



# The Benchmarks: Progress and Emerging Priorities in Epilepsy Research

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This issue of *Epilepsy Currents* includes 4 reviews reflecting progress in epilepsy research in the 4 benchmarks areas (“Benchmarks”) of the National Institute of Neurological Disorders and Stroke (NINDS)/American Epilepsy Society (AES) Benchmarks Stewards Committee. Here, we provide historical context for the formal organization of research priorities related to epilepsy. We review the benchmark areas and the processes through which the Benchmarks will continue to evolve to reflect scientific advances and community research priorities over time.

## Origins of the Current Benchmarks

The NINDS at the National Institute of Health (NIH) sponsored the first Curing Epilepsy conference in 2000 in partnership with nongovernmental organizations and other Federal agencies following an executive order from President Clinton. The goal was to shift the focus of epilepsy research from treating seizures to finding cures—in other words, to better understand the cause(s) of epilepsy to inform the development of more effective treatments. At that time, there were many anti-seizure medications on the market, but many had significant side effects and were, and continue to be, ineffective for approximately one-third of individuals with epilepsy. The NINDS then sponsored a conference in 2007 called Curing the Epilepsies (in recognition of the fact that there are many different types and causes of epilepsy) to assess the state of epilepsy research, identify research priorities shared by the research community, and collectively propose new directions. Participants in the first conference in March 2000 were eager to identify a way to evaluate progress resulting from this historic event, and a session was added to the conference in 2007 to “benchmark” the outcomes. The NINDS subsequently worked with more than a dozen Epilepsy Research Stewards—established leaders in the field of epilepsy research—to define a series of goals for the field that could serve as a research agenda.<sup>1</sup> The NINDS and the Stewards developed a series of Epilepsy Research Benchmarks based on the 3 major topic areas of the 2000 Conference: (1) interrupting and monitoring epileptogenesis, (2) genetic

strategies, and (3) developing new therapies. The Benchmarks were subsequently revised and updated in 2014<sup>2,6-9</sup> following the Curing the Epilepsies Conference in 2013, with a new area focused on epilepsy-related comorbidities across the lifespan.

The Benchmarks have been used to guide research priorities at NIH, as well as at nonprofit organizations that support epilepsy research. Substantial progress has been made since the conference in 2000 with a major shift in the focus of research and the development of new treatments to identifying the causes of epilepsy and development of targeted treatments. Major NINDS initiatives in these above research areas include large-scale studies such as the Epilepsy Phenome/Genome Project and Epi4K and Center Without Walls mechanisms focused on sudden unexplained death in epilepsy (SUDEP) and on epilepsy-related variant assessment.<sup>3-5</sup>

## Current Benchmarks Areas

The reviews in this issue provide summaries of progress in epilepsy research in each of the benchmark areas since the last such series of reviews in 2016.<sup>6-9</sup>

Epilepsy Benchmarks Area I, Understanding the Causes of the Epilepsies and Epilepsy-Related Neurologic, Psychiatric and Somatic Conditions, has seen major advances in the discovery of genetic epilepsies and autoimmune epilepsies, with new discoveries as well as the development of animal models of these causes. Emerging studies have begun to dissect the causes of epilepsy-related comorbidities.

The review on Epilepsy Benchmarks Area II, Prevent Epilepsy and Its Progression, presents developments in understanding several factors that influence epileptogenesis. There is exciting emerging progress in this area, for example, in conditions that can be defined genetically early in their course *before the onset of epilepsy* (eg, some cases of tuberous sclerosis complex), providing an opportunity for intervention. In parallel, emerging treatment strategies from drug repurposing to gene therapy are also considered. There is clearly substantial additional research required to better understand who is at risk for epilepsy due to various causes of epilepsy, including



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acquired epilepsy, and when and how best to intervene to limit or prevent epilepsy.

Epilepsy Benchmarks Area III, Improved Treatment Options for Controlling Seizures and Epilepsy-related Conditions without Side Effects, addresses a fundamental question raised at the inception of the Benchmarks: How can treatment be made more precise in mechanism and delivery such that effective treatment can be achieved without side effects? As progress in this area moves forward, with more causes detected and specific treatments contemplated, we will need to address critical features required for clinical trial design, both regarding seizure detection and monitoring for effects on comorbid conditions.

The review of research progress in Epilepsy Benchmarks Area IV, Limit or Prevent Adverse Consequence of Seizures and Their Treatment Across the Lifespan, focuses on better characterizing the seizure- and non-seizure-related effects on the lives of individuals with epilepsy. New attention has been afforded in this past cycle of review to nonepileptic seizures and to seizure-related mortality (SUDEP), reflecting more attention to seizure- and non-seizure-related effects on quality of life for people with epilepsy.


As may be evident, there are several themes that run through all of the areas: causes of epilepsies as a springboard for studies of basic underlying epilepsy mechanisms and treatment development (preclinical studies and clinical trials) for both seizure- and non-seizure-related symptoms in individuals with epilepsy. We have emphasized these areas of progress while drawing attention to continued gaps in the knowledge needed to drive the field forward.

New in the 2020 reviews are vignettes introducing each area, representing the voices of people with epilepsy or their family members. These vignettes represent a new partnership with the Epilepsy Leadership Council (ELC), representing epilepsy advocacy, professional, and governmental organizations working together. Epilepsy Leadership Council members have provided valuable feedback on the reviews in addition to providing the poignant, real-world vignettes to set the stage for each area's content, speaking to the very essence of why epilepsy research is needed. Knowing what we have learned thus far, how can we not ask why an individual has epilepsy? How can we not try to prevent sequelae of on-going epilepsy? As a field, how can we accept the status quo that essentially one-third of individuals with epilepsy still have seizures that are not controlled with available medications and that the ones who do are often forced to accept side effects? Research into each of the benchmarks areas seeks to inform clinical diagnosis and treatment of people with epilepsy. The involvement of the ELC in our discussions highlights the reason for epilepsy research—whether basic, clinical, or translational—to improve the lives of individuals with epilepsy.

## New Benchmarks for 2020 and Beyond

Despite continued progress in epilepsy research, many people throughout the world have epilepsy due to infection. Although the causes are often known (eg, cerebral malaria), strategies to


effectively predict, prevent, and treat both the primary infections and the potential ensuing epilepsies are still in development. The compilation of this issue's reviews provides an opportunity to evaluate our progress as a community and to reflect on priorities for the past versus the future. New research priorities and nuances to existing research priorities will be identified and refined through discussion at and following the 2020 NINDS Curing the Epilepsies Conference. We look forward to continuing the NINDS/AES partnership, including input from members of the ELC, with a diversity of Area Leads and Stewards and community members. We will have the opportunity to refine the research priorities in epilepsy together so that the most compelling and pressing hypotheses can be rigorously pursued, the most important questions answered, and the results ultimately translated back to individuals with epilepsy. The Benchmarks can and will adapt to advances in knowledge and to a changing research landscape that seeks to respond to the community's priorities and the needs of individuals with epilepsy who need more effective treatments.

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### Authors' Note

A.P. serves on the Scientific Advisory Board of Tevard and has a spouse/partner who receives a salary from Sanofi Genzyme.

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