NIH EPILEPSY BENCHMARKS
A Review

5/21/2021

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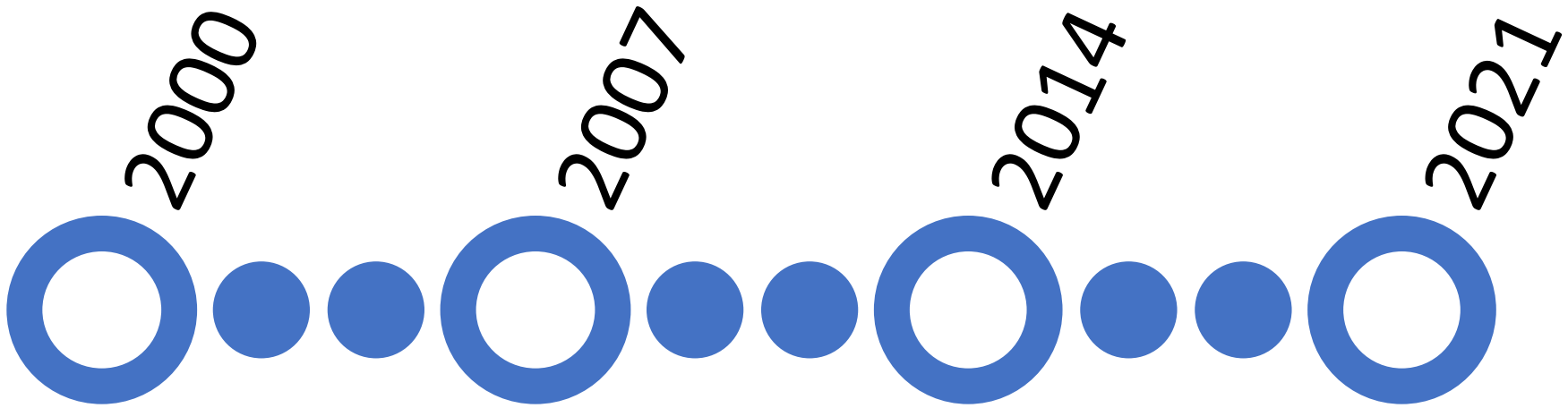
Evolution of the Benchmarks

- Purpose
- Dynamic process



EPILEPSY CURRENTS

Review

Epilepsy Benchmarks Area II: Prevent Epilepsy and Its Progression

Epilepsy Currents
2020, Vol. 20(1S) 14S-22S

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EPILEPSY CURRENTS

Review

Epilepsy Benchmarks Area III: Improved Treatment Options for Controlling Seizures and Epilepsy-Related Conditions Without Side Effects

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EPILEPSY CURRENTS

Review

Epilepsy Benchmarks Area I: Understanding the Causes of the Epilepsies and Epilepsy-Related Neurologic, Psychiatric, and Somatic Conditions

Epilepsy Currents
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Check for updates

EPILEPSY CURRENTS

Review

Epilepsy Benchmarks Area I: Understanding the Causes of the Epilepsies and Epilepsy-Related Neurologic, Psychiatric, and Somatic Conditions

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2014 Benchmarks

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.

2020-21 Benchmarks

Area I. Understand the causes of the epilepsies and their relationship to epilepsy-associated neurologic, psychiatric, and somatic conditions.

- A. Identify genes and pathways associated with all the epilepsies and epilepsy-related conditions, and determine how changes in genes, alone and in combination with other factors, contribute to the development of these conditions.
- B. Identify and understand the mechanisms by which infections, immune modulation, age, environment, vascular changes, perinatal factors, 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, gender, race/ethnicity, socioeconomic status, and other features of specific populations affect the risk of developing epilepsy and epilepsy-related conditions.
- E. Determine the relationship between the mechanisms that underlie the epilepsies and those that underlie commonly co-occurring epilepsy-related conditions (e.g., neuropsychiatric or neurodevelopmental disorders).

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.

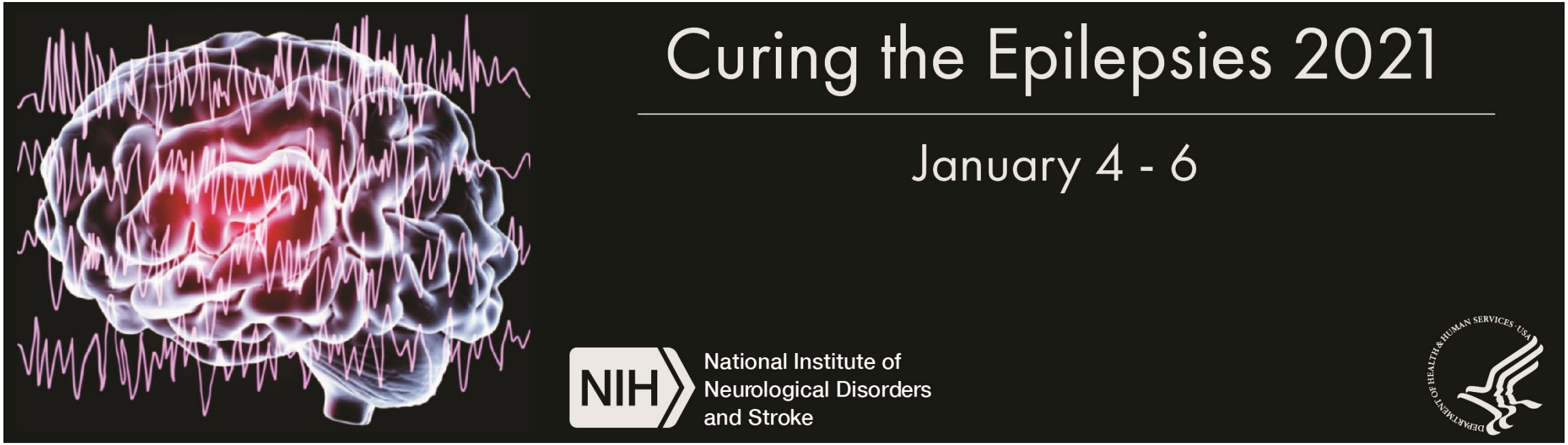
- A. In order to identify new antiseizure or disease-modifying therapeutic targets and mechanism-based therapies, we need to (1) understand the mechanisms of initiation, propagation, and termination of seizures at the cellular and network level for different seizure types, including status epilepticus, 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 and 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, mechanisms of pharmacoresistance, and 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 (e.g., childhood, pregnancy, 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 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 non-medical settings that allow ongoing assessment of treatment response, improve therapy adherence, and minimize adverse effects of therapies.

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 non-epileptic seizures (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 sudden unexpected death in epilepsy (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.

Benchmark changes 2014 to 2021

- Area I- Broadened the scope of our research into the genetic and other mechanisms of the epilepsies and epilepsy-associated conditions.
  - Not just identify new genes or causes but begin to look at gene-etiology interactions
  - Deeper understanding of the pathways and processes that are dysregulated by genetic or other etiology
- Area II- Added use of big data analysis to combine different lab and clinical data to better understand and find treatments for the epileptogenic process
- Area III-Added details and depth to what is needed to develop new treatments to control seizures and epilepsy related conditions including generating new outcome measures, wearables and various biomarkers
- Area IV-Extended research Non-epileptic Seizures and into the epilepsy-associated conditions into women's health and sleep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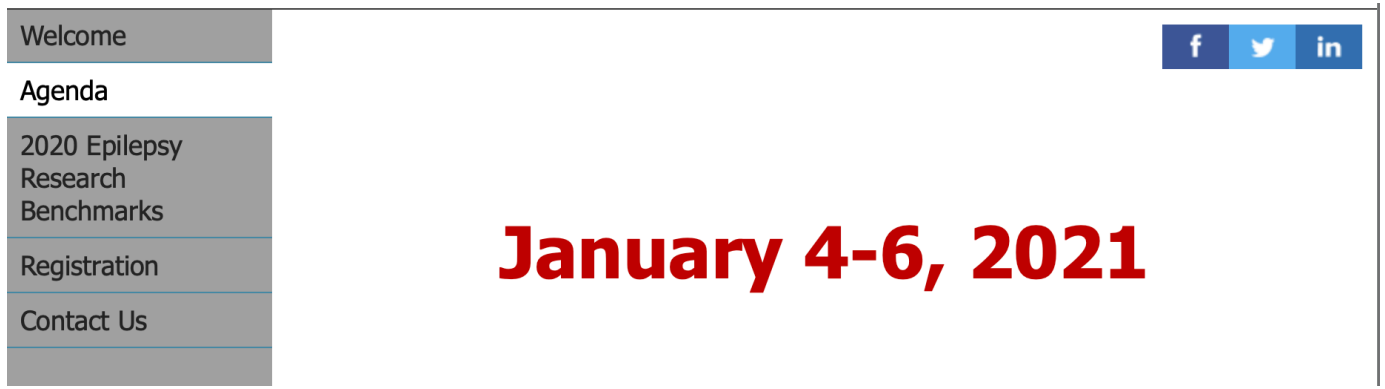

Session I: Introductions, Setting the Stage for Epilepsy Research Benchmarks and Transformative Research Priorities

Session II: Expediting Targeted Treatments for the Epilepsies

Session III: Modeling Human Epilepsies

Session IV: Biomarkers for Human Epilepsies

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

Session VI: Emerging Research Priorities in the Epilepsies

Session VII: Translating Research into Clinical Care

Transformative Research Ideas

- Big, fundamental questions
- Diversity of types of research

Challenges to Progress

- Culture of science
- Silos of research
- Insufficient connections between clinical and bench research (and bioinformatic research)

Strategies to move the field forward

- REMOVE SILOS → TEAM SCIENCE
  - SUPPORT AND INFRASTRUCTURE
- DATA SHARING → COLLABORATION
- NEW IDEAS → INNOVATION
- BASIC RESEARCH → CURES
- CLINICAL RESEARCH → NEW TOOLS

Strategies to move the field forward

- Culture change—promote partnerships
  - scientists, clinicians, clinician-scientists, advocacy partners, industry(?)
  - experts from other fields
- Research infrastructure—adapt to data sharing
- Training
  - Research focus on epilepsies & research mindset in clinical training
- Translation of research

Much of this is summarized and reported in an upcoming commentary in Epilepsy Currents entitled:**The 2021 Epilepsy Research Benchmarks—respecting core principles, reflecting evolving community priorities.**

There is also a companion piece from the ELC

Thank you

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