Curing the Epilepsies 2021: Setting Research Priorities

National Institute of Neurological Disorders and Stroke

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Acronym Definitions

AD	Alzheimer's disease
AED	antiepileptic drug
AES	American Epilepsy Society
AI	artificial intelligence
ASO	antisense oligonucleotide
ATAC-seq	assay for transposase-accessible chromatin with sequencing
BECTS	benign epilepsy with centro-temporal spikes
BRAIN	Brain Research through Innovative Neurotechnologies
CAE	childhood absence epilepsy
CB1	cannabinoid type I receptor
CHIPseq	chromatin immunoprecipitation sequencing
CNV	copy number variant
CWOW	Center Without Walls
DBS	deep brain stimulation
DEE	developmental and epileptic encephalopathy
ECHO	Extension for Community Healthcare Outcomes
EDEN	Epilepsy Digital Management Navigator
EHR	electronic health record
EMR	electronic medical record
ENIGMA	Enhancing Neuro Imaging Genetics through Meta Analysis
EpiMVP	Epilepsy Multiplatform Variant Prediction
ES	epileptic seizures
ETSP	Epilepsy Therapy Screening Program
FDA	Food and Drug Administration
GGE	genetic generalized epilepsy
GPX4	glutathione peroxidase-4
GTCS	generalized tonic clonic seizures
GWAS	genome-wide association study
HFO	high-frequency oscillation
HIPAA	Health Insurance Portability and Accountability Act
HSR	health services research
IC-EEG	intracranial EEG
IND	Investigational New Drug
IOM	Institute of Medicine
iPSC	induced pluripotent stem cell
IRB	Institutional Review Board
NGS	next-generation sequencing
NHP	non-human primate
NLP	natural language processing
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
PCORI	Patient-Centered Outcomes Research Institute

PK/PD	pharmacokinetic/pharmacodynamic
PMS	Phelan-McDermid Syndrome
PNES	psychogenic nonepileptic seizures
PTE	post-traumatic epilepsy
QOL	quality of life
SUDEP	sudden unexpected death in epilepsy
TBI	traumatic brain injury
TSC	tuberous sclerosis complex
WGS	whole genome sequencing

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Executive Summary

The National Institute of Neurological Disorders and Stroke (NINDS) convened the *Curing the Epilepsies: Setting Research Priorities* conference virtually via Zoom on January 4-6, 2021. This conference was the fourth in a series of *Curing the Epilepsies* conferences that has been held approximately every 7 years since 2000; this conference, originally scheduled to convene in person in April 2020, was postponed due to the COVID-19 pandemic. The purpose of the series is to evaluate the current state of epilepsy research and consider priorities for future efforts.

The goal of this conference was to bring together stakeholders—including researchers, clinicians, individuals with epilepsy, families, and advocates—to identify gaps and opportunities in epilepsy research. Although much progress has been made in epilepsy research in recent decades, the personal stories shared by advocates at this conference underscore the need to expedite progress so that research advances reach people with epilepsy faster. As such, participants were asked to focus on transformative research priorities for the field, including (1) accelerating the development of new treatments that can be translated to individuals with epilepsy, (2) increasing data sharing and collaboration, and (3) addressing the challenges faced by the research and advocacy communities.

Over the course of this 3-day conference, researchers, clinicians, and advocates shared their perspectives on the following topics: (1) expediting targeted treatments for the epilepsies, (2) modeling human epilepsies, (3) establishing biomarkers for human epilepsies, (4) harnessing big data to drive epilepsy research and clinical care, (5) emerging research priorities in the epilepsies, and (6) translating research into clinical care. These sessions included panel discussions and breakout groups to allow participants to suggest and refine a set of transformative research priorities that will drive epilepsy research forward.

The transformative research priorities discussed at this conference have the potential to accelerate progress and make a meaningful difference in the lives of individuals with epilepsy and their families. A recurring theme was the need to increase collaboration and break down the silos that separate basic researchers, clinicians, and advocacy groups. Concerted efforts to increase large-scale collaboration in real time, collect large multimodal datasets that can be integrated with extant datasets, build an infrastructure for the sharing of data and resources, and embrace new analytic strategies to mine these data will help to improve research and current care. Specific goals for these collaborations should include an understanding of the mechanisms that underlie the epilepsies, the development of an array of biomarkers for the epilepsies, the improvement of preclinical models of the epilepsies, the expansion of epilepsy research and care to underserved communities, and the creation of innovative tools and measures that will expand the capabilities of basic and clinical research alike.

As with earlier *Curing the Epilepsies* conferences, the Epilepsy Benchmark Stewards Committee, coordinated by the American Epilepsy Society, revised the Epilepsy Research Benchmarks prior to the conference, taking into consideration feedback from all stakeholders. These Benchmarks are intended to anchor research over the next 5-7 years in the issues that are key to

understanding the epilepsies and improving meaningful outcomes for people with epilepsy through research.

NINDS led public crowdsourcing campaigns in September and October 2020 to obtain feedback from the community on transformative research priorities and these priorities shaped the revised agenda for the virtual conference that was held in January 2021.

Meeting Summary

Session I: Setting the Stage for Epilepsy Research Benchmarks and Transformative Research Priorities

Welcome Remarks

Walter Koroshetz, MD, Director, NINDS/NIH

The National Institute of Neurological Disorders and Stroke (NINDS) is the leading funder of epilepsy research in the United States. The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and then use that knowledge to reduce the burden of neurological disease, including the epilepsies. NINDS pursues this mission by investing in basic, translational, and clinical research; training a talented and diverse workforce; identifying gaps in research and public health needs; supporting development of tools and resources to enable discoveries; communicating and collaborating with all stakeholders, including the public; and evaluating and continuously improving all NINDS programs. For the epilepsies, this effort includes sponsoring this conference and other workshops such as the *Metabolism-Based Therapies for Epilepsy* workshop held in November 2020 and the *Post-Traumatic Epilepsy: Models, Common Data Elements, and Optimization* workshop scheduled for March 2021. NINDS supports the Epilepsy Therapy Screening Program (ETSP) at the University of Utah, which provides numerous epilepsy models for testing new pharmacological therapies to treat and prevent the epilepsies. NINDS also supports Epilepsy Centers Without Walls (CWOWs), including EpiBios4Rx focused on post-traumatic epilepsy, the Channelopathy-Associated Epilepsy Research Center, and the Epilepsy Multiplatform Variant Prediction (EpiMVP) Center whish are both focused on identifying the mutations and mechanisms that underlie the epilepsies. In addition, the Brain Research through Innovative Neurotechnologies (BRAIN) Initiative continues to develop powerful tools that allow researchers to monitor, map, and modulate the circuits that generate epileptiform activity.

This *Curing the Epilepsies* conference provided an opportunity for NINDS to collaborate with stakeholders, including the public, to identify gaps and opportunities in epilepsy research. Participants were asked to consider what paradigm-shifting research could have the greatest impact on developing better treatments for people with epilepsy and potentially preventing epilepsy. They were also asked to provide input on transformative research priorities for the field, particularly on (1) research that accelerates the development of new treatments that can be translated to individuals with epilepsy, (2) opportunities for increased data sharing and collaboration, and (3) challenges faced by the research and advocacy communities and how they might be better addressed. Insights from this conference will be combined with previously solicited input on the Epilepsy Research Benchmarks to inform the work of the epilepsy research community over the next 5-7 years.

Epilepsy Research Benchmarks

Vicky Whittemore, PhD, NINDS/NIH

The Epilepsy Research Benchmarks were originally developed after the first *Curing Epilepsy* conference in 2000 as a way to communicate, address, and monitor the progress of important research priorities. At that time, the research focus had shifted from treating seizures to identifying cures—defined as "no seizures, no side effects"—and preventing epilepsy in individuals at risk. The original Epilepsy Research Benchmarks focused on three areas: (1) understanding how epilepsy develops, (2) finding ways to prevent seizures from developing in at-risk individuals, and (3) finding better ways to stop seizures without side effects in individuals with epilepsy. The Benchmarks were revised based on insights gleaned from subsequent conferences in 2007 and 2013 to emphasize comorbidities (i.e., neurologic, psychiatric, and somatic conditions) and causes of mortality in the epilepsies, including sudden unexpected death in epilepsy (SUDEP). The conference was also renamed *Curing the Epilepsies* in 2013 to recognize the many forms and causes of epilepsy.

As with earlier conferences, the Benchmarks have been updated and revised to take into account advances in the field. The revision process began before this conference via a NINDS public crowdsourcing campaign to solicit comments on the existing Benchmarks as well as the Transformative Research Priorities. These Benchmarks focus on four areas: (1) understand the causes of the epilepsies and their relationship to epilepsy-associated neurologic, psychiatric, and somatic conditions; (2) prevent epilepsy and its progression; (3) improve treatment options for controlling seizures and epilepsy-related conditions while limiting side effects; and (4) limit, treat, or prevent co-occurring conditions associated with epilepsy across the lifespan in general and special epilepsy populations.

Why Do the Benchmarks Matter?

Ilene Penn Miller, Epilepsy Leadership Council Benchmarks Work Group

The history of the Epilepsy Research Benchmarks and the *Curing the Epilepsies* conferences illustrate the evolution of epilepsy research over the past two decades. Coming off a decade of brain revelations, the first *Curing Epilepsy* conference in 2000 represented a landmark shift in mindset from treating to curing epilepsy. By the second *Curing Epilepsy* conference in 2007, it became clear that the community must move beyond merely convening to begin benchmarking to routinely measure progress toward addressing gaps and priorities in epilepsy research. The third *Curing the Epilepsies* conference in 2013 expanded the scope of work to embrace the many types of epilepsies, comorbidities, and affected populations across the lifespan. New benchmarks were added after that conference to address the cognitive, psychiatric, psychosocial, and other comorbidities of the epilepsies, beyond seizures.

A robust epilepsy ecosystem now exists to pursue the mission of curing the epilepsies. However, the current pace of research is too slow to realistically cure thousands of epilepsies in a meaningful timeframe. It is therefore critical to find fundamentally new ways to organize the epilepsy community so that it can identify cures faster and for many epilepsies at a time. Large-

scale initiatives inspired by the Benchmarks have led to major discoveries in epilepsy research, including hundreds of genes associated with the epilepsies. The expansion of consortia and collaborations and widespread data sharing could produce transformative change and overcome existing systemic impediments to progress—such as competition, disconnected data, and tenure-driven publishing incentives—that are undermining efforts to find cures for the epilepsies. It is time to overhaul the epilepsy infrastructure to integrate basic, translational, clinical, and implementation science because silos of research and care are failing individuals with epilepsy.

Laying the Groundwork for Transformation

Ann Poduri, MD, MPH, Boston Children's Hospital/Harvard Medical School

Epilepsy is an urgent health concern that impacts the morbidity and mortality of 1 in 26 people globally. Despite centuries of awareness and research, many questions remain to be answered on the path to curing the epilepsies. At this conference, participants were encouraged to consider three sets of questions: (1) Why focus on or prioritize research in epilepsy? (2) What should be the focus of epilepsy research efforts? and (3) What are the big unanswered questions that need to be addressed to cure the epilepsies? Specifically, what research needs to be done within, across, and beyond the Epilepsy Research Benchmark areas to further progress toward treatments, cures, and preventive strategies?

The field must pursue transformative approaches to research to better identify who is at risk for epilepsies, understand how seizures start and stop, generate superior models of epilepsies, and select the right biomarkers for epilepsies. Transformation requires a collective effort from bench scientists, clinical researchers, students, clinical partners, advocates, patients, and families. Conference participants were encouraged to continue the conversation about the important research questions that will transform the field and allow progress toward shared goals.

Introduction to the Transformative Research Priorities

Eric Marsh, MD, PhD, Children's Hospital of Philadelphia Research Institute

The principal components of the Epilepsy Research Benchmarks have been relatively stable since their inception. Remarkable progress has been made in epilepsy research, but many substantial questions remain, and the prognosis, treatment, or outcome of individuals with epilepsy has not changed significantly. Despite the improved ability to diagnose the genetics of a growing proportion of people with epilepsy, the genetics of the common epilepsies and the genetic predisposition of the acquired epilepsies remain unknown. With recent advances in computational power, molecular and genetic tools, pharmacological methods, and imaging and physiological techniques, epilepsy researchers can begin to tackle transformative research questions that will ultimately lead to a new set of Epilepsy Research Benchmarks in 2026 that radically differ from those that exist today. The goal of this conference is to further spark that debate.

The American Epilepsy Society (AES) Benchmarks Stewards Committee is responsible for revising the Epilepsy Research Benchmarks. The Benchmarks reflect shared Transformative Research Priorities that should (1) fundamentally improve our understanding of the epilepsies and the lives of people with epilepsy; (2) stimulate novel and innovative research to address challenges and open questions in the field; (3) encourage multidisciplinary approaches and attract new thinking to research on the epilepsies; and (4) identify specific areas of research that, if successfully undertaken, present opportunities to transform the understanding and treatment of epilepsy. During fall 2020, the epilepsy community submitted their priorities through the NINDS IdeaScale crowdsourcing campaign, many of which focused on fundamental changes to the performance of basic and clinical epilepsy research.

The ideas from the IdeaScale campaign and the AES Benchmarks Stewards Committee led to a reshaping of this conference following its postponement in April 2020. Thus, the central purpose of this conference became to define the Transformative Research Priorities for the epilepsy community. The scheduled presentations and panels were designed to serve as a springboard for new research questions and ideas that will address the outstanding unknowns in epilepsy research.

Session II: Expediting Targeted Treatments for the Epilepsies

Moderator: Daniel Lowenstein, MD, University of California, San Francisco

Why Epilepsy Research Matters: A Personal Story

Amber Freed, SLC6A1 Connect

SLC6A1 Connect is a non-profit organization that supports research on SLC6A1-related epilepsy, an autosomal dominant genetic form of epilepsy characterized by loss-of-function in one copy of the SLC6A1 gene. In fewer than 2 years, the organization has found a corporate sponsor to support gene replacement therapy, pursued numerous potential antisense oligonucleotide (ASO) treatment approaches, coordinated a drug repurposing trial that is scheduled to begin in spring 2021, and raised more than $2 million for SLC6A1 causes. SLC6A1 Connect members make many sacrifices and fight passionately to advance research that can improve the lives of their children. The organization recognizes that government funding for disease-specific translational programs is scarce, and therefore directs its funds toward translational opportunities with the potential to make a meaningful difference for affected children during their lifetime.

Moving Toward Targeted Treatments for the Epilepsies

Daniel Lowenstein, MD, University of California, San Francisco

Targeted therapies are interventions with a well-understood mechanism of action that either fully and permanently ameliorate the symptoms of a disease—without any clinical or biological side effects—or prevent a disease from occurring in the first place. Current treatments for epilepsies, which primarily include pharmacological and surgical approaches (e.g., implantable stimulators), fail to meet the full definition of targeted therapies and often do little to address

comorbid conditions. Although pursued throughout recorded history, targeted therapies for the epilepsies have seen relatively little progress since mainstay antiepileptic drugs (AEDs) were introduced more than 50 years ago. Although more AEDs are now available, newer AEDs have not been found to be superior to older AEDs and rates of seizure remission have not changed; roughly one-third of individuals with epilepsy continue to experience seizures and those whose seizures do remit often experience substantial side effects.

Multiple obstacles to achieving targeted therapies for the epilepsies exist. One obstacle is the limited validity of animal models. While important advances have been made using animal models, progress toward achieving targeted therapies will only become faster as the capacity to directly probe the human brain increases. Another obstacle is the extreme structural and functional complexity of the human brain, which necessitates sufficient investment in fundamental neuroscience to ensure the long-term success. In addition, the research community's relatively nascent understanding of the brain ecosystem will require open-minded approaches to investigating the factors that influence brain function.

Finally, next generation tools are needed to resolve this complex landscape, and the development of these tools will require the engagement of bioengineers, physicists, computational scientists, and other experts. Fortunately, the digital revolution has enabled the research community to scale team science and build knowledge networks that combine multiple levels of biological analysis, from the genome to the exposome, into large complex data sets that can be mined to understand the target and to discover targeted therapies.

Genetic Diagnosis in the Epilepsies: Challenges and Opportunities

Heather C. Mefford, MD, PhD, University of Washington/St. Jude's

Obtaining a genetic diagnosis of epilepsies offers many advantages to individuals with epilepsy and their care providers: it improves prognosis counseling, facilitates discussion of recurrence risk, influences medication choices, connects families with the same genetic diagnosis, and identifies potential therapeutic targets. Because the epilepsies are not a single disease, the process of reaching a genetic diagnosis may differ depending on whether the epilepsy is a genetic generalized epilepsy (GGE), a developmental and epileptic encephalopathy (DEE), or a focal epilepsy. Although the genetic architectures of these classes differ, they also overlap to a degree that may allow the identification of targeted treatments for one class to more broadly inform the treatment of other classes that share genetic risk factors.

Early epilepsy genetics relied heavily on linkage analysis in large families, which led to the identification of candidate genes and the channelopathy hypothesis of epilepsy. However, instances of familial epilepsies are rare, and those discoveries did not translate broadly across many affected individuals. The development of genome-wide technologies—including chromosome microarrays, next-generation sequencing (NGS), and genome-wide association studies (GWAS)—greatly accelerated progress in gene discovery, in part by shifting the focus from candidate gene approaches to hypothesis-free discovery.

Genome-wide approaches have highlighted the overlapping genetic architectures of the epilepsies. The adoption of NGS, which enabled the sequencing of entire genomes, was critical for gene discovery in DEE, because exome sequencing within families led to discovery of de novo mutations in affected children. This approach was the key to gene discovery in the severe DEEs; genetic diagnosis is now possible in 40-50 percent of patients with DEE. While the de novo mutations in DEE are not present in GGE and focal cohorts to the same degree, exome sequencing revealed rare or ultra-rare variants in the same genes that cause DEE, revealing overlapping genetic risk in these other classes of epilepsy. Use of GWAS to search for common genetic variants that might act as risk factors for epilepsy also highlights the overlapping genetic architecture of the epilepsies. This approach revealed, for example, that common variants in known epilepsy genes (e.g., SCN1A) are important for genetic risk. While the risk imparted by these variants is much smaller than that imparted by a de novo mutation in a severe DEE, some approaches to treatment that are identified in the severe DEEs may be applicable to the more general and common epilepsies. GWAS can also identify new gene candidates that can lead to potential effective therapies. These discoveries required large patient cohorts and were accelerated by large-scale collaboration such as the Epi4K Consortium.

Many of the genetic discoveries enabled by exome sequencing are single-nucleotide changes. Newer genetic technologies may reveal other kinds of genetic causes of epilepsy that are not captured by exome sequencing and short-read NGS, including noncoding variants, regulatory variants, structural variants, epigenetic variants, repeat expansions, somatic mosaic mutations, oligo/polygenic contributions, and inherited variants with decreased penetrance. The identification of these missing genetic mutations will require the application of novel technologies and analytical approaches, creative strategies, and large collaborative efforts.

New Genetic Causes of the Epilepsies

Erin Heinzen, PharmD, PhD, University of North Carolina at Chapel Hill

Many types of genetic variants are known to contribute to epilepsy risk, with large copy number variants (CNVs) and highly penetrant de novo variants the best understood. New genetic technologies can help to fill gaps in knowledge about the contributions of other types of gene variants. Advances in whole genome sequencing (WGS), for example, will allow the field to transition away from exome sequencing to identify genetic risk outside of protein-coding regions of the genome, where most genetic variation exists. Standard short-read WGS enables identification of non-coding regulatory variation as well as some structural variants, CNVs, and repeat expansions, but the short-read fragments (of 200 to 300 bases) are limiting. Newer long-read WGS, with sequences of 20 kilobases or more, pushes these capabilities even further, capturing a more comprehensive landscape of structural variants, CNVs, repeat expansions, haplotypes, and epigenetic marks as well as the entire mitochondrial genome.

When discovered through WGS, potential genetic risk variants must be interpreted in terms of their impact on protein expression. This interpretation can be facilitated by functional genomic methods, including expression quantitative trait loci (eQTL) mapping, assay for transposase-accessible chromatin with sequencing (ATAC-seq), chromatin immunoprecipitation sequencing

(CHIPseq), and Hi-C. These technologies can now be applied at the single-cell level, enabling the determination of a variant's effect on the protein expression landscape in particular cells of interest.

Technological advances also increase the capacity to study mosaicism and epilepsy risk. Postzygotic de novo variants that arise during development may be difficult to identify depending on when the mutation occurred and the location of the variant in the body; for example, late postzygotic brain-specific variants can play a role in brain malformations and in non-lesional focal epilepsy and are undetectable by standard blood-based genetic analysis. Single-cell sequencing and genetic analysis of resected brain tissue present opportunities to discover brain-specific mosaic variants that contribute to epilepsy risk. Moreover, significant advances in cell-free sequencing of DNA in the blood and cerebrospinal fluid (CSF) creates the potential to identify brain-localized mosaic variants in large patient populations without the need to perform surgery to collect brain tissue.

As these new technologies accelerate the generation of large, multidimensional data sets, the epilepsy research community must invest in shared processes and infrastructures to analyze and interpret these data to realize the full potential of the technology. Large-scale collaborative initiatives will also be critical for the discovery of oligogenic, polygenic, and single-variant risk factors for epilepsy because of the large sample sizes required for detection.

Framing Precision Trials Around Meaningful Outcomes

Dennis Dlugos, MD, MSCE, Children's Hospital of Philadelphia

As interventional precision medicine trials have begun in the epilepsy field, questions about meaningful outcome measures have become both more focused and the answers have become more challenging to interpret because the epilepsies do not have quickly measurable outcomes (e.g., viral load, tumor burden). Moreover, every precision medicine trial must be based on understanding the clinical and biological trajectories of the disease, both of which vary across the epilepsies.

Outcome measures in epilepsy precision medicine trials fall into three broad categories: seizures, development (e.g., behavior, cognition, socialization, quality of life [QOL], family stress), and biomarkers (e.g., EEG background). The relative meaningfulness of these outcome measures is a moving target. For example, the significance of a change in seizure-related outcomes varies by context: seizure freedom or complete prevention of seizure onset may be clinically meaningful, but seizure reduction may only be meaningful depending on the degree of reduction and the associated timeframe (i.e., a greater reduction in seizures may be required to maintain association with QOL over longer time periods). Ideally, meaningful outcome measures would include both seizure and non-seizure domains, although a strong seizure outcome such as seizure freedom or prevention would be a promising start for a candidate intervention. Similarly, biomarker outcomes (e.g., normalization of an abnormal EEG background) warrant further study to conclude whether they are sufficient to support the approval of an intervention.

When selecting meaningful outcome measures for a precision medicine trial, researchers must consider the onset—both clinical and biological—of the epilepsy being studied. In most genetic epilepsies, seizures have a defined age of onset, and the developmental consequences of the epilepsy may precede or follow this onset. Thus, the significance of changes in a developmental outcome may vary based on the unique developmental impacts of a given epilepsy. A strong understanding of the biological onset of the epilepsy can maximize meaningful outcomes in this domain because it may guide the optimal age of enrollment for a trial. However, although previous studies have shown that short-term interventions can improve a variety of cognitive domains and fine motor skills, these outcomes may be difficult to measure in some populations of individuals with epilepsy at the age when changes are especially meaningful, such as in infants and toddlers. As a result, there is an increased focus on the creation of measures for such development outcomes in infants and toddlers with DEE, including new measures of social and emotional skills and eye tracking paradigms.

Another important aspect of trial design is duration. To obtain approval, a new precision therapy must demonstrate superiority when compared to a concurrent, parallel control group. The randomized phase of these trials typically lasts approximately 3 months, and therefore outcome measures must demonstrate meaningful changes within this short timeframe.

Accelerating Translation from Bench to Bedside (One Patient at a Time)

Stanley Crooke, MD, PhD, n-Lorem Foundation

The mission of the n-Lorem Foundation is to apply the efficiency, versatility, and specificity of antisense technology created at Ionis Pharmaceuticals to charitably provide experimental ASO medicines to treat patients with ultra-rare diseases. Individuals can apply with a researcher to the n-Lorem Foundation, where their case is reviewed by the Access to Treatment Committee. This expert committee ensures that the affected individual is suitable for ASO treatment and is only exposed to prudent risks. When a person is accepted for treatment, the n-Lorem Foundation funds the discovery and development of the ASO at Ionis, assists with the preparation of an investigator-initiated Investigational New Drug (IND) application, and evaluates the performance of the ASO.

Unique automated procedures at Ionis can discover ASOs rapidly and cost-effectively. ASO treatments are efficient and versatile, with multiple post-binding mechanisms, routes of administration, and organ engagement. Moreover, the performance of ASOs is highly consistent within chemical classes. Ionis established databases that integrate all safety observations in humans and nonhuman primates (NHPs) for each chemical class under development and published these databases and shared them with the U.S. Food and Drug Administration (FDA).

Although critical, technology alone is insufficient to support n-Lorem Foundation's feasibility. Commercial approval for an ASO treatment for one person with an ultra-rare disease is unlikely to succeed and, if it does, would be prohibitively expensive for families. Consequently, the n-Lorem Foundation exists as a charitable foundation: these treatments are made available to affected individuals free of cost for life. The foundation also requires a great deal of information

to function, including access to the individual's diagnostic and genetic information, a detailed understanding of disease manifestations, a capable investigator to manage the patient under the IND, and a willing host institution. The n-Lorem Foundation also works with the FDA to foster an accepting regulatory environment and maintains numerous collaborations to achieve its goals.

Discussion

Participants divided into breakout groups to discuss transformative research priorities, gaps, and opportunities to expedite targeted treatments for the epilepsies. The ideas raised in these discussions benefit individuals with epilepsy and their families that live with DEEs, acquired epilepsies, and intractable epilepsies, especially if those epilepsies share common mechanisms that could be targeted by novel therapies. Clinicians and researchers will also benefit from more collaborative opportunities and resources.

Translating Big Data Research to Targeted Care of Individuals

Multiple gaps and opportunities must be addressed to effectively bridge the divide between big data and individualized care of individuals with epilepsy. To ensure their applicability to as many individuals as possible, outcome measures used in big data research should be standardized. A greater understanding of the natural histories of different genetic epilepsy syndromes will also help researchers to apply big data results more effectively to individual genetic diagnoses. Systematic genetic testing of more individuals at more life stages (including newborn screening) and from more inclusive populations will enhance the overall data set and capture changes in epilepsy across the lifespan. Genetic data can also be combined with other measures (e.g., circuit-level data) to elucidate the functional implications of genetic diagnoses. Machine learning and other computational methods should be leveraged to mine these multimodal data sets to expedite the discovery of targeted treatments.

Expanding the Focus on Comorbidities and Non-Seizure Outcomes

In addition to enhancing knowledge about specific genetic diagnoses, support for dedicated research on comorbidities and other aspects of the brain "ecosystem" is also important if treatments are to be truly targeted to an individual. These aspects will influence the differential likelihood of seizures at a given time even among individuals who share a genetic disorder. Moreover, comorbidities themselves warrant targeted treatment. Optimization of non-seizure outcomes will also improve and accelerate research on targeted treatments by focusing efforts on outcomes that are relevant and important to people with epilepsy and their caregivers, including developmental, cognitive, and behavioral outcomes.

Research Gaps for Targeted Treatments

Although targeted treatments for specific genetic diagnoses are becoming more promising, many research gaps remain to be addressed. It is still unclear how polygenic and non-genetic epilepsies can be targeted for treatment. There is also a pressing knowledge gap concerning the mechanisms of AEDs and their impact on infants, the immature brain, and pregnant women, which is critical for evaluating the safety of new treatments. Another research opportunity entails a greater focus on diagnostics and therapeutic devices to better meet the needs of

underserved epilepsy populations, including children and individuals who do not have access to epileptologists. Preclinical models also need to be better aligned with candidate mechanisms to determine common and disparate factors that underlie different epilepsies. Some conditions, such as refractoriness, must be defined more precisely in order to develop and align preclinical models that are more suitable for elucidating these mechanisms. In addition to the traditional emphasis on hypothesis-driven research, study sections should encourage replication of previous findings and more exploratory and descriptive research to address these gaps.

Infrastructure Needs

More resources are needed from all levels of government to translate research findings into targeted treatments for individuals with epilepsy. Establishing biorepositories for CSF, blood, and tissue samples would expedite research in this area by making valuable human specimens available to more researchers. Centralized repositories and high-throughput pipelines for genetic and other kinds of data that are collected in a shareable format would facilitate data mining, aggregation of multimodal datasets, and translation of big data findings to clinical outcomes. A standard set of protocols for generating shareable data for epilepsy research would bolster these efforts, and funding agencies may consider longer-term funding mechanisms to support the collection of genetic and natural history data needed for these resources. Learning health systems and other types of partnerships across repositories, institutions, and private companies would also promote data sharing and translation. Another valuable investment would be the funding of workshops and toolboxes that enable investigators to work with new technologies or to explore important epilepsy topics, such as rare diagnostics or translation of ideas from bench to clinic, in order to accelerate the adoption of new technologies and the sharing of expertise on a larger scale. Conventional trial design features (e.g., the 3-month window to demonstrate efficacy of a treatment) should also be reconfigured to better serve targeted groups of people with epilepsy who have rare diseases.

Collaboration

The creation of multidisciplinary consortia (e.g., Centers Without Walls) would be a transformative step toward accelerated progress in targeted epilepsy care. Resources should also be dedicated toward incentivizing researchers to contribute to shared resources (e.g., specimen or data repositories), including prior to publication. The epilepsy community should also strive to bridge the gaps between basic scientists and clinicians and between researchers and advocacy groups. Furthermore, researchers can learn from advances in other fields that have achieved success with targeted treatment and large-scale collaboration (e.g., cancer, psychiatry, autism, and other fields with large consortia) to accelerate discovery. Funding agencies can lead this effort by organizing meetings of this groups. This enhanced communication and collaboration at all levels will help optimize targeted treatments in ways that are meaningful to individuals with epilepsy and their families.

Session III: Modeling Human Epilepsies

Moderator: Alfred George, MD, Northwestern University

Discussants:

- Amy Brooks-Kayal, MD, University of California, Davis
- Gerald Downes, PhD, University of Massachusetts-Amherst
- Wayne Frankel, PhD, Columbia University
- Toshihiro Kitamoto, PhD, University of Iowa
- Jack Parent, MD, University of Michigan
- Charles Szabo, PhD, University of Texas Health Science Center
- Karen Wilcox, PhD, University of Utah
- John Wolf, PhD, University of Pennsylvania
- Greg Worrell, MD, PhD, Mayo Clinic

This session focused on the use of preclinical models to serve as surrogates, proxies, or avatars for the human brain in epilepsy-susceptible individuals. One goal of the session was to assess whether existing models are sufficient—or new models are needed—to help accelerate the discovery and development of new treatments for the epilepsies.

Why Epilepsy Research Matters: A Personal Story

Kim Nye, Tess Research Foundation

When newly discovered genetic causes for epilepsy are diagnosed, the research landscape is often sparse. There may be a complete lack of mechanistic understanding, treatment guidelines, predictive biomarkers, drugs in development, or even government funding to pursue any of this missing information. In the case of SLC13A5-related epilepsy, caused by a citrate transporter mutation, the TESS Research Foundation assumed the mission to accelerate therapeutic discovery for this newly discovered epilepsy and started by funding the creation of preclinical models. Because no perfect model system for SLC13A5-related epilepsy exists, the foundation has funded the generation of numerous animal and cellular models—including fly, fish, mouse, induced pluripotent stem cell (iPSC), and organoid models—that will inform research on mechanisms, drug screening and repurposing, metabolism-based therapy, and gene therapy. However, multiple distinct animal models are generally needed to address different types of research questions or therapeutic development, and animal models often do not faithfully recapitulate the human condition. SLC13A5-related epilepsy, for example, is a monogenic loss-of-function disease that should be modeled well by a knockout mouse, yet significant phenotypic disparities between the human and mouse presentations are common. If not for the efforts of advocacy organizations, it is not clear that models of rare genetic epilepsies would be generated. However, the challenges and limitations of faithfully modeling the epilepsies in animals raise many questions about the amounts of time and funding that these groups should spend on this endeavor. Above all, these challenges emphasize the need for transformative change in epilepsy research.

Modeling Human Epilepsies: From Organoids to Non-Human Primates

Amy Brooks-Kayal, MD, University of California, Davis

The best model of a human is a human, but non-human preclinical models are essential tools for research that cannot be conducted in individuals with epilepsy. Such research investigates the basic mechanisms of epilepsy and drug screening studies to examine the efficacy, pharmacokinetic/pharmacodynamic (PK/PD) qualities, blood–brain barrier permeability, and toxicity of drug candidates. All non-human models are imperfect and limited; therefore, the best model for a study depends on the question the study is trying to answer. Multiple models may be needed to determine whether a therapy will be safe and effective in human trials. The most commonly used models to study the epilepsies are described below in order of increasing biological complexity, with a focus on their common uses, advantages, and limitations.

Human iPSCs

Human iPSCs are used to build preclinical model systems for the study of genetic epilepsies. Because these cells are typically derived from fibroblasts from individuals with epilepsy, they contain the specific mutation and unique genetic background of the individual. These cells can be proliferated to generate an essentially unlimited supply and differentiated to become many cell types of interest to research, including neurons and glia. iPSC models are used to study structural brain development, electrophysiological activity, and calcium signaling, as well as to perform drug testing and genetic screening. Although iPSC models are unique among preclinical models in their human-specific neurodevelopmental features, they are an inherently reductionist system that develops slowly and exhibits incomplete maturation. Organoid iPSC models mature more than two-dimensional (2D) iPSC cultures, but still lack the in vivo network complexity of the brain and, like 2D iPSC models, also exhibit incomplete maturation.

Drosophila

Drosophila models are primarily used for genetic screening because they are a well-established model system with a sophisticated genetic toolkit. Moreover, many genes associated with human disease have orthologous genes in Drosophila, and a variety of seizure-prone mutants are available. Further, these models offer the benefits of short generation time and low-maintenance costs. They are limited by their simplistic brain anatomy and the fact that seizures in this model are almost always induced rather than spontaneous. In addition, Drosophila genes do not map identically to human genes, and Drosophila EEG patterns do not correspond to human EEG patterns.

Zebrafish

Zebrafish are a commonly used model for small molecule screening, genetic analysis, and personalized therapy development. Zebrafish models develop quickly, have a wide variety of genetic resources, and are inexpensive to maintain, and the transparent embryos are easy to image. Most epilepsy genes are conserved in Zebrafish, although the genes do not map identically to human genes. Other limitations of this model include a lack of neocortex and a failure to replicate the human disease phenotype in some mutants.

Mouse Genetic Models

Mouse models are the most common non-human model of human genetic diseases, and many mouse models for the epilepsies are in use. More than 360 mouse mutants have spontaneous seizures or low seizure thresholds, approximately 100 of which have construct validity for known human epilepsy variants. An estimated 85 models exist for DEEs alone, although significant gaps in coverage of the full range of epilepsies still exist. Technology has greatly improved control over mouse genetics, enabling the straightforward generation of single-gene mutations that can be targeted to specific cell types or temporal expression patterns. The large and growing collection of powerful genetic tools is a considerable advantage of working with mouse models. However, some human genetic features, such as CNVs and complex structural variants, remain difficult to replicate in mice. Other limitations of these models include the differences in mouse and human brain structures (e.g., mice do not have gyri), the lack of one-to-one correlation between seizure types and comorbidities, and difficulties in modeling some comorbidities, such as cognitive and psychiatric comorbidities. Furthermore, some applications are not feasible in such small animals, and high-throughput screening is more challenging and expensive in mice.

Rodents

Both mice and rats are used to model acquired epilepsy across the lifespan. A wide variety of such rodent models exist, including for temporal lobe epilepsy, post-traumatic epilepsy, infection-induced epilepsy, stroke, hypoxia, hyperthermia-induced early life stress, and focal models. Many (but not all) of these models demonstrate spontaneous seizures and have been used extensively to screen therapies and investigate mechanisms; mouse models of acquired epilepsy can be genetically manipulated to answer hypothesis-driven questions about mechanisms. Chronic video EEG can be performed in rodent models, though it is very time-consuming and expensive. These models have seizures, but they are often rare and require long time periods to record. Other limitations of these models include agyric brains, subtle behavioral seizures, and strain-dependent differences in seizure susceptibility.

Canines

Canines naturally develop epilepsy at a fairly high prevalence rate. Canine epilepsy models can be genetic or acquired, as in humans, or can be induced. Canine brains are larger than many other preclinical models, have gyri, and are closer in structure to humans. As such, canines are valuable models for surgical procedures and devices. Their intelligent, trainable, and social nature makes it easier to assess cognitive and social comorbidities. Furthermore, canines exhibit several features of intractable epilepsies, such as multi-drug resistance, comorbidities (e.g., sleep disorders, SUDEP), and status epilepticus. Limitations of this model include housing expenses and dogs' cultural status as a common pet.

Swine

Swine (pig) models are generally used to examine mechanisms of epileptogenesis. They are well suited for head injury studies, such as controlled cortical impact studies of post-traumatic epilepsy, because their brain size and gyral structure allow for application of multiple electrodes. Moreover, seizures in pigs are electrographically similar to those in humans. Blood

and CSF biomarkers can be measured in pigs, and their higher level of cognitive and social function compared to small animal model species facilitates the assessment of comorbidities. Pigs also have clinically-relevant neuroimaging and histopathological outcomes. Limitations of this model include housing expenses and the necessity of expert interpretation for EEG measurements.

Non-Human Primates

An established NHP model of epilepsy is the epileptic baboon. Epileptic baboons have a genetic predisposition to photosensitive and spontaneous seizures, which are often reminiscent of those experienced by patients with GEE, including myoclonic, absence, and generalized tonic clonic seizures (GTCS). Other similarities to human GEEs include childhood or juvenile seizure onset, a predisposition for seizures at sleep transitions, and scalp EEG with generalized seizures. These baboons can be used for intracranial EEG (IC-EEG), functional neuroimaging, genetic studies, device studies, and SUDEP studies. Studies in epileptic baboons are relatively translatable, particularly given their similar brain structure to human and higher level cognitive and social behavior, which enables assessment of cognitive and social comorbidities. Limitations include very high cost and low availability of epileptic baboons, as well as training requirements for researchers and seizure-induced morbidity. Future opportunities for research in epileptic baboons include prospective studies of genetic and epigenetic, electroclinical, neuroimaging, behavioral, and molecular biomarkers for epileptogenesis, similar to those conducted in humans; studies of long-term seizure detection and/or neurostimulation devices; prospective validation of proposed human biomarkers of SUDEP; and studies of the development pathophysiology underlying GEE.

Panel: How do we better model the human epilepsies or what can we learn from model systems?

Generating New Models and Improving Existing Models

To accelerate epilepsy research, new models must be generated. Some newer models, such as the domoic acid-poisoned sea lion, are naturally occurring, and others may be generated as genetic technologies advance. Eventually, researchers may be able to induce known genetic epilepsy mutations in more species—merging the powerful genetic tools available in lower-order species with the phenotypes more similar to human epilepsies that exist in higher-order species.

Another critical need is the alignment of existing models. The replication of a phenotype across models, for example, boosts confidence in the translatability and relevance of experimental results. In addition, different model systems can be combined to investigate different aspects of a given research topic, such as mechanisms or comorbidities. Rigorous experimental practices, including blinded experiments and appropriate statistical analysis, should always be applied to support the validity and translatability of all findings.

Researchers that work in different model systems can collaborate to identify and replicate findings that are more translatable to humans; these collaborations are often supported by patient advocacy organizations. In addition, determination of functional imaging correlates of

human phenotypes, especially in higher-order animals, has great potential to improve the validity of preclinical models. Ultimately, selection of the best preclinical model will vary based on the research question.

Genetic Variability and Translational Challenges

The validity and translatability of preclinical animal models is a major challenge in epilepsy research. Some mouse models of genetic and acquired epilepsies, for example, fail to develop seizures or other expected phenotypes. The failure to develop phenotypes can be strain-dependent in rodents and other species, and it is difficult to predict which genetic backgrounds will result in a phenotype for different mutations. Powerful genetic tools in drosophila and zebrafish models have led to discovery of new genes and pathways implicated in the epilepsies. However, differences between these organisms and humans are large enough that these discovered genes are not always relevant to human epilepsies, although they can be employed as candidate genes for testing in other model systems. Genetic variability is also an important consideration when working with human preclinical models such as iPSCs. Different cell lines from the same patient can exhibit genetic variation that must be controlled for to ensure proper interpretation of findings.

Modeling Comorbidities

Preclinical models have varying utility for the study of non-convulsive comorbidities that occur in human epilepsies. Swine models of acquired epilepsy were developed in part to investigate the cognitive comorbidities that follow traumatic brain injury (TBI). As such, complex tasks (e.g., touchscreen-based conditional association tasks) have been developed for use in pigs to evaluate episodic memory and other cognitive measures that are difficult to assess in lower-order animals. While many neurobehavioral assays are conducted regularly in rodent models to evaluate cognition, memory, and sociability, these assessments are more limited compared to those in higher-order animals. Epileptic baboons demonstrate behavioral phenotypes that may enable researchers to explore behavioral comorbidities in the preclinical space. The intelligence and trainability of other higher-order models, including canines, carry promise for the future development of more ways to model cognitive and other comorbidities in preclinical models.

Therapeutic Development

Therapeutic testing and development can leverage preclinical models in a variety of ways. Some genetic therapies have shown promise in ameliorating the symptoms of genetic rodent models, including non-convulsive comorbidities. Genetic mouse models are critical for the development of genetic therapies (e.g., ASOs) because they are among the highest-order species in which precise genetic mutations that are implicated in epilepsies can currently be induced. Other therapies, such as FDA-approved drugs, may be screened in zebrafish or Drosophila and then directly moved into clinical trials.

Breakout Group Discussion

Attendees divided into breakout groups to discuss transformative research priorities, gaps, and opportunities related to modeling epilepsies. The ideas raised in these discussions will benefit patients, advocates, researchers, and clinicians.

Collaboration and Data Sharing

Given the value of collaboration across labs that work with different preclinical models, the current barriers to data sharing—between basic science labs and between basic and clinical researchers—represents a major challenge for modeling human epilepsies. The addition of clinical trialists to research teams that work with animal models represents a potentially impactful step toward initiating more translational studies. Funding mechanisms that support human and animal model data collection within the same proposal could also help to bridge the translational gap between preclinical and clinical research.

Data repositories and bioinformatic resources represent another opportunity to bolster collaboration. Inter-agency collaborations across NIH or advocacy organizations could also catalog and collect available models to promote the sharing of resources and models among epilepsy researchers as well as researchers in related fields (e.g., other neurological or psychiatric research). Large collaborations, multi-site projects, and centralized infrastructures (e.g., "Centers of Technical Excellence" or CWOWs) offer additional opportunities to address current challenges related to rigor, reproducibility, coordination, and the adoption of common data elements within and across species in preclinical research; NIH supplements could be created specifically to fund reproducibility and replication studies. Enhanced communication among multiple stakeholders also enables researchers to align existing models in new ways that may be more conducive to clinical translation, such as by mechanism or by meaningful outcomes.

New Models

Many gaps exist among current epilepsy models. More and better models of refractory epilepsy, spontaneous seizures, epileptogenesis, comorbidities, and network phenomena are needed, which may require more frequent utilization of higher-order species. The development of new models is costly, and the research community should not need to rely on advocacy organizations to fund these endeavors. Naturally occurring animal models of epilepsies (e.g., domoic acid-poisoned sea lions) present a unique opportunity to investigate mechanisms of acquired and genetic epilepsies, although there are issues related to access to these models. Seizure-resistant mouse strains could also be leveraged to understand mechanisms that protect against seizures.

As models are developed and refined, the field must realize that different research questions will be appropriate for different models, both new and existing. Organoid models may be valuable bridge models, especially for drug sensitivity and screening; organoids and iPSCs may also be useful for studying non-genetic epilepsies. To facilitate the selection of appropriate models, researchers could develop a set of criteria that define the appropriate usages of existing models and the necessary steps for developing new models.

Leveraging New and Existing Tools

To improve preclinical modeling of epilepsies, more tools must be developed that will allow researchers to elucidate the basic biological mechanisms associated with epilepsy genotypes and phenotypes, as well as to better characterize existing models. Large unbiased phenotypic

screens can be leveraged to better understand disease and therapeutic mechanisms. Biomarkers for these mechanisms must also be developed and standardized.

Session IV: Biomarkers for Human Epilepsies

Moderator: Peter Crino, MD, PhD, University of Maryland

Discussants:

- Denes Agoston, MD, PhD, Uniformed Services University
- Martina Bebin, MD, MPH, University of Alabama, Birmingham
- David Henshall, PhD, Royal College of Surgeons
- Sam Lhatoo, MD, University of Texas Health Science Center Houston
- Steve Roberds, PhD, Tuberous Sclerosis Complex Alliance
- Brandon Westover, MD, PhD, Massachusetts General Hospital

This session focused on biomarkers for the human epilepsies. Six questions were posed as a platform for discussion: (1) How are different types of biomarkers (i.e., biomarkers for seizures, epilepsy, or epileptogenesis) conceptualized and approached? (2) Will biomarkers be the same, different, distinct, additive, or synergistic? (3) Will biomarkers be applicable to all seizures and epilepsies or to individual syndromes and causes? (4) Will biomarkers be phasic and dynamic or static and binary? (5) Will there be a predictive, temporal logic to biomarkers (i.e., will biomarkers elucidate onset, severity, intractability, or remission)? and (6) Will there be biomarkers for prognosis and comorbidities?

Why Epilepsy Research Matters: A Patient Advocacy Story

Steve Roberds, PhD, Tuberous Sclerosis Alliance

Tuberous sclerosis complex (TSC) is a rare genetic disorder that causes tumors to form in vital organs throughout the body and is highly associated with epilepsy, autism, and other neurological manifestations. TSC is a heterogenous disorder that affects no two people the same way, although epilepsy is very common and seizure onset often occurs in infancy. While risk of cognitive impairment in TSC is strongly associated with epilepsy, this risk is not absolute. Therefore, predictive biomarkers are needed to inform personalized trajectories. Transformative change is needed to discover the biomarkers that will move the field beyond treatment guided by population correlations and toward these personalized trajectories.

Why Do We Need Biomarkers?

David Henshall, PhD, Royal College of Surgeons

A biomarker is 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. For the epilepsies, a biomarker is a change (i.e., physiological or chemical) produced by a seizure or the epileptic zone that can be detected remotely. The three primary types of biomarkers are molecular, neurophysiological, and imaging. Molecular

biomarkers are among the most attractive and practical biomarkers because of their potential to be measured in a routine blood test. Blood proteins are the best researched molecular biomarkers for epilepsy, with an emphasis on proteins that are enriched in neurons and associated with inflammation, although there are challenges regarding the specificity of these biomarkers to the epilepsies. Another popular class of molecular biomarkers is microRNAs, which are simple to detect in multiple biofluids and are sometimes brain-specific, such that their detection in blood is a good indicator of brain damage. Furthermore, microRNAs have been manipulated in preclinical models to produce therapeutic benefits.

Biomarkers have several important applications for the epilepsies. One application is diagnosis, which is not always straightforward because seizures are not always witnessed and can be confused with other conditions. Biomarkers can also be used for prognostic purposes to assess risk of developing epilepsy or comorbidities and to forecast seizures before they occur. A related application for biomarkers is the prevention of epilepsy, which requires identifying individuals who are at risk. Biomarkers can also guide treatment selection and monitoring and inform selection of patients for clinical trials of anti-epileptic treatment.

Specific biomarkers measure unique aspects of epilepsy and are therefore useful in different contexts. Seizure biomarkers measure changes that result from a seizure and are beneficial in emergency situations (e.g., to identify a non-convulsive seizure) and to support epilepsy diagnosis (e.g., to identify non-epileptic seizures of psychogenic origin). A biomarker for epilepsy would indicate the existence of an altered brain network that is capable of triggering seizures but would not necessarily change before or after a seizure. A biomarker for epileptogenesis must be present before the first seizure and can be either unique to a given etiology or be more broadly applicable to multiple causes of epileptogenesis.

Ideally, biomarkers for epilepsy should be sensitive, specific, and directly relevant to the disease process. Practical considerations for biomarker selection include the stability of the biomarker's baseline values; the ease, speed, and cost of collecting and analyzing the biomarker; and the required timing of sample collection. Biomarkers that are only useful when collected in a small window of time following an event may be impractical. Moreover, the same sample timepoint may represent different stages of progression for different epilepsies. While studies in some animal models have demonstrated that epilepsy can develop rapidly over the course of days following status epilepticus, other studies have shown that epilepsy can take weeks or months to develop after stroke or TBI. Ideally, biomarkers should also be benchmarked against a gold standard, which currently does not exist for epileptogenesis.

Opportunities for future biomarker research include the discovery of new molecules; identification of biofluid sources; and elucidation of transfer mechanisms between the brain and circulating cells. Challenges include the need to identify and validate biomarkers in appropriate models; increase human epileptogenesis biomarker options; and determine the effects of age, timing, sex, and etiology on biomarker measures. A five-phase roadmap for research on biomarkers of epileptogenesis was developed after the NIH *Accelerating the Development of Therapies for Anti-Epileptogenesis and Disease Modification Workshop* in 2018

and includes (1) preclinical exploratory studies, (2) initial clinical assessment, (3) retrospective studies, (4) prospective diagnostic accuracy studies, and (5) disease burden reduction studies.

Panel: Biomarkers to Prevent Epilepsy, Predict Progression, and Response to Treatment

Types of Biomarkers

Given the range of epilepsies and their unique origins and processes, the epilepsy community will need to leverage panels of biomarkers rather than a single biomarker. Different types of biomarkers must be developed—distinct biomarkers for epilepsy, epileptogenesis, and seizures—and multiple biomarkers drawn from multiple modalities (e.g., molecular, neurophysiological) may be required within those type classes. For example, because epileptogenesis is a process, collection of multiple biomarkers for epileptogenesis at multiple timepoints will likely be necessary to capture sufficient information to understand the process. Multiple seizure biomarkers will also likely be necessary, because whether a common biomarker will emerge across epilepsies is unclear. Furthermore, a variety of factors unrelated to epilepsies (e.g., age, gender) may influence the utility of a biomarker for a particular individual. As biomarkers are discovered, guidelines for how to interpret and weight them in different contexts should be developed, because they will likely be probabilistic rather than binary. More cohesive efforts, including preclinical and clinical collaboration, will accelerate biomarker discovery and development. Large-scale multimodal sample collection and analysis would also expedite progress in this space.

Sources for Biomarkers

Blood is one of the easiest biospecimens to obtain from patients and is therefore a leading candidate source for biomarkers in epilepsy. Another valuable biospecimen for biomarker development is CSF, which is not commonly collected but has been leveraged for Alzheimer's disease (AD) research. CSF will capture potential molecular biomarkers that do not cross the blood–brain barrier, although the low levels of cellular material, RNA, and protein present in CSF present a challenge for detection. Signal detection can also be complicated with blood specimens because of the noise caused by regular fluctuations in biomarker levels (e.g., surrounding meals).

EEG

EEG is the current gold standard for biomarkers used to diagnose epilepsy. Serial EEG has also been used to detect progressing epileptogenesis in infants with TSC. The use of serial EEG in a predictive capacity can provide important information about the average time between the first epileptiform activity and the first seizure, which represents a critical window for early intervention and creates an opportunity to develop and conduct trials on preventive therapies. The use of EEG as a biomarker can be improved through development of better methods to interpret EEG signals that will increase inter-rater reliability, particularly for EEGs that contain many artifacts; automation is one potential avenue for this optimization.

Neuroimaging

Considerable volumes of neuroimaging data already exist in electronic medical records (EMRs) that may indicate an individual patient's risk for developing epilepsy, but these data are not yet leveraged to their full potential. Machine learning and artificial intelligence (AI) methods can be developed to mine these data for potentially valuable biomarkers. Numerous small studies have demonstrated the capacity to leverage different imaging modalities for biomarker discovery, but the field has not yet determined which neuroimaging modalities are best suited to identify biomarkers for epilepsies.

Sudden Unexpected Death in Epilepsy (SUDEP)

It is becoming increasingly possible to assess individualized risk for SUDEP by leveraging a range of putative predictive biomarkers, including electroclinical, imaging, biochemical, and genetic biomarkers. Evidence from animal models have implicated the brainstem as a potentially important region for the development of imaging-based SUDEP biomarkers. Researchers are also focusing on understanding the temporal aspects of SUDEP, which will influence the relative utility of different biomarkers in different time periods. A predictive biomarker for SUDEP would be a transformative shift for research and prevention of this fatal outcome.

Breakout Group Discussion

Participants divided into breakout groups to discuss transformative research priorities, gaps, and opportunities related to biomarkers for human epilepsies. The ideas raised in this discussion would benefit the epilepsy community, , including individuals at risk for developing epilepsy.

Research Gaps

The epilepsies are an especially complicated family of diseases for biomarker development because they can be phasic, dynamic, static, degenerative, or remitting, and sometimes exhibit all of these characteristics simultaneously. A trans-diagnostic approach to understanding the mechanisms that drive seizures, epilepsy, and epileptogenesis will be essential to development of biomarkers and will require study of not only the ictal period but also the inter-ictal, prodromal, and post-epilepsy (i.e., epilepsy-free) periods; biosensors may be leveraged to collect the longitudinal data needed to study these long time periods. A multimodal array of biomarkers will also likely be necessary to fully capture the many facets of epilepsy. Not every biomarker developed in the lab will translate to the clinic, but each will likely have utility for preclinical efforts (e.g., drug development) and should be studied extensively to gain insight that may expedite discovery of the next successful biomarker. Basic research in animal models and new technologies that enable experiments with higher spatial and temporal resolution will accelerate understanding of mechanisms and translation of biomarkers to the clinic.

Prioritizing Biomarkers

Because many different kinds of biomarkers will benefit epilepsy research and treatment, the field should prioritize the biomarkers with the greatest potential to address the epilepsy community's most pressing needs. This prioritization should be an iterative process that is informed by preclinical models, clinical findings, and patients or advocacy groups to arrive at

the most practical, beneficial, and meaningful biomarkers that warrant greater focus. Possible candidates for prioritization include biomarkers for (1) pharmacoresistance or drug response, (2) prediction of seizures, SUDEP, or refractoriness, (3) prognosis of seizures and comorbidities, (4) distinction between epileptic seizures (ES) and psychogenic nonepileptic seizures (PNES), and (5) prediction of epilepsy with first seizure. Development of biomarkers that may be assessed in a nonclinical setting (e.g., "home EEG") as well as biomarker classes that are currently underutilized (e.g., high-frequency oscillations [HFOs], behavioral biomarkers) could also be a transformative step for the epilepsy community.

Data Processing and Infrastructure

There are numerous ways to change the ways that scientists collect, store, share, and process data related to biomarker development that represent opportunities for transformative change in epilepsy research. A multimodal platform to integrate data, a human biospecimen repository, and a centralized infrastructure that promotes leveraging and sharing of existing data could expedite novel insights for biomarker development. Preclinical animal research in particular would benefit from establishment of a mouse biofluid repository to promote resource sharing. The research community should seek new ways to mine standard EEG data, including reaching consensus on the required minimum dataset to produce meaningful results (i.e., raw data vs. original clinical report). When machine learning and artificial intelligence (AI) are deployed to mine and analyze the data, existing data sets for epilepsies that are relatively well understood (e.g., childhood absence epilepsy [CAE], benign epilepsy with centro-temporal spikes [BECTS], post-traumatic epilepsy [PTE]) could be leveraged as training data sets to track potential biomarkers over clinical trajectories. More funding is needed for all of aspects of biomarker discovery, ranging from non-hypothesis-driven research that may reveal previously unknown candidate mechanisms to large-scale, long-term efforts (e.g., a CWOW or project similar to the Framingham Heart Study) to gather large volumes of longitudinal data, which would transform biomarker development but would demand substantial infrastructure.

Partnerships and Collaboration

Multidisciplinary collaboration is essential for the development of multimodal biomarkers for a range of epilepsies and timepoints over the course of epilepsy. Invested patient populations are valuable members of this collaboration, because they are often willing to contribute a lot of data to facilitate progress in epilepsy research and treatment. Researchers and individuals with epilepsy could develop partnerships in which large volumes of data are utilized from the medical record for analysis. Many advocacy groups are already collecting data for natural history studies that could also benefit these partnerships. Public–private partnerships, including with companies that already collect relevant data (e.g., genetic information), may be another opportunity to bolster funding and infrastructure for biomarker development.

Session V: Harnessing Big Data to Drive Epilepsy Research and Clinical Care

Moderator: Brian Litt, MD, PhD, University of Pennsylvania

Discussants:

- Jeffrey Buchhalter, MD, Phoenix, AZ
- Hisham Daoud, PhD, University of Louisiana, Lafayette
- Carrie McDonald, PhD, University of California, San Diego
- Megan O'Boyle, Phelan McDermid Syndrome Foundation
- Avtar Roopra, PhD, University of Wisconsin, Madison
- William Stacey, MD, PhD, University of Michigan

This session focused on major gaps and questions in epilepsy research and clinical care that can be addressed by harnessing big data. Attendees were encouraged to identify transformative research priorities related to big data no matter how challenging they may be to implement.

Why Epilepsy Research Matters: A Personal Story

Megan O'Boyle, Phelan-McDermid Syndrome Foundation

The Phelan-McDermid Syndrome (PMS) Foundation launched the PMS International Registry in 2011. This registry collects parent-reported genetic, developmental, and clinical data and provides these data to researchers. Although individuals with PMS and their families generously donate their data to such registries, they are not always informed about how their data will be used and shared across registries. When collecting this type of data, researchers must consider potential *future* uses—beyond analysis for their own studies—to maximize broad usage of these valuable data. These considerations could be included in the consent process to mitigate barriers to data sharing and access, including overly strict Institutional Review Boards (IRBs) that may prevent these data from being leveraged to their fullest potential.

The Promise of Big Data in the Epilepsies

William Stacey, MD, PhD, University of Michigan

For research on the epilepsies to advance, data must be acquired, collected and shared, processed and interpreted, and presented in a useful manner. While the clinical epilepsy field *acquires* massive amounts of data to inform clinical decisions (e.g., EMRs, patient histories, imaging, EEG, genetic information), the other steps in this process are not as well addressed. Most of these data are interpreted locally and then discarded. Moreover, data collected from the same patient in two separate locations are often incompatible and not linked. Differences in data formats and other barriers to data sharing across institutions create data silos that hinder treatment and research.

Clinicians have limited time to adequately process data and often do so visually. Furthermore, most clinicians—and many researchers—do not use modern data tools, such as machine learning or AI. Further, epilepsy data often are not presented in a useful manner, which makes it difficult for clinicians to effectively employ new pharmacological, imaging, EEG, and genetic data to improve outcomes for individuals with epilepsy. Therefore, although large volumes of data are acquired for the epilepsies, better methods of sharing, analyzing, and visualizing these data are essential to harness the power of big data for epilepsy research and care. The epilepsy

community can learn from other research areas and exemplar clinical trials (e.g., the Australia epilepsy trial by Neurovista) to develop the necessary infrastructure and to optimize data collection and processing.

Panel: How do we collect, harmonize, share, and use big data to improve clinical care?

Learning Health Systems

Learning health systems were popularized in 2007 by the Institute of Medicine (IOM) in response to the need for new methodologies to improve meaningful outcomes for people with epilepsy. The core principles of learning health systems include (1) a commitment to interventions based on data, (2) the collection of data in a standardized fashion at every clinical encounter, and (3) analysis of data in near-time that results in feedback to the network and iterative improvements in outcomes. Robust clinical informatics and direct involvement of individuals with epilepsy and their caregivers are key to the success of learning health systems. Learning health systems for the epilepsies are well situated to address reduction in seizure frequency, improvements for QOL, identification of comorbidities, and other potentially transformative priorities. In addition, learning health systems collect a wide range of standardized data from large numbers of individuals as part of routine clinical care, which could greatly reduce the cost and effort associated with building a large human data registry that would accelerate progress in epilepsy research.

Large-Scale Consortia and Collaboration

The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA)-Epilepsy consortium is an international network of 29 epilepsy research sites that leverages quantitative neuroimaging to predict clinical outcomes and generate data to improve biological understanding of the epilepsies. The consortium is an exemplar for large-scale collaboration and human data aggregation. Priorities for the consortium are set at regular meetings of investigators from member sites. While the unique capabilities of a given site prevent total harmonization across all sites, numerous steps are taken to reduce variance and produce meaningful and compatible data to share throughout the network, including a case-control study design and standardized post-processing algorithms and statistics. The epilepsy sites compose just one working group within the consortium; other working groups dedicated to other diseases collect data in the same standardized way, creating opportunities for the epilepsy community to learn from other fields. Preclinical consortia have also been established for epilepsy research and provide a roadmap for aggregation and alignment of animal model data; investment in more preclinical consortia represents a similarly transformative priority for the epilepsy community that will accelerate discovery of common mechanisms and development of novel tools and improve reproducibility across labs through a centralized infrastructure.

Machine Learning and Artificial Intelligence

Machine learning and AI are valuable tools for mining existing datasets for new insights and for producing models that can predict meaningful events for epilepsy care and treatment (e.g., occurrence of seizures). Success in employing these tools relies on three pillars: computational power, algorithms, and availability and labeling of big data. The computational power and algorithms are currently available to epilepsy researchers; however, there is a pressing need for

collaboration across sites to improve the labeling of data that will enable supervised learning to train these algorithms to effectively process and detect information within epilepsy datasets. The creation of well-annotated multimodal data sets—especially with multiple data types from the same patients—will improve the capacity to generate effective computational models (potentially through collaboration with engineers or private partners that specialize in writing these algorithms) for the extraction of novel information and insights.

Data Sharing and Security

To facilitate widespread data sharing, the field must emphasize the development of common data elements, protocols for data standards, and a robust infrastructure (e.g., a central preclinical and/or clinical database). Frameworks for widespread data acquisition and availability that already exist in other fields (e.g., cancer biology) can serve as templates to kick start large-scale data sharing in the epilepsy community. However, attention must be paid to the security concerns associated with the collection of large volumes of data. Individuals must be confident that their data will remain protected as epilepsy researchers increasingly embrace big data approaches (e.g., cloud computing). Study teams should regularly update consent procedures to provide the flexibility needed to share data at large scales while protecting data and abiding by Health Insurance Portability and Accountability Act (HIPAA) and IRB regulations. Furthermore, should researchers and clinicians choose to partner with private companies to develop new analytical approaches, data security concerns and implications for consent will need to be thoroughly assessed. However, the resulting consent procedures must not be so restrictive that they hinder data sharing, and researchers and regulatory entities (e.g., IRBs) should partner with advocacy organizations to develop consent procedures that align with the values of the individuals involved, including the choice to safely share identified data; the rare disease community may be more willing to share identified data than researchers or regulators assume.

High-Resolution Neurophysiology

Although EEG data have been collected for many years, the processing of these data has not appreciably changed. EEG resolution must improve to bridge the spatiotemporal gap of scale between seizure mechanisms and EEG signals. These innovations will also enable better interpretation and presentation of HFO data in ways that are more clinically actionable.

Breakout Group Discussion

Attendees divided into breakout groups to discuss transformative research priorities, gaps, and opportunities related to the use of big data in research and care for the epilepsies. The ideas raised in this discussion would benefit the epilepsy community, especially in the rare disease space, which needs a robust data infrastructure to aggregate and extract the greatest value from all available data.

Increased Data Acquisition and Access

Larger volumes of multimodal, well-annotated data are needed to advance many areas of epilepsy research, including biomarker and mechanism discovery. These data could be collected in numerous ways, including but not limited to (1) large collaborative studies (e.g., an expansive

GWAS); (2) digital platforms utilized by individuals with epilepsy (e.g., the Epilepsy Digital Management Navigator [EDEN], which shares self-reported and automatically anonymized data with care providers); (3) standardized acquisition of multi-layer omics and neurophysiology data from all resected tissue; (4) new procedures that modify how data are collected at points of care to facilitate downstream aggregation (e.g., adding common key fields to EHRs); and (5) incentives for individual clinicians, researchers, and patients to share more data with centralized repositories (e.g., an "S-index" to reflect how much an investigator has shared data).

As more data are collected, it will become increasingly important to establish and maintain an infrastructure with trusted brokers of these data, including centralized data repositories. These brokers must ensure that data are securely available to preclinical and clinical researchers as well as individuals with epilepsy and their families, which may require policy changes that make EHR data more accessible. Furthermore, it will be essential to develop common data elements and standardized data acquisition and annotation procedures to facilitate the creation and maintenance of these repositories in the long term.

A transformative priority to pursue in parallel with the goal of collecting larger data sets is the inclusion of more data from underserved, international, and community-based populations. To make large-scale data collection more feasible and encourage investment, medium-scale data collection would be a valuable intermediate stage whereby individual investigators establish the efficacy of different acquisition approaches and standards that can then be adopted more readily. Importantly, more funding opportunities—public, private, or both—will be essential to making this increased data acquisition and access a reality.

Novel Data Processing Approaches

The widespread adoption of machine learning, AI, and other existing statistical or computational tools is a transformative priority for epilepsy research and care, because these tools are currently underutilized. Computational tools will enable leveraging of existing data sets for new uses and may help to increase the utility and collective understanding of EEG data and the alignment of preclinical animal models with clinical data. Computational approaches can also be harnessed to develop methods for integrating data (e.g., linking human data to preclinical animal model data, combining data produced by different methodologies, pulling natural histories from EHRs) into multimodal data sets that will accelerate mechanistic understanding of the many kinds of epilepsy and facilitate more informed treatment decisions. These efforts will be especially helpful for epilepsies without a particularly strong signature within any one data stream (e.g., epilepsies that do not produce a strong EEG component). Automated data processing could even transform the way that epilepsies are categorized and diagnosed based on currently hidden trends across many data sets. There is also potential to develop algorithms that leverage real-time data collection (e.g., from digital diaries or wearable devices) to provide actionable feedback (e.g., seizure tracking and forecasting).

To rigorously implement these approaches, the epilepsy community should invest in training, fellowships, and related opportunities to build a robust data science workforce. In addition,

partnerships with industry and private companies that specialize in data management should be leveraged to accelerate the development and implementation of these novel data processing approaches.

Session VI: Emerging Research Priorities in the Epilepsies

Moderator: Lori Isom, PhD

Why Epilepsy Research Matters: A Personal Story

Gabi Conecker, Wishes for Elliott, DEE-P Connections

Wishes for Elliott promotes research on SCN8A-related epilepsy. The nonprofit's work is centered on audacious goals and transformative change to find better treatments and ultimately a cure for the epilepsies. New ideas are needed to address barriers to research progress, including the underutilization of data. Collaborative solutions among experts within and beyond the epilepsy research community, a national strategy, robust infrastructure, and increased funding and data integration can produce the transformative change that will improve QOL for individuals with epilepsy, reduce seizures, and cure the epilepsies.

Health Services Research and Access to Care

David Clarke, MD, Dell Medical School, University of Texas at Austin

Health services research (HSR) is a multidisciplinary field that studies how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviors affect access to health care, the quality and cost of care, and health and well-being. Applied HSR provides evidence to improve affordable, safe, effective, equitable, accessible, and patient-centered approaches to care.

Access to health care specifically refers to the timely use of personal health services to achieve the best health outcomes. It is often difficult to discern diagnostic delays from accessibility of care. Diagnosis can be delayed for multiple reasons, including failure to recognize medical events as seizures or clinician deferral of diagnosis. In some cases, delayed diagnosis and access to care are directly related, as when scheduling difficulties delay the ability to receive a diagnosis. Access to care remains a problem for some patients after diagnosis, with one-third of people with epilepsy in the United States remaining untreated for up to 3 years after they are diagnosed even when they have experienced a recent seizure.

While diagnostic and access issues permeate the entire epilepsy community, access to care varies by sociodemographic and socioeconomic factors and is particularly difficult for individuals who are of low socioeconomic status, have inadequate or no health insurance, live long distances from points of care, or are non-white (particularly, African Americans, Native Americans, and Pacific Islanders). These health disparities can have large impacts; for example, risk of SUDEP is higher among people with low socioeconomic status.

The IOM's 2012 recommendations seek to address problems with health care access in multiple ways. The recommendations span (1) collaborative surveillance, which can be accomplished

through consortia and learning health systems; (2) accreditation of epilepsy centers; (3) coordinated public awareness efforts; and (4) engagement with people with epilepsy and their families through education and advocacy. Novel approaches to expanding health care access that embody these recommendations include secure video sharing to improve remote care for people with epilepsy, the Extension for Community Healthcare Outcomes (ECHO) telementoring program to improve care for children and youth with epilepsy, the British Paediatric Neurology Association (BPNA) Paediatric Epilepsy Training (PET) courses, and the development of wearable EEG and other medical devices. In addition to these recommendations, clinical and public health research should address gender, race, insurance, and geographical variables whenever possible.

New BRAIN Initiative Technologies to Study the Epilepsies
Ivan Soltesz, PhD, Stanford University

A variety of innovative new technologies from the BRAIN Initiative present transformational opportunities to advance the understanding of the molecular, cellular, network, and behavioral events defining the epilepsies.

In contrast to traditional biochemistry techniques used in preclinical research, which cannot resolve crucial rapid signaling events associated with seizures, new approaches now enable the tracking of molecular events in real time in vivo. For example, a fluorescent biosensor for endocannabinoids based on the cannabinoid type I receptor (CB1) enables the monitoring of real-time endocannabinoid dynamics. Cannabinoid signaling is of particular interest to epilepsy researchers because CB1 can powerfully inhibit GABA and glutamate release and is also the target of various plant-derived cannabinoids. Using this biosensor, scientists have observed transient increases in endocannabinoid signaling induced by seizures that would escape detection by traditional molecular methods. Biosensors of this kind will likely be transformational tools that can dramatically accelerate understanding of the molecular events that occur in epileptic networks.

Epilepsy researchers can also take advantage of new technologies to monitor the activity of large populations of cells simultaneously in awake behaving animal models. Such tools include novel silicon probes to record spikes from large populations of cells as well as in vivo calcium and voltage imaging techniques. For example, mesoscale two-photon calcium imaging makes it possible to record from thousands of cells at the same time, even in deep brain structures while animals perform tasks. This approach can be used to identify unique activity patterns in specific neuronal subtypes that offer potential as biomarkers for cognitive comorbidities in preclinical models. In addition, the combination of acousto-optical deflector technology with two-photon imaging can be used to track the activity of large numbers of neurons in three dimensions, including diverse populations of interneurons scattered across large brain volumes, that play a crucial role in the epilepsies.

Novel tools now enable epilepsy researchers to selectively tag and manipulate neurons that play important roles in seizures. One such tool, known as scFLARE (single chain Fast Light- and Activity-Regulated Expression), is sensitive to both light and calcium activity—enabling the

specific labeling of cells that are active in a selected time period, which can then be used to label only cells that are active during a seizure. scFLARE activation can also be used to trigger opsin expression so that cellular activity can be selectively manipulated. Other advances in opsin technology, such as the development of red-shifted opsins, make possible the non-invasive manipulation of cellular activity in deeper brain structures than previously possible. Opsins such as ChRmine has been used to curtail spontaneous temporal lobe seizures in mouse models without the need for intracranial implants by shining light outside of the skull to activate specific inhibitory cell populations. Brain surgery for experiments such as these can now be avoided altogether by leveraging intraocular injections of vectors that induce opsin expression in desired cell populations. These technologies will be powerful investigational tools for the epilepsy field because they abolish the need for surgeries or intracerebral cannulas for closed-loop intervention experiments.

The field should strive to move beyond subjective assessments and develop objective behavioral biomarkers in preclinical epilepsy research. Novel tools such as Motion Sequencing, or MoSeq, enable automated objective analysis of behavior. MoSeq translates discrete behaviors into units, known as syllables, which are then strung together to form behavioral sequences, much like syllables come together to form words and sentences. Video recordings of mice can be processed by AI to objectively identify syllables in a motion sequence that occur more frequently in ictal or inter-ictal periods. These behavioral biomarkers can then be leveraged to strengthen preclinical testing of AEDs or other epilepsy research in an automated, objective, and reproducible manner. Similar technologies may be developed to analyze human epilepsy behaviors in the future.

Epilepsy in the Elderly

Alice Lam, MD, Massachusetts General Hospital

The highest incidence and prevalence of epilepsy is in older adults, who are the fastest-growing demographic for epilepsy in the United States. Epilepsy carries a two-fold higher risk of mortality and an increased risk of comorbidities in older adults, and its etiology is unknown in up to one-half of older individuals. Recent epidemiological advances have revealed that bi-directional relationships exist between late-onset epilepsy and dementia or stroke, such that incidence of dementia or stroke increases the risk of developing epilepsy and vice versa. All three of these diseases share vascular (e.g., hypertension, diabetes mellitus, smoking, microvascular disease) and genetic (e.g., Black race, APOE status) risk factors, although the mechanisms that underlie this shared risk are not yet known.

The research community has made notable progress in elucidating the relationship between epilepsy and Alzheimer's Disease (AD). While seizures were previously thought to arise only in late and severe stages of AD, it is now clear that seizures can begin early in the course of AD, even preceding cognitive decline. Most seizures in AD are non-convulsive and epilepsy is easily missed in this population, yet approximately 20-40 percent of people with AD who do not have a clinical history of seizures will demonstrate subclinical epileptiform activity in a scalp EEG, primarily during sleep. The clinical significance of epilepsy in AD is still unknown; although

seizure development in AD is associated with an earlier age of onset for cognitive decline, it is not clear whether these seizures accelerate the clinical course AD or instead act as a biomarker of aggressive AD. Mouse models of AD have revealed a potential feed-forward mechanism by which neuronal hyperactivity and classic AD pathologies (e.g., amyloid and tau aggregation) are directly and reciprocally linked; if found in humans, this mechanism could be a therapeutic target for disease modification in AD and would support more aggressive monitoring and treatment of epilepsy in people with AD.

Current knowledge gaps limit the ability to care for elderly patients with epilepsy. Elderly populations are often frailer, have more comorbidities, and are on more medications than other populations. More research is needed to determine the specific treatment outcomes (e.g., seizure freedom, side effect reduction, cognitive decline, or stoke prevention) that are most important to maximize QOL for elderly patients with epilepsy. More clinical data are also needed to guide prevention of adverse outcomes in elderly patients, because it is currently unclear how different seizure types, frequencies, or medications influence the development of incident stroke or dementia. In addition, the primary prevention of late-onset epilepsy is similarly a major challenge that will require more research focused on etiologies and mechanisms.

Research directions in this area are many and include (1) investing in large-scale prospective longitudinal studies of late-onset unexplained epilepsy, (2) leveraging biomarker advances in AD and cerebrovascular disease to better understand the bidirectional relationship between late-onset epilepsy and these diseases, (3) promoting research on the clinical significance of epilepsy and epileptiform activity in AD, and (4) exploring the mechanisms that underlie late-onset epilepsy to ultimately prevent epilepsy in the elderly.

Epigenetic Control of Brain Cell States

Anne Schaeffer, MD, PhD, Mt. Sinai

In epilepsy, an imbalance exists between the activity of excitatory neurons and reciprocal inhibition by inhibitory neurons. Thousands of types of neurons in the brain contribute to this balance between excitation and inhibition, each with unique physiological characteristics and genetic signatures that dictate these characteristics, thereby contributing to a complex regulatory landscape for neuronal activity in the brain. The unique patterns of gene expression–known as gene networks—in different neuronal cell types are modulated during development by epigenetic factors, including (but not limited to) transcription factors and chromatin modifications. Changes in epigenetic mechanisms caused by mutations or environmental influences can alter brain development and upset the balance of neuronal activity. Once gene networks are formed within the brain, they must also be maintained throughout the life course to prevent dysfunction, such as seizures, from developing later in life.

An increased understanding of epigenetic mechanisms may lead to the ability to reprogram neurons to restore the balance of activity in brain networks and reduce seizure susceptibility. This concept is currently being explored in mouse models using gene therapy and pharmacological approaches that were pioneered in other fields, such as cancer research. In

one example of the promise of epigenetic mechanisms in the epilepsies, modulation of the expression of a non-coding microRNA that regulates gene networks that determine neuronal circuit excitability was able to induce or reduce a fatal epilepsy syndrome in mice.

Neuronal activity is also modulated by glial cells. Microglia, which act as immune cells in the brain, can sense changes in neuronal activity and respond in ways similar to inhibitory interneurons, which may protect the brain from excessive neuronal activity and seizures. Moreover, the loss of this microglia function in mouse models leads to neuronal hyperexcitability and seizures. This finding suggests that an inflammatory episode that alters microglia function may be one mechanism by which environmental factors can influence the activity of neuronal circuits. It may therefore be possible to harness the network-level epigenetic mechanisms that control neuronal and glial states to restore healthy brain activity.

Metabolism

Manisha Patel, PhD, University of Colorado

Metabolic pathways can provide fuel sources to control neuronal excitability and therefore represent an opportunity for transformative change in epilepsy research. Metabolism-based approaches to research and treatment of epilepsies fall broadly into four areas: (1) fuels and diets (e.g., dietary therapies), (2) mechanisms that underlie the bidirectional relationship between metabolism and epilepsy, (3) structure and function of important metabolic organelles, such as mitochondria, in hyperexcitable circuits, and (4) metabolic technologies.

The brain selectively utilizes glucose as a fuel to produce excitatory signals, and glycolysis can be targeted for seizure control. Although ketogenic diets originated as a therapy for epilepsies, it is still unclear how the change in fuel source results in a pleiotropic metabolic response and how that response can be modified for seizure control. However, work in this area led to the discovery that glycolysis can be therapeutically targeted to achieve seizure control with compounds such as 2-deoxyglucose. More research is needed to identify the signaling pathways that are altered by fuel switches, determine which pathways can be safely targeted by therapies, understand how ketogenic diets can be optimized to enhance therapeutic effects, including by combination with small molecules, and establish how best to design and implement clinical studies that involve diet and small molecules.

Metabolic impairment can be a cause or consequence of epilepsies through many mechanisms. In one example, researchers identified a key structural feature of an antioxidant enzyme, glutathione peroxidase-4 (GPX4), that confers resistance to oxidative damage in the fast-spiking parvalbumin-positive interneurons that play a central role in epilepsy circuits. These interneurons have high metabolic demands and produce more reactive oxygen species than other cell types. Alteration of the enzymatic structure of GPX4 in a mouse model resulted in fatal seizures and loss of these interneurons. This finding highlights a crucial mechanism that improves the resilience of circuits to oxidative damage and suggests a potential novel therapeutic target for epilepsies.

Redox disruption represents another opportunity for metabolism-based therapeutic target development. Redox disruption occurs in both humans and animal models of epilepsies (genetic and acquired). There are multiple sources of redox disruption in epilepsy, and therapeutic compounds are available for research and clinical trials that may improve epilepsy outcomes and comorbidities. Challenges to this area of research include (1) quantitative measurement of evanescent and compartmentalized reactive oxygen species, (2) determination of whether these species are beneficial or deleterious, (3) identification of species that can be leveraged as therapeutic targets, and (4) selection of disease outcomes that can be targeted by such therapies.

Neurological networks that are associated with seizures have high energy demands and require high levels of mitochondrial performance. Advances in super-resolution microscopy (e.g., STED, STORM) have illuminated mitochondrial ultrastructure, which was previously only possible with electron microscopy. Use of these approaches to image neuronal mitochondria in networks associated with seizure activity has shown that mitochondria near high-performing synapses exhibit alterations in mitochondrial structure, function, and number. Such technological advances have created opportunities to further explore the structure and function of mitochondria in epilepsy, reveal novel interactions between these organelles and other cellular structures, and identify novel therapeutic targets rooted in metabolic activity.

Multiple technologies can be applied in transformative approaches to metabolism-based research in the epilepsies. Such technologies include omics tools, animal models, high resolution imaging, and biochemical assays (e.g., flux analysis). These technologies are widely available, user-friendly, and highly conducive to team science and collaboration because of their interdisciplinary nature.

Microbiome

Tore Eid, PhD, Yale University School of Medicine

The microbiome consists of the entire collection of microorganisms that reside throughout the body, including bacteria, viruses, fungi, and parasites. Most of these microorganisms do not cause harm to the human host, and some even produce beneficial nutrients (e.g., vitamin K produced by gut bacteria). These beneficial microorganisms also prevent colonization by pathogenic microorganisms that cause dysfunction or disease.

The gut microbiome of people with epilepsy differs from that of healthy individuals; moreover, the gut microbiome of patients with drug-resistant epilepsy differs from patients with drug-sensitive epilepsy. Furthermore, ketogenic diets have been shown to change the gut microbiome composition in an animal model of epilepsy in a way that is critical for the diet to be effective. The specific bacterial profile was further linked to changes in brain metabolism, such that there were increased levels of GABA (i.e., the major inhibitory neurotransmitter) and decreased levels of glutamate (i.e., the major excitatory neurotransmitter). In addition, many studies have shown that gut bacteria can affect orally ingested medications, which suggests that the microbiome might influence the efficacy of oral AEDs, and conversely that the ingestion of oral AEDs might change the microbiome.

Very few epilepsy studies have leveraged the microbiome as a therapeutic target, and it is not clear how well findings in preclinical models will translate to humans. However, some promising results have been obtained in this field. In one study, administration of probiotics in chemically kindled rats was shown to reduce epileptic activity compared to rats on a typical diet. Although probiotics were less effective than valproic acid, modification of the probiotic composition may produce a more effective treatment. In another study, fecal transplants from healthy rats suppressed stress-induced seizures in kindled rats, suggesting that fecal transplants may be able to alter the microbiome in a manner that holds promise for treating epilepsies.

The mechanisms through which the microbiome influences epilepsy are not yet understood. Currently hypothesized mechanisms include (1) release of metabolites by gut bacteria that alter levels of endogenous neurotransmitters in the brain, (2) infection by pathogenic organisms that triggers local (i.e., gut) or systemic (i.e., brain) inflammation, and (3) altered bioavailability of oral AEDs. More research is also needed to determine whether altered gut microbiota can cause or modulate seizures and epileptogenesis, change seizure thresholds, influence comorbidities, or alter the efficacy of antiepileptic therapies. Once microbes and microbial mechanisms that modulate epileptogenesis or comorbid conditions are identified, safe and effective therapies can be developed to target the microbiome for the treatment of epilepsies.

Breakout Group Discussion

Attendees divided into breakout groups to discuss emerging research priorities, gaps, and opportunities. The ideas raised in this discussion would benefit patients, families, and researchers within and beyond the epilepsy field.

Health Services Research

Pressing needs in the HSR field include inadequate funding and workforce; these two gaps also intersect because more funding is needed for fellowships and training opportunities to bolster the HSR workforce. In addition, the current infrastructure limits access to necessary resources, such as harmonized data sets from a wide range of data sources. Large academic centers with comprehensive epilepsy programs are exemplars for HSR, although there is a need to capture more data from populations that do not receive care at epilepsy centers and/or have access to health care. Multidisciplinary grants that support collaboration between health services researchers and other epilepsy researchers can advance the implementation and improvement of care for the epilepsies.

Dissemination of New Technologies

Although new BRAIN Initiative technologies hold great promise for epilepsy research, they can be expensive and difficult for labs to implement, which highlights the need to improve and fund both dissemination of the technologies themselves and opportunities for training. The research community must weigh the advantages and disadvantages of different dissemination methods. Commercialization and pre-packaging of new technologies may improve user-friendliness for non-experts but can be expensive and render technologies difficult to customize. The development of open-source options is an affordable way for labs to acquire customizable technologies, but also requires more technical expertise. Establishing collaborative networks or

centralized core facilities for epilepsy research would be a transformative change in the way epilepsy research is conducted and make new technology, expertise, and data more widely available and affordable. Centralized cores also offer a venue to support data replication, standardization, and sharing efforts. The epilepsy community should promote cross-collaboration between basic researchers and clinicians to realize the full potential of technologies that can move from the lab to the clinic (e.g., closed-loop neuromodulation using deep brain stimulation [DBS] electrodes). It will be necessary to address the lack of standardization in both clinical and preclinical data to facilitate this collaboration. Importantly, dissemination of new technologies should include an emphasis on health literacy and effective communication regarding the power of these tools with patients and families.

Applications for New Technologies

Emerging technologies can be applied to address many gaps and opportunities. One opportunity is to interrogate the mechanisms that underlie successful neuromodulation therapies and explore ways to target specific networks through neuromodulation. Epilepsy researchers can learn from examples set by other fields to effectively combine synergistic therapies to achieve better outcomes (e.g., the combination of drugs and neuromodulation for Parkinson's disease). Other opportunities are to leverage large-scale recording to better understand seizure mechanisms beyond the cell or circuit level, and to develop technologies that can better address questions regarding the developing brain. To enable these applications, study sections should consider funding projects that are pre-hypothesis-generating and designed primarily for exploration and data collection. Furthermore, there should be an emphasis on developing methods to safely translate these new technologies to humans.

Epilepsy in the Elderly

More advocacy is needed to promote research on epilepsy in the elderly. Efforts to raise support and awareness for this issue are hindered by the difficulty of diagnosing epilepsy in the elderly because of the subtlety of seizures or an inability of patients to tolerate a lengthy EEG. Researchers can leverage technological advances in other fields, such as AD research, to identify tools and biomarkers that can predict trajectories and improve outcomes in elderly populations with epilepsy. Furthermore, a wealth of data can be mined from these non-epilepsy sources to inform this research, including large AD research networks or EHR systems.

Epigenetics

Although genetic mutations are an important focus of epilepsy research, greater attention should be paid to the epigenetic mechanisms that regulate the implicated genes. More research is needed on many topics in this area, including (1) the role of non-coding sequences and various forms of DNA or RNA modifications, (2) the dynamic epigenetic changes during epileptogenesis, (3) the three-dimensional architecture of the genome, and (4) the influence of cell type-specific regulatory regions. Large-scale efforts to map the entire epigenetic landscape in genetic and acquired epilepsies would reveal both common and unique signals of dysregulated gene expression across diagnoses. These research efforts could lead to development of blood-based epigenetic biomarkers and identification of novel treatment targets. To accelerate this research, more collaboration is needed across labs that focus on

different epigenetic mechanisms or model organisms and, more broadly, on genomic questions and techniques. Further, researchers could leverage tools and learn from advances in other fields, such as cancer and psychiatry research, that have made considerable progress in understanding epigenetic influences on other diseases.

Metabolism

Epilepsy researchers should seek collaborations with and learn from other fields that have cultivated expertise in metabolism biology, including liver biology and immunology, to accelerate research on the epilepsies. Metabolism-based technologies can be leveraged to stratify patients, predict responses to metabolic therapies, and generate metabolic profiles that could predict responses to therapies more generally. To effectively interpret metabolic data in the context of the epilepsies, more research is needed to understand the unique contributions of individual cells to metabolic flux in different brain states. Cross-omics platforms and biobanks that include metabolism-specific data and specimens will support this research. There is also an opportunity to employ currently available metabolic therapies, including the ketogenic diet, more broadly, which will require more outreach and education to inform clinicians about the benefits of these therapies.

Microbiome

Dysbiosis has been observed in epilepsies, but whether it is a cause or consequence of seizures remains unclear. Other open questions relate to the specific microbes and mechanisms that are associated with epilepsies and comorbidities and how well data from animal models will translate to humans. More research on these questions may create opportunities to modulate epileptogenesis and comorbidities through the microbiome. Immediate translation of such interventions to clinical use may be possible, and many treatments (e.g., probiotics) are relatively safe, although controlled clinical trials are lacking. To accelerate this research, biorepositories should include stool samples collected from individuals with epilepsy at different time points.

Session VII: Translating Research into Clinical Care

Moderator: Brandy Fureman, PhD, Epilepsy Foundation

Discussants:

- Amy Brooks-Kayal, MD
- Peter Crino, MD, PhD
- Al George, MD
- David Henshall, PhD
- Lori Isom, PhD
- Brian Litt, MD, PhD
- Dan Lowenstein, MD
- Laura Lubbers, PhD
- William Stacey, MD, PhD

Why Epilepsy Research Matters: A Personal Story

Laura Lubbers, PhD, CURE Epilepsy

The need to develop strategies to address the risks that arise from epilepsy treatment side effects is long-standing. These side effects can significantly impact QOL for patients and families. Moreover, clinicians may not effectively communicate the treatment-associated risks, which impairs the ability of patients and families to proactively address these risks. Transformative change is needed to accelerate epilepsy research and develop more treatment options that will enable individuals with epilepsy and their families to make informed decisions that mitigate risks. This effort will require a culture shift that promotes a collaborative research infrastructure and engages more stakeholders to rapidly translate research findings to clinical practice.

Overview

Brandy Fureman, PhD, Epilepsy Foundation

Over the years, the epilepsies field has made major strides toward involving individuals with epilepsy and their families as partners in research and clinical care in order to embrace the advocate's mantra, "nothing about us without us." The field must continue to remove barriers and unite stakeholders, in particular by eliminating silos in research and clinical care. Although the progress in basic epilepsy research has been exciting, the current system has failed to translate these advances into better clinical outcomes despite multiple generations of new therapies. People with epilepsy and their families urgently need the transformational changes that will accelerate research and ultimately cure the epilepsies.

Panel: From Bench to Bedside—How Do We Accelerate the Research?

Infrastructure for Large Multi-disciplinary Collaboration and Multimodal Data Analysis

A major transformative research priority for the epilepsies is the establishment and support of more collaboration. Multi-center collaborative efforts that maximize the synergies across disciplines and stakeholders to acquire data from a wide range of modalities will accelerate a deeper understanding of the complex mechanisms that drive the epilepsies and expedite the development of valuable tools and treatments. Importantly, these new tools must be accessible to researchers and clinicians with variable degrees of funding and resources to contribute to the field. Another key component of the infrastructure for collaboration is a centralized repository for data and biospecimens to promote sharing of data and resources even among smaller groups that are not part of consortia or other official collaborations. Rather than developing one centralized database, an ecosystem of harmonized data repositories (including platforms that already exist) can be created to facilitate the sharing of information across the many specialized fields that compose epilepsy research, including imaging, neurophysiology, and genetics. The aggregation of large, multimodal data sets would provide an opportunity to use machine learning or AI-based approaches to mine extant data for hidden insights. Essential to the maintenance of these central databases is the prospective collection of data that utilizes standard formats or common data elements that allow for seamless annotation and integration with these databases. These databases must be easy to use and access in order to encourage

researchers, clinicians, and advocacy groups to contribute and work with data within the shared ecosystem.

Toward a Mechanistic Understanding of the Epilepsies

Among the greatest unanswered questions in the epilepsy field are the mechanisms that drive the epilepsies, including the basis for acquired and genetic epilepsies as well as comorbidities. In the genetics space, new technologies coupled with large-scale exome and whole genome sequencing efforts, including the Epi25 Collaborative, will accelerate the detection of currently unidentified variants and improve understanding of acquired brain-specific mutations. Furthermore, new BRAIN Initiative tools have greatly expanded the capability of preclinical research to answer these mechanistic questions. A transformative research priority is to develop ways to translate these tools into clinical practice and human research, because the best models for the epilepsies will ultimately be generated with human data. A bidirectional translation of technology between humans and various preclinical animal models will also help to align preclinical model data with clinical data to accelerate the discovery of mechanisms that are shared across species and therefore most likely to be relevant to human epilepsies.

Reconceptualizing the Practice of Epilepsy Research and Care

To support the continued accrual of knowledge about the epilepsies, the epilepsy community must be willing to reconceptualize core aspects of its approach to research and clinical care. For example, the classification of epilepsies may need to shift from descriptive characteristics to a molecular or mechanistic basis for identification. A dynamic classification system that is aligned with current knowledge will reveal which epilepsies share common (and potentially treatable) mechanistic roots and enable development of more mechanistically-targeted therapies. As these new promising therapeutic and disease-modifying candidates emerge, including ASOs, the epilepsy community will also need to rethink clinical trial design to support the evaluation and success of these therapies. Furthermore, clinical trials and care must be restructured in a more equitable way so that underserved communities have increased access to both proper health care and opportunities to participate in research. In addition to strengthening collective data sets through the recruitment of more inclusive and diverse participants, epilepsy researchers must be encouraged to contribute their data and specimens to shared resources, which may necessitate a new incentive structure that rewards them for collecting data for use beyond their own projects. In addition, grant mechanisms must be allocated so that discovery-driven research is not excluded or disadvantaged in favor of hypothesis-driven projects if epilepsy research is to truly reveal the "unknown unknowns" that currently remain elusive.

Preclinical Modeling of the Epilepsies

The range of preclinical animal models must be expanded and improved to include more types of epilepsy (e.g., refractory epilepsy) and non-convulsive comorbidities. Although a great deal of funding to develop new animal models currently comes from invaluable partnerships with advocacy groups (especially for rare monogenic epilepsies), the epilepsy community must generate new and more sustainable ways to fund or subsidize the development of these models that reduces the burden on people with epilepsy, families, and advocates. Also needed are funding mechanisms that enable open discovery (rather than hypothesis-driven research)

so that these preclinical models and new technologies can be used to accelerate the discovery of "unknown unknowns" that still exist in the epilepsy field.

Rigor and Reproducibility

A key component of improving preclinical modeling of epilepsies entails addressing current problems with rigor and reproducibility. Preclinical studies must be designed with comparable rigor to clinical studies to ensure adequate power and appropriate monitoring. Preclinical research teams should include (or be partnered with) researchers with expertise in reliable quantification of seizures, EEG signals, and behavior changes. This quantification must be consistent across labs to facilitate reproducibility. Further, the field should explore mechanisms to ensure that independent labs are sufficiently funded to perform replication studies and that researchers can replicate promising data collected in fly, zebrafish, and rodent models in more complex species.

Biomarkers

It is currently difficult to predict the trajectory of any one individual after the first seizure has occurred, as well as to retrospectively diagnose seizures. The development of new biomarkers is a transformative research priority that will improve clinicians' and researchers' ability to address these gaps as well as other major questions in the epilepsy field. Actionable biomarkers can be developed for a wide variety of important uses in epilepsy, including markers for prognosis following a first seizure, diagnosis of intractability, assessment of SUDEP risk, and prediction of treatment response. Collaboration among researchers, clinicians, and advocacy groups will be needed to mine the large volumes of extant data and systematically test biomarkers in preclinical models. A large collaborative study (similar to the Framingham Heart Study) that collects longitudinal, multiplexed data would be a truly transformative step toward defining and validating biomarkers across the epilepsies.

What Comes Next?

Ann Poduri, MD, MPH and Eric Marsh, MD, PhD

At this *Curing the Epilepsies* conference, participants discussed potentially transformative research priorities and methods that will drive epilepsy research forward. They discussed various research gaps, including unanswered questions about the mechanisms that underlie both genetic and acquired epilepsies, the necessary improvement and expansion of preclinical animal models, and the need to develop new biomarkers that can track multimodal features dynamically over time. They also discussed issues with research focus and care access, highlighting a need to pay greater attention to underserved communities and elderly populations across epilepsy initiatives. Fortunately, many opportunities exist to address these gaps through new technological advances, including novel tools and methods that have expanded to other fields (e.g., epigenetics, metabolomic, and microbiomics) but have not yet been fully adopted by epilepsy researchers.

At the core of discussions were several fundamental questions that the epilepsy research community still needs to answer, including (1) Who is at risk for epilepsy and what are the genetic, infectious, traumatic, and other risk factors? (2) Why is epilepsy so common? (3) How

can epilepsy researchers combine approaches and share data to develop the best model of epilepsy? (4) What are the right biomarkers for the epilepsies; and (5) Can we cure everyone with epilepsy and prevent future epilepsies before they develop?

These questions can only be answered if certain challenges to progress are addressed, including a culture of science that rewards individual success over collective success as well as research silos of many varieties (e.g., barriers between clinical and basic research or between different epilepsies). The research community will also have to balance competing priorities, including discovery- and hypothesis-driven projects.

Strategies that will accelerate progress in the epilepsy field include (1) the removal of silos and promotion of team science (e.g., CWOWs), (2) the establishment of an infrastructure for data sharing and collaboration (e.g., biobanks and repositories), (3) the generation of innovative ideas and tools, (4) the support of basic science to increase the likelihood of developing treatments and cures, and (5) the expansion of clinical research to develop new tools and measures for trials beyond those that fit within the standard 3-month randomized controlled trial. These strategies may require a culture shift and enhanced infrastructure that promote new partnerships and data sharing.

The Epilepsy Research Benchmarks were revised prior to the conference so that the discussions could focus on transformative research priorities. In the years before the next conference, the epilepsy community must continue work toward the common goal to adopt transformative research priorities to improve outcomes for people with epilepsy.

Appendix A: Agenda

Day 1: January 4, 2021

10:00 – 10:30 AM	**Session I: Introductions, Setting the Stage for Epilepsy Research Benchmarks and Transformative Research Priorities**
10:00 – 10:10 AM	Welcome – Walter Koroshetz, MD, Director, NINDS/NIH
10:10 – 10:15 AM	Epilepsy Benchmarks – Vicky Whittemore, PhD, NINDS/NIH
10:15 – 10:20 AM	Why do the Benchmarks matter? – Ilene Miller
10:20 – 10:25 AM	Laying the Groundwork for Transformation – Ann Poduri, MD, MPH, Boston Children's Hospital/Harvard Medical School
10:25 – 10:30 AM	Introduction to the Transformative Research Priorities – Eric Marsh, MD, PhD, Children's Hospital of Philadelphia Research Institute
10:30 AM – 1:30 PM	**Session II: Expediting Targeted Treatments for the Epilepsies** *Moderator: Daniel Lowenstein, MD, University of California, San Francisco*
10:30 – 10:35 AM	Why Epilepsy Research Matters: A Personal Story – Amber Freed, *SLC6A1* Connect
10:35 – 10:50 AM	Moving Toward Targeted Treatments for the Epilepsies – Daniel Lowenstein, MD
10:50 – 11:00 AM	Genetic Diagnosis in the Epilepsies: Challenges and Opportunities – Heather Mefford, MD, PhD, University of Washington/St. Jude's
11:00 – 11:10 AM	New Genetic Causes of the Epilepsies – Erin Heinzen, PharmD, PhD, University of North Carolina at Chapel Hill
11:10 – 11:20 AM	Framing Precision Trials Around Meaningful Outcomes – Dennis Dlugos, MD, MSCE, Children's Hospital of Philadelphia
11:20 – 11:30 AM	Accelerating Translation from Bench to Bedside (One Patient at a Time) – Stanley Crooke, MD, PhD, n-lorem Foundation
11:30 AM – 12:30 PM	Breakout Groups
12:30 – 1:30 PM	Report Out of Breakout Groups and Discussion
1:30 – 2:00 PM	Break
2:00 – 5:00 PM	**Session III: Modeling Human Epilepsies** *Moderator: Al George, MD, Northwestern University*
2:00 – 2:05 PM	Why Epilepsy Research Matters: A Personal Story – Kim Nye, Tess Research Foundation
2:05 – 2:20 PM	From Organoids to Non-Human Primates – Amy Brooks-Kayal, MD, University of California, Davis

2:20 – 3:20 PM Panel: How do we better model the human epilepsies or what can we learn from model systems?

Discussants:

- iPSCs and Organoids – Jack Parent, MD, University of Michigan
- Drosophila – Toshihiro Kitamoto, PhD, University of Iowa
- Zebrafish – Gerald Downes, PhD, University of Massachusetts-Amherst
- Genetic Mouse Models – Wayne Frankel, PhD, Columbia University
- Rodent Models – Karen Wilcox, PhD, University of Utah
- Rodent Models – Amy Brooks-Kayal, MD, University of California, Davis
- Dogs – Greg Worrell, MD, PhD, Mayo Clinic
- Pigs – John Wolf, PhD, University of Pennsylvania
- Non-human Primates – Charles Szabo, PhD, University of Texas Health Science Center

3:20 – 4:20 PM Breakout Groups

4:20 – 5:00 PM Report Out from Breakout Groups and Discussion

Day 2: January 5, 2021

10:30 AM – 1:30 PM Session IV: Biomarkers for Human Epilepsies
Moderator: Peter Crino, MD, PhD, University of Maryland

10:30 – 10:35 AM Why Epilepsy Research Matters: A Patient Advocacy Story – Steve Roberds, PhD, Tuberous Sclerosis Alliance

10:35 – 10:50 AM Why Do We Need Biomarkers? – David Henshall, PhD, Royal College of Surgeons

10:50 – 11:50 AM Panel: Biomarkers to Prevent Epilepsy, Predict Progression, and Response to Treatment

Discussants:

- Biomarkers of Epileptogenesis – Denes Agoston, MD, PhD, Uniformed Services University
- EEG as a Biomarker – Martina Bebin, MD, MPH, University of Alabama, Birmingham
- Multimodal Imaging as a Biomarker – Brandon Westover, MD, PhD, Massachusetts General Hospital
- Biomarkers for those at risk for SUDEP and epilepsy related mortality – Sam Lhatoo, MD, University of Texas Health Science Center Houston
- Need for biomarkers – David Henshall, PhD
- Patient Advocate Perspective – Steve Roberds, PhD

11:50 AM – 12:50 PM Breakout Groups

12:50 – 1:30 PM Report Out from Breakout Groups and Discussion

1:30 – 2:00 PM Break

2:00 – 5:00 PM **Session V: Harnessing Big Data to Drive Epilepsy Research and Clinical Care**
Moderator: Brian Litt, MD, PhD, University of Pennsylvania

2:00 – 2:05 PM Why Epilepsy Research Matters: A Personal Story – Megan O'Boyle, Phelan McDermid Syndrome Foundation

2:05 – 2:20 PM The Promise of Big Data in the Epilepsies – William Stacey, MD, PhD, University of Michigan

2:20 – 3:20 PM Panel: How do we collect, harmonize, share, and use big data to improve clinical care?

Discussants:

- Learning Health Systems – Jeffrey Buchhalter, MD, Phoenix, AZ
- ENIGMA – Carrie McDonald, PhD, University of California, San Diego
- AI and Machine Learning – Hisham Daoud, PhD, University of Louisiana, Lafayette
- Transcriptomics – Avtar Roopra, PhD, University of Wisconsin, Madison
- Big Data – William Stacey, MD, PhD
- Patient Advocate Perspective – Megan O'Boyle

3:20 – 4:20 PM Breakout Groups

4:20 – 5:00 PM Report Out from Breakout Groups and Discussion

Day 3: January 6, 2021

10:30 AM – 12:30 PM **Session VI: Emerging Research Priorities in the Epilepsies**
Moderator: Lori Isom, PhD

10:30 – 10:35 AM Why Epilepsy Research Matters: A Personal Story – Gabi Conecker, Wishes for Elliott

10:35 – 10:45 AM Health Services Research and Access to Care – David Clarke, MD, Dell Medical School, University of Texas at Austin

10:45 – 10:55 AM New BRAIN Initiative Technologies to Study the Epilepsies – Ivan Soltesz, PhD, Stanford University

10:55 – 11:05 AM Epilepsy in the Elderly – Alice Lam, MD, Massachusetts General Hospital

11:05 – 11:15 AM Epigenetics – Anne Schaeffer, MD, PhD, Mt. Sinai

11:15 – 11:25 AM Metabolism – Manisha Patel, PhD, University of Colorado

11:25 – 11:35 AM Microbiome – Tore Eid, MD, PhD, Yale University School of Medicine

11:35 AM – 12:00 PM Break Out Groups by Topic Area

12:00 – 12:30 PM Report Out from Breakout Groups

12:30 – 2:00 PM **Session VII: Translating Research into Clinical Care**
Moderator: Brandy Fureman, PhD, Epilepsy Foundation

12:30 – 12:35 PM Why Epilepsy Research Matters: A Personal Story – Laura Lubbers, PhD, CURE Epilepsy

12:45 – 12:50 PM Overview – Brandy Fureman, PhD, Epilepsy Foundation

12:50 – 1:45 PM Panel: From Bench to Bedside – How do we accelerate the research?

Discussants:

- Dan Lowenstein, MD
- Al George, MD
- Amy Brooks-Kayal, MD
- Peter Crino, MD, PhD
- David Henshall, PhD
- Brian Litt, MD, PhD
- William Stacey, MD, PhD
- Lori Isom, PhD
- Laura Lubbers, PhD

1:45 – 2:00 PM What Comes Next? – Ann Poduri, MD, MPH and Eric Marsh, MD, PhD