2014 NINDS Benchmarks for Epilepsy Research

On April 17-19, 2013, NINDS hosted Curing the Epilepsies 2013: Pathways Forward, the third in a series of *Curing the Epilepsies* conferences held in partnership with epilepsy advocacy and professional organizations to assess progress in epilepsy research and help set an agenda for future years. As an important outcome, these conferences have led to the development of *Benchmarks for Epilepsy Research*, which reflect priorities for research toward clinically meaningful advances in understanding and treating the epilepsies. Following this tradition, and with input received during and prior to the April 2013 conference, NINDS has developed 2014 Benchmarks for Epilepsy Research as a framework for focusing research and benchmarking progress over the next five to ten years. Responsibility for achieving goals highlighted by the Benchmarks is shared by all members of the broad epilepsy community. For example, NINDS looks to them to inform plans for research investments; investigators may pursue questions aligned with the Benchmarks; and other governmental and nongovernmental organizations may also identify opportunities to contribute. Since their initial development in 2000, the Benchmarks have helped to galvanize the research community around important goals, such as preventing epileptogenesis, addressing aspects of epilepsy beyond seizures, and confronting the challenge of SUDEP – all of which are now vibrant areas of investigation. NINDS looks forward to working with the community to achieve further success in the coming years.

Preamble

The 2014 Benchmarks for Epilepsy Research are organized into key research goals in four areas in which significant progress should be likely over the next five to ten years. While advances may arise from many different research directions and may not be predictable, these broad goals are intended to serve as a shared framework for focusing the community's efforts and benchmarking important advances in the field as they are achieved.

Several themes emerged during discussions to develop the 2014 Benchmarks. First, the epilepsies are a spectrum of rare and more common disorders that vary in cause and disease course, and this heterogeneity represents both opportunities and challenges for epilepsy research. Distinct forms of epilepsy may ultimately require unique approaches to treatment and prevention. It is also possible, however, that individual epilepsy syndromes with known causes or other well-defined features will serve as gateways for understanding mechanisms with broader relevance to other epilepsies. Either way, the broad range of both causes and clinical features associated with the epilepsies suggests that knowledge and expertise in medical disciplines outside the traditional boundaries of neurology, such as psychiatry, immunology, cancer biology, cardiology, and others, will be critical. As a second theme, there is growing appreciation of a spectrum of conditions beyond seizures that reduce quality of life for people with epilepsy, including cognitive impairment, neurodevelopmental, and intellectual disabilities; psychiatric and behavioral disorders; stigma and other psychosocial issues; and effects on sleep, bones, and endocrine, reproductive, and other body systems. These conditions, often called comorbidities of epilepsy, have complex relationships with the underlying causes of epilepsy, ongoing seizures and other pathological network activity, and the effects of seizure treatments. To better reflect this complexity, the 2014 Benchmarks refer instead to epilepsy-related conditions and consequences, within a revised organization that encourages the integration of these topics into research on the epilepsies as a whole. In addition, the 2014 Benchmarks also reflect recognition of a range of factors specific to certain populations that should be considered in understanding the development and treatment of epilepsy and related conditions and consequences, including issues relevant to children, women, the elderly, and other groups.

Across all areas of the Benchmarks, progress will depend on continued advances in research tools and methods and their application to epilepsy research, particularly as new and emerging research technologies provide unprecedented capabilities in brain imaging, electrophysiology, and genomics and other systems biology approaches. Like other biomedical fields, epilepsy research is accumulating vast amounts of data, and opportunities for capturing clinical data at the point of care are also increasing. Embracing a culture of data sharing, collaboration, and integration across scales and approaches may best enable the epilepsy community to capitalize on these resources. Efforts to develop, validate, and disseminate novel approaches to analyzing large datasets, including genomic data and high-density brain activity monitoring, will also be essential. In addition, although many useful animal models exist for epilepsy research, important opportunities exist for further development of model systems that more closely reflect the etiologies and

clinical features of human epilepsies. Translational experiments in preclinical models that are rigorously designed and conducted, and transparently reported to the community, will help to accelerate the pace of therapy development. Independent replication to determine the robustness of preclinical findings is likely to aid the successful translation of interventions to prevent epileptogenesis, modify disease, control seizures, or address epilepsy-related conditions and consequences beyond seizures.

As a final note, while the scope of the Benchmarks broadly encompasses many areas of biomedical research on the epilepsies, NINDS recognizes that important advances may also come from areas not explicitly highlighted. Moreover, focusing on the Benchmarks and biomedical research alone will not be sufficient to ensure better outcomes and improved quality of life for people with epilepsy. A report from the Institute of Medicine recently established recommendations and priorities that address public health aspects of the epilepsies beyond biomedical research, including issues related to surveillance and population research, measures for and access to high-quality care, patient and health care provider education, and public awareness. Together, the Benchmarks and the IOM report serve as complementary guides for the efforts of diverse stakeholders.

2014 NINDS Benchmarks for Epilepsy Research

I. Understand the causes of the epilepsies and epilepsy-related neurologic, psychiatric, and somatic conditions.
   A.   Identify new genes and pathways associated with the epilepsies and epilepsy-related conditions.
   B.   Identify new infectious, immune, age-related, environmental, or other causes and risk factors associated with the epilepsies and epilepsy-related conditions.
   C.   Determine whether factors related to age, gender, race/ethnicity, socioeconomic status, and other features of specific populations affect risk and mechanisms of epilepsy and epilepsy-related conditions.
   D.   Determine whether the bi-directional relationships that exist between the epilepsies and several co-occurring conditions (e.g., neuropsychiatric or neurodevelopmental disorders) result from the same underlying causal mechanisms, interacting mechanisms, or are a consequence of the first presenting condition.

II. Prevent epilepsy and its progression.
   A.   Understand epileptogenic processes involved in epilepsies with neurodevelopmental origins, including those due to genetic or presumed genetic 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.

III. Improve treatment options for controlling seizures and epilepsy-related conditions without side effects.
   A.   Understand the initiation, propagation, and termination of seizures at the network level in different forms of epilepsy.
   B.   Identify biomarkers for assessing or predicting treatment response, including markers that may identify specific populations that are likely to have good outcomes or develop adverse responses.
   C.   Develop or refine models that are aligned with etiologies and clinical features of human epilepsies, especially treatment resistant forms, to enable improved understanding of ictogenesis and preclinical development to improve seizure control with fewer side effects. Establish the sensitivity and specificity of these models with regard to current therapies.
   D.   Identify, develop, and improve interventions to detect, predict, prevent, or terminate seizures, including approaches suitable for use in the home and other non-medical settings.

    E.   Identify, develop, and improve anti-seizure therapies that target (either alone, or in combination) novel or multiple seizure mechanisms.

    F.   Develop, improve, and implement interventions for effective self-management, including treatment adherence.

    G.   Develop and validate objective patient-centered outcome metrics for clinical studies.

IV. Limit or prevent adverse consequences of seizures and their treatment across the lifespan.

    A.   Understand and limit adverse impacts of seizures on quality of life, including effects on neurodevelopment, mental health, intellectual abilities, and other neurological and non-neurological functions.

    B.   Understand and limit adverse impacts of anti-seizure treatments (medical, surgical, or other interventions) on quality of life, including effects on neurodevelopment, mental health, intellectual abilities, and other neurological and non-neurological functions.

    C.   Understand risk factors and mechanisms involved in non-epileptic seizures (NES). Develop effective approaches for earlier and accurate diagnosis and treatment.

    D.   Identify causes, risk factors, and potential preventive strategies for sudden unexpected death in epilepsy (SUDEP) and other epilepsy-related mortality (for example, suicide) in people with epilepsy.

    E.   Identify the impact of pharmacological treatment of the epilepsies on fetal and neonatal development. Develop strategies to control seizures in pregnancy without causing harm to either the mother or child.