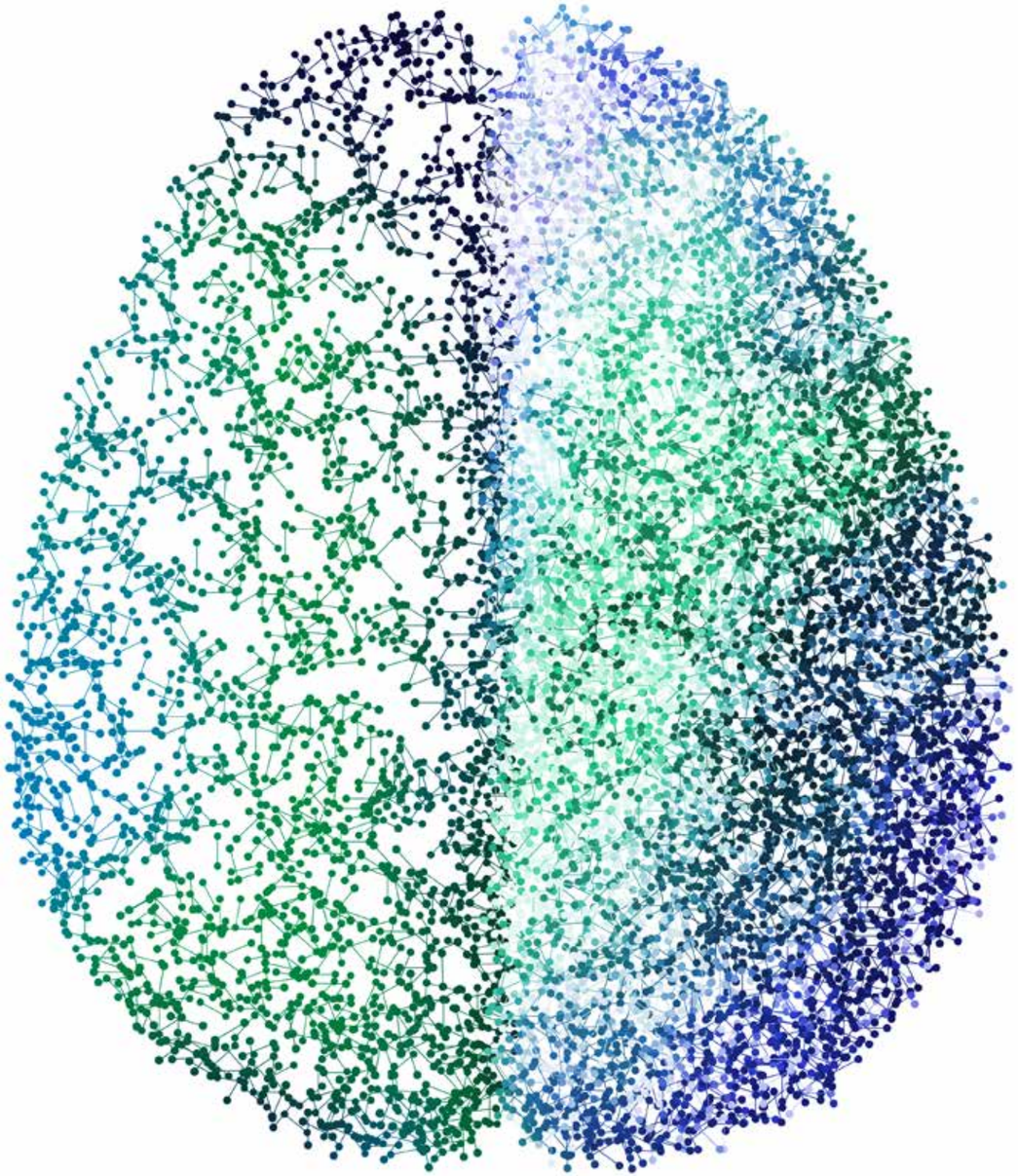
UTHealth®
Neurosciences
The University of Texas Health Science Center at Houston

UTHEALTH NEUROSCIENCES OUTCOMES REPORT 2019



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Dear Esteemed Colleagues,

As physicians, seeing our patients do well is the main joy of our profession. As a team, we hold each other accountable for the care we deliver. As we look back together on a decade of growth at UTHealth Neurosciences and UT Physicians Neurology we remain committed to raising the bar with first-rate clinical programs in all areas of neuroscience.

We're proud to join a handful of select facilities in Walmart's elite Centers of Excellence network providing the highest quality spine surgery to the company's associates. We will provide spine coverage for all Walmart associates in the southeastern United States, coordinating the entire experience for the patient from transportation from the airport through follow-up. Based on the success of the Walmart COE, we have expanded our spine program to other employers including HEB, McKesson Corporation, Lowe's and Jet Blue.

Our group now has more than 130 subspecialty providers in clinics located in suburbs throughout Houston, allowing us to coordinate the care of patients from all areas of Houston. In addition, the UTHealth Telemedicine Program has extended comprehensive neurological and neurosurgical care to 23 facilities in the southern half of Texas, providing 24/7 consultations for partner hospitals to ensure prompt diagnosis and help avoid unnecessary transfers to Houston.

Congratulations to our faculty who have received major recognitions, including neurosurgeon Arthur L. Day, MD, who received the prestigious Distinguished Service Award, the highest honor given by the Society of Neurological Surgeons, and Claudio Soto, PhD, who received a Michael J. Fox Foundation grant to develop a noninvasive biochemical test for early diagnosis of Parkinson's disease.

We're proud of our entire team of neuroscience providers, who do their best daily and consistently ask how to do things better.

Please feel free to contact us directly if you would like more information about our services, research and programs.

With best wishes,

Dong H. Kim, MD

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Neuroscience at Its Best

The providers at UTHealth Neurosciences have a reputation for innovation, high-quality outcomes and the best possible healthcare experiences, which draws patients from around the world. Together with UT Physicians Neurology, the group's clinicians, researchers and educators are nationally recognized for leading-edge medicine and consistently ranked by quality benchmarking organizations as leaders in clinical quality and patient safety. Their insights, technological innovations and success at applying research findings at the bedside are transforming the field of neuroscience.

Part of McGovern Medical School at UTHealth, the group is Houston's undisputed leader in neuroscience care and the foremost neuroscience provider in the southern half of Texas. The group has extended its continuum of care across the region, creating a citywide network of neurologists, neurosurgeons, neurointerventionalists, neuro-oncologists, interventional pain management specialists and advanced practitioners – and reduced referral wait times by building a new structure for the practice of neurology in the community. These providers analyze quality data and track outcomes as a group using the same standards employed by their counterparts at UTHealth Neurosciences at the Texas Medical Center. This helps them continually modify clinical practice and ensure exceptional patient experiences.

This comprehensive, integrated approach led to the creation of the Southwest's leading epilepsy program, a highly ranked neurotrauma program, a cerebrovascular center where physicians treat more aneurysms and arteriovenous malformations than any other center in the region, an established pediatric neurosurgery program in collaboration with Children's Memorial Hermann Hospital and The University of Texas MD Anderson Cancer Center, an unmatched spinal neurosurgery and reconstructive peripheral nerve surgery program and a Brain Tumor Center, where physicians diagnose and treat hundreds of new tumor patients each year. Physicians are also innovators in the treatment of multiple sclerosis, movement disorders, neurocognitive disorders, memory disorders and dementia, neuromuscular diseases, chronic pain and traumatic brain injury.

Through its telemedicine and neurocritical care programs, the group offers patients in outlying communities access to stroke,

neurology, and critical care expertise, as well as opportunities to participate in clinical trials. Twenty-three facilities in Texas are now linked through remote presence robotic technology. In addition, UTHealth physicians are reaching larger numbers of people and engaging them in a powerful way through patient access portals on the group's website.

Through the Innovation and Quality (IQ) Program, the group's leaders are organizing data to improve physician and service performance, fostering innovative ways to measure quality and track long-term outcomes, and increasing infrastructure support to enable faculty at McGovern Medical School to conduct more clinical trials and patient-centered research. The results of these novel treatments are quickly transitioned to clinical practice.

These efforts have led to a strong 12-year improvement in quality outcomes. During that time, our physicians have reported mortality rates well below the national expected benchmark and have seen a greater than 50 percent reduction in length of stay, despite the increased acuity of the patients they treat.

At a Glance

Physician Team

Staff Physicians	100
Clinical Residents and Fellows	85
Medical Students on Rotation	339
Research Fellows	40
Advanced Practice Providers	32

Inpatient Facilities

Total Neuro Beds	160
Neuro ICU Beds	38
Neuro IMU Beds	15
Neuro Acute Care Beds	61
Stroke Unit Beds	12
Neurorehabilitation Beds	12
Dedicated Operating Rooms	9
EMU Beds – Pediatric & Adult	13

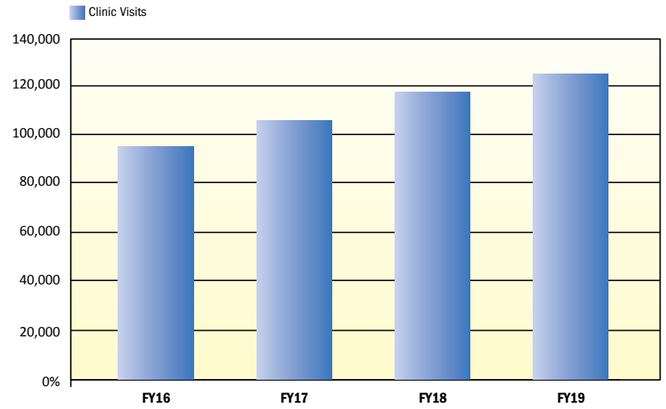
Research

Research Projects in Progress	More than 200
Grants Awarded	Over $50 million (Neurology and Neurosurgery)

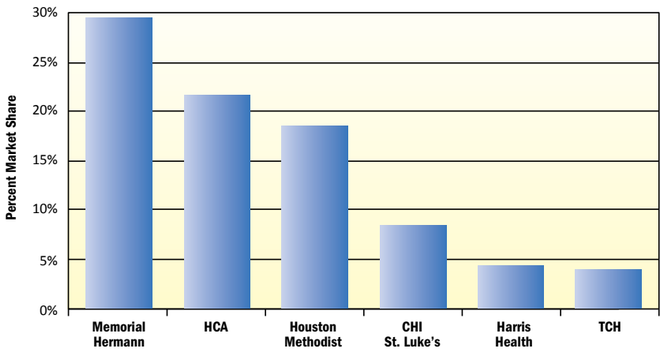
Specialty Equipment includes:

- Leksell Gamma Knife® Perfexion™
- Varian Trilogy Linear Accelerator
- Siemens Artis™ zee (intra-operative angiography suite)
- Robotic SEEG (ROSA)
- RP-7™ Remote Presence System
- 3D C-Arm
- Philips Healthcare endovascular temperature modulation system
- Simultaneous electroencephalography and polysomnography
- Continuous EEG monitoring
- Magnetoencephalography imaging (Magnes Elekta® Neuromag TRIUX)
- MRI capable of advanced spectroscopic and diffusion tensor imaging with tractotomy
- Portable CT machine
- Nihon Kohden EEG 1200 machine with NeuroWorkbench data management software
- Viking Nicolet EMG machines (2 freestanding) & Viking NicVue EMG Machine (1) portable
- Phillips CX50 sonography machine (4)
- LivaNova VNS therapy devices
- Allergan Botox injection amplifier
- Medtronic DBS programmer – Samsung tablet

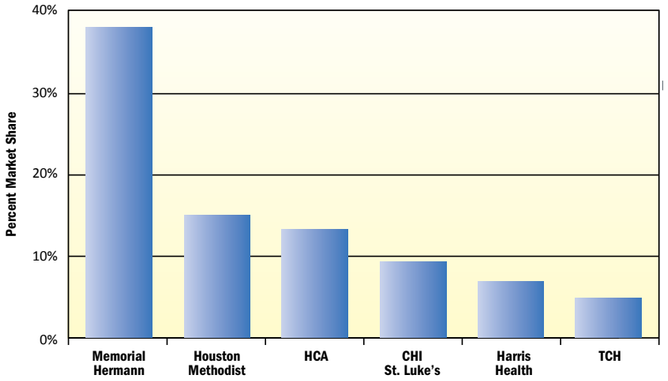
Patient Volumes in Clinic



Neurology Market Share FY18



Neurosurgery Market Share FY18



Source: Texas Hospital Association Patient Data System (FY2016 Q3 - FY2018 Q2) provided by Truven, formerly Thomson Reuters. Texas Hospital Inpatient Discharge Public Use Data File (FY2016 Q3 - FY2018 Q2) provided by Texas Department of State Health Services, Center for Health Statistics; FY2016 Q3 - FY2018 Q2 discharges estimated by using historical data by hospital. Excludes Normal Newborns and SNF and any hospital not reporting to THA or Truven. Expanded Greater Houston consists of 12 counties: Austin, Brazoria, Chambers, Fort Bend, Galveston, Harris, Liberty, Montgomery, San Jacinto, Waller, Walker and Wharton.

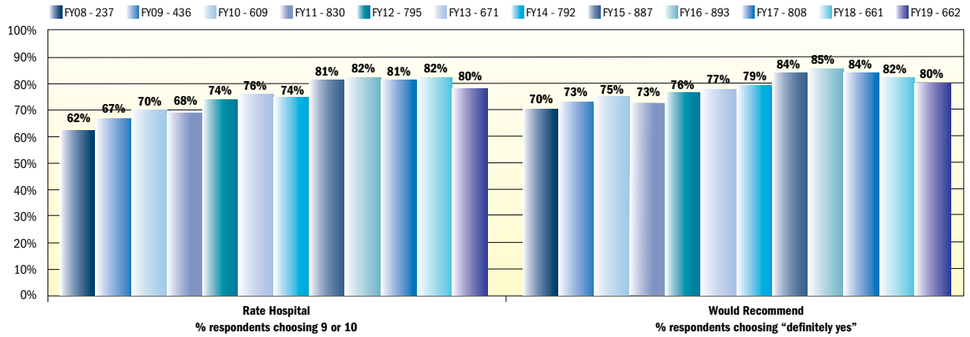
The Patient Experience

The impact of patient-centered care on clinical outcomes and patient satisfaction is well documented in medical literature. As institutions across the country struggle to improve outcomes and satisfaction while reducing costs, Mischer Neuroscience Institute is achieving both goals. The close cooperation of UTHealth physicians and an innovative administrative structure that gives nurses more time to coordinate patient care has led to an upward trend in patient satisfaction over the last 10 years. Data gathered by the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey shows consistent improvement in domains considered critical to a high level of patient satisfaction.

HCAHPS Overall Assessment

Surveys Received FY08-19

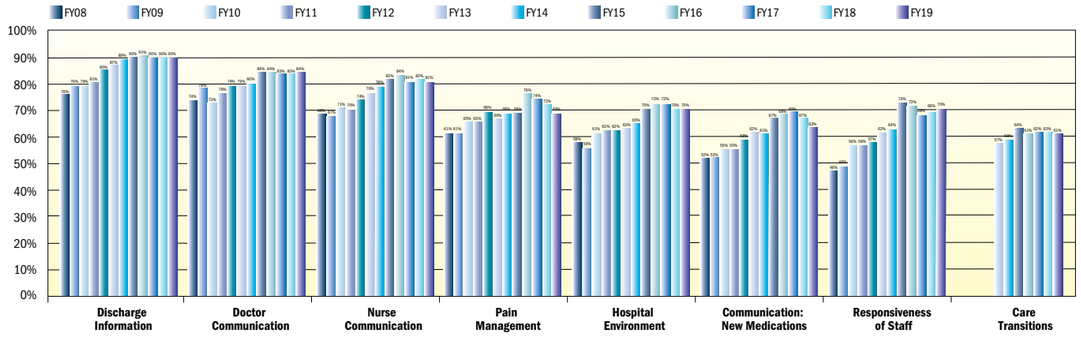
Total Survey Respondents Per Year:



HCAHPS Domain of Care

Surveys Received FY08-19

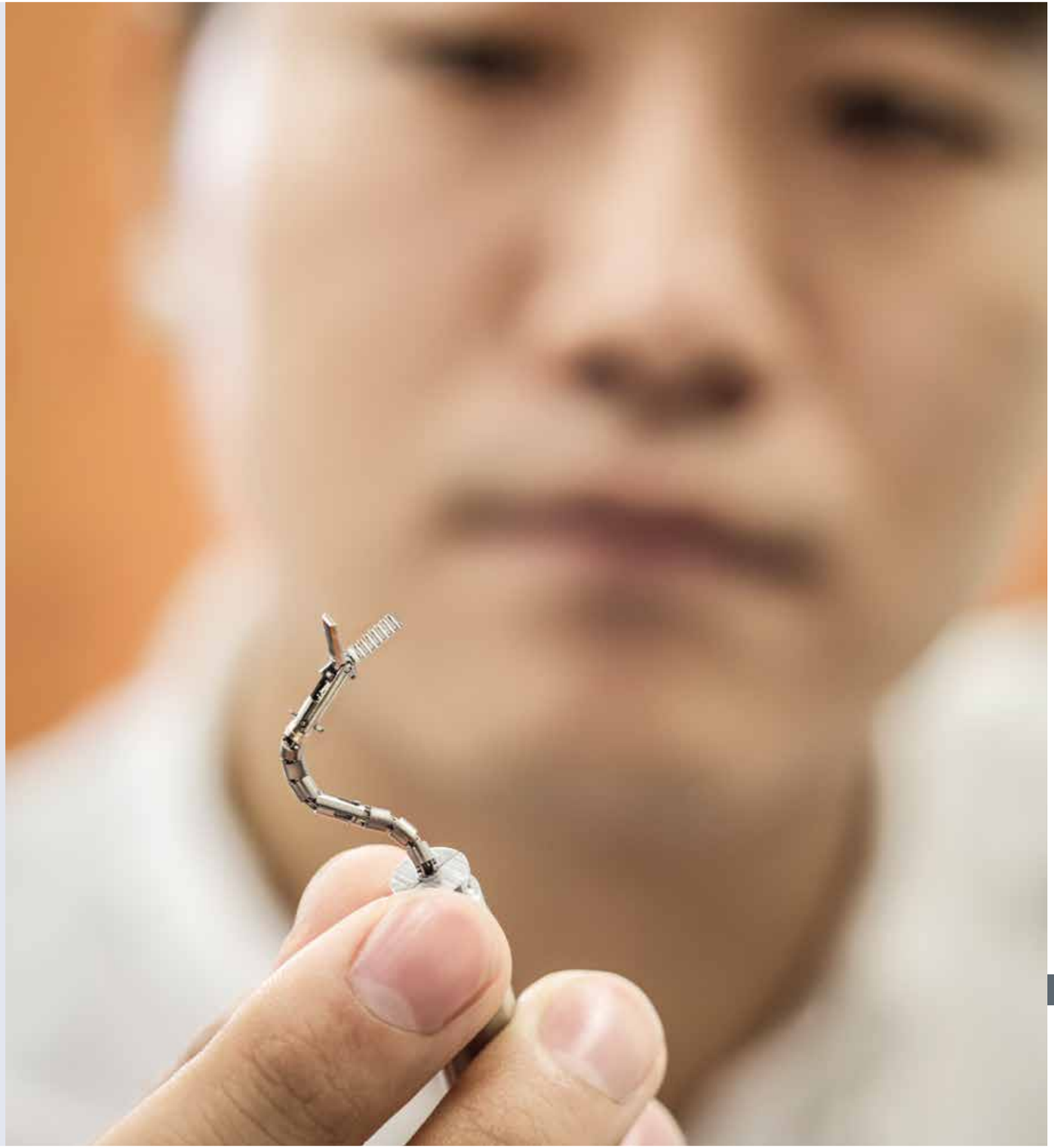
Respondents choosing "always" or "yes"



Source: Press Ganey, national hospital survey vendor, for all surveys received from patients discharged from 7 Jones, EMU, 5 Jones, NIMU, Stroke, Spine added as of FY14, NVICU added as of FY16. HCAHPS scores have not been adjusted to account for a survey mode administration change.

A History of Firsts

- The first center to discover a genetic mutation linked to intracranial aneurysms.
- The first stroke program in Texas and the only one in the region to meet The Joint Commission's rigorous standards for the highly coveted Comprehensive Stroke Center certification.
- Site of the first single-center clinical trial for recurrent medulloblastoma, ependymoma and atypical teratoid-rhabdoid tumors using the direct infusion of chemotherapy into the fourth ventricle; the first trial of infusion of 5-AZA into the fourth ventricle or resection cavity in children with recurrent posterior fossa ependymoma; and the first trial of combination intraventricular chemotherapy (methotrexate and etoposide) infusions into the fourth ventricle or resection cavity in children with recurrent posterior fossa brain tumors.
- The first neurosurgery center in the region to offer all advanced modalities of treatment for complex lesions: expert microsurgery, interventional neuroradiology/endovascular surgery and Gamma Knife® radiosurgery.
- The first hospital in the south-central United States and one of only a few in the country offering intra-arterial chemotherapy for retinoblastoma, the most modern treatment for the disease.
- The first in Texas to use robotic stereo-encephalography (SEEG) for 3-D mapping of epileptic seizures.
- The first in Houston to offer amyloid imaging, a diagnostic tool that enables physicians to diagnose Alzheimer's disease.
- The North American leader in studies of primary progressive multiple sclerosis and the most active center in Texas for organized clinical trials of new therapies for MS.
- The first facility in Houston and one of the first in the United States to test the clot-dissolving drug tPA for acute stroke.
- The first stroke center in Houston and one of the first dedicated stroke programs in the world.
- One of the first centers in the nation to offer MR-guided laser interstitial thermal therapy (MRgLITT) using the Visualase™ system for the treatment of well-delineated focal epilepsies.
- The first center in the region to use the NeuroPace® RNS® System, a new FDA-approved technique for responsive neurostimulation to treat adults with medication-resistant epilepsy.
- Mischer Neuroscience Institute brought the first clinical magnetoencephalography (MEG) sensor to Houston and has updated the technology to the Elekta Neuromag® TRIUX.
- The Institute houses one of only a few adult and pediatric inpatient Epilepsy Monitoring Units in the country with the unique capability of simultaneously performing electroencephalography and polysomnography.
- The first in the region to inject human central nervous system stem cells into the spines of spinal cord injury patients.



Walmart Partners with UTHealth Neurosciences to Provide High-Quality Spine Care to Associates in the Southeast Region

In an expansion of its elite Centers of Excellence network, Walmart has added UTHealth Neurosciences and Mischer Neuroscience Institute at Memorial Hermann-Texas Medical Center to its list of facilities offering the highest quality spine surgery to the company's associates. The group will provide spine coverage for all Walmart associates in the southeastern United States, which means that when a Walmart associate requires spine surgery, UTHealth Neurosciences coordinates the entire patient experience. Coordination begins with transport from the airport and includes constant communication and joint decision-making throughout the process, which is organized by a designated clinical navigator.

> "The care we provide through this program is truly end-to-end. We take full responsibility and accountability for every step of the care delivery process, just as it should be and just as we do with all of our patients."
> **– Dong Kim, MD**

Just a handful of select facilities are part of Walmart's existing Centers of Excellence program for spine surgeries, including Mayo Clinic hospitals in Arizona, Minnesota and Florida; Virginia Mason Medical Center in Seattle and Geisinger Medical Center in Danville, Pa.

"By selecting a small number of facilities that meet the criteria important to Walmart – quality care, exceptional service, a track record of appropriate patient selection for surgery versus conservative therapy – the company has found that outcomes are better and overall costs are lower, even when travel and hotel costs are included," says Amanda Spielman, senior vice president and chief operating officer of neurosciences at McGovern Medical School at UTHealth. "For spine patients, it's about much more than whether the surgeon did a good job in the OR- equally important are preoperative and postoperative care that set the patient up for recovery and return to function. We provide a seamless transition from arrival in Houston to preoperative evaluation, surgical or therapeutic intervention and postoperative care. Our focus is always on the patient."

Candidate centers undergo a thorough evaluation process, and fewer than 5 percent initially identified meet all the quality requirements for consideration. The process includes an extensive review of the system's quality, outcomes and patient satisfaction data. Hospitals must provide detailed clinical protocols, surgical patient selection criteria, clinical registry participation, information on multidisciplinary shared decision-making as well as institutional and physician performance metrics – length of stay, return to surgery, infection rates and procedure-specific outcomes. This approach to patient care, developed by Dong Kim, MD, director of Mischer Neuroscience Institute and professor and chair of the Vivian L. Smith Department of Neurosurgery at McGovern Medical School at UTHealth, and Spielman, easily matched the philosophy and approach of a Walmart Center of Excellence.

The spine surgeries are performed by neurosurgeons Daniel H. Kim, MD, FACS, FAANS; Arthur Day, MD; John Quinn, MD; and Albert Fenoy, MD. Pain management is a critical part of the spine program, and neurosurgeons

Photo courtesy of Memorial Hermann-Texas Medical Center

Behind the Scenes: Why Walmart Chose UTHealth Neurosciences Physicians for the Spine Center of Excellence

Patients in need of spine care have many options for treatment. Depending on the evaluation, the neurosurgeon may recommend injections for pain management or therapy. If surgery is indicated, the highest quality spine care is available through our providers.

"Our team of clinicians determines the best plan of care for each patient," says Rahil Tai, MD, director of clinical quality review for UTHealth Neurosciences. "When Walmart invited us to present a proposal, we provided our clinical quality data and volumes, and the guidelines and protocols we have in place to ensure evidence-based patient care. Our data showed our strong performance, which led to the program being named as the only Center of Excellence in Texas."

According to Walmart, the percentage of patients who have surgery is lower for those who are evaluated at Centers of Excellence than in local markets. The company selects its COEs based on whether they foster a culture of following evidence-based guidelines, and as a result perform surgeries only when necessary; whether they structure surgeons' compensation so that they are incentivized to provide care based on what's appropriate for each individual patient; and their geographic location. Research done by Walmart, as well as the company's own internal data, shows that about 30 percent of spine procedures done today are unnecessary. The service is 100 percent paid by Walmart, with no out-of-pocket expenses for employees.

"Our model focuses on providing the highest quality care, allowing us to avoid unnecessary costs and unnecessary readmissions," Dr. Tai says. "When patients get high-quality spine care, they recover and return to work faster, saving expenses associated with complications and loss of work time.

"Being part of a Walmart Center of Excellence for spine care, it's incumbent on us to show our performance and the efficient use of resources," he adds. "If we continue to improve on what we're already doing well, we can translate that improvement beyond Walmart employees to every patient population we serve."

work closely with interventional pain management specialists Ashley Amsbaugh, MD, and Nadya M. Dhanani, MD, for patients who may benefit from more conservative treatment. The program is based at the UTHealth Neurosciences Spine Center, located in the Texas Medical Center.

"The care we provide through this program is truly end-to-end. We take full responsibility and accountability for every step of the care delivery process, just as it should be and just as we do with all of our patients. But this is obviously different from the typical fee-for-service model. This is the future of health care, and we're excited to be at the forefront of the transition as the industry moves in this direction," Dr. Dong Kim says. "It's a win-win-win for all parties involved, and especially for the patients."

Mary Luscomb, 55, was doubtful at first. Luscomb lives north of Dallas in Gainesville, Texas, where she works as a logistics manager at the area Walmart distribution center.

"I had been suffering from severe neck and back pain for seven years due to multiple bulging disks. In the beginning, we tried to manage with injections, but the pain and numbness I was feeling was just getting worse and more frequent. A recent trip to our local physician indicated it was time for surgery. I figured I would have the surgery with him, but then I learned about our Centers of Excellence program," Luscomb says. "It was strange and a little nerve-wracking to think about. A doctor I'd never even met, more than 300 miles away from my home, was going to perform my surgery in a matter of days. Of course, I was skeptical."

Within a week of being told she needed surgery, Luscomb was contacted by the team at UTHealth Neurosciences and informed of her scheduled surgery date. They carefully detailed her upcoming itinerary. She would fly down on Sunday, come to the clinic on Monday to meet her surgical team, have the procedure on Tuesday, spend that night at the hospital, then spend Wednesday and Thursday in a nearby hotel suite with her daughter – all of which would be prearranged for her convenience. Her follow-up clinic visit was scheduled for Friday, and she would be home by Saturday.

"We were picked up at the airport in a shiny new Lincoln Town Car. Every step of the way, we were treated like VIPs. I've never experienced anything like it before," Luscomb says. "On Monday for our clinic visit, we were in an exam room within five minutes of our arrival. Dr. Kim spent time with me, walking me through what all he was going to do, quickly putting my mind at ease."

Luscomb wasn't just pleased with the service and care she received, she was also thrilled with her outcome. "No more numbness, no more pain. I could feel the difference immediately."

Normal rehabilitation time for her procedure can range from one to three months. Luscomb was back at work within four weeks. "It's been fantastic. The team at UTHealth Neurosciences has called and checked up on me since I've been home. Meanwhile, I get to see our local physician for my follow-ups. And most importantly, my neck is fixed, and now I can go on with my life. It's the best of all worlds."

Based on the success of the Walmart COE, the group has expanded its spine program to include other employers through a program offered by Pacific Business Group Health, which includes employers such as HEB, McKesson Corporation, Lowe's and Jet Blue.

Landmark UTHealth Study Shows that Intracranial Evaluation with SEEG Is Safer and Produces Better Outcomes than SDE

Minimally invasive stereoelectroencephalography (SEEG) to determine whether patients with drug-resistant epilepsy are candidates for brain surgery is safer, more efficient and leads to better outcomes than the traditional approach, according to investigators at McGovern Medical School at UTHealth and Mischer Neuroscience Institute at Memorial Hermann-Texas Medical Center. Their landmark study, published online in March 2019 in JAMA Neurology,[1] showed that patients who underwent SEEG experienced fewer complications and made quicker, less painful recoveries than patients who underwent craniotomy with subdural electrode (SDE) implantation. The SEEG patients who went on to neurosurgery for epilepsy also were more likely to be seizure free at one year, compared with those who underwent SDE implantations.

"We expected lower morbidity, less blood product use, less use of pain medications and an overall better patient experience with SEEG based on our surgical experience, but we were not expecting to see a difference in outcome," says Nitin Tandon, MD, professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School, director of the epilepsy surgery program at Mischer Neuroscience Institute and the lead author of the article. "These findings give new hope to epilepsy patients who previously may have ruled out surgery for various reasons."

The retrospective study reviewed the cases of 239 patients with medically refractory epilepsy who underwent a total of 260 procedures between 2004 and 2017 to locate the source of their seizures and determine their suitability for surgery.

Of those 260 procedures, 139 cases were traditional SDEs, which require a large craniotomy. A sheet of electrodes is placed on the surface of the brain to pinpoint the origin of the seizures, and the skull is closed for an observation period, usually a week to 10 days. If the seizure focus is identified, surgery to resect it is done immediately following the observation period to avoid a second craniotomy.

Another 121 cases were performed using robotic SEEG, in which electrodes are implanted via fine probes threaded through small drill holes in the skull, resulting in minimal blood loss and less pain. Patients undergo a similar observation period. Following electrode removal, patients are typically discharged from the hospital. If they are candidates for surgery, they will return in a few weeks for surgery for resection or laser ablation of the seizure focus.

Of the patients who underwent resection or laser ablation to remove the lesion causing their seizures, 76 percent of SEEG cases were either free of disabling seizures or had them rarely at the one-year mark, compared to 55 percent of SDE cases. The minimally invasive technique also produced more favorable outcomes among patients with nonlesional epilepsy, for which surgery tends to be less successful. Nearly seven of 10 SEEG cases (69.2 percent) had good outcomes at the one-year mark compared to just over a third (34.6 percent) of

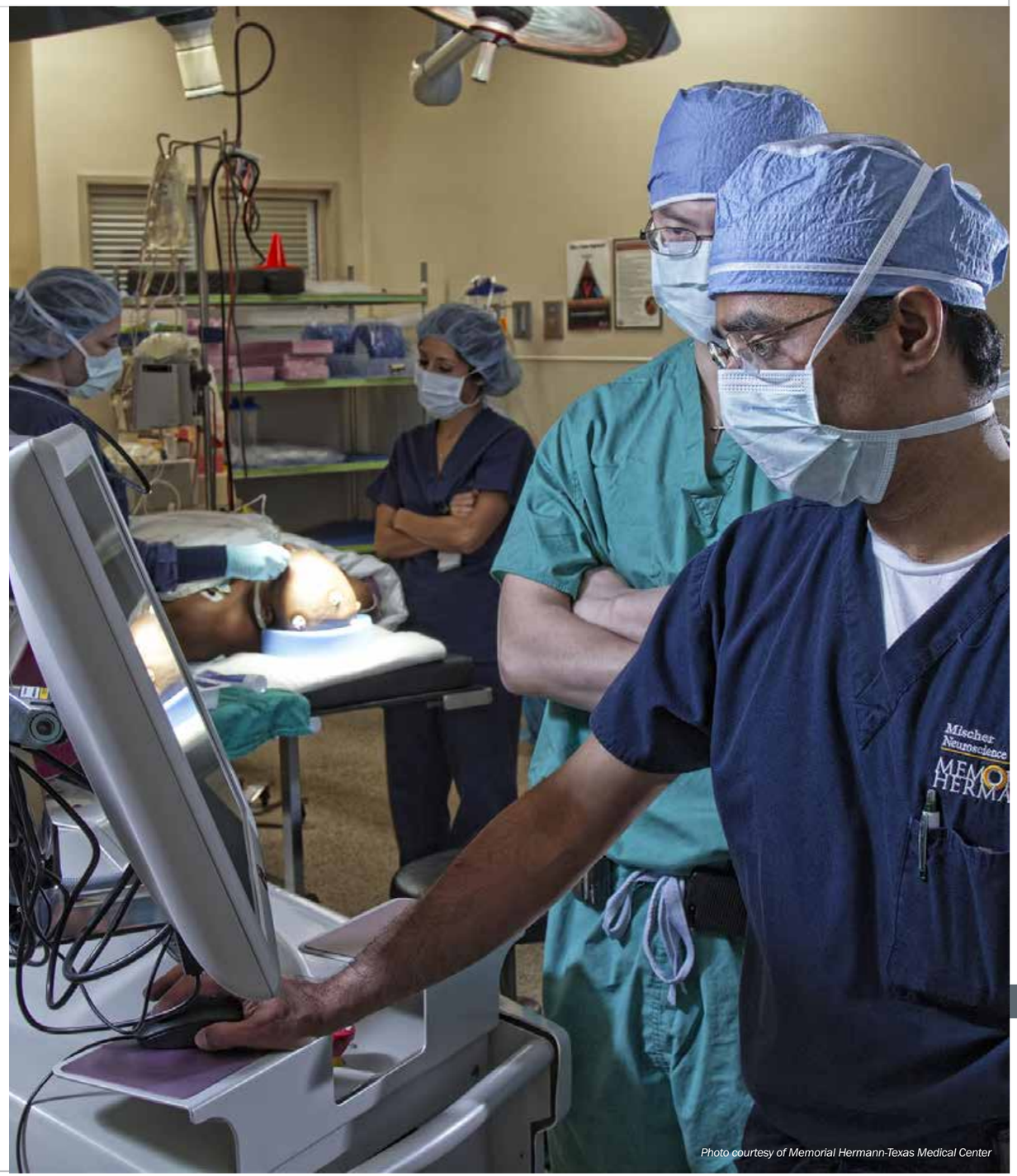


Photo courtesy of Memorial Hermann-Texas Medical Center

SDE cases. A greater proportion of SEEG cases were nonlesional epilepsy – 56.2 percent as opposed to 28.8 percent of SDE cases.

"This makes the case for SEEG even stronger," Dr. Tandon says. "There are three reasons why it can achieve better results. First, the technique doesn't constrain where the electrodes can be implanted, enabling us to study brain networks in a much more comprehensive fashion to pinpoint the seizure sources. Second, SEEG allows for precise targeting of deeper structures, which makes it better at localizing the epilepsy focus in many patients. Third, the absence of time pressure to evaluate the test results, and the fact that no craniotomy has been done, allows us to select patients likely to do well, fully consider various options and implement the optimal surgical plan. We also have a much better opportunity to discuss the data with patients and engage them in discussion of scenarios that might emerge from either resection or laser ablation."

In addition, results showed that SEEG patients required significantly less narcotic medication than SDE patients. Results also showed the minimally invasive procedure was more than twice as fast, with the average time in surgery at just over two hours for SEEG cases, compared to more than five hours for SDE cases.

This is good news for the vast numbers of undertreated patients with epilepsy who are candidates for surgery. "Patients with drug-resistant epilepsy constitute approximately one-third of the population with epilepsy, and this population has a high incidence of accidental injury, seizure activity for 30 minutes or more and sudden unexpected death," Dr. Tandon says. "Less than 10 percent of those eligible undergo surgery. Many have been discouraged by the invasiveness of subdural electrode implantation. SEEG is much less invasive and better tolerated by patients. In the study we showed a 6 percent risk of complications with SDE, and no complications with SEEG."

"If patients are refractory to three medications or just as commonly, unable to tolerate the doses that will control their seizures without losing their vocational or family life, they should be referred to a specialized epilepsy surgery center. In that way all options are laid out early, and patients are in charge of deciding when and if they want to move on beyond medications."
– Nitin Tandon, MD

The transition from SDE to SEEG was incremental and allowed for comparative analysis of outcomes using the two techniques. "Initially we used SEEG mostly in patients with deep lesions or those who had previous surgery, and in bilateral cases, which are challenging for subdural electrode implantation," he says. "With the availability of robotic technology, we switched from performing mainly SDE evaluations to SEEG in 2013. We were seeing a distinct difference in the patient experience. Today we're using SDE to evaluate neocortical epilepsy located around eloquent cortex and in young children, whose skulls are too thin to hold the anchor bolts for SEEG."

When should a general neurologist consider referring a patient to a tertiary or quaternary epilepsy center? "Stopping the seizures is always the goal. If that goal is not met, we should leave no stone unturned," Dr. Tandon says. "If patients are refractory to three medications or just as commonly, unable to tolerate the doses that will control their seizures without losing their vocational or family life, they should be referred to a specialized epilepsy surgery center," he says. "In that way all options are laid out early, and patients are in charge of deciding when and if they want to move on beyond medications." SEEG has moved epilepsy surgery to a better place. As the second site in the United States to have a robot for SEEG, the program has been at the forefront of the journey, using robotics for minimally invasive techniques that are much better tolerated by patients and more likely to be effective. The procedure can also be performed without robotic assistance.

"We hope these findings give more patients whose epilepsy cannot be controlled by medication the confidence to consider surgery, and also help other institutions transition more quickly to providing this minimally invasive procedure," Dr. Tandon says. UTHealth coauthors of the study were Brian Tong, a third-year medical student who played a crucial role in data compilation and analysis; Elliott Friedman, MD, neuroradiologist; Jessica Johnson, BSN, epilepsy nurse practitioner; and neurologists Giridhar Kalamangalam, MD, DPhil; Stephen Thompson, MD; Gretchen Von Allmen, MD; Melissa Thomas, MD; Omotola Hope, MD; and Jeremy Slater, MD.

[1]Tandon N, Tong BA, Friedman ER, Johnson JA, Von Allmen G, Thomas MS, Hope OA, Kalamangalam GP, Slater JD, Thompson SA. Analysis of Morbidity and Outcomes Associated With Use of Subdural Grids vs Stereoelectroencephalography in Patients with Intractable Epilepsy. JAMA Neurology. 2019 Jun 1;76(6). doi: 10.1001/jamaneurol.2019.0098.

Leveling Care Across Multiple Hospitals Through Telemedicine

Before Baptist Beaumont Hospital joined the UTHealth Telemedicine Program in 2002, there were no acute care hospitals equipped to treat ischemic stroke between Houston and Lake Charles, La. The two cities lie 132 miles apart in the southwest tip of the Stroke Belt, an area of the southeastern United States with an unusually high incidence of stroke and other forms of cardiovascular disease. With only a handful of neurologists available to provide on-call coverage for a 75- to 100-mile service area, the hospital was ill equipped to provide care for the area's older population. But thanks to telemedicine and its partnership with UTHealth, Baptist Beaumont Hospital has been accredited as a Primary Stroke Center since 2007 and has morphed into a local powerhouse for the delivery of tPA.

Baptist Beaumont Hospital and Memorial Hermann Southwest Hospital were early adopters of telemedicine through McGovern Medical School at UTHealth, originally funded by a grant from the U.S. Department of Defense and financial support from philanthropic gifts. Since then, 17 more sites in Texas have gone live with the technology: Memorial Hermann Memorial City Medical Center, Memorial Hermann Greater Heights Hospital, Memorial Hermann The Woodlands Medical Center, Memorial Hermann Katy Hospital, Memorial Hermann Pearland Hospital, Memorial Hermann Cypress Hospital, Memorial Hermann Sugar Land Hospital, Memorial Hermann Northeast Hospital, Huntsville Memorial Hospital in Huntsville, Matagorda Regional Medical Center in Bay City, the Medical Center of Southeast Texas in Port Arthur, Citizens Medical Center in Victoria, St. Joseph Hospital-Downtown in Houston, DeTar Healthcare System in Victoria, Tomball Regional Medical Center in Tomball, UTHealth Northeast in Tyler and Midland Memorial Hospital in Midland.

"Our ultimate goal is to build a collaborative network of hospitals working together to deliver comprehensive neurological and neurosurgical care in the southern half of Texas," says Tzu-Ching (Teddy) Wu, MD, medical director of UTHealth's Telemedicine Program and an associate professor of neurology. "As the Texas Medical Center hub, we provide 24/7 stroke consultations, as well as consults for other conditions, for our network hospitals. The program allows us to treat as many patients as possible at our partner hospitals, avoiding unnecessary patient transfers."

In addition to access to physicians who are experts in neuroscience care for telemedicine consultation, benefits to hospitals in the telemedicine network include higher quality of care and decreased treatment delays as patients receive prompt diagnosis with a treatment plan based on the best available protocols. "More patients and families receive treatment where they live, in the community, rather than having to drive long distances to Houston," Dr. Wu says. "Patients who require a higher level of care have a guaranteed transfer process that gives them access to the most advanced treatments and the best tertiary-care neuroscience partner in the region."

As the neurology telemedicine program grows across Texas, other neuroscience subspecialties are expanding their expertise beyond the Texas Medical Center. In summer 2017, UTHealth neurocritical care physicians at Memorial Hermann-TMC began providing support to critical care physicians at three suburban Houston hospitals when they need a higher level of neurocritical care expertise.

"The team at UTHealth Neurosciences includes nine neurointensivists who also practice at Memorial Hermann Memorial City Medical Center and Memorial Hermann Southwest Hospital," says H. Alex Choi, MD, interim vice chair of neurocritical care and assistant professor of neurosurgery in the Vivian L. Smith Department of Neurosurgery at UTHealth. "Telemedicine has allowed us to broaden our reach and provide neurocritical care coverage to outlying hospitals 24/7."

Under development is an outpatient telemedicine program that will allow patients from outside the Greater Houston area who choose UTHealth Neurosciences for neurosurgery to see their surgeon remotely in follow-up. "Telemedicine has taught us that you don't need a major medical center to provide good neurological care," says Louise McCullough, MD, PhD, professor and chair of the Department of Neurology at McGovern Medical School and chief of neurology at Memorial Hermann-TMC. "What you do need is expert physicians and a strong telemedicine program that levels care across Houston and in communities beyond the city. We've taken our original neurology telemedicine program and broadened it. We think the possibilities are virtually limitless."

UTHealth Neurosciences Extends Subspecialty Care Across the City

With more than 130 affiliated subspecialty providers, UTHealth Neurosciences and UT Physicians Neurology offer patients access to specialized care through clinics located in their home communities.

"The presence of UTHealth neurosurgeons and neurologists in outlying communities, plus the expansion of our subspecialty clinics, allows us to manage a variety of health conditions across the entire continuum of care – from outpatient consultations to inpatient care to outpatient follow-up," says Amanda Spielman, senior vice president and chief operating officer of neurosciences at McGovern Medical School at UTHealth. "We're now able to coordinate the care of patients from all areas of Houston."

If patients who live in West Houston see a subspecialist in an outpatient clinic at UTHealth Neurosciences-Katy and need a higher level of care, their physicians can refer them to a UTHealth Neurosciences or Neurology physician at another Memorial Hermann campus, such as Memorial Hermann-Texas Medical Center. "On the neurology side, we want to ensure that patients have access to subspecialty expertise in their home communities," says Louise D. McCullough, MD, PhD, FAHA, professor and chair of the Department of Neurology at McGovern Medical School and chief of neurology at Memorial Hermann-TMC. "We'll continue to populate clinics in the community with accomplished neurologists who can refer complex cases or diagnostic challenges to us in the Texas Medical Center. The clinics also give people access to any clinical trials we're conducting at McGovern Medical School."

Aparajitha Verma, MD, MBA, leads the outpatient neurology program for UTHealth Neurosciences across the city. "While the individual providers have autonomy, they are held to the same standards with the same mission, vision and values," she says. "If we find that we can improve a process or want to implement new evidence-based care, we can rally our group of physicians around it. To have that large a group across the city is pretty spectacular."

Specialized Care Across the City

BACK PAIN CLINICS
UTHealth Neurosciences-Memorial City
Joseph Amos, MD

UTHealth Neurosciences-Southeast
Hiral Patel, MD

UTHealth Neurosciences-Texas Medical Center
Mark Burish, MD, PhD
Nadya Dhanani, MD
Ashley Amsbaugh, MD

HEADACHE CLINIC
UTHealth Neurosciences–Southwest
Hamid Hamdi, MD

MEMORY LOSS CLINICS
UTHealth Neurosciences–Southwest
UTHealth Neurosciences–Sugar Land
Mimi Dang, MD

NEURO-ONCOLOGY CLINICS
UTHealth Neurosciences-Memorial City
Sigmund Hsu, MD

UTHealth Neurosciences-Southwest
Jay-Jiguang Zhu, MD, PhD

PARKINSON'S DISEASE CLINIC
UTHealth Neurosciences-Memorial City
Eddie Patton, MD

SEIZURE CLINICS
UTHealth Neurosciences–Greater Heights
Reza Sadeghi, MD

UTHealth Neurosciences–Southwest
Mimi Dang, MD

SLEEP DISORDERS CLINIC
UTHealth Neurosciences-Texas Medical Center
Aparajitha Verma, MD

STROKE CLINICS
All UTHealth Neurosciences neurologists see stroke patients. Clinics are:
UTHealth Neurosciences-Greater Heights
UTHealth Neurosciences-Katy
UTHealth Neurosciences-Memorial City
UTHealth Neurosciences-Southwest
UTHealth Neurosciences-Sugar Land

UT★Physicians
A Part of UTHealth
NEUROLOGY

EXPERT CARE FOR COMPLEX NEUROLOGICAL CONDITIONS

Located in the Texas Medical Center, UT Physicians Neurology offers the highest level of specialized care for both common and complex neurological disorders, including:

Epilepsy
Memory Disorders and Dementia
Movement Disorders and Other Neurodegenerative Diseases
Multiple Sclerosis
Neuromuscular Conditions
Sleep Disorders
Stroke and Other Cerebrovascular Conditions

2019 Accolades

Dr. Arthur Day Receives Society of Neurological Surgeons Distinguished Service Award

Arthur L. Day, MD, vice chair, program director and director of clinical education in neurosurgery at Mischer Neuroscience Institute at Memorial Hermann-Texas Medical Center and professor of neurosurgery at McGovern Medical School at UTHealth, has received the prestigious Distinguished Service Award, the highest honor given by the Society of Neurological Surgeons (SNS). Dr. Day received the award in recognition of his lifelong commitment and outstanding leadership, dedication and contributions to the field of neurosurgery.

Known as the Senior Society, the SNS is the American society of leaders in neurosurgical residency education, and is the oldest and most exclusive neurosurgical society in the world. Academic department chairmen, residency program directors and other key academicians comprise the active membership of the society, which is limited to 200 active members.

The Senior Society cited Day for his lifelong teaching and his stewardship of the organization's Committee on Advanced Subspecialty Training (CAST), which is responsible for accreditation of subspecialty training fellowships and for the development and updating of subspecialty training requirements. Under Day's leadership, CAST revamped the way fellowships are reviewed and standardized, and set standards for new fellowships in neuroendovascular surgery, critical care, tumor and others.

"I am incredibly honored to receive the Senior Society's Distinguished Service Award," Day says. "It is deeply humbling to be added to the group of prior award winners – a real honor roll in neurosurgery."

Day is a board-certified, fellowship-trained neurosurgeon with specific expertise in cerebrovascular and skull base neurosurgery. He also specializes in microsurgical treatment of brain tumors and minimally invasive spinal surgery.

Day was awarded his medical degree from Louisiana State University in New Orleans. He completed his internship training in Birmingham, Ala., and subsequently completed his neurological surgery residency and fellowship in brain tumor immunology at the University of Florida College of Medicine in Gainesville.

Before joining Mischer Neuroscience Institute and UTHealth, he practiced at the University of Florida for 25 years, ultimately rising to the positions of professor, co-chair and program director of the Department of Neurosurgery. In 2002, he moved to Boston as professor of surgery at Harvard Medical School and was also program director and chair of the Department of Neurological Surgery at the Brigham and Women's Hospital.

Day has held leadership positions in many medical professional societies, and received numerous awards and honors, including the Medal of Honor from the Neurosurgical Society of America, the Founders' Laurel Award from the Congress of Neurological Surgeons for his "exceptional service, lifelong dedication and meritorious accomplishments in the field of medical education" and the Harvey Cushing Medal from the American Association of Neurological Surgeons for his many years of outstanding leadership, dedication and contributions to the field of neurosurgery.

He served as president of the Society of Neurological Surgeons from 2011 to 2012, has also been a member of the neurosurgical RRC, and chaired the American Board of Neurological Surgery. He has also been named multiple times to Best Doctors in America®. Day has published 200 journal articles and book chapters, and co-edited two books about neurological sports injuries.

Dr. Claudio Soto Receives Grant to Develop a Noninvasive Biochemical Test for Early Diagnosis of Parkinson's Disease

One of the greatest obstacles to developing a disease-modifying therapy for Parkinson's disease (PD) is early and accurate diagnosis. With a $342,000 grant from the Michael J. Fox Foundation for Parkinson's Research, Claudio Soto, PhD, and his laboratory team are investigating the potential of a blood test to diagnose PD before the disease's debilitating symptoms manifest.

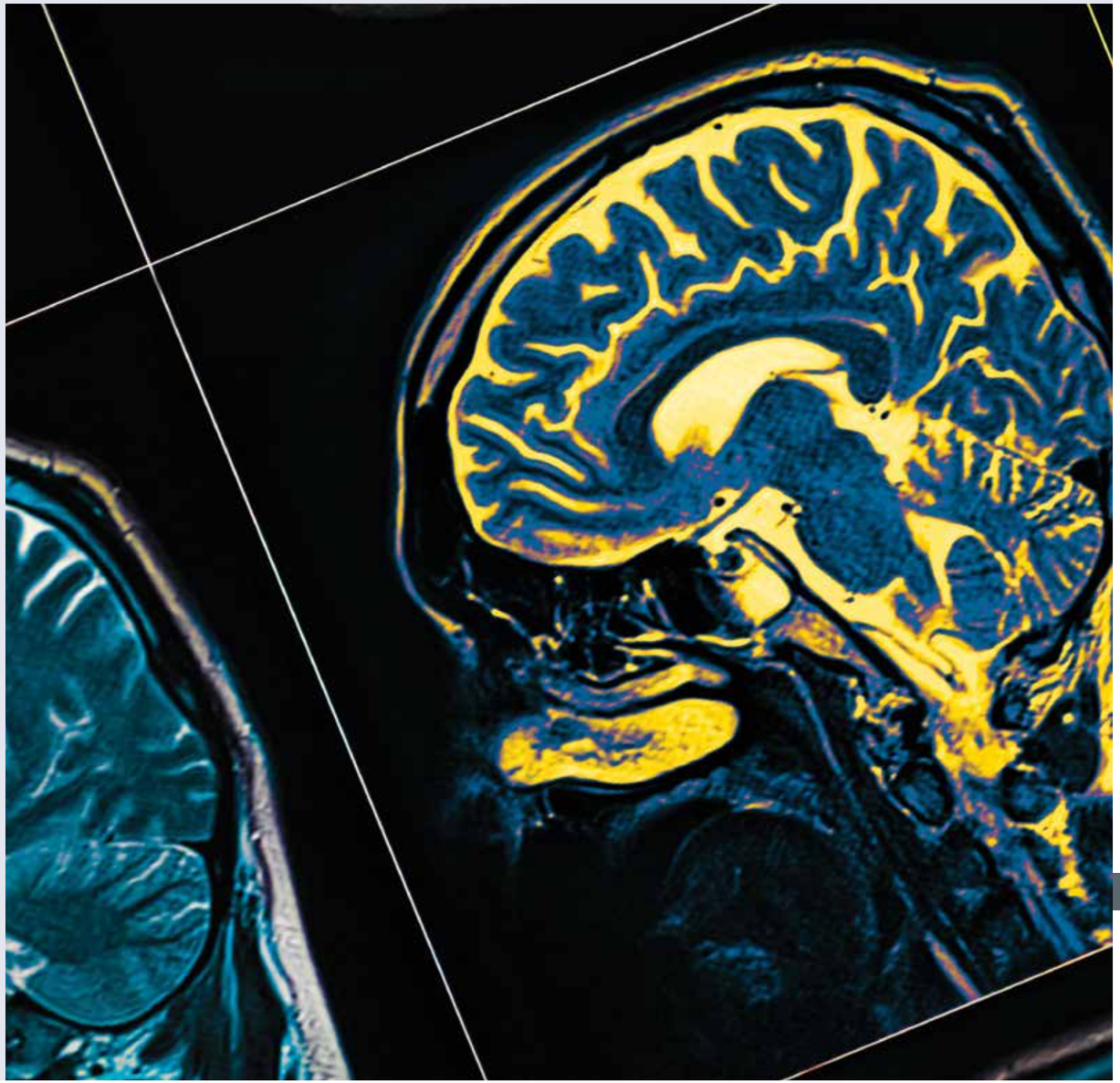
"By the time the motor symptoms of Parkinson's disease emerge, up to 70 percent of dopaminergic neurons in the substantia nigra, which plays an important role in movement, are already lost," says Dr. Soto, professor of neurology and director of the George and Cynthia W. Mitchell Center for Alzheimer's Disease and Other Brain-related Illnesses at McGovern Medical School at UTHealth. "We hope this one-year project will lay the foundation for the development of a sensitive, noninvasive, objective laboratory test to detect Syn oligomers in the blood plasma of people affected by PD and related diseases. The technology has the potential to have a tremendous impact, enabling the biochemical diagnosis of PD, possibly pre-symptomatically, to allow for the early initiation of appropriate therapy that could reduce the effects of the disease. It may also be very useful for tracking disease progression and developing new clinical trials for PD."

The newly funded study, entitled "Development of a biochemical test to detect synuclein (Syn) oligomers in blood and validation of CSF assay in Parkinson's disease patients," is a continuation of a previous award Dr. Soto received from the Michael J. Fox Foundation to initiate a study on PD. Grants personnel at the foundation approached Dr. Soto to write the original grant – a rare occurrence in the funding arena – based on novel work done in his lab related to Alzheimer's disease.

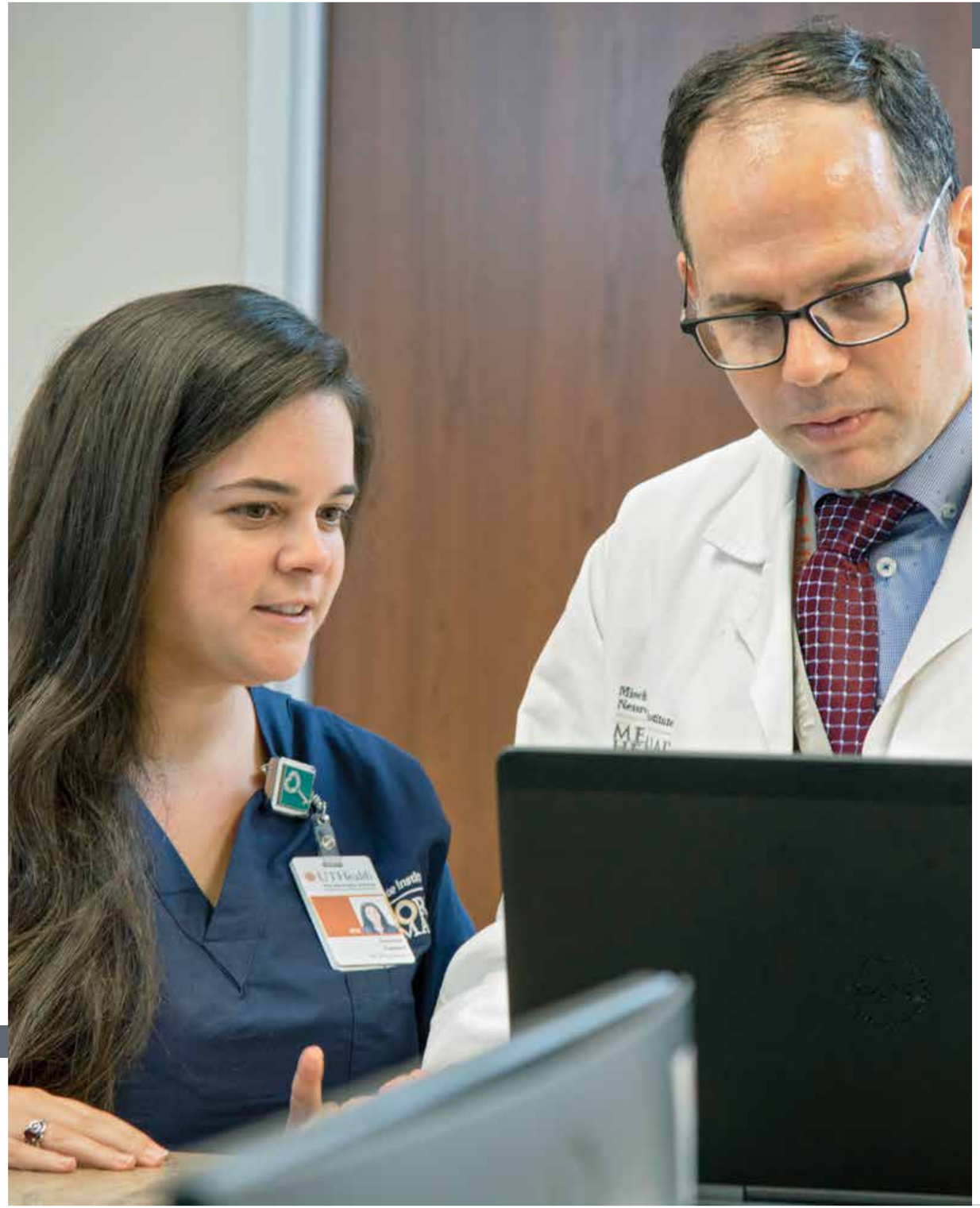
Dr. Soto's team focuses primarily on understanding the molecular basis of neurodegenerative diseases associated with the misfolding and brain accumulation of proteins, particularly focusing on Alzheimer's disease, Parkinson's disease and prion-related disorders. The vision of his group is to perform high-impact research with the potential to revolutionize understanding of brain diseases, and to translate the scientific knowledge gained into the discovery and development of novel strategies for diagnosis and therapeutic intervention. Dr. Soto invented and pioneered an innovative technology for high-sensitivity detection of misfolded proteins in biological fluids, which is currently being used in many countries as a noninvasive and high-sensitivity diagnostic test for various brain diseases. The novel therapies emerging from his work are currently being tested in patients affected by Alzheimer's disease.

Dr. Soto has published more than 160 peer-reviewed scientific publications and contributed to more than 20 books, including one of which he is the sole author. Many of his studies have been published in prestigious scientific journals, including Cell, Nature, Science, New England Journal of Medicine, Nature Medicine, PNAS, Neuron and The Lancet, among others. His publications have been cited more than 12,000 times, and articles written by scientific and lay journalists have highlighted his work. He has received numerous awards and has been an invited speaker at more than 200 international scientific meetings. Dr. Soto is the recipient of many grants from the federal government and private foundations for a cumulative funding total of more than $30 million.

"This one-year project will lay the foundation for the development of a sensitive, noninvasive lab test for Parkinson's disease," he says. "In our first study on PD, we worked invasively with cerebrospinal fluid collected through lumbar puncture. Our goal is to advance the technology so that we can work with blood samples to predict Parkinson's disease. Moving forward, we hope to gather sufficient data to show that our new techniques work with a good level of sensitivity and specificity. Our aim is to complete the studies in the next few years, and our final step will be to seek regulatory approval of the test."



Scope of Services and *Quality* Outcomes



Brain Tumor

Neuro-oncologists Jay-Jiguang Zhu, MD, PhD, and Sigmund H. Hsu, MD, continue to expand the capabilities of the Brain Tumor Center in UTHealth Neurosciences practices across Houston. Neuro-oncology services are now available in the Texas Medical Center and at UTHealth Neurosciences clinics in Memorial City, in Southwest Houston, and at TIRR Memorial Hermann rehabilitation hospital.

Dr. Zhu, fellowship trained at Massachusetts General Hospital, focuses his practice on primary brain tumors – gliomas, meningiomas, pituitary adenomas and primary CNS lymphomas – as well as brain metastases and leptomeningeal spread of systemic malignancies.
He is also interested in quality of life, including cognitive function during and after radiotherapy and chemotherapy; neurological complications of systemic chemotherapies; and clinical trials focused on developing new treatment options for primary brain tumors and CNS metastases. By working with other clinicians and research scientists, Dr. Zhu and his team are working on discovery of biomarkers for glioblastoma at recurrence, as well as identifying factors that may improve care and longevity of patients with gliomas using the National Cancer Database (NCDB).
Dr. Hsu, fellowship trained at The University of Texas MD Anderson Cancer Center, has clinical and research interests in the discovery of new and more effective therapies for patients with primary brain tumors, treatment of metastatic cancer to the brain and spinal cord, and the evaluation and treatment of neurological problems in cancer patients. Dr. Zhu is the site principal investigator in several trials that give eligible study participants access to new and advanced treatments. With funding from the National Cancer Institute, he is leading a Phase II/III clinical trial studying the efficacy of veliparib with temozolomide compared to temozolomide alone in treating patients with glioblastoma multiforme (GBM) or gliosarcoma. More than 400 patients have been enrolled at sites around the country.

Dr. Zhu was principal investigator in a randomized, double-blind, controlled Phase IIB clinical trial testing the safety and efficacy of the vaccine ICT-107 for newly diagnosed GBM patients following resection and chemoradiation. The trial, which began enrollment in August 2011 and was completed in December 2015, showed improved, progression-free survival of patients who are human leukocyte antigen (HLA) A2 positive. HLA genes are key to the activity of the immune system in identifying the body's own proteins versus proteins of foreign origin.

Dr. Zhu is the principal investigator for the Phase II randomized, 70-site multicenter worldwide clinical trial studying the Wilms tumor (WT1) protein-derived peptide vaccine, DSP-7888, Dosing Emulsion in Combination with Bevacizumab in Patients with Recurrent Glioblastoma. The trial is open to enrollment.

Two other trials led by Dr. Zhu have been completed, and the results have been published in prestigious journals. A Phase III multicenter, randomized, controlled trial is testing the efficacy and safety of a medical device called Novo TTF-100A (Optune) for newly diagnosed GBM

Improved Survival of Glioblastoma Patients Treated at Academic and High-volume Facilities: A Hospital-based Study from the National Cancer Database

Zhu P, Du XL, Zhu JJ,* Esquenazi Y* (*Equal contribution)

Journal of Neurosurgery. 2019 Feb 15;1-12. doi: 10.3171/2018.10.JNS182247.

Abstract:

Objective: The present study was designed to explore the association between facility type (academic center [AC] vs non-AC), facility volume (high-volume facility [HVF] vs low-volume facility [LVF]), and outcomes of glioblastoma (GBM) treatment.

Methods: Based on the National Cancer Database (NCDB), GBM patients were categorized by treatment facility type (non-AC vs AC) and volume [4 categories (G1-G4): < 5.0, 5.0-14.9, 15.0-24.9, and ≥ 25.0, cases/year]. HVF was defined based on the 90th percentile of annual GBM cases (≥15.0 cases/year). Outcomes include overall survival (OS), the receipt of surgery and adjuvant therapies, 30-day readmission/mortality, 90-day mortality, and prolonged length of inpatient hospital stay (LOS). Kaplan-Meier methods and accelerated failure time (AFT) models were applied for survival analysis, and multivariable logistic regression models were performed to compare differences in the receipt of treatment and related short-term outcomes by facility type and volumes.

Results: A total of 40,256 GBM patients diagnosed between 2004 and 2014 were included. Patients treated at an AC & HVF experienced the longest survival (median OS: 13.3, 11.8, 11.1, and 10.3 months; time ratio [TR]: 1.00 [Ref.], 0.96, 0.92, and 0.89; for AC & HVF, AC & LVF, non-AC & HVF, and non-AC & LVF, respectively), regardless of care transition/treatment referral. Tumor resection, radiotherapy, and chemotherapy were most frequently utilized in AC & HVF. Prolonged LOS, 30-day readmission, and 90-day mortality were decreased by 20%, 22%, and 16% ($p \leq 0.001$), respectively, at AC & HVF.

Conclusions: This study provides evidence of superior outcomes when GBM patients are treated at AC and HVF. Standardization of health care across facility type and/or volume and comprehensive neuro-oncological care should be a potential goal in the management of GBM patients.

patients in combination with temozolomide, compared to temozolomide alone. The device, which patients wear on their scalp, provides a constant, safe, low-voltage alternating electric field that has been shown to reduce tumor cell division and improve GBM patients' survival. The device was approved by the FDA for progressive GBM in April 2011. Interim analysis of the trial data showed significant improvement of progression-free survival time and overall survival duration in participants randomized to the treatment arm of the study. Based on this trial result, the FDA approved the device for newly diagnosed GBM in October 2015. The study was completed in July 2016. The results from 83 participating institutions showed significant improvement of progression survival time and overall survival duration in patients randomized to the treatment arm versus the control arm with temozolomide alone. In addition, the health-related quality of life (HRQoL) has improved and maintained for patients in the treatment arm.[1] The results were first presented at the annual meeting of the Society of Neuro-Oncology in November 2016. The full trial results were published in JAMA in December 2017.[2]

Dr. Zhu is also leading an open-label Phase I/II (safety lead-in) study of trans-sodium crocetinate (TSC) with concomitant treatment of fractionated radiation therapy and temozolomide in newly diagnosed GBM patients. The trial examines the safety and efficacy of TSC as a radiation sensitizer for the treatment of malignant tumors. The study is closed, and the results demonstrated the benefit to patients in the trial without any significant side effect.[3]

Dr. Hsu is principal investigator in several studies, including the trial of a novel Taxol chemotherapy compound, TPI 287, which crosses the blood-brain barrier and is administered in combination with bevacizumab versus bevacizumab alone in adults with recurrent glioblastoma. In addition, he is leading a

Triple-drug Therapy with Bevacizumab, Irinotecan, and Temozolomide Plus Tumor Treating Fields for Recurrent Glioblastoma: A Retrospective Study

Lu G, Rao M, Zhu P, Liang B, El-Nazer RT, Fonkem E, Battacharjee MB, Zhu JJ

Frontiers in Neurology. 2019 Jan 31;10:42. doi: 10.3389/fneur.2019.00042. eCollection 2019.

Abstract:

Clinical studies treating pediatric and adult solid tumors, such as glioblastoma (GBM), with a triple-drug regimen of temozolomide (TMZ), bevacizumab (BEV), and irinotecan (IRI) [TBI] have demonstrated various efficacies, but with no unexpected toxicities. The TBI regimen has never been studied in recurrent GBM (rGBM) patients. In this retrospective study, we investigated the outcomes and side effects of rGBM patients who had received the TBI regimen. We identified 48 adult rGBM patients with a median age of 56 years (range: 26-76), who received Tumor Treating Fields (TTFields) treatment for 30 days or longer, and concurrent salvage chemotherapies. The patients were classified into two groups based on chemotherapies received: TBI with TTFields (TBI+T, N = 18) vs. bevacizumab (BEV)-based chemotherapies with TTFields (BBC+T, N = 30). BBC regimens were either BEV monotherapy, BEV+IRI or BEV+CCNU. Patients in TBI+T group received on average 19 cycles of TMZ, 26 and 21 times infusions with BEV and IRI, respectively. Median overall survival (OS) and progression-free survival (PFS) for rGBM (OS-R and PFS-R) patients who received TBI+T were 18.9 and 10.7 months, respectively. In comparison, patients who received BBC+T treatment had OS-R and PFS-R of 11.8 ($P > 0.05$) and 4.7 ($P < 0.05$) months, respectively. Although the median PFS results were significantly different by 1.5 months (6.6 vs. 5.1) between TBI+T and BBC+T groups, the median OS difference of 14.7 months (32.5 vs. 17.8) was more pronounced, $P < 0.05$. Patients tolerated TBI+T or BBC+T treatments well and there were no unexpected toxicities. The most common side effects from TBI+T treatment included grade III hypertension (38.9%) and leukopenia (22.2%). In conclusion, the TBI regimen might play a role in the improvement of PFS-R and OS-R among rGBM patients. Prospective studies with a larger sample size are warranted to study the efficacy and toxicity of TBI+T regimen for rGBM.

Phase II dose-escalation study of TPI 287 in combination with bevacizumab in adults with recurrent or progressive glioblastoma following a bevacizumab-containing regimen.

The Vivian L. Smith Department of Neurosurgery at McGovern Medical School is the United States leader in enrollment for a highly active experimental drug, ABT-414. This drug is an antibody-toxin compound (similar to Kadcyla), made by ABBVIE, which showed promising early activity in Phase II testing, according to published results. Patients who have overexpression of epidermal growth factor receptor are eligible to enroll in the trial, where they receive the blinded agent in addition to radiation therapy and temozolomide.

Dr. Hsu is also the lead physician in the FoundationOne™ Registry study, a prospective observational study to examine practice patterns and the impact on clinical decision-making associated with the FoundationOne next-generation sequencing test. The study allows UTHealth Neurosciences physicians to recommend optimal advanced technologies, including motor and language mapping, functional neuroimaging, frameless stereotactic navigation in surgery and awake craniotomies performed under local anesthesia, as well as minimally invasive procedures, including neuroendoscopy and stereotactic radiosurgery.

The department has added two radiation oncologists to its neuro-oncology team: Shariq Khwaja, MD, PhD, and Mark Amsbaugh, MD. Together with Angel Blanco, MD, director of radiation oncology and stereotactic radiosurgery and an associate professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School at UTHealth, they provide radiation oncology services at the Brain Tumor Center at UTHealth and in collaboration with Mischer Neuroscience Institute. The Institute acquired the region's first Leksell Gamma Knife® in 1993, and is now using the more advanced Leksell Gamma Knife® Perfexion™. Patients who benefit from the Perfexion's sophisticated software with dose-to-target conformation include those with meningiomas and vestibular schwannomas; arteriovenous malformations; medically refractory trigeminal neuralgia; and metastases. Multiple intracranial metastases can usually be treated in a single outpatient procedure. UTHealth neurosurgeons have performed more than 5,000 Gamma Knife procedures. The Varian Trilogy linear accelerator is the first in a powerful new generation of cancer-fighting technologies, offering the highest dose rates for shorter sessions. The system delivers 3D conformal radiotherapy, IMRT, extracranial and intracranial stereotactic radiosurgery, fractionated stereotactic radiation therapy, stereotactic body radiosurgery (SBRT) and intensity-modulated radiosurgery for cancer and neurosurgical treatment.

The Brain Tumor Center is led by Dong Kim, MD, professor and chair of the Vivian L. Smith Department of Neurosurgery at McGovern Medical School at UTHealth. The team works closely with referring physicians throughout the radiosurgical treatment process. A neurosurgeon and a radiation oncologist assess each candidate to determine whether radiosurgical treatment is the best option. Nurse navigators work directly with patients on scheduling and pretreatment education, and provide support and care on the day of treatment. The Center also sponsors a well-attended brain tumor support group that meets the second Wednesday of every month.

The Brain Tumor Center at UTHealth offers patients specialized care through multiple clinics:

- Pituitary Tumor and Vision Change Clinic
- Skull Base Program
- Brain Metastases Clinic
- Cancer Neurology Clinic
- Gamma Knife Patient Care Clinic
- Neurogenetics Clinic

Analysis of Cerebrospinal Fluid Metabolites in Patients with Primary or Metastatic Central Nervous System Tumors

Ballester LY, Lu G, Zorofchian S, Vantaku V, Putluri V, Yan Y, Arevalo O, Zhu P, Riascos RF, Sreekumar A, Esquenazi Y, Putluri N, Zhu JJ

Acta Neuropathological Communications. 2018 Aug 31;6(1):85. doi: 10.1186/s40478-018-0588-z.

Abstract:

Cancer cells have altered cellular metabolism. Mutations in genes associated with key metabolic pathways (e.g., isocitrate dehydrogenase 1 and 2, IDH1/IDH2) are important drivers of cancer, including central nervous system (CNS) tumors. Therefore, we hypothesized that the abnormal metabolic state of CNS cancer cells leads to abnormal levels of metabolites in the CSF, and different CNS cancer types are associated with specific changes in the levels of CSF metabolites. To test this hypothesis, we used mass spectrometry to analyze 129 distinct metabolites in CSF samples from patients without a history of cancer (n = 8) and with a variety of CNS tumor types (n = 23) (i.e., glioma IDH-mutant, glioma-IDH wild type, metastatic lung cancer and metastatic breast cancer). Unsupervised hierarchical clustering analysis shows tumor-specific metabolic signatures that facilitate differentiation of tumor type from CSF analysis. We identified differences in the abundance of 43 metabolites between CSF from control patients and the CSF of patients with primary or metastatic CNS tumors. Pathway analysis revealed alterations in various metabolic pathways (e.g., glycine, choline and methionine degradation, diphthamide biosynthesis and glycolysis pathways, among others) between IDH-mutant and IDH-wild type gliomas. Moreover, patients with IDH-mutant gliomas demonstrated higher levels of D-2-hydroxyglutarate in the CSF, in comparison to patients with other tumor types, or controls. This study demonstrates that analysis of CSF metabolites can be a clinically useful tool for diagnosing and monitoring patients with primary or metastatic CNS tumors.

Drug Screening of Human GBM Spheroids in Brain Cancer Chip

Akay M, Hite J, Avci NG, Fan Y, Akay Y, Lu G, Zhu JJ
Scientific Reports. 2018 Oct 18;8(1):15423. doi: 10.1038/s41598-018-33641-2.

Abstract:
Glioblastoma multiforme (GBM), an extremely invasive and high-grade (grade IV) glioma, is the most common and aggressive form of brain cancer. It has a poor prognosis, with a median overall survival of only 11 months in the general GBM population and 14.6 to 21 months in clinical trial participants with standard GBM therapies, including maximum safe craniotomy, adjuvant radiation, and chemotherapies. Therefore, new approaches for developing effective treatments, such as a tool for assessing tumor cell drug response before drug treatments are administered, are urgently needed to improve patient survival. To address this issue, we developed an improved brain cancer chip with a diffusion prevention mechanism that blocks drugs crossing from one channel to another. In the current study, we demonstrate that the chip has the ability to culture 3D spheroids from patient tumor specimen-derived GBM cells obtained from three GBM patients. Two clinical drugs used to treat GBM, temozolomide (TMZ) and bevacizumab (Avastin, BEV), were applied and a range of relative concentrations was generated by the microfluidic channels in the brain cancer chip. The results showed that TMZ works more effectively when used in combination with BEV compared to TMZ alone. We believe that this low-cost brain cancer chip could be further developed to generate optimal combination of chemotherapy drugs tailored to individual GBM patients.

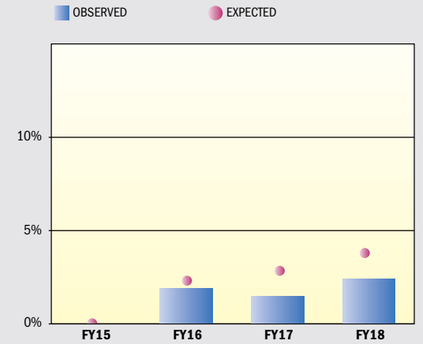
Breakthrough approaches to treatment provided by specialists at UTHealth Neurosciences have led to an increase in the number of patients treated for brain tumors. Since 2009, surgical volumes have increased by 50 percent, to nearly 500 cases per year.

[1]Zhu JJ, Demireva P, Kanner AA, Pannullo S, Mehdorn M, Avgeropoulos N, Salmaggi A, Silvani A, Goldlust S, David C, Benouaich-Amiel A, Zvi Ram on behalf of the EF-14 Trial Investigators. Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma. J Neurooncol. 2017 Dec;135(3);545-552. doi: 10.1007/s11060-017-2601-y. Epub 2017 Aug 28.

[2] Stupp R, Taillibert S, Kanner A, Read W, Steinberg DM, Lhermitte B, Toms S, Idbaih A, Ahluwalia MS, Fink K, Di Meco F, Liberman F, Zhu JJ, Stragliotto G, Tran DD, Bren S, Hottinger AF, Kirson ED, Lavy-Shahaf G, Weinberg U, Kim CY, Paek SH, Nicholas G, Burna J, Hirte H, Weller M, Palti Y, Hegi ME, Ram Z. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temoxolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA. 2017 Dec 19;318(23):2306-2316.

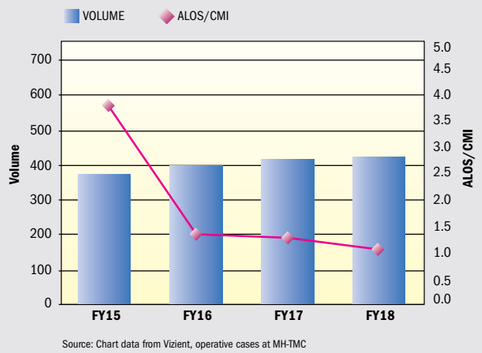
[3]Gainer JL, Sheehan JP, Larner JM, Jones DR. Trans sodium crocetinate with temozolomide and radiation therapy for glioblastoma multiforme. J Neurosurg. 2017 Feb;126(2):460-466. 10.3171/2016.3.JNS152693. Epub 2016 May 13.

Brain Tumor: Inpatient Mortality



Source: Chart data from Vizient, operative cases at MH-TMC

Brain Tumor: Volume & Length of Stay (CMI Adjusted)



Source: Chart data from Vizient, operative cases at MH-TMC

Gamma Knife Stereotactic Radiosurgery in Combination with Bevacizumab for Recurrent Glioblastoma

Morris SL, Zhu P, Rao M, Martir M, Zhu JJ, Hsu S, Ballester LY, Day AL, Tandon N, Kim DH, Shepard S, Blanco A, Esquenazi Y

World Neurosurgery. 2019 Apr 4, pii: S1878-8750(19)30873-3. doi: 10.1016/j.wneu.2019.03.193.

Abstract:

Background: Prior retrospective and prospective studies suggest improved survival with the use of stereotactic radiosurgery (SRS) and bevacizumab in the treatment of limited-volume glioblastoma (GBM) recurrences.

Methods: We retrospectively reviewed our experience with Gamma Knife SRS in combination with bevacizumab for the treatment of focal GBM recurrence during 2009-2015. Outcomes include overall survival, progression free survival (PFS), and radiation-related adverse events. Kaplan-Meier methods and multivariable Cox proportional hazards models were performed for survival analysis.

Results: Within a median of 13.7 months after diagnosis, a total of 45 patients with GBM underwent Gamma Knife SRS and bevacizumab treatment. Median age was 57 years (range: 20-78 years) and 63.3% were women. The median Karnofsky Performance Score (KPS) at recurrence was 80 (range: 40-100). Sixty-four percent of patients had single radiosurgery target (range: 1-4) and median target volume and margin dose were 2.2 cm3 (range: 0.1-25.2 cm3) and 17.0 gray (Gy) (range: 13-24 Gy), respectively. Median PFS and overall survival were 9.3, 31.0 months following diagnosis, and 5.2, 13.3 months after SRS, respectively. Factors associated with poor outcomes were KPS ≤70, SRS dose <18 Gy, and use of <2 chemotherapy agents prior to SRS. No radiation-related adverse events occurred.

Conclusions: SRS in combination with bevacizumab can be safely used to treat focal GBM recurrence. KPS, radiation dose, and multi-agent chemotherapy usage prior to SRS demonstrated significant impact on PFS. Bevacizumab may provide clinically relevant radioprotection.

Cerebrovascular

The UTHealth Stroke Center, led by the Department of Neurology at McGovern Medical School at UTHealth, has long been a leader in the treatment of stroke and other cerebrovascular diseases. UTHealth physicians helped Memorial Hermann-Texas Medical Center become the first in Texas to earn The Joint Commission's Comprehensive Stroke Center (CSC) certification in 2013, the highest quality standard for stroke care in the United States at the time. In addition, the American Heart Association recognized Memorial Hermann-TMC with the Get With The Guidelines®—Stroke Gold Plus Achievement Award and the Target: Stroke Honor Role Elite Plus in 2018.

In addition to breakthrough treatment for stroke, the cerebrovascular team provides coordinated care for patients with aneurysms, carotid occlusive disease and intracranial vascular malformations, including open surgical and endovascular treatments such as angioplasty, stenting and embolization. UTHealth neurosurgeons are skilled at microvascular clipping of aneurysms using the most advanced skull base approaches to minimize brain manipulation; extracranial-intracranial bypass procedures; carotid endarterectomy; and hemicraniectomy for severe strokes. State-of-the-art radiosurgery using the Leksell Gamma Knife® Perfexion™ is used regularly for vascular

malformations best treated nonsurgically. Also available is the Pipeline™ endovascular flow-diverting stent, a device that reconstructs the parent vessel lumen of difficult-to-reach aneurysms as an alternative to clipping or endovascular coiling.

The UTHealth Cerebrovascular Surgery Program is staffed by eight cerebrovascular specialists: Dong H. Kim, MD, Arthur L. Day, MD, P. Roc Chen, MD, Spiros Blackburn, MD, Mark Dannenbaum, MD, Gary Spiegel, MD, Joseph Cochran, MD, Yazan Alderazi, MD, and Sunil A. Sheth, MD. Drs. Chen, Blackburn, Dannenbaum and Cochran are dually trained in both open and endovascular neurosurgery and have extensive experience in skull base surgery. Dr. Spiegel is an experienced endovascular neuroradiologist, and Dr. Sheth is dually trained as a vascular and interventional neurologist. Dr. Alderazi is trained as a critical care and vascular neurologist, as well as an endovascular neuroradiologist. This multidisciplinary group and the Department of Neurology have extended the UTHealth cerebrovascular program to locations across the city. Patients at UTHealth Neurosciences and UT Physicians benefit from a comprehensive array of procedures ranging from diagnostic angiograms to thrombectomies and endovascular coiling.

Our physicians stand among an elite group of providers in the country focused on complex stroke care. Opened in 1988 as one of the first dedicated stroke programs in the world, the Memorial Hermann-TMC Comprehensive Stroke Center is home to the 10-county Greater Houston area's largest onsite stroke team. UTHealth neurologists and neurosurgeons use leading-edge technology to diagnose and treat more than 2,000 stroke and aneurysm patients annually, ensuring that each patient gets the appropriate treatment as soon as possible. By working closely with the Houston Fire Department and local EMS services, the stroke team has logged an impressive record of success in the administration of tPA- more than five times the national average of 5 percent.

Sean Savitz, MD, is director of stroke program development for the Memorial Hermann Health System and also heads two parallel efforts that extend stroke research and clinical expertise beyond the Texas Medical Center to Memorial Hermann hospitals across Houston: the new UTHealth Institute for Stroke and Cerebrovascular Disease and Memorial Hermann's Stroke Systems of Care. With funding from UTHealth, the new Institute serves as a multidisciplinary hub for research and best practices in acute stroke treatment, stroke prevention, stroke recovery, population health and health services. As the research infrastructure at the Texas Medical Center expands, the network for stroke research will be extended to Memorial Hermann's 15 acute-care hospitals.

UTHealth Neurosciences' cerebrovascular continuum of care spans the gamut, from pre-hospital ambulance care to the emergency center setting, and extends through a 12-bed dedicated inpatient stroke unit, to neurorehabilitation provided in a 12-bed inpatient unit at Memorial Hermann-TMC and at its sister hospital TIRR Memorial Hermann, an international leader in rehabilitation and research. Patients benefit from comprehensive inpatient and outpatient services, state-of-the-art technology and innovative therapies and techniques. They also have access to comprehensive outpatient stroke management through clinics, including the Stroke Transitions Education and Prevention (STEP) Clinic directed by Anjail Sharrief, MD. In the STEP Clinic at UT Physicians, practitioners aim to reduce the risk of stroke while improving the quality of life of stroke survivors through risk-factor control and

Sphingolipid Profiling Identifies Large Vessel Occlusion Stroke: Results of the ASPIRE Stroke Study

Sheth SA, Lee S, Iavarone AT, Wong GJ, Liou R, Malhotra K, Starkman S, Liebeskind DS, Saver JL, Savitz SI, Gonzalez NR

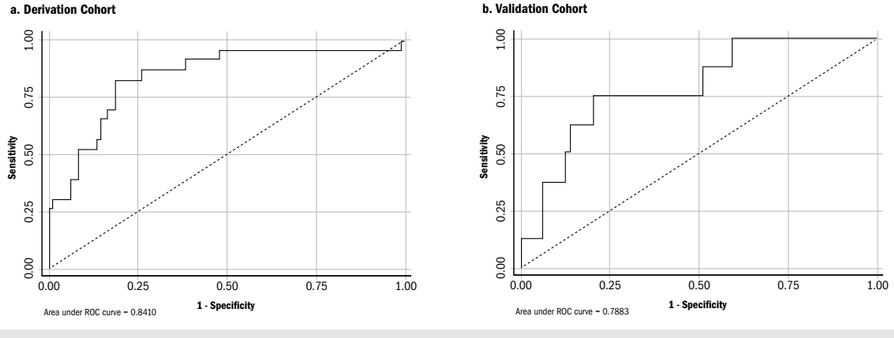
Background: Rapid identification and transport of patients with large vessel occlusions (LVO) to endovascular-capable hospitals has become increasingly important. We previously demonstrated that brain-specific sphingolipids (SLs) serve as useful plasma markers of brain injury. Here, we test and validate SL biomarkers to differentiate LVO from non-LVO acute ischemic stroke (AIS) and stroke mimics.

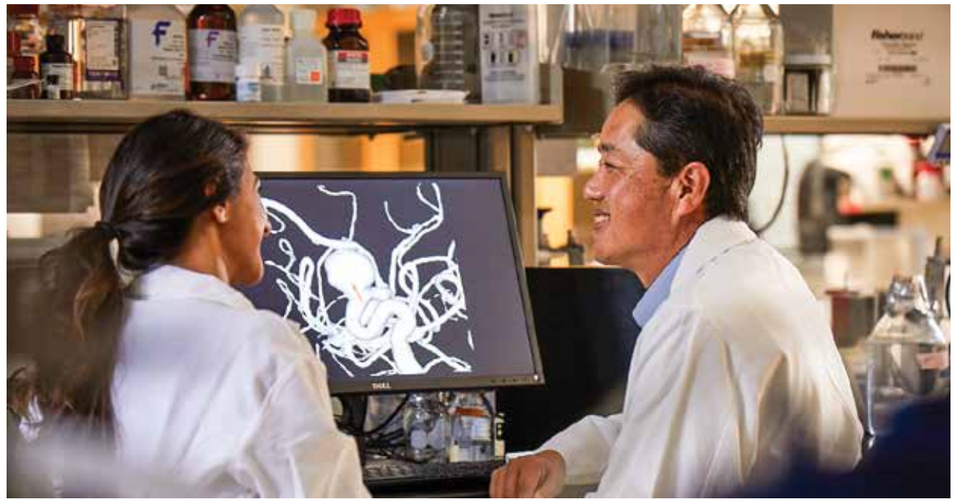
Methods: We enrolled consecutive patients with symptoms concerning for AIS and performed SL profiling using HPLC-MS/MS on blood samples obtained at hospital arrival. MS data were aligned and automated peak picking was performed using XCMS, and SLs were identified by exact mass. A classification method using SL plasma concentrations was created using step-wise logistic regression in a derivation arm, and then tested in an independent validation arm.

Results: Among 184 patients with AIS or AIS-mimics, 84 (46%) were female and average age was 73 years (IQR 63-84). 81 patients (44%) were diagnosed with AIS, 32 (17%) with TIA, and 71 (39%) as stroke mimics. Median time from last known well to blood collection was 124 minutes (IQR 65-275) and Los Angeles Motor Scale (LAMS) was 1 (IQR 0-2). Among patients with AIS, median NIHSS was 3 (IQR 2-8) and 33 (41%) had LVO on CTA or MRA. Among 24 SLs definitively identified, 3 (12.5%) were ceramides, 3 (12.5%) were sphingosines, and 18 (75%) were sphingomyelins. Using step-wise regression, a panel of 8 SLs differentiated LVO from non-LVO AIS or stroke mimic with very good accuracy (AUC 0.76 in derivation; 0.72 in validation), comparable to LAMS alone (AUC 0.73). Combining the SL panel with LAMS resulted in superior discrimination (AUC 0.84 in derivation and 0.79 in validation; Figure).

Conclusions: Plasma levels of SLs may serve as sensitive biomarkers of LVO stroke at early time points after onset.

Figure. ROC curves for model including LAMS and SL Panel





post-stroke complication management. They are also developing novel interventions to improve stroke care and outcomes.

The Memorial Hermann-TMC Comprehensive Stroke Center consistently achieves excellent-to-perfect metrics for quality of care and outperforms national and peer-based benchmarks. Under the direction of Farhaan Vahidy, MD, PhD, a robust data core is provided to physicians by a team of programmers, data scientists and medical abstractors, enabling leadership to monitor quality data in real time and use it to plan and implement evidence-based quality improvement measures.

The CSC also has the largest stroke fellowship program in the country, led by Amrou Sarraj, MD. The program has a rich history of preparing leaders in the field of stroke care by providing comprehensive clinical and academic training that covers all aspects of cerebrovascular disease.

The UTHealth Telemedicine Program, directed by Teddy Wu, MD, extends stroke and neurology expertise far beyond the hospital's walls, helping emergency physicians in suburban and community hospitals throughout southeast Texas make accurate diagnoses and save lives. Remote presence robotic technology has enhanced the telemedicine program by linking outlying hospitals electronically to the neurology department at McGovern Medical School, providing real-time visual interaction between neurologists and patients, and allowing UTHealth neurologists to review CT scans and advise local physicians on treatment protocols. Through telemedicine, physicians can now offer patients in outlying communities an opportunity to participate in clinical trials that otherwise would be unavailable to them, which expands medical knowledge as it saves lives. The Telemedicine Program is a flagship training program for residents and fellows in the stroke academic community, led by Amanda Jagolino-Cole, MD, and Tiffany Cossey, MD.

Physicians at UTHealth conduct more research than any other stroke program in the south or southwestern United States, participating in multicenter and single-center clinical trials testing new treatments for patients who cannot be treated elsewhere. McGovern Medical School, in partnership with the Memorial Hermann-TMC Comprehensive Stroke Center, was chosen as the only regional coordinating center in Texas and the southwestern United States to serve in StrokeNet, a national network funded by the National Institute of Neurological Disorders and Stroke to conduct clinical stroke trials across the country. UTHealth serves as the flagship to coordinate clinical stroke trials throughout the region.

Pioneering stroke research at UTHealth includes thrombolytic treatment for wake-up stroke, the safety of pioglitazone for hematoma resolution in intracerebral hemorrhage, multi-agent vasodilator infusion therapy versus current typical single-agent therapy for cerebral vasospasm, and stem cell-based therapies for acute ischemic stroke. Dr. Savitz is leading pioneering studies in stroke recovery with the use of stem cells with promising results. Investigations led by Andrew Barreto, MD, seek to increase the effect of standard-of-care treatment by combining tPA and other blood thinners to enhance recanalization of large artery clots in acute stroke.

Optimizing stroke patients' outcomes is one of the most important areas in acute stroke care. UTHealth is conducting the largest multicenter study on refining selection methods to determine how best to triage acute ischemic stroke patients prior to endovascular therapy (SELECT), led by Amrou Sarraj, MD.

A team of researchers led by Dong Kim, MD, discovered a genetic mutation linked to intracranial aneurysms (IA). After studying more than 500 people, including a large family with multiple incidents of IA, the team identified a specific protein-coding gene, THSD1, whose mutation is suspected to lead to the formation of weak or thin spots in cerebral arteries. After pinpointing the mutation, the researchers investigated the consequences of a loss of function of THSD1, using genetically modified mice and zebrafish. They discovered cerebral hemorrhage and increased mortality in both animal models when the gene's function was switched off.

By supporting interdisciplinary collaborative research from neuroscience, clinical neurology, vascular biology, immunology, cerebrovascular diseases and aging, the UTHealth BRAINS Research Laboratory is developing effective strategies for the diagnosis and treatment of stroke and brain injury – and moving new discoveries quickly from the bench to the bedside. Led by Louise D. McCullough, MD, PhD, the Group consists of nine other independent investigators – Jun Li, PhD, Fudong Liu, MD, Venu Venna, PhD, Sean Marrelli, PhD, Bharti Manwani, MD, PhD, Anjali Chauhan, MSc, PhD, Gab Seok Kim, PhD, Bhamu Priya Ganesh, PhD, and Akihiko Urayama, PhD. It is funded by the National Institutes of Health and the American Heart Association to study aspects of stroke and vascular disease, with programs ranging from neonatal stroke to post-stroke dementia. Research programs are investigating sex differences in stroke, how social factors such as depression and social isolation affect stroke outcomes, the mechanisms underlying pregnancy-associated stroke risk, the impact of aging of the immune system on stroke-related cognitive decline, chromosomal and hormonal contributions to sex differences in ischemic stroke, the hypothesis that microchimeric cells home to the site of injury as part of the immune response to stroke, the role of calcium signaling in stroke, the effects of X chromosome-linked proteins on sexual dimorphism in ischemic stroke, and how manipulation of the brain's resident immune cells may help limit ischemic injury and promote tissue repair after stroke. Dr. Liu examines how sex differences in inflammation alter outcomes after neonatal stroke, and Dr. Venna is working on understanding the role of an emerging cytokine, macrophage migration inhibitory factor, in post-stroke depression, cognitive impairment and post-stroke recovery. New work by Dr. Urayama in collaboration with Claudio Soto, PhD, a world-renowned UTHealth expert in neurodegenerative diseases, has shown that transfer of blood from young animals can reduce age-related inflammation. The group also is invested in training, and has numerous postdoctoral fellows and MD/PhD students actively engaged in research.

Led by Jaroslaw Aronowski, MD, PhD, and funded by multiple grants from the National Institutes of Health, studies in intracerebral hemorrhage – the stroke subtype with the highest mortality – are focused on the development of new treatments. Dr. Aronowski's group is examining various anti-oxidative and anti-inflammatory therapeutic strategies with a particular focus on how to reprogram immune cells to reduce inflammation, improve clearance of debris and ultimately improve brain repair after intracerebral hemorrhage (ICH) in experimental models. Discoveries from this research led to a clinical trial directed by Nicole Gonzales, MD, investigating factors linked to hematoma clearance as a new therapeutic approach in patients with ICH. Lastly, Dr. Vahidy, is leading studies comparing functional and quality-of-life outcomes in patients with intracerebral hemorrhage transferred to Memorial Hermann-TMC with those patients who remain at outside hospitals to determine which patients can benefit most from transfer.

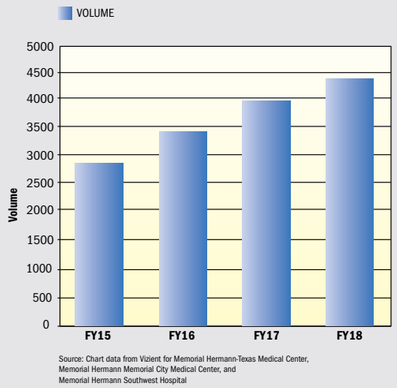
QUALITY & OUTCOMES MEASURES

Stroke Core Measures

GWTG Measure	MEASURE GOAL	2013	2014	2015	2016	2017	2018
VTE Prophylaxis	85%	99.1%	99.9%	100%	100%	99.9%	99.9%
Discharged on Antithrombotic Therapy	85%	98.8%	99.5%	100%	99.5%	99.5%	99.9%
Anticoagulation Therapy for Atrial Fib.	85%	97.9%	98%	97.2%	98.3%	99.2%	97.8%
Thrombolytic Therapy	85%	97%	94.6%	100%	100%	99.2%	99.2%
Antithrombotic Therapy by End of Hospital Day 2	85%	92.8%	97.8%	99.2%	98.8%	98.9%	98.2%
Discharged on Statin Medication	85%	98.2%	99.2%	100%	99.4%	99.7%	99.5%
Stroke Education	85%	96.1%	97.3%	98.4%	99.5%	99.4%	99.5%
Assessed for Rehabilitation	85%	99.2%	99.8%	99.7%	99.9%	99.7%	99.4%

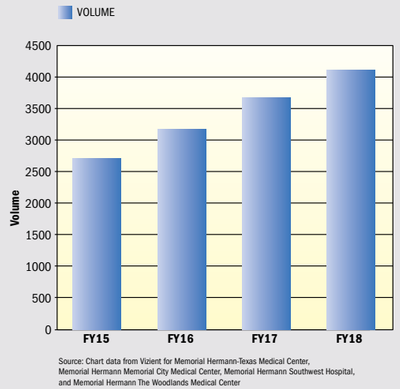
Source: Chart data based on fiscal year

Cerebrovascular Volume



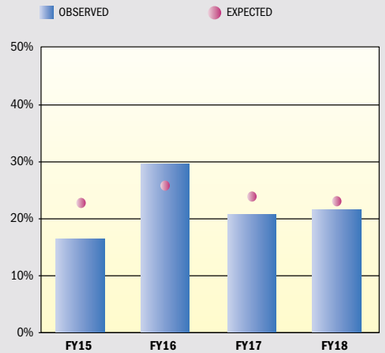
Source: Chart data from Vizient for Memorial Hermann-Texas Medical Center, Memorial Hermann Memorial City Medical Center, and Memorial Hermann Southwest Hospital

Stroke Volume



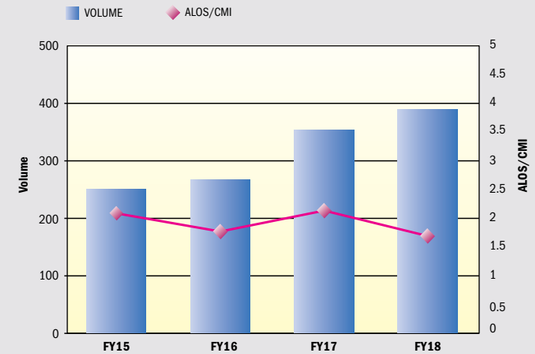
Source: Chart data from Vizient for Memorial Hermann-Texas Medical Center, Memorial Hermann Memorial City Medical Center, Memorial Hermann Southwest Hospital, and Memorial Hermann The Woodlands Medical Center

Subarachnoid Hemorrhage: Inpatient Mortality



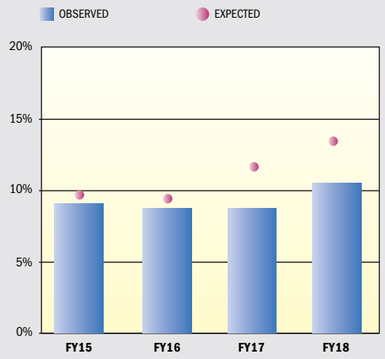
Source: Chart data from Vizient

Subarachnoid Hemorrhage: Volume & Length of Stay (CMI Adjusted)



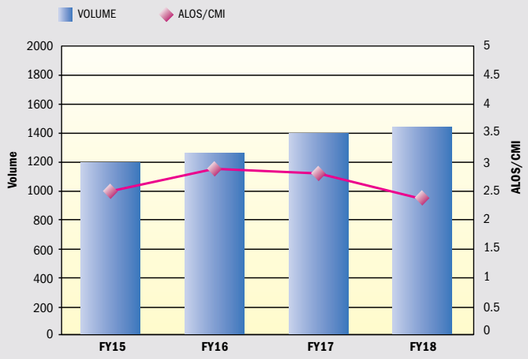
Source: Chart data from Vizient

Acute Ischemic Stroke: Inpatient Mortality



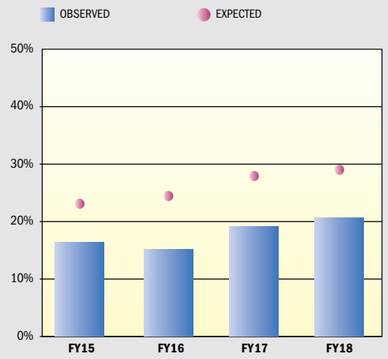
Source: Chart data from Vizient

Acute Ischemic Stroke: Volume & Length of Stay (CMI Adjusted)



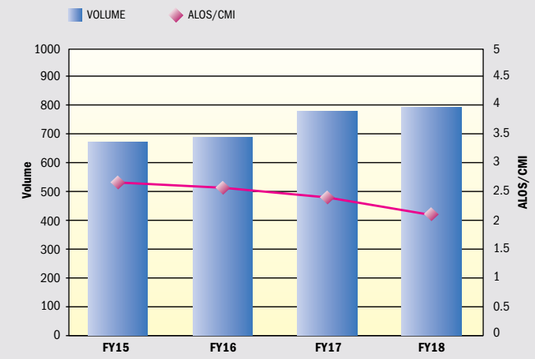
Source: Chart data from Vizient

Intracerebral Hemorrhage: Inpatient Mortality



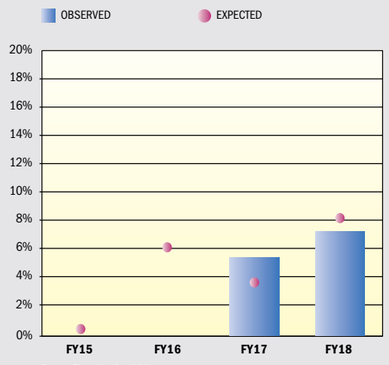
Source: Chart data from Vizient

Intracerebral Hemorrhage: Volume & Length of Stay (CMI Adjusted)



Source: Chart data from Vizient

Arteriovenous Malformation: Inpatient Mortality



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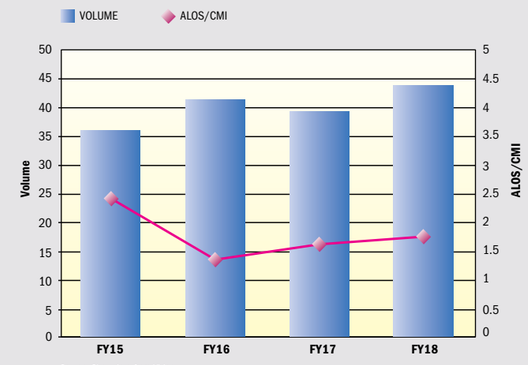
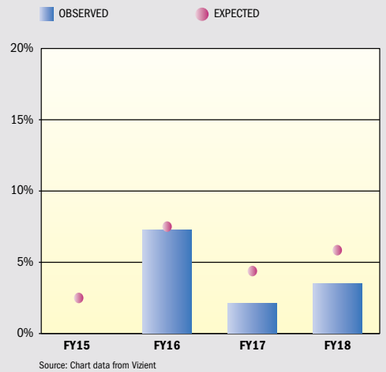
Arteriovenous Malformation: Volume & Length of Stay (CMI Adjusted)



Source: Chart data from Vizient

Unruptured Aneurysm: Inpatient Mortality



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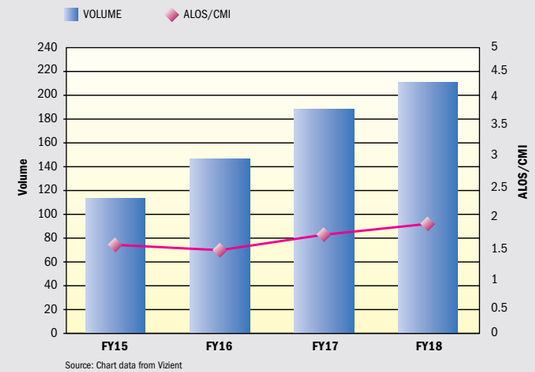
Unruptured Aneurysm: Volume & Length of Stay (CMI Adjusted)



Source: Chart data from Vizient

Children's Neuroscience

UTHealth pediatric neurosurgeons David Sandberg, MD, FAANS, FACS, FAAP, Stephen Fletcher, DO, and Manish N. Shah, MD, bring a broad range of clinical and research expertise to the Children's Neuroscience Center at UTHealth.

Translational studies conducted by Dr. Sandberg have demonstrated the safety of infusing chemotherapeutic agents directly into the fourth ventricle of the brain to treat children with recurrent malignant brain tumors. A pilot clinical trial completed in August 2015 demonstrated promising results in some patients who had failed all other prior treatments, and these results have led to two current trials available only at Children's Memorial Hermann Hospital in collaboration with McGovern Medical School. These two trials are open for enrollment: "Combination Intraventricular Chemotherapy Pilot Study," investigating methotrexate and etoposide infusions into the fourth ventricle in children with recurrent posterior fossa brain tumors, and a Phase 1 study "Infusion of 5-Azacytidine (5-AZA) into the Fourth Ventricle or Resection Cavity in Children with Recurrent Posterior Fossa Ependymoma."

Dr. Fletcher leads fetal pediatric neurosurgery efforts at The Fetal Center at Children's Memorial Hermann Hospital, a national leader in providing diagnosis, treatment and complete care for mothers with high-risk pregnancies and infants with congenital anomalies or genetic conditions. The multidisciplinary team performed the first fetal spina bifida repair in the region, and patients are now being referred to the Center for fetal myelomeningocele repair from throughout Texas and a number of surrounding states. The fetal surgery team continues to refine efforts at improving neurological outcomes in children with spina bifida with a robust research effort to determine the best method of repairing the abnormality; they also aim to reduce the risk to the mother by performing the procedure endoscopically. The combined efforts of basic scientists, general and fetal surgeons, neurosurgeons, pathologists and radiologists has led to a novel method to close the spinal defect, which remains under study. Their goal is to enroll more patients in ongoing studies to improve outcomes for children with spina bifida.

Dr. Shah, who has special expertise in the surgical management of spasticity and dystonia in children, directs the Texas Comprehensive Spasticity Center at UT Physicians Pediatric Surgery and McGovern Medical School, in collaboration with Children's Memorial Hermann Hospital. Dr. Shah performs selective dorsal rhizotomies, baclofen pump placement and advanced deep brain stimulation. He also has expertise in pediatric epilepsy, craniofacial surgery and craniocervical spine surgery. His research focuses on advanced imaging-based classifications of cerebral palsy and epilepsy patients.

To avoid the many complications of ventriculoperitoneal shunting for children with hydrocephalus, pediatric neurosurgeons from UTHealth routinely perform minimally invasive techniques such as endoscopic

Photo courtesy of Children's Memorial Hermann Hospital

third ventriculostomy, septostomy, choroid plexus coagulation and fenestration of arachnoid cysts. Selected brain tumors can be biopsied or removed completely via endoscopic techniques. All of these procedures are performed through very small incisions with minimal hair shaving. In collaboration with UTHealth otolaryngologists affiliated with Memorial Hermann-Texas Medical Center, neurosurgeons also remove some tumors via endoscopic transnasal approaches without an external incision. Together with nationally recognized UTHealth craniofacial plastic surgeons, UTHealth pediatric neurosurgeons affiliated with Children's Memorial Hermann Hospital perform both conventional and minimally invasive endoscopic surgeries to repair craniosynostosis and other complex craniofacial anomalies. The multidisciplinary Texas Cleft-Craniofacial Team was established in 1952 and has been a regional leader for pediatric craniofacial surgery for decades.

Children's Memorial Hermann Hospital is also a center of excellence for pediatric epilepsy surgery and comprehensive specialized care for children with refractory epilepsy. The pediatric Epilepsy Monitoring Unit is one of the largest and most comprehensive of its kind in the southwestern United States. In addition to MRI and CT with low radiation dose protocols for pediatric patients, UTHealth physicians use the Elekta Neuromag® for noninvasive functional mapping of brain activity with magnetoencephalography (MEG) to locate the source of epileptic seizures and minimize risk for children undergoing resective surgery for refractory epilepsy. For the most accurate diagnosis they also use stereo EEG, video EEG, PET, SPECT, memory and speech (Wada) testing and neuropsychological testing. Interventions include medical management and the ketogenic diet as well as surgery, including vagus nerve stimulation and laser ablation procedures. UTHealth

RESEARCH HIGHLIGHTS

Combination Intraventricular Chemotherapy Pilot Study: Methotrexate and Etoposide Infusions into the Fourth Ventricle or Resection Cavity in Children with Recurrent Posterior Fossa Brain Tumors

PRINCIPAL INVESTIGATOR: David I. Sandberg, MD
Director, Pediatric Neurosurgery, Mischer Neuroscience Institute
Professor, Vivian L. Smith Department of Neurosurgery and Department of Pediatric Surgery
Dr. Marnie Rose Professorship in Pediatric Neurosurgery
McGovern Medical School at UTHealth

For the first time in humans, our center demonstrated in a previous pilot clinical trial that chemotherapy can be delivered directly into the fourth ventricle of the brain in children with recurrent, malignant brain tumors. Promising results from a pilot trial with low-dose (2 milligram) methotrexate infusions has led to several additional clinical trials testing this novel treatment approach. There has been no neurological toxicity, and some patients have demonstrated decreased tumor burden after infusions. In a current trial, open to patients age 1 to 80 years with medulloblastoma and atypical teratoid rhabdoid tumor (ATRT), two chemotherapy agents (methotrexate and etoposide) are simultaneously being infused into the fourth ventricle to treat recurrent disease in the brain and/or spine. The researchers hope for continued demonstration of safety and even more robust clinical responses in this clinical trial.

Infusion of 5-Azacytidine (5-AZA) into the Fourth Ventricle or Resection Cavity in Children with Recurrent Posterior Fossa Ependymoma: A Phase 1 Study

PRINCIPAL INVESTIGATOR: David I. Sandberg, MD
Director, Pediatric Neurosurgery, Mischer Neuroscience Institute
Professor, Vivian L. Smith Department of Neurosurgery and Department of Pediatric Surgery
Dr. Marnie Rose Professorship in Pediatric Neurosurgery
McGovern Medical School at UTHealth

Open to patients age 1 to 80 years old with recurrent ependymoma that originated in the posterior fossa of the brain, this new study employs a novel means of treating ependymoma brain tumors that originate from the fourth ventricle: infusion of a chemotherapy agent directly into the fourth ventricle rather than systemic intravenous delivery. The agent being infused, 5-AZA, has been shown to effectively kill ependymoma cells in the laboratory and been shown to be safe when infused at a lower dose directly into the fourth ventricle in a pilot clinical trial. There will be no simultaneous systemic chemotherapy.

Pediatric Epilepsy Surgery Focus Identification with Resting State MRI

PRINCIPAL INVESTIGATOR: Manish N. Shah, MD
Director, Texas Comprehensive Spasticity Center
Director, Pediatric Spasticity and Epilepsy Surgery
Children's Memorial Hermann Hospital and Mischer Neuroscience Institute
Assistant Professor, Department of Pediatric Surgery
McGovern Medical School at UTHealth

Dr. Manish N. Shah and his research team hypothesize that preoperative resting state MRI data obtained with the routine structural MRI workup for epilepsy surgery can help predict brain seizure foci locations. The resting state MRI voxel-wise latency to the global mean signal was compared in a cohort of pediatric epilepsy surgery patients to a large cohort of normal pediatric brain latency maps. The voxel-wise latency maps are predictive of the type of operation and laterality of the cohort.

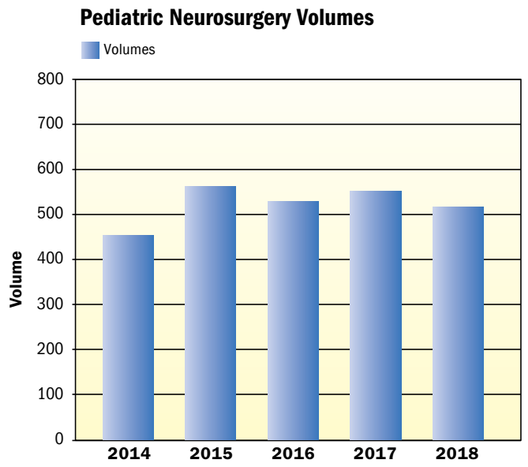
As these resting state MRI data are easily obtained with the preoperative clinical MRI, they may be of great adjunct utility in identifying potential seizure foci for further investigation with minimally invasive monitoring methods such as stereotactic electroencephalography (SEEG).

Pediatric Optical Tomographic Imaging

PRINCIPAL INVESTIGATOR: Manish N. Shah, MD
Director, Texas Comprehensive Spasticity Center
Director, Pediatric Spasticity and Epilepsy Surgery
Children's Memorial Hermann Hospital and Mischer Neuroscience Institute
Assistant Professor, Department of Pediatric Surgery
McGovern Medical School at UTHealth

Using a novel detection method, the researchers imaged four infants with varying skull thicknesses with a transcranial optical imaging paradigm. They hope a refined method of this technique will provide data on brain activation and deactivation with similarly excellent spatial and temporal resolution, without the need for sedation often required for functional MRI studies in children.

pediatric neurosurgeon Manish N. Shah, MD, directs the Pediatric Epilepsy Surgery Program at Children's Memorial Hermann Hospital. UTHealth's Gretchen Von Allmen, MD, is chief of pediatric epilepsy for the Texas Comprehensive Epilepsy Program and medical director of the Children's Memorial Hermann Hospital Pediatric Epilepsy Monitoring Unit. Along with pediatric epileptologists Jeremy Lankford, MD, and Michael Watkins, MD, they work together with other adult and pediatric epilepsy specialists to manage patients over their entire lifespan for a seamless transition of care.



Source: chart data based on surgical procedures per fiscal year.

Children's Memorial Hermann Hospital is a leading center for the treatment of retinoblastoma, a rare pediatric eye malignancy that affects only 250 to 350 new patients each year. It was the first hospital in Texas and one of only a handful of hospitals in the United States to administer intra-arterial chemotherapy, the most modern treatment for the disease, which enables children to have chemotherapy injected into the artery that feeds the eye, eliminating the side effects of systemic chemotherapy and maximizing the dose to the eye. Intra-arterial chemotherapy is a complex treatment that involves close collaboration among a 50-person retinoblastoma team at Children's Memorial Hermann Hospital. In addition to UTHealth ocular oncologist Amy Schefler, MD, and neurointerventionalist Mark Dannenbaum, MD, the team includes pediatric oncologist Deborah Brown, MD, pediatric anesthesiologist Michael Lin, MD, neuroradiologists and other physicians. Specialty-trained nurses in the oncology pharmacy, pediatric operating room, pediatric recovery area and angiography suite all play a role in caring for these special patients, as well as social workers, genetic counselors and Child Life specialists. Physicians are also engaged in research investigating new ways to save eyes that have failed conventional therapies.

The Children's Neuroscience Center at UTHealth provides a broad range of diagnostic and treatment services for children with complex neurological problems including autism, brachial plexus disorders, brain tumors and malformations, cerebral palsy, congenital hydrocephalus, craniofacial disorders, developmental disorders, epilepsy, chronic headache and migraine, head trauma, learning disabilities, movement disorders, myopathy, neurofibromatosis, neurometabolic disorders, neuromuscular disorders, pediatric stroke, peripheral nerve disorders, sleep disorders, spina bifida, Tourette syndrome and tuberous sclerosis complex. UTHealth physicians have specialized pediatric neurosurgical expertise in congenital

Cryopreserved Human Umbilical Cord for Repair of Fetal Spina Bifida Defects

PRINCIPAL INVESTIGATOR:
Ramesha Papanna, MD, MPH
Assistant Professor, Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School at UTHealth

CO-INVESTIGATOR: Stephen Fletcher, DO
Associate Professor, Department of Pediatric Surgery
McGovern Medical School at UTHealth

In-utero repair has been shown to improve neurological outcomes in children with open neural tube defects. In Dr. Papanna's lab, researchers are investigating the various tissues used to repair these defects in the spines of infants.

Preliminary data in various animal models suggest that the use of human umbilical cord for repair offers many advantages over commercially available products. Two patients were enrolled in an FDA-approved clinical trial and are being followed one year after surgery. Outcomes appear promising, and the fetal team at Children's Memorial Hermann Hospital is seeking approval for a study using this material in future fetal surgeries.

The research has been expanded to include an even more detailed analysis of the molecular and biochemical changes that occur with human umbilical cord, and the researchers are studying all options, from open fetal repair to endoscopic fetal repair for selected patients with open neural tube defects.

malformations, including Chiari malformation; endoscopic neurosurgery; and treatment for pediatric stroke, spinal deformities and traumatic brain and spine injury.

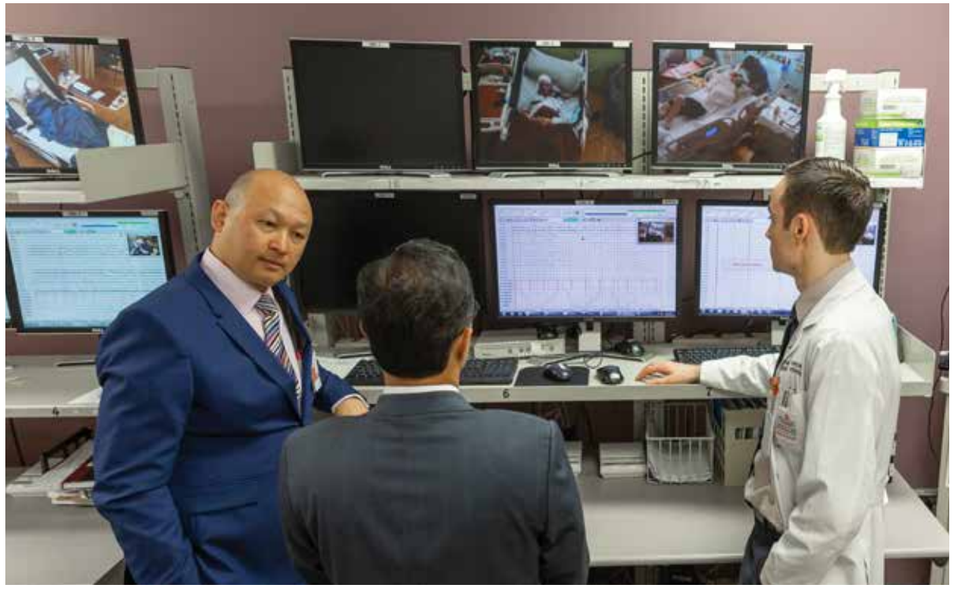
Care at Children's Memorial Hermann Hospital is delivered in a child-friendly, reassuring environment to promote wellbeing and the best possible outcomes. When surgery is required, UTHealth physicians use advanced imaging techniques and minimally invasive procedures that lower patient risk. Onsite sedation is available for imaging studies with care provided by specially trained pediatric anesthesiologists and pediatric nurses.

Photo courtesy of Children's Memorial Hermann Hospital

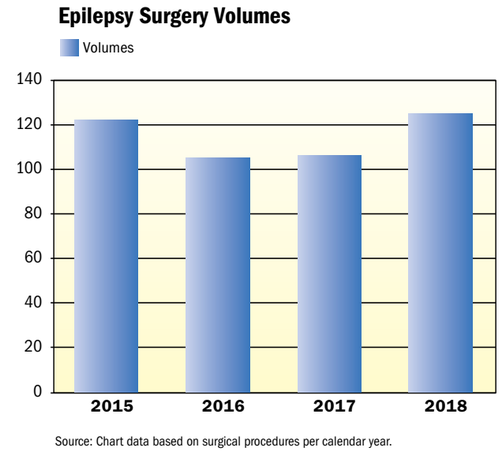
Epilepsy

Over the past five years, the Texas Comprehensive Epilepsy Program (TCEP), a Level 4 National Association of Epilepsy Centers-certified center, has seen accelerated growth in volumes of medically and surgically treated patients. UTHealth providers now include six fulltime adult and three fulltime pediatric epileptologists and an adult and pediatric epilepsy surgeon. A collaborative effort among UTHealth Neurosciences, McGovern Medical School at UTHealth, Memorial Hermann-Texas Medical Center, and Children's Memorial Hermann Hospital, the program is the premier destination for the diagnosis and treatment of epilepsy in patients of all ages in the southwestern USA. A host of etiologies, including genetic anomalies, brain trauma, structural abnormalities, stroke and brain tumors, can cause epilepsy, and a specific determination of the cause of seizures by experts in the field is crucial to planning the most effective treatment for individual patients.

The program expanded with the addition of Samden Lhatoo, MD, FRCP (Lon), in December 2018. He is now the John P. and Kathrine G. McGovern Distinguished University Professor of Neurology and executive vice chair of the Department of Neurology. He also serves as director of the Texas Comprehensive Epilepsy Program and co-director of the Texas Institute for Restorative Neurotechnologies at UTHealth.



At the heart of the program is a state-of-the-art seven-bed adult Epilepsy Monitoring Unit (EMU) and a six-bed pediatric EMU at Memorial Hermann-TMC and Children's Memorial Hermann Hospital, together making up the largest and most comprehensive monitoring unit of its kind in the region. The Video-EEG monitoring unit is one of a few inpatient units in the country with simultaneous electroencephalography/polysomnography capability.



Source: Chart data based on surgical procedures per calendar year.

Once a diagnosis is made, TCEP physicians at UTHealth offer the most advanced medical treatment options available, including combination drug therapy, the ketogenic and modified Atkins diet, and specialized measures for special populations (for example, hormonal manipulation for catamenial epilepsies). Under the leadership of UTHealth neurosurgeon Nitin Tandon, MD, the program is a world leader in epilepsy surgery. Dr. Tandon has performed more than 700 cranial procedures for the localization and treatment of epilepsy, with a zero percent mortality rate and a very low rate of permanent morbidity. In addition to the conventional procedures of focal cortical resection, lobectomy, hemispherectomy and corpus callosotomy, physicians have adopted several innovative surgical procedures for epilepsy. Prominent among these are robotic stereo-electro-encephalography (SEEG) for 3D investigation of epileptic foci in the brain with a stereotactic placement of intracerebral electrodes, MR-guided laser interstitial thermal therapy (Visualase®) and Responsive Neural Stimulation (RNS – NeuroPace®). The program was the second in the country to adopt robotic SEEG, and Dr. Tandon recently performed his 170th robotic SEEG implantation with 0 percent morbidity from the placement of nearly 2,400 electrodes.

UTHealth physicians are pioneering the use of Visualase, the application of laser surgery for well-delineated focal epilepsies, which is used to ablate seizure foci in a minimally invasive fashion. In addition to the conventional use of Visualase for the treatment of temporal lobe epilepsy associated with hippocampal sclerosis, UTHealth physicians use it in novel ways, including the treatment of deep-seated periventricular nodular heterotopia and hypothalamic hamartoma.

More than 50 Visualase procedures have been completed, with zero complications. The program also offers responsive neurostimulation therapy (RNS - NeuroPace®) to selected patients whose refractory disease is not amenable to conventional or laser surgery. Finally, the program goes beyond the medical and surgical treatment of epilepsy to offer general supportive measures via a network of community counselors who help patients cope with the psychosocial and emotional aspects of their condition. A patient and caregiver support group, overseen by physicians, a specialist nurse and coordinating administrative staff, meets every month at Memorial Hermann-Texas Medical Center.

The TCEP has been involved in drug-trial research related to most of the new epilepsy treatments approved in the United States in the last 16 years, including lacosamide monotherapy and adjunctive therapy for partial-onset seizures, and an open-label extension study of rufinamide as an adjunctive therapy in patients with refractory partial-onset seizures. Current drug trials include vigabatrin therapy with magnetic-resonance spectroscopy (MRS) for refractory partial epilepsy. UTHealth physicians have also contributed patient data to nationwide trials in epilepsy genetics (the Epilepsy Phenome-Genome Project) and epidemiology (Human Epilepsy Project). The program is a member of the National Critical Care EEG Monitoring Research Consortium.

TCEP physicians, all of whom hold academic appointments at McGovern Medical School, pursue several other lines of investigator-initiated clinical and scientific research. Research funding comes from a variety of sources including major National Institutes of Health and National Science Foundation grants. In addition, they pursue collaborative interdisciplinary research with numerous local, national and international institutions. Prominent research interests are in the area of the neuroimaging and electrophysiology of epilepsy and human cognitive function, such as the neurophysiology of human language and memory processing and the sleep-wake cycle; advanced MRI techniques to localize epilepsy when conventional methods fail; and signal processing of EEG to understand brain networks and the more fundamental aspects of how seizures arise and propagate using existing cognitive networks.

Advanced Diagnostic Technologies for Epilepsy

Board-certified physicians employ advanced diagnostic technologies that provide comprehensive datasets to help define and localize brain seizure networks.

- High-definition MRI employing specialized sequences to probe grey and white matter and eloquent function, including double-inversion recovery, diffusion tensor imaging and functional MRI
- Magnetoencephalography (MEG) coupled to high-density electroencephalography (EEG) for spike localization and cognitive function mapping
- State-of-the-art video-EEG for epilepsy electro-clinical classification
- Positron emission tomography (PET) and single photon emission computed tomography (SPECT) for probing cerebral metabolism
- Intra-carotid amytal (Wada) testing for language and memory lateralization
- Epilepsy-specific neuropsychological testing

RESEARCH HIGHLIGHT

Subdural Grids vs. Stereo-electroencephalography–Morbidity and Outcomes: A Comparative Analysis of 260 Consecutive Cases

LEAD PHYSICIAN: Nitin Tandon, MD
Professor, Vivian L. Smith Department of Neurosurgery
McGovern Medical School

Objective: Over the past five years, a dramatic change has occurred in the evaluation of epilepsy, involving the use of stereo-electroencephalography (SEEG) for seizure localization. This change, replacing the use of subdural electrodes (SDEs), has been motivated by the minimally invasive nature of SEEG coupled with a greater ease of its implementation than in decades past, due to technological advances. While both SDE and SEEG techniques have relative advantages in specific situations, in many patients, either one of these approaches could be applied. We performed a comparative analysis of the relative efficacy, morbidity and seizure outcomes using these two distinct techniques at a large volume epilepsy center, where SDE placement has largely been replaced by SEEG, to evaluate the relative safety, morbidity and outcomes following each of these procedures.

Methods: Details and outcomes following 260 intracranial procedures, consecutively performed by a single neurosurgeon between 2004 and 2017, were identified from a prospectively compiled surgical database. Patient demographics, epilepsy characteristics, procedural morbidity, duration of monitoring, six-month and eventual outcomes were determined in each case. Comparisons between the two groups were made using unpaired t-tests and chi-squared tests.

Results: The SEEG (n=121) and SDE (n=139) groups were similar in age (30.1 ± 12.2 vs. 30.6 ± 13.8 years), gender (SEEG = 47.1% male; SDE = 43.9% male), numbers of anticonvulsants failed and the duration of epilepsy (16.4 ± 12.0 years vs.17.2 ± 12.1 years). Duration of intracranial monitoring in these two groups was comparable (SEEG = 7.7 ± 3.9 days vs. SDE = 8.1 ± 2.8 days) and similar numbers of SDE (6) and SEEG (7) cases underwent the placement of additional electrodes after the initial implant, during the same hospital stay. A significantly larger proportion of SDE procedures (13.7%) underwent transfusion of blood products compared with SEEG procedures (0.8%, $p < 0.0001$). Pain medication requirements were also significantly greater in the SDE vs. the SEEG group (356 ± 233 mg vs. 201 ± 176 mg, $p < 0.0001$). There were 7 symptomatic hemorrhagic sequelae (with one long-term neurological deficit related to the intracranial evaluation) and two infections in the SDE cohort, but no clinically relevant complications occurred in the SEEG cohort, a marked difference in the complication rates ($p = 0.004$). A greater proportion of SDE cases led to resective or ablative surgery (91.4%), compared with SEEG cases (72.7%, $p < 0.0001$). Favorable epilepsy outcomes following (Engel I or II), significantly favored patients undergoing resection/ablation after SEEG relative to SDE at 6 months (83.7% vs 65.5%, $p = 0.004$) and at one year (71.6% vs 54.1%, $p=0.02$) post resection. While the SEEG cohorts were less likely to undergo definitive procedures, comparison of outcomes for all patients also trended to favor SEEG with good outcomes in 59.5% vs. 53.2% ($p = 0.31$) at 6 months and 43.8% vs. 38.1% ($p=0.35$) at one year, though these differences were not significant.

Conclusions: This is the first direct comparison of large and matched cohorts managed using SEEG and SDEs that reveals distinct benefits in procedural morbidity coupled with non-inferiority and likely more favorable epilepsy outcomes favoring SEEG. These considerations should factor into decision-making when patients with pharmaco-resistant epilepsy are considered for intracranial evaluations. Given that it is unlikely that prospective randomized comparative studies to contrast these two surgical approaches in the evaluation of epilepsy are unlikely, we look to validation of these observations from similar analyses done at other centers performing large volumes of these procedures.

Laser Ablation for Mesial Temporal Lobe Epilepsy: Surgical and Cognitive Outcomes with and without Mesial Temporal Sclerosis

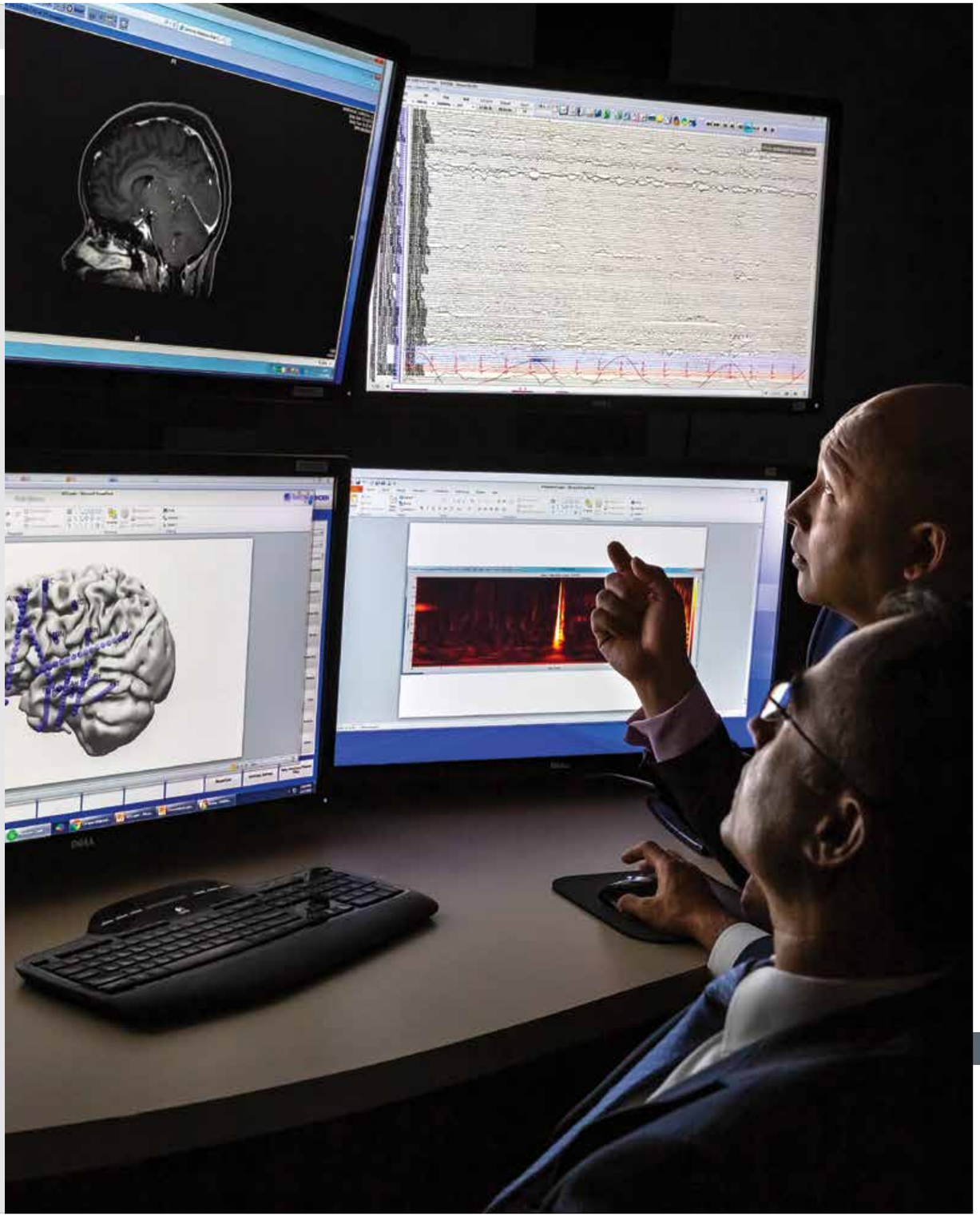
LEAD PHYSICIAN: Nitin Tandon, MD
Professor, Vivian L. Smith Department of Neurosurgery
McGovern Medical School

Objective: Laser interstitial thermal therapy (LITT) is a minimally invasive surgical technique for focal epilepsy. A major appeal of LITT is that it may result in fewer cognitive defects, especially when targeting dominant hemisphere mesial temporal lobe (MTL) epilepsy. To evaluate this, as well as to determine seizure outcomes following LITT, we evaluated the relationships between ablation volumes and surgical or cognitive outcomes in 43 consecutive patients undergoing LITT for MTL epilepsy.

Methods: All patients underwent unilateral LITT targeting mesial temporal structures. FreeSurfer software was used to derive cortical and sub-cortical segmentation of the brain (especially sub-regions of the MTL) using the preoperative MRI. Ablation volumes were outlined using a post-ablation T1 contrasted MRI. The percentages of the amygdala, hippocampus and entorhinal cortex ablated were objectively quantified. The volumetric measures were regressed against changes in neuropsychological performance before and after surgery.

Results: A median of 73.7% of amygdala, 70.9% of hippocampus and 28.3% of entorhinal cortex was ablated. Engel I surgical outcome was obtained in 79.5 % and 67.4% of the 43 patients at 6 and 20.3 months follow-up, respectively. No significant differences in surgical outcomes were found across patient subgroups (hemispheric dominance, hippocampal sclerosis or need for intracranial evaluation). Further, no significant differences in volumes ablated were found between patients with Engel IA vs. Engel II-IV outcomes. In patients undergoing LITT in the dominant hemisphere, a decline in verbal and narrative memory, but not in naming function, was noted.

Conclusions: Seizure-free outcomes following LITT may be comparable in carefully selected patients with and without MTS, and these outcomes are comparable with outcomes following microsurgical resection. Failures may result from non-mesial components of the epileptogenic network that are not affected by LITT. Cognitive declines following MTL-LITT are modest, but significant for the group and principally affect memory processes.



Memory Disorders and Dementia

Physicians at the UT Physicians Neurocognitive Disorders Center evaluate and treat patients with concerns about memory, language, judgment, mood, behavior and related issues. Because symptoms may have a range of causes – normal aging, early dementia, mini-strokes, infections, vitamin deficiencies, depression, hormonal deficiencies and sleep disorders, among others – they evaluate symptoms fully to ensure correct treatment. Several important advances are allowing them to determine a specific diagnosis in most patients, leading to better treatments. Research at the Center focuses on three key areas for dementia: improving diagnosis, determining its causes and improving treatment, either by preventing dementia or treating it in the early symptomatic stage.

UTHealth physicians were the first in Houston to diagnose Alzheimer's disease (AD) using amyloid-sensitive PET imaging, which is helpful in determining whether patients do or do not have AD. Now physicians

RESEARCH HIGHLIGHT

LEAD PHYSICIAN: Paul Schulz, MD
Professor, Department of Neurology
Director, Dementia and Memory Disorders
McGovern Medical School at UTHealth

Memory Disorder and Dementia Clinic

UTHealth neurologists at the UT Physicians Neurocognitive Disorders Center are currently engaged in cutting-edge pharmaceutical research in Alzheimer's disease (AD) and related neurodegenerative disorders. On the cellular level, AD starts decades before symptom onset, with the accumulation of amyloid protein in the brain. Once the amyloid levels reach a certain threshold, they lead to changes in neuronal activity. Another normal protein within the neurons, tau, then accumulates abnormally and leads to cell damage and the symptoms of memory loss. For decades, AD could be diagnosed only at autopsy, but new imaging and laboratory technologies allow physicians to identify amyloid harmlessly in living patients. By diagnosing early in the disease, or even before symptoms develop, novel opportunities to treat AD have emerged.

Alzheimer's Disease Treatment

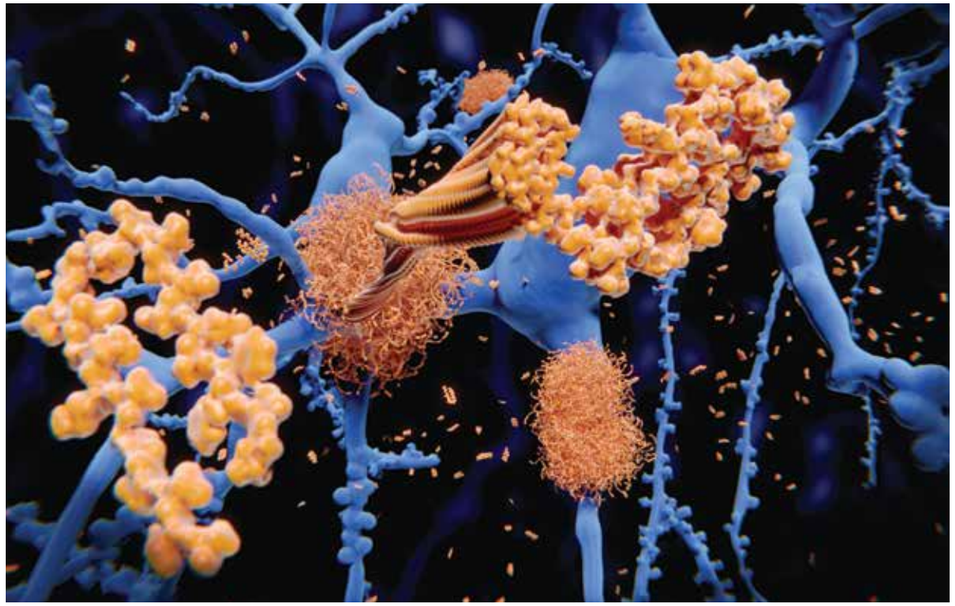
While all FDA-approved treatments for AD just treat symptoms, a new generation of drugs shows promise in modifying the underlying course of the disease by altering the production or accumulation of amyloid. Beta-secretase enzyme (BASE) inhibitors are oral drugs that alter the brain's metabolic pathways and reduce the production of amyloid. Monoclonal antibody IV infusions are also being used to target existing amyloid, such as in senile plaques, for destruction by the immune system. The researchers are currently testing both approaches in patients, with the hope that reduced amyloid burden will slow cognitive decline. Any patient with mild cognitive impairment or early Alzheimer's could be a good candidate for these studies.

Preventing Dementia in Healthy Patients

Perhaps even more exciting, patients who are concerned about getting AD because of a family history, but who are currently without cognitive symptoms, may be eligible to enroll in a long-term trial with this class of medication. The goal of these trials is to intervene before symptoms develop to prevent or reduce the risk of developing Alzheimer's. Patients between the ages of 60 and 75 are eligible to receive a simple genetic test for a major AD risk factor. Those who are at higher risk may then be screened for a multi-year trial of a daily BASE Inhibitor to delay or avoid the onset of Alzheimer's disease.

Related Diseases

Although AD is by far the most common disease related to the amyloid and tau proteins, tau is also involved in several other neurodegenerative disorders. One example is progressive supranuclear palsy (PSP), a rare disease similar to Parkinson's, which causes changes in walking, eye movements and the voice. Given that PSP currently has no FDA-approved treatments, the researchers are excited to be part of a clinical trial of an antibody infusion directed at the tau protein. Any patient with a diagnosis of PSP is eligible to screen for this trial. Should the anti-tau antibody prove beneficial in PSP, it could be expanded into AD another other disorders.



are working with laboratory scientists to develop new spinal fluid and blood tests for AD and Parkinson's disease (PD) and new imaging agents that will help diagnose other forms of dementia and provide insights into their underlying processes.

They are also using blood and spinal fluid to investigate the role of genetic mutations and chemical modifications of genes in dementia. UTHealth neurologists Paul Schulz, MD, and David Hunter, MD, are currently engaged in leading-edge pharmaceutical research in Alzheimer's disease. Phase II and III trials are now enrolling for several medications that aim to lower the production and accumulation of amyloid protein in the brains of AD patients. Current treatments for AD are symptomatic, but this new generation of drugs shows promise in modifying the underlying disease.

Patients with early stages of AD are eligible for screening. Even more exciting, patients with a family history of AD, but who are currently without cognitive symptoms, may be eligible to enroll in a long-term trial with this class of medication, with the aim of preventing Alzheimer's before symptoms develop.

In other trials at the Center, physicians are investigating the efficacy of deep brain stimulation in patients with major depressive disorder who have not responded to other treatments and developing stem cells for use in patients with neurodegenerative disorders.

Movement Disorders and Neurodegenerative Diseases

Using pioneering techniques and clinical expertise to diagnose, evaluate, manage and treat adult and geriatric patients, UTHealth MOVE has established a track record of providing outstanding care and management for patients. A collaboration between UT Physicians and McGovern Medical School at UTHealth, UTHealth MOVE provides patients with specialty clinics and faculty expertise. Conditions seen and treatments available include spasticity management, deep brain stimulation, neurotoxin injection therapy, Huntington's disease, Parkinsonian disorders, disorders of tremor, ataxia and those caused by traumatic brain or spine injury.

UTHealth MOVE offers pharmacological and surgical therapies, including the use of intrathecal baclofen pump therapy. Through the Deep Brain Stimulation (DBS) Program, candidates are selected for DBS therapy for the FDA-approved indications of Parkinson's disease, tremor and dystonia, which includes team management and programming of DBS therapy. At the Neurotoxin Injection Therapy Clinic, physicians use Botox®, Xeomin®, Myobloc® or Dysport® as indicated for abnormal states of dystonia, spasticity, chronic migraine and limb spasticity.

Deep brain stimulation for Parkinson's tremor, dystonia and essential tremor is known for low complication rates and outstanding outcomes. Based on the skill of the neurological and neurosurgical team and their expertise in DBS programming, Mya Schiess, MD, director of UTHealth MOVE, and her team advocate for early use of deep brain stimulation in appropriate patients. Surgeries are performed by Albert Fenoy, MD, who leads the Deep Brain Stimulation Surgery Program at McGovern Medical School.

In 2018, the DBS program recorded record growth. Two years earlier Dr. Schiess was the only representative from the United States participating in the international Consensus Panel to Formulate Criteria for the Selection of Parkinson's Disease Patients for DBS Therapy. Based on the panel's now published work, she is helping to develop and launch a version of the EARLY STIMULUS assessment tool for use in the United States. In addition, she is the U.S. spokesperson for an expanded FDA indication for the Activa® neurostimulator for DBS therapy in Parkinson's disease, a groundbreaking approval that will allow some patients to be eligible for DBS therapy earlier – at four years from disease onset with a minimum of four months of motor complications. DBS therapy continues to be appropriate for longer-duration motor complications in advanced disease, but there is no longer an upper-age restriction.

Phase 1 Study of Allogeneic Bone Marrow-derived Mesenchymal Stem Cell Therapy for Idiopathic Parkinson's Disease

PRINCIPAL INVESTIGATOR: Mya C. Schiess, MD
Professor and Adriana Blood Chair, Department of Neurology,
McGovern Medical School at UTHealth

This study is the first step in investigating the safety of using escalating doses of allogeneic adult bone marrow-derived mesenchymal stem cells (MSCs) delivered intravenously to patients with idiopathic Parkinson's disease (PD). The target population includes men and women of any ethnic, racial or socioeconomic background with sporadic late-onset clinically diagnosed Parkinson's disease with onset of motor symptoms > 4 years and ≤ 7 years between the ages of 45–70 years old at the start of the trial. Twenty-four men who meet the UK Brain Bank criteria for idiopathic PD and who have a Hoehn and Yahr of < 3 in the OFF medicine state will be recruited to participate. Each cohort of 5 study subjects will receive one of four doses of MSC; 1 X 106 MCS/kg of body weight, 3 X 106 MCS/kg, 6 X 106 MCS/kg, or 10 X 106 MCS/kg.

The researchers' primary outcomes will be safety, defined as the absence of an immediate transfusion reaction, adverse events or organ damage. Secondary outcomes will measure therapy impact on PD progression as defined by changes on UPDRS, MDS-UPDRS, TUG, PDQ-39, H&Y, C-SSRS and immunologic profile. A greater goal envisions additional studies using repeated MSC dosing to address progression in typical and atypical Parkinson's neurodegeneration.

Impact on Health Care: MSC therapy has the potential to slow the rate of PD progression and restore homeostasis to the neuronal-glial populations damaged by the degenerative process. Currently our PD therapies focus on symptom relief. If intravenous adult-derived mesenchymal stem cell therapy proves to be neuroprotective or neurorestorative, it would truly advance our care, which is the mission of UTHealth.

UTHealth faculty member Raja Mehanna, MD, has added depth and understanding to the program's legacy in DBS with numerous publications of reviews, articles and a book on DBS therapy and outcomes. In addition, UTHealth MOVE's referral program is thriving. Today, 25 percent of Stage 1 electrode-placement surgeries performed on patients by UTHealth MOVE and the DBS team are referred by community physicians.

UTHealth MOVE's comprehensive Huntington's Disease Program was named a Huntington's Disease Society of America (HDSA) Center of Excellence in 2016 and remains on the HDSA's list of top programs. Led by Erin Furr-Stimming, MD, the program is one of 47 centers of excellence across the country and the only one in Texas to receive the prestigious designation. At UT Physicians, UTHealth doctors operate the only specialty clinic in the Houston area for the diagnosis, management and support of patients and their families with Huntington's disease.

In addition, expertise in the management of traumatic brain injury is available in collaboration with the Halle Center for Traumatic Brain Injury and the appointment of Allison Boyle, MD, to the UTHealth MOVE team of physicians. The bimonthly, full-day UTHealth MOVE clinic was established at Memorial Hermann The Woodlands Medical Center in 2015 and has been expanded to two clinic days a week under Dr. Boyle's direction. The Woodlands clinic provides the same expert care available in the Texas Medical Center to this fast-growing community.

Enroll-HD: A Prospective Registry Study in a Global Huntington's Disease Cohort

LEAD PHYSICIAN: Erin Furr-Stimming, MD
Associate Professor, Department of Neurology,
McGovern Medical School at UTHealth

The primary objective of this worldwide observational, prospective multicenter study is to improve our understanding of Huntington's disease (HD). Researchers are collecting information about cognition, behavior and motor function to estimate how HD progresses in patients; collecting blood samples and data to identify genetic and environmental factors that affect HD phenotype and disease progression; and promoting interrogatory studies that may provide clues to the pathogenesis of HD. The study is enrolling.

HD-Clarity
LEAD PHYSICIAN: Erin Furr-Stimming, MD
Associate Professor, Department of Neurology
McGovern Medical School at UTHealth

The primary objective of this study is to generate a high-quality cerebrospinal fluid (CSF) sample collection for evaluation of biomarkers and pathways that will enable the development of novel treatments for Huntington's disease (HD). The secondary objectives are to generate a high-quality plasma sample collection matching the CSF collections, and to collect phenotypic and clinical data for each participant, which will also be used to evaluate biomarkers and pathways of relevance to HD research and development. The study is enrolling.

SIGNAL
LEAD PHYSICIAN: Erin Furr-Stimming, MD
Associate Professor, Department of Neurology
McGovern Medical School at UTHealth

The purpose of this Phase 2 study is to evaluate the safety, tolerability, PK and efficacy of VX15/2503 in subjects with late prodromal and early manifest Huntington's disease. This study is active but no longer enrolling.

Microglial Activation in HD: A Structural and Functional Study
PRINCIPAL INVESTIGATORS: Erin Furr-Stimming, MD
Associate Professor, Department of Neurology
McGovern Medical School at UTHealth

Natalia Pessoa-Rocha, PhD
Postdoctoral Research Fellow, Department of Psychiatry and Behavioral Sciences

Antonio Lucio Teixeira, MD, MSc, PhD
Professor, Department of Psychiatry and Behavioral Sciences

The objective of this study is to investigate the role played by microglia in the different stages of HD. The researchers will evaluate structural and functional parameters of microglial response in HD gene carriers in relation to the clinical features seen at various stages of disease.

The team's treatment philosophy is grounded in the early identification of disease and early use of neuro-modulating or neuroprotective approaches. Physicians maintain patients at the highest level of function possible, based on symptom-driven therapeutic goals set by the physician and patient. In developing and adjusting treatment plans, they consider the whole person, as well as the patient's environment and support groups. They also emphasize education, and encourage patients to stay mentally and physically active, to work at having fun and to create a positive environment with friends and family.

UTHealth supports and partners with the Houston Area Parkinson's Society (HAPS), which has been crucial in providing educational, exercise and social programs as well as support groups to Parkinsonian patients. The program partners with TIRR Memorial Hermann in a comprehensive UTHealth MOVE/Neurorehabilitation Program that incorporates neurological-driven rehabilitation as part of the treatment approach.

Research in movement disorders and neurodegenerative diseases at UTHealth MOVE is substantial, with partnerships and collaborations among clinical and basic science studies and multiple disciplines, and funding from federal, pharmaceutical and philanthropic sources. Faculty in the UTHealth program are members of the Movement Disorders Society, the Parkinson's Study Group, Huntington's Study Group, Tremor Research Group, Dystonia Coalition and Restless Legs Syndrome Study Group. Ongoing established research includes a longitudinal prospective study on biomarkers and pre-symptomatic biomarkers for Parkinsonian syndromes, which led in 2013 to the discovery of immune-mediated markers of disease activity and proposed cell therapy intervention for Parkinsonism.

Dr. Schiess is the primary architect and principal investigator for an FDA-approved Phase IA/B pilot safety study of the use of adult bone marrow-derived mesenchymal stem cells in Parkinson's disease. The trial, which began in January 2016, is evaluating the safety and tolerability of neuroimmune modulation with allogeneic stem cells in patients with Parkinson's disease. The UTHealth MOVE program continues as a participating site for the multicenter National Institute of Neurological Disorders and Stroke/Parkinson Study Group (NINDS/PSG) trial of isradipine as a neuroprotective drug in Parkinson's disease. In addition, the UTHealth MOVE program is recruiting for the Sure PD-3 clinical trial sponsored by NINDS/PSG to explore the manipulation of uric acid as a neuroprotective molecule in Parkinson's-mediated neurodegeneration.

Conditions Treated

The movement disorders medical team sees patients at UT Physicians, using proven and investigational medications and interventional methods to manage:

- Parkinson's disease and Parkinsonian disorders
- Generalized and focal dystonia
- Essential tremor and other tremor states
- Huntington's chorea
- Restless leg syndrome and other sleep disorders like REM sleep behavior disorder
- Cortical and subcortical dementias
- Cerebral palsy
- Spasticity, ataxias, gait disorders, spinal and brain trauma-related movement abnormalities
- Multiple sclerosis-related movement abnormalities and other inherited and acquired neurodegenerative diseases

Multiple Sclerosis

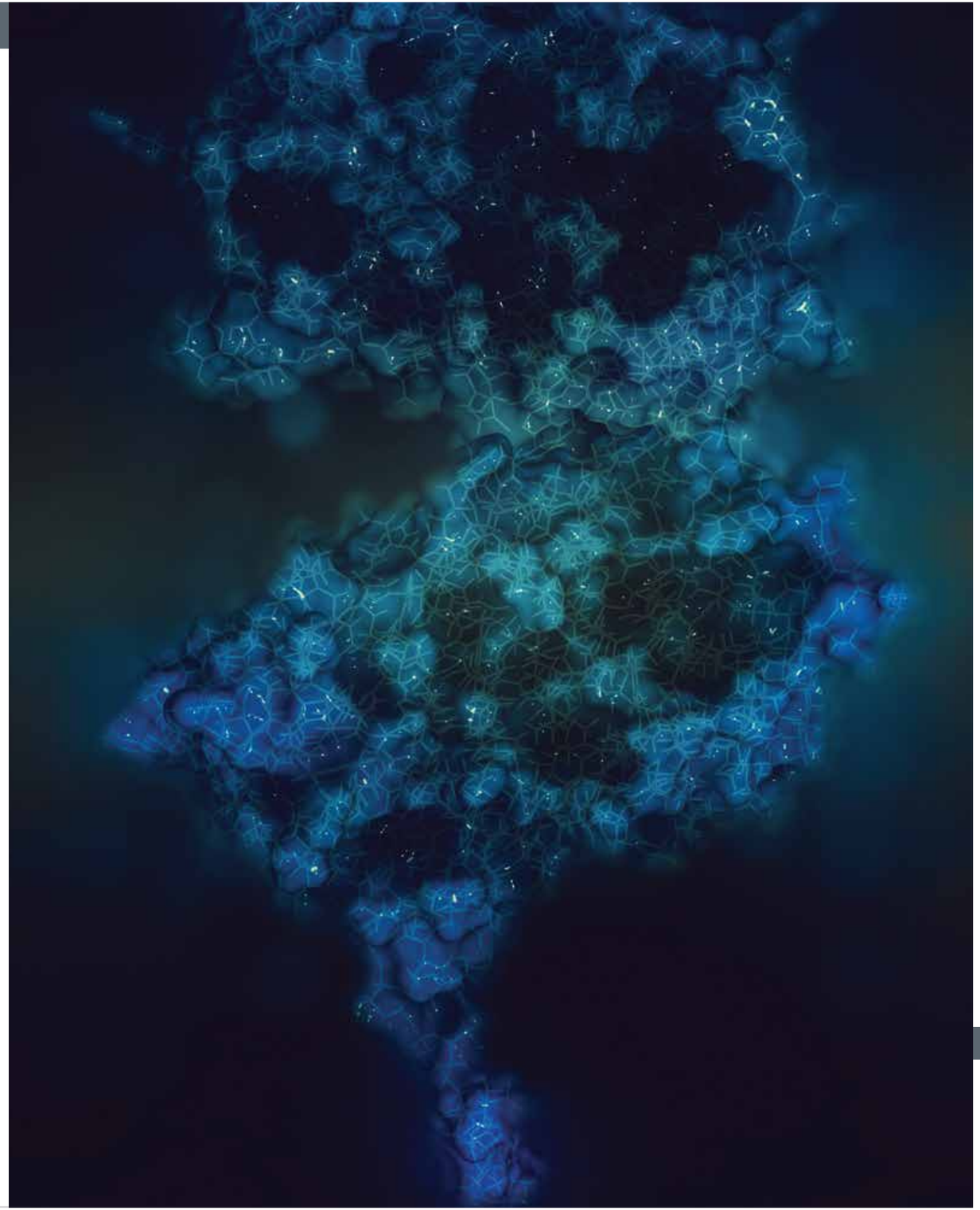
The Multiple Sclerosis Program at McGovern Medical School at UTHealth has established a track record of leading-edge care using groundbreaking techniques to diagnose, evaluate, manage and treat adult patients with MS and other demyelinating disorders. The scope of expertise of UTHealth physicians is broad and includes patients in all stages of MS, as well as those with neuromyelitis optica, transverse myelitis and optic neuritis. They are experienced in the appropriate use of aggressive therapies in severe cases.

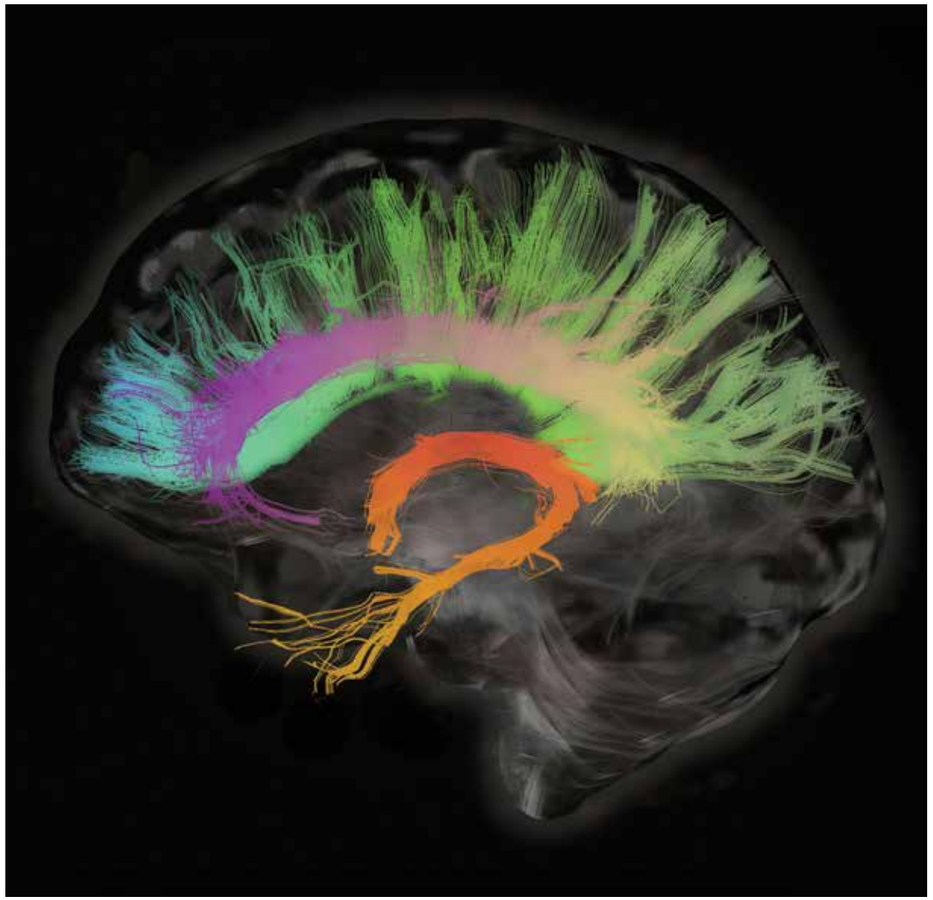
Organized in 1983, the Multiple Sclerosis Research Group has participated in numerous clinical trials of novel disease-modifying therapies, serving as the lead center for international studies, several of which were pivotal in gaining FDA approval of currently available treatments for MS. Recently completed clinical research includes two international randomized, controlled studies in primary progressive MS: INFORMS, which investigated the potential benefits of fingolimod, a drug that did not limit progression, and ORATORIO, which examined the effects of anti-CD20 (B-cell) therapy with the monoclonal antibody ocrelizumab and is the first study to show a positive outcome with this form of MS. The Group has also been involved in several studies of anti-CD20 therapies for relapsing MS, which demonstrated a marked benefit for this type of treatment.

The MSRG was founded under the leadership of Jerry S. Wolinsky, MD, professor emeritus of neurology.

Faculty members include J. William Lindsey, MD, acting division director; John Lincoln, MD, PhD; Rohini Samudralwar, MD; and Rajesh Gupta, MD. They practice at UT Physicians clinics for patients with MS and related disorders, participate in multiple clinical trials of new medications for MS and engage in research on imaging of MS and basic research aimed at defining the cause of MS. Current projects include studies aimed at defining the best treatment for people with MS, a novel Phase I trial of increasing blood flow to the brain as a treatment for MS and basic laboratory studies of Epstein-Barr virus infection as the cause of MS.

In the Department of Neurology's state-of-the-art Magnetic Resonance Imaging Analysis Center, physicians use spectroscopic and diffusion tensor imaging with tractotomy, as well as other advanced diagnostic tools. Following diagnosis, patients benefit from breakthrough treatment options that include injectable immunomodulators, immunosuppressives, monoclonal antibodies and all of the newer oral agents designed to treat the debilitating symptoms of MS. Investigators also use the MRI Analysis Center to monitor the effects of promising oral drugs in efficacy trials. The Center was pivotal in providing quantitative imaging data that supported the regulatory approval of the oral agent teriflunomide for use in relapsing forms of MS in the United States, Europe and a growing number of countries worldwide, determining the optimal drug dose and extending the results of its benefits when used in first symptom-onset disease.





The Multiple Sclerosis Program's goal is to maintain patients at the highest level of function possible, with early use of immunoactive agents to prevent disease progression. Because rehabilitation is integral to each patient's treatment plan, physicians work closely with the physical medicine and rehabilitation specialists and therapists at TIRR Memorial Hermann, a national leader in medical rehabilitation and research, as well as the inpatient neurorehabilitation team at Mischer Neuroscience Institute.

RESEARCH HIGHLIGHTS

Immune Response to Epstein-Barr Virus in Multiple Sclerosis

LEAD PHYSICIAN: J. William Lindsey, MD
Professor, Department of Neurology
McGovern Medical School at UTHealth

Epstein-Barr virus (EBV) has been linked to multiple sclerosis in many different ways over the last 30 years. The hypothesis of this study is that EBV causes MS through "molecular mimicry" or cross-reactivity. EBV elicits a vigorous and recurrent immune response, and the researchers believe that, in MS, the immune response targets a component of the virus that resembles a component present in the normal brain. As a result, every time that EBV reactivates, the immune system attacks the virus and also attacks the nervous system.

In work published in the last year, the researchers have shown that MS patients tend to respond more to certain EBV proteins than healthy people. They have also shown that the antibodies to these EBV proteins can bind to human proteins present in the normal brain. The next goal of this project is to demonstrate that this cross-reactive immune response can actually damage brain cells.

These studies could have a major impact on our understanding of the causes of MS and could lead to an effective treatment for MS with minimal side effects.

The Impact of Enhanced Cerebral Perfusion on the Evolution of Multiple Sclerosis Lesions

LEAD PHYSICIAN: John A. Lincoln, MD, PhD
Assistant Professor, Department of Neurology
McGovern Medical School at UTHealth

Global and regional changes in blood flow to the brain (cerebral perfusion) have been seen early in multiple sclerosis (MS) patients with both relapsing and progressive forms. Previous research in our laboratory has shown that reduced small-vessel perfusion is associated with the formation of gliotic lesions (lesions with permanent damage). Studies have suggested that virtual hypoxia resultant from the combination of diminished cerebral perfusion and increased energy demand contributes to permanent tissue damage that strongly correlates with clinical disability in persons with MS.

There are currently several potent anti-inflammatory medications available to treat patients with MS though none are known to enhance cerebral perfusion. Acetazolamide (ACZ) is a generic medication with a well-established safety and tolerability profile that is known to enhance cerebral perfusion in healthy subjects. Improving cerebral perfusion might improve energy supplies as well as reduce buildup and improve clearance of toxic metabolites, thereby decreasing permanent tissue injury.

The goal of this project is to determine if daily therapy with ACZ improves cerebral perfusion in MS patients and if improved perfusion enhances repair of previously formed and newly formed MS lesions, reducing irreversible neurological damage and disability.

Neuromuscular Disorders

Physicians with the UTHealth Neuromuscular Program subspecialize in complex neuromuscular disorders that are difficult to diagnose and treat, including neurodegenerative disorders, inflammatory nerve and muscle disorders, autoimmune neuromuscular junction disorders, traumatic nerve injuries and toxic metabolic disorders of the peripheral nerves and muscles. Led by Kazim A. Sheikh, MD, the program is a designated center of excellence for Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating poly-neuropathy (CIDP) and records more than 4,000 patient visits annually, primarily adults age 18 and older. About two-thirds of patients seen by physicians are over the age of 50.

Neurodiagnostic facilities at UTHealth include a state-of-the-art Electromyography (EMG) Laboratory and a Muscle and Nerve Laboratory. The EMG Lab, directed by UTHealth neurologist Thy Nguyen, MD, provides comprehensive nerve conduction studies and EMG evaluations performed by experienced staff.

Because electrodiagnostic evaluation is an extension of clinical findings, affiliated medical specialists perform a focused neuromuscular examination, including history and physical, before conducting the electrical test. In addition to nerve conduction and EMG, electrodiagnostic studies available at the lab include repetitive nerve stimulation, blink reflexes, cranial nerve studies, single-fiber electromyography and facial/trigeminal neuropathy. An invaluable diagnostic test, EMG provides evidence in support of diagnoses of peripheral neuropathies; motor neuron diseases such as amyotrophic lateral sclerosis and spinal muscular atrophy; muscle disorders such as myopathy and muscular dystrophy; neuromuscular junction disorders such as myasthenia gravis; entrapment neuropathies such as carpal tunnel syndrome, ulnar and peroneal neuropathies; and traumatic nerve injury, including evaluation of the brachial plexus and facial neuropathy. The UTHealth Neuromuscular Program is the only program in Houston that provides single-fiber EMG.

Studies conducted in the Muscle and Nerve Laboratory help improve diagnosis in cases with limited neuromuscular findings by locating abnormalities at a pathologic/microscopic level. Subspecialists perform muscle, nerve and skin biopsies, which are further processed by highly experienced staff. Their preferred technique is open biopsy under local anesthesia, which reduces the likelihood of missing abnormalities in cases of patchy involvement, such as in inflammatory myopathies. They also perform skin biopsies for the diagnosis of small-fiber neuropathy, and the lab is the only center in Houston that processes skin biopsy specimens for the diagnosis of small-fiber neuropathies. The laboratory provides technical services to regional neuromuscular experts as well. The Muscle and Nerve Laboratory is co-directed by Dr. Sheikh and Suur Biliciler, MD.

Current research is focused on developing new strategies to treat neuropathic disorders and enhance nerve repair. With funding from the National Institutes of Health and the GBS/CIDP Foundation International, investigators are evaluating the role and pathogenic mechanisms of inflammatory/autoimmune neuro-pathies; using diffusion tensor imaging to assess and quantify nerve degeneration and regeneration in patients with traumatic nerve injuries; investigating modulation of FcRn as a strategy to prevent autoantibody-mediated nerve injury; examining the pathobiologic effects of anti-ganglioside antibodies on nerve regeneration; and using monoclonal antibodies for delivery of cargo to nerve cells for peripheral nerve imaging and modulation of function. The group is also involved in clinical studies examining the predictors of short- and long-term outcomes in Guillain-Barré syndrome, comparing the efficacy of current treatments in the management of neuropathic pain and use of cellular therapies in patients with treatment-resistant Guillain-Barré syndrome.

In-vivo Imaging of Epidermal Nerve Fibers

Zhang G, Ghosh P, Lin J, Ghauri S and Sheikh KA

Assessment of epidermal nerve fiber density and its structure integrity is critical for the diagnosis and evaluation of the effectiveness of potential therapies in small-fiber neuropathies. Currently, skin biopsies at multiple sites are most commonly used to assess these diseases. These studies are expensive and time consuming due to cumbersome processing and quantification techniques, and serial biopsies over time are often not feasible due to costs and patient acceptance. Moreover, the vast majority of normative data for skin biopsies in humans is available only for a few distal sites, and a significant proportion of patients with small-fiber neuropathies have focal or regional symptoms not involving the commonly biopsied sites in the leg. Live imaging could overcome these limitations and provide a noninvasive real-time assessment of epidermal nerve fibers all over the body.

We previously found that anti-ganglioside antibody (AGA) is an effective neuronal delivery vector for transport of various cargos, such as fluorescent dyes, to peripheral nerves. In the current proof-of-concept study, we examined whether noninvasive multiphoton microscopy can be used to probe/image the epidermal nerve fibers in living animals after systemic and/or local delivery of fluorescently conjugated AGA. We found that the individual nerve endings in skin and cornea are distinctly labeled and visualized under a two-photon microscope. The epidermal nerve fiber labeling by fluorescent-tagged AGA was further validated using transgenic mice selectively expressing yellow fluorescent protein in their nervous systems.

In-vivo multiphoton imaging provides a tool with potential for dynamic longitudinal evaluation of small-fiber neuropathies, including nerve degeneration and regeneration, without tissue removal. Thus, the use of multiphoton microscopy in conjunction with fluorescently labeled AGA as neuronal vector can have many research and clinical applications, such as labeling and live visualization of epidermal nerve fibers to assess small sensory nerve fibers in health and disease.

Neurotrauma and Neuroscience Critical Care

The Neurotrauma and Neuroscience Critical Care Program is internationally recognized for the treatment of high-acuity brain and spinal cord injuries. UTHealth Neurosciences physicians manage severe neurotrauma cases, with neurointensivists and experienced mid-level practitioners staffing the 32-bed Neuroscience ICU (NSICU) at Memorial Hermann-Texas Medical Center around the clock to provide ongoing intensive care to critically ill patients. The program continues to grow and now operates a total of 74 NSICU beds in three hospitals, including Memorial Hermann Southwest Hospital and Memorial Hermann Memorial City Memorial Medical Center, making it one of the largest programs in the country.

UTHealth is an international leader in research conducted on innovative treatments following neurotrauma and participates in several multicenter trials. Investigators at McGovern Medical School at UTHealth and TIRR Memorial Hermann collaborate in a cutting-edge comprehensive research program incorporating basic science, translational research, clinical trials and comparative effectiveness research. Led by H. Alex Choi, MD, assistant professor in the Vivian L. Smith Department of Neurosurgery, the program utilizes the most advanced medical technologies and devices.

McGovern Medical School offers a two-year neurocritical care fellowship to applicants who are board certified or eligible in neurology, emergency medicine, anesthesia or internal medicine. A one-year fellowship track is open to eligible candidates who have completed postgraduate training in neurosurgery, medical critical care, anesthesia critical care or surgical critical care. The educational curriculum is specifically designed to train physicians with a strong base in general critical care, with an emphasis on neurological and neurosurgical emergencies. The NSICU is equipped with multimodality monitoring capability including ICP, CPP, continuous video EEG monitoring, continuous cardiac output, non-invasive cerebral blood flow monitoring and brain oximetry. The NSICU is a truly academic training environment where UTHealth fellows work with neurosurgery, neurology, anesthesia and emergency medicine residents, as well as rotating fellows from other critical care programs. Fellows may rotate through the medical, surgical/trauma and cardiovascular ICUs and are offered a number of electives including anesthesiology, stroke, EEG, TCD, neuroradiology and burns. They also have the opportunity to work on the UTHealth Mobile Stroke Unit, the nation's first.

In April 2019, McGovern Medical School and Mischer Neuroscience Institute hosted the Seventh Annual Neuro ICU Symposium, a three-day course designed to educate physicians and other healthcare professionals on optimal management of patients using a team approach. The symposium emphasizes expanding the horizons of neurocritical care, focusing on comprehensive patient care and optimizing critical care delivery. Highlights this year included discussion of the results of the pivotal DAWN trial, a focused session on neuroanesthesia, different viewpoints on hot topics and real patient experiences from the ICU. The Eighth Annual Neuro ICU Symposium will be held April 1-3, 2020.

Patients with acute neurological injuries benefit from the Memorial Hermann Red Duke Trauma Institute – one of only two Level 1 trauma centers in the area and one of the busiest in the nation – and from Memorial Hermann Life Flight®, the first air medical transport service established in Texas and the second in the nation. Built on the hospital's long-term collaboration with McGovern Medical School, the 200-bed Red Duke Trauma Institute provides high-quality care to both adult and pediatric trauma patients and offers a full spectrum of service including access to Houston's only verified burn center. Physicians at UTHealth drive innovations in trauma care by moving research quickly from the laboratory to the bedside.

UTHealth Neurosciences physicians have expanded the team's active role in saving the lives of critically ill patients by expanding critical care services at two

RESEARCH HIGHLIGHTS

SAHRANG (SubArachnoid Hemorrhage Recovery ANd Galantamine)

PRINCIPAL INVESTIGATOR: H. Alex Choi, MD
CO-PRINCIPAL INVESTIGATORS: Dash P, Grotta JC, Barreto A, Hergenroeder G, Liu Y, Savarraj J

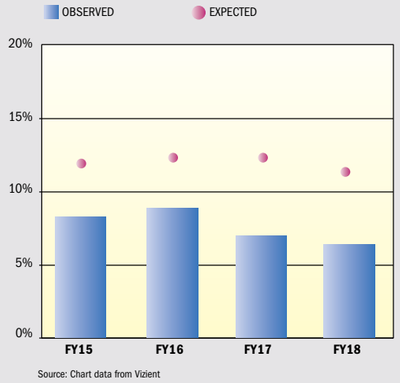
Researchers led by Dr. H. Alex Choi are studying the potential for Galantamine, a medication used for Alzheimer's disease, to improve outcomes after subarachnoid hemorrhage (SAH). Preclinical studies in Dr. Pramod Dash's laboratory have shown that Galantamine has the ability to stabilize the blood-brain barrier, provide neuroprotection and improve outcomes after brain injury. With financial support from the Center for Clinical and Translational Sciences at McGovern Medical School at UTHealth, Dr. Choi is translating these findings from the bench to a placebo-controlled, randomized clinical trial. The study aims to investigate the potential for Galantamine to improve clinical outcomes after aSAH, as well as help researchers understand the immune modulatory effects of Galantamine.

Systemic Model of Peripheral Inflammation After Subarachnoid Hemorrhage

In an article published in Neurology, researchers used bioinformatics and network modeling techniques to develop a model of peripheral inflammation after aneurysmal subarachnoid hemorrhage (aSAH). The researchers studied inflammatory markers in blood samples from 45 patients with aSAH. Several biomarkers including IL-6, CCL2, CCL11, CSF3, IL-8, IL-10, CX3CL1 and TNF play a role in inflammation and were identified as potential candidates for therapeutic intervention. Network models revealed that systemic inflammatory activity peaks at 24-48 hours after hemorrhage. By using bioinformatics tools, a more comprehensive view of the biologic processes that occur to cause brain injury after aSAH was depicted.

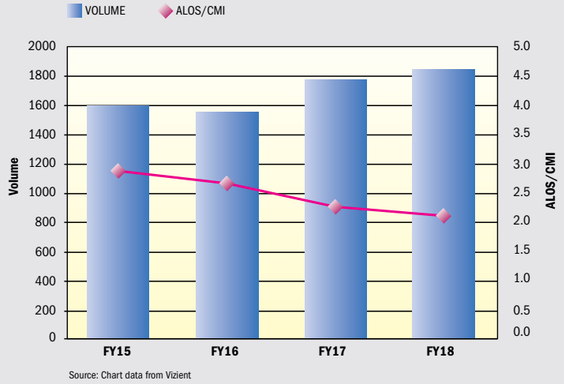
Savarraj JP, Parsha K, Hergenroeder GW, Zhu L, Bajgur SS, Ahn S, Lee K, Chang T, Kim DH, Liu Y, Choi HA. Systematic model of peripheral inflammation after subarachnoid hemorrhage. Neurology. 2017. Apr 18;88(16):1535-1545.

Traumatic Brain Injury:
Inpatient Mortality



Source: Chart data from Vizient

Traumatic Brain Injury:
Volume & Length of Stay (CMI Adjusted)



Source: Chart data from Vizient

hospitals. At Memorial Hermann Southwest Hospital, a new neurotrauma and neuroscience critical care service opened in March 2016. The hospital's state-of-the-art Neuroscience ICU is staffed 24/7 by UTHealth physicians, all of whom are fellowship trained in neurocritical care. These neurointensivists work hand in hand with neurosurgeons to provide superior care after neurological surgery. Memorial Hermann Memorial City Medical Center operates a 19-bed dedicated neurocritical care unit combining intensive and acute care. The hospital's Neuroscience ICU is also staffed 24/7 by fellowship-trained UTHealth physicians. The unit sees a large volume of neurotrauma and stroke patients and is equipped with continuous EEG capabilities.

Both centers have 24/7 neuroendovascular surgical care available for immediate stroke care and the treatment of complex cerebral vascular diseases. Both are also equipped with the most advanced tele-robot capabilities allowing expert practitioners to be at the virtual bedside in minutes.

The Subarachnoid Hemorrhage Early Brain Edema Score Predicts Delayed Cerebral Ischemia and Clinical Outcomes

In an article published in *Neurosurgery,* UTHealth researchers developed a new radiological scoring system to quantify early brain edema after aSAH. They studied CTs from 164 aSAH patients to describe a new radiographic scoring system called the Subarachnoid Hemorrhage Early Brain Edema Score (SEBES), which is loosely based on the ASPECTS Score commonly used in ischemic stroke. It is a qualitative scoring system from 0-4. One point was assigned for the (1) absence of visible sulci caused by effacement of sulci or (2) absence of visible sulci with disruption of the gray-white matter junction at two predetermined levels in each hemisphere: (a) at the level of the insular cortex showing the thalamus and basal ganglion above the basal cistern and (b) at the level of the centrum semiovale above the level of the lateral ventricle. The SEBES was shown to predict both the dreaded complication of delayed cerebral ischemia as well as long-term clinical outcomes.

Ahn SH, Savarraj JP, Pervez M, Jones W, Park J, Jeon SB, Kwon SU, Chang TR, Lee K, Kim DH, Day AL, Choi HA. The Subarachnoid Hemorrhage Early Brain Edema Score Predicts Delayed Cerebral Ischemia and Clinical Outcomes. Neurosurgery. 2017 Jul 7. [Epub ahead of print]

Pain Management

Pain management is a critical part of UTHealth Neurosciences' overall program. Specialists in interventional pain management and physical medicine and rehabilitation treat acute and chronic pain arising from trauma, nerve damage, degenerative conditions, cancer and systemic metabolic disorders such as diabetes. The multidisciplinary team works in close collaboration to provide a variety of interventions and strategies for pain self-management to help people regain control of their lives.

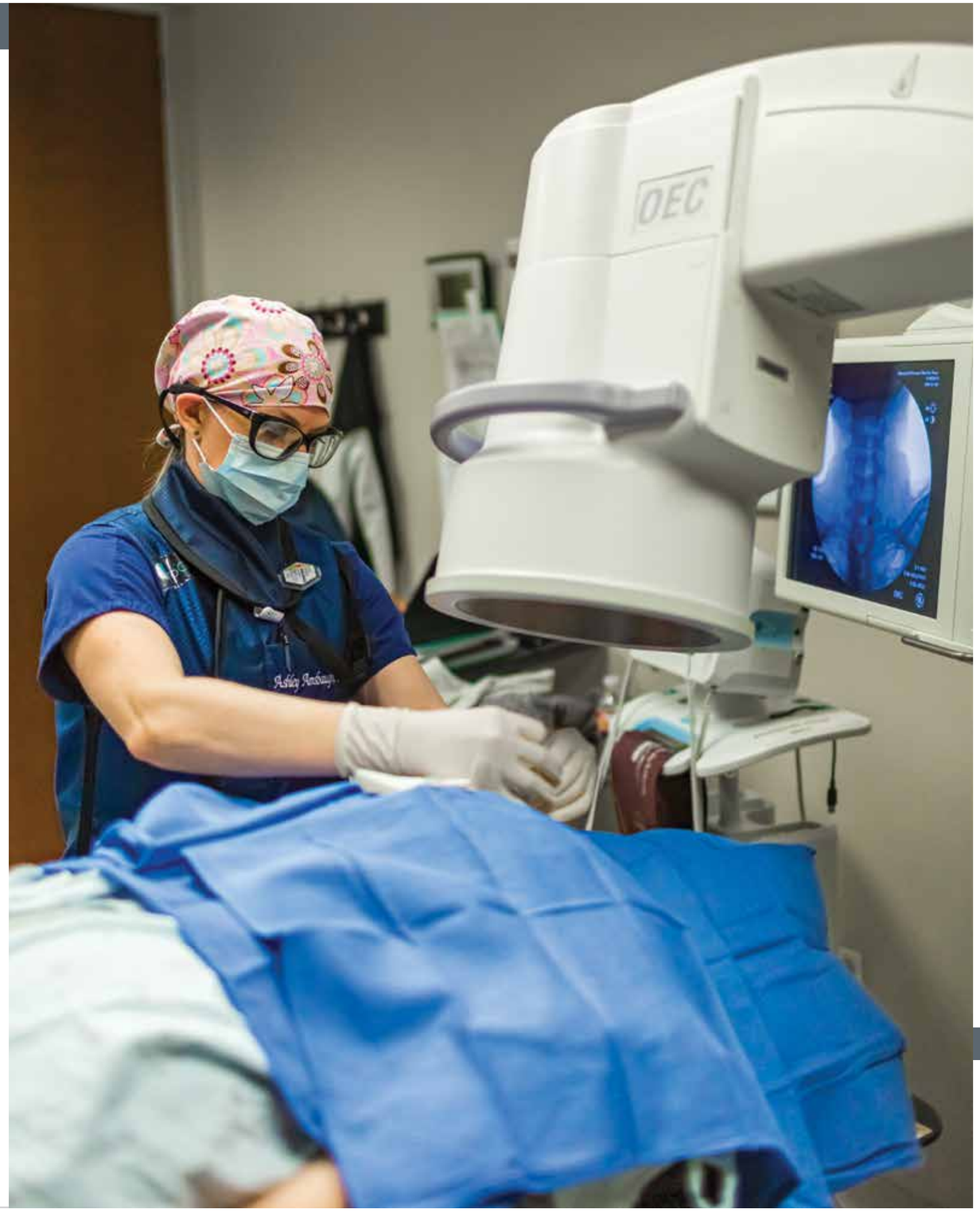
UTHealth physicians Nadya Dhanani, MD, Mark Burish, MD, PhD, Joseph Amos, MD, Ashley Amsbaugh, MD, and Hiral Patel, MD, are key members of the UTHealth Neurosciences Pain Management Program. A board-certified anesthesiologist and interventional pain management specialist, Dr. Dhanani joined the team in 2014 after completing her residency training in anesthesiology at Massachusetts General Hospital and a fellowship in pain medicine at The University of Texas MD Anderson Cancer Center. She heads the Pain Management Program at UTHealth Neurosciences.

Dr. Burish was recruited in 2015 after completing his neurology residency and pain management fellowship at the University of California at San Francisco. In addition to treating patients with spine and neuropathic pain, he directs The Will Erwin Headache Research Center at Memorial Hermann and McGovern Medical School at UTHealth. Established with a $20-million pledge from The Will Erwin Headache Research Foundation, the Center includes a group of experts dedicated to the study of cluster headaches and other debilitating headaches and facial pain diseases.

Dr. Amos completed his residency in physical medicine and rehabilitation at the Baylor College of Medicine/UTHealth Alliance for Physical Medicine and Rehabilitation and his fellowship in pain medicine at the University of Washington in Seattle. Prior to joining UTHealth Neurosciences, he was in private practice serving the Houston community. He now directs pain management at the group's Memorial City location and serves as an expert panelist in pain management for the Texas Medical Board.

The program further expanded in 2017 with the addition of interventional pain management specialists Hiral Patel, MD, and Ashley Amsbaugh, MD. Dr. Patel completed her residency training in anesthesiology at McGovern Medical School at UTHealth and a fellowship in chronic pain management at The University of Texas MD Anderson Cancer Center. Dr. Amsbaugh completed her residency training in anesthesiology and a fellowship in pain medicine at the University of Louisville School of Medicine in Kentucky.

Physicians and researchers working with the Will Erwin Headache Research Center include neurosurgeon Dong Kim, MD; researcher Georgene Hergenroeder, BSN, MHA, RN, CCRC; researcher Pramod Dash, PhD, Chair of Neurobiology and Anatomy at McGovern Medical School,



Disorders Treated

- Cervical and lumbar radiculopathy and facet arthropathy
- Sacroiliac dysfunction
- Spinal stenosis
- Carpal tunnel syndrome
- Vertebral compression fractures
- Neuropathic pain conditions, including peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia and central post-stroke pain

Treatments Available

- Kyphoplasty and vertebroplasty for vertebral compression fractures
- Stellate, celiac plexus, lumbar sympathetic, superior hypogastric, and ganglion impar blocks and neurolysis
- Facet injections, medial branch nerve blocks and radiofrequency ablation (RFA)
- Sacroiliac joint blocks and strip lesioning using RFA
- Transforaminal, interlaminar and caudal epidural steroid injections
- Greater and lesser occipital, supraorbital and suprascapular nerve blocks
- Joint and muscle injections
- Spinal cord stimulation

and genetic counselor Krista Qualmann, MS. The group will work with other institutions across the country to develop a consortium of centers to identify patients with cluster headache and other debilitating types of headaches, with the goal of better understanding and treating the disorders. Projects under way at the Center include clinical research into cluster headache features and treatments, as well as an investigation of genetics, epigenetics and metabolomics of cluster headaches through collaborations with basic science researchers.

RESEARCH HIGHLIGHT

The Will Erwin Headache Research Center Study of Cluster Headache: Building a Registry of Cluster Headache Patients

PRINCIPAL INVESTIGATOR: Mark Burish, M.D., Ph.D. Assistant Professor, Department of Neurosurgery, McGovern Medical School at UTHealth

The Will Erwin Headache Research Center Study of Cluster Headache is a large observational repository of information related to cluster headache. The researchers' goal is to collect clinical data from consenting patients through online questionnaires and biological samples such as blood and saliva, which will be studied in the lab and shared with other researchers interested in greater access to cluster headache samples. The study has partnered with basic scientists in the field of circadian research to build a laboratory model of the disease. Currently in its third year, the study will continue for 10 years with pledged funding from the Will Erwin Headache Research Foundation.

Previous research into cluster headache has been limited by access to large samples of patients: cluster headache affects only 1 in 1,000 people. The registry at The Will Erwin Headache Research Center is the first of its kind in the United States devoted to cluster headache, and can be used to study genetics, biomarkers and pain signaling. The researchers hope to gain insights that will be used to develop new treatments for the disorder.

Spine Disorders

The renowned UTHealth Neurosciences spine surgeons who lead the Spine Center at UTHealth offer the most advanced treatments available today, both surgical and nonsurgical. They perform more than 2,600 procedures annually, making the spine program the largest in the region. The Center is among a handful of select practices in Walmart's elite Centers of Excellence Program for spine surgeries.

Nationally and internationally renowned UTHealth neurosurgeon Daniel H. Kim, MD, FACS, FAANS, has expanded the spinal neurosurgery program and added expertise in reconstructive peripheral nerve surgery, complex spinal reconstruction and minimally invasive spinal surgery, both endoscopic and robotic. A clinical and educational leader in his field, he has authored hundreds of papers and published 20 surgical textbooks, many of which are used at leading medical schools to teach standard-of-care techniques for neurosurgery. Dr. Kim is a preeminent researcher in peripheral nerve repair through nerve transfer and nerve graft, and is also recognized for his work in neurorehabilitation through robotics and cortical stimulation, spinal biomechanics and innovative neuromodulation treatments for chronic pain.

With the addition in 2016 of fellowship-trained neurosurgeon John Quinn, MD, the program has expanded further. Dr. Quinn has expertise in complex reconstructive surgery in children and adults for the treatment of spinal deformities such as scoliosis, kyphosis and flatback syndrome, and also performs cervical and thoracolumbar deformity reconstruction and complex revision surgery. Cyrus King, MD, joined UTHealth in 2018 and practices at the group's Memorial City and Sugar Land locations. He is fellowship trained in spine surgery with a focus on complex spine and deformity surgery.

The multidisciplinary team at the UTHealth Spine Center works in new operating rooms equipped with advanced instrumentation and dynamic imaging systems. They are skilled in minimally invasive spine procedures and innovative treatment options for patients with back pain resulting from trauma, degenerative disc disease, osteoporosis and related stress fractures, and deformity. Rehabilitation begins in the hospital following surgery.

Our physicians care for patients in a state-of-the-art 16-bed Neuroscience Elective Unit at Memorial Hermann-Texas Medical Center, with 10 beds dedicated to patients who choose to have spine surgery. Six beds are ICU level, reserved for patients admitted for brain surgery – for conditions such as trigeminal neuralgia, Chiari malformation, pineal cysts and brain tumors.

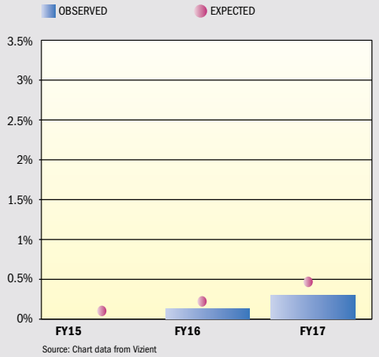
Pain management is a critical part of the group's spine program, and neurosurgeons work closely with specialists in physical medicine and rehabilitation and interventional pain management to help patients manage chronic back and neck pain. The multidisciplinary team works together to provide a variety of interventions and strategies for self-management to help people regain control of their lives.

The Center's clinicians provide exceptional care for patients with traumatic spine injury, including the 10 to 20 percent of admissions through the Level I Red Duke Trauma Institute that involve neurological damage. Based on benchmark Vizient data, the UTHealth Neurosciences spine surgeons' inpatient mortality outcomes for spine trauma, degenerative spine disease and elective spine surgery has been consistently lower than expected for the past nine years.

As faculty at UTHealth, neurosurgeons at the Center educate the next generation of spine experts and shape the future of medicine through basic science research, clinical discovery and the development of new, breakthrough treatments. Research under way at UTHealth is focused on bringing promising therapies for spinal cord injury (SCI) patients from the laboratory to clinical trials in a manner that will provide evidence of effectiveness, with maximum safety, to patients undergoing treatment. Investigation is currently focused on tissue engineering matrices and axon regeneration, gene transmission and regulation of stem cell differentiation, the safety of the anticonvulsant drug riluzole in patients with SCI, and novel neuroprotection therapeutic approaches to SCI, among other projects.

QUALITY & OUTCOMES MEASURES

Spine Degenerative or Elective: Inpatient Mortality



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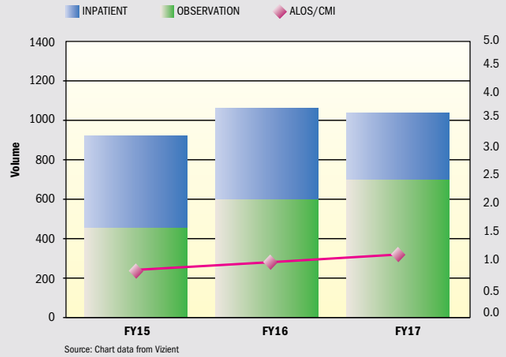
Spine Degenerative or Elective: Volume & Length of Stay (CMI Adjusted)



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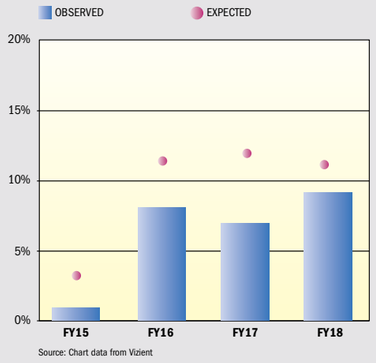
Spine Trauma: Inpatient Mortality



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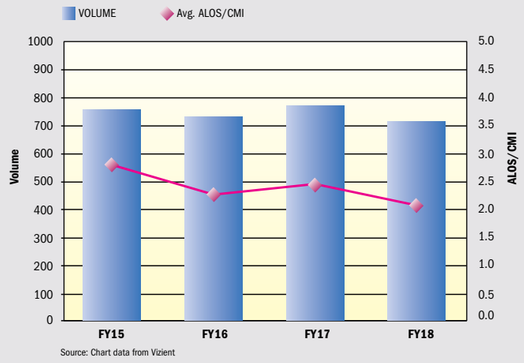
Spine Trauma: Volume & Length of Stay (CMI Adjusted)



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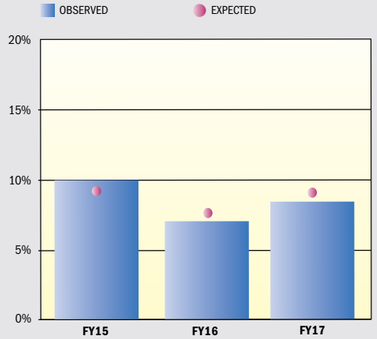
Spine Tumor: Inpatient Mortality



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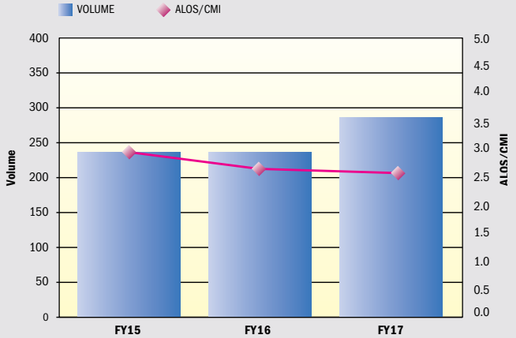
Spine Tumor: Volume & Length of Stay (CMI Adjusted)



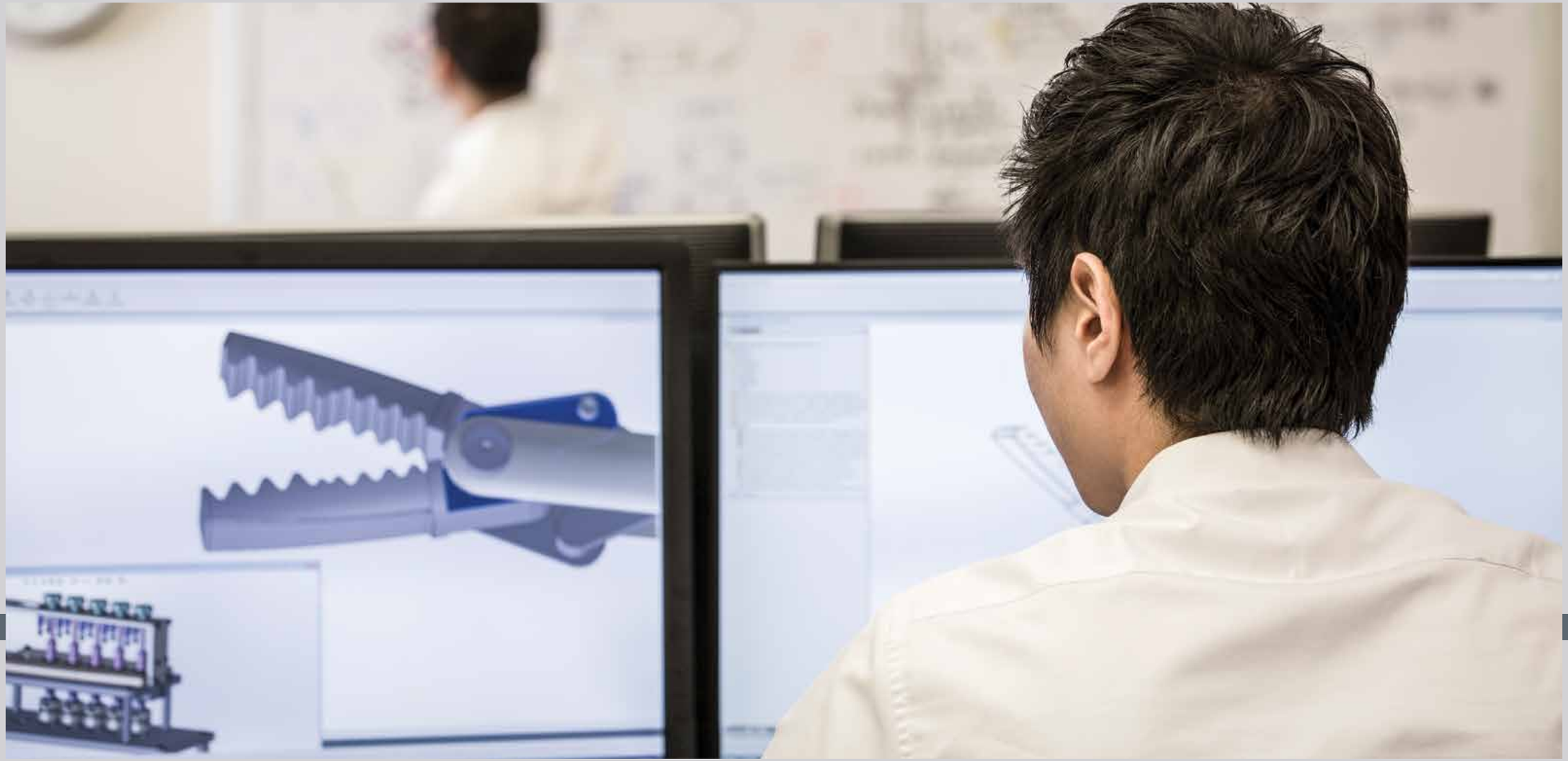
Source: Chart data from Vizient

Spine Disorders Treated

Physicians at UTHealth Neurosciences are committed to providing exceptional clinical care with a strong focus on patient safety and the highest quality outcomes for patients. They specialize in:

- Artificial disk replacement
- Birth palsies
- Brachial plexus injuries
- Carpal tunnel syndrome
- Congenital spine disorders
- Median nerve injuries
- Nerve sheath tumors
- Neurofibromatosis
- Neuromodulation for nerve injuries and for chronic headache
- Pelvic plexus injuries
- Peripheral nerve injuries
- Peroneal nerve injuries
- Pudendal nerve entrapment
- Piriformis syndrome
- Radial nerve injuries
- Sciatic nerve injuries
- Spinal AVMs
- Spinal stenosis
- Spine and spinal cord tumors
- Spine deformity
- Spine disk herniation
- Spine fractures
- Spine infection
- Tibial nerve injuries
- Ulnar nerve entrapment

Research and Innovation



Physicians at McGovern Medical School at UTHealth are engaged in a broad and intensive research program focused on the mechanisms, treatment and cure of neurological disease and injury. They use diverse approaches – molecular, transgenic and electrophysiological techniques – in biomedical studies, translational research, clinical trials and technology development and assessment.

Grants to researchers at UTHealth are awarded by the National Institutes of Health, the Vivian L. Smith Foundation for Neurologic Disease, the American Stroke Association and other granting agencies. Investigations cover major areas of neurological disease, including stroke, aneurysm, spinal cord injury, brain tumor, stem cell therapies, neuroprotection, hypoxic encephalopathy, epilepsy, traumatic brain injury and Parkinson's disease.

Research funding for the Department of Neurology for the 2019-20 academic year exceeds $28.5 million, including grants and contracts. Research funding for the Vivian L. Smith Department of Neurosurgery for the same time period is more than $17.4 million, including grants and contracts. The following listing is a sample of ongoing or recently completed research projects.

CEREBROVASCULAR

A Randomized, Placebo-controlled Study of the Efficacy and Safety of Intracerebral Stem Cells (CTX 0E03) in Subjects with Disability Following an Ischemic Stroke (PISCES III)

Study Steering Committee Member and Investigator:
Peng Roc Chen, MD

Patients with persistent disability 6 to 12 months following an ischemic stroke will be enrolled in this randomized, placebo-controlled, multicenter study following confirmation of eligibility and consent. Patients will be randomized 1:1 to undergo a stereotactic surgery and receive a single administration of CTX0E03 Drug Product by intracerebral implantation or undergo sham surgery only (placebo). Patients will be followed for 12 months after surgery with follow-up assessments occurring at various time points over the 12 months. All eligible patients will be assigned a standardized physical therapy (PT) program. Patients will complete their daily PT exercises at home for 12 weeks after their surgery.

Brain AVM Genetic and Molecular Study

Co-Investigators: **Eunhee Kim, PhD, and Peng Roc Chen, MD**

This study is focused on understanding the pathophysiology of brain arteriovenous malformation (bAVM). Researchers are investigating the role of several molecular factors related to endothelial dysfunction, angiogenesis, and inflammation in bAVM pathophysiology. The goal is to provide insight on gene regulation of bAVM formation and risk of its hemorrhage.

Extracorporeal Filtration of Subarachnoid Hemorrhage via Spinal Catheter (PILLAR)

Site Principal Investigator: **Spiros Blackburn, MD**

In this prospective clinical trial, physicians are investigating a novel device used to filter out blood in the spinal fluid after aneurysmal bleeding. The goal of the study is to demonstrate safety of the device and show that blood removal may improve clinical outcome.

Role of Haptoglobin Genotype on Neuroinflammation and Coagulation Following Aneurysmal Subarachnoid Hemorrhage

Principal Investigator: **Spiros Blackburn, MD**

This project seeks to investigate the promising finding that the haptoglobin genotype predicts outcome after aneurysmal subarachnoid hemorrhage, and beyond this, novel mechanisms of inflammation and coagulation to determine future therapeutic targets.

SEdation versus General Anesthesia for Endovascular Therapy in Acute Ischemic Stroke (SEGA)

Study Chair: **Peng Roc Chen, MD**

This study aims to estimate overall treatment benefit (improvement in disability) among acute ischemic stroke patients randomized to general anesthesia (GA) compared with sedation (CS) during endovascular therapy. Researchers will assess safety as measured by incidence of symptomatic intracranial hemorrhage; rates of endovascular therapy (EVT) procedural complications, reperfusion; and quality of life.

The Intra-arterial Vasospasm Trial (iVAST)

Principal Investigator: **Peng Roc Chen, MD**

This study is designed to compare the outcome effect between intra-arterial (IA) infusion of a combination of multiple vasodilators and a single agent in treatment of cerebral vasospasm.

Venous Sinus Balloon Angioplasty vs. Stenting for Pseudotumor Cerebri: A Prospective Single-Center Clinical Pilot Study

Lead Physician: **Peng Roc Chen, MD**

This study evaluates the outcomes of intracranial venous sinus balloon angioplasty and balloon angioplasty followed by stent placement in treating venous sinus stenosis induced intracranial hypertension.

CHILDREN'S NEUROSCIENCE

Combination Intraventricular Chemotherapy Pilot Study: Methotrexate and Etoposide Infusions into the Fourth Ventricle or Resection Cavity in Children with Recurrent Posterior Fossa Brain Tumors

Principal Investigator: **David I. Sandberg, MD**

For the first time in humans, our center demonstrated in a previous pilot clinical trial that chemotherapy can be delivered directly into the fourth ventricle of the brain in children with recurrent, malignant brain tumors. Promising results from a pilot trial with low-dose (two milligram) methotrexate infusions has led to several additional clinical trials testing this novel treatment approach. There has been no neurological toxicity, and some patients have demonstrated decreased tumor burden after infusions. In a current trial, open for patients age 1 to 80 years with medulloblastoma and atypical teratoid rhabdoid tumor (ATRT), two chemotherapy agents (methotrexate and etoposide) are simultaneously being infused into the fourth ventricle to treat recurrent disease in the brain and/or spine.

Infusion of 5-Azacytidine (5-AZA) into the Fourth Ventricle or Resection Cavity in Children with Recurrent Posterior Fossa Ependymoma: A Phase 1 Study

Principal Investigator: **David I. Sandberg, MD**

Open to patients age 1 to 80 years old with recurrent ependymoma that originated in the posterior fossa of the brain, this new study employs a novel means of treating ependymoma brain tumors that originate from the fourth ventricle: infusion of a chemotherapy agent directly into the fourth ventricle rather than systemic intravenous delivery. The agent being infused, 5-AZA, has been shown to effectively kill ependymoma cells in the laboratory and been shown to be safe when infused at a lower dose directly into the fourth ventricle in a pilot clinical trial. There will be no simultaneous systemic chemotherapy.

Cap-based Transcranial Optical Tomography

Principal Investigator: **Manish N. Shah, MD**

In this IRB-approved human study, a novel optical imaging device was designed that obtained high spatial resolution optical tomographic imaging from infants. The preliminary results with cap-based transcranial optical tomography (TCOT) lay the groundwork for further investigation of pediatric neurological conditions such as hydrocephalus, cerebral palsy and epilepsy.

EPILEPSY

A Unified Cognitive Network Model of Language

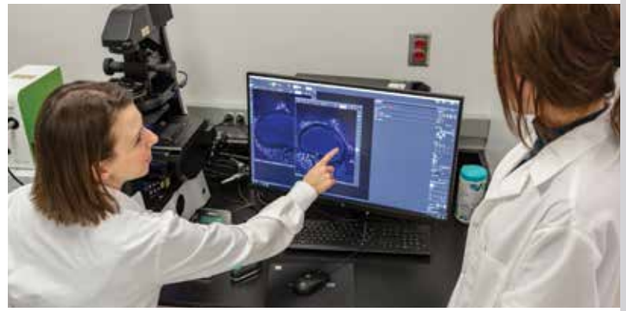
Lead Physician: **Nitin Tandon, MD**

The researchers are using advanced methods for intracranial EEG recordings and stimulation to generate a model of the network behavior that enables us to read letters, words and derive meaning from sentences. This will yield novel insights into language organization that are applicable to normal language capacity and language dysfunction in a wide variety of patients with neurologic and psychiatric illnesses.

Brain Networks of Noun Generation

Lead Physician: **Nitin Tandon, MD**

Researchers are using intracranial electroencephalographic (icEEG) recordings and direct cortical



stimulation to generate and validate network-based descriptions of brain dynamics and critically evaluate current neuro-linguistic models of object and people naming.

Functional and Anatomical Imaging of Brain Regions Involved in Language

Lead Physician: **Nitin Tandon, MD**

In this study, researchers developed the software and tools necessary to make accurate intermodal comparisons of modalities used for preoperative functional mapping, including fMRI and electrical cortical stimulation mapping.

How Inhibitory Control Modifies Stimulus Value and Motivation

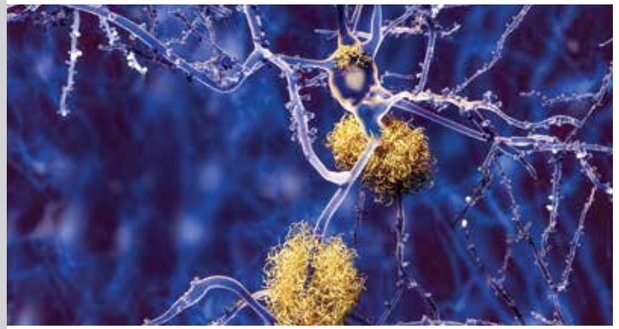
Lead Physician: **Nitin Tandon, MD**

The researchers are studying the neural architecture underlying how people are able to control inappropriate urges. Functional MRI and electrocorticography are being used to understand the substrates and timing of the network involved in modulating and stopping action.

Intracranial Electrophysiology and Connectivity of Language Regions in Humans

Lead Physician: **Nitin Tandon, MD**

The investigators are making intermodal comparisons between intracranial EEG, fMRI, DTI, and electrical cortical stimulation mapping.



Selective Laser Ablation in Temporal Lobe Epilepsy Trial (SLATE)

Lead Physician: **Nitin Tandon, MD**

SLATE is a three-year, multicenter trial for FDA-specific approval of laser interstitial therapy for mesial temporal lobe epilepsy.

MEMORY DISORDERS AND DEMENTIA

A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety Study of Gantenerumab in Patients with Early (Prodromal to Mild) Alzheimer's Disease

Site Principal Investigator: **Paul Schulz, MD**

The goal of this trial is to test the safety and efficacy of an anti-amyloid antibody, which is injected monthly, and to determine whether lowering the Aβ levels will delay the progression of Alzheimer's disease

A Randomized, Double-blind, Placebo-controlled, Two-cohort Parallel Group Study to Evaluate the Efficacy of CAD106 and CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease: AP1015A2201J, The Generations 1 Trial

Site Principal Investigator: **Paul Schulz, MD**

Alzheimer's disease is due to the accumulation of an abnormal protein called Aβ. BACE inhibitors reduce the activities of the enzyme that produces the abnormal Aβ. The goal of this trial is to test whether a daily BACE inhibitor medication can delay or prevent the onset of AD in persons who are ApoE 4/4 positive, who have amyloid PET imaging-proven frequent plaques, but are asymptomatic.

A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease: CNP520A2202J, The Generations 2 Trial

Site Principal Investigator: **Paul Schulz, MD**

The goal of this trial is to test whether a daily BACE inhibitor medication, which reduces Aβ production, can delay or prevent the onset of AD in persons who have one ApoE 4 allele, who have amyloid PET imaging-proven frequent plaques, but are asymptomatic.

Deep Brain Stimulation for Refractory Major Depressive Disorder

Principal Investigator: **Jair Soares, MD, PhD**

Co-investigator: **Paul Schulz, MD**

The goal of this study is to test the safety and efficacy of deep brain stimulation of the median forebrain bundle on the symptom of depression, in patients with refractory major depression disorder.

Detection of Amyloid-Beta and Tau Misfolded Oligomers in Biological Fluids of TBI and AD Patients

Principal Investigator: **Claudio Soto, PhD**

Co-investigator: **Paul Schulz, MD**

With funding from the Department of Defense, the researchers are using protein misfolding cyclic amplification (PMCA) technology for sensitive diagnosis of patients affected by traumatic brain injury.

Highly Selective Detection of Tau Oligomers in Biological Fluids for the Diagnosis of Alzheimer's Disease

Principal Investigator: **Claudio Soto, PhD, and Ben Vollrath, PhD**

Co-investigator: **Paul Schulz, MD**

The purpose of the study is to develop and test protein misfolding cyclic amplification (PMCA) technology for highly sensitive detection of misfolded Tau oligomers implicated in Alzheimer's disease.

M15-562: A Randomized, Double-blind, Placebo-controlled Multiple Dose Study to Assess Efficacy, Safety, Tolerability and Pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy

Principal Investigator: **Paul Schulz, MD**

The goal of this trial is to test the safety and efficacy of a monthly IV-infused Tau protein antibody for delaying the progression of progressive supranuclear palsy (PSP).

M15-563: Clinical Study Protocol M15-563, An Extension Study of ABBV-8E12 in Progressive Supranuclear Palsy (PSP)

Site Principal Investigator: **Paul Schulz, MD**

This is an extension trial of M15-562 for which the goal is to test the safety and efficacy of a monthly IV-infused Tau protein antibody for delaying the progression of PSP.

M15-566: A Phase 2 Multiple-dose, Multicenter, Randomized, Double-blind, Placebo- controlled Study to Evaluate the Efficacy and Safety of ABBV-8E12 in Subjects with Early Alzheimer's Disease

Site Principal Investigator: **Paul Schulz, MD**

Another abnormal protein deposited in the brains of people with Alzheimer's disease is Tau protein. The goal of this trial is to test the safety and efficacy of a monthly IV-infused Tau protein antibody and determine whether lowering the level of Tau protein in the brain delays the progression of Alzheimer's disease.

Management of Parkinson's Disease Psychosis in Actual Practice: The INSYTE Study

Site Principal Investigator: **Paul Schulz, MD**

The goal of this study is to compare the safety and efficacy of pimavanserin versus best medical therapy for the treatment of Parkinson's disease psychosis.

Misfolded Protein Aggregates in HIV Infection

Principal Investigator: **Claudio Soto, PhD, and Roberto C. Arduino, MD**

Co-investigator: **Paul Schulz, MD**

The goal of this project is to study comprehensively the presence of misfolded protein aggregates in the brains and biological fluids of HIV-infected people.

Plasma Exchange to Treat Alzheimer's Disease

Site Principal Investigator: **Paul Schulz, MD**

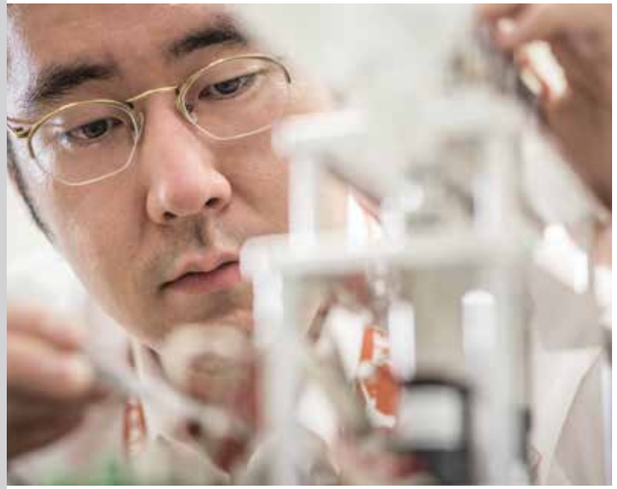
The researchers' goal is to test the hypothesis that plasma exchange will lower blood Aβ, Tau and inflammatory molecules, and that this will improve clinical outcomes in AD, probably through reducing brain levels of these three classes of molecules. This is a single-site, investigator-initiated translational trial from mice to humans.

Sports-related Concussion: Emotional Distress and Hypothalamic Hormone Levels in Female Adolescent Athletes

Principal Investigator: **Summer Ott, PhD**

Co-investigator: **Paul Schulz, MD**

The researchers are investigating why young females with concussion have a longer recovery time versus males, and why Anglos have a longer recovery time than African-Americans.



Stem Cells to Treat Parkinson's Disease

Principal Investigator: **Paul Schulz, MD**

This single-site, investigator-initiated translational trial is testing the safety and efficacy of stem cells to treat Parkinsonism in mice, and also in humans with Parkinson's disease.

MOVEMENT DISORDERS AND NEURODEGENERATIVE DISEASES

Enroll-HD: A Prospective Registry Study in a Global Huntington's Disease Cohort

Lead Physician: **Erin Furr-Stimming, MD**

The primary objective of this worldwide observational, prospective multicenter study is to improve our understanding of Huntington's disease (HD). Researchers are collecting information about cognition, behavior and motor function to estimate how HD progresses in patients; collecting blood samples and data to identify genetic and environmental factors that affect HD phenotype and disease progression; and promoting interrogatory studies that may provide clues to the pathogenesis of HD. The study is enrolling.

HD-Clarity

Lead Physician: **Erin Furr-Stimming, MD**

The primary objective of this study is to generate a high-quality cerebrospinal fluid (CSF) sample collection for evaluation of biomarkers and pathways that will enable the development of novel treatments for Huntington's disease (HD). The secondary objectives are to generate a high-quality plasma sample collection matching the CSF collections, and to collect phenotypic and clinical data for each participant, which will also be used to evaluate biomarkers and pathways of relevance to HD research and development. The study is enrolling.

Microglial Activation in HD: A Structural and Functional Study

Lead Physician: **Erin Furr-Stimming, MD, Natalia Pessoa-Rocha, PhD, and Antonio Lucio Teixeira, MD, MSc, PhD**

The objective of this study is to investigate the role played by microglia in the different stages of HD. The researchers will evaluate structural and functional parameters of microglial response in HD gene carriers in relation to the clinical features seen at various stages of disease.

Nuedexta® and Irritability in Huntington's Disease

Lead Physician: **Erin Furr-Stimming, MD**

Researchers are valuating the safety and efficacy of dextromethorphan/quinidine in the treatment of irritability in Huntington's disease.

Pivotal Trial BN 40423

Lead Physician: **Erin Furr-Stimming, MD**

This Phase III study is investigating the ASO-HTT molecule in the Huntington's disease patient population.

Restore: A Clinical Study of Patients with Symptomatic Neurogenic Orthostatic HypoTension to Assess Sustained Effects of Droxidopa Therapy

Sponsor: **Lundbeck NA**

Principal Investigator: **Raja Mehanna, MD**

The purpose of this research study is to determine the long-time effectiveness and safety of a study drug called droxidopa (also known by the trade name NORTHERATM) in people with symptoms of neurogenic orthostatic hypotension (NOH) associated with Primary Autonomic Failure [Parkinson's disease (PD), Multiple System Atrophy (MSA) or Pure Autonomic Failure (PAF)], or Non-Diabetic Autonomic Neuropathy (NDAN) or Dopamine Beta Hydroxylase (DBH) deficiency.

SIGNAL

Lead Physician: **Erin Furr-Stimming, MD**

The purpose of this Phase 2 study is to evaluate the safety, tolerability, PK and efficacy of VX15/2503 in subjects with late prodromal and early manifest Huntington's disease. This study is active but no longer enrolling.

Study to Measure Cerebrospinal Fluid Mutant Huntington Protein in Participants with Early Manifest Stage I or Stage II Huntington's Disease

Lead Physician: **Erin Furr-Stimming, MD**

A multisite, longitudinal, cohort study measuring cerebrospinal fluid-mutant Huntington protein in patients with Huntington's disease.

NEURO-ONCOLOGY

A Study of DSP-7888 Dosing Emulsion in Combination With Bevacizumab in Patients With Recurrent or Progressive Glioblastoma Following Initial Therapy

Lead Physician: **Jay-Jiguang Zhu, MD**

This is a randomized, active-controlled, multicenter, open-label, parallel-group, Phase 2 study of DSP-7888 dosing emulsion plus bevacizumab versus bevacizumab alone in patients with recurrent or progressive glioblastoma multiforme (GBM) following treatment with first-line therapy consisting of surgery and radiation with or without chemotherapy.

SPINE

Identifying Novel Molecular Targets for Chronic Spinal Cord Injury

Principal Investigator: **Jiaqian Wu, PhD**

The Wu Lab is identifying novel potential therapeutic targets for chronic SCI gliosis using purified astrocytes from mouse contusive SCI models, and testing their functions.

Selected Publications

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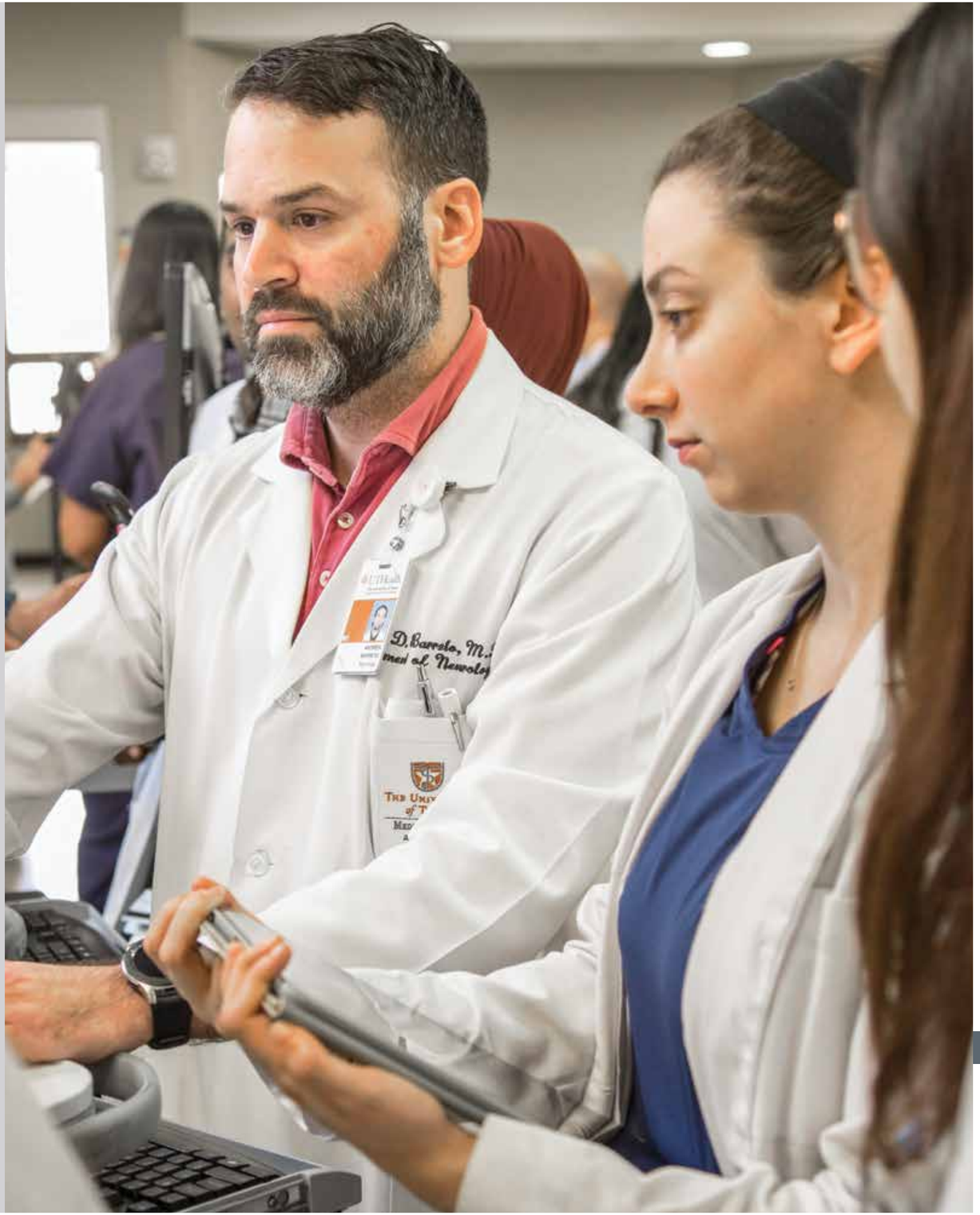

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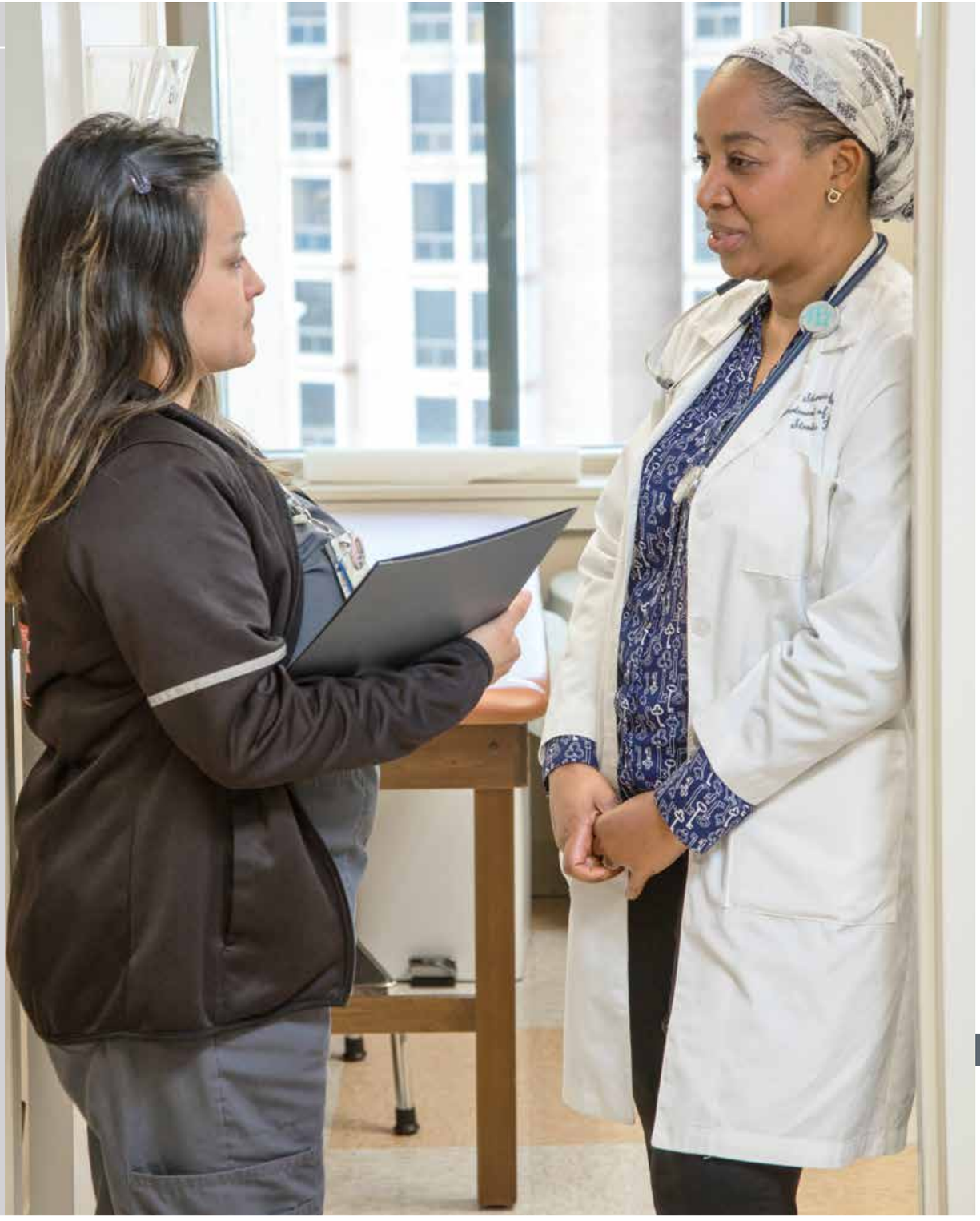

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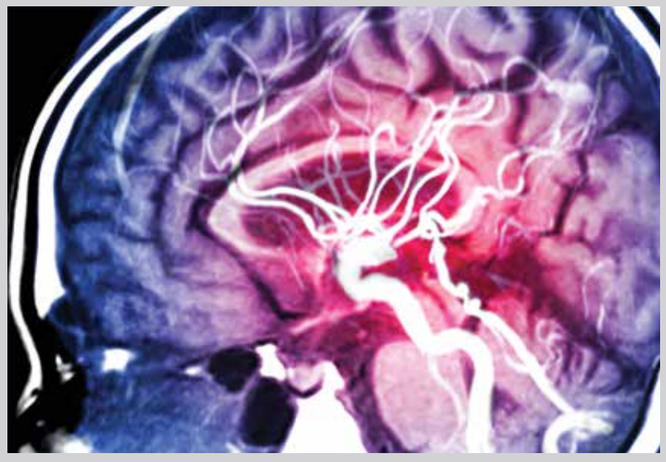

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Patient Stories

Jim Huddleston :
Beating Back Pain Without Surgery

Jim Huddleston's problems with sciatica date back to the mid-1960s. To deal with the pain, he strengthened his core muscles with sit-ups, pushups and leg raises – any type of exercise that would help support his spine.

"I was able to play soccer and football and enjoy other outdoor activities without any consequences for quite a while," says Huddleston, who took up cycling 15 years ago after injuring his knee. "Then about eight years ago I started having intermittent sciatica attacks that were severe enough to limit my activity."

His sciatica continued to worsen, with pain that radiated down the nerve through his hips, buttocks and both legs. He had trouble getting comfortable while sleeping or sitting for any length of time, but when he was cycling, he was without pain.

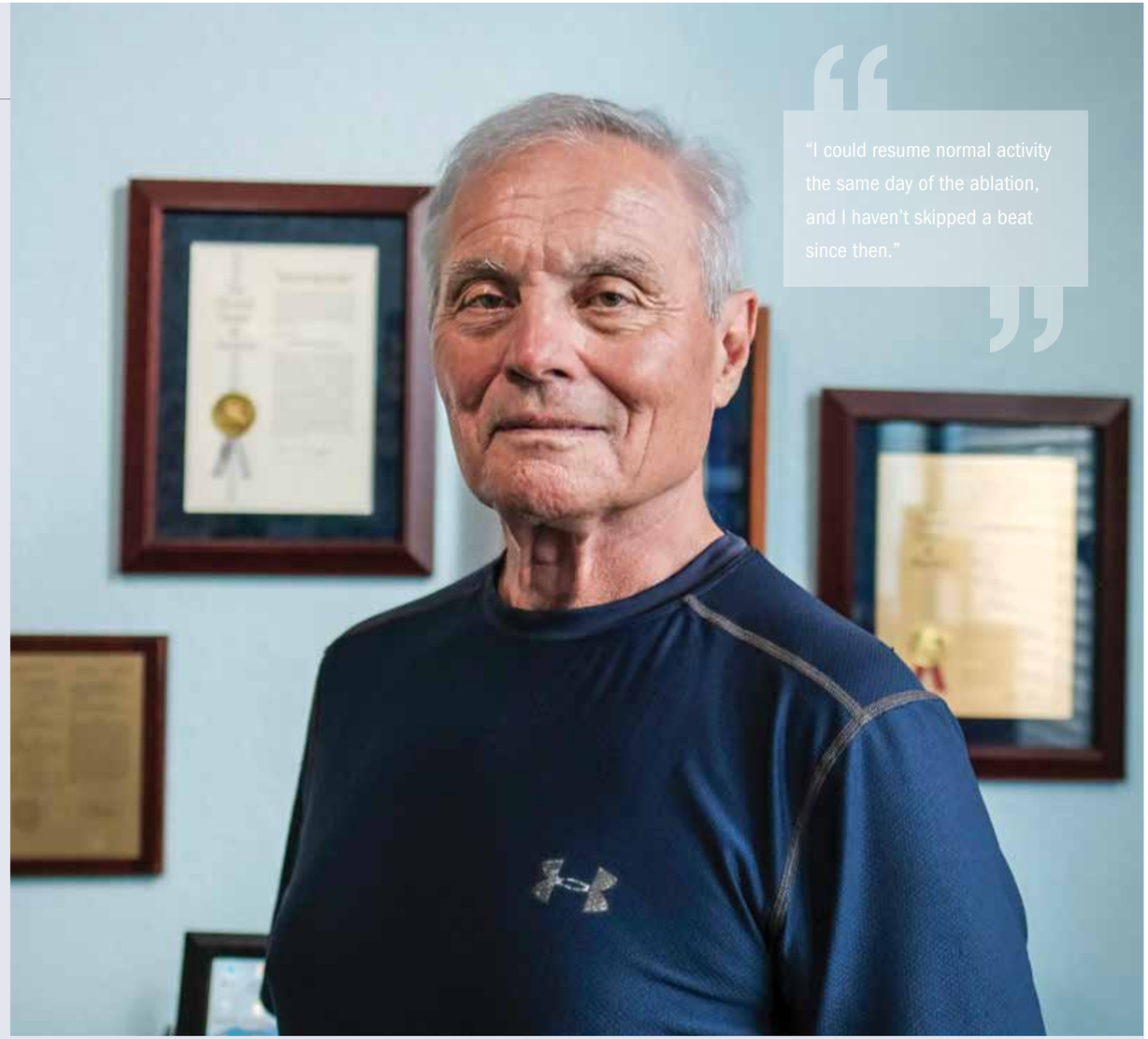
An orthopedic surgeon in Houston referred him to John Quinn, MD, a fellowship-trained UTHealth neurosurgeon who sees patients at the Spine Center at UTHealth. After a thorough evaluation, Dr. Quinn asked Huddleston if he was open to exploring ways to manage the pain without major spine surgery.

"Mr. Huddleston's case shows how important the clinical examination is," says Dr. Quinn, an assistant professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School. "He had a complicated diagnosis – degenerative scoliosis with disk degeneration at every level of his lumbar spine, a common finding in older adults. But the source of his pain turned out to be his sacroiliac joint."

Dr. Quinn referred Huddleston to UTHealth staff physician Ashley Amsbaugh, MD, who is double board certified in anesthesiology and pain management, specializing in interventional pain management. She practices at the Spine Center at UTHealth.

"We suggested managing the inflammation in the sacroiliac joint with a steroid injection," says Dr. Amsbaugh, a clinical assistant professor in the Vivian L. Smith Department of Neurosurgery. "The first go-round with steroids improved his ability to sleep, get in and out of bed easily and engage in activity, but the relief was short term. We subsequently did radiofrequency ablation on the sensory nerves that supply the sacroiliac joint on the left and right sides."

Radiofrequency ablation (RFA) uses radio waves delivered through a needle tip to heat and destroy nerves that carry pain signals to the brain. Patients are lightly sedated, and the procedure takes 30 to 45 minutes. On the right side, Huddleston had ongoing relief. On the left side, he still had some pain after the first month following RFA. Dr. Amsbaugh did a second ablation on the left side six months after the first ablation.



"In most people it can take four to six weeks to get maximum benefit, but Jim responded well," she says. "He was able to return to his exercise routine focused on strengthening his core right away."

Huddleston rides four or five times a week, anywhere from 30 to 55 miles in open air, depending on the destination, and for 35 minutes to an hour and a half on an indoor trainer while watching cycling videos. "I'm very pleased with the whole experience, from the staff who made my appointments, my interaction with the nurses, and new appointment and follow-up scheduling. Dr. Amsbaugh is a consummate professional," he says. "I could resume normal activity the same day of the ablation, and I haven't skipped a beat since then."

Christine Melody: **Back in the Driver's Seat**

Getting your driver's license is a liberating moment, but for Christine Melody it meant so much more than the freedom of the open road. Finally getting behind that wheel marked an end to the phase of her life where she was held captive by epilepsy and the happy beginning of living life to the fullest.

It had been a torturous journey of frightening seizures and a search for a successful treatment spanning almost two decades. The crucial turning point came when Christine and her parents, Martha and Tom, met Nitin Tandon, M.D., professor in the Vivian L. Smith Department of Neurosurgery at McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth) and director of the Epilepsy Surgery Program at the Mischer Neuroscience Institute at Memorial Hermann-Texas Medical Center.

"We spent years traveling across the country searching for answers and for hope. But no one gave us the confidence to proceed with surgery. Then right here on our doorstep in Houston, we met Dr. Tandon, who was amazing and made us realize not having surgery could be even more dangerous," Christine says.

Tandon is at the forefront of cutting-edge brain surgery that can effectively treat epilepsy, through pinpointing the source with fine electrode probes and tackling it with laser precision to eliminate seizures from patients' lives.

Wanting to lead a normal life, Christine and her parents had tried to do everything possible to avoid letting seizures hold her back. Raised with three brothers, she was tough, and despite warnings from doctors, took it upon herself to excel in gymnastics and in cheerleading. She became so adept at masking her condition, people were often oblivious to it. But sometimes concealing a seizure simply wasn't possible.

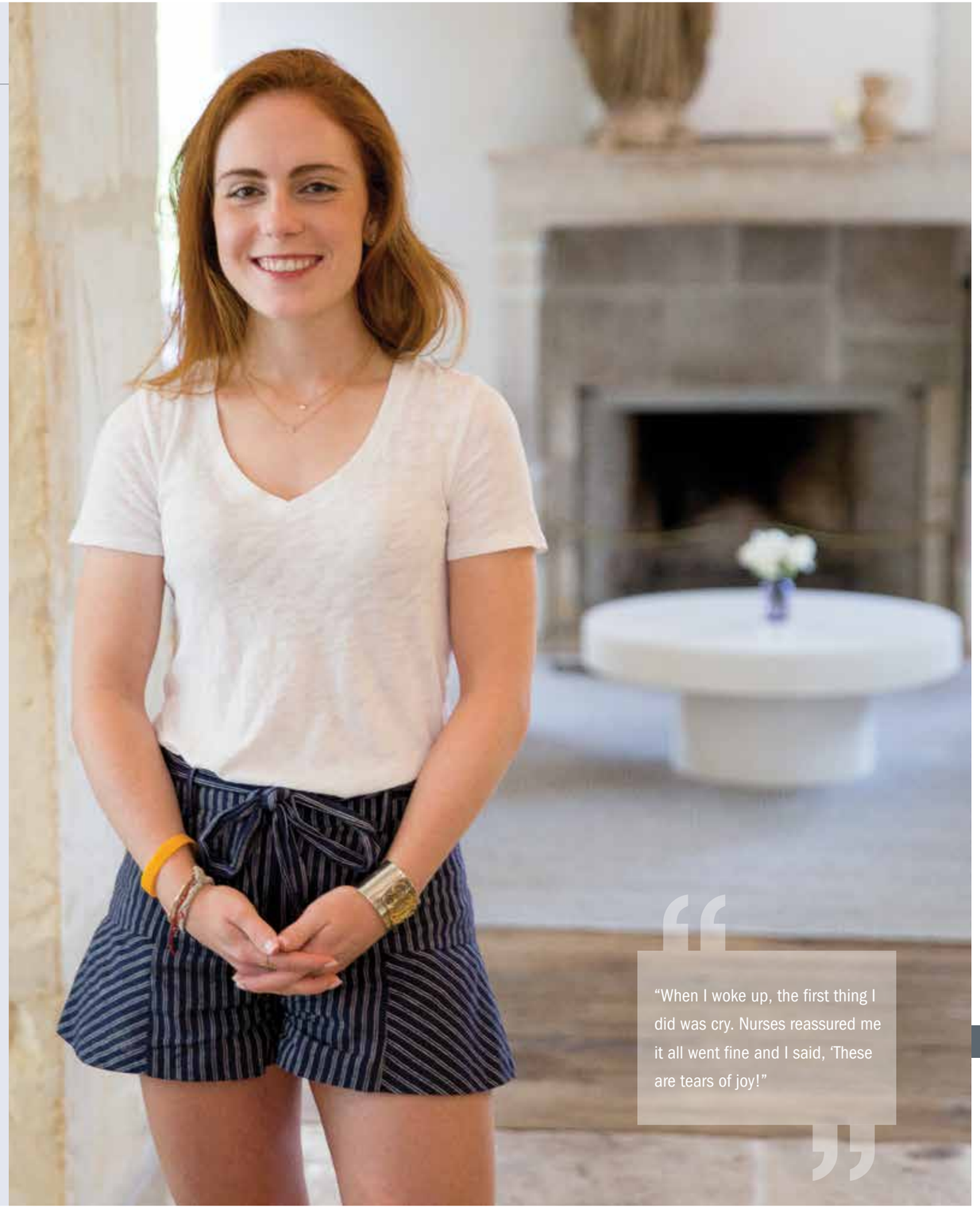
"At a cheerleading competition I suddenly sensed a bad episode coming. I walked away from the line and started mumbling and fidgeting. Unable to fully control my movements, it was like being a puppet controlled by someone else," Christine says, "I hated it – I felt so embarrassed, frustrated and alone."

Often, only her closest friends and family could spot the telltale signs of a seizure. So when she moved away to study at college, the frightening reality of her vulnerability was evident.

"Things went downhill fast. I was having up to 20 seizures a day and being away at college became a constant struggle. I had trouble concentrating and during seizures, I couldn't even write," Christine says.

"Once I found myself wrapped in a towel in the middle of my dorm lobby. I remember getting out of the shower, but that's when the seizure must have taken hold. It was quite scary and of course my mom was worried sick on the end of the phone calling me, frantically asking 'What happened?'"

Her parents realized something had to change, and, thankfully, Tandon's surgical talents held the key.



"He was the answer to all our prayers. From the first consultation we knew we were finally on the right path," says her mother, Martha. To this day, she is still haunted by the memory of when she found her little 2-year-old girl lying unconscious in her crib after suffering a fever-induced static seizure. "Doctors said she was lucky to survive and escape major brain damage. We felt so relieved and grateful," Martha says. "Then one day at preschool she had another seizure. Her life continued to be plagued by them, and I worried endlessly, especially when she went swimming and horse riding. It constantly preys on your mind."

Mesial temporal lobe epilepsy, which affects Christine, represents around a quarter of all epilepsy cases. The least invasive surgical option is called laser interstitial thermal therapy, more commonly known as laser ablation, which burned away the scar on her brain left by the aftermath of her very first seizure.

"After Dr. Tandon explained the procedure and his track record in performing it, we didn't hesitate. He even put me in touch with other patients who had been through the same thing," Christine says.

Armed with the precious 'Dammit Doll' given by a friend in recognition of her plight, a special prayer bracelet and a symbolic bracelet in memory of her priest Father T.J. Martinez, Christine went in for surgery more than a year ago. It was a success.

"When I woke up, the first thing I did was cry. Nurses reassured me it all went fine and I said, 'These are tears of joy!' The biggest weight had been lifted from my life and my whole family. Finally I was free — we all were," Christine says.

A few months later, to celebrate her newfound independence, Christine received something extra special for her 21st birthday. "I couldn't believe it when my parents led me outside to a brand new car on the driveway. I'd wanted to drive so long and had almost lost hope," she says.

Making the most of her new life, there have been plenty of road trips as well as a Bruno Mars concert in Las Vegas. "Before, I always worried that bright lights might trigger a seizure, but now I can just relax and enjoy it. Everything about my life is different," she says.

Passionate about helping others, Christine is volunteering with the Epilepsy Foundation and speaks with people who have the condition and may be considering surgery. "I just want people to know there's light at the end of that long, dark tunnel, and it's really worth getting there," Christine says. "I couldn't be happier right now." Her parents are equally thrilled.

"It's hard to express how blessed we feel. Dr. Tandon hasn't just given our daughter the ability to drive — he has given her wings to fly," Martha says.

Such transformational results are the driving force behind Tandon's work.

"Outcomes such as these, and the enormous impact we have on the lives of not just the individual, but the whole family, is exactly what motivates us each day to come up with new approaches and cures for epilepsy," Tandon says. "Being able to help people lead more fulfilling lives is such a privilege, and I'm delighted to have been given the opportunity to put Christine back in the driving seat."

—Written by UTHealth Media Relations

Jay McIntosh:
Improved Quality of Life with Deep Brain Stimulation

Imagine a world where the smallest tasks can make day-to-day life incredibly difficult. At times, life can be stressful enough without having to worry about menial things. But for those suffering with tremors, even the smallest tasks can present an enormous challenge.

For Jay McIntosh, he began noticing issues with tremors during his teenage years. A slight, but constant tremor in his thumbs was more of a nuisance than anything life threatening, but it made small tasks like pouring and measuring in his high school science labs a difficult task. However, as McIntosh aged, he noticed the tremor began to progress throughout his body as well, affecting his hands, feet, and head.

"I started noticing difficulty when administering the Lord's Supper," says McIntosh, who is a Baptist pastor. "My hand would shake in the process of distributing. Then I noticed difficulty with holding hands with a member to pray with them before surgery. It was just a nuisance, but it started to worsen in my 40s."

"Tremors are uncontrollable shaking usually displayed in the hands, feet, and head," says Raja Mehanna, MD, a neurologist with UT Physicians and assistant professor at McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth). "They can lead to minor issues such as a shaky voice or a head nod, but can markedly affect quality of life."

Tremors affect more than 10 million people in the United States and have an incidence rate of 23.7 out of every 100,000 people. Passed down hereditarily (50 percent chance of inheritance from the parent), the cause of tremors is unknown; however, it is thought to be related to abnormal activity in the cerbello-thalamo-cortical network of the brain.

By adjusting his daily routine, McIntosh was able to adapt to the spreading tremors. For example, if he was distributing communion, he would fill his glass only half way to avoid spilling because of a tremor. However, by the time McIntosh reached the age of 45, he decided it was time to begin seeing Mehanna.

McIntosh's treatment began with medication to try to address the tremors. He had some success with the medication, but after a couple of years he noticed that it began to provide no relief. Mehanna began to observe rigidity in McIntosh's elbows, prompting imaging to test for Parkinson's disease. After the test came back negative, Mehanna informed McIntosh that brain surgery was the next step.

"Oh no you're not," McIntosh recalls thinking at the time.

In what he describes as a 'Whatchu talkin' bout, Willis?' moment, McIntosh could not wrap his head around the fact that he was going to be having brain surgery.

He was even more surprised when he learned that he would be awake for the entire process. "That added a little bit more anxiety initially," McIntosh says. "Then I did some research and realized the brain does not feel

or experience pain. I learned the most difficult part of the surgery would be just getting through the skull, and once they were in the brain, there would be no pain issues at all. The only pain I experienced was that normal pain you have from the local injection."

McIntosh underwent deep brain stimulation (DBS), on February 17, 2017. The surgery consists of electrodes being implanted into the vicinity of the thalamus. Wires from the electrodes are then threaded underneath the skin to a neurotransmitter, a pacemaker device that sends electric pulses into the thalamus, helping to control the effects of tremors.

"It was pretty exciting to be awake and be aware of everything happening in the operating room," McIntosh says of being fully cognizant during the surgery. "Very early on, I thought it was the coolest thing I ever did. When people hear me say that, they can't believe it, but it was really an incredible experience."

Albert J. Fenoy, MD, a neurosurgeon and associate professor at McGovern Medical School, performed McIntosh's surgery at UTHealth's partner hospital, Memorial Hermann-Texas Medical Center. Having performed the surgery nearly 500 times, McIntosh knew he was in good hands, but was even more reassured to know Mehanna would be in the room as well.

"It was a great encouragement at the time," McIntosh says. "Then being awake during the surgery, after Dr. Fenoy placed the electrodes at target, and Dr. Mehanna turned the device on I could literally see the tremor leave. It was a feeling of 'Hey, this is going to work.'"

The surgery did work for McIntosh, who says he now has close to 95 percent relief from his tremors. The only times he notices any symptoms at all are when picking up something light, like a Styrofoam coffee cup, or at the end of a long day, when he notices his speech will have a slight slur. Although, his neurotransmitter has a solution for that too.

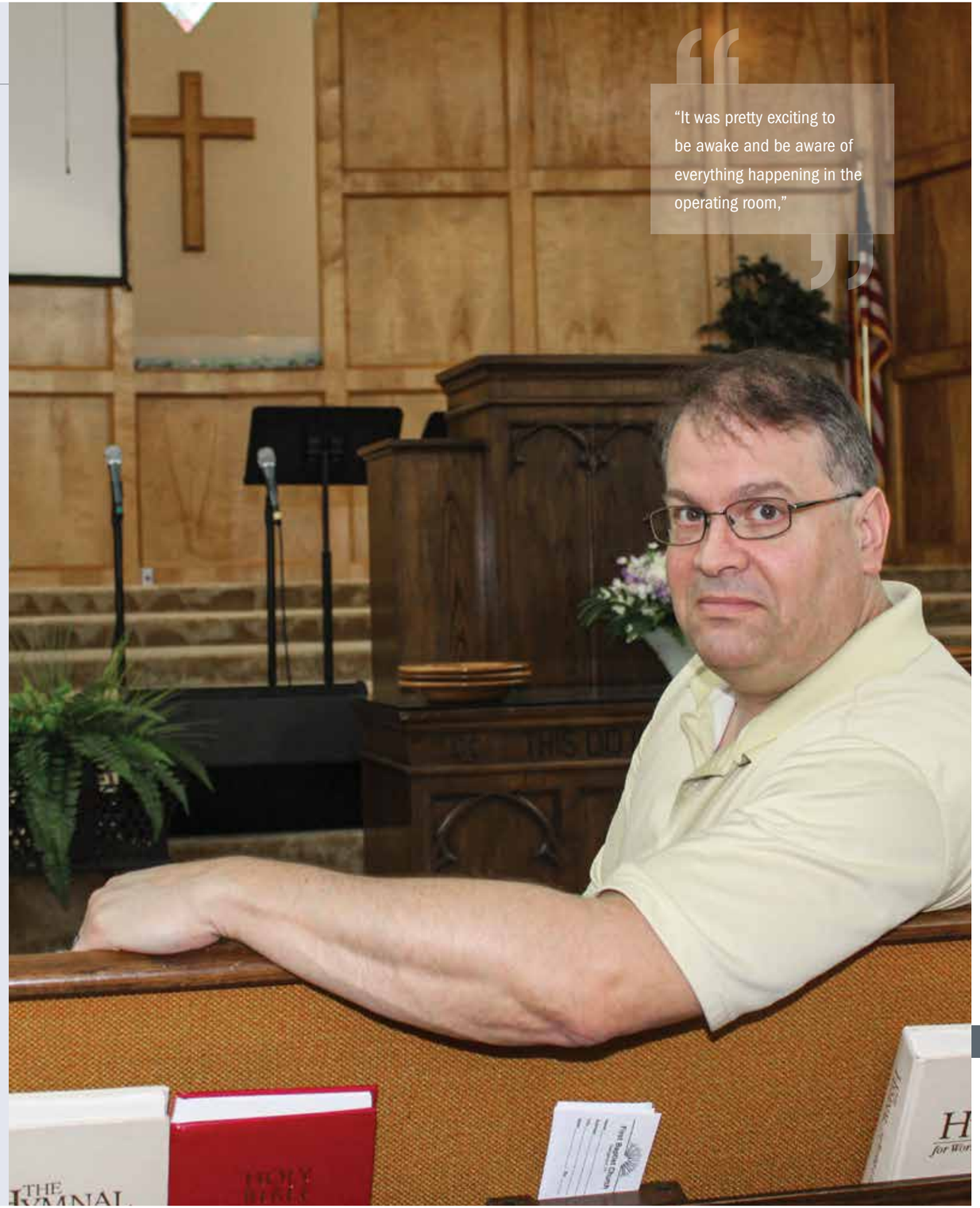
The neurotransmitter, which McIntosh keeps on at all times unless he needs to turn it off for a doctor checkup, is programmable for certain situations, including a speech function to help him get through the slurring. However, he notes he has only had to adjust the settings once in two years.

So now, the only nuisance that McIntosh has to deal with, which he admits is a small one, is remembering to charge the battery for the transmitter. He does this for 15 minutes every other day, and the battery will not need to be replaced for 15 years. McIntosh still sees Mehanna every four months to check on the device, but those trips will soon move to biannual appointments.

McIntosh has begun to spread the word about treatments for the world's most common movement disorder. He enjoys being able to inform current patients about his journey and has even spoken to future doctors at McGovern Medical School.

And of course, McIntosh also points out the incredible care he received from his doctors at UT Physicians. "My care has been outstanding," he says. "I had a level of comfort that when surgery was recommended I was open to investigating it myself, and I'm glad I did. I will continue to recommend UT Physicians for neurology and neurosurgery matters."

—Written by UT Physicians



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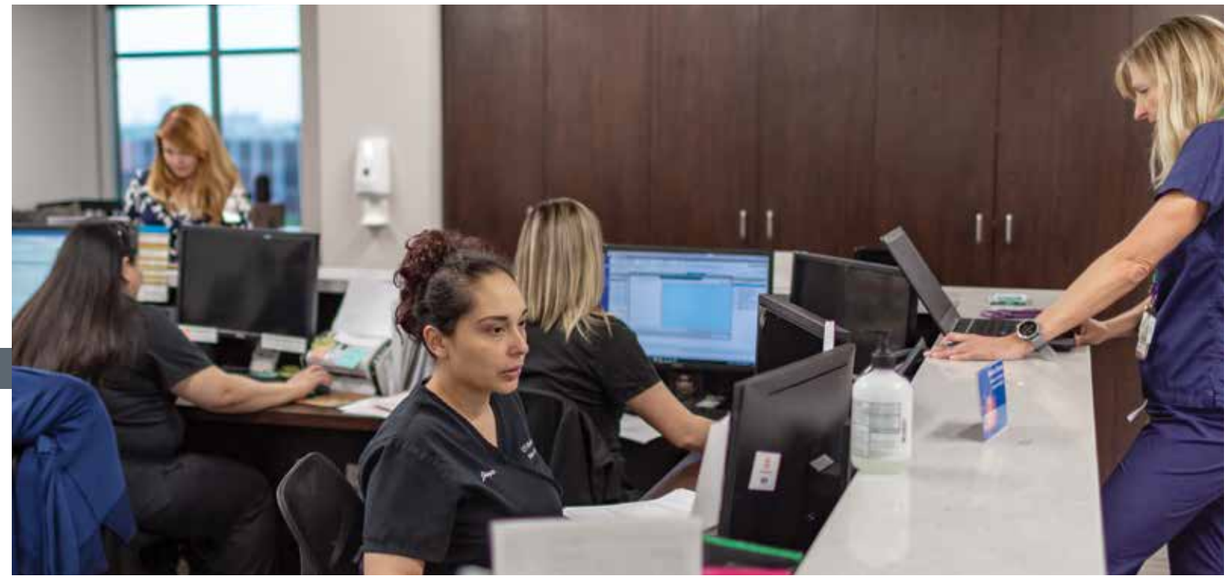

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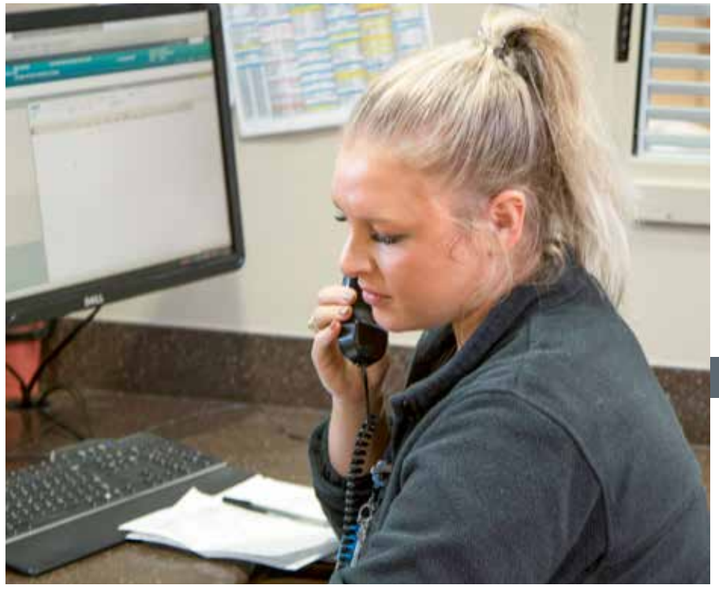

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