Epilepsy Research Benchmarks 2007-2012 Progress Summary Snapshot

This table provides a general summary of progress related to the 2007 Epilepsy Research Benchmarks, based on input from the Benchmarks Stewards in their 2007-2012 Progress Report and in annual research updates. This summary was developed to inform discussions about updating the Benchmarks, but it is not intended as an evaluation of the effectiveness or quality of research in current Benchmarks areas or an assessment of which areas should remain priorities. Areas with substantial progress may continue to represent important research needs, and understanding why progress has been limited in other areas may point to new challenges or changes in scientific direction to address in the future.

Benchmarks Area I - Prevent epilepsy and its progression.	**Stewards**	**Progress summary**
A. Identify as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune and infectious).	Lowenstein/Poduri	Substantial progress; new genetic links and other causes have been identified (also see B1)
B. Identify underlying mechanisms of epileptogenesis.		
1. Identify at least one susceptibility gene or other risk factor (e.g., viral, trauma, autoimmune) and identify how it predisposes to changes in network excitability.	Lowenstein/Poduri	Some progress; new genetic and autoimmune causes identified, but functional validation and understanding disease mechanisms are ongoing needs
2. Identify at least one epileptogenic mechanism that is reversible, or has influence at critical developmental times.	Stafstrom/Wong	Substantial progress; depolarizing GABA, insights into HIE-related neonatal seizures and epilepsy
3. Identify at least one specific role for non-neural mechanisms (e.g., glia, immune cells, angiogenesis) in epileptogenesis.	Anderson/Rotenberg	Substantial progress; advances related to astrocyte glutamate transport; also see metabolic processes
4. Identify at least one neuronal mechanism in microcircuits that contributes to epileptogenesis.	Anderson/Rotenberg	Substantial progress; advances in several areas (GABA/ inhibitory signaling, circuit maturation, mTOR pathway effects)
5. Identify convergent pathways or mechanisms of epileptogenesis in multiple models and human epilepsy syndromes.	Stafstrom/Wong	Substantial progress; candidate mechanisms include mTOR pathway disruption and inflammatory mechanisms such as IL-1β activation
6. Identify the underlying cellular and molecular properties that are associated with electrophysiological and functional abnormalities.	Dingledine/Roopra	Substantial progress; multiple signaling pathways identified related to inflammation, BBB breakdown, metabolic processes (also see B5)
7. Identify homeostatic mechanisms that prevent spread of microsynchrony.	Dingledine/Roopra	Substantial progress; some mechanisms identified that can be targeted to prevent microsynchrony or seizure activity, some of which may be “homeostatic”. Also see D1 below.
C. Identify biomarkers for epileptogenesis.		
1. Identify and validate one biomarker to predict progressive or intractable epilepsy in new-onset patients.	Dichter	Limited progress; clinical research to stratify intractable and treatment-responsive patients, but no predictive markers identified and notion of “progression” remains controversial
2. Identify and validate one biomarker (e.g., imaging, electroencephalographic (EEG), blood test) to predict development of epilepsy in at-risk individuals (human or animal).	Kuzniecky	Some progress; no single marker identified and validated, but candidates include specific EEG and MRI features; and growing area of research

D. Identify approaches to prevent epilepsy or its progression.		
1. Identify at least one homeostatic mechanism that protects against the development of epilepsy or its progression.	Engel/Staba	Some progress; potential mechanisms and targets identified in animal models of acquired epilepsy, with some demonstration of antiepileptogenic effects.
2. Identify interventions that prevent, interrupt or reverse the epileptogenic process.	Engel/Staba	Some progress; See D1.
E. Develop new animal models to study epileptogenesis.		
1. Develop at least one new animal model of the development and progression of epilepsy.	White	Substantial progress; viral encephalitis model, TSC model
2. Develop at least one new animal model of the epileptic encephalopathies of infancy and childhood.	Moshe/Galanopoulou	Substantial progress; new models for infantile spasms, early epileptic encephalopathy
3. Develop at least one new animal model that recapitulates the unique aspects of epileptogenesis in the aging brain.	White	Some progress; models relevant to particular epilepsy etiologies seen in the elderly have been developed (stroke, tumor, TBI, Alzheimer's), but not using aged animals
F. Test the efficacy of prevention strategies.		
1. Test the efficacy of prevention strategies identified above in animal models and in human clinical trials.	Bautista	Substantial progress; mTOR inhibitors, adenosine augmentation, and traditional AEDs have been tested in animal models (and in humans for AEDs) with mixed results

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Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy.	**Stewards**	**Progress summary**
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, physiological).	Wilcox	Substantial progress; new and improved methods for recording neural activity yielded new insights
2. Define the functional networks in the brain that are responsible for seizure generation in clinical epilepsy using biosensors, imaging and other methods.	Litt/Stacey	Substantial progress; new technologies for recording network activity at higher spatial and temporal resolution and algorithms for analysis
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.	Litt/Davis	Some progress; potential markers (HFOs, functional imaging, inflammatory, gene expression) identified but not validated
2. Identify new molecular targets for pharmacotherapy development.	Wilcox	Substantial progress; proteins (neuropeptide receptors), signaling pathways (e.g., mTOR, JAK/STAT pathways), and inflammatory pathways involved in epilepsy, but therapies targeting specific clinical etiologies remains need
3. Develop valid screening strategies and biomarkers and surrogate markers (e.g., genetic, pharmacogenomic, electrophysiologic, imaging, biochemical) to identify patients who are likely to respond to, or develop adverse effects from specific therapies.	Glauser	Some progress; pharmacogenetic marker identified (HLA markers) for adverse carbamazepine reaction), but less progress in other areas
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.	French/Carlson/Worrell	Some progress; improvements to diagnostic and pre-surgical evaluation approaches; barriers to progress remain (more focus needed on non-TLE, variability in classification and pre-surgical evaluation across centers, difficult to implement highly technical approaches)
2. Develop new approaches (e.g., gene therapy, brain stimulation, cellular therapy, pharmacotherapy) for targeted therapies.	Bertram	Some progress; advances in brain stimulation and in preclinical gene therapy and focal delivery research, but challenges remain for effective clinical application
3. Develop higher-throughput cost-effective models for screening pharmacotherapies for specific types of epilepsy.	White	Some progress; zebrafish model appears promising
4. Initiate clinical trials of new, modified, and combination approaches to enhance cure rates.	French	Some progress; but with limited positive results

Epilepsy Research Benchmarks 2007-2012 Progress Summary Snapshot

Benchmarks Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment.	**Stewards**	**Progress summary**
A. Identify and characterize the full range and age specificity of comorbidities in people with epilepsy.		
1. Determine the types, frequency and severity of various comorbidities in the general population of people with epilepsy.	Berg	Some progress; prevalence determined but less focus on severity
2. Identify at least one new susceptibility factor each for cognitive, neuropsychiatric, and other medical comorbidities in people with epilepsy.	Berg	Some progress; potential factors identified
3. Delineate the natural history of comorbidities in epilepsy including the nature of the relationship between specific co-morbidities 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).	Hermann/Berl	Some progress; work to understand comorbidity causes and relationship to seizures ongoing
B. Identify predictors and underlying mechanisms that contribute to comorbidities.		
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 co-morbidities in epilepsy.	Swann/Asato/Lin	Substantial progress; increasing application of structural and functional neuroimaging techniques to study cognitive, mood, and behavioral comorbidities in adults and children with epilepsy
2. Develop and validate at least one animal model of a co-morbidity of epilepsy.	Swann/ Brooks-Kayal	Substantial progress; several types of comorbidities in different rodent models of epilepsy
3. Develop and implement a standardized protocol for screening pharmacologic and non-pharmacologic treatments of epilepsy for their amelioration or exacerbation of neuropsychiatric and cognitive co-morbidities.	Swann	Some progress; some screening tools/methods developed, and research suggests basis for others
4. Determine contributions of epileptogenesis, seizures, interictal epileptiform events, and homeostatic protective processes to the development of comorbidities.	Swann/Benke/Huntsman	Some progress; animal model studies of specific features, some clinical research; protective processes not reported
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.	Swann/Drane	Some progress; growing focus of research to understand comorbidities, but limited comparison with people without epilepsy
C. Determine optimal treatments for neuropsychiatric and cognitive comorbidities in people with epilepsy.		
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.	Kanner	Some progress; limited controlled data, but consensus recommendations that treatments are applicable to PWE

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.	Kanner/Schafer	Some progress; self-management approaches show benefit
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.	Kanner/Langfitt	Some progress; focus has been on existing treatments and also self-management and behavioral interventions
D. Prevent or limit other adverse consequences occurring in people with epilepsy.		
1. Sudden unexplained (or unexpected) death in epilepsy (SUDEP).		
a. Develop and validate at least one prevention strategy to decrease the occurrence of SUDEP.	So/Lhatoo	Limited progress; prevention strategies under study, with insights from progress toward identifying patients at risk, risk factors, and SUDEP mechanisms
2. Sleep Disturbances		
a. Identify the range and frequency of sleep disorder subtypes associated with epilepsy.	So/Loddenkemper	Some progress; further characterization, particularly for obstructive sleep apnea syndrome (OSAS) and continuous positive airway pressure (CPAP) intervention
b. Identify the influence of sleep disorders on the incidence of seizures.	So/Loddenkemper	Some progress; seizure patterns relationship to sleep/wakefulness and sleep disorders
c. Identify the influence of sleep disorders on at least one co-morbidity of epilepsy.	So/Loddenkemper	Substantial progress; studies on sleep-dependence of behavioral comorbidities, memory, and cognitive dysfunction
3. SUDEP.		
a. Identify the mechanisms responsible for SUDEP (including effects of seizures on autonomic functioning, particularly cardiac and respiratory).	So/Goldman	Some progress; neuro-cardiac, autonomic, and respiratory compromise as candidate mechanisms
4. Identify optimal strategies to avoid systemic disorders associated with epilepsy and its treatment (e.g., osteopenia, endocrine disturbances, reproductive disorders, and teratogenicity).	So/Pack	Some progress related to adverse effects of in utero exposure and osteopenia; limited progress to better understand fertility or endocrine dysfunction
E. Develop effective methods for diagnosis, treatment and prevention of non-epileptic seizures (NES).		
1. Determine the types and frequency of NES in the general population and in people with epilepsy.	La France/Syed	Some progress; V-EEG remains gold standard for diagnosis, no population-based study
2. Identify common susceptibility factors and etiologies for NES.	La France/Doss	Some progress; risk factors identified mostly from retrospective data
3. Validate at least one effective treatment for NES.	La France	Some progress; CBT seems effective but further validation needed