genotypes. This is not easy stuff to convey --- no bumper sticker phrasing here, but rather a need to be patient and clear about the expectations for effective therapies. To mount an all-out national effort, we need to be very clear about the endpoint, "aspirational" or not. 3. Suggest at least the order of magnitude of the resources needed to achieve the goal. It has been pointed out that setting these objectives is risky business. Particularly in AD, but not unique to the field, some researchers and others have raised false hope and expectations repeatedly with promises of a "cure within the next five years" for a long time. Credibility for this effort and responsibility to patients and their families demands that we define our objectives as carefully as we can within the context of an aspirational goal. Finally, we need to emphasize that this focus on research is not at the expense of, but in support of clinical efforts to help people already affected. The language concluding this goal does this and should be retained and if anything, strengthened. HHS will prioritize and accelerate the pace of scientific research and ensure that as evidence-based solutions are identified they are quickly translated, put into practice, and brought to scale so that individuals with Alzheimer's disease can benefit from increases in scientific knowledge.
Beth Bishop (Volunteer – Alzheimer's Association (via Alz Forum))	One thing that strikes me over and over is that when people go to their "regular" practioners, they often get very vague information and appropriate diagnoses. People who go to most geriatricians get the latest information. Somehow we need to have training for the variety of family and internal medicine practioners, and even specialists to enable them to recognize the early/all signs of

	the various dementias and the overlaps of the various complications such as diabetes, concussions, and Parkinson's etc. Without specific education of the medical community in the form of continuing education, all the research in the world won't be disseminated and used to its potential. We need further training of all doctors to recognize the problems, and make the connections to a disease that devastates! I hope these ideas will be included as part of the national plan proposed.