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

Washington, DC and Virtual Meeting

January 22, 2024

Advisory Council Members in Attendance

- *Non-Federal Members Present*: Adrienne Mims (Chair), Randall Bateman, Deke Cateau, Fawn Cothran, Roberta Cruz, Susan DeMarois, Keun Kim, Helen Bundy Medsger, John-Richard Pagan, Joanne Pike, Yakeel Quiroz, Rhonda Williams

- *Federal Members Present*: Arlene Bierman (Agency for Healthcare Research and Quality); Bruce Finke (Indian Health Services [IHS]); Sarah Fontaine (U.S. Department of Defense); Richard Hodes (National Institutes of Health, National Institute on Aging [NIH/NIA]); Shari Ling (Centers for Medicare & Medicaid Services [CMS]); Erin Long (Administration for Community Living [ACL]); Lisa McGuire (Centers for Disease Control and Prevention [CDC]); Tisamarie Sherry (Office of the Assistant Secretary for Planning and Evaluation [ASPE]); Joan Weiss (Health Resources and Services Administration [HRSA])

- *Quorum present?* Yes

- *Advisory Council Designated Federal Officer*: Helen Lamont (ASPE)

General Proceedings

The Advisory Council on Alzheimer's Research, Care, and Services was convened for its first meeting of the year at 9:42 a.m. Eastern Standard Time on January 22, 2024, in Washington, D.C., and virtually. Dr. Adrienne Mimms, Advisory Council Chair, welcomed meeting participants and reviewed the meeting agenda. Advisory Council members introduced themselves. The meeting was open to the public.

Federal Updates

- ***ACL*** -- Erin Long reported that the Alzheimer's Association has been awarded a cooperative agreement of over $5M per year for 5 years to increase availability of dementia-specific respite care. At least 80% of funds will go to home and community-based service (HCBS) providers to deliver respite services. The Association will provide training and technical assistance to advance respite care capacity nationwide. ACL has funded four 4-year cooperative agreements to

support the 2022 National Strategy to Support Family Caregivers. Awardees will develop and disseminate new approaches for supporting family caregivers. Funding for new Alzheimer's Disease Program Initiative (ADPI) grants is expected in 2024. ACL will continue to fund the Alzheimer's Association's call center and Title VI dementia activities in Tribal communities. The Lifespan Respite Program and Assistive Technology Program grantees are reporting successful activities.

- ***ASPE*** -- Helen Lamont reported on ASPE publications and evaluation activities. ASPE supported development of a long-term services and supports projection model, resulting in four published reports on caregiving networks and needs. Projects on Medicaid HCBS examined state modifications to 1915(c) waivers during the pandemic and how HCBS service claims are classified in the Transformed Medicaid Statistical Information System. ASPE published reports on interventions to prevent suicide in older adults (September 2023), homelessness among older adults--rising rates, existing resources, and challenges (October 2023), and the relationship between nursing home ownership structures, facility traits, and quality of care (November 2023). A September 2023 study on state implementation of wage increase related policies for direct care workers found that even with wage increases, direct care worker compensation lags other entry-level jobs. ASPE is examining gaps in HCBS workforce research, considering priority worker populations and sources of data that can be used. Many departments within HHS and Department of Labor are participating in these research efforts.

- ***CDC*** -- Lisa McGuire reported on *Healthy Brain Initiative (HBI) Road Map for Indian Country* is being revised, guided by a leadership committee with significant Tribal representation. Public input will be reviewed in March 2024. The CDC continues to add supplements to the *State and Local Public Health Partnerships Road Map*, to help states tailor the materials. The 2024 cohort of HBI Road Map Strategists was recently awarded to public health departments.

  The BOLD Center on Dementia Risk Reduction released "A Public Health Approach to Dementia", a new, free online interactive curriculum, and state-specific fact sheets and heat maps on the prevalence of six risk factors for dementia (available via the Alzheimer's Association website or by email at centerofexcellence@alz.org). The BOLD Center on Early Detection has an upcoming webinar on dementia screening and linking clients to diagnostic and social services. The BOLD Center on Caregiving published public health strategies in dementia caregiving, has a related January 24 webinar, and developed an advance care planning resources guide and publication on the intersection of social determinants of health and family caregiving for dementia.

  The International Association for Indigenous Aging developed a video on dementia and a related Bingo card. As part of HBI, the University of Illinois-Chicago has created a HealthMatters coaching program for people with

intellectual and developmental disabilities (IDD) and brochure on the *6 Pillars of Brain Health* for people with IDD. CDC released a new communication guide, *Integrating Alzheimer's Messages into Chronic Disease Programs*, for public health professionals. UsAgainstAlzheimer's produced a guide on culturally sensitive and relevant public health messaging around dementia. Dr. McGuire recently presented a session on Dementia vs. Alzheimer's to the American Medical Association. Dr. McGuire reminded the Council of the Healthy Brain Resource Center that includes over 300 publicly available resources.

- ***HRSA*** -- Joan Weiss reported on Geriatric Workforce Education Program (GWEP) fiscal years (FY) 2021-2024 activities and funding updates. GWEP is determining its FY2024 awards, which have increased from $750,000 to $1M per year. GWEPs provided 529 dementia trainings to over 113,000 learners in FY2022-2023. HRSA's 16 dementia focused training modules will be updated in FY2024. Twelve GWEPs are finalizing 24 training modules for the nursing home workforce, including on dementia. Additional FY2023 funding has supported curriculum development on nursing home care of older adults within the Age Friendly Health Systems 4M framework and aims to increase the number of nurses practicing in nursing homes. HRSA is working with ASPE on a congressional report on the current capacity of dementia care specialists. HRSA is supporting primary care practices in attaining Age Friendly recognition through GWEPs; 272 practice sites have received training as Level 1 participants, and 144 practices have achieved Level 2 status, Committed to Care Excellence.

- ***IHS*** -- Bruce Finke reported that IHS continues to build out its Alzheimer's Grant Program (funded in 2021), with most resources going to Tribal communities. Funding supports workforce development education and training, caregiver support coaching, outreach and dementia awareness, program support and data. Total funding is about $5M per year. The first four grants were awarded in 2022, and another eight in 2023. The tribes provide direct care and services. In 2024, funding will be directed to programs with established efforts, providing an additional 3 years of funding to further develop models of care and focus on sustainability. IHS has been building its technical assistance to grantees. Site visits, a learning collaborative, data dashboard, and annual report are in development. The Indian Health Geriatric Scholars Pilot has scholars from 14 sites completing intensive training. A Geriatric Nurse Fellowship Pilot was launched in partnership with the IHS Division of Nursing. IHS will hold a clinical and community services meeting in summer 2024. The Indian Country Dementia Clinical and Caregiver Extensions for Community Healthcare Outcomes are in their second year, with 526 participants since the May 2023 launch. IHS has an Request for Quote out for training and technical assistance support and has been working on more consistent messaging for outreach and awareness.

- ***NIH*** -- Richard Hodes shared upcoming events (NIA 50th anniversary, March 2024 Cognitive Aging Summit, and September 23-25, 2024, NIH Alzheimer's Disease Research Summit) and recommended cautious spending due to future

funding level uncertainty: NIH is currently operating under a continuing resolution of the congressional budget, which provides funding through March 8, 2024. Dr. Hodes highlighted recent, significant expansion in Alzheimer's Disease and Related Dementias (ADRD) related trials and increased diversity in targets of pharmacologic trials. There are currently nearly 500 trials on topics including dementia care and caregiving, pharmacological treatments, non-pharmacological approaches, diagnostic tools, assessments, and imaging studies, and treatments for neuropsychiatric symptoms. Non-pharmacological research is examining interventions such as exercise, neurostimulation, cognitive training, sleep, diet and supplements, and stress and mindfulness. The two biggest areas of focus in dementia care and caregiving research are formal care settings and caregiver health and well-being. A National Academies of Sciences, Engineering, and Medicine ad hoc committee established in Fall 2023 will recommend research priorities for preventing and treating ADRD in its final report (anticipated in early 2025). A change in published funding announcements will streamline clinical drug trials and neuroscience research infrastructure build out in Africa. A EUREKA Challenge was launched in September 2023, with a prize for the best data methods for early prediction of ADRD. Future research directions include detection and diagnosis at earlier stages; evolving technologies for drug delivery; addressing drug side effects; progress in diagnostic methods, options for symptom management, and additional disease-modifying therapies; and targeted risk reduction interventions.

- ***National Institute of Neurological Disorders and Stroke (NINDS)*** -- Walter Koroshetz shared updates from a November 2023 Research Roundtable with non-governmental organizations and people with lived experience. Workgroups discussed biomarkers, therapies, and practical considerations for early detection and treatment. Multiple funding opportunities are currently open for research on biological mechanisms, stress, models for ADRD, Tau DNA-binding protein 43 (TDP-43), COVID-19 effects on dementia, co-pathologies, effects of anti-amyloid therapies on blood vessels, training, therapy development, biomarker, and clinical trials. Funding for vascular contributors to cognitive impairment and dementia (VCID) research is also available. Future NINDS interests include genome editing therapy.

Discussion

How does the work of the federal agencies fit into the broader goals of the Advisory Council? How can we gauge how many people are educated and are reached?

- Erin Long shared that ADPI grant projects support the goals outlined earlier by NAPA--education, detection, taking science and evidence-based interventions and translating them to the community. All materials created through ADPI grants are available via the National Alzheimer's and Dementia Resource Center website.
- CDC grants are forming coalitions within their jurisdictions and developing area plans, creating infrastructure that previously did not exist. Grants are funded in

43 states, and the BOLD Centers of Excellence are a resource to the whole nation. The initiatives that the various federal agencies have mentioned help bridge gaps in care and services.
- Bruce Finke said that the tribes use resources produced by ACL, CDC, and HRSA.
- John-Richard Pagan asked that the terminology “Alzheimer’s and related dementias” continue to be used, as dementia is broader than just Alzheimer’s disease.
- Joan Weiss indicated that HRSA is very committed to underserved populations. GWEP includes 8-week rotations in a Tribal organization, rural, or underserved primary care site, with the goal that candidates will continue to practice in these areas after graduation. Sixty-five percent of Teaching Health Center program participants remain in the site where they trained.

LEGISLATIVE UPDATES

- Rachel Conant, Vice President of Federal Affairs at the Alzheimer’s Association, provided updates. Through the appropriations process, FY2024 requests include a $321M increase for NIH ADRD research and $35M for implementation of the BOLD Infrastructure for Alzheimer’s Act. The U.S. Senate has proposed a $100M increase for NIH research and a total of $34.5M for BOLD. The House has proposed level funding for research and for BOLD.

- The NAPA Reauthorization Act expires in 2025; the new, draft reauthorization bill has co-sponsors in the House (97) and Senate (36). The Senate passed legislation out of committee in June 2023. The Alzheimer’s Accountability and Investment Act has strong bipartisan support. It is hoped that both bills will be passed by the end of the year. The Comprehensive Care for Alzheimer’s Act called on the Center for Medicare and Medicaid Innovation to develop a dementia care management model and has resulted in the Guiding an Improved Dementia Experience Model, announced by CMS in June 2023.

- Three bills that require reauthorization in 2024 are the BOLD Act (reauthorized every 5 years), the Older Americans Act (reauthorized every 3-5 years), and Lifespan Respite Care Act (reauthorized every 3 years).

RESEARCH PANEL: RESEARCH ON IMPLEMENTATION OF DISEASE-MODIFYING THERAPIES

“Opening Remarks”
Randall Bateman

Research developments were highlighted, including Food and Drug Administration (FDA) approval of Lecanemab in July 2023 as a disease-modifying treatment for Alzheimer’s disease, improvements in diagnostic testing, and progressive research on

modifiable risk factors such as high blood pressure to prevent ADRD. Bateman acknowledged the impact of NIH funds, the National Plan to Address Alzheimer's, and increased funding from Congress. Areas of future exploration include how to best implement and extend impact of new disease-modifying treatments, development and testing of drug candidates, better biomarkers and treatments for ADRD, risk and protective factors, and development of precision medicine. Increased annual research funding from Congress is an urgent need, however, under the current continuing resolution, funding is limited. Consequences to not having a full approved budget include increased research costs over time due to slowed research and missed discoveries resulting from rewriting and resubmitting many grant applications.

"Treating Alzheimer's Disease with Lecanemab"

Erik Musiek, MD, PhD, Washington University School of Medicine

Lecanemab does not improve cognitive impairment but may slow disease progression meaningfully by attacking amyloid plaques during a narrow window early in the progression of the disease as evidenced in the 18-month clinical trials for FDA approval. Reported downsides to the drug include cost, inconvenience of bi-weekly infusions, and possible side effects (e.g., an inflammatory response and micro-hemorrhages). About 21% of people in the trial developed side effects, most of which were asymptomatic; 9% of people on the placebo developed these side effects. People with the APOE4 gene appear to be at higher risk for side effects.

WashU Diagnostic Center is using similar criteria as the FDA clinical trials to determine suitable candidates for receiving Lecanemab. Eligible patients have mild cognitive impairment or very mild Alzheimer's disease and show biomarkers of amyloid. Requirements to receive treatment include a recent MRI, absence of certain neurological risk factors, and no other major medical conditions. To qualify, patients are referred by their primary care physician to a neurologist, with whom they complete a dementia workup, biomarker testing, and genotyping, not all of which is covered by insurance. About 25% of people going through this process qualify for the drug. Treatment involves bi-weekly infusions and repeat MRIs. About 15-20% of people offered the drug choose to proceed with treatment. Lecanemab administration is very work-intensive and requires a large clinical team made up of dementia-trained neurologists, neuroradiologists, and support staff as well as infusion center and MRI capacity. This makes it difficult for a non-memory center to administer Lecanemab. Patients are treated indefinitely, which is not sustainable for any practice due to exponential growth of patient numbers. WashU and other centers will have to decide how long it is feasible to treat people. Challenges for patients include limited access to the Memory Center, the need for clinic proximity to infusion centers and MRIs, insurance coverage, and cost. Medicare covers about 80% of the cost; people without Medicare often cannot afford treatment. There remain many unanswered clinical questions, particularly around the length of treatment, how to deal with logistical interruptions to treatment, safety and long-term effects, and the helpfulness of registries.

"Outstanding Research Questions for Alzheimer's Disease DMTs"
Randall Bateman, MD, Washington University School of Medicine

Dr. Bateman highlighted clinical trial evidence and future research questions. Clinical trials indicate the earlier people are treated with Lecanemab, the larger the benefit. More information is needed about who will benefit, the magnitude of benefit, variation at different disease stages and under different diagnostic and treatment models, and how patient subgroups may differ (e.g., men vs. women, racial and ethnic groups, people with APOE4, mixed dementia pathologies, co-morbid diseases and conditions, Down syndrome, or certain risk factors that excluded them from clinical trials, including those with five or more micro-hemorrhages). There remain many unanswered research questions, particularly around early identification, ongoing testing during treatment, optimization of treatment, and precision medicine.

Discussion

- Transportation can be a huge barrier to receiving treatment. A holistic approach to helping patients get treatment is needed.
- Some Medicare billing codes can be used to cover certain aspects of this care.
- Younger people who are not eligible for Medicare have few treatment options, despite need. Some insurance companies are not willing to cover Lecanemab and have limited awareness of early onset dementia. Eventually, insurance companies will have to provide some coverage.
- The advocacy community must help educate and move health systems and payers forward on this issue, including building in implementation quality measures and answering questions about the diagnostic and treatment process (e.g., recent Alzheimer's Association summit).
- Primary care medicine is already on "life support." Often resources are limited even for providing basic care such as treatment for high blood pressure. How can we find ways to better invest in primary care as the backbone of the health care system?
- Additional considerations include people with mixed dementias, interactions between different dementias, and how to optimally treat them.

RESEARCH PANEL: RESEARCH GAPS AND OPPORTUNITIES

"Down Syndrome and Alzheimer's Disease"
Elizabeth Head, MA, PhD, University of California, Irvine

Head provided syndrome and disease background and highlighted the Alzheimer Biomarker Consortium--Down Syndrome (ABC-DS). People with Down Syndrome have an average life expectancy of 58 with variation by race and ethnicity. The most rapidly growing cohort is people aged 40-50. People with Down syndrome produce excessive amyloid, even prenatally, and by the age of 40, many have sufficient pathology for an Alzheimer's disease diagnosis. Approximately 10-15% of people with Down syndrome reach their late 60s or early 70s without cognitive decline, despite Alzheimer's disease

neuropathology in their brains. For those who do show signs of Alzheimer's disease, the disease tends to progress quickly, with a typical duration under 5 years. The average age of Alzheimer's disease onset is 50-55, and Alzheimer's disease is likely a primary cause of death for people with Down syndrome. People with Down syndrome are typically excluded from clinical trials. ABC-DS, a longitudinal study, examines biomarkers of Alzheimer's disease in adults with Down syndrome age 25 and over. The goal is to understand biological changes underlying Alzheimer's disease in people with Down syndrome and provide insight into clinical trial design for people with Down syndrome. Participants can co-enroll in a trial-ready cohort to examine genetic contributions to Alzheimer's disease in Down syndrome and biomarkers for Down syndrome that can help predict who is going to "convert" to Alzheimer's disease.

People with Down syndrome often have significant cerebrovascular pathology, which can be a risk factor for side effects from new Alzheimer's disease treatments and may impact Down syndrome clinical trials. Including people with Down syndrome in Alzheimer's disease research may help expand the knowledge base for people without Down syndrome.

Discussion

- Is there a way to leverage existing registries, such as the CMS registry, to track people with Down syndrome who are already receiving treatment? This can be very informative, regardless of the number of people receiving treatment. For example, is the amyloid-related imaging abnormalities rate different in Down Syndrome? Most people with Down syndrome are covered by Medicare/Medicaid, which would facilitate tracking their care and data analysis.
- People with Down syndrome are likely be excluded from eligibility for Lecanemab early in the process because of the high rate of risk factors like micro-hemorrhages.

"Lewy Body Dementia"

Jennifer Goldman, MD, MS, Barrow Neurological Institute, JPG Enterprises, LLC

Lewy Body Dementia refers to the clinical syndromes dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD). DLB is the second most frequent neurodegenerative disease after Alzheimer's disease, affecting about 1.4M people in the United States. People with DLB make up about 3.8% of new dementia diagnoses and about 4-30% of the total population of people living with dementia. Among people with Parkinson's disease, there's a 75-80% risk of developing dementia, with about 10% of patients developing dementia each year. DLB affects men more than women, but we need to know more about sex differences.

Delayed diagnosis and misdiagnosis are common; it often takes about 18 months and three doctors for patients to receive an accurate diagnosis. Other challenges include a myriad of clinical symptoms and seeing specialists who lack expertise to identify DLB. The neuropsychiatric symptoms, cognitive fluctuations, and motor features of DLB can significantly impact functioning and quality of life, and often result in significant

economic burden and caregiver stress. There are currently no disease-modifying treatments, and some medications given due to a misdiagnosis can cause psychosis.

Diagnostic criteria have undergone several iterations; the latest was approved in 2017 and includes biomarkers that can support diagnosis. DLB and PDD share many symptoms but often progress differently. On autopsy, about two-thirds of people with DLB have mixed dementias with Alzheimer's disease, vascular dementia, or limbic-predominant age-related TDP-43 encephalopathy (LATE). About one-third of people with PDD show mixed dementias. An abnormal dopamine transporter scan was approved by the FDA in the past year for DLB diagnosis. The pathology of DLB is complex. Recent studies suggest the presence of co-pathologies in DLB. Genes seem to be less of a causal factor in DLB than in Alzheimer's disease.

Research recommendations:

- Increase the number of clinical trials. Research challenges include cognition fluctuation (over hours, days or weeks) and most PDD trials still focusing on motor symptoms.
- Develop and refine neuroimaging biomarkers that track progression, assist in diagnosis, and provide therapeutic targets. A few biomarkers are slated for release, including alpha-synuclein.
- Expand existing and develop new longitudinal DLB study cohorts, including diverse populations, from the pre-symptomatic phase to autopsy to support a range of research studies.

Governmental agencies should provide support for efforts targeting improving diagnosis, access to care, coverage for diagnostic tests and research advancements; help patients and families reduce disability and disease burden through a variety of care models and treatment options; and identify people in the early stages and follow cohorts longitudinally.

Discussion

- It is important to raise awareness about available trials to participate in.
- Diagnostic modalities: There are several PET scans and a cerebrospinal fluid (CSF) test for diagnosing DLB. As we are doing spinal taps for Alzheimer's disease, could we test for DLB too and track the information in a registry to see how effective treatments are in removing amyloid in people with DLB markers? These tests were previously only available to and used by researchers, but tests are starting to be made available commercially. As the tests become more widely available, adding DLB markers to those tests may be useful both clinically and to researchers. Are there clinical differences in the presentation of DLB among racial/ethnic groups? This is an area that needs more attention. There is often later diagnosis and greater co-morbidities in some racial/ethnic groups.

"Frontotemporal Lobar Degeneration"

Brad Boeve, MD, Mayo Clinic

Frontotemporal Dementia (FTD) is an umbrella term covering many clinical syndromes. Frontotemporal lobar degeneration (FTLD) includes a spectrum of pathologies that are manifested as syndromes. Between 2 and 20 people out of 100,000 are diagnosed with FTD. The risk of FTD increases with age, but unlike Alzheimer's disease and other dementias, it often begins in midlife. It affects men and women equally and is uncommon in non-White populations, but it is not clear if this is a biological difference or a result of underdiagnosis in certain communities.

Because FTD often affects people in their working years, the economic and familial impact is great and can include fractured relationships, job loss, loss of insurance and income, and financial devastation due to poor decisions. The initial symptoms can often be mistaken for a "midlife crisis" or a psychiatric condition. Costs of this disease are estimated as twice those for Alzheimer's disease, and caregivers rate the quality of life of their loves ones very poorly.

Diagnosis is often delayed. It is based on a neuropsychological profile, imaging (which depends on the FTD variant), and the absence of alternate etiology. Current diagnostic measures include the Clinical Dementia Rating Scale (CDR), the National Alzheimer's Coordinating Center FTLD module scale, neuropsychiatric measures, MRI imaging, and a plasma neurofilament light chain (NfL). About 20% to 40% of cases are associated with variants or mutations in a known FTLD gene. There are dozens of genes now known to be associated with FTLD and amyotrophic lateral sclerosis (ALS), but there is not a one-to-one correlation between specific genetic variants and FTLD syndromes.

Research recommendations:

- Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affect risk and manifestations.
- Develop an array of biomarkers for diagnosis, prediction, disease monitoring, target engagement and patient stratification. Biomarkers do appear to change prior to clinical onset, but there is no blood or CSF marker that clearly identifies FTD. NfL (which is non-specific) is currently the only clear marker that tracks with disease progression.
- Accelerate evaluation of novel FTD treatments. Many clinical trials are in progress, but there are no FDA approved treatments currently.
- Identify overlapping pathogenic mechanisms between FTD and other neurodegenerative disorders and syndromes.
- Define generic and molecular modifiers of FTD as well as other modifiers of FTD. For example, increased physical activity is associated with decreased longitudinal NfL rate in familial FTD.

Finding and maintaining residential care can be very challenging for families. Affordable support care models that promote quality of life are needed. Government should support coverage of tests to aid in diagnosis. The FDG-PET is covered by Medicare but

often not by other insurance. People with FTD need expedited processing of Social Security Disability enrollment. Dr. Boeve recommends that agencies support and protect individuals with known or suspected genetic mutations and consider coverage of costly preimplantation genetic testing in IVF, which is not typically covered by insurance. NAPA recommendations can identify FTD research as a high priority.

Discussion

- Without accurate biomarkers, it has been difficult or impossible to determine prevalence and identify potential avenues of treatment. Identifying biomarkers is key to progress.

"Candidate ADRD Fluid Biomarkers and their Challenges and Opportunities"
Donna Wilcock, PhD, Indiana University

Our knowledge base about the types and causes of dementia and Alzheimer's disease has slowly evolved and highlights the complexities and overlap of aging related brain changes. There are now reliable Alzheimer's disease biomarkers, and many fluid biomarkers that can help predict brain plaques and the severity of tau pathology. Identification of fluid and imaging biomarkers for TDP-43/LATE, DLB, and VCID is needed. PET scans are the next best option for validating biomarkers due to sample size limitations of autopsy studies. Current imaging for VCID is not very sensitive. A NINDS consortium is specifically targeting biomarkers for VCID.

More research is needed to explore inflammatory and vascular contributions to dementia, and there may be multiple biomarkers for identifying VCID. Therapeutically, inflammatory responses occur across multiple pathologies, and genetic evidence points to inflammation as having a role in risk for Alzheimer's disease.

Cerebral small vessel disease has an additive effect on cognition when co-morbid with Alzheimer's disease. Therapeutics that address vascular components of dementia, and plaques and tangles could greatly impact dementia. Different biomarkers may be needed for each of VCID's many vascular pathologies and mechanisms.

Researchers are investigating candidate biomarkers for many types of ADRD and fluid biomarkers of inflammation. Some of these seem to correlate with levels of amyloid plaques and decline. The RT-QuIC technique for detection of alpha-synuclein pathology in spinal fluid is a promising biomarker that is specific and quite sensitive for PDD and DLB. There are also promising biomarker candidates for TDP-43 proteinopathy, LATE, and FTLD-TDP.

Scalable, sensitive, and specific biomarkers (i.e., blood tests) are needed to advance preventing and treating ADRD. Autopsy studies with matched antemortem biofluids can help advance biomarker discovery for ADRD but may be limited by sample sizes since some dementias are rare. PET ligands may be the best approach for advancing biomarker discovery for dementias beyond Alzheimer's disease.

Discussion

- What is known about COVID-19 and inflammation? Usually with infections like COVID-19, there may be an acute cytokine storm and then a resolution stage. In chronic neurogenerative conditions, there is an apparent burnout of these systems because of constant taxing.

Public Comments

- ***Angela Taylor***, Vice President of Strategic Partnerships for the Lewy Body Dementia Association (LBDA), expressed appreciation to the Advisory Council and NIH for the growing recognition of "other dementias" over the past 20 years. LBDA celebrates the approval of a disease-modifying treatment for Alzheimer's. She encouraged researching synuclein biomarkers to learn more about how many people with Alzheimer's disease have co-existing LBD.
- ***Trish D'Antonio***, Vice President, Policy & Professional Affairs at the Gerontological Society of America (GSA), shared GSA's new toolkit, Addressing Brain Health in Adults with Intellectual Disabilities and Developmental Disabilities: A Companion to the KAER Toolkit for Primary Care Providers. The free toolkit (available on GSA's website) was developed in collaboration with the National Task Group on Intellectual and Developmental Disabilities and Dementia, Ohio Council on Cognitive Health, and Ohio Association of County Boards of Developmental Disabilities.
- ***Maureen Japha***, Executive Director of Eli Lilly's Neuroscience Business Unit, emphasized that the realization of the potential benefits of the new amyloid-plaque targeted therapies is contingent upon equitable and timely patient access to diagnostics and therapeutics. CMS's decision to severely restrict access to these therapies through its April 2022 national coverage decision undermines the NAPA goal of advancing Alzheimer's disease treatments. CMS made its coverage decision when there was only one FDA-approved drug in this class and stated that coverage decisions would be revisited pending new evidence. Lilly 's forthcoming, peer-reviewed manuscript addresses the three criteria CMS set forward for revisiting its coverage decision. CMS's reconsideration process can take 9 months or more, but as many as 3,000 Alzheimer's disease patients with Medicare may progress to moderate or severe stages of dementia a day. The NAPA Council should urge CMS to remove Coverage with Evidence Development (CED) restrictions where positive, confirmatory data is available and immediately reconsider the use of CED for these new Alzheimer's disease therapeutic products.
- ***Dawn Kirby***, Association for Frontotemporal Degeneration (AFTD) Ambassador, shared the story of her daughter, a nurse and mother of a baby boy, who was diagnosed with FTD at age 29, and had never heard of FTD. She enrolled in the research center for support but rapidly declined, required 24/7 care, and was unable to show any emotion or pain. She passed away at age 33. Dawn expressed appreciation for everyone's work, AFTD staff, and research progress. Her daughter donated her brain for research.

- ***Sue Peschin***, President and CEO of Alliance for Aging Research, requested that the Advisory Council receive a 6-month update from CMS on Medicare access to Leqembi, including how many: Medicare and Medicaid claims have been paid; people are enrolled in the three CMS-approved research studies; private insurance claims have been paid for Leqembi; and patients have had to access treatment through private pay. The Alliance for Aging Research is concerned about complicated treatment coverage barriers and that CMS will tie the NIA's $300M real-world data platform to Medicare coverage as its designated registry. Section 1801 of the Medicare law bars CMS from supervising or controlling clinical care, yet that is how its Medicare CED coverage policy is being applied, which undermines the FDA's authority.
- ***Dana Sciullo***, National Programs Coordinator for the National Down Syndrome Society (NDSS), shared that the risk of developing Alzheimer's disease is over 90% for people with Down Syndrome. NDSS recently developed a guidebook and hosted a webinar on Down Syndrome and Alzheimer's disease (both available on the NDSS website). She shared the story of her brother, Anthony, who has a job and a full life. He began having seizures at a young age, and his brain has already showed the impact. Their grandmother is declining from Alzheimer's disease. They are asking for increased education of medical providers and funding for medical research, inclusion in clinical trials, access to treatments. covered by insurance, and educating long-term care about needs of people with Down Syndrome and Alzheimer's disease.
- ***Terry Walter***, AFTD Ambassador, noted that six members of her family have died from FTD and ALS. A specific gene was discovered because of their family contribution to the research. Families experience emotional and financial turmoil going through this process. She advocated for funding for FTD, ALS, and other dementias.
- ***Helen Lamont*** will send another public comment along with meeting materials.

Concluding Remarks

Adrienne Mims, Chair, thanked all presenters and public commenters. Meeting focal points included the importance of reauthorizing NAPA, new treatments, future research and funding needs, and factors preventing the development of effective treatments, including knowledge gaps about the true prevalence of DLB and FTD due to lack of biomarkers. The next NAPA Advisory Council meeting will take place April 29-30, 2024.

The meeting adjourned.

Minutes submitted by Helen Lamont (ASPE).

All presentation handouts are available at https://aspe.hhs.gov/collaborations-committees-advisory-groups/napa/napa-advisory-council/napa-advisory-council-meetings.