1. New models to study the development of epilepsy and co-occurring conditions

New models of epileptogenesis must mimic human etiologies - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

The AES views this as the most important research endeavor for the next 5 years. We suggest a revision to explicitly state that new models must mimic human etiologies.

The lowest hanging fruit for epilepsy models is to use CRISPR-knock-in (KI) strategies to create mice expressing human gene variants rather than simply presuming gene knockout or over-expression will accurately model a loss- or gain-of-function mutation. The technology is widely available to most labs, not that costly, and could provide a strategy to re-evaluate the effects of gene variants on epileptogenesis. For example, a missense mutation that causes a loss-of-function may have very distinct effects on neuronal (or astrocyte) function compared with simply knocking a gene out.

What would success look like if this research priority was achieved? :

These new models would of course provide new pre-clinical platforms for drug screening, behavioral analysis, and e-phys analysis. This approach would also provide us with a platform to functionally validate the myriad of epilepsy variants reported in the literature or identified in clinical evaluations that have not yet been tested in vitro or in vivo. These models are much more accessible, experimentally tractable, and replicate the human condition better than for example models for TBI-, stroke-, neurodegeneration-, or tumor- associated seizures and epilepsy. Of course, these latter models also need much more development to bring them closer to human disorders but may be more challenging than genetic epilepsies above.

Who would be most impacted by this research? : those with intractable epilepsy

2. Progression of epilepsy from the acute to chronic phase

Broaden understanding of epileptogenesis - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

The American Epilepsy Society considers this a high priority. As in human cancer, there will likely be common and overarching processes or mechanisms that lead to the establishment of the epileptic network. By analogy, all cancers stem from abnormally exuberant cell proliferation, and epilepsy reflects abnormal synchrony of neural networks. But the processes and mechanisms leading to seizures in SCN1A may be very different than CDKL5 and likely, from TBI- or tumor-associated seizures. From a treatment perspective, we have moved from big mechanisms drugs i.e., phenytoin, to targeted therapies i.e., everolimus, fenfluramine. Consider editing the priority to emphasize that understanding of epileptogenesis should include pan and etiology-dependent mechanisms.

What would success look like if this research priority was achieved? :

There will likely be common and overarching processes or mechanisms that lead to the establishment of the epileptic network.

Who would be most impacted by this research? : Those requiring targeted therapies

3. Solving the unsolved genetic epilepsies, 1. New models to study the development of epilepsy and co-occurring conditions

Unsolved genetic epilepsies- improve models first - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
The American Epilepsy Society does not recommend this for the top 4-5 priorities for the field. It should instead be a goal for 5-10 years from now, after the ability to develop improved models (priority #1 above) is achieved.

There are a myriad of known gene variants found within intronic or untranslated gene regions or at splice-sites that will require functional validation in vitro by expression of the variant in a CRISPR-edited cell and ultimately in a CRISPR-edited fly, fish, or mouse. Epigenetics (miRNAs, transposable elements, silencers) are tantalizing mechanisms for epileptogenesis but we are at embryonic stages in research. Efforts should bring in epigenetics experts from cancer, genetics, and immunology world to help drive this. We need a fresh canvas to think about this, as most existing studies on epigenetics are still focusing on gene/protein expression in a linear fashion. There needs to be a "big data" analysis of how non-coding, movable genetic elements affect the genome and in particular the epilepsy genome. The natural histories of genetic / phenotypic variants remain to be elucidated, and a clinical informatics approach is needed.

What would success look like if this research priority was achieved? :
There needs to be a "big data" analysis of how non-coding, movable genetic elements affect the genome and in particular the epilepsy genome. The natural histories of genetic / phenotypic variants remain to be elucidated, and a clinical informatics approach is needed.

Who would be most impacted by this research? : genetic epilepsies

3. Solving the unsolved genetic epilepsies, 9. Models of the epilepsies that have real human relevance, 5. Focus on specific groups of people with epilepsy, 11. Other! Add another Transformation Research Priority, 8. Precision (targeted) treatment for the epilepsies

Accelerating precision diagnosis to precision treatment – Ann Poduri

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
This priority will transform epilepsy research by integrating modern science into modern care for patients with epilepsy.

For example, a patient with as yet unexplained non-acquired epilepsy should be considered to have genetic epilepsy until proven otherwise and appropriately evaluated. If the first line of evaluation is unrevealing he or she should have an iterative re-analysis of cause in tandem with empiric therapy. One

a cause is identified, he or she should be offered enrollment in an appropriate cohort study that will allow for natural history data to be collected for the sake of scientific knowledge as well as to serve as baseline data regarding important outcomes for subsequent trials of treatment. Precision treatments should be offered from across a network of clinical trials.

If other, please add brief description. :

Common themes across many of the Transformative Research Priorities are precision diagnosis and precision treatment. The many priorities highlighted above connect to this theme and will have greatest impact when integrated through connections to a network of specialized centers or linked institutions through a center without walls model.

What would success look like if this research priority was achieved? :

Success would look like identification of a cure for patients with one or more well-defined epilepsies, particularly genetic epilepsies.

In short, we should follow the blueprint of the cancer field with a Cancer Oncology Group model guiding treatment through clinical trials. There are already some groups of epilepsies that would lend themselves to this model, and there are corresponding well-organized communities of patients and families with whom researchers and clinicians can partner. Such work is being done today but not integrated across centers, and access to precision diagnosis and precision treatment is not available to all patients with epilepsy. The example of genetic epilepsies provides a focus around which such a model could be developed.

Who would be most impacted by this research? : Patients with well-defined epilepsy, including genetic epilepsies. Other groups of epilepsies could equally benefit from precision diagnosis, establishment of measures to follow, and a clinical trials model to approach treatment.

3. Solving the unsolved genetic epilepsies, 8. Precision (targeted) treatment for the epilepsies, 5. Focus on specific groups of people with epilepsy, 7. Biomarkers to track progression of disease and response to treatment

Multicenter networks to foster transformative clinical research – Community Member

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

We advocate for a deliberate investment in collaborative, national or international efforts to rapidly and rigorously collect and share clinical data on patients with epilepsy, particularly those with rare genetic variants. Development of an infrastructure of clinical informatics tools that can plug into a national or international network for epilepsy centers could transform the field. A learning healthcare system model could provide the opportunity for natural history studies, disparities & healthcare delivery research, discovery of clinical biomarkers of disease progression and response to treatment, identify people with rare epilepsies for potential participation in treatment trials, etc. These priorities are critical as we move forward with disease-modifying therapies.

This approach has dramatically improved health outcomes for children with cancer, inflammatory bowel disease, and hypoplastic left heart syndrome. The epilepsy community is now poised to do the same.

What would success look like if this research priority was achieved? :

A broad network of clinical epilepsy centers whose electronic health records are harnessed for systematic clinical data extraction to enable efficient analysis and rapid dissemination to change practice and improve outcomes. Development of an array of computable phenotypes and common data elements for a range of pediatric and adult epilepsies will augment efficiency of data collection (Rather than collect data wholly through labor-intensive individual chart review, automated collection of a large number of data elements by extracting information already in the electronic health record can be merged with clinical data collected at the point of care).

This approach could facilitate natural history studies and catalyze cycles of comparative effectiveness research, such that the state of the art for epilepsy management would be driven more by data and less on expert opinion.

Who would be most impacted by this research? :
A network of learning healthcare systems could span the range of pediatric and adult epilepsies (including both the rare and more common epilepsy syndromes) and engage clinicians and researchers across multiple centers to change the trajectory of the advancement of knowledge for our field.

4. Biomarkers for epilepsy-related death

Identify those at higher risk for SUDEP - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
AES believes this is high public health priority as it will save lives i.e., to identify patients at higher risk for SUDEP and thus particularly in need of pharmaco-treatments or preventative devices (AICD) or patient surveillance. It will, however, be a major challenge due to ascertainment and low (sporadic) sample size worldwide. A genetic approach to identify genes associated with SUDEP is laudable though it seems doubtful that ALL SUDEP results from a genetic mutation and instead genomic pre-disposition (susceptibility variants, SNPs) and other factors may contribute.

What would success look like if this research priority was achieved? :
Ability to identify those at higest risk for epilesy-related mortality

Who would be most impacted by this research? :
Patients at higher risk for SUDEP and thus particularly in need of pharmaco-treatments or preventative devices (AICD) or patient surveillance

5. Focus on specific groups of people with epilepsy

Research between association late term pregnancies and epilepsy – Tracey Short

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
If more research was done, specifically on the link between epilepsy and late stage pregnancy, more OB/GYNs could be educated on the need to induce earlier to prevent epilespy.

Indicate which Transformative Research Priority your submission addresses?

If other, please add brief description.

Infants born at early term (born at 37 or 38 weeks of completed gestation) appear to have increased risk of epilepsy, childhood death and needing disability support. The causal routes in this group are complex, and further work is needed to see if the impact appears to come from the cause of the early birth or the impact of it per se. In addition we found that infants born at 41 weeks gestation or more also appear to have increased risk of developing epilepsy as they grow, and higher risks of needing disability support.

Reference: - Associations between early term and late/post term infants and development of epilepsy: A cohort study

David Odd, Alessandra Glover Williams, Cathy Winter, Timothy Draycott, PLOS x

What would success look like if this research priority was achieved?

A link between late stage pregnancies and epilepsy would be either proved or disproved. It is were proved, a large scale education program should be implemented to inform pregnant mothers and their OB/GYNs.

Who would be most impacted by this research?

Children of late term pregnant mothers.

6. Shared mechanisms and pathways across the epilepsies

Autoimmune, Immune and Infectious Causes - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

The American Epilepsy Society views this topic as a high priority that should encompass strategy to incorporate the expertise from experts in immunology and neuroimmunology. Some revisions would help to ensure its transformative nature.

This focus should be on epilepsy alone, as the co-morbidities add a level of complexity that may make progress slow.

With genetic and epigenetic mechanisms represented strongly in other stated priorities, this priority might instead hone-in on autoimmune, immune, and infectious causes of the epilepsies. The term "immune" should be included. In developing countries, infectious etiologies for epilepsy remain a major public health challenge. There is growing and compelling evidence that autoimmune mechanisms may contribute to epileptogenesis by mechanisms in sporadic seizures or status epilepticus (e.g., NORSE) beyond the clinically well-defined auto-antibody associated encephalopathies.

What would success look like if this research priority was achieved? :

In developing countries, infectious etiologies for epilepsy remain a major public health challenge. There is growing and compelling evidence that autoimmune mechanisms may contribute to epileptogenesis by mechanisms in sporadic seizures or status epilepticus (e.g., NORSE) beyond the clinically well-defined auto-antibody associated encephalopathies.

Who would be most impacted by this research? :

Those impacted by autoimmune, immune, and infectious causes of the epilepsies.

7. Biomarkers to track progression of disease and response to treatment

Accelerate development and validation of biomarkers - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
The American Epilepsy Society agrees that topic is a VERY high priority. We suggest a revision to include "onset of epilepsy" in its scope.

To date there have been numerous studies and meta-analyses on epilepsy biomarkers. Biomarkers for epilepsy versus seizure have often been blurred but should be considered distinct. Clinically useful biomarkers for seizures (i.e., a blood test), would have great value in the emergency department, intensive care unit, labor and delivery areas, operating rooms, and urgent care centers, as well as a huge impact in developing countries where conventional clinical tools and resources are scarce (i.e., EEG, brain imaging). These biomarkers will likely reflect phasic changes in the expression of biomolecules

(e.g., protein, mRNA, miRNA) and could easily derive from systemic changes (i.e., muscle, T-cells, gut, etc), rather than brain specific changes released systemically.

In contrast, biomarkers for epilepsy, meaning the change in network functioning causing recurrent seizures, may be more challenging. A diagnostic biomarker for "epilepsy" would obviously have huge prognostic and predictive value from a public health perspective in diagnosis, distinguishing response to medications, clinical course, likelihood of intractability, and potentially genetic risk assessment. We note that development of epilepsy biomarkers requires robust examination of human data.

Likely these discoveries will require large collaborative, multi-center approaches with "big data" analysis, separating "seizures" from "epilepsy". Cohort will need careful and broad stratification for medical co-morbidities i.e., cancer, immune disorders, obesity, diabetes, social determinants of health.

What would success look like if this research priority was achieved? :
A diagnostic blood test for seizures or epilepsy would be particularly transformative. A diagnostic biomarker for "epilepsy" would obviously have huge prognostic and predictive value from a public health perspective in diagnosis, distinguishing response to medications, clinical course, likelihood of intractability, and potentially genetic risk asses

Who would be most impacted by this research? :
all persons with or at risk of epilepsy and seizure disorders

8. Precision (targeted) treatment for the epilepsies

Modifier genetics – Erin Heinzen

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

For many genetic epilepsies the pathomechanisms are not known making rapid identification of novel drug targets challenging. Identifying genetic modifiers of high-risk epilepsy alleles using a variety of approaches (CRISPR screens, leveraging natural genetic diversity in model organisms, human modifier studies using large patient repositories) may inform key genes involved in disease mechanisms and could illuminate drug targets more rapidly than traditional mechanistic studies.

What would success look like if this research priority was achieved? :

Modifier alleles are identified for several forms of genetic epilepsy which illuminate viable treatment targets for epilepsies with similar underlying mechanisms

Who would be most impacted by this research? :

Drug-resistant epilepsy patients

Parents driving precision therapies for genetic epilepsies – Kim Nye

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

Some of the greatest progress right now in precision therapies for genetic epilepsies is the result of parents of children with genetic epilepsies forming nonprofit organizations. These non-profits then raise funds for medical research. These organizations understand the urgency of the situation and they drive progress by being laser-focused on a specific genetic epilepsy. These genetic epilepsies are arguably among the most likely candidates for currently available precision treatments (ASOs, gene therapies, etc). However, these organizations are also always short on funds and often have to reinvent the wheel in terms of infrastructure. Many of the genetic epilepsies will remain largely unexplored because there is no affected family with the bandwidth to advocate for them. We are all trying to create the same research toolkits of animal and cellular models. We are all trying to organize our patient populations with registries, natural history studies and biobanks. There needs to be a system in place to streamline these processes without putting the financial burden on the affected families to raise funds for these models and repositories.

What would success look like if this research priority was achieved?

Success would look like more animal and cellular models for more genetic epilepsies that would be available to all qualified researchers. This would lead to more drug repurposing and more precision therapies for epilepsy.

Who would be most impacted by this research?

Initially, those with specific genetic epilepsies would be the most impacted. However, I would hope that with time and research, a better understanding of the mechanisms of the genetic epilepsies would also shed light on epilepsy in general.

Precision Diagnosis; an Etiology for Everyone – Brandy Fureman

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

Precision diagnosis – right now there are a large number of people with epilepsy with an unknown cause. This means that our understanding of the phenotypes that we currently associate with a specific etiology (such as genetic) may be skewed to only the most severe phenotypes, which are often also the most rare, and therefore understudied. A grand challenge is to develop ways to rapidly diagnose an epilepsy etiology—whether that is genetic, infectious, autoimmune, injury, etc. – for every person so that

the full spectrum of phenotypes associated with those etiologies can be determined. This foundational project has the potential to impact basic science, clinical development, and clinical care in the epilepsies. Precision diagnosis leading to an etiology for everyone is a necessary foundation for developing precision treatments that can apply to the broadest possible numbers of people.

What would success look like if this research priority was achieved?

Success would look like new diagnostic approaches that efficiently detect genetic, infectious, injury, autoimmune, or other causes of epilepsy are ready to be implemented into the clinical workflow so that every person diagnosed with an epilepsy has an associated etiology or etiologies identified. This would result in larger numbers of people with epilepsy eligible for clinical studies and clinical trials of new precision interventions. Success would also be apparent if new mechanisms involved in an etiology are revealed by identifying larger cohorts.

Who would be most impacted by this research?

Precision diagnosis tools would impact both the populations of people with rare epilepsies by making the diagnostic odyssey shorter, and populations of people with "garden variety epilepsy" but no known cause. Precise diagnosis of epilepsy with etiology can point to treatment options that are more likely to be effective, treatments that are likely to cause adverse effects or exacerbations, and can increase the numbers of people available to participate in precision therapy trials.

Stem Cell Therapy - Sandra Fernandes

How effectively can autologous stem cell therapy be considered as a line of treatment for LGS patients who are resistant to anti-epileptic drugs

9. Models of the epilepsies that have real human relevance, 1. New models to study the development of epilepsy and co-occurring conditions

Translational models with human relevance - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

The American Epilepsy Society suggests that this priority be merged with priority (#1).

It is indeed a high priority to make models in cells and multiple organisms (fly, fish, mouse) that actually replicate the human mechanisms, e.g., gene knockout may not be the same as gene inactivation from a missense variant. All models have REAL human relevance, it is just HOW relevant. Another way to say it might be: Develop cell and animal models predicated on gene variants identified in genetic epilepsies or on well-defined cellular mechanisms in acquired epilepsies i.e., brain injury, brain cancer, neurodegeneration, neuro-infection, or neuro-inflammation.

Note that the phrasing of "treat genetics of epilepsies" is unclear but should likely be phrased as "treat acquired and genetic epilepsies"

What would success look like if this research priority was achieved? :

To make models in cells and multiple organisms (fly, fish, mouse) that actually replicate the human mechanisms

Who would be most impacted by this research? : people with genetic and acquired epilepsies

10. Network interactions in the epilepsies

Macroscopic network mechanisms of focal epilepsy – David Mogul

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
Much of the field of epilepsy still harbors long-held ideas about what creates the patterns of neural electrophysiology that results in focal seizures, a lot of which has not been experimentally established. Much of this activity may have the spatiotemporal characteristics that would be unlikely to be captured with standard imaging protocols. Better understanding of these mechanisms will not only better reveal the underlying dynamics of seizure generation and progression but may lead to the kind of improved understanding that would impact treatment options. This would be especially true for drug-resistant seizures.

What would success look like if this research priority was achieved? :
Epilepsy patients with identical diagnoses often exhibit starkly different seizure patterns. The ability to map out network electrophysiological dynamics specific to each patient would then allow for the possibility of personalized therapies for epilepsy patients that might guide a better understanding of the true etiology of this pathological condition. One potential vision of success -- at least with respect to currently available technologies -- is that patients who undergo invasive brain electrical recording prior to surgery may be able to construct personalized maps as seizures evolve to indicate true regions of ictogenesis beyond simply where large energy electrical activity is first recorded.

Who would be most impacted by this research? :
This is likely to most impact those approximately one-third of epilepsy patients with drug-resistant seizures. Whether it be improved surgical outcomes, better targeting of exogenous brain stimulation or some other targeted therapy, it's difficult to assign those targets without truly understanding the network etiology of seizures.

Network interaction including comorbidities AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
The American Epilepsy Society considers comorbidities of epilepsy a high priority endeavor. Patients themselves, often independent of actual seizure frequency, remain underemployed or underachieving because comorbidities affect function in equal or greater measure than epilepsy itself. Furthermore, accumulating evidence finds that comorbidities and epilepsy have bilateral interactions; improvement in one comorbid domain may affect seizure occurrence.

What would success look like if this research priority was achieved? :
The sheer incidence of comorbidities (for example, chronic insomnia affects between 30-50% of patients with epilepsy and about 10% of the total population) makes opportunities for interventions that can in parallel fashion improve comorbidities, epilepsy, and quality of life. Finally, the public health burdens of

widespread comorbidities mean that improvements in these domains can have disproportionate cost savings and family health.

Who would be most impacted by this research? :
PWE impacted by comorbidities associated with epilepsy and seizures

11. Other! Add another Transformation Research Priority

If other, please add brief description. :
I am both epileptic and type 1 diabetic. It would be easy to spend most of my time feeling sorry for myself, afraid to leave my apartment. What if I have a seizure at the nail salon? What if my blood sugar plummets on the subway? Well, both of these have happened, but I'm prepared. I take public transit and wear a medical ID bracelet whenever I'm out on my own. I've spent years volunteering in the neurology units at major hospitals in Denver and New York, talking with epilepsy patients. When they learn that I also have epilepsy, they're typically shocked that I'm out and about on my own. I learned that many of these patients are afraid to leave their homes, and I found this very disturbing.

What would success look like if this research priority was achieved? :
The "beta" version was already a success. When working as a volunteer at Denver Health, I developed a much smaller scale *SEEZ* brochure for epilepsy patients there. Two examples: "Tom" was overwhelmed in the classroom and had dropped out of college. I gave him the brochure, and when I visited the next week, he had registered for two online classes and was talking about his future goals. "Sherry" was reluctant to wear a medical ID bracelet because she didn't want to look like something was wrong with her. When she admired the one I was wearing, I told her I got it from Lauren's Hope. The contact info was in the brochure, and she ordered the same one in blue. SEEZ can have this type of impact nationwide.

Who would be most impacted by this research? :
People with disabilities, particularly those who may be uncomfortable with the idea of going out into the world, would benefit most from *SEEZ*. *SEEZ* has a spokeshero named Epilectra (www.epilectra.com) who is the main character of a graphic novel I've written and am in the process of trying to get published. She has epilepsy and can channel the errant electrical activity in her brain through her fingertips in the form of lightning. She leads a team of superheroes who all have disabilities they've morphed into super-abilities. Epilectra's motto is "Your Difference Is Your Strength." *SEEZ* can help people with disabilities learn how to be their own superhero, embrace their difference, and go into the world with confidence.

Cross-disciplinary investigation - AES

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :
This should be a clear mandate for future and collaborative investigation in epilepsy, as it provides an opportunity to bring in scientists from disciplines outside of the epilepsy field.

If other, please add brief description. :
The AES recommends a different priority of, "Define the relationship between network abnormalities leading to seizures (epileptogenic process/epileptogenesis), maintenance of the epileptic network,

success with or resistance to pharmacotherapy, and neurobehavioral co-morbidities." One example of this need is the link between gut microbiome i.e., the highly unique and individualized repertoire of healthy and in some cases unhealthy (due to overgrowth, selection), bacteria in the human gut (and really everywhere in the body), and neurological disease. There are data demonstrating a link between neurodegeneration (especially Parkinson's disease), brain inflammation, autism, TBI, and recently seizures. The identification of gut flora that are linked to any of these is inordinately complex requiring immunology, gut biologists, bioinformatics and neuroscientists to decipher.

What would success look like if this research priority was achieved? :

Define the relationship between network abnormalities leading to seizures (epileptogenic process/epileptogenesis), maintenance of the epileptic network, success with or resistance to pharmacotherapy, and neurobehavioral co-morbidities.

Who would be most impacted by this research? : all patients with epilepsy

Laying the Foundation for an Epilepsy Moonshot – JayEtta Hecker

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

More substantive research priorities, however well framed and targeted, can not alone overcome the inefficiencies and silo-ed structure for clinical care and research in the epilepsies.

By integrating clinical care and research—the standard for decades in pediatric oncology—we will get on a path where we will start seeing improvements in the quality of life for all those living with and too often dying from epilepsy.

If other, please add brief description. :

In the preface to their 10 research priorities, the AES Benchmarks Committee references being charged with "identifying paradigm-shifting research priorities" with goals on improving "understanding" and stimulating "novel", "multi-disciplinary approaches".

While the Benchmarks Committee proposes 10 research priorities that offer promise for new "understanding" of epilepsy causes, prevention, treatment, and comorbidities, it is not clear how these 10 areas capture the kinds of bold paradigm-shifting measures needed to genuinely put the nation on a path for "Curing the Epilepsies". As families with loved ones whose degrading quality of life has barely improved over the past 20 years, our hope is for research priorities holding real promise of improving OUTCOMES – not just "understanding".

To many in the epilepsy community of patients and families, it is clear that **research and innovation is required to determine how we can shift the landscape to integrate epilepsy research and clinical care.**

- how the full spectrum of stakeholders need a new robust consortium to collaborate seamlessly to develop applied research strategies for capturing vital data and learning from every clinical encounter with rare patients,

- how the vast but heavily silo-ed sources of data from clinical care, research, trials, registries and more can be standardized, integrated, analyzed, and applied to accelerate and support learning, better treatments, and improved outcomes.

We do not believe the 10 additional research priorities proposed by the Benchmark Committee address the urgent need to shift the status quo, moving us to a system that integrates epilepsy clinical care, research and clinical trials to optimize critical data and maximize learning and improved outcomes. We strongly believe that **by integrating clinical care and research—the standard for decades in pediatric oncology—we will finally start seeing improvements in the quality of life for all those living with (and far too often dying from) epilepsy.**

Well-targeted investigations could identify the critical procedures and infrastructure attributed to successes in pediatric oncology and adapting them to the epilepsy environment. This would include defined processes for preparing and testing new protocols (including standardized data collection at every observation), getting treatment centers to adopt these protocols, and enrolling all children with epilepsy in longitudinal monitoring and research.

Fortunately, there are many fronts of innovation which already exist in our community on which to build and integrate into a comprehensive strategic effort – examples include the Pediatric Epilepsy Research Consortium/Foundation (PERC/PERF), Epilepsy and Pediatric Epilepsy Learning Health Systems (ELHS and PELHS), Institute for Advanced Clinical Trials with Children (I-ACT-C), Pediatric Trials Network (PTN), Precision Medicine Consortium, Platform for Vector Gene Therapy (PAVEGT), NCATS Clinical Data to Health (CD2H), emerging platforms for data integration, sharing, and analyses (including RDCA-DAP, VIVLI, YODA Project, Rare X), and diverse standard-setting efforts (including CDISC and OMOP).

Patients and families cannot wait another 7 years in the hopes that the proposed national benchmarks and cross-cutting research priorities might result in urgently needed improvements in the quality of lives of the 470,000 children or the 1 in 26 Americans living with epilepsy. Far too many lives are often debilitated or lost due to the glacial rate of progress in epilepsy clinical care. **The overriding national priority should be to identify and implement systemic structural transformation that will truly put us on a path to "Curing the Epilepsies".**

What would success look like if this research priority was achieved? :

The decades of evidence from pediatric oncology strongly suggests that by integrating clinical care and research we will finally start giving neurologists the ability to use data to make informed decisions about care, thereby improving the quality of life for those living with epilepsy.

The structure and culture for disseminating and applying lessons from clinical care, research, and clinical trials would be transformed to be patient-centered and laser focused on improving outcomes.

Who would be most impacted by this research? :

The quality of life of the 470,000 children and 1 in 26 Americans struggling with epilepsy and their families would improve.

Researchers and clinicians, being part of a robust environment for "continuous learning" from every patient, would be more informed and more effective.

The cost to society of epilepsy, both human and financial, could be dramatically reduced.

Other – Detlev Boison

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

Metabolic and biochemical pathways are an understudied research area in the epilepsies. Biochemical pathways provide crucial links between gene expression (e.g. via epigenetic modification), energy

metabolism (mitochondria, ATP), neuron-glia interactions, and finally neuronal excitability. Derailment of metabolic functions can affect a complex system such as the brain on multiple different levels and metabolism or biochemistry based therapies offer novel therapeutic opportunities aimed at restoration of network homeostasis and epilepsy prevention.

If other, please add brief description. :

Define the role of metabolism in epileptogenesis and understand the mechanistic basis of disease modifying metabolic therapies.

What would success look like if this research priority was achieved? :

Development of a metabolism or biochemistry based intervention capable of preventing the development of epilepsy or its progression.

Who would be most impacted by this research? :

Everyone at the risk of developing epilepsy.

Active, Involved Life Can Ward Off Depression in Adult Epileptic – S Sesserman

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

These patients' reluctance to go out and live life to their lives to its fullest is what motivated me to develop my nonprofit, *SEEZ* (www.SEEZ.us) -- Support & Empower Everyone Zealously. *SEEZ* offers the resources, information, camaraderie, and support to people with epilepsy and other disabilities, along with their loved ones, through social media, local events, and more that will help them feel more confident embracing life and marching toward their goals. Health professionals are great while you're in their office and with medical needs. *SEEZ* addresses patients' needs once they leave their doctor's offices and venture into the real world. It provides resources for a host of essential goods and services -- from transportation options to top online educational facilities, from medical identification to service animal requirements, and from food delivery to groups support.

Large-scale clinical data and outcomes in rare epilepsies – Ingo Helbig

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

During the last decade, we have seen tremendous progress in understanding the genetic basis of rare epilepsies. However, while genetic studies can be performed at scale, review of clinical data and outcomes still remains a largely manual tasks. This discrepancy has resulted in a significant "phenotyping gap" where the genetic cause of many rare epilepsies is known, but natural history is not well understood. Novel data science technologies using harmonized clinical data, including large-scale information from the Electronic Medical Records, allow for a systematic analysis of clinical data. In addition, progress has been made in enabling documentation of seizure and non-seizure outcomes in standardized ways. This enables frameworks to assess treatment effects, natural history, and comparative effectiveness studies to help better understand the longitudinal history and responses to new and established treatments in rare epilepsies.

If other, please add brief description. :

I am proposing a Transformative Research Priority that addresses the "phenotyping gap" by facilitating the ability to analyze large-scale clinical information and outcome data to better understand natural histories in rare epilepsies. The proposed research priority suggests the development of harmonization tools for existing clinical data derived from clinical data to enable meaningful data analysis to understand disease course and treatment responses.

What would success look like if this research priority was achieved? :

This priority would be successful if a common framework was achieved to report and share harmonized large-scale clinical data including outcome data, in parallel to data standards for genomic information in rare epilepsies. Successful completion would also include implementation in collaborative framework to enable data generation for subsequent analysis. Such a research priority would supplement other approaches for Natural History Studies.

Who would be most impacted by this research? :

Individuals with rare epilepsies, including genetic developmental and epileptic encephalopathies.

Advancing genetic therapies for monogenic epilepsies – Laura Lubbers

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

This idea would accelerate promising treatments for the many stakeholders interested in advancing genetic therapies. Many of the patient advocates for monogenic epilepsies are viewing genetic therapies and a potential path towards a cure, with many working independently to achieve their goals. There have been innumerable advances in genetic diagnoses, availability of genetic testing (although there is more to do) and development of generic tools and technologies that have been essential in enabling the promise of genetic therapies; however, many obstacles remain. Some include, development and availability of appropriate viral vectors, a lack of understanding of topics that range from dosing paradigms for the different approaches through safety issues and translatability to people. In addition, there are ethical considerations that will require thoughtfulness and input from the broad community. This topics could be advanced and accelerated by a deep and focused investment in topics that cut across the needs of the different groups working in this space to accelerate the progress for many.

If other, please add brief description.

Accelerating advancements for gene therapies

What would success look like if this research priority was achieved?

Rapid development of genetic therapies that are ready for testing in human populations.

Who would be most impacted by this research?

People and families affected by monogenic epilepsies

Solving the question, What is a seizure? – Laura Lubbers

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

This idea would assist the basic research community in transforming preclinical findings to clinical application.

If other, please add brief description.

One powerful thing the basic research community could do to advance epilepsy research and support those who will or do suffer with epilepsy is to come up with consensus about 'what is a seizure', especially in the process of epileptogenesis. Electrographic signals can be difficult to interpret with existing tools. However, subtle changes in EEG have been used successfully already, in combination with other risk factors, as key biomarker of epileptogenesis (Rensing et al., Epilepsia (2020), Wu et al., Pediatr Neurol (2016) and employed in the clinic, e.g., PReVENT trial biomarker. Other preclinical EEG signatures are now being recognized and defined following head injury (Andrade et al., Journal of Neurotrauma (2020)). Efforts like this must be expanded to understand who is at risk for developing epilepsy whether due to genetic or acquired causes.

Challenge: develop new and more sensitive methods for detecting electrographic changes in the brain, broaden our thinking to characterize EEG signatures that may relate to non-convulsive seizures, come together as a community to define at least some consensus so that this area of study can move forward and toward patient benefit.

What would success look like if this research priority was achieved?

More people would understand their relative risk for developing epilepsy

Who would be most impacted by this research?

People with various defined genetic and acquired epilepsies

Instituting Research Collaborations Across Rare Epilepsies - Ilene Miller

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

As a parent, rare epilepsy organization co-founder, and lifelong advocate, I undertook a Rare Epilepsy Landscape Analysis (RELA) (bit.ly/RELAanalysis) and (https://bit.ly/RELAappendix) in 2019. The RELA identified 75 Rare epilepsy organizations (there are over 100 today!) and developed a 111 question survey developed by and for the Rare epilepsy organizations and other key stakeholders. 44 rare epilepsy organizations participated illuminating their priorities and challenges across 5 key domains including information & support, research, professional education, advocacy. and operations.

Despite many different underlying causes, disease incidence and prevalence, and organization resources and maturity, this first-of-its-kind analysis found that **Rare organizations were struggling with many similar challenges and aligned across many collaborative opportunities.** Three 3 areas of shared priorities, obstacles, and collaborative solutions that rely on basic, clinical and translational research follow below. Additionally, an editorial titled **Raring for Change** was published in Epilepsy & Behavior, Epilepsy Behav. 2020 Oct; 111: 107276. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7395595/)

1. **The Rares prioritize connecting patients to specialists to expedite diagnosis and ensure the most up-to-date care.** Broadly dispersed patients as well as a broad spectrum of patients even within each disease and lack of professional collaboration are roadblocks to this priority. <u>The Rares are aligned in creating rare centers of excellence and establishing multi-disciplinary clinics.</u>

2. **The Rares prioritize understanding the mechanism of their diseases, developing natural history registries, and funding translational research.** Connecting researchers to seed collaborations, acquiring sufficient patient data for clinical trials, and access to funding are among the most prevalent challenges. The Rares are aligned in developing resources like registries, biorepositories and other tools that could be used across diseases. They also see opportunities to co-develop clinical quality care scales for use across diseases.
3. **The Rares prioritize updating researcher thinking on rare conditions, educating professionals to detect and diagnose disease, and developing and disseminating best clinical practices.** Small patient numbers, disparate experts, the underutilization of genetic and imaging testing to accurately and expeditiously diagnose patients, and unwillingness among some clinicians to learn beyond their scope of practice presents roadblocks. The Rares are aligned in developing and disseminating clinical diagnostic, evaluation and treatment guidelines as well as outreach/training/education to medical trainees and across multiple disciplines including geneticists, psychiatrists, neuropsychologists, endocrinologists etc.

Research investment and advances in genetics, imaging, and basic science accelerated the diagnosis of rare epilepsies. Precision medicine offers future promise for many of these diseases. However, to realize that promise we need investments in the infrastructure and tools now. With 100's of diseases, our community needs to find ways to be more efficient in developing resources that cut across the rare epilepsies.

If other, please add brief description.

Capitalizing on alignment of priorities, challenges and collaborative opportunities across the Rare Epilepsies to use resources that support basic, clinical and translational research more efficiently and effectively.

What would success look like if this research priority was achieved?

Better utilization of scarce resources across hundreds of rare epilepsy diagnosis. Faster learning across the epilepsies - both the rares and generalized.

Who would be most impacted by this research?

Patients and their families.

Call to Structurally Transform the Epilepsy Ecosystem – ELC

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

As a community of 19 patient and professional groups across the epilepsy community, we applaud the work of the Benchmark Committee and NINDS for launching this open call for transformative priorities for "Curing the Epilepsies". Looking back over the 20 years invested in national conferences toward Curing the Epilepsies and 3 cycles of Benchmarks to set priorities, we are concerned that **progress for persons living and struggling each day with epilepsy and all of its complexities has not been commensurate with the time or effort invested over two plus decades**.

• Epilepsy diagnosis has continued to increase.

• Epilepsy control has not changed with 30-40% of patients still refractory or uncontrolled.

• Anti-epilepsy medications have doubled in numbers and the cost of care has doubled although seizure control has not significantly improved.

• Surgery continues to be underutilized despite large numbers of eligible candidates.

• Federal and private investment in epilepsy is outpaced by Alzheimers, MS, and Parkinsons despite epilepsies higher prevalence.

• Quality of life has not improved across the patient spectrum for both well controlled to severe patients.

• Financial toll can be extraordinary in both direct costs including access to care, treatment and management as well as indirect costs including work productivity, employment status, and caregiver burden.

• Epilepsy mortality rates have increased and deaths by SUDEP have remained largely the same.

• Our capacity to measure basic statistics of epilepsy incidence, prevalence, and death by age and by cause and other key criteria are lacking.

We believe that **significant gaps in the current epilepsy research and healthcare ecosystem are preventing research progress from translating to meaningful change for patients.**

To catalyze a new era of research in the epilepsies, **we recommend the creation of a NIH supported national network of specialty centers across the United States actively engaged in clinical trials and other research studies to expedite the diagnosis and treatment of all epilepsies** in children and adults, including those that are rare and complex.

The **reimagined NIH funded network would expedite clinical evaluation and diagnosis, hasten the development and dissemination of treatment protocols, accelerate the monitoring of standardized outcomes, address deficits and disparities in care, and strengthen registry participation and collaborative research.** The network would have as a primary focus improving tangible outcomes for patients and their caregivers including both seizure cessation and control as well as the quality of life for a broad range of individuals struggling with epilepsy comorbidities, and treatment effects regardless of the cause or functional status.

This **call for transformative action to really put us on a path to "Curing the Epilepsies" is endorsed by 19 patient and professional organizations across the epilepsy spectrum** including:

1. Child Neurology Foundation
2. CURE Epilepsy
3. Danny Did
4. Dravet Syndrome Foundation
5. Dup15q Alliance
6. Epilepsy Foundation
7. FamilieSCN2A Foundation

8. Hope for Hypothalamic Hamartomas

9. Hope for ULD

10. International Foundation for CDKL5 Research

11. LGS Foundation (Lennox-Gastaut Syndrome)

12. Milestones for Maxwell & SLC6A1 Connect

13. National Association of Epilepsy Centers (NAEC)

14. Phelan-McDermid Syndrome Foundation (PMSF)

15. Ring14 USA

16. TESS Research Foundation

17. The Brain Recovery Project: Childhood Epilepsy Surgery Foundation

18. Tuberous Sclerosis Alliance

19. Wishes for Elliott

If other, please add brief description.

For 20 years we have made significant but incremental progress because the underlying infrastructure has not been conducive to widespread, permanent progress. The time is now to Integrate clinical care and research—the standard for decades in pediatric oncology. This transformative change will put epilepsy on a path where we will start seeing improvements in the quality of life for all those living with and too often dying from epilepsy.

What would success look like if this research priority was achieved?

We believe **our recommended focus on structural reform**, **improving the linkage between research and clinical care**, lays the groundwork for advancing many of the benchmarks the Committee's suggested 10 priorities, as well as promising new transformative ideas submitted by the community. Structural reforms are needed to seamlessly integrate a wide range of important but siloed initiatives to generate: (1) direct improvements of treatment and outcomes and (2) facilitate transformative research by easing identification and participation of participants for research/trials

DIRECT IMPROVEMENTS OF TREATMENT AND OUTCOMES:

- Annapurna.Poduri: "Accelerating precision diagnosis to precision treatment." This priority will transform epilepsy research by integrating modern science into modern care for patients with epilepsy.
- Community Member: "Multicenter networks to foster transformative clinical research." We advocate for a deliberate investment in collaborative, national or international efforts to rapidly and rigorously collect and share clinical data on patients with epilepsy, particularly those with rare genetic variants.
- Seserman: "Active, Involved Life Can Ward Off Depression in Adult Epileptic."
- Monika Jones: "Epilepsy surgery deserves its own benchmark and more funding." Epilepsy surgery is no longer considered a last resort for patients with drug-resistant seizures; however, there remain significant and systemic barriers to prompt referral to epilepsy surgery evaluation.
- JayEtta Hecker: "Laying the Foundation for an Epilepsy Moonshot." More substantive research priorities, however well framed and targeted, cannot alone overcome the inefficiencies and

silo-ed structure for clinical care and research in the epilepsies. By integrating clinical care and research—the standard for decades in pediatric oncology—we will get on a path where we will start seeing improvements in the quality of life for all those living with and too often dying from epilepsy

- Anny Reyes: "Research in Health Disparities." There is a huge gap in this research area that pertains to Hispanic/Latinx patients with TLE and other epilepsy syndromes. Specifically, very little is known of whether Spanish-speaking patients with epilepsy have similar cognitive trajectories and post-operative cognitive outcome to other racial/ethnic groups.
- Janelle Wagner "A cure is important but so is the person" Area IV… does not appear to account for non-pharmacological interventions in the treatment of mental health disorders.
- JayEtta Hecker: "We need clinical trials with an N of EVERYONE." Coming from the world of families with children ravaged by the many rare and catastrophic epilepsies, we suggest consideration of a benchmark where every child with epilepsy is enrolled in a clinical trial. Our children are already guinea pigs, but their experiences are not treated with the respect of a common lab rat.

Adam Hartman, MD: " Improve treatment options for controlling seizures and epilepsy." Incorporate findings from the NINDS workshop entitled

- Helbigi: "Large-scale clinical data and outcomes in rare epilepsies." While genetic studies can be performed at scale, review of clinical data and outcomes still remains a largely manual task
- Erin Heinzen: "Modifier genetics. " For many genetic epilepsies the pathomechanisms are not known making rapid identification of novel drug targets challenging. Identifying genetic modifiers of high-risk epilepsy alleles using a variety of approaches (CRISPR screens, leveraging natural genetic diversity in model organisms, human modifier studies using large patient repositories) may inform key genes involved in disease mechanisms and could illuminate drug targets more rapidly than traditional mechanistic studies.
- AES Networ: "interaction including comorbidities."The American Epilepsy Society considers comorbidities of epilepsy a high priority endeavor.
- ++Raconwit: "++Studying Telehealth in Epilepsy." Teleheath may have an important role in monitoring epilepsy clinical research subjects and may be particularly helpful for following established research subjects/patients and may permit ongoing clinical investigations during clinical trials.
- AES: "Accelerate development and validation of biomarkers." Biomarkers for epilepsy versus seizure have often been blurred but should be considered distinct. Clinically useful biomarkers for seizures (i.e., a blood test), would have great value in the emergency in the emergency department, intensive care unit, labor and delivery areas, operating rooms, and urgent care centers, as well as a huge impact in developing countries where conventional clinical tools and resources are scarce
- AES: "Identify those at higher risk for SUDEP." AES believes this is high public health priority as it will save lives i.e., to identify patients at higher risk for SUDEP and thus particularly in need of pharmaco-treatments or preventative devices (AICD) or patient surveillance. It will, however, be a major challenge due to ascertainment and low (sporadic) sample size worldwide.
- AES: "Cross-disciplinary investigation." This should be a clear mandate for future and collaborative investigation in epilepsy, as it provides an opportunity to bring in scientists from disciplines outside of the epilepsy field.
- Gerry Nesbitt: "Merge and share datasets across different research studies." Epilepsy patients' research data are typically collected and stored in standalone de-identified database silos,

making it impossible to merge or compare data across disparate research studies or give feedback to the patient.

- AES: "Broaden understanding of epileptogenesis." As in human cancer, there will likely be common and overarching processes or mechanisms that lead to the establishment of the epileptic network.
- ++Steve Roberds: "++Strategically integrating the benchmarks for clarity." Few benchmarks will have large clinical impact if accomplished alone. Most benchmarks, specifically those relating to integrating large data sets and developing models, depend upon integrating knowledge gained from progress toward other benchmarks.
- Vio.H: "The integration of human values and ethics into all DRE research." Incorporate ethics approaches and use human values to guide innovation in research and technology for drug resistant epilepsy (DRE).
- Gerry Nesbitt: "Epilepsy-related "training" datasets for machine learning. "Most epilepsy-related Machine Learning (ML) tools tend to focus on seizure detection using readily available EEG "training" datasets. ML has potentially many other epilepsy-related use cases beyond seizure detection that are yet to be discovered, but the lack of "training" data is likely hindering its use.
- Daniel Goldenholz: "Cure epilepsy." The current benchmarks never say the words "cure epilepsy". It is vaguely suggested by Area II, component E, but why be vague? We want to CURE EPILEPSY. Lets say that loud and clear, right?
- Kvossel: "Understanding the etiology of late-onset epilepsy." One third of late-onset epilepsy have no known etiology.

Who would be most impacted by this research?

Every person newly diagnosed and living with epilepsy including newborns through the elderly as well as those are controlled and refractory, moderately and severely impacted.

Learning Healthcare System – Jeff Buchalter

It is clear that although current research efforts have improved the lives of people living with epilepsy in a variety of ways, large gaps persist. While continuing basic science research, drug and device development, comparative effective research, other options should be considered. In this regard I would like to propose that the information sciences, specifically embodied by the concept of "learning healthcare systems (LHSs)" be embraced and developed by the epilepsy community. (LHSs) have a variety of manifestations as described by the American Medical Informatics Association (https://www.amia.org/education/webinars/learning-health-system-overview-and-update) in addition to more specific applications within the severe pediatrics diseases (https://www.cincinnatichildrens.org/research/divisions/j/anderson-center). These methodologies which are based in Quality Improvement have been demonstrated to reduce the severity of disease and provide meaningful improvement in clinical outcomes without the introduction of new therapies. Currently, there are two LHSs in the epilepsy domain- the Epilepsy Learning Healthcare System (coordinated by the Epilepsy Foundation) and the Pediatric Epilepsy Learning Healthcare System (sponsored by the Pediatric Epilepsy Research Foundation). These systems are examples for what could fundamentally change the way epilepsy is practiced but require resources to continue the research/knowledge that is gained in theory from every patient interaction.

Epilepsy Ontology – Jeff Buchalter

The enormous amount of information that is currently available in the basic and clinical sciences within and outside the domain of epilepsy makes it clear that past means of curating and exploring past and emerging information. "Databases" have traditionally been considered the means of information storage and retrieval. The suggestion is the development and use of biomedical ontologies as means of addressing these information related issues. Ontologies are information structures that are based in the definition of fundamental concepts of knowledge and the relationships between the concepts. An example would be to search "SCN1A" mutations and immediately be "connected" to all of the gene products, physiological pathways, phenotypes, EEG, imaging, etc features that are associated with the mutation. This would provide a structure in which animal models could be *computationally* linked to all aspects of clinical information. It could be used to explore all of the reported genotypes, phenotypes, epidemiology, basic mechanisms, and animal models relevant for SUDEP. Two epilepsy related ontologies (EpSO and ESSO) already have been started and are housed in the NIH repository (https://bioportal.bioontology.org/). These ontologies are awaiting further resources to continue development and application to many research efforts relevant for epilepsy.

Collaborative Tech for Epilepsy Surgery, Devices and Therapies- Brian Litt

Why would this research priority transform epilepsy research, our understanding of the epilepsies, and/or treatment of the epilepsies? :

We propose a bold initiative to share data, infrastructure, new technologies and methods across centers to tackle some of the major challenges in treating refractory epilepsy. There is a clear gap between recent advances in technology to treat refractory seizures and their clinical translation. This is largely because individual centers do not have a sufficient number of patients or technical know-how to do the statistically robust studies required to expedite discovery. For this reason, despite tremendous improvement in hardware, wearables, algorithms and implantable devices, progress in treating patients moves slowly. We propose to build tools and infrastructure, leveraging existing centralized and federated platforms, to allow (some examples):

1. Collaborators to aggregate and standardize data from patients implanted with intracranial electrodes and devices for research and trials. This includes imaging, metadata, electrophysiology and other supporting information.

2. Scientists to share and federate algorithms so that they can be run either centrally or on multiple sites and pool results

3. Centers to rapidly propose and execute retrospective and prospective clinical trials related to intracranial EEG, wearable and implantable devices, laser ablation, an innovations in hardware, software, algorithms and systems, both alone and in collaboration with industry.

Indicate which Transformative Research Priority your submission addresses? 11. Other! Add another Transformation Research Priority

If other, please add brief description.

Major unanswered questions of vital translational significance that could be enabled by this proposal include:

1. What is the optimal spatial sampling of intracranial EEG and approach: electrode spacing, size, grid, stereo EEG and other techniques? How can we estimate and eliminate sampling error with intracranial investigations?

2. What is the optimal temporal sampling of electrophysiology (sample rate) and at what scale

3. What are the best multimodal techniques, protocols and resolution to map epileptic lesions, networks and techniques to coregister and display electrode locations, and how do we standardize them and make them universally available across platforms?

4. Identify the best biomarkers to localize epileptic networks and to track device response in a rigorous fashion (e.g. HFOs, seizures, interictal coherence, other methods)

5. Determine the best network methods to quantify and display EEG analysis to characterize epilepsy networks, and localize sites for surgical resection, ablation or device implantation. The goal here is to simulate and choose the best surgical or device therapy prospectively.

6. Determine the best invasive treatment for specific epilepsy syndromes in rigorous, multicenter trials

These are only a sampling of the kinds of questions that could be answered by an appropriate collaborative infrastructure to facilitate multi-center collaboration.

What would success look like if this research priority was achieved?

Success would include having most or all major epilepsy centers share their imaging, electrophysiology and meta data (genetics as well) centrally, as well as their algorithms and analysis tools. These centers and other investigators would together establish standards for terminology, data formats, imaging and electrophysiology and then collaborate to answer major diagnostic, therapeutic and scientific questions. This has been done for individual projects involving multiple centers, but never spread community wide. Success here does not mean that individual centers have to give up control of their data, or traverse Major unanswered questions of vital translational significance that could be enabled by such collaborations and tools to guide invasive epilepsy treatments include:

Who would be most impacted by this research?

The proposed collaborative infrastructure would initially benefit children and adults with refractory epilepsy, though it will rapidly be leveraged to treat all individuals with seizures, tracking biomarkers as well as localizing epileptic networks. We propose to establish a rich, translational, community-wide collaboration that melds quantitative disciplines with state-of-the-art clinical epilepsy data in order to establish the following:

1. A central cloud-based platform and tools for standardizing imaging, electrophysiology and clinical metadata for annotation, analysis and sharing. The platform should allow visualization, annotation, analysis, data sharing and publishing via the cloud. It should also handle and analyze multimodal imaging and connect with existing epilepsy imaging consortia. We already have several powerful resources available that can be linked and adapted for this purpose. This infrastructure could include either a central repository, like ieeg.org, or powerful tools that allow investigators to standardize, find, process, access and analyze data federated across centers or platforms, without the need for moving the data to a single location.

2. An infrastructure for establishing rigorous standards for electrophysiology and multimodal analysis (e.g. together with imaging).

3. A large cache of multi-scale and high-resolution electrophysiology data from patients implanted with intracranial electrodes who have undergone resective surgery, laser ablation, grid, strip or stereo EEG. These data should include multimodal imaging and implement standardized electrode co-registration and seizure marking, manually and with quantitative tools, and be of high quality. We would encourage all US centers engaged in these activities to contribute data collaboratively.

4. A pool of experts to develop and test network models, biomarker detection algorithms, and retrospective quantitative clinical trials of seizure localization and different therapies across a large number of patients, to set up data for prospective trials.

5. Establish a large, multicenter "sandbox" of high-quality data upon which to train and test new analytic tools, which will greatly accelerate and economize future quantitative epilepsy research. This "sandbox" can also serve as the best place to train new investigators interested in quantitative research and engineering solutions applied to epilepsy care.

We point to the successes of IEEG.org in establishing now gold standard algorithms for seizure detection and prediction that are used worldwide, as well as an infrastructure on which to benchmark and publish new algorithms that may have promise to improve upon these standards. We believe this same infrastructure or type of infrastructure could dramatically improve invasive epilepsy treatment, research and training. It will also accelerate basic and translational epilepsy research and clinical trials at numerous levels, including in biomarkers, antiepileptic medications and comorbidities.

Tags

- **epilepsy**
- **neurotech**