ADVISORY COUNCIL ON ALZHEIMER'S RESEARCH, CARE, AND SERVICES

Washington, DC

January 26, 2018

WELCOME AND CHARGE FOR MEETING

Laura Gitlin, Ph.D., Johns Hopkins University, Chair
Dr. Gitlin opened the meeting at 9:05 a.m. and invited Council members to introduce themselves. Participating by telephone were: Joan Weiss, Health Resources and Services Administration (HRSA); Susan Cooley, U.S. Department of Veterans Affairs (VA); Debra Olster, National Science Foundation (NSF); and Ellen Blackwell, Centers for Medicare & Medicaid Services (CMS).

Dr. Gitlin read Donna Walberg's letter of resignation from the National Alzheimer's Project Act (NAPA) Advisory Council. Debra Cherry, Ph.D., will take her place as chair of the Long-Term Services and Supports Subcommittee.

Rohini Khillan acknowledged the passing of Joshua Wiener, Ph.D., who had contributed much to NAPA's deliberations.

PROGRESS SINCE THE OCTOBER MEETING

Laura Gitlin, Ph.D.
Dr. Gitlin is updating and organizing the NAPA Plan to enable it to be more impactful, namely by having an executive summary, tracking updates, updating strategies under the goals, and soliciting and tracking non-federal items for Plan updates. This level of organization is needed so we can see how NAPA recommendations fit with the Plan by goal and strategy. Dr. Gitlin and Ms. Khillan are engaged in ongoing conversations with subgroup chairs about the central roles that non-federal members can play. The first step is to generate recommendations, followed by deciding what to keep and move forward from previous years. Discussions are also being held regarding the best strategies to take advantage of openings in Congress where we can push forward key issues to appropriate members of Congress and other organizations. These measures respond to comments and discussion from the last meeting.

Rohini Khillan, Office of the Assistant Secretary for Planning and Evaluation
Ms. Khillan will discuss this approach with Department of Health and Human Services (HHS) planners to ensure that the NAPA Plan is up to date (e.g., with work from the National Institute on Aging [NIA] and the International Alzheimer's Disease Research Portfolio). Some matters fall under survey territory. Evaluation of progress fits into the

driver program. Subcommittees and federal workgroups should continue to tie their activities back to the Plan.

To enable tracking of public comments, Brenda Veazey, webmaster for NAPA, has reviewed and categorized 6 years of comments.

DISCUSSION OF THE NAPA COUNCIL DRIVER DIAGRAM

Bruce Finke, M.D., Indian Health Service
A Driver Diagram is a logic model to help everyone see what is necessary to reach the NAPA aim (i.e., eliminating the burden of Alzheimer's Disease [AD] by 2025). It is an action model but differs from other action models in its acute focus on the aim, the key leverage points to reach the aim, and the ideas and specific actions within each Driver Diagram. Everyone agrees on what we want to accomplish, and this model unifies how we get there by providing us with a broad overview of where things fit together and affect they each other.

Notably, a Driver Diagram is not fixed in time. It is a theory about the actions needed to achieve the stated goal and it must have clearly defined aims, but it is intended to be flexible to allow us to see progress made over time. Measurement is an important aspect, and usually the aim is reflected through some measure. Drivers needed to achieve the measure are the key levers within each aim. At the same time, no measures are perfect, but some offer a view of what is happening over time. This will give us a way to see what we are doing as an advisory committee and what the federal staff are doing.

In the first round, the primary drivers are the five Goals of the National Plan. The secondary drivers map to the strategies under those five Goals. The subcommittee and federal workgroup chairs have met to discuss and further refine the diagram. The work of the "Enhance Care Quality and Efficacy" and the "Expand Supports for People with AD and Related Dementias and Their Families" subcommittees overlap significantly.

Rohini Khillan
Ms. Khillan noted that actions should be referred to as themes and concepts. Certain themes (e.g., scientific roadmap for achieving the goal by 2025) keep recurring and we need to develop recommendations around them. Then we need activities conducted by either the federal agency or non-federal partners to address the recommendations made.

Laura Gitlin, Ph.D.
Dr. Gitlin said that the specific actions and measurements present challenges. She emphasized that this is a dynamic product that will continue to be revised.

Comments and Questions

- ***Robert Egge*** fully supports the use of the Driver Diagram because of its goals, strategies, and actions. It illuminates where we are now and where we are headed. He also wondered whether that is collectively sufficient. ***Dr. Gitlin*** would like to keep documenting these questions as the Council continues working. ***Dr. Finke*** thought Mr. Egge hit the two most important points, namely that the Diagram is not a substitute for action but a way to achieve action, and that, if it is to be effective, it must prompt these sorts of questions. ***Ms. Khillan*** gave the example of issues that keep coming up every year.

- ***Gary Epstein-Lebow***: The Driver Diagram could be simpler if the right side listed only immediately impending actions and not the ones already accomplished. ***Dr. Gitlin*** was thinking of that as the categorization of plans. ***Dr. Finke*** thought it made sense for an active diagram that shows the work we need to do to get where we want to go, but not where we have been. Are the nice ideas really necessary to get us where we want to go? ***Ms. Khillan***: We are starting this process in the middle rather than at the beginning, and we have to give some account of what has already happened, although not necessarily in this document. ***Dr. Gitlin***: The diagram is a presentation, not a conceptualization.

- ***Becky Kurtz***: The Diagram is comprehensive, but it does not help subcommittees prioritize. ***Shari Ling***: How do we consider day-to-day situations and illustrate and bring forward the barriers and impediments? There may be lessons learned. Nevertheless, visual management helps in many ways. Measuring impacts is particularly challenging and to do it we must measure the sub-actions. It is a complex problem that could lead to lost momentum.

- ***Laura Gitlin***: Many of these things are place-holders. Once they are filled in, we need to discuss strategy. We are talking about prioritization. ***Dr. Finke***: A Driver Diagram is generally a prioritization document--if we want to get to A, we have to do the following. And we do what we can do when we can do it. The tool is meant to help you prioritize. One challenge over the last 5 years is that agencies work on a year-to-year budget, but as a committee we need a longer view. Prioritizing does not mean we are doing everything at once, but that we think that action is important. ***Ms. Khillan*** will be working with subcommittee chairs on the fourth column (i.e., actions/change ideas). If we have all recommendations for the past 6 years, those priorities will emerge. Going forward, it will be more of a living document.

- ***Laura Gitlin***: We have to think through the barriers and how they are documented--that measurement is really important. Agencies often have their own measurement strategies, which could be useful.

- ***Erin Long***: At the Administration for Community Living (ACL), we have a wide range of measurements. ACL tries to validate the things they are funding and the work of the people. Recently we have been developing a tool for how people across the board have "moved the needle." Enhancing care is a metric for how many people are using various kinds of care. They also measure quality of life issues (e.g., through education or outreach) and whether the work achieves the goal. Broadly, this will keep things moving forward.

- ***Laura Gitlin***: How many states use evidence-based programs for various goals? If only 20 states use them, we may need a recommendation to expand that. That would allow subcommittees to think through the issue. The federal agencies' existing measures could be a place to start. What measures does each agency use that could apply here to give us an integrated document? For example, can we document reduction in psychotic episodes? How do we take the success of those long-term care facilities and incorporate them?

- ***Shari Ling***: Making the measurement visible is the first step. We can document behavior by state, calculate targets, and share those targets (which would involve a national partnership). A partner can do one thing or another to contribute to the overall process. For any metric we need reliable data sources. Optimally, we need to know whether we are improving outcomes while recognizing that there are limitations.

- ***Bruce Finke***: Usually in this kind of improvement work, the right of the diagram shows process while the left shows outcomes. Measurement is often seen as an additional expense. Therefore, it would be a good idea to use existing measures if they help inform our view. Do they give a working view of how well we are progressing? This is a different use of measurement than usual.

- ***Becky Kurtz***: Reducing the use of anti-psychotic drugs is an example of something that is not a strategy for how to measure, but a measure to figure out a strategy. Measurement implies a huge amount of work with meetings and the education component. Even if we use an existing measurement, it will require a lot of work to adjust it for our purposes. ***Ms. Khillan*** noted that we need to show what the National Plan is.

- ***Laura Gitlin***: We need to give more thought to the secondary drivers. Where is the data point to know our baseline? We need recommendations as to how to get at some of these measures.

- ***Rohini Khillan***: Another problem is that the Driver Diagram keeps getting bigger and bigger. One criterion for inclusion would be whether the entry helps explain to other people what we do.

- ***Bradley Hyman***: An underlying assumption of this method of organization is the time frame. The National Plan's first goal is to "prevent and effectively treat

Alzheimer's disease by 2025." That imposes a temporal order. Is there a way to organize these aims according to when they are needed? ***Dr. Gitlin***: That is a great point. The time dimension is another way to cut this. Perhaps we could do something within the subcommittees.

- ***Anthony Pacifico***: Some of the ideas here sound like programmed research. To prioritize, the Army uses Peer-Reviewed Alzheimer's Research Programs, which are technology training cycles. You wind up with a product, but have difficulty incorporating innovation. Some results are not only products but also infrastructure.

Dr. Gitlin summarized:

- We agree that a Driver Diagram can be helpful.
- We can evaluate to help move forward.
- We will ensure that we don't get "stuck in the weeds."
- She wants to follow up on Mr. Egge's comments that the diagram is not a substitute for action, but a way to achieve action, and whether the diagram is collectively sufficient to prompt the needed questions.
- We want to think through the measures.
- We need to consider the concept of reliable data sources.
- We need to think about barriers.

Ms. Khillan outlined action items and will work with subcommittee chairs to get to prioritization. She may develop a list of what each agency uses. Subcommittees should insert these considerations into their 2018 recommendations.

FEDERAL WORKGROUP UPDATES

Long-Term Services and Support Subcommittee

Erin Long, Administration for Community Living, Administration on Aging
Since October, ACL has been involved in giving awards; 11 programs were funded in September. Data on the impact of these programs will begin to be compiled soon (Goal 3 and 4 of the Plan). A huge part is education, training, and community building. Specific activities include a webinar on Lewy body dementia (LBD) last year and frontotemporal degeneration (FTD) this year. When the webinars began, 30-50 people attended, but now as many as 1,000 attend. ACL has partnered with Sharon Denny and the Association for Frontotemporal Degeneration (AFTD). Next week a webinar will be presented on the international perspective, highlighting Scotland. In November, a webinar was presented for the Native American community, and provided education under Title VI (education and nutrition).

Lisa McGuire, Ph.D., Centers for Disease Control and Prevention
The Centers for Disease Control and Prevention (CDC) is developing a new roadmap of action items for state and local officials; 35 action items address cognitive function. This was developed in partnership with the Alzheimer's Association. We now have 25 draft action items under review. We are focusing on early diagnosis and disclosure, and the next steps that should be taken at the public health level. We are working with tribal organizations to develop ancillary material that will be applicable to these populations. CDC initiated the process in June and will release the roadmap in mid-2018.

Comments and Questions

- ***Laura Gitlin***: In light of current privacy laws, how do you evaluate impact? ***Ms. Long***: It is challenging, but we use a survey to solicit comments on whether people are getting what they want. Also, the webinars offer continuing education credits (CEUs), so we can get some information by the number and type of professionals who use them, and what organizations are involved. ***Dr. McGuire***: Although we cannot collect personal information, we get numbers of people who participate in the webinars and the kind of professionals who are getting the CEUs. ***Dr. Gitlin***: The reach is what we're trying to get at. We provide education, but it is challenging to measure how and whether that gets used.

- ***Robert Egge***: CDC has done great work on this. Adis data are expected, but how? ***Ms. Long***: All grantees are required to evaluate their projects. The Office of Management and Budget has approved this data collection tool, and all programs are required to report with it. The research division will outline how each program has furthered its outcome measures. Only three are closed now, so the first closed-grant report will probably be ready next year.

- In response to ***Debra Cherry***, ***Dr. McGuire*** said the target of the third roadmap is much like that of the second. We want to have actions that are doable and that make sense for the target audience

- Replying to ***Cynthia Huling Hummel***, who asked whether they include people living with dementia, ***Dr. McGuire*** said CDC involves the early stage group from the Alzheimer's Association.

- ***Laura Gitlin*** asked about dissemination. ***Dr. McGuire*** replied that they are working through organizations and their chapters, using conferences, webinars, etc. ***Mr. Egge*** stated that the association perspective will be major for his state. ***Dr. McGuire***: We may also get the news media involved. ***Dr. Finke*** noted that the Alzheimer's Association has reached out to Indian Health Service (IHS).

Clinical Care Subcommittee

Shari Ling, M.D., Centers for Medicare & Medicaid Services

CMS identified specified actions and provided a link to more information on each. Each year in December, they have to propose a list of quality measures to be included for implementation; this is the Measures Under Consideration list. The measures are discussed based on what they are, how they will be used, and what purpose they serve. For example, nursing home care may only be needed for a few days and collecting information on patients' experience could be helpful. However, gathering and documenting patients' perception of their care remains a gap. CMS addressed this issue by asking discharged patients whether they would recommend the facility to friends and family, how they rated the staff, how they rated the care received, and how they rated whether discharge needs were met. Results are under deliberation.

In December, CMS's Medicare-Medicaid Coordination Office sponsored a five-part webinar on interdisciplinary care teams for older adults. Meanwhile, they are producing resource guides, which are available on the website. We can collect information on how many viewers were reached in training.

The Center for Medicare and Medicaid Innovation is implementing two new plans. One is the Value-Based Insurance Design Model for 2019, which encourages customized benefit designs and flexibilities to address the specific health needs of beneficiaries and allows for care and services that go beyond the scope of usual care. The other plan is Comprehensive Primary Care Plus (CPC+), presented by Janel Jin. CPC+ is an alternative payment model. It is being demonstrated with more than 60 care partners, nearly 3,000 care practices, and more than 13,000 practitioners supporting more than 1.8 million Medicare beneficiaries. CPC+ involves national and regional learning communities. We ask care partners to commit to a similar level of support.

In November, CMS posted the Community-Based Care Transitions Model's final report. They found that while it did not have hospital-wide impact, it did affect those who received the services. Hospital administrators evaluate for specific conditions and adjust practices accordingly. Because this practice runs concurrent with many models, its effects on the model are difficult to discern.

In 2015, CMS introduced a Chronic Care Management Service to improve primary care for Medicare beneficiaries and enhance continuity of care, coordination, and care planning. The code is available to those who have more than one condition. In the first 2 years, 665,000 beneficiaries received CCM services. Although the impact still remains to be determined, both beneficiaries and providers indicated satisfaction with the service.

This fall, CMS's Office of Minority Health, working with the Substance Abuse and Mental Health Services Administration, issued a Roadmap to Behavioral Health as a companion guide to the Coverage to Care Roadmap to Better Care and a Healthier

You. It addresses behavioral health needs in general, which is particularly relevant as many people with dementia also have depression.

The National Partnership to Improve Dementia Care in Nursing Homes 2017 report for the second quarter indicates that the national prevalence of antipsychotic medication use has decreased from 35% to 15.5%. In a few states, prescribing increased rather than decreased. This information can be used to direct more resources to these states.

The Focused Dementia Care Survey, released in November 2015, has been updated and is available on the National Partnership website.

Real change relies on partnerships, and CMS plans for more partnership activities in 2018, such as collaboration with State Dementia Care Coalitions, CMS Regional Offices, and State Survey Agencies; comprehensive focus on poorly performing nursing homes; revision of "Hand in Hand" training series; and data tracking and distribution.

Joan Weiss, Health Resources Services Administration [via telephone]
HRSA, along with federal partners and public stakeholders, created the Alzheimer's Disease and Related Dementias Caregiving Training Curriculum to provide training about dementia care for the primary care workforce and caregivers. The curriculum consists of 11 modules (4 to assist providers and 7 to help family members and other caregivers). The curriculum is free and can be adapted (without permission) to the particular needs of specific trainees. It can be accessed online at https://bhw.hrsa.gov/grants/geriatrics/alzheimers-curriculum.

Susan Cooley, U.S. Department of Veterans Affairs [via telephone]
The VA has instituted the Psychotropic Drug Safety Initiative, a system-wide program to improve medication-prescribing practices based on evidence and clinical practice standards. Phase 2 (October 2015-June 2017) focused on improving psychopharmacologic prescribing practices for veterans older than 75, both in the community and in Veterans Health Administration community living centers. Each participating facility reduced its use of antipsychotics.

The VA Geriatric Scholars Program is a workforce development program intended to integrate geriatrics into primary care practices. This continuing education for health care professionals offers intensive, self-paced learning through webinars and online learning communities. The focus is rural VA clinics, including rural IHS clinics. Activities include Rural Interdisciplinary Team Training for the Tohono O'Odham Nation, webinars for VA staff, and Geriatric Scholars Toolkits available online at http://www.gerischolars.org/course/view.php?id=29 and http://www.gerischolars.org/course/view.php?id=2.

Comments and Questions

- ***Laura Gitlin*** asked for more information on CPC+. ***Ms. Jin*** explained that CPC+ is a practice-wide innovation. CMS does not provide explicit directions to primary

care givers; rather, providers use their own methods. CPC+ encourages forming relationships with specialists in the community. ***Dr. Finke*** said this creates a better platform within primary care. It specifically calls out patients with dementia. CMS has added a risk adjustment payment for dementia care, which requires additional resources. It works to build specific capabilities around care management within primary care, and then it allows practitioners to do what they know how to do. CPC+ does dictate to practitioners how to take care of patients; it provides resources for them to do it. It will be interesting to see the impact on early diagnosis.

- Replying to ***Allan Levey***, ***Dr. Ling*** said ß-amyloid scanning was covered with evidence development. The national requirement is that the beneficiary be enrolled and participating in a study that addresses specific questions within the context of these studies. CMS must be able to review and approve each study. Data are coming back for CMS review, but CMS may not have enough data to review the progress yet.

- ***Gary Epstein-Lebow***: How can a primary caregiver involve in the Care Plan those who are unable to complete the study? ***Ms. Jin***: That was not one of our outcomes. ***Dr. Finke***: The Care Plan is a flexible idea. Each person must understand his or her role in care and away from care. CMS commits to enabling care giving, rather than dictating how caregivers provide care. They use practices that yield the best results to guide requirements. This is moving from building capability to how the practices are used. ***Dr. Gitlin***: It is practice-changing. A tremendous amount of work must be done to educate care providers. ***Ms. Jin***: CMS offers webinars, etc., to educate people. The learning community is a support, but CMS does not tell them how to do their day-to-day work. In person and online they have their own virtual community.

- ***Bruce Finke*** hopes CMS is creating a market for the HRSA curriculum modules. The work of a model is to create that pull. ***Ms. Jin*** cautioned that this is not a top-down process, but a matter of how it can be linked. ***Dr. Ling***: No single product will work everywhere, so the more resources we can make available, the better. The Care Plan has to be a flexible, living document that follows a person through the course of the disease. Nevertheless, we can identify criteria that characterize a successful Care Plan. Use of information--and data that are not necessarily information--about diagnostic products is another issue. This involves use as a guide to management without judging that management. ***Ms. Kurtz*** wanted another opportunity to have more discussion on this topic. ***Ms. Jin*** suggested lunch or email for the immediate future.

- ***Katie Brandt*** wants to expand the education model. People want to care for and be cared for by someone who is like them. Modules allow flexibility to target and add to what caregivers are already bringing to those communities. Education is empowering to caregivers. What evaluation or payback can be provided after using the modules? ***Dr. Ling***: CMS is eager for feedback so they can design for

the needs of the user. A hard job may not be caused by the tool, but because of other factors in the situation.

- ***Katie Brandt*** asked what could be clearly identified for evaluation. ***Ms. Weiss*** said HRSA updates the module every 6 months, and they are converting the caregiver module to YouTube videos, although they will still have the PowerPoint presentations. If you want to suggest revisions or additions, please send suggestions to Joan Weiss. HRSA will release the next revision in June.

- ***Cynthia Huling Hummel*** applauded this progress. She was diagnosed in 2016 when there was no Care Plan. She had to develop her own plan and found that the patients were educating the caregivers.

Research Subcommittee

Richard Hodes, M.D., National Institute on Aging
The first AD summit was held in 2012 and we are moving to a pattern of having a summit every 3 years. The fiscal year (FY) 2018 budget calls for a 40% decrease in AD funding. However, the National Institutes of Health (NIH) are further involved in Alzheimer's research in creating their Bypass Budget, which goes directly to Congress. Priorities are translated into milestones and needs. Recent investments have allowed us to accelerate milestones.

AD/AD-related dementias (AD/ADRD) research areas specifically named in the National Plan are LBD, FTD, and vascular cognitive impairment/dementia (VCI/D). Diversity in AD/ADRD research is illustrated by focuses on: cognitive outcomes in population studies; research on disease mechanisms; gero-science; aging metabolic changes in AD; comparative biology of neurodegeneration; basic biological processes of AD; biomarkers; research on care and caregiver support; and disparities, sex differences, and AD risk. To recruit and mobilize, NIH is intent on considering a broad spectrum of the disease, which is illustrated by the funding opportunity announcements (FOAs) for which both the categories and the numbers of grants have increased.

The AD/ADRD research investment has quadrupled between FY2014 and FY2017, and translational programs and enabling infrastructure for AD/ADRD now include AD drug development, blueprint neurotherapeutics, drug discovery, and more than 140 active clinical trials. Clinical trials vary from early-stage interventions for people without symptoms (~40) to late-stage clinical drug development (8), non-pharmacological interventions (62), and care and caregiver interventions (37). Public-private partnerships have been established (e.g., for animal model studies). They have developed collaborations to compile data in a common database and identify the most promising candidates for interventions. The result is new hope and translation through new targets.

Opportunities for small business through the Small Business Innovation Research program include: Advancing Research on AD and ADRD, Tools for Clinical Care and

Management of AD and its Comorbidities, and Development of Socially Assistive Robots to Engage Persons with AD.

The next NIH AD research summit--Path to Treatment and Prevention--will occur March 1-2, 2018.

Comments and Questions

- ***Allan Levey*** thanked Dr. Hodes and NIA for changing the tenor of science regarding AD. The biggest impact is changing the way we conduct science, in that a collaborative spirit has been successfully promoted. ***Dr. Hodes*** agreed the change has been dramatic. This is one of the first major private-public partnerships in which the private organization had no financial incentive. NIA funded a series of individual investigations and the resulting research data were stored in a common database. Thus, AD research has seen one of the most important evolutions of this kind of success.

- ***Laura Gitlin***: The clear and consistent message is that we need to change the way we do research. The ultimate question is: Are we shortening the time to develop new therapies, drug and non-drug? ***Dr. Hodes***: It is too early to be definitive. We must compare treatment identified through to clinical trials. The process has the potential to shorten the time to treatment development. The Food and Drug Administration (FDA) has been an important partner in furthering this. ***Dr. Levey***: Before we get to clinical trials in humans there is a long development phase. One way to shorten the pipeline is to repurpose existing drugs. Here is a real opportunity to revise the recommendations to increase the number of Phase II trials (e.g., we need a trial on inflammation).

- ***Bruce Finke***: From the care and services perspective, we have work to do on building a communication structure as we move from care to diagnosis. Primary care and specialty care must move closer together.

PUBLIC INPUT

Matthew Sharp, Association for Frontotemporal Degeneration
Multiple pathologies in FTD underlie a confusing mix of clinical presentations and symptoms and make it exceedingly difficult to design studies and clinical trials and to identify clinically meaningful endpoints by which to measure the effectiveness of treatments. Due to the many and varied challenges, the AFTD has sought to maximize the success of research efforts by working collaboratively with other organizations and combining resources to find creative solutions. Last spring, AFTD and its partner, the Bluefield Project, launched the FTD Disorders Registry. More than 1,000 people have registered and they are ready to inform pharmaceutical companies, academic researchers, and regulatory and policy groups about patient-focused trial design and to cultivate a collaborative environment for drug development.

In addition, AFTD has announced a new pilot grant to support the development of non-pharmacological therapies for FTD and has released a request for proposals for non-pharmacological interventions and tools with the potential to improve the quality of life for persons diagnosed and their families. This 1-year grant of up to $60,000 is open to United States and international investigators. Details are posted on the AFTD website.

Feng-Yen Li, Ph.D., Physicians Committee for Responsible Medicine
The Physicians Committee for Responsible Medicine recognizes that research is in need of a paradigm shift that would move away from the use of animal models, focus on risk factors rather than pathological hallmarks, and evaluate lifestyle interventions as first-line, disease-modifying treatments. It urges the Council to consider the following three research paradigm shifts, which may help us develop a disease-modifying treatment for AD/ADRD:

1. **Replace animal models with human-relevant models**. Animals do not develop AD like humans do, and scientists should discontinue using genetically engineered animal models for disease mechanistic studies and drug development. The long history of recurrent drug trial failures in humans despite successes in the animal models also strongly supports the notion that these models are not reliable. We need to push Alzheimer's drug discovery pipelines to replace animal models with human-relevant research models and methods (e.g., human stem-cell-derived mini-brains, patient tissues, and predictive toxicology frameworks such as adverse outcome pathways).
2. **Focus on modifiable lifestyle risk factors as targets, instead of pathological hallmarks**. While amyloid and tau are well-recognized pathological hallmarks of AD, they may only be observable abnormalities that result from the disease process rather than drivers of the disease process, and we should not disproportionately invest in targeting amyloid and tau for AD. The fact that there is no cognitive benefit in patients despite evidence confirming the reduction of amyloid load with candidate drugs in clinical trials suggests that amyloid and tau may not be driving the disease. Moreover, they are not particularly sensitive nor specific biomarkers for the disease. We should consider developing treatments to modify lifestyle risk factors that may drive the disease, such as saturated fat, cholesterol, and inflammatory biomarkers. One lesson from disease-modifying treatments in other chronic diseases is that treating these lifestyle risk factors can effectively modify diseases such as heart disease and diabetes.
3. **Evaluate lifestyle interventions as first-line, disease-modifying treatments**. AD, like other chronic diseases, may be driven by lifestyle factors such as poor diet and physical inactivity. Hence, changing lifestyle habits may prevent or reverse symptoms, as demonstrated by lifestyle modification trials (e.g., the FINGER trial). We need public funding to support research in this area because the private sector does not have a financial incentive to invest in research in these types of treatments. Lifestyle interventions offer the greatest potential to curb the course and financial burden of this disease.

The many failed trials in the past decades suggest that we ought to do something different. Given the unreliability of animal models and the poor candidacy of amyloid and tau as drug targets, the Physicians Committee for Reliable Medicine recommend that the Council focus on supporting research for human-relevant models, lifestyle risk factors as targets, and non-pharmacological lifestyle interventions for the therapeutic development pipeline.

Ian Kremer, Leaders Engaged on Alzheimer's Disease
Mr. Kremer applauded the Council's continued work, citing CMS's targets for outcomes, not just measuring change but setting objectives around those targets. He suggested that the Council add two additional avenues for objective outcomes: (1) the speed of moving through the target-discovery pipeline. We need to establish a typical baseline and set targets for how much time you want to shave off the pipeline and how to get there. (2) Care Plans. The importance and value of CMS benefits have been accepted. Now we need to identify subgoals around disease etiology and subpopulations enabling social justice to inform population selection.

Above all, this Council should harness its opportunities around being an advisory council. It should emphasize the need for an increased budget for AD research (and this Council has been effective in increasing the budget in the past). It should delineate the prospects for continuing the status quo and prevent rolling back the current funding. The will of Congress to continue to do the right thing cannot be taken for granted. The Council must describe the consequences of rolling back funding. For example, there are plans to eviscerate coverage for funding care and services. This Council can explain the consequences of doing that in ways that advocacy groups cannot. Mr. Kremer urged the NAPA Council to embrace the role of being an advisory council in a positive and defensive way.

Matthew Janicki, Ph.D., National Task Group on Intellectual Disabilities & Dementia Practices
Drs. Seth Keller and Matthew Janicki co-chair the National Task Group on Intellectual Disabilities and Dementia Practices (NTG), an affiliate of the American Academy of Developmental Medicine and Dentistry and associated with the Rehabilitation Research and Training Center on Developmental Disabilities and Health at the University of Illinois at Chicago.

Among the genetic causes of intellectual disability, Down syndrome is the one most commonly associated with dementia because adults with Down syndrome are at high risk of AD and generally manifest early onset dementia. These distinct areas deserve due consideration by NAPA, and their remedies warrant inclusion in the National Plan, especially since this population is disproportionally affected. NTG asks that the Council recognize that dementia has a particularly devastating impact on people with an intellectual disability and their friends, families, and staff involved with them as advocates and caregivers. The NTG believes that the federal Council should continue to include--and expand on--concerns and considerations for people with intellectual

disabilities in its annual updates of the National Plan. To this end, NTG stands ready to assist and contribute to such efforts.

Mary Hogan, National Task Group on Intellectual Disabilities & Dementia Practices

Ms. Hogan is a steering committee member of NTG, which is co-chaired by Dr. Janicki. NTG was formed late in 2010 primarily to ensure that individuals with intellectual disabilities and their families were included in the National Plan to address AD and other dementias. As a small grassroots organization, NTG is focused on increasing support and improving caregiving standards for those with intellectual disabilities and their families. To this end, NTG has accomplished the following:

- Produced an early-detection screening instrument along with a user manual available in 13 languages on the NTG website.
- Identified and disseminated best practice guidelines and community supports guidelines.
- Created a health practitioner assessment protocol that was published in the *Mayo Clinic Proceedings*.
- Provided health advocacy guidelines, critical for assuring improved medical care.
- Assisted the Commission on Accreditation of Rehabilitation Facilities with national program standards for dementia care in rehabilitation facilities.
- Designed a national training curriculum--Dementia Capable Care of Adults with Intellectual Disabilities and Dementia (with a train-the-trainer component)--that has been offered across the United States.
- Partnered with colleagues in Canada to develop a training curriculum.
- Has offered ongoing training and webinars for professionals and family members.
- Helped organize an International Summit on Intellectual Disabilities and Dementia that was held in Glasgow, Scotland, in October 2016.
- Published articles in professional journals related to intellectual disabilities and dementia.
- Has offered technical assistance to professional organizations.
- Explored grant-based innovative programs including the exploration of telehealth and tools for dementia assessment with an electronic data storage component.
- Partnered with organizations that received grants from ACL to ensure that their capacity to serve this population increases and that standards of care improve.
- Has interacted with the National Association of Councils on Developmental Disabilities, National Association of State Directors of Developmental Disabilities Services, and National Association of States United for Aging and Disabilities, regarding state activities.
- Presented at national conferences, including the National Home and Community-Based Services Conference, to increase awareness of the needs of those with intellectual disabilities and dementia and their family members.
- Represented those with intellectual disabilities and dementia and their caregivers at the National Research Summit on Care, Services, and Supports for Persons with Dementia and Their Caregivers.

- Partnered with The Arc, National Down Syndrome Society, and Alzheimer's Association on training and publications, and with the National Down Syndrome Society and National Alliance on Caregiving on the planning of the Adult Down Syndrome Summit to be held in Arlington, Virginia, in April 2018.
- Provides information to families and hosts a monthly online family support group for family members across the United States.

As people age and are at increased risk for AD or other dementia, partnerships are critical for addressing the many demands that lie ahead. NTG supports the efforts of the NAPA Advisory Council and hopes it will be inclusive of all people in future plans, that it try to understand this special population, and that, in taking note of NTG's appeals, it will reflect on what life must be like for those who face a lifetime of challenges.

Carolyn Johnson, Caregiver [read by Ms. Khillan]
Ms. Johnson's husband was recently diagnosed with FTD. In going from doctor to doctor, they realized that few know about this horrible disease, which is robbing the lives of young men and women. FTD now falls under the umbrella of AD, but it is not AD. Aphasia is common with this disease and because FTD causes the afflicted to behave irrationally, people wind up in state psychiatric hospitals and jails, as happened to Ms. Johnson's brother, a noted architect, who was unable to calmly explain his actions to a police officer. We need to educate doctors, hospitals, judges, and the general public about this disease.

Nihal Satyadev, Youth Movement Against Alzheimer's [read by Ms. Khillan]
The Youth Movement Against Alzheimer's (YMAA) is working on two projects. Firstly, YMAA was recently approved to launch its low-cost caregiver respite program in partnership with the University of Southern California, Leonard Davis School of Gerontology. More information can be found online at http://www.theyouthmovement.org/#/futureOfCare. Secondly, YMAA is leading efforts to pass a California Care Corps Act, building on the framework proposed by Congresswoman Michelle Lujan-Grisham in her National Care Corps Act, which was originally introduced in the 114th Congress and is being reintroduced in the current Congress as a demonstration act. We believe that this legislation is critical to offering care solutions beyond the longstanding In-Home Supportive Services allocations and will help foster an intergenerational culture.

Sharon Hall, Caregiver and Advocate [read by Ms. Khillan]
Ms. Hall's husband has FTD. The FTD population is often overlooked because the afflicted are young, while most programs in memory care do not cater to people under age 65. Additionally, programs and services for those with FTD and their care partners are difficult to find. The cost of FTD care is twice that of AD, leaving many younger families destitute. Many affected families still have young children at home, so a parent often has to work while hiring help at home. The afflicted who have left jobs may have to endure a 2-year wait for Medicare's Social Security Disability Insurance to become effective.

In addition, we need national certification for those working in memory care so they are trained to deal with all dementias and the symptoms of all dementias. Care partners of those diagnosed at a young age need real respite programs. We are losing too many care partners to stress and stress-related diseases. We need to make programs and services available to the community of those afflicted with dementias who are not part of the aged population.

RESEARCH SUBCOMMITTEE AGENDA: THE JOURNEY FROM TARGETS TO TREATMENTS

Allan Levey, M.D., Emory University
NAPA's stated goals are to prevent and effectively treat AD by 2025, optimize care quality and efficiency, expand supports for people with AD and their families, enhance public awareness and engagement, and track progress and drive improvement. The NIH AD/ADRD Research Summits help drive the recommendations. In 2015, recommendations for AD were interdisciplinary research to understand the heterogeneity and multifactorial etiology of disease; transforming AD therapy development from targets to trials; new strategies for prevention; innovating disease monitoring, assessment, and care; empowering patients and engaging citizens; and enabling partnerships for open innovation. In 2016, recommendations for ADRD were to include multiple etiology dementias, non-governmental organizations, AD/ADRD health disparities, LBD, FTD, and vascular contributions to cognitive impairment and dementia.

Several challenges for developing AD treatments stand out. Prevention, disease-modifying, and symptomatic treatments may have substantially different therapeutic targets, and require different clinical trial designs. Disease heterogeneity and varied rates of progression make trials complicated to run, with a typical trial enrolling thousands of patients followed for two or more years at a cost of hundreds of millions of dollars per trial. This is a complicated disease with potentially different "phases," which may require a right-person, right-time, right-drug approach, similar to chronic diseases such as atherosclerosis or cancer in which different therapies are used to prevent illness or treat established disease. Moreover, recent high-profile failures led to caution in new investments.

In this family of diseases, all pathologies are heterogeneous and all begin before symptoms occur. The research community has been focused on the development of amyloid plaques, but we also need to consider how to use genomics, or whatever drives the disease, to inform both drug and non-drug treatments. The community has begun to consider getting people involved in trials at an earlier stage.

Bradley Hyman, M.D., Alzheimer's Disease Research Center
We are not just talking about AD, but also FTD and LBD. Pathology begins years before symptoms emerge. This challenges trial designs, as well as thinking about therapeutics at various stages of the disease. How do you design an experiment for a condition that

evolves over 15 years? How do you muster our joint efforts to overcome the challenges?

We can intervene at various points, but we must validate that. Another variable is that no two people respond the same. For example, Dr. Hyman treated 80-year-old twins in whom one was symptomatic but the other was not. Yet, at death, both were found to have tangles and plaques. This indicates heterogeneity of disease, but also heterogeneity of bases of disease. Despite the failure of some well-defined trials, we must maintain the momentum to keep trying.

Overview of NIA Preclinical Pipeline for AD

Eliezer Masliah, M.D., National Institute on Aging

Dementias characterize the aging population, but there are many points in the process before damage is visible. Among the things we have learned are: AD could coalesce with LBD, vascular dementia, and FTD; a number of proteins accumulate in addition to tau and TDP-43; and accumulation is progressive, propagating and jumping from cell to cell.

More than 120 drugs have been developed, but, regardless of the large pipeline, very few drugs have made it to the finish line. The fault could be drug interventions too little or too late, lack of target engagement, or the wrong target. To solve this problem, we are making all data publicly available to be shared. This has resulted in better integration of the various programs centered on public-private partnerships. The overarching topic is open science. This approach addresses key AD summit recommendations: employ new research paradigms, such as systems biology and systems pharmacology; enable rapid and extensive sharing of data, disease models, and biological specimens; develop computational tools and infrastructure for storage, integration, and analysis of large-scale biological and other patient-relevant data; build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate; support and enable open science; and develop new precompetitive public-private partnerships.

Six academic teams created networks of information, all made publicly available (e.g., intracellular tracking of organelles, a new target for drug development, and single genes that belong to networks of genes). The program has been working on this for 5 years. One example of an identified drug target is VGF. Protein networks are being used as novel biomarkers. NIA Translational Center for Animal Model Resources (MODEL-AD) uses genetic data. An important enabling infrastructure on this pipeline is to develop next-generation AD models.

We want greater transparency on data generated and we want everyone to have access to all the data to further drug discovery and drug development programs. NIA has offered almost 140 funding opportunities, with more to come. Our main theme for the forthcoming summit is that we have to test the right target with the right drug at the right time. Specific topics include complex biology and heterogeneity, precision

medicine, translational tools, emerging therapeutics, the impact of environment to advance disease prevention, disease monitoring, and open science research ecosystem.

Overview of the Clinical Trial Pipeline for AD

Laurie Ryan, Ph.D., National Institute on Aging

NIH-supported clinical interventions for AD/ADRD include trials of 105 agents--70% for pathology and the rest for cognitive or neuropsychiatric symptoms. Almost 80 are clinical trials--half pharmacology, half non-pharmacology. Pharmacological targets include amyloid, ApoE, lipids, lipoproteins, neurotransmitter receptors, metabolism and bioenergetics, vasculature, growth factors and hormones, oxidative stress, and multi-targets.

The Anti-Amyloid Treatment in Asymptomatic AD Trial is a secondary prevention trial in clinically normal adults (aged 65-85) who have evidence of amyloid-ß pathology on screening with PET imaging. The goal is to slow disease progression to cognitive decline. The drug being tested (Phase III) is solanezumab; 7,000 participants have been screened. The hypothesis being tested is that altering “upstream” amyloid accumulation will affect “downstream” neurodegeneration and cognitive decline. In LM11A-31, in patients with mild to moderate AD, the molecule modulator of the P75 neurotrophin receptor is being tested for activation of degenerative processes and protection of nerve cells and their connections.

Non-pharmacological treatments include exercise, diet, cognitive training, technology, and care (medication) management. The EXERT Study tests whether supervised aerobic exercise can slow cognitive decline, slow brain atrophy, or delay onset of AD dementia. Another study is the MIND Diet (a hybrid of the Mediterranean and DASH diets) Intervention to Prevent AD, which randomizes 600 adults aged 65-84 to the MIND diet + calorie restriction or usual diet + calorie restriction.

Seven clinical trials of neuropsychiatric symptoms are underway--five pharmacological and two non-pharmacological. One is prazosin for agitation in AD (PEACE-AD). Data, including those from brain tissue studies, suggest that noradrenergic stimulation via the central nervous system α-1 adrenergic receptor contributes to the pathophysiology of agitation in AD.

Clinical trials infrastructure is being addressed by establishing the Alzheimer’s Clinical Trials Consortium (ACTC) to run clinical trials focused on interventions that prevent, delay, or treat symptoms of AD and other age-related dementias. ACTC provides a state-of-the-art clinical trial infrastructure to facilitate rapid development and implementation of protocols, including a centralized Institutional Review Board (IRB). It also provides leadership in innovative trial design methods, outcomes, and analyses, as well as recruitment strategies. A separate FOA will solicit applications for clinical trials to be managed and supported by ACTC. Data sharing will be achieved through ACTC resources. Data and sample sharing are expected at the time of publication of the

primary results or within 9 months of database lock. Moreover, emerging data from ongoing late-stage prevention trials will be made available as soon as possible.

Other funding mechanisms being established include the AD-Development Program, Pilot Clinical Trials for the Spectrum of AD and Age-Related Cognitive Decline (three phases), and Advancing Research on AD and ADRDs.

The Collaboration for Alzheimer's Prevention (CAP) was founded by representatives from the Alzheimer's Disease Cooperative Study A4, Alzheimer's Prevention Initiative (API), Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), Alzheimer's Association, FDA, NIA, and the Fidelity Biosciences Research Initiative. CAP was founded as a convening, harmonizing, and consensus-building initiative to help stakeholders advance AD prevention research with rigor, care, and maximal impact. CAP's goals are to standardize procedures and harmonize data collection to facilitate future comparisons, seek methods of sharing data and samples in the research community, and assist in planning prevention trials. CAP is primarily focused on drug trials, but non-pharmacological preclinical AD trials would also benefit from CAP efforts. Six clinical trials are underway. This also presents an opportunity for Small Business Innovation Research trials.

A National Strategy for Recruitment and Participation in AD Clinical Research has been established with the goal of engaging broad segments of the public. It is aimed at capacity building and connecting at the local level, with a particular focus on underrepresented populations. In 2016, NIA began its National Strategy Development initiative, which is now accepting public comments and will finalize the strategy in June/July 2018.

AbbVie's R&D Vision for AD

Eric Karran, Ph.D., AbbVie Inc.

AD is an emerging global crisis. Besides the scientific component is the unmet medical need. Therefore, AbbVie is increasing its global AD effort and now has more than 200 scientists devoted to neurodegenerative disease. In order to be successful, programs need access to excellent scientists doing fundamental research into disease mechanisms, to clinicians who know the disease and treat patients, and to patients and patient material (genome, fluids, samples, biomarkers, brain banking). Four conditions are prerequisite for drug discovery success: hire excellent people, provide well-equipped labs and sufficient budgets, set a clear mission, and give it time.

Genetics has informed AD research, but genes tell about predisposition (disease initiation) rather than disease progression. Choosing the right target is critical. The gap between academia and pharma is closing, but still, drug targets are sometimes lost in translation from one to the other. A pharma scientist's drug target should be possible to trace to pathways with genetic evidence and have drug-able sites or activities. It should have evident polarity of modulation--do we want to increase, decrease, or modulate the

drugs effect? The target has to be without side effects and it must have a favorable tissue distribution, and preferably not be a member of a gene superfamily.

NIA's Accelerating Medicines Partnership-Alzheimer's Disease target analysis has been an excellent vehicle to bring together academic and pharma scientists. It highlights the technical challenge in choosing the right target to pursue and emphasizes the need to do a better job of selecting targets. There is also a direct relationship between what gets funded and the number of drugs approved.

As George Box said, "All models are wrong; some models are useful." It would be useful to have an animal model of AD, but currently, we are not good at modeling. Furthermore, there is a difference between having a bad model and modeling badly.

Pharma uses *in vivo* models for proof of pharmacology/mechanism; biomarker/pharmaco-dynamic marker discovery; assessment of safety vs. efficacy of therapeutics; projecting doses to humans; target validation/hypothesis testing; and, rarely, to understand disease processes *de novo*. It would be useful to have a model of AD in mice, but that is not a realistic objective. A realistic objective is acquiring additional *in vivo* systems that model different aspects of neurodegenerative disease (e.g., mechanisms of neuronal death; the relationship between synaptic and neuronal dysfunction, neuronal death, and animal functional decrement; and differential neuronal selectivity to pathology).

Clinical development has undergone many failures for no single reason (e.g., a good agent may not have been tested at the right time). We need to know how early that should be. If we had something that worked, it would provide more information. Understanding the genetic atmosphere is necessary, but so is understanding the patient's environment, as both affect the course of disease. Blood biomarkers would be extremely useful, as would better clinical instruments.

AbbVie's AD disease-modifying clinical pipeline extends from Phase I to Phase III trials. Amyloid plaques and tau pathology (leading to cognitive impairment) define AD. But, there is no correlation between amyloid and cognitive impairment, whereas tau pathology correlates well with cognitive impairment. Everyone hopes one of these agents will work, but hope should not replace science.

In conclusion, a number of highly successful public-private consortia have been established that have significantly advanced our understanding of AD. Sustaining and increasing the interaction between all stakeholders--funders, academics, advocacy groups, patients, regulators, and pharma--will increase the probability that we shall succeed. The current degree of collaboration and sense of a shared mission is unprecedented.

Participating in an Alzheimer's Clinical Study: Perspectives on Involvement of a Person Living with Dementia and Her Study Partner

Cynthia Huling Hummel, Council Member
Ms. Huling Hummel began experiencing impairment in 2003, but was not diagnosed until 2016 when she found that she has two copies of the *ApoE4* gene. She participates in the clinical trial ADN13 at the University of Rochester. It has changed her life and given her hope and strength. Participating in Alzheimer's clinical research can be empowering because it gives her a purpose and helps her move from being a victim to a worker for the future. It also gives her access to excellent medical care and procedures not yet available to the general public. The ADN13 study requires one personal visit per year. Following this, the patient can participate by computer. In order to participate, the individual must have a study partner.

Participating in a new study raises new possibilities and new challenges, including whether the study is observational or interventional, distance from the testing site, availability of a study partner, and time commitment. The chance to participate in an interventional tau study raises questions for Ms. Huling Hummel: Should she move closer to the university? Should she pay a study partner? She has already designated her two children as study proxies.

Some say they would like to participate in a clinical study, but they do not know where the studies are or how to enroll. We need to enhance recruitment and focus on diversity. Ms. Huling Hummel offered these recommendations: encourage primary care physicians to provide the newly diagnosed (and care partners) with information on the benefits of enrolling in clinical studies; use faith communities to promote studies and host field research; send researchers into the field; provide vouchers for those in need to cover hotel, food, and transportation costs; and promote non-family study partners.

Marion Weisse, Study Partner
Ms. Weisse has been involved as a study partner since 2009. ADN13 requires a study partner to accompany the subject to all clinic visits or be available via telephone to answer questions from study staff. The partners must provide general information about themselves, such as age, gender, and relationship to the participant.

Comments and Questions

- ***Eric Karran***: The most compelling data are coming from Canada, but nothing that has been brought forward so far that will affect the 2025 target.

- ***Robert Egge***: Recruitment and data-sharing are important topics.

- ***Eliezer Masliah***: As with the public-private partnerships for data, we could share reagents, but we need financial help from an organization like the Gates Foundation. Making all data available to be shared is good, but utilizing the data requires additional funding. ***Dr. Hodes***: Data-sharing requires special

considerations around maintaining confidentiality. ***Dr. Ryan***: We are beginning to see partnerships for non-pharmacological studies, with MIND Diet and EXERT, etc.

INITIATIVES, PARTNERSHIPS, AND COLLABORATION TO HELP PATIENTS WITH THE HIGHEST UNMET NEED: DOMINANTLY INHERITED AD TRIALS UNIT AS A CASE EXAMPLE

Randall Bateman, M.D., Washington University School of Medicine

AD is a uniquely human condition for which we have ancient clinical descriptions. In 1906, Dr. Alois Alzheimer described an AD patient, characterized by plaques and tangles in the brain. In 1991, mutations were discovered, and in the 2000s, the first drugs were developed targeting ß-amyloid as a cause of AD.

Less than 1% of AD results from autosomal dominant mutations in three genes directly involved in ß-amyloid--*APP*, *PSEN1*, and *PSEN2*. Sufferers of autosomal dominant AD (ADAD) usually show symptoms of the disease at approximately the same age as their parents did. The goal of DIAN-TU was to enroll family members. The DIAN Observational Study established the framework and, in 2011, established the study design for DIAD.

AD starts two decades before the first symptoms appear, by which time two-thirds of the memory neurons are gone. Amyloid plaques occur 20 years before death, and the brain begins to shrink 5-7 years before death. DIAN-TU's aim is to prevent symptom onset.

The stages of proteinopathy in DIAD exhibit a cascade of effects over time. The rationale of the DIAN therapeutic trials is that clinical onset of symptoms can be predicted at any point in life, allowing therapeutic trials years or even decades before the clinical onset. ADAD has a clear cause of disease due to ß-amyloid and offers uniquely informative scientific information on disease progression, biomarkers, and changes due to therapeutic treatments. Its common pathophysiology supports general AD indication. Successful implementation of prevention and symptomatic studies will provide information as to the cause of AD and provide guidance for future therapeutic development.

Working with patients is an essential part of designing clinical trials. DIAN-TU participant, Brian Whitney, gave his perspective via video. He stated that the study has changed his life. He has known the disease has been in his family for generations, but this is the first time they have had hope that they and their children might not die from it.

Participant interaction and partnership have resulted in the DIAN Expanded Registry, which serves as a key information and referral source for the DIAN Observational Study and DIAN-TU trials. In addition, patients and family members began advocating for themselves, which led to an annual DIAD Family Conference, allowing researchers and

caregivers to hear directly from family members. This has had an impact on regulators and pharma representatives.

Successful research means testing multiple targets in multiple drugs at the right stage of the disease. DIADs have a 100% chance of getting the disease. DIAN-TU NexGen is testing multiple drugs, so only 25% (instead of the usual 50%) of participants are assigned a placebo. They developed novel biomarkers and statistical methods, and use the DIAD-specific Disease Progression Model based on DIAN observational data, which is flexible to allow for changes as new information emerges (e.g., increasing the dosage mid-trial). Each drug covers a different target in the brain, and they are looking for new targets. DIAN-TU investigators are also working with regulatory groups such as FDA and the European Medicines Agency. This model is making a difference.

Comments and Questions

- ***Richard Hodes*** asked for a comment on the attitude of sufferers and their families to the DIAN Family Conferences. ***Dr. Bateman*** remarked on the intense sense of isolation among these people. At the meetings, there was incredible bonding and emotional release among the participants. They had thought they were the only families with this disease. In addition to being disabused of that idea, they saw the many dedicated and caring people who were trying to prevent and treat the disease.

- In response to ***Dr. Levey***, ***Dr. Bateman*** said that of the remaining obstacles to be addressed, the greatest limiting resource is participants and the ability to implement studies around the world. It takes time to establish centers and conduct outreach to enroll patients. We do not know ahead of time what an effective treatment will be, and we are having too few shots on goals, so we need to increase the pipeline. The only thing that will change the current situation is more drugs, more patients, and more shots on goal.

- Replying to ***Dr. Gitlin***, ***Dr. Bateman*** said that although the best-known symptom of AD is memory loss, under-recognized symptoms include clinical depression resulting from biological changes in the brain and loss of executive function. Therefore, DIAN-TU has extensive questionnaires to track the manifestations of the disease.

- ***Gary Epstein-Lebow***: How many in the DIAN Observational Study do not opt to participate in the DIAN-TU? ***Dr. Bateman***: Once the family members meet, they like to stay in touch with each other. They form groups and interact with each other. However, everyone in the observational study is not eligible for the trials. Eligible persons may decline trial participation because they are not at a point in life when they want to invest that much time in treatment. More interesting is that the reason they do commit so much time is that they want to help their children.

CARE SUMMIT REPORT

State of the Science for Pragmatic Trials of Non-Pharmacological Interventions to Improve Outcomes Among Persons with Dementia and Their Caregivers

Laura Gitlin, Ph.D., and Rohini Khillan
[Katie Maslow, Gerontological Society of America, contributed, but could not attend the meeting]

A post-summit opportunity (December 1, 2017) for a working group of approximately 30 people was organized by Brown University School of Public Health and Hebrew Senior Life, and supported by NIA. They wanted to establish criteria for determining which interventions are ready for launch as pragmatic clinical trials (PCTs), and to consider the infrastructure necessary to prepare to conduct, translate, and disseminate such a program of research. Their report is available online.

PCTs are designed primarily to inform decision-makers regarding the comparative balance of benefits, burdens, and risks of a biomedical or behavioral health intervention at the individual or population level. The rationale for PCTs is that we need evidence to inform decisions that lead to improved, efficient, and affordable care. There has been a disconnect between research and clinical care. We need to overcome the shortcomings of traditional randomized clinical trials, namely that they occur in stand-alone settings to ensure validity, involve non-diverse populations, are underpowered and expensive, and are not applicable to the real world. We need to move toward a "learning health system," embed clinical trials into that health care system, and ensure the rapid feedback of evidence into clinical care (i.e., clinical care informs evolution of evidence). This would result in continuous learning at a lower cost. Pragmatic characteristics require a different method of organization. In fact, people were surprised by the amount of information that we do have.

Pragmatic trial criteria include an implementation protocol that is well-defined, standardized, and replicable; evidence (do not start with discovery) that on some level demonstrates intervention efficacy; minimal risk of potential adverse events or unintended consequences; alignment of priority areas for all key stakeholders (outcomes are influenced by different stakeholders); acceptability (i.e., upstream "buy-in" from providers and health care systems); feasibility (i.e., it can be implemented by providers and systems under real-world conditions); business case, in that it results in cost savings or improvement in quality metrics; and measurement, as outcomes are important to all stakeholders and will inform clinical and policy decision-making.

The recommended infrastructure for PCTs would be a robust research infrastructure to improve dementia care and accelerate the testing and dissemination of effective programs. Ideally, we would have a support center with expertise related to research methods, design, and statistics, as well as data linkage and integration into daily routines. Measurement, including data outcomes and data acquisition, would be integrated into the infrastructure, as would ethics, regulatory compliance, and IRB

protocols; PCT training; and provider network relations and stakeholders. NIH will be releasing a Request for Applications to address this.

Comments and Questions

- Responding to ***Dr. Bateman***, ***Dr. Gitlin*** said PCTs will depend on different strategies. For example, on the behavioral side, there are practical issues of why community-based organizations (senior centers, long-term care networks) are or are not involved in research; this requires education. Ten years ago, researchers would have had to justify why they wanted to reach out to a different agency; if funding were cut, the agency might have to drop out of the trial. The conversation is very different now.

- ***Randy Bateman*** asked what needs to be done to accelerate the process. Even if investigators are encouraged to develop more drugs, targets, etc., it will cost $200 million and more. Cancer research has the advantage that it can be integrated with medical care. AD research needs a pipeline to the facility of clinical trials. ***Dr. Gitlin***: That would require a 1-2 year model.

- ***Richard Hodes***: An additional challenge is that other PCTs are carried out in settings that are already involved in patient care, whereas the would-be institutions we are considering have never been involved in clinical trials.

CARE SUMMITS AND THE WORK OF THE NATIONAL PLAN

We at HHS are committed to having this kind of summit. NIA is taking the lead on the next summit, which is on care services. It will have a different structure to accommodate all stakeholders. We want to develop a plan and infrastructure, which will be discussed in other meetings. We are now in discussions with NIA on how to keep the involvement of all stakeholders.

We have approximately 680 recommendations. Ms. Khillan, Ms. Maslow, and Dr. Gitlin have been working to define how they can be acted upon. They have adopted a style and organized the recommendations by 11 themes. For each theme there are focal areas under which there are research recommendations and examples. The summit themes are:

1. Heterogeneity
2. Clinical approaches and the lived experience of persons with dementia
3. Caregiver relationships, roles, and networks
4. Comprehensive models of care across trajectories and care settings
5. Strategies for scaling and disseminating existing evidence, drawing upon implementation science
6. Dementia-related terminology and stigma: words matter
7. Financial burden and costs

8. Living arrangements, care settings, and persons with dementia who live alone
9. Technology
10. Workforce
11. Research methodology

They have already completed 7 themes, and when all 11 are done, they will review them for redundancy and will ask for volunteers to also review them. Then it will become part of the final report (the outline was disseminated). They want to pull out a list of recommended working groups and are also considering listing ways of conducting research differently. RTI is writing a report that focuses on the process.

The last part is a dissemination plan that includes posting the report on the website and sending it to stakeholder groups.

CONCLUDING REMARKS

Dr. Gitlin adjourned the Council meeting at 4:30 PM.

The next meeting will be held April 27, 2018.

Minutes submitted by Rohini Khillan (ASPE).
All presentation handouts are available at http://aspe.hhs.gov/advisory-council-alzheimers-research-care-and-services-meetings.

PARTICIPANTS

Advisory Council Members

Present

Ellen Blackwell, CMS [*via telephone*]
Katie Brandt, Massachusetts General Hospital
Debra Cherry, Ph.D., Alzheimer's Greater Los Angeles
Susan Cooley, VA [*via telephone*]
Gary Epstein-Lubow, M.D., Brown University
Robert Egge, Alzheimer's Association
Bruce Finke, M.D., IHS
Laura Gitlin, Ph.D., Johns Hopkins University
Richard Hodes, M.D., NIA
Cynthia Huling-Hummel, a person living with Alzheimer's disease
Bradley Hyman, M.D., Alzheimer's Disease Research Center
Rohin Khillan, HHS/ASPE
Becky Kurtz, Atlanta Regional Commission, Area Agency on Aging
Allan Levey, M.D., Emory University
Shari Ling, M.D., CMS
Erin Long, ACL/Administration on Aging
Lisa McGuire, Ph.D., CDC
Debra Olster, Ph.D., NSF [*via telephone*]
Anthony Pacifico, Ph.D., U.S. Department of Defense
William Spector, Ph.D., Agency for Healthcare Research and Quality
Angela Taylor, Lewy Body Dementia Association
Sowande Tichawonna, caregiver
Kara Townsend, HHS/ASPE
Joan Weiss, Ph.D., HRSA [*via telephone*]

Absent

Richard Allman, VA
Billy Dunn, FDA

Public

Speakers

Randy Bateman, M.D., Washington University School of Medicine
Eric Karran, Ph.D., AbbVie, Inc.
Eliezer Masliah, M.D., NIA
Katie Maslow, Gerontological Society of America
Laurie Ryan, Ph.D., NIA
Marion Weisse, study partner

Attendees

Amiee Aloi
Joe Balintfy
Marie Bernard
Dawn Beraud
Erin Cadwalader
Phil Cronin
Patricia D'Antonio
Katie Donnini
Sanjay Dubé
John Dwyer
Elena Fazio
Lori Frank
Jordan Gladman
Kristi Guillory
John Haaga
Scott Hayton
Mary Hogan
Judit Illes
Matthew Janicki
Janel Jin
Kristen Karlberg
Ann Marie Kolanowski
Ian Kremer
Christopher Laxton
Feng-Yen Li
Rachel Maisler
Melissa McGowan
Brett McReynolds
Madelyn Morrison
Stephanie Oh
Creighton Phelps
Jennifer Pollack
Colleen Reilly
Stephen Scango
Denise Scruggs
Matthew Sharp
Michael Simmons
Sarah Smith
Eric Sokol
Laura Thornhill
George Vradenburg
C. Grace Whiting
Debbi Witham

January 26, 2018 -- Advisory Council Meeting #27

The meeting was held on Friday, January 26, 2018, in Washington, DC. The Research Subcommittee took charge of this meeting's theme, focusing on the process from targets to treatments. The Council heard speakers on the preclinical pipeline, the clinical trial pipeline, and the industry perspective. The meeting also included discussion of a driver diagram to guide the Council's future work, updates and a report from the October Care Summit, and federal workgroup updates. Material available from this meeting is listed below and is also available at https://aspe.hhs.gov/advisory-council-alzheimers-research-care-and-services-meetings#Jan2018.

Comments and questions, or alerts to broken links, should be sent to napa@hhs.gov.

General Information

Agenda	[HTML Version] [PDF Version]
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Meeting Summary	[HTML Version] [PDF Version]
Public Comments	[HTML Version]

Handouts

Care Summit Report Themes	[PDF Version]
NAPA Driver Diagram Draft Examples	[PDF Version]
Outline for Care Summit Final Report	[PDF Version]

Presentation Slides

AbbVie's R&D Vision for Alzheimer's Disease	[HTML Version] [PDF Version]
Care Summit Report	[HTML Version] [PDF Version]
Clinical Subcommittee Update	[HTML Version] [PDF Version]
Initiatives, Partnerships and Collaboration to Help Patients with the Highest Unmet Need: Dominantly Inherited Alzheimer's Disease Trials Unit (DIAN-TU) as a Case Example	[HTML Version] [PDF Version]
Long-Term Services and Supports Committee Update	[HTML Version] [PDF Version]

NAPA Driver Diagram	[HTML Version] [PDF Version]
Overview of the Clinical Trial Pipeline for AD	[HTML Version] [PDF Version]
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Participating in an Alzheimer's Clinical Study: Perspectives on Involvement of a Person Living with Dementia and Her Study Partner	[HTML Version] [PDF Version]
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Research Subcommittee Agenda: The Journey from Targets to Treatments	[HTML Version] [PDF Version]

Videos

Updates since October meeting	[Video]
NAPA Driver Diagram	[Video]
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