

Opportunities and Challenges in the Use of Blood-Based Biomarkers in Clinical Research and Population Studies on Alzheimer's Disease and AD-Related Dementias

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Acronym Definitions

A4	Anti-Amyloid Treatment in Asymptomatic Alzheimer's
AA	African ancestry
ACTC	Alzheimer's Clinical Trials Consortium
AD	Alzheimer's disease
ADL	activity of daily living
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRC	Alzheimer's Disease Research Center
ADRD	Alzheimer's disease-related dementia
AI	artificial intelligence
APOE	apolipoprotein E
ARIA	amyloid-related imaging abnormality
ATN	amyloid/tau/neurodegeneration
ATRI	Alzheimer's Therapeutic Research Institute
AUC	area under the curve
BAL	Biomarker Assay Laboratory
BB	blood-based
BBB	blood-brain barrier
BBM	blood-based biomarker
BD	brain-derived
BEST	Biomarkers, Endpoints, and Other Tools
BEYONDD	Biomarker Evaluation in Young Onset Dementia from Diverse Populations
BHR	Brain Health Registry
CAL-BHR	California Latino Brain Health Registry
CAP	College of American Pathologists
cfRNA	cell-free RNA
CLARITI	Consortium for Clarity in ADRD Research through Imaging
CLEAR-AD	Centrally Linked Longitudinal Peripheral Biomarkers of Alzheimer's Disease
CLIA	Clinical Laboratory Improvement Amendment
COA	Clinical Outcome Assessment
COU	context of use
CPAD	Critical Path for Alzheimer's Disease
CSF	cerebrospinal fluid
CTE	chronic traumatic encephalopathy
DD	defining disease
DIAN	Dominantly Inherited Alzheimer's Network
EMA	European Medicines Agency

EOD	early onset dementia
ER	emergency room
FAIR	findable, accessible, interoperable, and reusable
FDA	Food and Drug Administration
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FNHI	Foundation for the National Institutes of Health
GAAIN	Global Alzheimer's Association Interactive Network
GBSC	Global Biomarker Standardization Consortium
IDEAS	Imaging Dementia Evidence for Amyloid Scanning
IHC	immunohistochemistry
IL-9	interleukin-9
iPSC	induced pluripotent stem cell
LATE-NC	limbic-predominant age-related TDP-43 encephalopathy-neuropathologic change
LEARN	Longitudinal Evaluation of Amyloid Risk and Neurodegeneration
LIMS	Laboratory Information Management System
LMIC	low/middle income country
LOS	Letter of Support
MTBR	microtubule-binding region
NACC	National Alzheimer's Coordinating Center
NCRAD	National Centralized Repository for Alzheimer's Disease and Related Dementias
NDUF	NADH:ubiquinone oxidoreductase
NfL	neurofilament light chain protein
NHB	non-Hispanic Black
NHW	non-Hispanic white
NIA	National Institute on Aging
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
PACC	Preclinical Alzheimer Cognitive Composite
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography
PHI	protected health information
PII	personal identifiable information
PPV	positive predictive value
QoL	quality of life
ROC	receiver operating characteristic
RT-QuIC	real time quaking-induced coercion

SE	surrogate endpoint
SEABIRD	Study to Evaluate Amyloid in Blood and Imaging Related to Dementia
SES	socioeconomic status
SMAD3	mothers against decapentaplegic homolog 3
SUNBIRD	Study to Understand Novel Biomarkers in Researching Dementia
TDP-43	transactive response DNA-binding protein 43
UCSF	University of California, San Francisco
UX	user experience
VCID	vascular contributions to cognitive impairment and dementia

Executive Summary

In Session 1, on the state of the art and molecular underpinnings of Blood Based Biomarkers for AD/ADRD, speakers reviewed biomarkers for brain amyloidosis, tauopathy and neurodegeneration (ATN). It emerged that robust blood-based biomarkers for amyloidosis are at hand, such as the amyloid beta 40/42 ratio and p-tau217. We are on a good path for blood-based biomarkers of tauopathy with several candidate p-tau isoforms or tau peptides whose CSF or plasma levels show promising correlation to the presence of tau fibrils and/or tangles and perhaps neurodegeneration. We still need to have robust and validated biomarkers to complement the ATN framework for AD/ADRD to mark and follow processes that contribute to the pathophysiology of AD, such as neuroinflammation and vascular contributions to dementia. We need biomarkers for non-AD dementia: LBD, FTD and LATE that exists as co-pathologies in a substantial segment of the AD patients, especially in older subjects. Seed amplification assays are emerging as robust biomarker for alpha-synucleopathies, but they require CSF or skin punch biopsies, and their performance still needs to be clinically validated. Moreover, we don't have PET tracers for alpha-synucleopathies and for TDP 43 aggregates, so we need to rely on autopsy as a ground truth.

In Session 2, focused on the use of biomarkers in clinical research and trials, speakers introduced a revised diagnostic framework that now incorporates well validated blood-based biomarkers for amyloid beta, but still relying on imaging for tauopathy and neurodegeneration. The revised diagnostic framework identifies Inflammation and cerebrovascular disease as major contributors to AD/ADRD, but, in session 3, we also learned that genomic/gene-expression studies, as well as animal models, provide strong evidence for other processes, such as mitochondrial dysfunction. We need to have robust and validated biomarkers to complement the ATN framework for AD/ADRD, which can contribute to precision medicine approaches to early disease diagnosis, prognosis, disease staging and monitoring response to intervention. Speakers shared examples of how we can successfully use amyloid beta blood-based biomarkers as tools in clinical trials, leading to optimized experimental design and facilitating reaching out to potential candidates, thus contributing to trial success, and lowering trial costs. Overall, there is confidence that the combination of different biomarkers will allow us not only to screen for and diagnose AD at the individual level with precision-medicine, but to accurately stage the disease, and perhaps turn these biomarkers into surrogate end-points for adjudicating outcomes of trials, with sufficient evidentiary support for acceptance by regulatory agencies.

In Session 3, focused on population-level and community-level studies, speakers underscored that we need to do a better job at ensuring external validity of blood-based biomarkers for AD/ADRD by understanding the impact of race/ethnicity, social determinants of health (e.g., poverty and education), and comorbidities on the disease. Additional research is needed regarding the impact of these factors as contributors to AD/ADRD pathophysiology and/or modifiers, and how these factors may impact current and novel blood-based biomarker levels and performance. It will also be critical to educate health care providers on when/what to order as blood-based biomarker, how to interpret AD/ADRD biomarkers,

and provide them with a structured/sensitive approach for disclosure. The Alzheimer's Association has already been taking steps in these directions such as publishing recommendations.

In Roundtable 1 speakers shared experiences in build infrastructures to leverage registries, using digital technologies for engaging subjected, cognitive screening and remote blood collections, which can be employed successfully to reach out to underrepresented minorities. Platforms that ensure coordination and bidirectional communication among parties (researchers-care providers-study subjects-contract laboratories) are critical for successful using these infrastructures. But, as we heard in Session 2, achieving a culture of reciprocity is critical: we need to do a more thoughtful, compassionate job when reaching out to diverse/underrepresented populations, not with open hands, but with an attitude to “give back”.

We also have infrastructure at hand for integrating and sharing multi-modal data from animal models, and from living human subjects, in one single sharable platform. Panelists underscored that platforms/data repository are vital for retrospective studies. Standardization of methods and harmonization of measures is critical to ensure that data across sites and time points are comparable. Metadata is also critical, as it provides context and therefore, meaning to the data.

We have infrastructure for collecting/storing/distributing samples for use by the wider scientific community. Centralized repository and centralized/consistent assays are critical for longitudinal studies, but we need best practices for collection/handling/storing and assay execution to allow standardization and harmonization of the data. Building, maintaining and managing these infrastructures need high level of coordination and pragmatism. Some of the specific necessities are:

- “Smart” material transfer agreements, to facilitate wide user access
- Reliable reference controls, to use as internal standard. Certified reference materials may not be available for all analytes/assays.
- (pooled plasma).
- Dedicated/need-based/customized lab management/informatics (LIMS)
- Strategies for Integrating sample sharing with data sharing (to save samples if assay already done)
- Strategies to monitor usage and Success metrics (Number of users/publications-Need to be streamlined/automatic tracking: who is using it, for what? Tracking downloads)
- Diversified biorepositories. Need to go global: Going global as a tool not only to reach out to diverse groups but as a road to making biomarkers more robust.
- Automatization

Challenges to establishing/ maintaining/managing these infrastructures are:

- Cost and Sustainability
- Privacy Protection Policies/used of different Informed Consent forms with different coverings
- Scalability
- Reliance on endogenous control samples or pooled plasma

- Inconsistent identification numbers used for study subjects in different studies (NAAC IDs vs other identifiers, such as GUID)

In Roundtable 2 stakeholders from patient advocacy groups, foundations, not-for-profit organizations, public/private partnerships and regulatory agencies shared their expertise and of view on platforms that enable networking and facilitate pipelines towards regulatory approval and/or commercialization. Panelists underscored that engaging different stakeholders (including pharma) in communications early in the process of biomarker development is instrumental to accelerate the process of validation and commercialization. Sharing Datasets and tools for the analysis of existing data through platforms that support a Workspace for collaborative research allows access to wider breadth of data and enables discovery. Also, robust, aggregated datasets and validated disease models can facilitate drug development and may also accelerate the processes of regulatory approval. Similarly access to data and public biorepositories on the part of for profit, and, vice versa, public access to dataset/repositories established by for profit can help the process of analytical validation and drug development.

Meeting Summary

October 30, 2023

Welcome: Day 1

Alessandra Rovescalli, Division of Neuroscience, National Institute on Aging

Dr. Rovescalli welcomed attendees to the workshop. When NIA started putting it together about a year and a half ago, it had just heard about the FDA designation of a blood assay for amyloid beta 42/40 as a breakthrough device. A little later, it learned of a long-awaited disease-modifying therapy able to slow down cognitive decline. Now multiple assays are coming up as viable blood biomarkers for amyloid and tau pathologies, with two or three different therapy strategies approved as disease-modifying interventions for AD. Things are moving very fast, and it is critical to know both the capabilities, barriers, as well as the research terrain. This workshop is an overview of the amazing potential of blood biomarkers for AD/ADRD and a critical reflection on how to use them in the battle against age-related dementias.

Opening Remarks

Richard Hodes, National Institute on Aging

Dr. Hodes noted that the past decade has seen enormous progress in the area of multiple blood biomarkers with the potential to detect disease early, track the response to treatment, and look at the course of pathologies in individuals affected by Alzheimer's disease.

Plenary Lecture

The Potential and Promise of Alzheimer's Disease Blood Biomarkers

Randall Bateman, Washington University in St. Louis

Dr. Bateman commented that the field has reached an inflection point, where what it can do for patients with Alzheimer's disease today is worlds different from what it could do just five years ago. For the first time, biomedical science is changing the course of the disease, removing and reversing amyloid plaque pathology and approving disease-modifying drugs.

Alzheimer's is a molecular disease. At the individual molecular level, it has an action and effect leading to a cascade of events that ultimately affect the brain and cause dementia. Autosomal dominant Alzheimer's disease starts with mutations in genes, producing stickier forms of amyloid beta. In sporadic Alzheimer's disease, the pathogenesis appears to be impairment in

the clearance of amyloid beta, converging with pathophysiological cascade of autosomal dominant AD amyloid plaque growth up to 20 years before symptom onset in both forms of the disease.

The Dominantly Inherited Alzheimer's Network (DIAN) has studied people destined to get Alzheimer's disease at a very specific age. A substantial buildup of amyloid plaques in the brain is observable 15 to 20 years prior to symptom onset, and hypometabolism and cortical atrophy sets in about five to seven years in advance. When an individual becomes symptomatic, substantial amounts of tau tangles can be seen in the brain as measured by tau PET.

In addition to pathologies, there is a map of dozens, hundreds, or perhaps even thousands of molecular signatures that can be determined in Alzheimer's disease. These signatures can be used to identify not only if someone will get the disease, but when that person will first exhibit symptoms and possible interventions.

One of the great limitations in the field has been the need to collect cerebrospinal fluid by lumbar puncture or spinal tap. The advent of blood-based biomarkers has provided simple and easy access to molecular signatures, and what used to take years to accomplish is now done in months.

Sensitive and specific biomarkers can be used to independently identify and quantify amyloid plaques and tau tangles in Alzheimer's disease pathology. The tau tangle pathology markers are strongly associated with clinical impairment and cognitive decline, which suggests a high clinical utility of biomarker panels.

The Study to Evaluate Amyloid in Blood and Imaging Related to Dementia (SEABIRD) is a community-based validation of plasma biomarkers as a screening for blood amyloidosis. SEABIRD met its recruitment goals in most demographic categories, including sex, race, and most comorbidities, but not yet in education. The classification accuracy of plasma biomarkers demonstrates outstanding performance in the general population, with the percent p-tau217 ratio performing as well as CSF or PET standard testing. The Study to Understand Novel Biomarkers in Researching Dementia (SUNBIRD) aims to determine diagnostic and prognostic performance of blood-based biomarkers in cross-sectional and longitudinal comparisons with AD tau and amyloid pathologies and clinical cognitive impairment in primary care clinics.

Three different drugs (aducanumab, lecanemab, and donanemab) have demonstrated in separate Phase III trials disease modification and improved outcomes of clinical progression, ADLs, and QoL.

There are several outstanding questions, including: How do the biological measures of pathology and pathophysiologic biomarkers relate to cognitive, clinical, and functional outcomes? How can the biological impact of treatments be used to design more effective treatments? Is the biology telling us how to better target the disease? Should we treat to biologic resolution on an individual patient level for optimal outcomes?

Dr. Bateman offered a guidelines recommendation that for blood-based biomarkers with similar performance as PET or CSF, blood testing can be used to confirm the presence of amyloid plaques, and support diagnosis, enrollment, and treatment monitoring without the need for PET or CSF. He predicted continuous development and approval of disease-modifying treatments for symptomatic patients; implementation of rapid, accurate diagnosis for all; delivering on the promise of changing the course of disease, keeping more patients with their cognition and function intact, and delaying the onset of dependency; and successful prevention trials enabling the screening of the general population in primary care, preventing the onset of Alzheimer's disease for millions.

Session 1: State of the Art and Validation

Chair: Henrik Zetterberg, University of Gothenburg

ATN Biomarkers: Current State and Biological Underpinnings

Thomas Karikari, University of Pittsburgh

ATN biomarkers fall into at least one of the following categories: the aggregated amyloid beta or associated pathologic state (A), the aggregated tau or associated pathologic state (T), and neurodegeneration or neuronal injury (N). It is possible blood biomarkers could be included in the next update.

Individuals negative in all three categories have normal AD biomarkers; those positive in A but negative in the other two are in the Alzheimer's pathologic change category; those positive in A and one or both of the other two are on the Alzheimer's continuum; and those negative in A but positive in one or both of the other two are in the non-AD pathologic change category.

ATN marker agreements increase with disease severity. Current A markers have high agreements between modalities. T and N markers have poorer agreements. Plasma markers show good agreements with CSF. Partial correlations may affect the capacity to fully replace CSF biomarkers. CSF MTBR tau markers better correlate with tangle pathology than the current p-tau.

Plasma BD-tau monitors disease progression in A-positive individuals. Plasma p-tau and BD-tau allow staging of emerging AD pathology, which is useful for identifying patients at increased risk of cognitive impairment and important for the prioritization of amyloid beta-positive patients to receive therapies. Plasma BD-tau might be useful for tracking ARIA, but further studies are needed.

Candidate Fluid Biomarkers for the ADRDs

Donna Wilcock, Indiana University

The traditional view of dementia is a siloed pie chart, with Alzheimer's, vascular dementia, Lewy body dementia, and other forms in distinct categories. In reality, there is considerable overlap among the different pathologies. The new ATN criteria add the concepts of inflammation (I) and vascular (V). Increasing evidence supports inflammation playing a role in Alzheimer's disease. Cerebral small vessel disease has an additive effect on cognition when comorbid with AD.

The challenge with vascular biomarkers is VCID reflects varied vascular pathologies and mechanisms. It is absolutely critical to develop clinical outcomes, biomarker measures, and interventions that match the targeted vascular injuries and disease. The challenge with adding inflammation is there are multiple stages of microglial activation, and it is unclear which stage inflammation biomarkers are identified with.

The RT-QuIC method is being used to detect alpha synuclein pathology. It seems to be specific and sensitive, but does not appear to indicate disease severity. A study by Rissman et al. examined extracellular vesicles from the plasma of autopsy-confirmed LATE-NC along with non-TDP-43 dementia cases and age-matched controls. Astrocyte-derived extracellular vesicles showed significantly elevated TDP-43 in LATE-NC cases compared to TDP-43-negative cases.

To advance biomarker discovery for ADRDs, Dr. Wilcock suggested autopsy studies with matched antemortem biofluids, mouse models, and iPSC studies to identify fluid biomarkers that match specific subtypes of inflammation and cerebrovascular pathologies, PET ligands for TDP-43 aggregation and alpha synuclein pathology, and improved technologies to optimize brain-derived exosome approaches that will broaden the potential biomarkers that can be assessed.

Validation of Blood-Based Biomarkers for Alzheimer's Disease

Suzanne Schindler, Washington University in St. Louis

Key metrics of analytical validation include precision, accuracy, sensitivity, linearity, and interferences. Pre-analytical factors, such as blood collection protocol, blood processing protocol, and storage of sample, can affect measurements. After you have an analytically

validated assay and a standard protocol for processing samples, you have to validate it clinically.

Amyloid status as determined by amyloid PET is often used as the reference or gold standard for evaluating the performance of CSF or blood tests. The ability of a CSF or blood test to classify individuals as amyloid PET-positive or negative is often described with the ROC AUC. A cutoff is typically applied to categorize individuals as positive or negative, which allows calculation of the sensitivity and specificity. In clinical practice, the interpretation of the test also depends on the pretest probability or prevalence of amyloid in the population. The use of two cutoffs can improve accuracy.

Traditionally, cutoffs have been applied to dichotomized individuals as biomarker-positive or negative. Biomarker levels associated with brain amyloidosis and/or symptomatic AD may vary by individual level factors. Biomarker ratios may perform more consistently across different racial and ethnic groups and in individuals with medical comorbidities. Plasma p-tau217 and amyloid beta 42/40 perform consistently in classifying amyloid status.

Given the major capacity constraints and drawbacks of PET and CSF testing, the use of high performance BBM tests in clinical care may enable more patients to access an accurate diagnosis and appropriate treatments. Many BBM tests are being developed, but most have inaccuracies that would misclassify approximately 25 percent of patients in a dementia clinic. Some tests may perform more consistently across racial groups and medical conditions. High standards of BBM test performance are needed because of the potential major implications of biomarker testing for patients. Head-to-head comparisons between FDA-approved CSF tests and BBM tests may be especially helpful for determining whether a BBM test has acceptable performance for clinical use.

Q&A

Moderators: Henrik Zetterberg, University of Gothenburg; Yuan Luo, Division of Neuroscience, National Institute on Aging

Dr. Luo asked how the DIAN studies aimed at early onset of AD, representing less than five percent of the AD population, translate to late onset AD. Dr. Bateman replied that the DIAN studies provide incredible accuracy in predicting who gets the disease and when they get it. People with early-onset AD tend not to have as many comorbidities as those with late-onset AD, allowing scientists to study the disease in its most pure form. The DIAN studies have predicted the outcomes in all sporadic AD trials that have been completed to date.

A virtual participant asked about the status of biomarkers measuring oligomers of tau and beta amyloid. Dr. Karikari answered that those biomarkers are not available at present, but several are in the works. The challenge is determining the standard of truth.

Another virtual participant asked if the aim is for a complex, dynamic signature in biomarkers. Dr. Wilcock said she feels like biomarkers, therapies, and therapeutic development run in parallel with each other, and that as therapies become more precision-targeted, more complex biomarker profiles that will be needed to identify who should receive the therapies.

Another virtual participant observed that some data indicate there might be diurnal variation in the blood biomarkers and that food intake might have an effect. Dr. Schindler responded that it is useful to collect both fasted and nonfasted samples, and that only collecting fasted samples reduces their clinical relevance.

Dr. Robert Rissman commented that it would be great to have five percent test-retest but questioned whether that is realistic. Dr. Schindler said that a lot depends on the specific test, but she agreed that five percent is largely aspirational, and noted that there is not much data on how achievable the five percent threshold is. It helps to identify individuals with an intermediate level of pathology. Dr. Bateman pointed out that these tests are being compared to other tests, which have their own error rate, so there will never be 100 percent accuracy. A better question might be: can we identify tests which tell us something important or relevant beyond what we already have?

Dr. Nilufer Ertekin-Taner said she likes the concept of ground truth, but argued that there needs to be a clear definition of what that is. Dr. Wilcock agreed, noting that a key consideration is determining which pathology is driving the clinical syndrome.

Dr. Sudhir Sivakumaran opined that the biggest variable in Dr. Karikari's research is tau. He asked how tau could be a biomarker for ARIA if anti-amyloid therapies drive it down. Dr. Karikari replied that it is not clear that anti-amyloid therapies have that effect on tau.

A participant asked the panelists how they reconcile transient changes with finding predictable biomarkers for disease stages. Dr. Schindler responded that a lot depends on what you are looking for in terms of biomarkers, but for predictions of amyloid PET, it is possible to get to almost perfect AUCs despite differences in age, sex, and medical comorbidities, which will help in the development of biomarkers for other pathologies. Dr. Zetterberg added that the struggle is between confounding factors and disease-relevant effects on the biomarkers. Dr. Karikari noted that there are a lot of factors that potentially affect the biomarkers.

Session 2: Use of Blood-Based Biomarkers in AD/ADRD Clinical Research

Chair: Robert Rissman, University of California, San Diego

Blood Biomarkers and Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup

Clifford Jack, Mayo Clinic

The core principles from previous workgroups on Alzheimer's disease are that the syndrome is separate from biology, and that AD is defined by its biology, with a series of implications. Several developments since 2018 prompted revised criteria, including approved treatments that target core disease pathology; the development of plasma biomarkers, some with excellent diagnostic performance; and the recognition that imaging and fluid biomarkers within a category are not interchangeable for some intended uses. The current workgroup's objectives are to develop criteria to inform the diagnosis and staging of AD that reflect current science and bridge research and clinical practice, but the goal is not to produce clinical practice guidelines themselves.

The workgroup has divided biomarkers into Core 1 and Core 2. The diagnosis of Alzheimer's disease can be established by abnormality on specific Core 1 biomarkers. Core 1 biomarkers are useful for the early detection of AD in people without symptoms and the confirmation that AD is an underlying pathology in someone with symptoms. Core 2 biomarkers are not typically standalone tests for the diagnosis of AD but can be combined with Core 1 to stage biological disease severity, provide information on the likelihood that symptoms are associated with AD, inform on risk of progression in people without symptoms, and inform on the likely rate of progression in people without symptoms.

Only biomarkers that have been proven to be accurate with respect to an accepted reference standard should be used for clinical diagnostic purposes, and the same criteria apply for PET, CSF, or BB biomarkers. The minimum benchmark the workgroup recommends is an accuracy of 90 percent for the identification of moderate to frequent neuritic plaques or an approved surrogate in the intended use population. For BB biomarker assays, this translates to an accuracy equivalent to that of approved CSF assays. The specification of accurate "in the intended use population" addresses positive and negative predictive value, which depends on the prior probability of AD in the population of interest. Clinical judgment is paramount in the clinical application of biomarkers. Staging of AD applies only to individuals in whom the disease has been diagnosed by an abnormal core biomarker.

Evolution towards Practical Biomarkers for Research and Diagnosis in Alzheimer's Disease

Adam Fleisher, Eli Lilly

The key value for biomarkers in clinical trials is in population screening, as a pharmacodynamic marker of drug effects, as surrogates for a clinical endpoint, and for faster and more efficient drug development. In clinical practice, they foster earlier disease detection and screening, improved diagnostic accuracy, prognosis and disease monitoring, and treatment management.

Additional data are needed to determine whether the BBMs have high enough positive predictive values to serve as standalone biomarkers for trial inclusion. Their use as longitudinal markers of change and drug effects is encouraged, but further validation is needed before they can be used as primary endpoints. The ideal diagnostic for a positive plasma biomarker is one that maximizes overall cut point accuracy for identifying the gold standard. Biomarker selection for clinical trial designs depends on intended use and need, design value, type of therapeutic being developed, the stage and size of trial, and the stage of disease.

Plasma biomarkers are becoming available to assess the full ATN paradigm in AD. Blood-based biomarkers show promise to transform the way we enroll, design, and interpret clinical trials, improving trial efficiency and specificity, and become an important part of clinical patient management. The use of surrogate biomarkers for short efficient treatment approval pathways is within reach with the standardization of positivity cut points within and across assay platforms. As more data become available on plasma biomarkers, and biomarkers become more widely used in clinical trials and clinical practice, appropriate use guidelines will be important for real world implementation.

Use of Blood-Based Biomarkers in Participant Screening in AD Clinical Trials

Rema Raman, University of Southern California

Three types of trial designs use biomarkers: stratification, which collects biomarkers on all participants and uses stratified randomization; enrichment, which uses defined biomarker assessment for trial inclusion; and strategy, which applies randomization to biomarker-based treatment strategies instead of treatments. The use of the enrichment design through identifying amyloid burden is a common study design used in AD clinical trials.

The addition of amyloid beta 42/40 plasma tests using blood plasma algorithms was shown to reduce participant and site burden, as well as study costs, through the reduction in the number of negative PET scans in a preclinical AD trial. Adding the p-tau 217 ratio to the screening algorithm further reduces PET failure rates. These algorithms are influenced by the prevalence

rates since positive predictive value (PPV) rates decrease with prevalence. As a result, it is not possible to estimate true prevalence since people are screened out based on plasma screening eligibility. The heterogeneity in prevalence rates observed across sites in this trial may be a function of participant characteristics.

Among plasma-eligible participants in this trial, similar amyloid PET eligibility rates were observed across race and ethnicity, suggesting that a single cut point across groups may be appropriate. Data from the recently completed A4 and LEARN studies show a strong association between baseline p-tau 217 levels and cognitive decline and that baseline p-tau 217 is a better predictor of PACC decline than any other predictor.

Ongoing work includes evaluating test-retest variability and accuracy across different p-tau 217 assays and assessing performance in study screening, evaluating the performance and impact of prevalence while continuing to reach and screen a demographically diverse sample, and establishing the criteria required to use p-tau 217 as the sole selection criteria for preclinical trials.

FDA Perspective on the Use of Biomarkers in Drug Development Programs

Jeff Siegel, Center for Drug Evaluation and Research, Food and Drug Administration

FDA defines biomarker as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. The BEST Resource is a glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care created by the NIH-FDA Biomarker Working Group. Susceptibility/risk, diagnostic, prognostic, and monitoring biomarkers measure disease presence and status. Predictive, pharmacodynamic/response, safety, and monitoring biomarkers measure aspects of response to treatment.

In considering a biomarker's utility, FDA looks at context of use (COU): its BEST category and how it impacts the clinical trial or drug development program. The specific COU for a biomarker drives the extent of evidence needed for qualification. Analytical validation establishes performance and acceptance characteristics of the biomarker assay. Clinical validation establishes that the biomarker acceptably identifies, measures, or predicts the concept of interest. There are three pathways for biomarker integration into drug development: the drug approval process, scientific community consensus, and the biomarker qualification program. These paths can and do interconnect.

Per the 21st Century Cures Act, a letter of intent requests the qualification of a specific biomarker for a proposed COU in drug development. A qualification plan describes biomarker

development plans for the COU and provides data on analytical validation of the biomarker measurement. The full qualification package contains all accumulated data to support the qualification of the biomarker for the proposed COU. FDA determines qualification based on a full review of the full qualification package.

A validated surrogate endpoint is where the FDA accepts that the biomarker predicts a specific clinical outcome and is used to support traditional approval. A reasonably likely surrogate endpoint is one supported by strong mechanistic and/or epidemiologic rationale such that an effect on it is expected to be correlated with a clinical benefit, but not yet reaching the standard for validation. It is used for accelerated approval intended to treat a serious or life-threatening disease or condition. Surrogate endpoints do not directly measure how a patient feels, functions, or survives, so the benefit-risk assessment must be based upon assumptions and predictions of benefit.

Encouraging the identification and use of reliable biomarkers can facilitate the development of new, safe, and effective drugs. Consortia can contribute to successful development of biomarkers by engaging diverse stakeholders. Validations of biomarkers as surrogate endpoints (SEs) require data from multiple sources. A sequential approach may validate the facilitation of novel candidate SE.

Q&A

Moderators: Robert Rissman, University of California, San Diego; Nada Radoja, Division of Neuroscience, National Institute of Aging

Dr. Radoja noted that Dr. Fleisher said different biomarkers tell different stories for different stages of the disease, and asked if this suggests the disease changes its signature over time. Dr. Fleisher allowed that a lot depended on timing, adding that the question is a broad one that Dr. Zetterberg or Dr. Bateman might be better able to answer.

Dr. Ozioma Okonkwo pointed to one of Dr. Raman's slides, which appears to show plasma- and PET-eligible data, and asked if the PET-eligible data is a subsequent analysis to the plasma-eligible. Dr. Raman explained that the plasma-eligible data looks at those who moved on to PET and what the eligibility rate for PET is.

A virtual participant asked Dr. Raman about the mixing of risk factors like age and APOE with objective disease measures like p-tau 217 and amyloid beta 42/40. Dr. Raman replied that she accounted for factors that she knew were risk factors as she looked at the impact of biomarkers on positive rates. Dr. Rissman added that the different factors have different weights depending on the algorithm being used.

Dr. Bateman asked if the use of biomarkers would be restricted to the methods for enrolling people in clinical trials, or if generalization would be possible, and if so, what it would look like. Dr. Siegel said the most extreme example would be if it is not possible to safely and effectively prescribe the medication unless the patient has the biomarker that was used to select patients for the trial. In many other situations, the biomarkers used to enroll patients in clinical trials do not really restrict prescribing to just that group. Much depends on what the evidence indicates in terms of benefit and risk.

A virtual participant posited that it might be useful to combine new biomarkers with amyloid and tau and use them to have better predictions of outcomes. Dr. Fleisher agreed that there are other exciting biomarkers to be discovered within the amyloid and tau categories as well as beyond. Dr. Jack noted that there is a difference between biomarker combinations that predict cognitive outcome and those useful for diagnosis and staging of one disease.

Dr. Sivakumaran commented on Dr. Siegel's use of the total kidney volume example and pointed out that there was also an iBox scoring system for transplant therapeutics. Ultimately, sponsors are encouraged to use as many biomarkers as possible in an effort to generate more data. Dr. Siegel agreed that there are parallel pathways to acceptance of biomarkers, adding that EMA and FDA have mechanisms for interagency communication.

Dr. Chi Udeh-Momoh noted that recent evidence shows a lower incidence of neuritic plaques and a lower amyloid burden in people of African descent. She asked Dr. Raman to explain her results in that context. She also asked Dr. Jack to what extent social constructs are being considered with the development of diagnostic guidelines for Alzheimer's. Dr. Raman responded that there has been a lot of talk in the field about the need for cut points based on groups, but the PET eligibility rates seem to be similar across all racial and ethnic groups. The use of blood plasma at the first stage of screening seems to be addressing the issue. Dr. Jack said the position of his committee is that AD is not a different disease on the basis of race or socioeconomic status, but the likelihood of cognitive decline may indeed vary as a function of race or other social determinants of health. Poverty needs to be considered as well as race and ethnicity. Dr. Fleisher added that risk factors for adverse effects of some of the drugs may differ by race and ethnicity. Dr. Ertekin-Taner observed that AD may be one disease from the standpoint of plaques and tangles, but how we get there may be very different based on race, ethnicity, and other factors. Dr. Raman pointed out that the model she used does account for APOE and age.

Session 3: Use of AD/ADRD Blood-Based Biomarkers in Population Studies and towards Personalized Medicine

Chair: Ozioma Okonkwo, University of Wisconsin

Implementing Blood-Based Alzheimer's Disease Biomarkers at the Population Level

Michelle Mielke, Wake Forest University

Blood-based biomarkers have many benefits for population diagnosis. They are less invasive, less costly, and more accessible than CSF or PET, and they have the potential to lessen health disparities. However, most studies to date have focused on clinical, white, and higher SES populations. There is an urgent need to understand how the blood markers perform in heterogeneous, diverse populations and what factors might affect their interpretation at the population level. There is also the need to consider diagnosis on an individual and prognostic basis.

Some studies suggest that AD fluid and imaging biomarker levels differ by race and ethnicity, but others do not. Comorbidities affecting blood markers are often more prevalent in underrepresented groups, which should be considered when examining race and ethnic differences in blood markers, as well as sex and gender differences. Many studies including racial and ethnic groups are not representative due to higher education or eligibility exclusion criteria.

The accuracy of tests in real world settings is not clear. Most of the work is done in specialized memory clinics and/or with younger populations. Older adults with cognitive impairment tend to have multiple comorbidities. Collection conditions are not as ideal for primary care. Assay platforms differ in accuracy, but health care systems often have contracts with a certain lab, and no information is given to providers as to what assays are better or if they can send the blood to certain labs. Blood biomarker assays will likely differ across care settings.

AD pathologies begin decades prior to symptoms and increase with age. It is possible that a positive test could be incidental. At present, a blood test in isolation of a clinical assessment for cognitive changes should not be done. Multiple brain pathologies increase with age, so pure AD is rare in older adults. There is the potential for suboptimal treatment due to disregard for other pathologies. It is important to determine the cost-benefit ratio of assessing AD pathology among individuals with multiple chronic conditions and limited life expectancy. Guidelines need to be developed in line with patient input. The impact of including the biomarker result in the patient record also needs to be considered. There is a critical need for qualitative studies to

understand what patients, families, and caregivers across diverse settings understand about biomarkers, and what they want to know and when.

Towards Personalized Medicine Biomarkers in ADRD: From Brain to Blood and Back

Nilüfer Ertekin-Taner, Mayo Clinic

Dr. Ertekin-Taner proposed it is possible to use molecular signatures as potential future precision medicine biomarkers in AD. She started by citing a study Mayo Clinic conducted in blood biomarkers for AD in African Americans. The study asked the question, can we exploit cell-free RNA (cfRNA) to discover novel and mechanistically informative biomarkers of AD? It then measured cfRNA levels of 50 target molecules in plasma of an AD case control series. Plasma cfRNA levels were found to have predictive value in AD and hold promise as novel biomarkers, increasing diagnostic accuracy of AD by seven to eight percent.

Another study looked at gliovascular molecular alterations in Alzheimer's disease as precision medicine therapeutic targets and biomarkers. Its aim was to bridge the knowledge gap about coordinated molecular changes within gliovascular unit cells in AD and their implications in BBB dysfunction. Pericytes were found to be the most affected vascular cell type in AD brains using single nucleus gene expression measurements. SMAD3 is a pericytic molecule perturbed in AD and highly connected with other gliovascular molecules. Its genetic variants associate with fewer infarcts of neuroimaging. Higher blood levels of SMAD3 also associate with less brain amyloid and cortical atrophy antemortem, suggesting its potential to serve as a biomarker of BBB function.

A third study looked at precision medicine biomarkers of cognitive resilience. It asked the question: are there blood transcriptomic changes associated with cognitive resilience in those at risk for AD? The top gene co-expression network module that is conserved between blood and brain and that is associated with cognitive resilience is enriched for mitochondrial biological processes. This module is enriched in mitochondrial NDUF genes, and higher blood NDUF levels are associated with better memory. Brain NDUF levels are also down in amyloid and tau mouse models. Furthermore, blood NDUF levels increase diagnostic accuracy of AD and mild cognitive impairment, suggesting their potential utility as precision medicine biomarkers of cognitive resilience.

To establish precision medicine biomarkers in AD, we need molecular profiling in matched brain-blood samples from the same individuals of deeply phenotyped cohorts and studies in multiethnic cohorts. The CLEAR-AD U19 program will conduct such studies to dissect the multilayered complexity of AD and is expected to identify precision medicine biomarkers of AD.

ADRD Blood-Based Biomarkers in Diverse Populations: Avenues for Early Detection and Prevention

Chi Udeh-Momoh, Imperial College of London

Dr. Udeh-Momoh referred to a study that aims to determine if abnormal BBMs can result in valid predictions of the presence of AD pathological changes, reducing the need for PET and CSF in AD trials. Plasma p-tau 217 is able to distinguish participants with neuropathologically defined AD from participants without diagnostic levels of AD histopathology, and its performance is not significantly different from key CSF- or PET-based measures. The use of blood-based amyloid assays as a prescreening tool prior to amyloid beta PET scans for clinical trial recruitment significantly reduced the total screening cost expected in an AD prevention trial.

The prevalence of dementia in low- and middle-income countries is expected to rise significantly, but to date the amount of data or research in these settings is less than 0.1 percent, and the number of AD biomarker studies in Africa remains at zero percent. Several efforts are now underway to address this discrepancy.

A clinical trial in cognitively normal subjects enrolled in an AD prevention study found lower levels of amyloid pathology in NHBs than NHWs. This finding was corroborated in the IDEAS Cohort Study. People of African ancestry report higher inflammation linked to age-related chronic illnesses. The postmortem IHC revealed upregulation of IL-9-related mechanistic factors only in AAs. Distinct mechanisms may contribute to AD etiology in Africans, possibly the influence of sociocultural factors and/or coexisting pathologies. Blood-based biomarkers hold promise for LMICs.

About seven percent of the Ibadan Dementia Project cohort developed dementia during a mean follow-up time of about seven years. Significant predictors included being female, smoking, low social engagement, and a history of stroke. The Africa-FINGERS initiative is a multimodal intervention to promote healthy aging in Africans based on the FINGER model. An AD biomarker-enriched study will address biomarker access inequities.

Dr. Udeh-Momoh is leading an effort to identify novel biomarkers of pathologic aging and resilience in Africans. She hopes to extend protocols to large populations in the U.K. and U.S. and surveillance sites in Kenya and Pakistan.

In & For the Community: Advancing Health Equity through AD/ADRD Blood-Based Biomarkers

Monica Rivera-Mindt, Fordham University

Black and Latinx adults are up to twice as likely to develop ADRDs as non-Latinx white adults, with a younger age of onset and a greater severity of initial cognitive symptoms. Older Black and Latinx adults are 30-40 percent less likely to access outpatient neurology care than non-Latinx whites, and are more likely to receive care in the ER, with longer hospital stays and higher inpatient costs, after neurologic diagnosis.

The BEYONDD study seeks to transform EOD research by making it more inclusive, culturally informed, community-engaged, and accessible via plasma biomarker, digital, and at-home methods. Community members will receive education and empowerment, study support and payments, compensation for transportation, and results disclosure. Potential participants can register through the BEYONDD website created by Alaniz Marketing. The BEYONDD study portal was built by BHR and includes an eligibility screener, participant and optional study partner questionnaires and surveys, and facilitation of mobile phlebotomy and accompanying assessments. The study is currently limited to fluent English speakers, but an expansion into other languages is planned.

Participants will be invited to come to a BEYONDD clinical site for an on-site visit. Central staff will reach out to participants to schedule this results disclosure visit. Those who decline will then be asked if they would like to receive their results from the remote phase. Interested participants will be able to access educational materials, a disclosure menu for selection of desired results, and a separate consent form.

Q&A

Moderators: Ozioma Okonkwo, University of Wisconsin; Jonathan King, Division of Behavioral and Social Research, National Institute on Aging

Dr. King asked Dr. Rivera-Mindt to describe the BEYONDD study's culturally informed approach, how it is implemented, and what has and has not worked well. Dr. Rivera-Mindt explained that one way of implementing such an approach is meeting with community science partnership board members quarterly to get their input on all aspects of the study.

A virtual participant asked how AD-specific population study findings are, and to what extent they merely demonstrate AD comorbidities rather than the disease process. Dr. Ertekin-Taner replied that both ADNI and Mayo Clinic Study of Aging participants have defined presence of biomarkers. Initial analyses have been confined simply to the clinical diagnosis of AD and mild cognitive impairment.

Dr. Jack noted that a basic tenet of epidemiologic research is the notion of a random sample of a geographically defined population, and the notion of active recruitment violates that assumption. He asked about the possibility of a solution to this problem. Dr. Rivera-Mindt

pointed out that her studies are community-based studies, not epidemiologic or classic prevalence studies. For many years, studies have oversampled non-Latinx whites, the highly educated, and affluent, and it is necessary to conduct community-based studies among underrepresented populations. Dr. Jack asked if there are established methods to do something like propensity weight from a convenient sample back to the population to get real estimates of prevalence. Dr. Mielke explained that in general, it is really hard in the U.S. Dr. Jack maintained that it was difficult but not impossible. Dr. Rivera-Mindt and Dr. Mielke agreed. Dr. King commented that he was a project scientist on the Health and Retirement Study, and that there are difficulties identifying samples and meeting people where they are, but there are ways of determining where there may be some mismatches.

A virtual participant perceived a tension where blood-based markers will increase the penetrance of AD research to under-included communities, but that these areas tend to be places with increased comorbidities. Furthermore, those additional factors influence the performance of blood-based markers, but the lack of resources might preclude the careful differential of values on these markers. Dr. Mielke responded that if blood-based biomarkers are good enough, they will lessen some of the disparities in terms of diagnosis for etiology, and that one of the goals of the new network is to come up with an algorithm that provides a standard deviation for certain comorbidities. Dr. Ertekin-Taner noted that at the same time we are talking about blood-based biomarkers of AD, another part of the equation is the need to ensure that primary care physicians who can administer these biomarkers are equitably distributed across the globe. Dr. Mielke added biomarkers should not be observed in isolation, but that a cognitive assessment and a general medical history are also necessary, and as these things are reimbursed, they will become more equitable.

Welcome: Day 2

Alessandra Rovescalli, Division of Neuroscience, National Institute of Aging

Dr. Rovescalli welcomed attendees to the second day of the workshop. The first day was a journey from the lab to the clinics, trials, populations, and communities. The second day would focus more on sharing resources and data. Two roundtables were scheduled.

Roundtable 1: Infrastructure for Enabling Research and Resource Sharing, Standard Operating Procedures, and Data Harmonization

Moderator: Cerise Elliott, Division of Neuroscience, National Institute on Aging

Remote Blood Collection for Plasma AD Biomarkers in ADNI and the Brain Health Registry

Rachel Nosheny, University of California, San Francisco

The UCSF Brain Health Registry (BHR) is an internet-based registry with over 100,000 participants. It includes digital, unsupervised cognitive tests; longitudinal cognitive and health data collected using self-report questionnaires; accumulating evidence for feasibility and validity; and the infrastructure for including biomarker and genetic data. The BHR Pilot study sought to evaluate the feasibility, usability, and validity of remote blood collection for AD biomarkers in older adults. Additional studies using the BHR remote blood collection infrastructure include the California Latino Brain Health Registry (CAL-BHR) Blood Biomarker Study, BEYONDD, and Bank CTE.

Key features of remote plasma biomarker infrastructure include automated, two-way communication between the BHR study management system and various vendors; automated communications and events, triggered by study status; an identification code generator; and integration of biomarker data with other BHR data questionnaires.

ADNI is a longitudinal, multicenter study to develop biomarkers for early detection and tracking of AD. In ADNI4, over 20,000 individuals will complete online questions and digital cognitive assessment remotely within an ADNI-specific web portal. It provides a unique opportunity to validate novel digital assessments; evaluate feasibility of a national, remote blood collection at a larger scale; and validate novel, multitier recruitment, screening, and prioritization.

Taken together, the results support the feasibility and usability of remote, unsupervised blood collection in older adults. Increasing diversity and accessibility is a major challenge. Results demonstrate selection biases at each step, even with a diverse pool of potential participants. Many participants need one-on-one help with scheduling and other things. To scale up efficiently, strategies are needed to further automate and streamline infrastructure.

AD Knowledge Portal: Enabling Infrastructure for Research on AD/ADRD

Laura Heath, Sage Bionetworks

The AD Knowledge Portal feeds on data from ADRD systems biology consortia and translational centers. It disseminates resources to the broader AD research community and supports consortium-wide efforts. Its resources encompass more than 180,000 data files. The submission process ensures that the data are curated, contextualized, and FAIR (findable, accessible, interoperable, and reusable). It includes 13 programs, 105 projects, 124 studies, 165,000 data files, 1,756 publications, 455 contributing researchers, 65 experimental models, 24 computational tools, and 84 target-enabling resources. For any given data file, there are three levels of metadata files: individual, biospecimen, and assay(s). One can navigate the portal to find data and resources either by using the explore menu to select studies, data, or experimental models, or browsing and filtering to identify resources of interest.

Data harmonization for cross-study comparisons is challenging. Each data contributor uploads what they collected for their study. Units, terms, diagnosis criteria, and data codings can all be different from study to study. Data templates, models, and dictionaries can help allow for more apples-to-apples comparisons. True harmonization often requires domain expertise. Governance is an integral part of data curation and release, with contract, regulatory, and participant protections review; account verification and qualification requirements; and data use agreements and conditions.

The AD Knowledge Portal is more than a data repository. It is a documentation and help site, a monthly newsletter, a discussion forum, and a center for hands-on workshops. Data coordination is an interdisciplinary endeavor, involving scientists, data engineers, governance analysts, software developers, and UX designers.

Expanded Blood Biomarker Data Integration and Sharing via the New National Alzheimer's Coordinating Center's Data Platform

Sarah Biber, University of Washington

NACC serves as the data coordination hub and centralized data repository for NIA's ADRC Program. Independent ADRCs collect standardized longitudinal data. NACC collects,

harmonizes, integrates, and shares that data. It recently moved its existing data onto a modern, cloud-based multimodal data integration and harmonization platform. The new platform is scalable to new data streams; allows for real-time data search, visualization, and access; and is ready for AI-driven discovery. The NACC Data Front Door is a one-stop shop for all ADRC data.

NACC provides an opportunity to validate blood-based biomarkers, disentangle heterogeneity, and facilitate the early detection and prediction of disease progression. Gaps that need to be addressed include expanding data to all ADRC participants, standardization, participation diversity, and better blood biomarker access prioritization.

The ADRC Biomarker Steering Committee was established in 2017 and serves as a collaboration between NACC and the ADRC Program. It recently launched two workgroups, one for best practices and one for data variables and data quality. There is also the ADRC Consortium for Clarity in ADRC Research through Imaging (CLARITI), which maintains a strong focus on inclusion and equity.

Experiences and Perspectives from the National Centralized Repository for AD and Related Dementia

Jeff Dage, Indiana University

NCRAD supports AD/ADRC research through providing a standardized, efficient, and quality focused resource with extensive capacity to enable sample procurement and banking from many global studies. In addition, they have a distribution infrastructure to make stored samples globally available while ensuring result return and tracking. It has established a quality system, and hopes to be CAP-accredited by the end of 2024. All data that NCRAD handles are standardized. Samples NCRAD banks include blood fractions, nucleic acids, human tissue (brain and skin), derived cells, and many other biofluids or sample types (CSF, saliva, urine, stool).

The Biomarker Assay Laboratory (BAL) offers robust and reliable longitudinal data acquisition and boasts a projected annual capacity of 15,000 assays going forward. Dr. Dage cited p-tau 181 as an example of a cut point to determine the presence of Alzheimer's pathology but also has qualified assays for p-tau217, NfL, GFAP, and A β 42/40.

The NCRAD infrastructure and quality system provide an excellent environment for a biomarker laboratory. Robust and reliable biomarker results are achievable with the appropriate focus on quality. Harmonization is possible and critically important but has become more challenging with the widespread deployment of the new assays across many research biomarker laboratories. Standardization is possible by following on from the work of the Global Biomarker Standardization Consortium efforts on CSF but will require significant investment and time.

Data Lakes, LIMS, and -80 Freezers: Strategies for Efficient Sharing of NIA Data and Biospecimens

Robert Rissman, University of California, San Diego

ATRI aims to share data, software, instruments, biospecimens, and expertise on trial design to accelerate the pace of AD clinical research. Through its DataShare program, it develops infrastructure to support open science and data sharing. Biospecimen and biomarker data sharing requirements include protecting participant privacy, protecting the scientific integrity of trials, timeliness, sustainability, data and biosample request management, data standards, and measure impact. Its informatics platform for sharing centers around a semi-structured repository called a data lake, which stores, catalogues, and secures structured and unstructured data and can be combined with a structured data warehouse to support a full range of data use cases.

A4 data and biospecimen sharing has been successful, but there are challenges with data preparation, measuring impact and assessing needs, user support, sample sharing, and biomarker data sharing. ATRI plans to share all A4 and LEARN data by the second quarter of 2024. Preparing biospecimens and biomarker data for sharing requires relabeling participant IDs with random ones, removing association with a study site, transforming and/or shifting dates, removing any remaining PII or PHI fields, and removing or hashing long text and comment fields.

LIMS is a sample management system. It is part of a lab automation initiative, integrating with clinical trials IT systems. Next steps include integrating with logistics IT systems and predictive analytics. ATRI continues to add more information to the LIMS. Its goal is to track all infrastructure, equipment, biospecimens, workflows, and analysis results in the system.

Panel Discussion

Dr. Elliott asked the panelists what metrics they use to evaluate efficient usage of the data. Dr. Dage acknowledged that NCRAD tracks literature citations, signed agreements and data sharing requests. Dr. Rissman noted that we need to find some way to more efficiently track requests and how we are impacted. Dr. Biber said NACC has deployed a new data request system that allows for automatic tracking.

For her next question, Dr. Elliott asked Dr. Nosheny how she is measuring the outcome of various studies adopting her methods. Dr. Nosheny replied that it is still early and she hopes many more studies will use the infrastructure she built for the remote blood collection, and as it grows, she will need more robust and standardized ways of measuring the number, type, and

outcome of studies. Dr. Heath said she does track downloads, but it is tricky determining who they are from. Dr. Dage commented that it is useful to track requests from investigators.

A virtual participant asked if users can query clinical information for ADRC biospecimen requests at NCRAD. Dr. Dage said there is some data available to search and query on the NCRAD website, but the best route is probably to conduct a search through NACC. Dr. Biber added that NACC recently received funding to collaborate further with NCRAD to incorporate the top five biomarkers into the NACC data platform. Dr. Rissman mentioned that some of the ADRC participants are also participating in clinical trials but have been effectively de-identified. Dr. Biber said she believes a lot of ADRCs do track which of their participants are involved in clinical trials.

Dr. Ertekin-Taner pointed out that if a clinical trial is driven by industry, it is extremely difficult or impossible to get access to biospecimens. Dr. Rissman responded that ACTC does a lot of public-private partnerships, which require that vendors share biospecimens and data from the trial. Dr. Ertekin-Taner asked if there are similar requirements for trials outside ACTC. Dr. Rissman asserted that ATRI as an institute and the University of Southern California as a university both have a duty to share everything that they do.

Dr. Zetterberg asked Dr. Nosheny about the attrition rate for people giving blood samples. Dr. Nosheny replied that this is due to a number of factors: some people have scheduling issues; some have trouble finding the right center; some find it too time-consuming; and some just leave without citing a reason. Barriers to completion tend to be amplified in minoritized groups. Dr. King lauded the rise in remote blood collection and agreed that scheduling can be a hurdle.

Dr. Elliott asked the panel how we determine the data and samples we are stewarding address or advance biomarker discovery. Dr. Biber said all the metrics the panel discussed need to be measured. Dr. Rissman expressed concern about doing different things in silos and advocated a uniform approach. Dr. Dage commented that access to samples is necessary, but so is access to multiomics data to allow for novel analysis techniques. Dr. Heath pointed out that AD Knowledge Portal is not directly involved with blood-based biomarker development but agreed that access to samples is important. Dr. Rissman pointed out that some of the samples are overlapping, and we need to find a way to link all the data. Dr. Nosheny perceived a need to think broadly about what advancing biomarkers means.

Dr. Karikari proposed the development of cut points and reference standards as a way to take advantage of the opportunity presented by the explosion of data. Dr. Dage responded that NCRAD has already begun some harmonization efforts and pointed out that the quality system at each lab needs to have some basic minimum criteria for this to be achieved. Dr. Rissman argued that the assays need to fit the samples, not the other way around. He suggested

working on defining what we need in terms of practicality and collecting samples and where the assays need to go.

Roundtable 2: Dissemination and Implementation Networks and Pipelines

Moderator: Jennie Larkin, Division of Neuroscience, National Institute on Aging; Guest Panelist: Teresa Buracchio, Center for Drug Evaluation and Research, Food and Drug Administration

Learning from the Alzheimer's Association: Global Standardization, Biorepositories, Data Sharing, Guidance, and Implementation Research for Blood-Based Biomarkers

Rebecca Edelmayer, Alzheimer's Association

Launched in 2009, the Association's Global Biomarker Standardization Consortium (GBSC) is a forum for key leaders in the field to achieve consensus standardization and validation of biomarker tests for global clinical use. Through the GBSC, the Association has developed international guidelines for handling of CSF for routine clinical measurements of amyloid beta and tau and are now working on similar guidance for blood. The Association recommends creating inclusive cohort biorepositories of well characterized samples from clinical studies and treatment trials for future research. Working with ATRI and many others, the Association funds national clinical biorepositories (e.g., U.S. POINTER, New IDEAS, ALZ-NET, AHEAD 3-45), which house blood samples for current and future analysis and make them available to the research community. The Association also promotes data sharing through resources like the Global Alzheimer's Association Interactive Network (GAAIN), which provides a global federated approach to data sharing of clinical data with an easy-to-use interface.

The Association recognizes the importance and need for translating biomarker results for the patient, recognizing that quantification informs treatment and care. It is critical to support guidance development and research that supports clinical implementation of new plasma and blood biomarker technologies. In 2022, the Association published the first appropriate use recommendations for blood biomarkers in AD. The Association convened the 'Revised Criteria For Diagnosis and Staging of Alzheimer's Disease' workgroup. This workgroup's charge is to examine the 2011 NIA-AA clinical guidelines and 2018 NIA-AA research framework in the context of the current scientific knowledge, and, if appropriate, revise the criteria for diagnosis and staging of Alzheimer's disease which includes guidance on the use of blood biomarkers. In addition, the Association is funding research to support the prospective validation of high-performing blood biomarkers and digital cognitive tests in specialist memory clinic and general

primary care settings, as well as a primary care-based screening pathway and care bundle for persons with early cognitive impairment using an algorithm, remote clinical assessment, and blood biomarkers.

Developing Robust Datasets to Drive Drug Development and Regulatory Decision-Making

Erin Rosenbaugh, Foundation for the National Institutes of Health

FNIH, a not-for-profit organization, partners with public and private sector leaders to accelerate medical breakthroughs. Its Biomarkers Consortium seeks to improve health through meaningful measurements. An approved project, which includes three or more private funding partners, must address significant unmet scientific and medical needs, have achievable goals, and involve a precompetitive team science approach building technical and lived experience expertise. Biomarkers Consortium projects advancing AD blood biomarkers include the Plasma Amyloid Beta Project and the AD Biosignature Project Concept.

Establishing the performance characteristics of the biomarker assay are acceptable for context of use (COU) is important. As certified reference materials are often not available, endogenous quality control samples enable evaluation of variability among batches or lots. It helps to actively engage in cross-stakeholder consortia and discussions for optimized resource allocation.

Dr. Rosenbaugh left attendees with two questions: how do we define acceptable performance of blood-based biomarker assays? How do we ensure that analytical performance data are available to investigators?

Creating an Enabling Environment for the Research Community: Progress and Challenges

Matt Clement, Alzheimer's Disease Data Initiative

The AD Data Initiative is a coalition of leading organizations working in partnership to accelerate progress towards new diagnostics, treatments and cures in ADRD. It was created by a coalition to change the status quo by increasing interoperability, unlocking new datasets, and empowering researchers. To achieve these goals, it launched the AD Workbench and AD Connect platforms.

A workspace is a secure, private cloud-based environment to curate, combine, analyze, and visualize data. A user can invite team members to their workspace to collaborate. AD Connect has a community forum function to allow for interactive discussions, as well as closed groups and private fora that can be created upon request.

The Initiative partnered with Roche Diagnostics and the NeuroToolKit consortium to develop a suite of apps to aid researchers around the globe with the curation, analysis, and comparison of their biomarker data. The William H. Gates, Sr. Fellowship encourages and supports researchers from around the world to be bold, creative, and innovative in their ADRD research. Seven Fellows were selected from the inaugural cohort from over 90 applications submitted by researchers based in 26 different countries.

Dr. Clement left attendees with two questions: what gaps and needs can be considered by this group as actions? What are the mechanisms by which this audience can help galvanize researchers to engage with the resources that have been surfaced today?

CPAD: Transforming Precompetitive Collaboration into Advances in Alzheimer's Disease Drug Development

Sudhir Sivakumaran, Critical Path for Alzheimer's Disease

In response to the FDA Critical Path Initiative, the Critical Path Institute was formed as an independent 501(c)(3) in 2005 to foster development of new evaluation tools to inform medical product development. Patient-level data sharing facilitates innovation. CPAD's mission is to create new tools and methods to increase the efficiency of the medical product development process, leading to treatments for neurodegenerative diseases that progress to dementia with the shared characteristics of AD.

CPAD's regulatory strategy is to integrate knowledge gained into existing clinical trial simulation tools for AD. Its research has shown a direct relationship between a decrease in amyloid plaque and slowing in the rate of disease progression, as well as a relationship between plasma p-tau 217 and the slowing of clinical decline.

CPAD's database boasts over 465,000 neuroimaging scans from over 350 different organizations in 55 countries around the world. Its user-friendly, web-based interface includes an Actionable Data Model tool and dashboard with variable lists, summary statistics, and visualization. It has longitudinal models of cognitive decline in 3,742 amyloid-PET-positive individuals across the AD spectrum. Disease progression models feed into a clinical trial simulation tool and a bidirectional modeling platform. Extensive data sharing and a federated data analysis approach have facilitated the evaluation and validation of a standardized scale for quantification of tau PET across tracers and cohorts.

CPAD leverages other data repositories and sources through partnerships and collaborations. C-Path and CPAD are trusted members of the global drug development community. Dr. Sivakumaran said CPAD owes it to every single individual living with AD and those who participated in clinical trials to maximize the utility of every single data point.

Panel Discussion

Dr. Larkin asked the panelists what they see as the greatest challenge to data discovery, sharing, and reuse. Dr. Buracchio answered that the biggest barrier at a foundational level has to do with informed consent issues. Dr. Sivakumaran added that CPAD gets data from various trials and studies done with various kinds of assays. Dr. Zetterberg interjected that he is impressed by the way bioinformaticists and statisticians can combine data across different platforms. Dr. Sivakumaran agreed. Dr. Rosenbaugh noted that one of the considerations for the AD biosignature is harmonization or standardization across datasets. She cited sample collection as one of the big challenges she faces. Dr. Edelmayer said she is struck by the need to develop biorepositories in a way that would allow for collection of samples that could be used for a variety of purposes. Dr. Clement noted that governance in general can pose a barrier. Dr. Larkin pondered whether NIST should have been included on the panel given the emphasis on standardization.

A virtual participant asked what the Alzheimer's Association is bringing besides CLIA and FDA. Dr. Edelmayer was not sure she understood the question. Dr. Larkin proposed tabling the question and allowing the person who put it in the chat to expand upon it.

Another virtual participant expressed enjoyment of the Biomarker Consortium presentation but asked why plasma and not PBMCs, as well as how to define the gold standard for validating the new blood biomarkers. Dr. Rosenbaugh explained that FNHI wants to make sure whatever matrix it uses is noninvasive and relatively easy to collect, and that validation for plasma is robust. As for defining a gold standard, it is important that analytical and clinical validations show you are measuring changes in fluid biomarkers. Dr. Buracchio noted that the biomarkers for clinical use are overseen by FDA's devices group, so she could not speak too much to validation. Dr. Rosenbaugh said the standard would depend on the context of use.

Dr. Larkin asked the panelists about their greatest hope for the future of the field. Dr. Edelmayer replied that the trajectory of developing plasma-based biomarkers is incredible. Dr. Rosenbaugh added that she has seen considerable progress in the fluid biomarker space. Dr. Sivakumaran remarked that in addition to raising people's hopes, the advances have actually led to the development of new therapies. Dr. Buracchio said that in her time at FDA, she had seen a tremendous increase in the use of biomarkers in drug development.

Dr. Clement pointed out that there is a project called the European Platform for Neurodegenerative Diseases, which is working to create a federated biorepository network.

Wrap-Up and Closing Remarks

Alessandra Rovescalli and Eliezer Masliah, National Institute on Aging

Dr. Rovescalli shared her takeaways from the workshop: that we have robust blood-based biomarkers for amyloidosis, and we are on a good path for biomarkers for tauopathy and neurodegeneration. There is a revised diagnostic framework that can incorporate well-evaluated blood-based biomarkers for amyloid beta, but tauopathy and neurodegeneration still rely on imaging. Amyloid beta blood biomarkers can be successfully used as tools in clinical trials, creating the potential for more successful trials at lower costs.

A lot of work still needs to be done inside and outside the lab. Robust and validated biomarkers are needed to complement the ATN framework for AD to mark and follow processes other than amyloidosis and tauopathy. The revised diagnostic framework acknowledges inflammation and cerebrovascular disease as the two major contributions to neurodegeneration in AD. Genomic, gene expression, and translation studies provide strong evidence for other processes.

Biomarkers are needed for non-AD dementia. There are several pathologies that coexist in a substantial segment of the AD patient population, especially as they age. There are good options for seed amplification assays as biomarkers, but they still require CSF or skin punches. Another challenge is the lack of tracers for imaging specific isoforms of tau, alpha-synuclein, and TDP-43 aggregates.

There is a lot of confidence that the combination of different biomarkers will allow not just the screening and diagnosis of AD, but also getting to the individual level with a precision medicine approach, which would allow precise staging of the disease for each individual patient, and perhaps turn these biomarkers into surrogate endpoints with sufficient evidentiary support for acceptance by regulatory agencies.

We are gaining experience in how to build infrastructures that can help us to leverage registries. Good coordination and direct communications are essential.

A better job of understanding the impact of race, ethnicity, poverty, comorbidities, and social determinants of health and their respective roles as contributors to the pathophysiology or modifiers of the disease, and how they can impact baselines and the performance of biomarkers, is necessary. There needs to be a more thoughtful and compassionate effort of reaching out to underrepresented minorities. Both communication and reciprocity are critical.

Health care providers need to be educated on when and how to use AD biomarkers, as well as have structure and guidance for disclosure. The Alzheimer's Association is already taking steps

toward this objective with their published recommendations for the use of blood-based biomarkers.

Infrastructure exists for the integrating and sharing of multimodal data from animal models and human subjects. These data platforms are critical for longitudinal studies. However, standardization and harmonization are critical for using these platforms. Data must be comparable, but metadata must be collected, harmonized, and delivered in the proper way to give context and meaning to the data. There is some infrastructure for collecting and disseminating samples in place.

Dr. Masliah informed attendees of a NOFO for applications to accelerate the establishment of effective biomarkers of AD and ADRD for use in medical product development, clinical trials, and/or clinical practice. The 2024 NIH Alzheimer's Disease Research Summit is scheduled for September 23-25.

Appendix A: Agenda

All times listed are Eastern Daylight Time.

Day 1: Monday, October 30, 2023

9:30 a.m. Welcome

Alessandra Rovescalli, Division of Neurosciences, National Institute on Aging

9:35 a.m. Opening Remarks

Richard Hodes, National Institute on Aging

9:45 a.m. Plenary Lecture:

The Potential and Promise of Alzheimer's disease blood biomarkers

Randall Bateman, Washington University in St. Louis

Session 1: State of the Art and Validation

Session Chair: Henrik Zetterberg, University of Gothenburg

10:20 a.m. ATN biomarkers: current state and biological underpinnings

Thomas Karikari, University of Pittsburgh

10:40 a.m. Candidate fluid biomarkers for the ADRDs

Donna Wilcock, Indiana University

11:00 a.m. Validation of blood-based biomarkers for Alzheimer disease

Suzanne Schindler, Washington University in St. Louis

11:20 a.m. FDA Regulatory Process for Alzheimer's Disease (AD) Devices

Woosung (David) Cho, Center for Devices and Radiological Health, Food and Drug Administration

11:40 a.m. Q&A

Session 2: Use of Blood-Based Biomarker in Participant Screening in AD Clinical Trials

Session Chair: Rob Rissman, University of California, San Diego

12:40 p.m. Blood biomarkers and Revised NIA-AA Criteria for Diagnosis and Staging of Alzheimer's Disease

Clifford Jack, Mayo Clinic

1:00 p.m. Evolution towards practical biomarkers for research and diagnosis in Alzheimer's disease

Adam Fleisher, Eli Lilly

1:20 p.m. Use of blood-based biomarkers in participant screening in AD clinical trials

Rema Raman, University of Southern California

1:40 p.m. FDA perspective on the use of biomarkers in drug development programs

Jeff Siegel, Center for Drug Evaluation and Research, Food and Drug Administration

2:00 p.m. Q&A

Session 3: Use of AD/ADRD Blood-Based Biomarker in Population Studies and Towards Personalized Medicine

Session Chair: Ozioma Okonkwo, University of Wisconsin

- 2:50 p.m. Implementing blood-based Alzheimer's disease biomarkers at the population level
Michelle Mielke, Wake Forest University
- 3:10 p.m. Towards personalized medicine biomarkers in ADRD: From brain to blood and back
Nilüfer Ertekin-Taner, Mayo Clinic
- 3:30 p.m. ADRD blood-based biomarkers in diverse populations: avenues for early detection and prevention
Chi Udeh-Momoh, Imperial College of London
- 3:50 p.m. In & For the Community: Advancing Health Equity through AD/ADRD Blood-Based Biomarkers
Monica Rivera-Mindt, Fordham University
- 4:10 p.m. Q&A
- 4:50 p.m. Wrap Up and Adjourn for The Day

Day 2: Tuesday, October 31, 2023

10:30 a.m. Welcome

Alessandra Rovescalli, National Institute on Aging

Roundtable 1: Infrastructure For Enabling Research and Resource Sharing, Standard Operation Procedures, Data Harmonization

Moderator: Cerise Elliot, National Institute on Aging

- 10:40 a.m. Remote Blood Collection for Plasma AD biomarkers in ADNI and The Brain Health Registry
Rachel Nosheny, University of California, San Francisco
- 10:50 a.m. AD Knowledge Portal: Enabling Infrastructure for Research on AD/ADRD
Laura Heath, Sage Bionetworks
- 11:00 a.m. Expanded Blood Biomarker Data Integration and Sharing via the New National Alzheimer's Coordinating Center's Data Platform
Sarah Biber, University of Washington
- 11:10 a.m. Experiences and perspectives from The National Centralized Repository for AD and Related Dementia
Jeff Dage, Indiana University
- 11:20 a.m. Data Lakes, LIMS and -80 freezers: Strategies for efficient Sharing of NIA Data and Biospecimens

Robert Rissman, University of California, San Diego

11:30 a.m. Panel Discussion

12:00 p.m. Break

Roundtable 2: Dissemination and Implementation-Networks and Pipelines

Moderator: Jennie Larkin, National Institute on Aging

1:00 p.m. Learnings from the Alzheimer's Association: Global Standardization,
Biorepositories, Data Sharing, Guidance and Implementation Research for Blood
Based Biomarkers

Rebecca Edelmayer, Alzheimer's Association

1:10 p.m. Developing robust datasets to drive drug development and regulatory decision-
making

Erin Rosenbaugh, Foundation for the NIH

1:20 p.m. Creating an Enabling Environment for the Research Community: Progress and
Challenges

Mat Clement, Alzheimer's Disease Data Initiative

1:40 p.m. CPAD: Transforming precompetitive collaboration into advances in Alzheimer's
disease drug development

Sudhir Sivakumaran, Critical Path for Alzheimer's Disease

1:50 p.m. Panel Discussion

Wrap-Up and Closing Remarks

Alessandra Rovescalli and Eliezer Masliah, National Institute on Aging

Appendix B: List of Participants

Nandini Arunkumar
National Institute on Aging

Randall Bateman
Washington University of St. Louis

Sarah Biber
*University of Washington National
Alzheimer's Disease Coordinating Center*

Teresa Buracchio
Food and Drug Administration

Woosung (David) Cho
Food and Drug Administration

Matt Clement
Alzheimer's Disease Data Initiative

Rebecca Edelmayer
Alzheimer Association

Cerise Elliott
National Institute on Aging

Nilüfer Ertekin-Taner
Mayo Clinic, Jacksonville

Adam Fleisher
Ely Lilly & Co

Paul Grothaus
National Institute on Aging

Laura Heath
Sage Bionetworks

Richard Hodes
National Institute on Aging

John Hsiao
National Institute on Aging

Soledad Ivaldi
National Institute on Aging

Clifford Jack
Mayo Clinic, Rochester

Gus Jimenez-Maggiora
University of Southern California

Thomas Karikari
University of Pittsburgh

Jon King
National Institute on Aging

Jennie Larkin
National Institute on Aging

Yuan Luo
National Institute on Aging

Eliezer Masliah
National Institute on Aging

Michelle Mielke
Wake Forest University

Jordan Moore
NIH Center for Scientific Review

Nadira Mussabekova
National Institute on Aging

Ozioma Okonkwo
University of Wisconsin

Suzana Petanceska
National Institute on Aging

Nada Radoja
National Institute on Aging

Rema Raman
University of Southern California

Robert Rissman
University of California, San Diego

Monica Rivera-Mindt
Fordham University

Erin Rosenbaugh
Foundation for the National Institutes of Health

Alessandra Rovescalli
National Institute on Aging

Laurie Ryan
National Institute on Aging

Jeff Siegel
Food and Drug Administration

Sudhir Sivakumaran
Critical Path Institute

Erika Tarver
National Institute on Aging

Chi Udeh-Momoh
*Imperial College, London, UK/Wake Forest
University*

Jaya Viswanathan
National Institute on Aging

Donna Wilcock
Indiana University

Henrik Zetterberg
*University of Gothenburg, University of
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