ACT-AD

Accelerate Cure/Treatments for Alzheimer's Disease

11th Annual FDA/Alzheimer's Disease Allies Meeting

The Promise and Challenges of Big Data Approaches for Biomarker Discovery, Drug Repositioning and Combination Therapy Development for Alzheimer's

December 5, 2018

SUMMARY

I. Building an Open Science Ecosystem to Enable Predictive Drug Development for AD

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

Prior to sharing an array of multi-stakeholder National Institute of Aging (NIA) initiatives, Dr. Petanceska emphasized the urgency needed to deconstruct the complexity of Alzheimer's Disease (AD) and asserted that open science, an overarching objective of the NIH AD Research Summits, is a vehicle to accelerate translational learning, collectively find the underlying reasons for drug failures in the clinic, and utilize precision medicine. NIA is incentivizing the sharing of data, methods, and research tools through a data driven and predictive drug development infrastructure. The Accelerating Medicines Partnership-Alzheimer's Disease (AMP-AD) program is a collaboration of government, industry, academic, and nonprofit partners that uses an open science research model. The new Agora platform has more than 100 model targets, and the AMP-AD Knowledge Portal, which is being upgraded will be relaunched in 2019, makes the models, data, and shared evidence available to the community for analysis and potential development. To illustrate the success of open science, Dr. Petanceska new disease insights reported by AMP-AD Consortium members and external groups using AMP-AD datasets. She also announced that NIA is investing $60 million over the next five years in the second phase of AMP-AD, with Sage Bionetworks leading the data coordinating center.

Dr. Ryan discussed various clinical trials and their mechanisms and the new NIA clinical trial infrastructure. The AD Neuroimaging Initiative (ADNI), a wide-ranging public-private partnership, the Alzheimer's Biomarkers Consortium- Downs Syndrome (ABC-DS), and the AMP-AD Biomarkers Trial, all make or will make data and bio samples available. The Alzheimer's Clinical Trial Consortium (ACTC), recently formed to create a streamlined infrastructure, provides operational support for funded clinical trials on promising interventions for cognitive and neuropsychiatric symptoms in individuals with AD and age-related dementias. Elements of ACTC include looking at novel agents, repurposing drugs, and novel approaches to recruitment and assessment, including technology-based recruitment and assessment innovations. The ACTC infrastructure welcomes both academic and industry partners. Dr. Ryan clarified that there are many more AD trials at NIA than those in the ACTC network and that the NIA ecosystem makes data, research models, and bio samples available to the research community, especially from terminated and negative trials.

<u>Session Discussion</u>

Initial discussion recognized the timely priority of sharing data from negative trials. The AMP-AD, Anti-Amyloid Treatment in Asymptomatic AD (A4) and Dominantly Inherited Alzheimer Network (DIAN) trials have agreed to the Collaboration for Alzheimer's Principles (CAP) for data sharing, so it is hoped that

with NIA leadership, this principle will be embraced by other trial leaders. Adding to the pragmatic dimension of this issue, the moral dimension was discussed, noting the aspirations of patients and their tangible contributions. When an investigator asked about ways to incorporate the expense of data sharing in clinical trial budgets, it was agreed that this area needs to be more proactively broadcast in clinical trial applications, and for existing trials, it could be addressed through budgetary supplements.

There also was discussion about data security and use of the cloud. Filtered access on the cloud was suggested. An NIH participant commented that when sharing human data, key to enablement is having proper data governance and big data infrastructure, such as a transparent process on restricting access, allowing for varying levels of access, and proper covenants and institutional review board (IRB) approval platforms. An example cited was the Synapse platform used by the AMP-AD portal and Agora.

A participant acknowledged that companies are already sharing data, and it was agreed that as more data are shared, there will be greater momentum to continue the process. Another participant recommended bio-repositories as an additional resource for obtaining shared data. From an intellectual property perspective and for NIA partnerships, it was recommended that discussions on data sharing begin early in the engagement process. Another participant mentioned that several pharmaceutical companies have joined the United Kingdom (UK) Biobank Regeneron Initiative to find creative ways of data access. The insights from the UK's central system may provide helpful examples.

FDA representatives said this was one of the reasons FDA in combination with the Critical Path Institute (C-Path) had formed a Critical Path consortium, launching an aggressive data sharing effort for all industry partners. The agency is a member of this group, which will be working with other agencies to push data sharing in the pre-competitive space. The group, led by industry members, has the technical infrastructure and expertise to control access and has had success with implementation. They already have downloaded information about placebo trial arms and models in AD.

FDA representatives commented on the timeliness of the discussion and that they expect advances from this initiative in 2019. Noting that the C-Path exists specifically to support commercial drug development and approval, FDA representatives explained that the C-Path, which is well funded and supported by the agency, is a good place to focus. There is cross-pollination among C-Path, ventures Bill Gates is funding, and NIA. In the overall effort to eliminate silos, in addition to direct engagement in AD, Gates supports C-Path and FDA works with NIA and NIH.

II. Integrative Proteomics for Biomarker Discovery in AD – Are we There Yet?

Nick Seyfried, Ph.D., Emory University School of Medicine

Dr. Seyfried provided a high level overview of his research focused on the integration of proteomics, systems biology, and molecular biology to tackle fundamental questions related to the pathogenesis of AD and its relationship to the robust pipeline of AMP-AD. He described using discovery and validation proteomics for therapeutic feasibility – finding novel targets and discovering biomarkers. Dr. Seyfried used weighted gene co-expression network analysis (WGCNA) and a multi-network approach to identify protein-specific co-expression in AD. He described how he moved from deeply integrated analysis of the brain with the cerebral spinal fluid (CSF) proteome for AD biomarker discovery and validated AD biomarkers in CSF by targeted mass spectrometry. Measuring these markers in patients' blood or CSF could provide the basis for tests that would help doctors diagnose or even predict AD before the onset of symptoms.

Major questions moving forward are: How early AD can be detected in CSF or blood plasma? Are these biomarkers diagnostic, and from an industry viewpoint, are they theragnostic? What can be learned from healthy as well as pathological aging studies?

Session Discussion

It was suggested that when looking at CSF proteins, it warranted to compare the choroid plexus and its changes because it produces many CSF proteins, is full of amyloid, and no data exists on this. It was explained that there is a need for blood biomarkers and that work on plasma and CSF needs to be integrated. The presenter currently has a grant from the Molecular Mechanisms of the Vascular Etiology of AD (MOVE-AD) Consortium and is partnering with Oxford, conducting research peptide panels similar to those he developed for CSF and integrating correlations with other biomarkers and clinical measures. In a proposed AMP-AD grant, he is looking to correlate and find the signatures most relective of AD. As for lipidomics, Duke plans to analyze the 300 CSF samples.

As for comparing molecules in the brain with the expression and findings from the central nervous system (CNS) -- a co-expression analysis, it was maintained that this will provide meaningful biological insights. The speaker said that he had done this in amyotrophic lateral sclerosis (ALS) and is doing it now for AD; observing communities of proteins completely independent of what he sees in the brain. He sees a CSF signature which he thinks is coming from the periphery, but he has not yet validated this. He believes that doing integrated network analysis in both –omes is important, doing it in plasma and CSF in the same people. It was suggested to compare the gene co-expression networks already generated across all RNA-Seq samples in AMP-AD.

III. **Digital Biomarkers in the Era of Precision Medicine**
Larsson Omberg, Ph.D., Sage Bionetworks

Dr. Omberg focused on precision medicine and digital biomarkers. He presented on the use of remote sensors and mobile devices to remotely capture severity of disease. Although most of the work presented was in diseases other than AD, the lessons learned are applicable.

Sage Bionetworks has done more than 30 mobile health studies which together have recruited more than 160,000 study participants. Traditional health research in the clinic is episodic, offers a partial view of the patient and is expensive whereas in mobile health using digital tools, such as mobile phones and wearable devices, assessments can be low-cost, frequent, even daily, or continuous with passive monitoring. Mobile health assessments can be paired with clinical assessments, with information extrapolated long term for progression monitoring. Reporting on results from studies in Parkinson's Disease and Multiple Sclerosis, he showed multiple measures extracted from the sensor data showed association with clinical severity and showed large intra-individual variation. Building personalized models from longitudinal data for variation in motor symptoms related to levadopa medication in Parkinson's Disease shows great potential for better understanding of population variation of phenotypes and how disease modifying medication can be better targeted

He pointed out that the vast majority of data collected commercially is not available and emphasized the need for open data and analysis. Sharing the data allows for more rapid development of digital biomarkers and outcomes and once developed allows for continual benchmarking and improvements as new devices and technologies are developed. Dr. Omberg illustrated his commitment to this concept by

describing how they have developed e-consents that allow the research participants to share their data with anyone and how they are publically releasing data.
Recently his team launched a crowd-sourcing "DREAM Challenge," in which his team posted data and a question online and offered a monetary reward for anyone who could best what had been done by five collaborating teams. After three weeks the 420 individual competitors from around the world had developed measures that were 58% better at predicting disease and 34% better at predicting disease severity. Subsequently they made the model available so others could benchmark the measures with their own data.

Summary Discussion

There was interest in the broader distributional measurements described. It was noted that a higher quantity of data can be captured so that there can be more rapid assessment of the measured effects, and there can be more variation in data that helps with the thoroughness of the assessment.

As for engaging with technology companies, Sage worked with Apple to help them launch its Research Kit and is currently co-developing the product. In general, Apple was interested in the use of their devices rather than the actual research, so Sage built the infrastructure for collecting the raw data; therefore Apple did not need to host human research data on their servers. Sage also worked with Samsung on a new device to measure blood pressure. However, in general, most companies developing wearables may do small pilots with researchers but are reluctant to share raw data, as they see it as having strong commercial value.

From an FDA perspective, transitioning observations into drug development is a complex issue for which there is no one roadmap. The FDA is open to technology supporting drug development and sees significant commonalities between the newer tools and the more traditional ones. Among the questions that need to be answered for both: Are the captured outcomes the intended outcomes? Do the outcomes provide evidence of meaningful change(s) or difference(s) for the patient? Key reasons for using new technology include doing something better and doing something that cannot be done.

IV. Quantifying Brain Wellness and Disease with Digital Biomarkers

Rhoda Au, Ph.D., Boston University

Dr. Au discussed the progression of AD and where there are new opportunities to detect evidence of cognitive changes earlier. She noted the heterogeneity of the disease, as seen in neuropathology, imaging and cognition, and she briefly reviewed how she leveraged the dementia research of the Framingham Heart Study (FHS). The limits of standard neuropsychological testing used in the FHS as she aimed to detect impairment earlier led her to apply the Boston Process Approach (BPA) to increase the sensitivity of the tests. The BPA includes tracking error and extraneous responses and the FHS is the first to apply this method to epidemiologic research. NIH funding of FHS extends to a younger third-generation cohort so FHS dementia studies now span the entire adult age range. Recently Dr. Au integrated digital technology into the cognitive assessment process while preserving the traditional pencil and paper test experience. Use of digital voice and digital pen to capture cognitive performance underlie her current work of determining the potential for digital cognitive biomarkers as surrogate indices for more expensive and invasive fluid and imaging biomarkers. She is interested in how "big data" analytics can better inform our understanding of disease pathways and treatment.

In addition to her work on FHS, Dr. Au is focused on building multi-sector ecosystems to enable solutions for chronic disease prevention, optimizing brain health specifically, and moving the primary focus of health technologies from precision medicine to a broader emphasis on precision health. She is developing a brain health monitoring system, testing and validating the platform through NIA funding. Among its initiatives is an AD Center at Boston University, where they are setting foundational protocols and which she is sharing with AD Centers across the nation so they can build their own platforms.
Session discussion

Session Discussion

Initial discussion centered on the choice of the term "digital biomarkers." Not using the term in the traditional way but thinking of it as a surrogate biomarker is a means to expand the basis of traditional thinking. The term is analogous to the lesson of FHS, a model that spans multiple health areas and began as a heart study, which now has the richest cognitive database in the world. Biomarker also is a timely term that interests investors. FDA representatives, commenting on the language used, said the term is a pragmatic one. From their perspective, considering biomarkers as multipurpose tools, including more traditional ones, like electroencephalography (EEG), as well as those that measure clinical outcomes or performance, it is more relevant initially to discuss the information a biomarker captures, such as likelihood or certainty, and the setting in which it is utilized, before discussing its status as a "biomarker."

Discussion about the metadata used for cognitive assessment elicited an explanation that the research presented is in the exploratory phase. It also was explained that to control for aging vocal cords in the voice analysis research, a range of features are combined so that a constellation of features are analyzed.

Additional information about iCarbonX , a company that makes high tech products, was discussed. Headquartered in Guangdong Province, China, it is in an acquisition phase, focusing on products for precision health – finding the right solution for the right person at the right time.

V. **Industry Perspective on Digital Biomarkers for AD/ADRD**
Jim Harris, Roche Diagnostics
Denise Heaney, Ph.D., Roche Diagnostics

Mr. Harris provided an overview of Roche, the pharmaceutical company and number one provider of diagnostics worldwide. Their current five year strategy is to drive integrated solutions and shape and drive digital diagnostics. He described the clinical diagnosis of AD based on patient clinical history, cognitive assessment, neuroimaging tests, and CSF biomarkers, referencing the NIA and Alzheimer's Association Diagnostic Research Framework 2018. He emphasized that with the high cost and a high number of people with AD, even with disease-modifying therapies, there would be an inadequate number of neurologists and technicians, for diagnosis and care management; digital measures can assist in accelerating data collection, integration, and analysis in combination with personalized information for the benefit of patients. Mr. Harris also stressed the significance of partnerships among healthcare stakeholders to provide information solutions that improve patient care, and partnerships in academia and the healthcare industry to help recreate and redefine how data drives patient care and research and development. He maintained Roche's commitment to AD and to taking treatment for patients to the next level with an advanced personalized healthcare strategy and multiple digital innovations.

Dr. Heaney discussed the rationale for digital biomarkers, Roche's experience with NAVIFY, a software solution for managing tumor boards and aligning oncology care teams on treatment. Roche views this product as a model for software solutions for other diseases, such as AD. Dr. Heaney explained that Roche regards digitalization as an opportunity to access meaningful data and create insights to improve patient care and outcomes. She described decision support in both the laboratory, where it encompasses improving operations, workflow and analytics, and in the clinic, where it includes providing insights to inform patient care. She cited NAVIFY as a clinical decision support platform that puts information in context in one place - a dashboard - that both providers and patients can use to make better decisions. Currently more than 130 institutions are evaluating this system, and according to new study results, because of this diagnostic optimization platform, oncologists and radiologists respectively spent 53% and 12% less time in tumor board meeting preparation.

Summary Discussion

Initial discussion centered on lessons learned from growing and merging evolving technologies like digital biomarkers with traditional phase measurements. There was agreement among industry participants that even with great markers, there is much complexity and uncertainty around having day-one readiness. Outstanding questions for the field include: Are clinicians educated and are labs ready? How does one transition from a trusted clinical diagnosis to a biologic? How does one partner with pharmaceutical colleagues?

There was agreement that the FDA was a good partner, recently issuing guidance on digital companion diagnostics. Allowing time for clinical access to have enough trained pathologists and cytologists on a specific test for adequate day-one capacity is required.

Integration was cited as the most important obstacle for institutions and hospitals that adopt a decision support system. Whereas institutions would like it up and running immediately, a fully integrated system needs to deal with multiple departments and security levels, so it can take from six to nine months to be fully integrated.

VI. **Leveraging Diverse Types of Big Data to Advance Rational Drug Repurposing in AD**

Mark Albers, M.D., Ph.D., Harvard University

Dr. Albers discussed leveraging diverse types of big data to repurpose drugs in AD. He illustrated how he integrates three data sources, beginning with discovery in chemical proteomics from data systems and validating his findings in *in vitro* central nervous system (CNS) cells from AMP-AD. He described these processes as a systems pharmacology approach. Subsequently he validates his research in electronic health records (EHR), and in his experience with a recent discovery, he merged these results with laboratory data, processes he described as a real-world approach. Now he is planning a clinical trial. Repurposing FDA-approved drugs is one approach to probe potential pathways in proof-of-concept, and ultimately therapeutic, clinical trials.

As a result of Dr. Albers' integrating new approaches, he discovered that cellular context matters and that drug-induced patterns of differentially expressed genes in CNS cell types predict the stage of AD better than drug-induced patterns derived from non-CNS cell types. He found that genes differentially expressed by JAK inhibitors in human CNS cell types predict the cell stage of AD in human brains. He also concluded that *in silico* drug trials in EHR can evaluate repurposed drug candidates. Preliminary data support a therapeutic role for JAK inhibitors in preclinical AD, and a clinical trial on this currently is

being designed. Dr. Albers also discussed his work with the drug metformin, which reduces progression to dementia relative to sulphonylurea in diabetics.

Among the obstacles faced by Dr. Albers is that more data cleaning needs to be done with the AMP-AD data. Other challenges, such as missing data, propensity matching of covariates and fewer data with newer, more precise drugs, occurred in the *in silico* drug trial in EHR. Likewise, he is determining how best to share the EHR data so others can use and re-validate it without compromising patient confidentiality. He also has had difficulty with access to the drug ruxolitinib for clinical trials.

Summary Discussion

The discussion began with a researcher's question about whether there is a correlation of an anti-mortem PKR phosphorus ratio to post-mortem TDP-43 within the brain because there is not a good biomarker for TDP-43. The presenter replied that he is working with autopsied ALS and AD brains, in which he sees high PKR levels and is looking to correlate the brains with CSF.

A participant commented that many patients are on JAK inhibitors, which are expensive, and asked whether the speaker had looked at whether patients had reported a cognitive benefit. He said that in some ways, that is what he is trying to do by looking at EHR. He is looking at changes in cognition over time in patients that are taking inhibitors for other reasons, but there are few data. Access to clinical trial data would be very useful, as JAK inhibitors with different scaffolds that clearly inhibit JAK are not yet understood.

The same participant asked about the gamma interferon signature and its effect in the periphery, and whether serum and blood have been saved from recent clinical trials for the presenter to analyze for signals. The response was that there is good reason to think that ruxolitinib has profound effects on macrophages and its effects on macrophages might extend to microglia. With many caveats, the speaker suggested that the drug may have a peripheral and/or innate effect, which is why he wants to do a proof-of-concept trial.

FDA representatives were asked whether it is possible to repurpose an already FDA-approved drug, like JAK inhibitors, for a different indication such as AD, and achieve breakthrough designation. They responded that the breakthrough process expedites the development and review of drugs to treat a serious or life-threatening condition for which preliminary clinical evidence indicates the drug may demonstrate substantial improvement over an available therapy on significant clinical endpoints. It does not matter if the drug has a previous indication, and if it meets these criteria, it is a good candidate for breakthrough status.

Another participant suggested that it could be useful to connect with the interventions testing program at NIA, the Division of Aging Biology and/or the Division of Neurology, or the National Center for Complementary and Integrative Health. An NIA representative suggested that going to the MODEL-AD Consortium could be beneficial to test the drug because it is creating the infrastructure to vet therapeutic candidates nominated by the community.

VII. **Clinical Analytics Platform for Linking Outcomes to Trends in Complex Data**
Nikhil Gopinath, M.S., Saama Technologies

Mr. Gopinath asserted that digital technology, mobile solutions, novel data collection modalities and integrated systems are becoming features of modern clinical trials. He discussed applications in clinical operations, feasibility, and extensions in clinical and safety sciences. Saama has experience with trial management and is beginning a roadmap with patient data. Showing a clinical analytics platform for linking outcomes to trends in complex data, a "multilayer hypergraph," Mr. Gopinath illustrated how to connect various data sources – clinical trials, management systems, biomarkers, claims and electronic records - and find associations among multiple facets, including disease symptoms and treatments. He aims to connect patient response to medical history and physiology and pinpoint the most effective responders and those with the least safety events. Currently, he is building the architecture for this long-term vision. As an initial step, using machine learning, he has been able to find the best clinical research sites for a specific trial and the best principal investigators and offer reasons why they would be best for recruitment, solving the huge problem on non-recruitment. Similarly, he believes that this methodology could review recently published Phase 3 clinical trial failure results, differentiating them by other endpoints, biomarkers and adverse events, to expedite and validate the process of new cohort design. Mr. Gopinath says that this neural network model or algorithm finds solutions through operational efficiencies and coordinated outcomes. Instead of scanning huge data sets, one can click on the dots to find specific information, even exploring the data in 3-D.

Summary Discussion

Initial discussion centered on selecting clinical trial sites and participants outside of the AD space and drilling down to get the right population and save time. It was explained that the majority of outside limitations dealt with trial management across three areas – inflammation and immunology, the central nervous system (CNS), and oncology.

He currently is deploying predictive models across both areas, that is, "intelligent risk-based-monitoring," and rolling out models for inflammation and immunology. As for extending this work, he is interested in models of subgroup analysis and updated protocol design. Like multiple database models, he would focus on randomized clinical trials (RCT), electronic medical records (EMR), and real-world data.

VIII. **Developing AI Technologies to Enable Data-Driven Drug Development**
Rong Xu, Ph. D., Case Western Reserve University

Dr. Xu's cutting-edge research is concentrated in biology and biomedical informatics and her presentation focused on developing artificial intelligence (AI) technologies and other computational techniques to enable data-driven drug development and discovery. She discussed how she used AI, including machine learning and natural language processing, to understand human language and reverse engineer drug development. Because there is a huge translational gap between animals and humans, and many drugs that work in mice do not work in humans, Dr. Xu designed a process that begins with humans and proceeds to animals. She developed novel computational algorithms to create, integrate, and analyze large amounts of heterogeneous and complex biological and health data. This includes the automatic construction of disease and phenotype knowledge bases; integration with existing databases; and healthcare big data. For example, in the dementia phenome, there are five million unique drug side-effect pairs for more than 8,000 drugs and 14,000 side effects.

Dr. Xu is currently building a mind-disease phenome knowledge base that will contain deep phenotypic relationships among thousands of drugs. In her reverse engineering approach for rapid drug

repurposing for AD, she combines novel computational predictions with clinical corroboration through patient EHR, experimental testing through "virtual clinical trials," and validation through pre-clinical testing *in vitro* and *in vivo.* Dr. Xu's goal is to identify unique, viable drug candidates and move them into patient trials efficiently and cost-effectively. She plans to disseminate her research through the AMP-AD Knowledge Portal.

Summary Discussion

One participant noted that because there is not a good translation in AD from animal to human, going back to a pre-clinical animal model to validate a finding in human data may not be very helpful. It was explained that for the pre-clinical animal model for a repurposed drug, there are expectations for failure and that this phase is mostly to figure out the mechanism of action, not to test the efficacy of the drug. It may not always be a necessary step, if there is strong evidence in clinical trials.

Discussion about the classification of blood-brain barrier predictions, big molecules and antibodies prompted a clarification that the described model currently applies to big and small molecules but that other computational models currently apply to only small molecules.

Because many new compounds and chemical entities are reviewed in early drug development, it was noted that the described approach uses only clinically identified features. A participant suggested that the approach would not provide that much documented clinical information and that this should be considered for the model's broader application. It was asserted that there are approximately 1,500 FDA-approved drugs and about 8,000 drugs, including failed ones, on which there is information published in the biomedical literature. Rather than just directly use a drug's clinical phenotype to predict its efficacy, the researcher uses indirect reasoning to make inferences about the drug's potential clinical impact on the disease.

In a discussion about coordinating with others, like those at IBM and with Eric Schott at Mount Sinai, differences were explained. IBM's Watson matches study articles with patients and the speaker's model extracts knowledge from articles, using a natural language process to understand their content. The presenter's model employs a systems approach to integrate knowledge and make predictions.

Additional discussion focused on the fact that working with computational algorithms to understand human language and medical texts is extremely difficult, tedious and slow. Because there is no existing database to extract from the literature the phenotypic relationship of data on drugs and diseases, NIA is working to build this computational algorithm. There now are 500 curated AD articles. Discussing relationships across various databases and how one would interact with the model described, the presenter said that they are planning to link with other databases and are building interactive web applications so people can tap on the disease, which will give them disease data, like causation; relationships about the disease; and supporting evidence, including research articles.