Mayo Clinic continuously evaluates its use of quantifiable CT perfusion imaging in acute ischemic stroke, fine-tuning the approach to optimize patient outcomes. The adjustments, which build on recent advances in stroke imaging technology, are implemented enterprisewide for consistent patient care.

“We are in a period of very rapid change in the evolution of stroke imaging,” says E. Paul Lindell, M.D., a neuroradiologist at Mayo Clinic in Rochester, Minnesota. “This dynamic environment requires continuous monitoring of developments and of clinical cases to determine the best care for patients.”

The DAWN and DEFUSE 3 clinical trials demonstrated that quantifiable CT perfusion can widen the treatment window for acute ischemic stroke. “There is now strong evidence to support the adoption of mechanical thrombectomy all the way up to 24 hours after stroke onset. But patients in this extended time window need to be carefully selected,” says Bart M. Demaerschalk, M.D., a stroke neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona, and enterprise chair of cerebrovascular neurology. “We’re committed to compiling what we collectively learn across our enterprise to better stratify patients for treatment.”

Mayo Clinic’s considered use of perfusion CT (Figure 1 and Figure 2, see page 2) provides an individualized approach to acute ischemic stroke. “Instead of treating every patient the same, we’re making sure we use this technology appropriately to identify patients who can benefit from endovascular treatment,” says James P. Klaas, M.D., a stroke neurologist at Mayo Clinic’s campus in Minnesota. “There’s no question that time is brain. But not every brain’s time is the same.”

**Unique perspective**

Mayo Clinic has stroke neurologists not only at its three main campuses in Arizona, Florida and Minnesota but also within Mayo Clinic Health System and at satellite sites via Mayo’s telesstroke network. This expertise, coupled with the high volume of patients treated for acute ischemic stroke, is advancing the application of CT perfusion to patient care.

“When a clinical trial is transformative, the results must still
be translated into daily practice,” Dr. Klaas says. “Our learning about CT perfusion is based on individual patient cases where certain aspects didn’t precisely match up with the clinical trials. We don’t want to miss a treatment option for a patient, but we also want to avoid treatment that would expose a patient to risk.”

Mayo Clinic’s refinements to CT perfusion rest on close collaboration among stroke neurologists, neurosurgeons, neurointerventionalists, neuroanesthesiologists and neuro-radiologists. “We have a unique perspective, as an academic medical center and a health system, that informs our discussions,” Dr. Lindell says. “Our multidisciplinary approach allows us to improve upon the results of clinical trials as we put them into practice.”

Disseminating that knowledge enterprise-wide benefits individuals in geographic areas where the risk of acute ischemic stroke is high. Through the telestroke network, Mayo Clinic stroke neurologists manage care in more than 30 hospitals in seven states as well as in telemedicine-enabled ambulances en route to hospitals.

“Our telestroke capability brings our expertise to communities that don’t have subspecialized stroke neurologists,” says Michelle P. Lin, M.D., M.P.H., a stroke neurologist at Mayo Clinic in Jacksonville, Florida. “The telemedicine assessment can select the patients most likely to benefit from thrombectomy. If a center doesn’t have CT perfusion imaging, we can transfer patients promptly to a main campus.”

Overall, the volumetric precision offered by quantifiable CT perfusion is benefitting patient care. Traditionally, patients who presented six hours after the onset of acute ischemic stroke were simply monitored. “The best we could do was try to manage the medical complications that arise with a large stroke,” Dr. Demaerschalk says. “Now the expanded therapeutic window is translating into carefully selected patients having visible improvement in the first 24 to 72 hours after treatment. These patients are able to undergo rehabilitation and to stand, walk, talk and go home. It’s quite striking.”

In an era of rapid technological advancement, refining the application of this technology will remain key. “Right now, CT perfusion software treats every milliliter of brain the same. But we know that some areas are more critical for predicting neurological dysfunction,” Dr. Klaas says. “One question is whether we should weight those areas differently.”

Another potential development is a role for artificial intelligence in CT perfusion. “We think that artificial intelligence may be able to discriminate features that humans aren’t able to discern in the images,” Dr. Lindell says. “The images that we acquire probably aren’t going to change a lot — it’s the analysis that’s so in flux.”

**Figure 2.** D. Angiogram after surgical removal of the clot shows normal blood flow. E. Diffusion-weighted imaging (left) and apparent diffusion coefficient mapping (right) done two days after the initial presentation show that the patient’s stroke was very small. She experienced no clinical deficits.
Whole-Patient Epilepsy Care: Uniting Technology and Psychosocial Expertise

Mayo Clinic combines the latest technology with a holistic approach for the optimal management of epilepsy. Sophisticated imaging and surgical techniques, and a multidisciplinary focus encompassing psychosocial problems associated with epilepsy, are the cornerstones of this patient-centered care.

“Epilepsy is more than just having seizures. There are significant comorbidities associated with it, particularly depression and anxiety. We understand that, and truly consider the whole picture for each patient,” says Joseph I. Sirven, M.D., a neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona.

Psychiatrists and neuropsychologists are involved in the diagnostic process and the consideration of treatment options. “Patients need a lot of support to get through these diagnostic procedures and through surgery, if that’s done. In our pre-surgical conference, we always discuss the psychosocial situation for the patient and the family, and what the best options might be for this patient,” says Richard S. Zimmerman, M.D., a neurosurgeon at Mayo Clinic’s campus in Arizona.

The technology available at all Mayo Clinic campuses for managing epilepsy includes:
- High-density electroencephalography (EEG)
- Subtraction ictal single-photon emission computerized tomography (SPECT) coregistered to MRI (SISCOM)
- Stereo electroencephalography (stereo EEG)
- Surgery performed in the MRI suite
- Laser interstitial thermal therapy for mesial temporal lobe epilepsy
- Neuromodulation, including responsive neurostimulation

Having that range of technology allows Mayo Clinic to meet the complex needs of patients. “These technologies all test the brain in different ways — structure, electrical activity, blood flow and metabolism. It’s best not to rely on one of these tests alone,” says Amy Z. Crepeau, M.D., a neurologist at Mayo Clinic in Arizona. “We can use a number of these imaging options together to determine where seizures originate when someone has uncontrolled epilepsy.”

Pinpointing seizure origin sites
High-density EEG uses as many as 256 electrodes to noninvasively capture seizure activity. “The abnormal surges in brain activity during a seizure — and often, even when a seizure is not happening — are small and can be difficult to pick up. High-density EEG can record smaller changes involving smaller areas of the brain. That gives us additional information that a routine EEG might miss,” Dr. Crepeau says.

SISCOM, developed by Mayo Clinic and used clinically since 2003, is an additional tool for localizing seizure origins (Figure 1). SISCOM provides precise measurement of blood flow during a seizure. Testing is performed in the epilepsy monitoring unit. When a seizure starts, a specially trained nurse immediately injects a tracer, and the patient is given a SPECT scan.

A second SPECT scan is performed when the patient isn’t having a seizure — typically, about 24 hours after the first scan. Radiologists perform a subtraction analysis that highlights how blood flow differs during a seizure versus at rest. These images are then superimposed on the patient’s MRI to allow the epilepsy neurologist and the neurosurgeon to identify where seizures originate.

If noninvasive tests don’t provide sufficient information, stereo EEG might be used. This procedure combines MRI and intraoperative neural navigation to map seizures originating in deeper brain areas (Figure 2, see page 4).

“We may have some idea of where the seizure originates, based on what the seizure does to the patient — for example, hand jerks,” Dr. Zimmerman says. “Computers that link the patient’s anatomy in real time to his or her MRI allow us to place as many as 20 very narrow electrodes into specific areas of the brain to localize seizure origin. Craniotomy isn’t required. We can cover large areas of the brain by inserting wires into extremely small holes.”

After the electrodes are placed, seizures are recorded over several days to determine where they start. “Although it is always preferable to

Figure 1. Axial and sagittal subtraction ictal SPECT coregistered to MRI (SISCOM) images show the location of seizure onset.
Mayo Clinic is among a handful of centers in the United States that offer fetoscopic repair of myelomeningocele. The procedure can provide surgical outcomes for the fetus that are similar to those of open surgery while lessening the risk of preterm birth.

“There’s a big learning curve for this minimally invasive surgery, which we have met through extensive training and simulations. We believe that the challenge is worthwhile to achieve more full-term deliveries of these babies,” says Edward S. Ahn, M.D., a neurosurgeon at Mayo Clinic in Rochester, Minnesota.

Open surgery has been the standard of care for prenatal myelomeningocele repair. Although the open procedure generally improves outcomes for children with myelomeningocele, it increases the risks of preterm birth and uterine rupture. Women who have open surgery for prenatal myelomeningocele repair must have a cesarean section for that pregnancy and all future pregnancies, as well as wait at least two years before becoming pregnant again.

“The objective of fetoscopic repair is to achieve the same outcomes for the babies but reduce maternal obstetric risks,” says Rodrigo Ruano, M.D., Ph.D., chair of Maternal and Fetal Medicine at Mayo Clinic’s campus in Minnesota. “After fetoscopic surgery these women will be able to have vaginal delivery during that pregnancy and any future pregnancies.”

**Fetoscopic Repair of Myelomeningocele: A Minimally Invasive Option**

Mayo Clinic also uses responsive neurostimulation devices, which continuously monitor brain activity and discharge stimulation as needed to stop a seizure when it occurs. As a lead participant in the approval process for responsive neurostimulation devices, Mayo Clinic has extensive experience with this treatment.

“These devices provide long-term recording of the patient’s brain activity. That allows us to change the level of stimulation or even to change a patient’s medication based on data, as opposed to relying on the patient’s memory of seizures,” Dr. Zimmerman says.

Chronic subthreshold stimulation of the cortex, which acts earlier than conventional neurostimulation devices to prevent seizure onset, is another treatment pioneered at Mayo. The levels of electrical stimulation used in subthreshold cortical stimulation are low enough to stop seizure initiation without causing loss of function in that part of the brain.

Research is underway at Mayo Clinic to improve the protocols for neuromodulation devices. Mayo Clinic researchers are also working to find new EEG biomarkers for better anatomical location of seizure origins.

“Research is a key aspect of our approach to clinical practice,” Dr. Sirven says. “All of our efforts focus on improving outcomes, both surgical and psychosocial, in these very complex patients.”
this strong collaboration,” Dr. Ruano says.

Myelomeningocele is generally diagnosed through routine fetal ultrasound during the second trimester of pregnancy. The surgery can be performed between 19 and 26 weeks of gestation. “We usually prefer to do the procedure at around 24 or 25 weeks, when the fetus is a little bit bigger,” Dr. Ahn says.

The fetoscopic procedure takes about 2.5 hours. General anesthetic is first given to the mother. That anesthetic relaxes the uterus and the fetus before the fetus receives intramuscular pain medication. Carbon dioxide is inserted into the uterus to improve visualization of the spinal defect. The repair is performed by inserting 2-millimeter instruments through tiny ports (Figure).

Babies who have prenatal myelomeningocele repair generally experience fewer complications than do babies who have postnatal treatment. Prenatal repair reduces the incidence of Chiari malformation, which can occur when cerebrospinal fluid leaks through the myelomeningocele.

“The Chiari malformation will not reverse without intervention,” Dr. Ruano says. “But we have an 80% to 90% chance of reversal if the myelomeningocele is fixed in utero.”

Chiari malformation can lead to hydrocephalus. “The increase in prenatal myelomeningocele repair has dramatically reduced the incidence of hydrocephalus in these babies,” Dr. Ahn says. “Only about 40% of babies with myelomeningocele require treatment for hydrocephalus, compared with 80% previously.”

Prenatal repair also prevents the spinal cord’s exposure to amniotic fluid, which may be toxic to the spinal cord. “In the long term, babies whose myelomeningoceles are closed prenatally tend to have better leg function,” Dr. Ahn says.

Mayo Clinic’s obstetric and pediatric specialists have experience caring for babies born with myelomeningocele. The Cerebral Palsy/Spina Bifida Clinic on the Minnesota campus coordinates care for children and teenagers with spina bifida.

“Mayo Clinic is structured to provide multidisciplinary care,” Dr. Ahn says. “From simple matters such as scheduling appointments to the routine conferring of specialists, everything is well coordinated.”

Nanotechnology: Potential Options for Glioblastoma Treatment

Mayo Clinic is developing ways to use nanoparticles to deliver anti-cancer therapy directly to glioblastomas (Figure, see page 6). The goal is to devise treatments that effectively target tumor-initiating cells while sparing normal brain cells.

“This technology is extremely promising. We have greater understanding of how these nanoparticles can better penetrate the brain and deliver knockout punches,” says Alfredo Quinones-Hinojosa, M.D., chair of Neurosurgery at Mayo Clinic in Jacksonville, Florida, and director of the Brain Tumor Stem Cell Research Laboratory.

Novel therapies for glioblastoma are urgently needed, as life expectancy after diagnosis is 14 to 15 months. Mesenchymal stem cells are an attractive potential drug carrier because they can bypass the blood-brain barrier, travel long distances within the brain, target migrating cancer cells and be modified to deliver anti-cancer agents to tumors.

Viruses, which also are being investigated as potential therapeutic vehicles, pose challenges associated with toxicity and immunogenicity. Nanoparticles are a potential alternative.

“We have observed that cancer cells have a high affinity for the uptake of the nanoparticles we have tested. At the same time, the nanoparticles quickly release their cargo, which improves efficacy,” says Hugo Guerrero Cazares, M.D., Ph.D., director of the Neurogenesis and Brain Tumors Laboratory at Mayo Clinic’s campus in Florida.

No opportunity wasted

With funding from the National Institutes of Health, Mayo Clinic is studying nanoparticles in vitro and in vivo using laboratory mouse

Figure. Illustration shows fetoscopic repair of a myelomeningocele.
models. One project involves using nanoparticles to modify adipose-derived mesenchymal stem cells to secrete anti-tumor proteins. The nanoparticle-engineered mesenchymal stem cell therapy can be delivered directly into the surgical cavity at the time of tumor resection. “It’s a wasted opportunity not to fight the cancer then and there, before we leave the operating room,” Dr. Quinones-Hinojosa says.

The project’s aims include determining whether nanoparticle-modified stem cells decrease glioblastoma proliferation and invasion in vitro and in vivo. The researchers will also assess the safety and efficacy of treatment with the modified stem cells in combination with targeted radiotherapy in mice with growing patient-derived glioblastomas.

“This technology is becoming much smarter as we develop it,” Dr. Quinones-Hinojosa says. “We have learned that these nanoparticles can be loaded with DNA, short interfering RNA and microRNA that will then target the molecular engines that allow cancer cells to migrate. We know the formulation of the most efficient nanoparticles as well as how to make these nanoparticles high throughput and store them for up to three years. Someday, we hope to use these nanoparticles off the shelf in the operating room.”

Unlike viruses, Mayo Clinic’s novel synthetic nanoparticles can carry many copies of different types of short interfering RNA within single particles. In a study published in the July 2019 issue of *Biomaterials*, the Mayo Clinic researchers demonstrated that short interfering RNA delivered by the nanoparticles can target several anti-glioblastoma genes simultaneously while avoiding healthy brain cells.

“That opens for us the possibility of combination short interfering RNA therapy, which might be crucial for effective cancer treatment and overcoming tumor resistance,” Dr. Guerrero Cazares says. “Glioblastoma is very heterogeneous — some part of the tumor might respond to a therapy and others won’t. We need to find the right combination of therapies to target all of these tumor pathways.”

**Exploring new ideas**

At Mayo Clinic, research and clinical practice are entwined. With patient consent, tumor tissue is donated to the laboratory for implantation and growth in laboratory mice. Individuals who donate tissue occasionally visit the laboratory; clinicians routinely interact with researchers to advance patient care.

“We work closely with patients and constantly explore new ideas with our surgical department,” says Rachel Sarabia Estrada, D.V.M., Ph.D., who assists with directing the Brain Tumor Stem Cell Research Laboratory. “We are very close to moving this technology to the clinic.”

“What makes Mayo Clinic thrive is the fact that with every discovery we make, we try to see first and foremost how it can benefit patients,” Dr. Quinones-Hinojosa adds. “We can’t take care of the needs of the patients unless we translate our discoveries from the lab back to patient care.”

**For more information**


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**Figure.** Mayo Clinic is using nanoparticles for both direct and cell-based delivery of anti-cancer therapy to glioblastomas. The direct delivery method uses a synthetic poly(beto-amino ester) (PBAE) nanoparticle delivery vehicle developed by Mayo Clinic in conjunction with Johns Hopkins University. The cell-based delivery method uses mesenchymal stem cells derived from the patient’s adipose tissue.
Research Highlights in Neurology and Neurosurgery

**Lumbosacral Radiculoplexus Neuropathy: Incidence and Association With Diabetes**

Lumbosacral radiculoplexus neuropathy is a monophasic illness characterized by microvasculitis with resultant ischemic nerve injury. Patients typically present with acute or subacute motor-predominant painful lower limb neuropathy; they often improve, although recovery is frequently protracted and incomplete. Lumbosacral radiculoplexus neuropathy is classified as having a diabetic and a nondiabetic form. However, it's unclear whether diabetes mellitus is a disease association or true risk factor for the neurological syndrome. Mayo Clinic researchers surveyed the medical records of residents of Olmsted County, Minnesota, between 2000 and 2015 to determine the incidence of lumbosacral radiculoplexus neuropathy and to test whether diabetes mellitus is a risk covariate for the neuropathy’s development. Of the 1,892 medical records reviewed, 59 individuals were identified as having lumbosacral radiculoplexus neuropathy. The incidence of that neuropathy in the population — 4.16 per 100,000 new cases a year — makes the neuropathy more common than other inflammatory neuropathies, such as Guillain-Barre syndrome, studied previously in the same population. In the recent study, individuals with diabetes mellitus had an eightfold higher risk of developing lumbosacral radiculoplexus neuropathy. However, prediabetes mellitus wasn't found to be a risk factor, suggesting that the neuropathy might not be caused directly by glycemic factors alone. The researchers conclude that diabetes mellitus is a major risk factor for lumbosacral radiculoplexus neuropathy, justifying the continued classification of the neuropathy into diabetic and nondiabetic forms.


**Measuring Tau in Living Former NFL Players**

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with a history of repetitive head impacts. Diagnosis involves the postmortem detection of a specific pattern of tau deposition with minimal amyloid-beta deposition. This pattern differs from those of other disorders, including Alzheimer’s disease. In a descriptive study led by Boston University, Mayo Clinic and collaborating institutions found that compared with control individuals with no history of traumatic brain injury, a group of living former National Football League (NFL) players with cognitive and neuropsychiatric symptoms had higher tau levels — but not elevated amyloid-beta levels—in brain regions affected by CTE. A total of 26 former players and 31 control individuals were included in the analysis. Study participants underwent positron emission tomography (PET). The symptomatic former NFL players had elevations in flortaucipir PET measurements of tau in the bilateral superior frontal, bilateral medial temporal and left parietal regions, all of which have been implicated in postmortem diagnoses of CTE. Although 35% of the symptomatic former NFL players had impaired delayed-recall scores on an objective memory test, they didn’t have higher amounts of amyloid-beta deposition than did control individuals, as measured by florbetapir PET. These findings suggest that the cognitive difficulties reported by former NFL players weren’t related to Alzheimer’s disease amyloid-beta deposition. The researchers note that further studies are needed to determine whether elevated CTE-associated tau levels can be detected in individual persons. (Stern RA, et al. Tau positron-emission tomography in former National Football League players. *New England Journal of Medicine*. 2019;380:1716.)

**Impact of 1p/19q Codeletion on Extent of Resection in Grade II Glioma**

Although benign, grade II glioma tends to progress to malignancy years after diagnosis. Previous studies have indicated that biomarkers such as 1p/19q codeletion status might influence the success of glioma resection, in particular affecting the survival benefit conferred by greater extent of resection. Mayo Clinic researchers have found indications that the survival impact of gross total resection in grade II glioma might be affected by 1p/19q codeletion status within the first five years after surgery, based on overall survival. Using the National Cancer Database, the researchers evaluated the records of all adults diagnosed with grade II glioma between 2004 and 2014. Among the 1,498 records studied, 47% lacked codeletion and 53% had codeletion. Kaplan-Meier modeling and univariate regression analyses indicated that gross total resection was significantly associated with greater five-year overall survival in both the non-codeletion and the codeletion groups. However, multivariate analysis incorporating adjuvant therapy status showed that the significance of gross total resection was retained only in the 1p/19q non-codeletion group after post-hoc adjustment. The results suggest that molecular diagnostics have potential clinical application in surgery outcomes. Larger, prospective studies are needed to clarify the validity of the reported observations and to determine how they would be best incorporated into optimizing the postoperative management of grade II glioma.


To read more about Mayo Clinic neurosciences research and patient care, visit [www.MayoClinic.org/medical-professionals](http://www.MayoClinic.org/medical-professionals).
Education 2019, 2020 and 2021 Neurology and Neurologic Surgery Continuing Medical Education Programs

2019 courses

November

- Mayo Clinic Cerebral Bypass and Advanced Neuroendovascular Course 2019
  Nov. 4-14, 2019
  Mayo Clinic, Rochester, Minn.
- Neuroscience Convergence 2019
  Nov. 7-9, 2019
  The Ritz-Carlton, St. Thomas, U.S. Virgin Islands
- Parkinson’s Disease and Other Movement Disorders 2019
  Nov. 15-16, 2019
  Mayo Clinic Franke Education Center, Phoenix

February

- Mayo Clinic Multidisciplinary Spine Care Conference 2019
  Nov. 22-23, 2019
  The Ritz-Carlton, Amelia Island, Amelia Island, Fla.

2020 courses

January

- Electroencephalography (EEG), Electromyography (EMG) & Neurophysiology in Clinical Practice 2020
  Jan. 26-31, 2020
  Mayo Clinic Franke Education Center, Phoenix

February

- 8th Annual Acute Care of the Complex Hospitalized Patient for NPs & PAs 2020
  Feb. 12-15, 2020

March

- 3rd Annual Mayo Clinic Advances and Innovations in Complex Neuroscience Patient Care: Brain and Spine 2020
  Feb. 27-29, 2020
  Enchantment Resort, Sedona, Ariz.

April

- Advances in Brachial Plexus Reconstruction: A Surgical Skills Course 2020
  April 23-25, 2020
  Mayo Clinic, Rochester, Minn.

October

- 12th International Conference on Frontotemporal Dementias 2020
  Oct. 7-10, 2020
  Hilton Minneapolis, Minneapolis

November

- Neuroradiology: Practice to Innovation 2020
  Nov. 9-13, 2020
  The Ritz-Carlton, Grand Cayman, Cayman Islands

2021 courses

February

- Practical Neuroradiology: Excellence Through Evidence and Guidelines
  Feb. 7-11, 2021
  Four Seasons Resort and Residence, Whistler, British Columbia, Canada

March

- 4th Annual Mayo Clinic Advances and Innovations in Complex Neuroscience Patient Care: Brain and Spine 2021
  March 4-6, 2021
  Enchantment Resort, Sedona, Ariz.

Information and registration

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Expediting Patient Referrals to Mayo Clinic

Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease

Contact Us

Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.