November means voting season! Like many Research Quarterly readers, I voted this November. But I also served as an election judge in my home district for the first time. I had never been part of the process before, and I got to see from the inside what it takes to hold a free and fair election where people make their voices heard. It was exhilarating to feel that I had an important role to play in our democracy, even at a small scale.

For families living with epilepsy, becoming involved in the research process can be the same kind of experience. Talking with scientists about your journey and learning about their work to better understand epilepsy and find new treatments and cures can also be exhilarating. Making sure that your voice is heard in setting research priorities, or enrolling as a participant in a research study, can be a way to take back some control and help to change the outcome for others with epilepsy. It reminds me of our new End Epilepsy campaign slogan, “Epilepsy can affect anyone with a brain, and anyone with a brain can affect epilepsy.”

This issue of the Research Quarterly highlights the many ways that we are supporting innovation, ecosystem building and solving problems. Our Chief Scientific Officer, Dr. Jacqueline French shares her insights on new and developing epilepsy therapies. Read about the research being done by scientists supported by Epilepsy Foundation grants in partnership with the American Epilepsy Society and the American Brain Foundation. Learn about the exciting research being done to empower people by improving seizure forecasting and mapping the brain. Become part of the process of building a learning healthcare system that makes people living with epilepsy equal partners in clinical research aimed at optimizing diagnosis, finding the best treatment options, improving seizure control and striving for seizure freedom. Let’s make our voices heard!

Sincerely,

Brandy Fureman, PhD
VP of Research & New Therapies

www.epilepsy.com/research
In October, the Epilepsy Innovation Institute awarded a $3 million grant to an international team of scientists, researchers and interoperability experts to evaluate biosensors that can track an individual’s physiology, behavior, and environment to improve seizure prediction.

Team members from Mayo Clinic, King’s College London and Seer Medical/The University of Melbourne will evaluate biosensors in a range of commercially available devices. The team will recruit, and collect data from, people with epilepsy who have received an implanted device that can measure brain activity — such as electroencephalogram (EEG) devices — to better understand changes in the body that induce or allow for seizure activity. The team receiving the grant was selected following a seven-month long, peer-reviewed process. The ultimate goal of this award is to definitively assess the types of measurements that are needed for a reliable seizure forecasting prototype device.

"Unpredictability, not knowing when or why a seizure starts, is a major challenge for those living with epilepsy. . . we have a unique opportunity to create an individualized seizure gauge that will allow a person with epilepsy to monitor the likelihood of a seizure on a daily basis."
- Sonya Dumanis, Ph.D., Senior Director of Innovation, Epilepsy Foundation

The Epilepsy Foundation’s Epilepsy Innovation Institute launched the My Seizure Gauge Challenge in October 2017 following a workshop that discussed and assessed the state of the science behind seizure forecasting. During the collaborative workshop, clinicians, engineers, data scientists, and pharma/device companies reviewed feedback from people living with epilepsy and their families and decided to take on seizure forecasting as their first innovation project.

"The My Seizure Gauge initiative lays the groundwork for a person with epilepsy to know when a seizure is likely or unlikely. This knowledge can empower people to feel more in control of their lives, take action to stop a seizure before it starts, and may help to explain why certain environments or states may trigger a seizure in an individual. It may also aid in developing personalized medication dosing and device stimulation to reduce side effects."
- Jacqueline French, M.D., Chief Scientific Officer at the Epilepsy Foundation and Professor of Neurology at NYU Langone Health’s Comprehensive Epilepsy Center

In the initial phase of the award, the team will evaluate biosensors that can track an individual's physiology, behavior and environment from a range of commercially available devices. Following testing, the team will select up to three peripheral sensors to move forward for seizure forecast testing in year two. People with epilepsy will be pairing the peripheral sensors selected with their already implanted EEG recording devices. The EEG system used will depend on the recruitment site: Mayo Clinic (Medtronic RC+S intracranial device), King’s College London (UNEEG ambulatory subscalp EEG), and the Seer Medical/The University of Melbourne (Seer Medical ambulatory video EEG, SeerGP app, and subscalp EEG). The vision is to measure a few components along with myriad factors, and then mine the data for new clues about what happens in the body in the hours and minutes before a seizure. Once the data has been collected it will be shared with the research community through crowd-sourcing platforms to facilitate algorithm development.

The Epilepsy Innovation Institute is an innovation incubator, tackling high-risk, high-reward projects through a series of million-dollar challenges. Each challenge is focused on “beginning-to-end solutions” directed toward specific patient-centered challenges and carried out by multidisciplinary solution teams. For more information about the My Seizure Gauge initiative, please go to, http://bit.ly/2OO7IP5.

How could seizure forecasting transform your life? Share your thoughts on social media.

Tag us @EpilepsyFdn #EpilepsySolutions
Imagine having a Google Map for your brain that highlights your unique brain traffic pattern. With this map, you could better identify the routes your seizure could take, where the potential traffic jams might be, and how activity can get re-routed in the brain during those situations.

Such a dynamic map would lay the groundwork to:

- Identify key brain regions unique to the individual that could be critical for seizure control
- Improve our abilities to visualize how a seizure spreads, which may improve surgical options and outcomes
- Optimize neurostimulation therapies to the individual
- Better understand the biological profiles of epilepsy syndromes, which in turn could improve diagnosis and address why seizures occur

Although there was clear agreement that such a tool could transform current clinical practice by allowing clinicians to tailor treatment to the individual and identify novel treatment strategies, the roadmap to getting there was less clear. We are still in the early days of brain mapping.

The Roadblocks

- Access to data. We need to attract outside experts in mathematics and computer science to test new approaches for modeling brain maps. How can we as a community support data sharing and data analysis initiatives on data already collected?
- Development of noninvasive tools to measure brain activity (outside of EEG) during a seizure. If we could couple EEG measurements with other brain activity measurements, we would get a better overview of what is happening during the spread of a seizure. How can we as a community encourage the further development of new imaging tools?

In September 2018, the Epilepsy Innovation Institute hosted a workshop to assess the state of the science on how such a Google Map could be created to model an individual’s seizure spread patterns in the brain. The workshop convened multiple stakeholders including people impacted by epilepsy, basic scientists, clinicians, mathematicians, engineers, and industry representatives.

Our Solution

The Epilepsy Innovation Institute wants to push the field forward in brain network modeling. We are currently raising funds to support seed funding for pilot studies that would:

- test new mathematical approaches to model seizure propagation networks, or
- test the development of novel noninvasive tools to improve our ability to visualize the network for future modeling.

A key deliverable of any of these studies would be new visualization tools that could show how an individual’s seizure propagation network spread throughout the brain.

If you are interested in financially supporting this initiative, please contact Geoff Hoyt at ghoyt@efa.org. More details to follow in 2019.

Learn more at www.epilepsy.com/mybrainmap

How would you want to visualize your unique brain activity? Share your thoughts on social media.

Tag us @EpilepsyFdn #EpilepsySolutions
Over the past 25 years there have been a great number of antiepileptic drugs (AEDs) and devices that have gone through development, have been rigorously tested, and ultimately approved for use by the FDA (U.S. Food and Drug Association). Most of these have been approved for seizures beginning in a focus (focal epilepsy), which is the most common type of epilepsy in adults. Despite the wealth of new drugs, unfortunately one-third of people with epilepsy are still having seizures despite treatment. For this reason, it is very important that we continue to test and approve new drugs and devices for epilepsy.

Fortunately, there are still a large number of new treatments undergoing development and in the epilepsy pipeline, in addition to several others that have just been approved.

New and emerging drugs can be “evolutionary” or “revolutionary”. Evolutionary antiepileptic drugs improve on older AEDs with the same mechanism, with the expectation that they may have improved ability to treat seizures, or they may be safer. An example of an “evolutionary” drug would be brivaracetam (Briviact™) which is similar in its action in the brain to levetiracetam (Keppra™). Brivaracetam binds to the same brain location as levetiracetam but binds with greater strength (affinity). Now that brivaracetam is in the clinic, we will see if it has different effects on human epilepsy. One drug that spans the landscape between “evolutionary” and “revolutionary” is padsevonil, which combines 2 previously known mechanisms (that of levetiracetam and that of benzodiazepines, like diazepam). In animal models, the combination worked better than either drug alone. Padsevonil recently entered human clinical trials, so soon we should know if this benefit seen in the laboratory also translates to benefit for people with epilepsy.

Revolutionary drugs work in new ways. Examples include cannabidiol (Epidiolex™) and cenobamate (mechanism of both novel but currently unknown), perampanel (Fycompa™, works to reduce excitation in the brain), and low dose fenfluoramine (releases serotonin in the brain). Cenobamate has been quite effective in clinical trials in adults whose focal seizures could not be controlled with other seizure medications. It will be submitted to the FDA for review in the near future.

Recently drug development has shifted to include development of antiepileptic drugs for “orphan” syndromes. These are the less common epilepsies, often seen in childhood, and very devastating in their impact on the developing brain. New therapies are urgently needed for the orphan epilepsies. Drugs undergoing development for one orphan epilepsy, Dravet syndrome, include fenfluoramine and huperzine. Cannabidiol (Epidiolex™) and stiripentol (Diacomit™) were recently FDA approved for Dravet syndrome, becoming the first ever drugs specifically approved for Dravet syndrome. Fenfluoramine is also in development for Lennox-Gastaut syndrome and cannabidiol (Epidiolex™) was recently FDA approved for this syndrome.

Another new concept in drug development is the introduction of drugs that are disease-modifying (that is they work on the underlying disease processes rather than just suppressing seizures). Our current drugs (including most of the drugs under development) are really “anti-seizure” rather than “anti-epilepsy” because they don’t do anything to “fix” what is wrong in the brain that causes epilepsy. The first FDA approved disease-modifying epilepsy drug is everolimus (Affinitor™). Everolimus reduces the activity of a key substance in the brain (M-Tor) which is overly produced in some genetic epilepsies (i.e., Tuberous Sclerosis Complex). Studies now show that “knocking down” this protein’s activity can reduce epilepsy burden. Scientists need to continue the hunt for key mechanisms that have gone astray in people with epilepsy, that could be normalized to help improve outcomes.

Overall, there are many exciting drugs in the epilepsy pipeline, and more being discovered all the time. Hopefully, this will lead to better options in terms of both seizure control and improved quality of life.
What was the primary goal of your research award? The primary goal of my research is to develop new tools to accurately and non-invasively diagnose epilepsy in people with Alzheimer’s disease (AD).

What is the actual prevalence of epilepsy in the AD population? High quality studies that address this question are needed. A reasonable estimate would be approximately 4-5%. This number represents the population of AD patients who sought medical care for a clinically obvious seizure or unusual spell, which led to a diagnosis of epilepsy. In reality, many more people with AD may be having seizures that go unrecognized and untreated.

What makes it so difficult to diagnose epilepsy in the AD population, and what approaches are you taking to improve this? Seizures in AD can be subtle and can present as just a minute of unresponsiveness, or a brief spell of increased confusion. Given memory and other cognitive problems that people with AD have, you can imagine that many of these seizures go unrecognized by patients, caregivers, and even physicians. Some people with AD have seizures that occur without any symptoms, and you would never know they were having seizures unless you monitored their brain’s electrical activity. Another major reason that epilepsy in AD is difficult to diagnose is that seizures and epileptiform activity in AD most likely arise from the mesial temporal lobe (mTL), a structure that lies deep within the brain. Most epileptiform activity from the mTL is not visible on a scalp EEG, our standard clinical test for diagnosing epilepsy. In people with epilepsy, we sometimes use invasive intracranial electrodes to visualize mTL epileptiform activity, but this kind of approach is almost never used in AD patients.

One primary focus of my research is to understand how common epileptiform activity is in people with AD. If we take people with AD who do not have a diagnosis of seizures, how many of them have epileptiform activity on their scalp EEG? Remember, most mTL epileptiform activity is not visible on a scalp EEG. Developing computational approaches that improve our ability to detect mTL epileptiform activity on scalp EEG is critical.

Do you think this could lead to new treatments for AD? I hope so! Before we get there though, we need to better understand the role of epileptiform activity in AD. How common is it, and does it contribute to memory problems in AD, as we know it does play a role in people with epilepsy? An interesting hypothesis is that epileptiform activity might even accelerate disease progression in AD. If that’s correct, we could potentially develop new medical therapies to reduce epileptiform activity and improve memory in people with AD.

How could this work transform clinical care in epilepsy? Neurodegenerative diseases like AD are among the most common causes for new onset epilepsy in the elderly. A better understanding of which AD patients are likely to develop epilepsy and how abnormal brain electrical activity affects cognition will be important for informing our approach on how to screen for and treat epilepsy in AD. From a general standpoint, this work will provide tools to non-invasively detect mTL epileptiform activity. This will improve our ability to diagnose temporal lobe epilepsy and may reduce need for invasive intracranial electrode studies we currently use.

How do you envision the future of epilepsy research moving forward? From a clinical standpoint, we are still “in the dark” with regards to how to treat epilepsy. Medication selection and adjustment is largely a trial and error process. How do we select the correct medication for an individual, and how do we know when a person is on an adequate dose to prevent seizures? Similarly, when we diagnose epilepsy, can we determine early on whether that person’s seizures are unlikely to respond to medications, so that we can avoid subjecting them to years of failed medication trials before pursuing surgical or other treatment options? There is a need for biomarker development on these fronts, and advances in our understanding of epilepsy from molecular, genetics, and –omics perspectives as well as the advent of big data and machine learning approaches that will help us get there. For people who are refractory to medications, we will start seeing development of more targeted surgical approaches. Brain stimulation and network modulation treatments for epilepsy are in their infancy. Improving our understanding of which networks to target and how to effectively do so for different types of epilepsy will expand treatment approaches. Last, while most of our treatments are geared towards stopping seizures in people who have already developed epilepsy, we really have no methods to prevent epilepsy from developing after brain injuries like stroke or traumatic brain injury. Advances in our understanding of epileptogenesis will be essential for developing epilepsy-preventative therapies.
Imagine building a learning health system in which all people – family and community members, clinicians, researchers and health system leaders – work together. They design, implement, and share the results of collaborative research and quality improvement efforts. And this work leads to better health outcomes and increased quality, experience, and value in care. A learning health system approach can dramatically accelerate the ability to generate new knowledge and put it into practice.

In 2018, the Epilepsy Foundation was awarded a PCORNet Learning Health System Network Pilot Collaborative grant to establish an Epilepsy Learning Healthcare System (ELHS).

**Our mission** is to design and implement a system of co-production that will improve outcomes for people with epilepsy and their families in the following specific ways:

- Improve quality of life
- Improve seizure control
- Improve seizure freedom

**Our vision** is a healthcare system in which we learn from every person with epilepsy, and in turn, improve outcomes for everyone with epilepsy. We do this by regularly collecting information about patient diagnosis, evaluation and care from doctors and hospitals, then gathering and analyzing it centrally in a standardized way. This information is then rapidly returned to answer questions about:

- Quality care
- Diagnostic processes
- Comparative effectiveness of treatments
- Utility of self-management strategies and healthcare and community-based services

Ultimately, a learning healthcare system in epilepsy will also support multi-site quality improvement projects, clinical trials, and observational research studies to improve seizure control for all people living with epilepsy.

With the support of the Epilepsy Foundation, the National Association for Epilepsy Centers, the Patient Centered Outcomes Research Institute and the Anderson Center for Health Systems Excellence, the ELHS is building a quality improvement and research network dedicated to improving outcomes for children and adults with epilepsy.

By connecting epilepsy centers and including people with epilepsy and their families, the ELHS will empower all people with epilepsy to live their highest quality of life, striving for freedom from seizures and treatment side effects. ELHS centers learn from every patient at every visit. Data is gathered from ELHS clinics across the country into a registry. The data is analyzed centrally to find best practices that will lead to better outcomes for patients and their families. At each center, experts will facilitate in person learning sessions. Monthly webinars will be held in which providers can share improvement on practices with the entire network. New ideas are generated and tested in ELHS centers using iterative Plan-Do-Study-Act (PDSA) cycles. Patients and families are integrated at every step to drive priorities, design new initiatives, and provide insight.

The ELHS strives to improve quality of life and to reduce or eliminate seizures for all people with epilepsy. The Epilepsy Foundation is proud to be working with the following partners in this effort:

- Rare Epilepsy Network
- National Association of Epilepsy Centers
- American Epilepsy Society
- American Academy of Neurology
- Child Neurology Society
- Child Neurology Foundation
- Epilepsy Study Consortium
- Healthcare providers and researchers

**To Learn More Please Contact:**
ELHS Program Manager
Dr. Kathleen Farrell at kfarrell@efa.org
Or visit us at: epilepsy.com/elhs

**Publication Alert**

In October 2018, the Epilepsy Foundation co-authored a paper in *Journal of Pediatrics* that describes how rare epilepsies are more than just seizures.

Click here to learn more: http://bit.ly/2Qg92pf
Assistant Professor of Neurology at Northwestern University, Dr. Gemma Carvill was just awarded the prestigious NIH New Innovators Directors Award. This award supports exceptionally creative investigators who propose innovative, high-impact projects. We are proud to have supported Dr. Carvill early in her career and congratulate her on this new accomplishment!

In 2013, the Foundation awarded Dr. Carvill a postdoctoral fellowship to study epilepsy. In 2017, through our partnership with the American Epilepsy Society (AES), the Foundation also funded her work in genetics through an AES/EF Junior Research Investigator Award.

Over the past few years, there has been tremendous progress in identifying novel genetic causes for pediatric epilepsy subtypes. The overall mission of Dr. Carvill’s lab is to define the genetic basis of epilepsy, understand disease mechanisms, and develop new therapeutics. Current medications only treat the outward symptoms of a seizure but not the underlying cause. Genetics provide a clue to the potential mechanisms for why the epilepsy begins. Dr. Carvill studies how genetics can impact brain function in epilepsy as well as how prevalent these mutations are in the population.

“This NIH New Innovators Directors Award focuses on identifying genetic and epigenetic variation in epilepsy. Much of the preliminary work and ideas in this award stem from research supported by the Epilepsy Foundation, both as a postdoctoral fellow, and last year as a Junior Investigator Awardee. Early career support from the Epilepsy Foundation gives young scientists, including myself, the opportunity to explore new and innovative ideas that can serve as a spring board to getting their independent labs off the ground. More importantly they sponsor research that will impact the lives of patients by facilitating better diagnoses and cures.” - Dr. Gemma Carvill

Many of today’s educators, senior investigators, and thought leaders for epilepsy were supported in their early careers with financial assistance from the Epilepsy Foundation. Since the 1960’s, we have been planting the seeds for our future, supporting the careers of over three thousand epilepsy researchers. Recently, we have partnered up with the American Epilepsy Society to continue our longstanding support of the next generation.

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**Epilepsy Foundation Research to be Shared at the 2018 American Epilepsy Society (AES) Annual Meeting**

The AES Annual Meeting is the largest gathering on epilepsy in the world and provides an opportunity for Foundation teams to link with key partners in basic science, clinical practice, industry, and advocacy. The following research will be presented,

**A 3 Year Review of Epilepsy Foundation 24/7 Helpline: Utilization, Constituent Needs, Resource Referral**

*Rationale:* Health helplines are integral to present-day healthcare, offering fast, low-cost, and geographically unrestricted access to health information, psychosocial support and links to resources and referrals. This study examines the utilization of the Epilepsy Foundation’s 24/7 Helpline service which offers information, support, resources and referrals for people living with epilepsy, their families, and healthcare professionals.

**Comorbidities of rare epilepsies: Results from the Rare Epilepsy Network (REN)**

*Rationale:* Although many studies have examined epilepsy-associated comorbidities, very few studies have reported comorbidities in rare epilepsies. Despite being rare, these understudied conditions with epilepsy are associated with a broad spectrum of serious comorbidities and high mortalities. We describe prevalence and characteristics of a range of comorbidities across different groups of rare epilepsies.

**Feasibility of Depression Screening by a 24/7 Epilepsy Helpline**

*Rationale:* People with epilepsy are at greater risk for depression and suicide than people without epilepsy. Currently, there is no routine screening for depression in people with epilepsy outside of an encounter with a healthcare provider (HCP). The Epilepsy Foundation’s 24/7 Helpline received 10,310 inquiries in the past year offering a possible venue for depression screening and referral for mental health care and education in adults with epilepsy.
Focused Ultrasound for Treatment of Epilepsy

The University of Virginia Comprehensive Epilepsy Program is conducting a research study on the use of focused ultrasound to treat deep lesions in the brain causing intractable epilepsy in adults 18 to 80 years old. The study will evaluate the effectiveness and safety of an investigational device that uses ultrasound or sound waves from outside the head to treat seizures that are not well controlled by medication and are due to a small growth of abnormal cells in the middle of the brain, most commonly hypothalamic hamartomas.

Partial-Onset (Focal) Seizures Trials

Eslicarbazepine Acetate (ESL) As First or Later Add-On Therapy for the Treatment of Partial-Onset Seizures

This study is looking at how effective and safe eslicarbazepine acetate (also known as ESL) is in people 18 years of age or older with partial-onset (focal) seizures, when it is added to their current anti-seizure medication(s).

Epilepsy Foundation’s Human Epilepsy Project (HEP2): Resistant Focal Seizures Study

The Epilepsy Foundation is launching a new partnership, called the Human Epilepsy Project, in collaboration with the Epilepsy Study Consortium. This study, the Human Epilepsy Project 2: Resistant Focal Seizures (HEP2) is designed to better understand the challenges of living with focal seizures that do not respond to medication and determine biomarkers of epilepsy severity and treatment response.

Focal or Generalized Seizures Trials

Effectiveness of Inhaled Staccato Alprazolam in Treating an Episode of Focal or Generalized Seizures

A new clinical trial is looking at how effective and safe orally-inhaled alprazolam (also known as STAP-001) is in people 18 years of age or older with focal or generalized epilepsy when given at the time of a seizure episode. This study is commonly referred to as StATEs (Staccato Alprazolam Terminates Epilepsy Seizures).

Epilepsy Genetics Initiative (EGI)

The Epilepsy Genetics Initiative (EGI) was created by Citizens United for Research in Epilepsy (CURE) to bridge the gap between people with epilepsy, clinicians, and researchers and tailor advances in medical care and decision-making to individual patients. The EGI has created a centralized database to hold and analyze the genetic data of people with epilepsy.

Learn more at: www.epilepsy.com/clinical_trials
Upcoming Conferences
Antiepileptic Drug and Device Trials XV
May 22 - 24, 2019, Miami, FL
https://aedtrials.com/

The International Conference for Technology and AnaLysis of Seizures (ICTALS)
September 2-5, 2019, University of Exeter, United Kingdom
http://exeter.ac.uk/ictals2019

Have a conference that you want to share?
Email ahansell@efa.org

Upcoming Research Grants
Shark Tank Ideas
Letter of Intent due December 14, 2018
Award up to $200,000

New Therapy Commercialization Grants
Submissions open December 14, 2018
Letter of Intent due January 28, 2019
Award up to $350,000 over 2 years

SUDEP Biomarker Challenge
Now accepting submission entries
Deadline October 10, 2020
Award up to $800,000

AES Early Career Funding Opportunities
Submissions open November 1
Letter of Intent due December 20, 2018
Awards range from $30,000 to $50,000

Rare Epilepsy Network
Now accepting research data requests

Learn more at www.epilepsy.com/research under Upcoming Grants

Have a grant opportunity that you want to share?
Email grants@efa.org

Want to join the Epilepsy Foundation Research Team?

JOB OPENING: Clinical Research Coordinator

www.epilepsy.com/make-difference/careers/clinical-research-coordinator