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# The NINDS Epilepsy Research Benchmarks

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## HISTORY

The field of epilepsy research has undergone a dramatic transformation in the past decade. However, substantial gaps exist in our understanding of epilepsy, from its causes and prevention to its clinical impact and treatment. In March 2000, prominent epilepsy research scientists, health care providers, and leaders of epilepsy organizations came together for a seminal conference to discuss what it would take to reach a cure for epilepsy, defined as the prevention of epilepsy in people at risk, and by effective and safe therapy ("no seizures, no side effects") for those with the disorder. Cosponsored by the National Institute of Neurological Disorders and Stroke (NINDS), the American Epilepsy Society, Citizens United for Research in Epilepsy, the Epilepsy Foundation, and the National Association of Epilepsy Centers, this White House–initiated conference highlighted advances in neuroscience, imaging, genetics, and clinical research related to mechanisms of epileptogenesis, and emphasized the vital need for further research that would lead to new treatments and cures.

Participants were eager to identify a way to evaluate progress resulting from this historic event, and a session was added to the conference 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. The NINDS and the Stewards developed a series of Epilepsy Research Benchmarks based on the three major topic areas of the 2000 Conference: (1) interrupting and monitoring epileptogenesis; (2) genetic strategies; and (3) developing new therapies. The first of these Benchmarks entailed goals that would hasten progress toward understanding the fundamental causes of epilepsy at the anatomic, physiologic, and genetic/molecular levels; and defining markers of epileptogenicity. This Benchmark also encouraged the validation and use of improved animal models for therapeutics testing. The second

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NINDS 2007 Epilepsy Benchmark Stewards: Matthew Anderson, M.D., Ph.D., John J. Barry, M.D., Jocelyn F. Bautista, M.D., Anne Berg, Ph.D. (cochair, Area III), Edward Bertram, M.D., Ph.D., Amy Brooks-Kayal, M.D. (cochair, Area III), Ray Dingledine, Ph.D. (cochair, Area I), Jerome Engel, Jr., M.D., Ph.D. (cochair, Area I), Tracy A. Glauser, M.D., Bruce P. Hermann, Ph.D., Ruben Kuzniecky, M.D.,W. Curt LaFrance, Jr., M.D., Brian Litt, M.D., Solomon Moshé, M.D., Susan Spencer, M.D. (cochair, Area II), Carl Stafstrom, M.D., Ph.D., John W. Swann, Ph.D., William Theodore, M.D., H. Steve White, Ph.D., and Karen Wilcox, Ph.D.

Benchmark focused on prevention through the use of epileptogenicity markers to identify tissue targets for preventive therapies, and the completion of large clinical trials of neuroprotective or antiepileptogenic compounds in high-risk individuals. The third Benchmark highlighted the development of improved therapies. Markers of epileptogenicity were again emphasized, in this case for the efficacy testing of therapeutics. Other factors were recognized as important for improved personalization of therapies, including an individual's developmental stage, hormonal status, and genetic profile. Multiple treatment strategies were encouraged, including the continued refinement of bio-sensors and seizure suppression systems, new approaches for epilepsy surgery, and novel therapies such as cell transplants or vaccines. This Benchmark also called for the achievement of a complete cure for a form of genetic epilepsy through appropriate translation through preclinical research studies. A complete list of the original Epilepsy Research Benchmarks is available at: http://www.ninds.nih.gov/funding/research/epilepsy-web/epilepsybenchmarks.htm. Over the subsequent 5 years, the research community made substantial progress on these Benchmarks, including but not limited to advances such as:

- Improvements in neurotransmitter imaging through the development of magnetized nanoparticles.
- The development of a collaborative project to understand changes in gene expression associated with epileptogenesis in different animal models.
- The establishment of a database that enables researchers to search nonproprietary structural and biologic data on anticonvulsant drugs.
- The initiation of clinical trials designed to prevent the development of epilepsy after brain injury.
- An improved understanding of both age and hormonal influences on the underlying cellular mechanisms of epilepsy.
- New discoveries related to epilepsy pharmacogenetics/pharmacogenomics.
- Progress in seizure detection and brain stimulation to control epilepsy, as well as other surgical approaches to treatment.
- The development of the Epilepsy Phenome/Genome Project to facilitate the discovery of genes responsible for more common forms of epilepsy.

These and other advances associated with the original Benchmarks—as well as roadblocks to progress in some Benchmark areas—are detailed in a series of reports available at: http://www.ninds.nih.gov/funding/research/epilepsyweb/epilepsybenchmarks.htm.

As these reports illustrate, research goals are never static, and the evolving needs of the research community, along with the increasing recognition that the comorbidities of epilepsy present a significant challenge to the goal of "no seizures, no side effects," strongly indicated that a reassessment of the Benchmarks was warranted.

In March 2007, this reassessment took place, with more than 400 researchers, physicians, patients, family members, and epilepsy organization leaders convening on the National Institutes of Health campus to participate in the "Curing Epilepsy 2007: Translating Discoveries into Therapies" Conference. Organized by the NINDS in collaboration with epilepsy research and voluntary organizations, the meeting was a follow-up to the successful conference in 2000. Participants reviewed the original Epilepsy Research Benchmarks and prioritized topic areas felt to be most promising, as well as those in need of attention. The NINDS solicited public input on these changes to the Benchmarks, and the Epilepsy Benchmark Stewards gathered in October 2007 to discuss the input received and to finalize

the new set of goals, outlined below and available (along with the specific Stewards who contributed to each of these goals) at: http://www.ninds.nih.gov/funding/research/epilepsyweb/2007_benchmarks.htm.

## THE 2007 EPILEPSY RESEARCH BENCHMARKS

### Benchmarks Area I: Prevent epilepsy and its progression

**A.** Identify as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune, and infectious).

**B.** Identify underlying mechanisms of epileptogenesis.

Short-term* goals include:

1. Identify at least one susceptibility gene or other risk factor (e.g., viral, trauma, and autoimmune) and identify how it predisposes to changes in network excitability.
2. Identify at least one epileptogenic mechanism that is reversible, or has influence at critical developmental times.
3. Identify at least one specific role for nonneural mechanisms (e.g., glia, immune cells, and angiogenesis) in epileptogenesis.
4. Identify at least one neuronal mechanism in microcircuits that contributes to epileptogenesis.

Longer-term** goals include:

5. Identify convergent pathways or mechanisms of epileptogenesis in multiple models and human epilepsy syndromes.
6. Identify the underlying cellular and molecular properties that are associated with electrophysiologic and functional abnormalities.
7. Identify homeostatic mechanisms that prevent spread of microsynchrony.

**C.** Identify biomarkers for epileptogenesis.

Short-term goals include:

1. Identify and validate one biomarker to predict progressive or intractable epilepsy in new-onset patients.
2. Identify and validate one biomarker [e.g., imaging, electroencephalographic (EEG), or blood test] to predict development of epilepsy in at-risk individuals (human or animal).

**D.** Identify approaches to prevent epilepsy or its progression.

Short-term goals include:

1. Identify at least one homeostatic mechanism that protects against the development of epilepsy or its progression.

Longer-term goals include:

2. Identify interventions that prevent, interrupt or reverse the epileptogenic process.

*Short-term goals are expected to be achievable in less than 5 years.
**Longer-term goals are expected to be achievable in approximately 5–10 years.

**E.** Develop new animal models to study epileptogenesis.

Short-term goals include:

1. Develop at least one new animal model of the development and progression of epilepsy.
2. Develop at least one new animal model of the epileptic encephalopathies of infancy and childhood.
3. Develop at least one new animal model that recapitulates the unique aspects of epileptogenesis in the aging brain.

**F.** Test the efficacy of prevention strategies.

Short-term goals include:

1. Test the efficacy of prevention strategies identified previously in animal models and in human clinical trials.

## Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

(*For this Benchmarks Area, the Stewards indicated that all goals should be considered as "Short-term."*)

**A.** Identify basic mechanisms of ictogenesis (seizure generation) that will lead to the development of cures.

1. Define underlying mechanisms of initiation, propagation, and cessation of seizures in the epileptic brain as targets for treatment (electrical, biochemical, cellular, molecular, and physiologic).
2. Define the functional networks in the brain that are responsible for seizure generation in clinical epilepsy using biosensors, imaging, and other methods.

**B.** Develop tools that facilitate the identification and validation of a cure.

1. Develop and validate biomarkers and surrogate markers to localize the epileptogenic networks and aid in the discovery and testing of new antiepileptic therapies.
2. Identify new molecular targets for pharmacotherapy development.
3. Develop valid screening strategies and biomarkers and surrogate markers (e.g., genetic, pharmacogenomic, electrophysiologic, imaging, and biochemical) to identify patients who are likely to respond to, or develop adverse effects from specific therapies.

**C.** Optimize existing therapies and develop new therapies and technologies for curing epilepsy.

1. Determine factors and approaches associated with best outcomes for surgical therapies.
2. Develop new approaches (e.g., gene therapy, brain stimulation, cellular therapy, and pharmacotherapy) for targeted therapies.
3. Develop higher-throughput cost-effective models for screening pharmacotherapies for specific types of epilepsy.

4. Initiate clinical trials of new, modified, and combination approaches to enhance cure rates.

## Benchmarks Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment

(*For this Benchmarks Area, the Stewards indicated that the goals highlighted in bold are priorities of the group*.)

**A.** Identify and characterize the full range and age specificity of comorbidities in people with epilepsy.

Short-term goals include:

1. Determine the types, frequency, and severity of various comorbidities in the general population of people with epilepsy.
2. Identify at least one new susceptibility factor each for cognitive, neuropsychiatric, and other medical comorbidities in people with epilepsy.

Longer-term goals include:

3. **Delineate the natural history of comorbidities in epilepsy, including the nature of the relationship between specific comorbidities and the underlying causes of epilepsy, specific features of epilepsy (e.g., age of onset, frequency of seizures, interictal epileptiform abnormalities), and treatment [e.g., antiepileptic drugs (AEDs), surgery].**

**B.** Identify predictors and underlying mechanisms that contribute to comorbidities.

Short-term goals include:

1. **Identify and utilize promising techniques and paradigms from other areas within the behavioral neurosciences [e.g., structural and functional neuroimaging, EEG, magnetoencephalography (MEG), genomics], and apply at least two of these approaches to the study of cognitive and behavioral comorbidities in epilepsy.**
2. Develop and validate at least one animal model of a comorbidity of epilepsy.
3. **Develop and implement a standardized protocol for screening pharmacologic and nonpharmacologic treatments of epilepsy for their amelioration or exacerbation of neuropsychiatric and cognitive comorbidities.**

Longer-term goals include:

4. **Determine contributions of epileptogenesis, seizures, interictal epileptiform events, and homeostatic protective processes to the development of comorbidities.**
5. Determine if the affective, attentional, and cognitive disorders in people with epilepsy are the same as those in people without epilepsy with respect to natural history, presentation, treatment, and underlying mechanisms.

**C.** Determine the optimal treatments for the neuropsychiatric and cognitive comorbidities in people with epilepsy.

Short-term goals include:

1. **Determine whether the treatments used for at least two of these conditions in isolation are effective when utilized in people with epilepsy or if these comorbidities require different strategies.**
2. Develop at least one efficacious care model for the diagnosis and treatment of epilepsy and validate that it improves the outcomes for patients with comorbidities.

Longer-term goals include:

3. Develop and validate novel treatments and management strategies for cognitive and neuropsychiatric disorders of people with epilepsy that are not adequately treated with currently available therapies.

**D.** Prevent or limit other adverse consequences occurring in people with epilepsy.

Short-term goals include:

1. Sudden unexplained (or unexpected) death in epilepsy (SUDEP).
    a. **Develop and validate at least one prevention strategy to decrease the occurrence of SUDEP.**
2. Sleep disturbances.
    a. Identify the range and frequency of sleep disorder subtypes associated with epilepsy.
    b. Identify the influence of sleep disorders on the incidence of seizures.
    c. Identify the influence of sleep disorders on at least one comorbidity of epilepsy.

Longer-term goals include:

3. SUDEP.
    a. **Identify the mechanisms responsible for SUDEP (including effects of seizures on autonomic functioning, particularly cardiac and respiratory).**
4. Identify optimal strategies to avoid systemic disorders associated with epilepsy and its treatment (e.g., osteopenia, endocrine disturbances, reproductive disorders, and teratogenicity).

**E.** Develop effective methods for diagnosis, treatment and prevention of nonepileptic seizures (NES).

Short-term goals include:

1. Determine the types and frequency of NES in the general population and in people with epilepsy.
2. Identify common susceptibility factors and etiologies for NES.
3. **Validate at least one effective treatment for NES.**

## THE FUTURE

These Epilepsy Research Benchmarks are designed to be a collaborative tool that assists researchers in identifying prominent gaps in the field, new areas to explore, and consensus priorities. They are practical goals for researchers to work toward, and are meant to be

achievable within the time frames indicated and to offer an opportunity to measure the successes in the field. An important feature of their development was the involvement of a number of junior investigators in the most recent group of Benchmark Stewards. This resulted in an integration of new ideas with the experience of the returning Stewards that will ensure a continuity of leadership in monitoring and updating the Benchmarks in the coming years. Another important feature of the 2007 Benchmarks is the addition of a new Benchmark area focused on the comorbidities of epilepsy—those associated with epilepsy itself as well as those resulting from treatment—which present a significant challenge for both individuals with epilepsy and the medical community. The NINDS looks forward to working with the epilepsy research community to facilitate the implementation of all of the research goals outlined in the Benchmarks, through investigator-initiated proposals as well as workshops and solicitations, as appropriate.

## ANNOUNCEMENTS

### Innsbruck Colloquium on Status Epilepticus 2009

The Innsbruck Colloquium on Status Epilepticus will take place April 2–4, 2009. The conference (chaired by S. Shorvon and E. Trinka) will focus on the following topics: bridging the gap from experimental models to clinical practice; infectious causes and inflammatory mechanisms in status epilepticus (SE); SE in the developing brain; and new treatment options. Registration opens September 1, 2008. For further information, contact the conference secretariat: PCO Tyrol Congress, Rennweg 3, A-6020 Innsbruck, Austria, e-mail: se2009@comeinnsbruck.at or visit the conference website: http://www.innsbruck-se2009.eu

### Epilepsy and Stigma: How Do We Conquer It in Africa?

This international conference on Epilepsy and Stigma in Africal will take place in Lusaka, Zambia on April 13–17, 2009. The conference is sponsored by the Epilepsy Association of Zambia working in conjunction with the Ministry of Health, the University of Zambia School of Medicine, the Middle Tennessee Chapter of the Society for Neuroscience (USA) and other co-operating partners. It will offer participants the opportunity to explore the neurological and psychosocial impact of epilepsy over the course of a lifetime, and will give individuals from many walks of life and opportunity to learn about the latest in epilepsy research and treatment. For details, please visit the website at http://www.epillepsyzambia2009.org or e-mail info@epilepsyzambia2009.org

### Antiepileptic Drug Trials X

April 15–19, 2009 in Coral Gables, FL, USA. http://www.aedtrials.com