Quality Neurological Care without the Commute

It was an idea that started a little over five years ago: place Penn Medicine neurologists in the community to provide easier access for people with chronic neurological conditions. Today, that idea has blossomed into a thriving community network of about 15 providers at six locations in Pennsylvania and New Jersey. The reason for this growth can be summed up in one word: demand.

"Neurology is increasingly becoming an extremely in-demand specialty area," shares Frances Jensen, MD, FACP, Professor and Chair, Department of Neurology, Penn Medicine. "There’s a lot of need in the community, so our initial thought was to bring in more subspecialists to manage things like epilepsy and stroke and increase general neurology access for conditions that are being followed in partnership with family physicians."

Even with this change, however, the department was still experiencing bottlenecks at its main campus location. So, Dr. Jensen took things one step further and tried placing experienced Penn general neurologists in local primary care centers in West Chester and Kennett Square. The concept was so well received that neurologists were soon added to centers in Valley Forge, Woodbury Heights, Cherry Hill and Rittenhouse Square. To help oversee and unify this thriving network, Dr. Jensen appointed Roderick Spears, MD, FAHS, FAAN, as Regional Director.

“All of the practices have done really well and have grown significantly since they were established,” says Dr. Spears. “A lot of this has to do with the quality of care but also with the comprehensive services we provide.”

“For example, at Penn Medicine Valley Forge where I practice, we offer interventions such as Botox® for migraines, spasticity and cervical dystonia,” he says. “We also

A MESSAGE FROM THE CHAIR

It’s almost impossible to not be awed by the way the nervous system seamlessly unites and mobilizes all of the disparate parts that make up a healthy human body. This idea of connecting and organizing is one that I think beautifully mirrors the current activities of our department at Penn.

In our field, it’s becoming clear that to push the boundaries of medical knowledge and advance care, we need to think beyond the comforts of our own clinical specialty. Increasingly, our department is prioritizing connections with other clinical specialties such as psychiatry, neurosurgery and neuroscience in the pursuit of discovery. We’re also working on cross-cutting research that involves neuroimmunology, gene therapy, and brain stimulation—major strengths of Penn Medicine and ideas that weren’t even thought possible as recently as a decade ago. These collaborations have allowed us to make significant inroads in several neurological diseases and have yielded some truly exciting results.

Among these is the identification of new targets around specific immune cell populations, which can be harnessed for potential treatment or staging of neurological disease. As we increase our understanding of the common threads between immune system dysfunction and neurological disease, discoveries
A Message from the Chair

such as this allow us to open new avenues for research and patient care.

Gene therapy is new territory for our specialty and one where Penn is poised to be a national leader thanks to our strength in this field. Already, we are the site of some of the first FDA-approved gene therapies for the brain and nervous system, including one for spinal muscular atrophy and another for blindness. There are several other early-stage trials in the pipeline and we’re hopeful these will be successful as well.

In the third area—brain stimulation—we are exploring invasive stimulation as well as the non-invasive ways of modulating brain function which include transcranial magnetic stimulation and transcranial direct current stimulation. Researchers are finding that these modalities can be useful in treating depression as well as promoting recovery from brain injury and stroke, and potentially managing other movement disorders. Additionally, Penn is one of the first with a focused ultrasound unit (another way to modulate the brain without surgery). Already FDA approved for tremor, we’re exploring its application in Parkinson’s disease and epilepsy.

Efforts such as these exemplify our department’s mission of service to our patients and our commitment to pursuing therapies and treatments for neurological conditions that have hitherto been incurable. I feel that this environment, which fosters forward-thinking and multidisciplinary collaboration, is an ideal setting for future leaders to learn, discoveries to take place, and for patients to receive care.

I hope that you enjoy this issue of Penn Neurology Advances and invite you to contact me anytime, come in for a visit and connect with us. Thank you for your past and future support of our department and staff.

Best regards,

Frances E. Jensen, MD, FACP
Professor and Chair, Department of Neurology
Penn Medicine

Quality Neurological Care without the Commute

have an infusion service for headaches and offer dedicated programs for neuromuscular and peripheral nerve disorders as well as a full radiology suite and lab services for diagnostic tests. Other sites offer specialized services such as EMG and nerve conductive studies."

Additionally, the network sites serve as gateways to clinical trials for qualifying patients. "When we hear about trials, we’re able to share this information with our patients and refer them downtown for the initial uptake appointment," Dr. Spears explains. "After that, patients can often be seen locally by their regular Penn neurologist. This is really the main difference between the community sites and main campus. We’re clinically focused, and the main campus is research focused."

As the network sites became a reality, one thing became very clear, says Dr. Jensen: the department needed to maintain a strong connection with its neurologists practicing in the community.

“The field is changing rapidly with innovative treatments and protocols emerging at an incredible pace,” she says. “Within the last three years we’ve seen new therapies for multiple sclerosis, spinal muscular atrophy, and epilepsy as well as several cutting-edge diagnostic tools. It’s very important that we keep our general neurologists up to speed on these options so they can continue providing exceptional care.”

One way in which they are doing this is by providing network neurologists with access to streamed lectures and CME courses. Some of these neurologists also teach and mentor residents at the main campus, thereby helping these future neurologists gain a better understanding for the community setting.

“This model has really worked well, and we fully anticipate adding more physicians to our network practices in the future,” says Dr. Jensen. “Ultimately, it comes down to providing our patients with the care they need in a setting that works for everyone, and I think we’ve found a great way to do that.”

“Neurology is increasingly becoming an extremely in-demand specialty area. There’s a lot of need in the community, so our initial thought was to bring in more subspecialists to manage things like epilepsy and stroke and increase general neurology access for conditions that are being followed in partnership with family physicians.”

—Frances Jensen, MD, FACP, Professor and Chair, Department of Neurology, Penn Medicine
While new surgical techniques and implantable devices are increasingly available for up to 1 million people in the United States with drug-resistant epilepsy, rates of seizure freedom after surgery haven’t significantly improved.

It’s not for lack of tools, says Brian Litt, MD, Director of the Penn Epilepsy Center and Penn’s Center for Neuroengineering and Therapeutics. The missing piece is a standardized blueprint to guide their use.

“Today, a patient who goes to five epilepsy centers might be offered five different implants and five different approaches to surgery,” Litt explains. “That’s because surgical mapping is done manually by marking seizures on intracranial EEG (iEEG) by eye, and then trying to determine seizure onset time, location, and the regions of origin.”

Enter virtual cortical resection (VCR): a promising method for quantitively mapping epileptic networks and simulating interventions to better predict patient outcomes. Dr. Litt is developing this technology together with Danielle Bassett, PhD, Associate Professor of Bioengineering and the recipient of a 2014 MacArthur fellowship during her first year at Penn.

**Mapping Epileptic Networks with Virtual Cortical Resection**

The brain network model was validated on a retrospective cohort of 28 patients with drug-resistant epilepsy who received intracranial electrodes prior to surgical resection. With their outcomes in hand, Litt and his team compared their model to the patients’ outcomes.

“We’ve had quite a bit of success so far,” Litt says. “Using a simulation to ‘treat’ different areas in a patient’s brain, the model accurately pinpointed places that were good candidates for ablation, resection, or modulation with an implantable device. It’s really a game-changer.”

Litt identifies additional benefits of virtual cortical resection. First, VCR could end the practice of provoking seizures in patients to map epileptic networks. Furthermore, it should reduce sampling bias and error, which are looming challenges to iEEG and epilepsy interventions.

“Knowing whether implants have missed vital seizure generators is key,” Litt says. “Together with Dr. Bassett’s team, we’re developing methods to assess the robustness of network models to under-sampling and to predict missing information.”

**Advancing the State of the Art**

Over the last four years, Litt’s team—a group of neurologists, neuro- and bioengineers, radiologists, and others—has been studying VCR to develop novel algorithms that may soon replace today’s imprecise, manual method for guiding epilepsy surgery.

This research, published in the October 2019 issue of *Brain*, was R01-funded and received additional grant funding from the National Institutes of Health, Jonathan Rothberg, and the Mirowsky Family Foundation.

Validation by Crowd-Sourcing

With what appears to be a viable process, the team’s next goal is to generalize and validate the methods and port them to clinical trials as quickly as possible.

This will require solving the major practical obstacles to validating and translating the method into clinical care. “Two major goals are to eliminate sampling and bias errors,” Litt explains, “and to validate the methods on a larger number of patients across centers. We also want to adapt our methods to Stereotaxic EEG.”

To clear these hurdles, Litt and his team have turned to epilepsy centers across the country.

“We’ve assembled a group of 15 major epilepsy centers to collaborate with us on validating the method,” he explains. “This larger group will aggregate and share data, algorithms and code in order to better position this method for a prospective clinical trial and patient care. The response from leading epileptologists has been enormous.”

Brian Litt, MD, pictured with John Bernabei, MD, PhD, (right), is exploring the use of virtual cortical resection as a means of guiding epilepsy surgery.
Neurogenetics Team Forms with ‘Tsunami’ of Breakthroughs Looming

The wealth of information that’s become available over the last 10 to 20 years coupled with the rapid evolution of the technology that can analyze it has dramatically transformed neurogenetics. The growing field is exploring how genetic abnormalities cause neurological disease and how genetic information can be manipulated to treat neurological disease.

Now, Pedro Gonzalez-Alegre, MD, PhD, Co-Director of the Division of Movement Disorders and Director of the Huntington’s Disease Center of Excellence, both at the University of Pennsylvania, and the Director of Clinical Programs at the Raymond G. Perelman Center for Cellular & Molecular Therapeutics at the Children’s Hospital of Philadelphia, believes researchers like himself are on the verge of what he describes as a “tsunami” of breakthrough therapies.

“It’s not here yet. We’ve got a few drops of water, basically,” Dr. Gonzalez-Alegre says. “But we’ve got to get ready for it. And I absolutely want to be a part of that wave because we are the world’s leading institution in gene therapy.”

Gradually, the scale of that research has also been growing. Faculty and students from the School of Engineering and Applied Science are developing more effective methods to administer gene therapy, Dr. Gonzalez-Alegre says. And that’s only the tip of the iceberg.

At the moment, a growing group of researchers within Penn’s Department of Neurology is studying neurogenetics from many different angles.

“We’re identifying new genes that cause neurological disease. We’re trying to better define the clinical symptoms and signs that people with specific gene mutations and a neurological disease have so that we can teach people to look for those mutations,” Dr. Gonzalez-Alegre says. “We’re trying to develop personalized approaches to treatment for patients that have a neurological disease caused by a specific gene defect. And we’re trying to develop ways to manipulate the genome of a patient so that we can provide a benefit in therapy.”

Gradually, the scale of that research has also been growing. Faculty and students from the School of Engineering and Applied Science are developing more effective methods to administer gene therapy, Dr. Gonzalez-Alegre says. And that’s only the tip of the iceberg.

Five years ago, the department began assembling a group of clinicians, including Dr. Gonzalez-Alegre, with the main goal of developing the ability to systematically diagnose patients with neurogenetic conditions.

“Even though that sounds simple, it was not,” he says. “Most centers don’t do it. We’re really unique in the region in that regard. Now we’re confidently and routinely diagnosing patients with common and very rare genetic conditions.”

The next phase entails expanding the group beyond the Perelman School of Medicine to ultimately include engineers and Penn Health-Tech, to develop delivery devices and tools to measure their effectiveness; economists, to forecast how the onslaught of new therapies is going to impact the insurance market; and ethicists, to help the researchers navigate these uncharted waters.

“The overarching objective for this group is to enable things to happen,” Dr. Gonzalez-Alegre says. “If there’s a pioneering therapy that someone at Penn, or even outside of Penn, is developing and they don’t have the means or expertise to get
it to a proper clinical trial, we want to fill in all of those voids and facilitate that process."

Another big piece of that puzzle, the research site itself, is also on the cusp of falling into place. Dr. Gonzalez-Alegre expects the Translational Center of Excellence for Gene & Molecular Therapy in Neurology to formally launch in early 2020. He will serve as its director. The center will be the fourth of its kind established by Penn Neurology, with another two currently in the planning stages, all with the aim of supporting pilot projects to accelerate high-impact areas uniquely suited to the department.

"We want to be a site for many first-in-human trials. And not only a site; we want to be a leading site and a principal investigator for many of them," Dr. Gonzalez-Alegre says. "Several companies that are heavily invested in this area have expressed an interest in partnering with us based on the infrastructure that we already have in place and our plans for the near-future."

A process that has moved at a methodical pace is likely to escalate over the coming months as the shadow of that tsunami looms larger.

"We’re going to see remarkable changes in the next few years. We’re going to be treating diseases we felt were incurable a few years ago. There’s a lot of potential to not just do more but to do it faster," he says. "It’s going to take a large investment initially. But if it’s made wisely—and, right now, there is no better place to invest than here at Penn—the yield is going to be enormous."

Pedro Gonzalez-Alegre, MD, PhD, pictured with research assistant Shareen Nelson (right) is working to position Penn as a leader in the area of neurogenetics.

To put into perspective just how much ground has been covered over the course of the young career of Tanya M. Bardakjian, MS, LCGC, consider this: BRCA1 was discovered only 25 years ago. And BRCA2 followed a year later. It was in the wake of those heady times that Bardakjian became a genetic counselor.

"The number of genes that we knew of at that time that are associated with conditions was still very small, and they were concentrated in pediatrics and prenatal. And hereditary cancer was just coming to the forefront," says Bardakjian, Co-Director of the Neurogenetics Program and the Huntington’s Disease Center of Excellence and the lone genetic counselor in Penn’s Department of Neurology.

Poised now on the cusp of what fellow Neurogenetics Director Pedro Gonzalez-Alegre, MD, PhD, describes as a “tsunami” of breakthrough therapies, Dr. Bardakjian is optimistic, but cautious.

“When I was working in pediatric and prenatal genetics in the beginning of my career, I used to have to tell people their children with spinal muscular atrophy were going to die. Now, that’s not always the case. I never dreamed we would be able to say that,” she says. “My biggest concern is the resources that will be needed over the coming years. There are only 5,000 board-certified genetic counselors in this country. In order to provide the therapeutics for these conditions, we have to know who has them. So, we have to diagnose them efficiently. We have to make sure that this is done responsibly, yet not too slowly so that people who do have these conditions can be identified, counseled appropriately, and then have access.”

Between the Neurogenetics Program’s plans and her own prominent positions as Co-Chair of the Neurogenetics Special Interest Group of the National Society of Genetic Counselors (NSGC) and member of the NSGC Public Policy and Abstract committees, Bardakjian says she feels an added responsibility to ensure a safe and ethical environment. But, then, she’s not one to shy away from responsibility.

“I always wanted to make sure that bad news was given appropriately in a manner that an individual could process and understand," Bardakjian says of what drew her to genetic counseling. “So much of genetic counseling and clinical genetic testing back then, and even now, was just not understood. So it was a perfect niche for me: I had an expertise and a desire to be there during a family’s and an individual’s journey with a rare disorder.”

Pedro Gonzalez-Alegre, MD, PhD

Guided by Cautious Optimism

Tanya M. Bardakjian, MS, LCGC
Grants Totaling $10 Million Facilitate Traumatic Brain Injury Research

Three grants awarded to Penn Neurology in recent months are facilitating ancillary studies to two major, multicenter clinical trials exploring the effects of traumatic brain injury (TBI). The grants total approximately $10 million.

“There’s been a significant increase in the amount of funding provided by the federal government for the study of TBI over the last 10 years,” says Ramon Diaz-Arrastia, MD, PhD, Presidential Professor of Neurology and Attending Neurologist at Penn Presbyterian Medical Center. “It’s come as a consequence of the recent combat in the Middle East as well as the evolving realization that athletes who participate in contact sports often suffer head injuries that have consequences.”

BOOST3 (Brain Oxygen Optimization in Severe TBI Phase 3) is a large, multicenter study, launched last year through a $32-million investment by the National Institute of Neurologic Disorders and Stroke (NINDS). The randomized, clinical trial is attempting to determine the comparative effectiveness of two strategies for monitoring and treating patients with TBI in the intensive care unit. Dr. Diaz-Arrastia is the protocol principal investigator (PI) for BOOST3. He was the contact PI for BOOST Phase 2. One of the three new grants is called Bio-BOOST, which will collect blood and spinal fluid samples from a subset of patients enrolled in BOOST3. Funded by the Department of Defense, Bio-BOOST will determine the relationship between brain injury biomarkers and abnormal physiology monitored by invasive intracranial probes.

The other two grants are earmarked for supplemental studies to TRACK-TBI (Transforming Research and Clinical Knowledge in Traumatic Brain Injury), a multi-institutional, observational study that began several years ago. In collaboration with public-private partners, researchers are collecting and analyzing detailed clinical data on subjects at 18 sites in the United States across the injury spectrum, along with CT/MRI imaging, blood biospecimens, and detailed clinical outcomes.

During the initial phase of TRACK-TBI, 3,000 patients were enrolled and followed for one year after their injuries. “We’re very interested in continuing to follow-up with them because we know that not everything that’s important in their recovery happens within the first year,” says Dr. Diaz-Arrastia.

One of the ancillary studies, called TRACK-TBI Epi, will focus that ongoing follow-up on post-traumatic epilepsy. People who have had a TBI are at an increased risk of developing epilepsy—in severe cases, the risk is over 25%—and it often occurs several years after the injury, according to Dr. Diaz-Arrastia. Through TRACK TBI Epi, which is also being funded by the Department of Defense, the follow-up will be extended through five years for all 3,000 patients enrolled in TRACK-TBI.

“A telephone evaluation will be part of TRACK-TBI Epi, and will include a screening questionnaire to see if they’re having events that could be post-traumatic seizures,” Dr. Diaz-Arrastia says. “Those who screen positive will be invited to come in for an in-person evaluation, which will include an MRI, EEG, and an evaluation by an epilepsy specialist to adjudicate whether they’re in fact having epilepsy or they’re having some other kinds of spells that may be non-epileptic.”

TRACK-TBI Epi is the first study of this magnitude that will allow prospective assessment of the development of post-traumatic epilepsy in people for whom so much data was collected during their acute period, according to Dr. Diaz-Arrastia. “We’re very interested in this project allowing us to identify predictive biomarkers that ultimately inform the design of potential anti-epileptogenic therapies because the therapies we have now can only control the seizures once the epileptogenic process has already taken place,” he says.

TRACK-TBI Bio is the second ancillary study funded by one of the newly-awarded grants. This NINDS-funded study will analyze neurofilament light—a protein found in the axons—in blood samples collected through TRACK-TBI. Samples were taken on the day of the patient’s injury, three days later, five days later, two weeks later, and six months later. “We’re going to evaluate how the elevations of neurofilament light correspond to the MRIs that we have,” Dr. Diaz-Arrastia says. “There are studies that point in this direction, but this will be by far the largest study to date to assess whether neurofilament light is a biomarker of external injury.

“One of the major pathologies in people that have had a brain injury is diffuse axonal injury to the large myelinated axons in the central nervous system,” Dr. Diaz-Arrastia. “Much of that occurs early on, but it appears to continue for a long period as well.”

There’s early evidence that people who have sustained a TBI are at greater risk of developing dementia later in their lives. Neurofilament light measured in the subacute and chronic period after injury could be helpful in identifying the subset of people who have suffered a TBI and are at risk of developing progressive neurodegeneration and dementia.
‘Dementia Pathway Project’ Aims to Better Align Patients with Resources

Approximately 5.7 million people in the United States are living with dementia, with Alzheimer’s disease accounting for 60% to 70% of the cases. But the number of new cases of dementia is increasing each year both here and around the world. In fact, a 2018 study projects that 13.9 million people in the US alone will be diagnosed with Alzheimer’s or related dementias by 2060.

An initiative being developed by Penn’s Department of Neurology and the neurosciences and primary care service lines is attempting to better align that growing population with the limited available resources.

“Most patients with dementia are seen by their primary care doctors. A few of them trickle over to neurology, but most of them are taken care of locally, out in the community,” says Sanjeev Vaishnavi, MD, PhD, Assistant Professor of Neurology at the Perelman School of Medicine and a Physician Researcher at the Penn Memory Center. “So the idea is, how can we best take care of those individuals? And, how can we in neurology, along with other specialists in psychiatry and geriatrics, help the primary care doctors provide the best and most appropriate care for those individuals, while also finding people who may be appropriate for more specialized care or research here at our facility?”

The initiative was a finalist for the Penn Medicine Center for Health Care Innovation Accelerator Program, which provides grants to applicants from the Penn Medicine and University of Pennsylvania community for concepts that illustrate potential to: achieve better health outcomes, redesign care, improve the clinician and care team experience, enhance the patient experience, and/or leverage nontraditional data and technology to support patient engagement, improve care, and uncover new clinical insights.

Dr. Vaishnavi says the “dementia pathway project,” as he describes it, is still in its earliest phase, which made it difficult to quantify in the grant application how much of an impact it could ultimately have.

“There’s been no implementation yet,” he says. “Right now, it’s kind of more getting all the key players in the same room and discussing how we currently take care of these individuals. We’ve gone through establishing who is seeing what here in our system. The next step will be to look at processes to see how we can improve care.”

Dr. Vaishnavi says he expects to reapply for the accelerator program grant next year, once the specific nature of the intervention is developed.

“The goal,” he says, “is that by the end of the academic year, we would have a pilot project, in terms of something that we could take out to the community with changes to how dementia patients are referred or managed.”

—— Sanjeev Vaishnavi, MD, PhD, Assistant Professor of Neurology at the Perelman School of Medicine and a Physician Researcher at the Penn Memory Center
“To push the boundaries of medical knowledge and advance care, we need to think beyond the comforts of our own clinical specialty.”
— Frances E. Jensen, MD, FACP
Professor and Chair,
Department of Neurology
Penn Medicine

To make an appointment with a Penn neurologist, please call 800-789-PENN (7366)
To make a referral, please call 877-937-7366
To donate to Penn Neurology, please call Lindsey Walker at 215-898-3037

Department of Neurology Welcomes New Faculty
This year, Penn’s Department of Neurology expanded its faculty with the addition of the following doctors:

Rachel Brandstadter, MD
Multiple Sclerosis

Christopher Perrone, MD
Multiple Sclerosis

Baochan Tran, PsyD
Neuropsychology

Colin Ellis, MD
Epilepsy

Ramya Raghupathi, MD
Epilepsy

Thomas Tropea, MD
Movement Disorders

Penn Neurology in the News
Select media stories from the past few months

The New York Times: The Loneliness of Frontotemporal Dementia
Sara Manning Peskin, MD, MS, a fellow in Cognitive Neurology, penned a piece about FTD, featuring Murray Grossman, MD, Director of the Penn FTD Center.

Netflix Explained: Beauty, Explained
Anjan Chatterjee, MD, Director of the Penn Center for Neuroaesthetics, was featured in an episode of the Netflix series Explained, discussing what makes things such as art and architecture aesthetically pleasing and enjoyable to look at.

PBS NOVA: The Violence Paradox
Roy Hamilton, MD, MS, an Associate Professor of Neurology, was interviewed about research to understand if stimulating the prefrontal cortex reduces a person’s intention to commit a violent, criminal act.

CBS3: ‘It’s Not A Death Sentence’: Growing Number Of Young Women Being Diagnosed With Multiple Sclerosis
Dina Jacobs, MD, Associate Director, Multiple Sclerosis Center, spoke with CBS3 about MS and her patient Danielle Bourgeon, a dancer who performed a piece about her experience with MS.