The 2021 Epilepsy Research Benchmarks—Respecting Core Principles, Reflecting Evolving Community Priorities

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Through a process that began formally in 2000, scientists, healthcare providers, and patient advocates from across the country convened with representatives of governmental and private agencies, recognizing the complexity of the epilepsies, the magnitude of the human burden, and the need for dedicated research focused on epilepsy. The resultant Epilepsy Research Benchmarks represent overall goals and concrete research priorities developed by and for the epilepsy research community. The first 3 benchmark areas, published online by the National Institute of Neurological Disorders and Stroke (NINDS) in 2000, centered on understanding how epilepsy develops, finding ways to prevent seizures in those at risk for epilepsy, and optimizing treatment ("stop seizures without side effects").[1] Over the years, the Benchmarks have evolved, incorporating input formally through the American Epilepsy Society (AES) Benchmarks Stewards Committee. This committee, co-led by AES and NINDS representatives, reviews progress in the field at regular intervals and surveys the priorities of the community through a variety of mechanisms, including the NINDS Curing the Epilepsies conferences. The benchmarks have thus evolved to reflect research progress, continued unanswered questions, and newly recognized

priorities. Revised benchmarks emerged in 2007[1-3] and again in 2014,[4-8] extending the short- and long-term goals of the community and resulting in the current framework with 4 benchmark areas (see Table 1).

Between 2014 and the present, the Benchmarks Committee reviewed progress in each of the 4 benchmarks areas, noting remarkable discoveries across basic epilepsy research, highlighting the major gains in understanding the causes of epilepsy, but also noting many continued gaps in all areas.[9-13] We have experienced a cultural shift through which the voices of patients and advocates are not only acknowledged but included in the discussions of the AES, including with the Benchmarks Committee, through the work of Epilepsy Leadership Council members, whose working group and leadership provided input into the Benchmarks process (and whose commentary accompanies this one). To further invite community input into the Benchmarks, in 2020 the NINDS published a Request for Information and launched a crowdsourcing campaign using the ninds.ideascale.gov platform. What was different about the most recent process of revision to the Benchmarks is that we relied less heavily on in-person discussion and debate. The Benchmarks Committee and ELC members last met in person at

Table 1. The 2021 AES/NINDS Epilepsy Research Benchmarks.

Area I: Understand the causes of the epilepsies and their relationship to epilepsy-associated neurologic, psychiatric, and somatic conditions	(A) Identify the many genes and molecular pathways associated with the epilepsies and epilepsy-related conditions. Define the many trajectories to hypersynchrony and demonstrate how these trajectories are modified by genetic background
	(B) Identify and understand the mechanisms by which infections, inflammation, environment, vascular changes, perinatal exposures or insults, trauma, and other causes and risk factors, alone and in combination, contribute to the development of the epilepsies and epilepsy-related conditions
	(C) Determine how alterations in molecular and cellular function interact with alterations in circuit and network function in the pathogenesis of cortical hyperexcitability and the clinical epilepsies
	(D) Identify and understand the mechanisms by which factors related to age, sex, race/ethnicity, socioeconomic status, and other demographic features modulate epilepsy risk, drawing from discoveries in basic, translational, clinical, and population-level investigation
	(E) Define the various mechanisms that explain why seizures commonly present with neuropsychiatric and neurodevelopmental comorbidities, drawing from discoveries in basic, translational, clinical, and population-level investigation
Area II: Prevent epilepsy and its progression	(A) Understand epileptogenic processes involved in epilepsies with neurodevelopmental origins, including those due to genetic or epigenetic causes
	(B) Understand epileptogenic processes involved in the development of epilepsy following traumatic brain injury, stroke, brain tumor, infections, neurodegeneration, or other insults to the brain
	(C) Identify biomarkers that will aid in identifying, predicting, and monitoring epileptogenesis and disease progression, including markers early after injury/insult that identify those people at risk for epilepsy
	(D) Develop or refine models aligned with the etiologies of human epilepsies to enable improved understanding of epileptogenesis and rigorous preclinical therapy development for epilepsy prevention or disease modification
	(E) Identify new targets and develop interventions to prevent or modify epileptogenesis and the progression of epilepsy and epilepsy-related conditions
	(F) Combine complex systems and/or machine learning approaches with laboratory studies in order to identify convergent phenotypes or pathways, examine background genetic or epigenetic effects, or consider novel molecular reclassifications of disease and the epileptogenic process
Area III: Improve treatment options for controlling seizures and epilepsy-related conditions while limiting side effects	(A) In order to identify new anti-seizure or disease-modifying therapeutic targets and mechanism-based therapies, we need to (1) understand the mechanisms of initiation, propagation, and termination of seizures at the cellular and network level for different seizure types, including status epilepticus, and in different forms of epilepsy; (2) understand the neural circuits, cell types, cellular interactions, and genetic factors that participate in interictal activity, different seizure types in different forms of epilepsy; and (3) understand the cellular, molecular, and network and systems basis for treatment side effects
	(B) Identify genetic, molecular, imaging, immunological, and electrophysiological biomarkers; determine mechanisms of pharmacoresistance; and develop clinical informatics tools so that the most appropriate pharmacological, biological, surgical, or device therapy can be selected for an individual with a common or rare epilepsy. These efforts should take into consideration time, an individual's unique set of personal characteristics, including sex and life stage (eg, childhood, pregnancy, and elderly), and consider inclusion of non-seizure outcome measures reflecting other epilepsy-related risks
	(C) Develop, refine, fully characterize, and deploy epilepsy and seizure models (including in non-rodents) that align with the etiologies, clinical features, rhythmicities, treatment responses, and development of resistance of human epilepsies to improve understanding of epileptogenesis, ictogenesis, seizure initiation, seizure termination, disease progression, and therapeutic targets. Explore the utility of new technologies to model human epilepsies and screen for therapies in a high throughput fashion, including iPSCs and organoids
	(D) Identify, develop, and improve pharmacological, surgical, genetic, epigenetic, neuromodulatory, dietary interventions and devices to detect, predict, prevent, or terminate seizures and mitigate other epilepsy-related health risks while minimizing adverse effects
	(E) Develop, improve, implement, and validate strategies, protocols, and interventions for epilepsy self-management in the home or other nonmedical settings that allow ongoing assessment of treatment response, therapy adherence, and adverse effects of therapies

Table 1. Continued.

Area IV: Limit, treat, or prevent co-occurring conditions associated with epilepsy across the lifespan in general and special epilepsy populations	(A) Understand and limit the impact of epilepsy on non-seizure outcomes such as neurodevelopment, mental health, cognition, health-related quality of life, and other functions (B) Understand and limit the impact of anti-seizure treatments (medical, surgical, and other interventions) on non-seizure outcomes, such as neurodevelopment, mental health, cognition, health-related quality of life, and other functions (C) Understand mechanisms (psychiatric and neurological) involved in NES. Develop effective pediatric and adult treatments and assess outcomes in NES including psychopathology and quality of life (D) Identify causes, risk factors, and potential preventative strategies for SUDEP and other epilepsy-related mortality due to co-occurring conditions including depression, anxiety, and suicide in people with epilepsy (E) Identify the impact of epilepsy on women's health outcomes (fertility, pregnancy, bone health, hormones, mental health, QOL) and health of their offspring (fetal and neonatal development) (F) Understand the role of sleep and circadian rhythms in cognitive and psychiatric and other health-related outcomes. Identify and treat sleep as a target to improve non-seizure outcomes, such as neurodevelopment, mental health, cognition, health-related quality of life, and other functions

Abbreviations: AES, American Epilepsy Society; NES, non-epileptic seizures; NINDS, National Institute of Neurological Disorders and Stroke; SUDEP, sudden unexpected death in epilepsy.

the December 2019 AES annual meeting, and our discussions and deliberations have since relied on the technology of the digital age for virtual meetings and shared documents to continue this important conversation about research priorities in the epilepsies.

The 2021 Epilepsy Research Benchmarks are presented in detail in Table 1. We have maintained the structure of the 4 areas, modifying some areas where progress has been made, and emphasizing the need for continued and new research in several aspects: for Area I, to deepen our understanding of the many causes of the epilepsies and their comorbidities and their mechanisms; for Area II, to employ models, biomarkers, and novel methodologies to understand epileptogenesis with a goal of preventing seizures, acknowledging emerging newly discovered causes; for Area III, to develop new treatments and new modalities of treatment for the epilepsies and associated conditions; and for Area IV, to focus attention on epilepsy-related developmental and psychiatric comorbidities, risk of sudden death, and associated conditions (eg, non-epileptic seizures) for individuals across the lifespan and for populations historically not well studied, including women with epilepsy.

We recognized that there are many themes running through all 4 benchmarks areas. Collectively, we acknowledged the importance of affirming these core research priorities that continue to reflect basic, unanswered questions in the field. In addition, now 20+ years after the original framing of the benchmarks, we felt the need to outline specific areas in which transformative research could move the field forward. The 2021 Curing the Epilepsies conference launched a conversation around transformative research priorities that will likely shape the Benchmarks in years to come.

Review of Curing the Epilepsies Meeting

The NINDS convened the *Curing the Epilepsies: Setting Research Priorities* conference virtually via Zoom on January 4-6, 2021.

This conference, originally scheduled as an in-person conference in April 2020, was postponed due to the SARS-CoV-2 pandemic. The January 2021 Curing the Epilepsies conference was focused on considering priorities for future efforts, by bringing together stakeholders—including researchers, healthcare providers, individuals with epilepsy, families, and advocates—to identify gaps and opportunities in epilepsy research. Although significant progress has been made in epilepsy research in recent decades, the personal stories shared by advocates at this conference underscore the need to transform progress so that research advances reach individuals 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 all stakeholders.

Over the course of this 3-day conference, attendees 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. Sessions focused on these topics included panel discussions and breakout groups to allow participants to suggest and refine 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. Several recurring themes were discussed throughout the conference and will continue to be the topics of ongoing discussions:

1. Progress in the field will be accelerated by increased collaboration and breaking down of the 'silos' that

traditionally have separated researchers, healthcare providers, and advocacy groups.

2. Concerted efforts are needed to foster and support *large-scale* collaborations that will expedite the discovery of the mechanisms of disease, the development of new therapies, and the translation of these therapies to clinical care.

3. Enormous amounts of data are being collected on individuals with epilepsy, including in the course of routine healthcare delivery, that could be shared and utilized in large multimodal datasets that could be integrated with extant datasets. This would require infrastructure and resources for data sharing and the use of new analytic strategies to mine high-quality data in order to improve research and clinical care.

4. The epilepsy community would benefit from learning from successful models for research and clinical care that have been implemented for other diseases.

5. More specifically, there is a need to
   (a) understand the mechanisms that underlie the epilepsies in order to develop targeted and more precise therapies;
   (b) develop and validate an array of biomarkers for the epilepsies to identify those most at risk for developing epilepsy and SUDEP, measure progression of disease, and response to treatment;
   (c) improve preclinical models of epilepsies so that they better recapitulate the human condition;
   (d) expand epilepsy research and clinical care to underserved communities and diversify the workforce in both areas; and
   (e) create and utilize innovative new tools and measures, such as those being developed in the BRAIN Initiative[14] that expand the capabilities of basic and clinical research on the epilepsies.

Challenges and Barriers to Transformation in Epilepsy Research

The Curing the Epilepsies conference shifted from reviewing benchmarks to seeking transformation because the fundamental scientific understanding of human epilepsy and of single genes, circuit dysfunction, and emerging cellular and animal models that aim to reflect human epilepsy has critically advanced in the last 7 years. While these advances are real, during the Curing the Epilepsies conference there was much discussion through formal talks, informal discussion in the "chat" feature of the teleconference platform, and in the moderated breakout groups about impediments to further transformation in epilepsy research. From this discussion, it was clear that there are barriers to collaboration and sharing in science, which appear to be consequential in epilepsy research. While there are structural and cultural aspects of academia and industry that encourage a "go-it-alone" spirit, there are examples of effective collaboration, most recently with rapid and effective convergence of science in the face of the SARS-CoV-2 pandemic, but more

consistently within pediatric oncology clinical research. While a major barrier to sharing is an existing lack of shared databases, the crowdsourcing campaigns portion of the Curing the Epilepsies/Benchmark revision 2020 process did not generate widespread responses. There are many potential explanations for the relatively small number of responses to the IdeaScale campaign, but the absence of novel ideas that emerged through this platform suggests a need for the community to further embrace a culture of publicly sharing ideas in order to maximize data sharing and collaborative work.

The goal of the conference was to generate transformative scientific ideas, as the key core epilepsy research questions have been outlined in the updated Benchmarks. There was excellent discussion about how to advance the current questions, but there was a lack of transformative research ideas discussed. This may either reflect that recent advancements in epilepsy science are on the cusp of solving the fundamental problems in epilepsy or it may mean that researchers are in a collective "idea valley." The current nature and pace of epilepsy research requires acceleration in technologies to truly understand the complexities of the brain. With the BRAIN Initiative and novel techniques and tools emerging, the field could quickly move forward in bigger steps, instead of the modest increments with which we currently advance. Another reason for lack of discussion of specific transformative ideas could be that academic and personal incentives are primarily centered around individual success reducing the motivation to publicly discuss transformative ideas. A final reason could be that we need more fresh ideas, new minds, to ask new questions, speaking to the need to engage and encourage young scientists and new researchers in epilepsy research.

Some potential solutions to these impediments that were discussed included formal mechanisms to advance sharing and collaboration, such as a greater use of "center-without-walls" and other team science models, harnessing the potential of the many available National Institutes of Health (NIH) grant mechanisms and resources, not just those geared to epilepsy, and partnering with non-NIH funding agencies. Finally, the need to reach out to leaders at academic institutions to rethink and change the incentives for success in our field was oft repeated throughout the conference.

What Will Benchmarks Process Look Like in the Future?

The 2021 Curing the Epilepsies conference sought to drive a more forward-looking approach to epilepsy research. We emerged from this conference with momentum building about ways to ask big questions, to build more multisite collaborations, to engage scientifically with people that we have not previously met, and to share large datasets. To keep this momentum going forward, we envision a more active role for the Benchmark Stewards Committee, including working with the NINDS to extend and deepen the conversations on specific topics and areas from the 2021 conference through workshops or other platforms. These discussions could reach an even broader audience

through presentations at annual AES meetings. Future Curing the Epilepsies conferences and revisiting of the Benchmarks should occur more frequently than every 7-8 years to keep pressure on the research community to drive transformative research and to adapt priorities to evolving times. Learning from the 2021 Curing the Epilepsies Conference, future conferences can implement some aspects of the virtual meeting format, such as random assignment of participants in discussion breakout groups and allowing people to participate remotely, that pushed some of the discussion in new directions and allowed broad participation, including from junior investigators, patient advocates, and others who might not always be able to travel to in-person meetings. An achievable goal for the next conference is to have inclusive representation at all discussion groups from trainees to senior investigators and from basic and clinical researchers to clinicians and patient advocates.

The revised 2021 benchmarks will serve an important need to continue to foster a breadth of research on the epilepsies across all 4 benchmark areas, including identifying causes and risk factors, understanding mechanisms of epileptogenesis, identifying biomarkers and new targeted treatments, with overall goals of improved understanding of the causes and consequences of the epilepsies, and limiting the presence and consequences of seizures, comorbidities, and treatment side effects. With a focus not only on what the epilepsy research community has achieved but also on what we as a community aspire and challenge ourselves to achieve, we hope that the 2021 Curing the Epilepsies conference inspires a new era of epilepsy research. Future Curing the Epilepsies conferences should be able to review major advancements, not just incremental ones, and generate even greater transformative research goals in an accelerated pace toward new treatments and cures that will impact every person with epilepsy.

Declaration of Conflicting Interests

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