Quantifying Neuroimaging: A Revolution in Patient Care

Mayo Clinic is at the forefront of imaging innovations that are upending neurological care. Aligned with the enterprise’s commitment to evidence-based medicine, these innovations apply quantifiable methods to neuroimaging, for individualized prognosis and treatment of brain tumors and epilepsy.

“This is going to revolutionize how we practice neuroimaging. The benefits for patients will be phenomenal,” says Bradley J. Erickson, M.D., Ph.D., director of the Radiology Informatics Laboratory at Mayo Clinic in Rochester, Minnesota.

The data-centered approach includes:
• Applying artificial intelligence to extract maximum information from MRIs of brain tumors
• Building mathematical models to predict tumor progression
• Using sophisticated functional imaging to precisely locate seizure origin sites in the brain.

“Imaging already drives what’s done daily in the clinic. But clinicians may not have all the tools necessary to help navigate individualized decisions. The power of these quantifiable approaches is that they can be applied to individual patients in ways that would otherwise be unattainable,” says Kristin R. Swanson, Ph.D., director of the Mathematical Neuro-Oncology Laboratory at Mayo Clinic in Phoenix/Scottsdale, Arizona.

Informatics to optimize cancer treatment
Applying modern machine learning methods to medical images has the potential to substantially improve brain tumor diagnosis, particularly prior to tissue-based diagnosis. In cases of glioma, an increasingly important aspect of diagnosis is the identification of molecular biomarkers, which can be used to group diffuse gliomas that have similar clinical behavior, response to therapy and outcome.

Mayo Clinic’s Radiology Informatics Laboratory recently succeeded in identifying the IDH1, 1P19Q and TERT glioma markers from routine MRI data, with 90% to 95% accuracy. “That’s far beyond what any human visual system can do,” Dr. Erickson says. The laboratory’s similar success identifying MGMT methylation status — another important glioma biomarker — was described in the October 2017 issue of the Journal of Digital Imaging.

Large data sets are used to train deep-learning algorithms to predict genomic patterns in tumors. “These algorithms seem to be able to identify textures or other properties of images that can be subtler than what we can visually perceive,” Dr. Erickson says.

Additional investigations focus on what this imaging can reveal about tumor biology. “We can tell that in some cases of IDH1 mutation, at least some of the MRI signal is coming from just outside the tumor margin. That’s probably where tumor cell invasion is occurring,” Dr. Erickson says. “Maybe those cells have a different physiology that affects how they resist the tumor invasion. The imaging may be reflecting something we don’t yet understand about the tumor biology. Eventually, imaging may help us determine whether a patient will respond to a certain treatment.”

Mathematical models are other tools in these efforts. Using large patient-centric data sets, the Mathematical Neuro-Oncology Laboratory...
Figure 2. A. MRI shows a brain tumor. B. Colored areas indicate portions of the image that a Mayo Clinic algorithm finds important for determining whether the tumor is IDH mutant. The colored areas don’t match the area of signal abnormality, which may reflect microinvasion as a signal of IDH wildtype versus mutant.

Pinpointing seizure focus

Mayo Clinic has developed quantifiable imaging to identify seizure focus, paving the way for treatment for people with medically intractable epilepsy that is multifocal or poorly localized. “We are able to provide options for people with the most challenging cases of epilepsy,” says Erik H. Middlebrooks, M.D., a neuroradiologist at Mayo Clinic in Jacksonville, Florida.

One of those options, deep brain stimulation (DBS), was recently approved by the Food and Drug Administration for epilepsy treatment. The target of DBS — the anterior nucleus of the thalamus (ANT) — is difficult to visualize in standard MRI sequences. Mayo Clinic has extensive experience with DBS and has developed imaging methods to better guide the procedure for optimal outcomes.

“When examining the existing clinical trials of DBS in epilepsy, off-target DBS placement is a real concern. The neuroimaging technology that we have developed allows us to be more accurate in electrode placement and to improve the programming of the devices to prevent seizures,” Dr. Middlebrooks says.

In the August 2018 issue of Neurosurgical Focus, Mayo Clinic researchers described a novel use of the fast gray matter acquisition T1 inversion recovery MRI sequence to delineate the mammillothalamic tract for direct targeting of the ANT (Figure 3). In a pilot study in the same Neurosurgical Focus issue, the researchers used functional MRI to demonstrate that successful ANT DBS in people with epilepsy correlated with increased connectivity in the default mode network and potential inhibition of the hippocampus — suggesting a potential mechanism of ANT DBS.

“We are very excited about the current DBS research taking place at Mayo Clinic. The field of brain ‘connectomics’ continues to revolutionize our understanding of the brain, and these developments are providing us important clues about which patients may benefit from DBS or other forms of neuro-modulation,” Dr. Middlebrooks says.

Another imaging innovation developed at Mayo Clinic is ictal single-photon emission computerized tomography (SPECT), which compares brain imaging taken during a seizure and at baseline. The baseline activity is subtracted from seizures to create images that can reveal seizure origin locations. Testing is performed in the epilepsy monitoring unit.

“Mayo remains fairly unique in offering ictal SPECT,” says Benjamin (Ben) H. Brinkmann, Ph.D., a biomedical engineer in the Epilepsy and Neurophysiology Laboratory at Mayo Clinic’s campus in Minnesota.

Morphometric MRI analysis (MAP), also developed at Mayo Clinic, can detect the subtle signs of focal cortical dysplasia. As described in the February 2018 issue of Epilepsy Research, MAP uses voxel-by-voxel comparisons between patient MRIs and a normative sample to detect abnormal thickening in cortical brain matter and abnormal blurring of the gray matter-white matter border.

“Those signs of focal cortical dysplasia are very difficult to detect otherwise,” Dr. Brinkmann says.

Stereo-electroencephalography (EEG), in which multiple electrodes are surgically
implanted in the brain, can determine the source of epileptic activity by identifying the electrodes that are activated during a seizure. “Stereo-EEG imaging allows us to sample the deep brain areas — the cingulum, the insula — that we just couldn’t record from before,” Dr. Brinkmann says.

Mayo Clinic’s imaging expertise rests on the enterprise’s multidisciplinary approach, in which neurologists, neurosurgeons, neuroradiologists and neuropsychologists collaborate to improve patient care. “As neuroradiologists, we are an integral part of the multidisciplinary team,” Dr. Middlebrooks says. “Imaging has become a pivotal diagnostic tool in the neurosciences and continues to be one of the key predictors of seizure freedom.”

For more information


**Objective Testing for Sports-Related Concussion**

Despite increased awareness of the dangers of sports-related concussion, most young athletes aren’t routinely evaluated for that traumatic brain injury. The Mayo Clinic Concussion Check Protocol can be used by parents or other adults on the sidelines to quickly assess whether a young athlete should be removed from play.

“In less than four minutes, these tests can help detect whether an individual has been concussed,” says David W. Dodick, M.D., a neurologist and the director of the concussion program at Mayo Clinic in Phoenix/Scottsdale, Arizona. “We know it’s not practical or feasible at this time to put a health care provider on the sidelines of every youth game and practice. But there are objective tests, which can be done by a trained adult, that can consistently and reliably detect whether a concussion may have occurred.”

More than half of concussions aren’t reported. Athletes may not recognize the symptoms or may be reluctant to speak up and risk removal from play. Even when an athlete is taken out of play after a big hit, a standard sidelines evaluation can miss a concussion.

“The exam has to be concussion focused and objective,” Dr. Dodick says. “A lot of sidelines evaluations are very subjective. In addition, even in the best of circumstances when a trained health care professional is examining the athlete, he or she may interpret a test differently than the person who performed a baseline examination. And some of the signs considered typical — such as the ability to stand on one leg — may not be abnormal even if there is a concussion, or may be abnormal when there isn’t a concussion.”

Mayo Clinic’s Concussion Check Protocol is printed on a small card. The three basic steps are:

- **Recognize and Remove** — Watch for concerning hits or signs of concussion, and remove the player.
- **Memory Assessment** — Ask the athlete the orientation questions listed on the back of the card.
- **King-Devick Test** — Give the athlete this two-minute test of eye movement.

Athletes who fail any of these steps should be removed from play until cleared by a medical professional.

The concussion check protocol requires testing each athlete at the start of the season to provide a baseline for comparing subsequent sidelines testing. A Mayo Clinic study comparing the results of preseason and postseason King-Devick tests found that concussion hadn’t been recognized in 10% of the athletes whose test results were abnormal at the end of the season.
Anthony L. Ritaccio, M.D., a neurologist at Mayo Clinic in Jacksonville, Florida, answers questions about Mayo Clinic’s approach to medically refractory epilepsy. The National Association of Epilepsy Centers rates all three Mayo Clinic campuses as Level 4 epilepsy centers — the highest rating, given to centers that provide the most-complex forms of intensive neurodiagnostic monitoring as well as extensive medical, neuropsychological and psychosocial treatment. Level 4 centers also offer a complete evaluation for epilepsy surgery and a broad range of surgical procedures.

Q: What options can Mayo Clinic offer to the 40% of people with epilepsy whose seizures don’t respond to medication?
Surgical resection is a potentially curative option, if the seizure origin site is identified. In addition to utilizing stereo-electroencephalography, we are able to use imaging and brain-mapping techniques developed at Mayo Clinic to make that determination. (See related story on page 1.)

Q: How does Mayo Clinic identify eloquent tissue in patients undergoing resection?
We are proponents of awake craniotomy to avoid postoperative deficits. At Mayo Clinic in Florida,
we perform on the order of 50 awake brain surgeries a year, for both epilepsy and tumor resection. We also have a unique intraoperative grid, developed at the Jacksonville campus of Mayo Clinic, that can surround small areas of the brain to identify seizure origin location. We are committed to constantly innovating devices to help make functional brain mapping more reliable.

**Q: What other technology is in development for functional brain mapping?**

With a grant from the National Institutes of Health (NIH), we are studying an innovative mapping technology that avoids applying electricity to the brain. This passive functional mapping uses an electrode that has been surgically implanted in the brain to capture electrocorticographic broadband gamma signals. Broadband gamma activity has been shown to be a reliable indicator of neuronal activity directly underneath an electrode. We record that activity while the patient listens to some short stories, and while the patient is at rest. Analyzing that data allows us to passively map eloquent tissue.

**Q: What options are available for patients who aren’t surgical candidates because the tumor focus is in eloquent tissue?**

We have extensive experience with implanted neuromodulatory devices that detect abnormal electrical activity and interrupt seizures before patients experience them. Data from the devices is streamed to the cloud, which allows us to monitor our patients’ seizures.

**Q: How does Mayo Clinic’s multidisciplinary approach facilitate the management of medically refractory epilepsy?**

Our neurologists, neurosurgeons and neuroradiologists work as a team to provide the latest imaging technology and surgical techniques. We have enormous collective experience evaluating people with intractable epilepsy for higher order therapies, both surgical and neuromodulatory. As a Level 4 center, Mayo Clinic is able to offer the panoply of services that these patients need.

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**Preserving Vision, Easing Headaches: Timely Multidisciplinary Care for Idiopathic Intracranial Hypertension**

Mayo Clinic’s cerebral spinal fluid (CSF) dynamics clinic provides a multidisciplinary, specialized approach to the management of idiopathic intracranial hypertension (IIH). Within a few days, patients can see a neurologist and neuro-ophtalmologist, have diagnostic testing, and see a neurosurgeon if needed. Timely diagnosis and treatment are essential for the optimal treatment of IIH.

“We have multiple specialists working side by side and early on to coordinate this care,” says Jeremy K. Cutsforth-Gregory, M.D., a neurologist at Mayo Clinic in Rochester, Minnesota, who leads the CSF dynamics clinic. That group also provides a team approach to care for normal-pressure hydrocephalus and spontaneous CSF leaks.

IIH is often misdiagnosed, and standard surgical treatment with a shunt frequently requires one or more re-operations. Mayo Clinic has experience with sophisticated imaging and lumbar puncture to confirm the diagnosis, as well as venous sinus stenting for treatment.

Most people with IIH are women between the ages of 15 and 50. “Up to 40% of patients with this condition can have permanent vision loss,” says John J. Chen, M.D., Ph.D., a neuro-ophthalmologist at Mayo Clinic’s campus in Minnesota. “With early and accurate treatment, we can preserve their vision. That’s why it is so important for them to be seen and treated in a timely manner.”

**Accurate diagnosis and stepwise treatment**

At Mayo’s CSF dynamics clinic, neurologists and neuro-ophtalmologists work together to confirm the diagnosis of IIH. The results of MRI, magnetic resonance venography (MRV) and lumbar puncture are carefully evaluated to exclude a diagnosis of tumor, venous sinus thrombosis, infection or inflammation.

“We find that as many as 40% of patients referred to us for IIH may not actually have the condition,” Dr. Chen says. “A lot of patients are given a diagnosis of IIH based on having headaches and a single, spurious lumbar puncture that shows elevated pressure. However, the lumbar puncture might have been done in the wrong position or while the patient was not...
appropriately relaxed. Also, what has previously been considered an elevated opening pressure can be seen in normal patients.

Once the diagnosis of IIH is confirmed, initial treatment focuses on lowering intracranial pressure to relieve papilledema (Figure 1). Depending on the degree of papilledema, medications such as acetazolamide might be tried. If the IIH is fulminant or medication fails to adequately reduce pressure, surgery is recommended.

The classic surgical treatment involves the implantation of a shunt. Although shunts can relieve pressure and papilledema, and sometimes headaches, they often clog or malfunction. “We can almost guarantee that patients will have a shunt failure within a handful of years — which means repeat surgeries or, at the very least, multiple scans and testing to prove that the shunt is still working,” Dr. Cutsforth-Gregory says.

To avoid that scenario, Mayo Clinic often uses venous sinus stenting as a surgical option (Figure 2). The procedure involves inserting a catheter into the venous sinus and measuring the pressure above and below the transverse sinus stenosis that’s typically associated with IIH. If a significant pressure gradient is detected, a stent is placed.

“The gradient disappears, and intracranial pressure is normalized in a nontraumatic way.

The papilledema almost always improves or resolves,” says Giuseppe Lanzino, M.D., a neurosurgeon at Mayo Clinic’s campus in Minnesota.

Managing headaches and obesity

Two-thirds of patients continue to have headaches after intracranial pressure is normalized and papilledema is resolved. The CSF dynamics clinic uses its multidisciplinary approach to manage the next phase of those patients’ care.

“Headache is often the major complaint of patients with IIH. Once we’ve addressed the risk of vision loss, we want to help patients with their headaches,” Dr. Cutsforth-Gregory says.

About two-thirds of these headaches are migraines. “We use the standard migraine approaches, up to and including Botox. Ultimately, most of our patients have fewer headaches and improved quality of life,” Dr. Cutsforth-Gregory says.

Because about 90% of people with IIH are obese, dietitians and nutritionists are often involved. “The initial intervention to protect patients’ vision is really a bridge to their losing weight to prevent IIH from recurring,” Dr. Cutsforth-Gregory says. In addition, Mayo Clinic endocrinologists help manage care for patients with polycystic ovary syndrome, which can occur with obesity and IIH.

To learn more about the optimal treatment of IIH, Mayo Clinic is participating in the Surgical Idiopathic Intracranial Hypertension Treatment Trial (SIGHT), a randomized, multicenter clinical trial comparing treatments for IIH involving moderate to severe vision loss. Study participants will receive medical therapy, medical therapy plus optic nerve sheath fenestration or medical therapy plus cerebral spinal fluid shunting.

Other research efforts include a clinical trial investigating the use of MR elastography (MRE) to evaluate raised intracranial pressure. “We think raised pressure will cause the brain to become stiffer. MRE might provide a noninvasive alternative to lumbar puncture for detecting raised intracranial pressure,” Dr. Chen says.

An additional project, in conjunction with NASA, is investigating why astronauts — who aren’t obese — often develop papilledema in outer space. “We’re looking at astronauts and more typical patients with IIH to see if there’s a genetic polymorphism that they might share that predisposes them to papilledema. Not all people who are obese get papilledema, and we’d like to find a clear cause,” Dr. Chen says.

“The field is evolving — it’s pretty exciting,” he adds. “Having a plethora of research collaborators helps us advance the field, while our clinical approach through the CSF dynamics clinic helps us to provide optimal care for patients.”

Figure 1. Image shows grade 4 papilledema in a 27-year-old woman with idiopathic intracranial hypertension.

Figure 2. Magnetic resonance venography images show transverse venous sinus stenosis (arrows) in a 30-year-old woman with obesity and idiopathic intracranial hypertension. She subsequently underwent uncomplicated angioplasty and stenting of the right transverse sinus, which normalized a pressure gradient across the transverse-sigmoid sinus junction.
Research Highlights in Neurology and Neurosurgery

Checkpoint Inhibitors and Neurological Immune-Related Adverse Events
The expanding use of immune checkpoint inhibitors highlights the importance of accurate diagnosis and prompt management of neurological immune-related adverse events. These events may present atypically and with overlapping signs and symptoms; optimal management is unknown. Comprehensive phenotypic characterization and long-term outcome data would therefore be clinically useful. Mayo Clinic researchers and colleagues at Massachusetts General Hospital have described the clinical spectrum, management and outcomes of neurological immune-related adverse events in a large cohort of patients who received immune checkpoint inhibitors. Twenty-eight (1.5%) of the 1,851 patients who received immune checkpoint inhibitors at Massachusetts General from 2011 to 2017 had grade 3 or 4 neurological immune-related adverse events. The rate of adverse events was significantly higher with the use of anti-CTLA-4 therapy alone or in combination with anti-PD-1 therapy compared with anti-PD-1 monotherapy. Most of the adverse events (68%) occurred within the first one to four cycles of immune checkpoint inhibitor therapy. (Dubey D, et al. Immune checkpoint inhibitor-related neurological adverse events: Clinical spectrum, management and outcomes. Presentation at: American Academy of Neurology Annual Meeting; 2019; Philadelphia, Pa.)

Tissue Biomarker for Patients With Parkinson's Disease
Mayo Clinic previously reported that submandibular gland biopsy detects Lewy-type synucleinopathy (LTS) in patients with early and advanced Parkinson’s disease (PD). Mayo Clinic researchers recently found that repeat biopsies can demonstrate increased LTS density over time. The researchers performed repeat biopsies on seven patients with PD who previously underwent bilateral transcutaneous needle biopsies of the submandibular gland. Staining with a monoclonal antibody was performed. All study participants had sufficient submandibular gland tissue on at least one side; 12 of the 14 glands biopsied had sufficient tissue for assessment. All 12 glands were positive for LTS, with an average fourfold increase in LTS density. The study is the first to demonstrate that bilateral biopsies can be performed safely and that LTS density increases over time. (Adler C, et al. Repeat submandibular gland biopsies as a progression marker in Parkinson’s disease. Presentation at: American Academy of Neurology Annual Meeting; 2019; Philadelphia, Pa.)

Glioma-Related Seizures and Tumor Molecular Markers
Gliomas are commonly associated with the development of seizures; the two conditions sometimes share common pathogenic mechanisms. Mayo Clinic researchers have found that glioma-related preoperative seizures may be more closely associated with tumor molecular markers than with glioma grade or histopathology. In a prospective cohort study, the researchers gathered clinical data from 68 patients with glioma. The presence of glioma-related preoperative seizures, electroencephalography, the characteristics of patients’ tumors and postoperative seizure freedom were assessed. Forty-six of the 68 patients had glioma-related preoperative seizures; 31 of the 46 (67%) had seizure freedom at a mean follow-up of nine months after surgery. Neither the presence of glioma-related preoperative seizures nor postoperative seizure freedom differed by the patients’ age or sex, or by the glioma’s location, grade or histopathological subtype. However, patients with IDH1 mutation had an increased likelihood of preoperative seizures and postoperative seizure freedom. (Feyissa A, et al. Glioma-related seizures: Beyond glioma grade and histopathology. Presentation at: American Academy of Neurology Annual Meeting; 2019; Philadelphia, Pa.)

Imaging Factors Related to Cognitive Aging
Three anatomically distinct regions play an important role in cognitive aging: entorhinal cortex, parietal lobe and frontal lobe. The entorhinal cortex is susceptible to aging and pathology; the parietal lobe is an integrative functional hub; and the frontal lobe may reflect early cerebrovascular disease. Mayo Clinic researchers have identified imaging biomarkers in those regions that capture unique aspects of cognitive aging. The researchers analyzed imaging from 796 participants in the population-based Mayo Clinic Study of Aging to identify protective and risk factors for entorhinal cortex thickness, superior parietal lobe thickness and diffusion-tensor imaging-based genu corpus callosum (GCC) fractional anisotropy. Among study participants ages 30 to 49, higher GCC fractional anisotropy was related to greater total brain volume, and higher entorhinal cortex thickness was related to better memory performance. Among 50- to 64-year-olds, higher imaging measures were related to lower current metabolic and vascular risk, greater total brain volume, higher global cognition, lower history of smoking and alcohol misuse, and higher prevalence of marriage. People ages 65 and older with high imaging measures had a higher prevalence of marriage and lower history of alcohol misuse compared with young adults with high imaging measures. (Neth B, et al. Factors related to higher neurobiological capital across the lifespan: Mayo Clinic Study of Aging. Presentation at: American Academy of Neurology Annual Meeting; 2019; Philadelphia, Pa.)

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

2019 courses

**September**
11th Annual Stroke and Cerebrovascular Disease Review 2019
Sept. 26-28, 2019
The Ritz-Carlton Amelia Island, Amelia Island, Fla.

**October-November**
4th Annual Epilepsy and EEG in Clinical Practice 2019
Oct. 31-Nov. 2, 2019
The Ritz-Carlton Orlando Grande Lakes, Orlando, Fla.

**November**
Mayo Clinic Cerebral Bypass and Advanced Neuroendovascular Course 2019
Nov. 4-14, 2019
Mayo Clinic, Rochester, Minn.

Mayo Clinic Convergence Neuroscience 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

2020 courses

**January**
Electromyography (EMG), Electroencephalography (EEG), & Neurophysiology in Clinical Practice
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**
Multidisciplinary Neuro-Oncology Symposium: Updates in Medical and Surgical Management of Brain Tumors 2020
March 6-7, 2020
Wyndham Grand Orlando Resort Bonnet Creek, Orlando, Fla.

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

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Website: https://ce.mayo.edu/neurology-and-neurologic-surgery

Expedited 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

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