## Contents

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
<td>Chairman’s Letter</td>
</tr>
<tr>
<td>04</td>
<td>Neurological Institute Overview</td>
</tr>
<tr>
<td>08</td>
<td>Highlights from Our Centers</td>
</tr>
<tr>
<td></td>
<td>EEG-Correlated fMRI: A Promising Tool in the Multimodal Evaluation of Refractory Epilepsy</td>
</tr>
<tr>
<td></td>
<td>Rollout of Research and Tech Innovations Takes the Fight to Athletic Brain Injuries</td>
</tr>
<tr>
<td></td>
<td>Visualizing Glioblastomas Intraoperatively as a Way to Maximize Resection</td>
</tr>
<tr>
<td></td>
<td>Making Freedom from Disease Activity an Achievable Goal in Multiple Sclerosis</td>
</tr>
<tr>
<td></td>
<td>Taking on Subarachnoid Hemorrhage Across Multiple Research Fronts</td>
</tr>
<tr>
<td>22</td>
<td>Research and Clinical Innovation</td>
</tr>
<tr>
<td></td>
<td>Spine Carepath Embeds Evidence-Based Care Strategy into the EMR</td>
</tr>
<tr>
<td></td>
<td>Using Advanced Neuroimaging to Pinpoint the Singularities of Blast-Related TBI</td>
</tr>
<tr>
<td></td>
<td>Study Charts New Territory in Profiling Predictors of Obstructive Sleep Apnea in Epilepsy</td>
</tr>
<tr>
<td></td>
<td>A New Tool for Alzheimer Evaluation — And Counseling to Support It</td>
</tr>
<tr>
<td>26</td>
<td>Neurological Institute Leadership and Staff</td>
</tr>
<tr>
<td>32</td>
<td>Locations</td>
</tr>
<tr>
<td>32</td>
<td>Cleveland Clinic Information and Resources</td>
</tr>
</tbody>
</table>

Cover image: Visualization of a glioblastoma resection margin under blue light following use of 5-aminolevulinic acid demonstrates the presence of residual tumor cells (pink). See article on pages 16-17.
Dear Colleagues,

Recent issues of our Year in Review have highlighted the Neurological Institute’s expansion in the past few years. From the creation of new disease-specific centers to the opening of our Lou Ruvo Center for Brain Health location in Las Vegas to the expansion of specialized services at our community hospitals and our Florida site, our reach has grown substantially.

In view of this, a key focus for the Neurological Institute in 2012 was on maximizing connectivity and standardizing care at the highest level across our many treatment settings. A big part of these efforts are the carepaths we have developed for a growing number of neurological conditions. Carepaths are evidence-based care models that are embedded in the electronic medical record (EMR) to guide clinicians through the care process for a specific condition. The aim is to reduce harmful or needlessly expensive practice variation and ensure evidence-based care for all patients.

Concussion and spine care are among the multiple conditions for which we have developed carepaths, as discussed on pages 14-15 and 23. And our sights are set on a carepath for relapsing-remitting multiple sclerosis once we achieve our goal of forging consensus on an operational definition of disease-free status, as detailed on page 19.

The abovementioned piece on concussion care is a good example of the centrality of technology to these efforts to standardize evidence-based care across multiple settings. This past year saw wide deployment of the Cleveland Clinic Concussion (C3) mobile application for baseline function testing in thousands of young athletes across Northeast Ohio who now can be assessed for concussion with the C3 app immediately after a head injury during play.

In addition to reducing variability of care, our carepaths are integrated with our Knowledge Program© interactive database to allow us to mine the EMR and continually monitor outcomes. This gives us an unprecedented window into which treatments are working, which workups are truly needed and similar issues that will fuel tomorrow’s clinical innovations — the stuff of future issues of this publication.

For now, I invite you to review the 2012 developments that we spotlight in these pages, which also include the following:

- Pioneering work combining EEG and fMRI to better understand the brain regions involved in epileptic activity
- Initial results from the most comprehensive study to date of chronic traumatic encephalopathy in professional fighters
- Our leading role in a trial of 5-ALA to enhance intraoperative visualization of glioblastomas during resection
- A confluence of research efforts to blunt the impact of subarachnoid hemorrhage

I welcome your comments and ideas for potential collaboration in the year ahead.

Michael T. Modic, MD, FACR
Chairman, Cleveland Clinic Neurological Institute
modicm1@ccf.org
Neurological Institute Overview

The multidisciplinary Cleveland Clinic Neurological Institute includes more than 300 medical, surgical and research specialists dedicated to the diagnosis, treatment and rehabilitation of adult and pediatric patients with disorders of the brain and central nervous system.

The institute is anchored by specialized, disease-specific centers. Each center incorporates a multidisciplinary approach to the diagnosis and management of a particular disease or group of diseases, combining the expertise of physicians and allied health professionals to foster collaboration and improve patient access.

The institute comprises four departments — Neurology, Neurological Surgery, Psychiatry and Psychology, and Physical Medicine and Rehabilitation — that integrate resident training, academics and research.

Additional diagnostic tools are found in our epilepsy monitoring units, sleep laboratories, neuropsychological testing facilities, electromyography laboratory and cutaneous nerve laboratory.

The Latest Treatment Modalities
Patients find leading-edge treatment options at the Neurological Institute, where we continue to advance such innovations as deep brain stimulation, laser interstitial thermal therapy for brain tumors, epilepsy surgery, stereotactic spine radiosurgery, endovascular treatment of cerebral aneurysms and vascular malformations, and neuroendoscopy. Joint Commission certification as a Primary Stroke Center and accreditation by the American Academy of Sleep Medicine are just two reflections of our commitment to provide the most advanced, highest-quality care to our patients.

Relevant Research
We conduct research directly related to conditions experienced by our patients, including translational research and clinical trials of drug and device interventions. In 2011, some 229 clinical research projects involving 6,227 patients were under way in the Neurological Institute. Neurologically based research grants and contract awards totaled nearly $12 million.

Convenient Care in the Community
We are committed to making access to world-class care convenient for all patients. Neurological Institute services are available at Cleveland Clinic community hospitals and family health centers throughout Northeast Ohio, as well as in Nevada and Florida. As a result, patients can easily...
access specialists who treat the most complex neurological conditions. This approach is predicated on the notion that those we serve are entitled to a uniformly high level of care and that location should never be an issue.

Key components in our regional network include:

- Cleveland Clinic Neurological Institute at Lakewood Hospital and Cleveland Clinic Neurological Institute at Hillcrest Hospital, providing comprehensive services throughout the community
- 120 acute inpatient rehabilitation beds at facilities across Northeast Ohio
- A team of more than 750 specialty-trained therapists at more than 45 locations offering physical medicine and rehabilitation services
- Cleveland Clinic at Home, within the Center for Home Care and Community Rehabilitation, bringing in-home and distance healthcare to individuals in an expansive area encompassing 14 Ohio counties and providing home infusion/pharmacy services in eight states

Integrated Nursing

Nurses in the Neurological Institute rank as respected members of the care team. They are encouraged to offer their input to physicians and administrators and to engage in problem-solving and process improvement. Patients benefit from this integration through improved coordination of care and shared provider goals.

Nurses with at least two years’ experience in the institute can aspire to certification in neuroscience nursing. These subspecialists staff areas such as the neurological intensive care unit and neurological stepdown units that treat the most complex patients.

Each November, Cleveland Clinic’s “Innovations in Neuroscience” conference convenes in Cleveland. One of its goals is to foster increased provider collaboration among attendees, which include nurses, physician assistants and medical assistants.

<table>
<thead>
<tr>
<th>Neurological Institute Volume, 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Total outpatient visits</td>
</tr>
<tr>
<td>Admissions</td>
</tr>
<tr>
<td>Inpatient days</td>
</tr>
<tr>
<td>Procedures</td>
</tr>
<tr>
<td>Surgical/interventional</td>
</tr>
<tr>
<td>Neuroimaging studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Research Funding, 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant and contract research dollars funding neurological investigations in the Neurological Institute totaled nearly $12 million.</td>
</tr>
<tr>
<td>New clinical research projects</td>
</tr>
<tr>
<td>Total active clinical research projects</td>
</tr>
<tr>
<td>Staff leading clinical research projects</td>
</tr>
<tr>
<td>New patients enrolled in clinical research projects</td>
</tr>
<tr>
<td>Total patient enrollment in clinical research projects</td>
</tr>
<tr>
<td>Federal grants and contracts</td>
</tr>
<tr>
<td>Nonfederal grants and contracts</td>
</tr>
</tbody>
</table>

Pioneering the Collection of Data and Outcomes

The Neurological Institute’s Knowledge Program® has captured data from more than 1 million self-administered patient questionnaires. One of the world’s first interactive clinical patient databases, the Knowledge Program is demonstrating its value as it evolves, with collection and correlation of electronic information on patient health status, quality of life and outcomes.

We are aggregating this patient-generated data with information from other sources — such as imaging results, information collected during patient encounters and data from our growing number of condition-specific clinical carepaths — to optimize clinical decision-making, quality improvement and research opportunities.

All these data are accessible to physicians through an interface with the patient’s electronic medical record. The Knowledge Program is proving to be among our most constructive tools for delivering individualized care to improve outcomes and quality of life, in line with Cleveland Clinic’s guiding principle: Patients First.
Schematic illustration of an EEG spike predominantly involving EEG electrodes recording from the left frontal and central regions of the patient’s brain. During simultaneously recorded EEG/fMRI, correlation is sought between the time of EEG spike and the brain activation pattern.

Schematic illustration of cortical activation revealed with functional MRI within the left basal frontal lobe and anterior insula. Areas of interest are superimposed on sagittal and axial images of the patient’s structural MRI. Red indicates activation; green indicates deactivation.

The use of scalp electroencephalography (EEG) simultaneously with functional magnetic resonance imaging (fMRI) allows measurement of electrical brain activity in correlation with the hemodynamic response in the brain. Known as EEG-correlated fMRI, or simply EEG/fMRI, this noninvasive multimodal neuroimaging technique is being used at Cleveland Clinic’s Epilepsy Center in an effort to better understand the pathophysiologic mechanisms and patterns of epileptic activities, particularly the generators of interictal discharges (spikes).

Cleveland Clinic is one of only a few clinical centers in the United States to employ EEG/fMRI, which currently serves as a research tool in the study of brain regions involved at the time of epileptic activity.

Eventually, EEG/fMRI may become clinically valuable as a multimodal tool for evaluating individuals with epilepsy, including patients whose seizures are difficult to control with medications and in whom identifying the seizure focus is challenging. Localizing the brain regions that show changes in neuronal activity during interictal spikes through the use of fMRI may one day enhance the evaluation of surgical candidates and may help guide surgical strategies in patients with refractory seizures.

The software used to execute simultaneous EEG and fMRI has been approved by the U.S. Food and Drug Administration for research applications. Cleveland Clinic is in a unique position to validate the clinical use of EEG/fMRI because of the high volume of evaluations and surgeries it performs in patients with seizures refractory to medications.

EEG-Correlated fMRI: A Promising Tool in the Multimodal Evaluation of Refractory Epilepsy

A Spatiotemporal Snapshot of Brain Activity

Integrating data obtained from EEG/fMRI may provide a spatiotemporal snapshot of brain activity that is not available through either modality alone (see images on facing page). With EEG, temporal resolution is excellent because it directly measures electrical activity in the brain, but spatial resolution is poor. Therefore, the accuracy of EEG in localizing the neuronal source from measurements of voltages at the scalp is limited. In contrast, spatial localization of brain activity is much better with fMRI, but temporal resolution is poor. These differing profiles make the two techniques complementary for measuring brain function.

With EEG/fMRI, MRI-compatible EEG electrodes are attached to the patient’s head outside the MRI scanner. Once the patient enters the scanner, these electrodes are connected to an amplifier in the MRI suite and to a recording computer outside the scanner room using a fiber-optic cable. This configuration helps to ensure patient safety during acquisition of the EEG/fMRI study.

Because patients must be placed inside the scanner for this procedure, the duration of the recording is limited to about one hour, so capturing activity during an actual seizure is rare. This duration is usually sufficient, however, to capture several interictal epileptic spikes and record the timing of these activities. The simultaneous acquisition of data using EEG and fMRI allows measurement of blood oxygen levels in specific brain regions to be correlated with the spike activity, offering evidence of the origin and spread pattern of each spike. The hemodynamic response in the brain is referred to as the blood-oxygen-level-dependent...
**BOLD** effect. Multiple spikes originating from the same brain region provide important localizing information and represent a strong indication that the epilepsy is focal and potentially amenable to surgical therapy.

Cleaning Up Signal Artifacts

The EEG recording environment in the MRI scanner is electromagnetically noisy because of the inductive effects of strong switching magnetic gradient fields. Removing artifacts from the EEG recording can be accomplished through several methods that use software to filter or clean up the signal (see images above). The EEG tracing is reviewed to determine the exact timing of epileptic spikes. The timing is then correlated to changes in the fMRI BOLD signal, which measures the corresponding hemodynamic response.

Studies of focal epileptic spikes caused by different types of brain pathologies have shown reliable activations in the fMRI BOLD signal within the expected location of the epileptogenic focus. In addition, these studies reveal areas of activation and deactivation at locations distant from the pathological focus, and thus provide a unique glimpse into the underlying networks of brain activity. The significance of distant responses in the study of brain connectivity and pathological epileptic networks is one of the issues under active investigation at Cleveland Clinic’s Epilepsy Center.
As sports-related head injuries garner more and more public attention, researchers and clinicians across Cleveland Clinic’s Neurological Institute are pursuing multiple initiatives to better understand these injuries and curb their impact. One initiative is a large, unprecedented study exploring how repeated blows to the head contribute to neurodegenerative disease in professional fighters. Another is the broad deployment of an inexpensive technology solution to take the guesswork out of concussion assessment in youth athletes. Both initiatives began yielding important practical payoffs in 2012.

Professional Fighters Study: Brain Changes Surface Long Before Symptoms
The link between repetitive head trauma and the neurodegenerative condition known as chronic traumatic encephalopathy is not new, but little is known about the condition’s natural history or risk factors.

To fill that knowledge gap, researchers with Cleveland Clinic Lou Ruvo Center for Brain Health launched the Professional Fighters Brain Health Study (PFBHS) in 2011. The trial is combining annual MRI studies with computerized cognitive and mood testing, speech sample analysis and other tests in a large group of professional fighters (boxers and mixed martial arts athletes) for at least four years. It has several aims:

- To examine the cumulative effects of repetitive injuries to the brain in real time
- To assess the earliest and most subtle signs of brain injury via MRI and other clinical measures
- To determine which factors make development of chronic neurodegenerative disorders more likely
- To identify fighters who are progressing to long-term neurodegenerative disease

In 2012, lead researcher Charles Bernick, MD, Associate Medical Director of the Lou Ruvo Center for Brain Health, presented one-year PFBHS findings from 146 fighters — more than had ever been collected in a single research report. This level of recruitment was made possible by the center’s location in Las Vegas, billed as the “fight capital of the world,” and trial enrollment continues to grow.

The one-year results showed that structural changes were detectable in the brain even before any cognitive symptoms appeared. Specific findings included the following:

- Greater numbers of fights and years of professional fighting are associated with lower volumes of several cortical and subcortical structures, but only after five years of professional fighting.
- A much higher threshold is needed to show a relationship between the number of fights and reduced performance levels, such as decreased speed in processing information.

Although these initial findings need to be confirmed longitudinally, they are consistent with what is known so far about subclinical disease in neurodegenerative conditions such as Alzheimer disease and Parkinson disease.

Indeed, results of the PFBHS may ultimately guide the use of MRI monitoring to identify degenerative brain disease before cognitive symptoms surface in a wider population subjected to repeated head blows, including young athletes.
and combat soldiers. Meanwhile, Lou Ruvo Center for Brain Health researchers say their findings may start to guide professional fighting’s regulatory agencies in how to better protect their athletes, including when to require brain evaluation.

Changing the Trajectory of Sports Concussion Care
Even broader and more immediate impact is resulting from the Cleveland Clinic Concussion (C3) application for the Apple® iPad® 2, a validated tool for convenient point-of-care assessment of concussion symptoms in athletes.

In 2012, Cleveland Clinic athletic trainers used the C3 iPad app to conduct baseline assessments of motor and cognitive function in nearly 6,000 high school and college athletes across Northeast Ohio who play contact sports. After baseline data are collected, the C3 app can be deployed in the locker room or on the sidelines for immediate objective assessment for concussion if an athlete sustains a head injury during play.

The C3 app was designed to collect objective data on motor and cognitive functions affected by concussion and to provide those data to clinicians in a meaningful way that permits interaction with the data. An athlete’s balance and postural stability are assessed while he or she performs clinical balance tests with an iPad strapped to the waist (see image). Other relevant functions are assessed by the app in other ways, such as trail-making tests conducted on the iPad with a stylus.

The app-based assessment generates a “performance polygon” plot (see image) that visually displays the extent of impairment (vs. baseline) across various functional domains as well as the speed of recovery in each domain over continued follow-up. This plot pinpoints the areas of most concern and helps guide therapy over time, says Jay L. Alberts, PhD, lead developer of the C3 app and Director of Cleveland Clinic’s Concussion Center.

In addition to the nearly 6,000 student athletes who underwent baseline functional assessment, the C3 app was made available in 2012 for post-injury assessment among an additional 6,000 young athletes who are managed by Cleveland Clinic athletic trainers but who play noncontact sports or were not yet scheduled for baseline assessment.

Cleveland Clinic’s next aim is to explore broader deployment of the C3 app for coordinated use by schools and hospitals across the country, along with the Cleveland Clinic Concussion Carepath, an online evidence-based protocol to reduce variability of care and improve patient outcomes. Because the app is highly transferable and designed for an affordable, widely used device, its potential for dissemination is great. When used with an evidence-based protocol like the Concussion Carepath, it holds the promise of taking much of the guesswork out of concussion management for athletes around the nation.
Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center is investigating fluorescence-guided resection of glioblastoma using 5-aminolevulinic acid (5-ALA), a prodrug that causes fluorescent porphyrins to accumulate in the cells of malignant gliomas.

When 5-ALA is administered orally, it is taken up by malignant glioma cells, which convert it to protoporphyrin IX. Protoporphyrin IX fluoresces pink under blue light, thereby offering the potential to identify residual tumor cells intraoperatively.

Cleveland Clinic received permission from the U.S. Food and Drug Administration to conduct a phase 2 study comparing 5-ALA with intraoperative MRI for tumor visualization with the endpoint of completeness of tumor resection in patients with suspected new or recurrent glioblastoma or suspected upgraded glioblastoma.

The extent of bulk tumor resection has been shown to correlate with prognosis in glioblastoma. Because most recurrences of glioblastoma are at the margin of surgical resection, identifying and removing all of the bulk or contrast-enhancing tumor is expected to delay recurrence and potentially improve outcomes.

Intraoperative MRI is used at some centers in an effort to remove all contrast-enhancing tumor, but it requires significant capital expenditure for the MRI and room modifications and it provides only a snapshot in time. Moreover, obtaining images intraoperatively is cumbersome and time-intensive, as it requires interruption of the procedure and the need to re-establish the surgical field.

In contrast, fluorescence-guided resection with 5-ALA provides information on a continuous basis, is easy to perform, requires only a modification to existing surgical microscopes and does not interrupt the procedure. A potential drawback to 5-ALA is that its efficacy requires direct visibility of fluorescent areas, so that a layer of normal tissue may obscure the appearance of tumor cells or an angle of vision without direct line of sight may lead to incomplete tumor cell removal.

Cleveland Clinic is one of only about 10 centers in the United States to investigate the use of 5-ALA for resection of brain tumors.

The study at Cleveland Clinic is led by Michael Vogelbaum, MD, PhD, Associate Director of the Burkhardt Brain Tumor Center. Forty patients with glioblastoma deemed to be surgical candidates based on current neurosurgical standards of care are being enrolled. Patients undergoing fluorescence-guided resection of tumor will receive a single oral dose of 5-ALA two to four hours before the scheduled surgery.

The primary objective involves comparing the volume of tissue removed with 5-ALA-guided resection vs. the measured enhancing tumor evaluated on a preoperative MRI. Patients will be assessed for completeness of tumor resection one to two days after surgery using gadolinium-enhanced brain MRI. Tumor progression will be assessed subsequently with images obtained when clinically indicated.
The prospect of achieving freedom from disease activity in relapsing-remitting multiple sclerosis (MS) is potentially within reach, given advancements in the ability to monitor disease activity and the emergence and expanded use of potent disease-modifying therapies.

To date, freedom from MS disease activity has been a therapy goal defined only in the clinical trial setting. Adoption of this treatment target in clinical practice will mean overcoming challenges, including the need for agreement on how to define the target and accurately measure response to MS therapies. Nevertheless, consensus is building that definitively stopping MS activity early in the disease course is a worthwhile and achievable patient management goal.

Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research is a leading proponent of this concept. To that end, the Mellen Center hosted an MS Experts Consensus Summit in September 2012, bringing together more than 50 experts in MS to focus on the use of existing monitoring tools and treatment strategies to achieve disease-free status in relapsing-remitting MS.

The summit heralded the beginning of an attempt to standardize the monitoring tools on which an operational definition of freedom from MS disease activity can be constructed. Over the course of two days in Cleveland, summit faculty discussed methods for measuring and monitoring disease activity and treatment efficacy. Several key concepts emerged:

• A consensus definition is needed to serve as a treatment target for appropriate patients in the clinic as well as to drive research on the concept of disease-free status.

• Multiple objective measures are candidates for inclusion in a definition of disease-free status, including relapse counts/recovery, the Expanded Disability Status Scale, MRI with and without quantitative analysis, a timed 25-foot walk, optical coherence tomography, and emerging biomarkers in the blood and cerebrospinal fluid.

• There is a high level of interest in using patient-reported outcomes to expand the patient’s role in defining the treatment target and measuring health status.

Cleveland Clinic’s Neurological Institute is uniquely positioned to monitor the stability of MS and the effectiveness of disease-modifying therapies over time, thanks to its Knowledge Program© database. The Knowledge Program collects patient-reported measures (e.g., health status, quality of life, symptoms) at every visit, aggregates these data with clinician-collected measures (e.g., laboratory and imaging results) and embeds them in the electronic medical record (EMR). This transforms the EMR from a simple repository for physicians’ notes and test results into a dashboard of clinical tools with which Cleveland Clinic neurologists can design patient management plans.

The goal is to use an operational definition of disease-free status in relapsing-remitting MS as the basis for a carepath — a comprehensive care interface embedded in the EMR — to provide treatment guidance, feedback and real-time reminders that empower neurologists to help patients bring their disease activity to a standstill.
Subarachnoid hemorrhage (SAH) often results from rupture of an aneurysm in the brain. While it’s a potentially devastating disease in its own right, SAH also brings a number of complications that can lead to further brain damage. Physician researchers in the Neurological Institute’s Cerebrovascular Center are joining forces to conduct broad-based studies into aneurysmal SAH and its potential complications.

**Platelets and SAH Outcomes**

The effect of platelet aggregation on functional outcomes in patients with SAH is being evaluated by Jennifer Frontera, MD. Recently, she discovered elevations in markers of platelet activation and inflammation during the first 72 hours after aneurysm rupture, which suggests that platelet activation is involved in early brain injury.

The role of microthrombosis after aneurysmal SAH as a contributor to early cerebral injury is the focus of a research grant awarded to Dr. Frontera by the American Heart Association. If microclot formation is found to be a significant player in early damage after SAH, its attenuation by early antiplatelet therapy might represent a new treatment paradigm. Discovering the optimal timing and intensity of such therapy to discourage rebleeding, an unwanted side effect of antiplatelet therapy, is of paramount importance.

**Innate Immune Mechanisms in Vasospasm After SAH**

The pathways by which neutrophil infiltration and activation lead to delayed cerebral injury as a complication of SAH are being explored by J. Javier Provencio, MD, a Cerebrovascular Center neurointensivist who also works in the Lerner Research Institute’s Neuroinflammation Research Center.

Support for Dr. Provencio’s work on this type of delayed cerebral injury (also called vasospasm) includes a grant from the National Institute of Neurological Disorders and Stroke. His laboratory is studying preclinical models of SAH to understand the immune mechanisms responsible for delayed deterioration, with the hope of developing immune-based treatments to prevent or treat this complication.

His laboratory is also collaborating with Neurological Institute neuropsychologist and researcher Cindy Kubu, PhD, to conduct studies of patients with SAH in order to evaluate the role of inflammation in the long-term cognitive deficits seen after SAH.

**Iron Overload in ICH and SAH**

The release of iron into the brain has been shown to be a mechanism of injury in intracerebral hemorrhage (ICH), a disease related to, but different from, SAH. The Cerebrovascular Center is involved in a multicenter national trial of early deferoxamine mesylate, an iron chelator, for treatment of brain injury secondary to ICH. As a corollary to this study, Joao Gomes, MD, is investigating whether iron accumulation is similarly involved in the pathogenesis of early brain injury following SAH in humans. If it is, this may open the door to acute administration of deferoxamine as a potential strategy for preserving neurons in patients with SAH.

**A Broad Mix of Neurointensive Investigations**

These three physician researchers form the core of a larger neurointensive care group that includes five other neurointensivists who all have research and quality projects based in Cleveland Clinic’s neurointensive care unit. By sharing clinical data and lab resources, these neurointensive care researchers are rapidly working toward treatments for some of the most deadly and debilitating diseases of the brain.
In our most recent reporting year, the Neurological Institute had 229 clinical research projects — involving 6,227 patients — actively under way.

Research and Clinical Innovation

Cleveland Clinic’s Neurological Institute carries out a robust research program that fosters a culture of innovation and collaboration. Physician investigators and scientists pursue laboratory-based research whose findings are applied to improve patient care. In 2011, we were awarded nearly $12 million in neurologically based research grants and contracts and had 229 clinical research projects actively under way.

In addition to the innovations featured in the preceding pages, below are snapshots of other innovative Neurological Institute initiatives that saw significant developments in 2012 and will continue to evolve in the years ahead.

Spine Carepath Embeds Evidence-Based Care Strategy into the EMR

Fragmented, variable and costly: Despite the recent proliferation of clinical practice guidelines for managing back pain, treatment of back pain remains fragmented among multiple providers, varies widely from evidence-based recommendations, and too often involves inappropriate use of expensive therapies and imaging tools.

To address the stubbornly poor compliance with spine care guidelines, Cleveland Clinic’s Center for Spine Health has developed the Cleveland Clinic Spine Carepath, an evidence-informed algorithmic strategy for managing back pain that is embedded in the electronic medical record (EMR). Key elements of care are captured in structured documentation (“clinical notes”) in the EMR, and diagnostic and therapeutic orders are recorded in a retrievable data set. This design allows retrospective study of the process of care and its impact on clinical outcomes. The Spine Carepath’s utility for outcomes research is further enhanced by its linkage with Cleveland Clinic’s Knowledge Program® database, which elicits patient-reported validated outcome measures at appropriate points throughout the course of care.

The carepath provides an opportunity to reduce potentially harmful variability in spine care while improving patient outcomes and reducing inappropriate or premature use of medical resources. The latter may reduce the cost of care and improve value. And because the carepath systematically analyzes process and outcomes data to continually re-evaluate and revise its clinical algorithm, it will keep itself on its toes — and ensure that patients get the most up-to-date, value-driven care.
Using Advanced Neuroimaging to Pinpoint the Singularities of Blast-Related TBI

Traumatic brain injury (TBI) following explosive blasts in military combat is different from other forms of TBI, but insight into exactly how it differs has been limited. Cleveland Clinic’s Schey Center for Cognitive Neuroimaging is one of a select group of research centers to win funding from the U.S. Department of Defense to study blast-induced TBI in military personnel in order to sort out those differences and how best to treat them.

The differences in blast-induced TBI are thought to stem from changes in air pressure caused by the blast. Conventional MRI has failed to elucidate the resulting damage to both gray and white matter in the brain. In response, Cleveland Clinic researchers have been using advanced neuroimaging techniques — functional MRI with diffusion tensor imaging and high-angular-resolution diffusion imaging — to identify biomarkers that may continue to indicate TBI-related neural changes long after the injured individual’s cognitive function has returned to normal. They are combining these imaging studies with comprehensive neuropsychological testing in a controlled study of 160 individuals, including active-combat military personnel with and without blast-induced TBI and civilians with mechanical TBI and other traumatic injuries. Neuroimaging is conducted at least one year after TBI to help ensure that relatively permanent neural changes are being measured.

Data collection ended in the last few months of 2012. While image analysis is continuing into 2013, initial findings appear to provide preliminary evidence that conventional MRI has failed to elucidate the resulting damage to both gray and white matter in the brain. In response, Cleveland Clinic researchers have been using advanced neuroimaging techniques — functional MRI with diffusion tensor imaging and high-angular-resolution diffusion imaging — to identify biomarkers that may continue to indicate TBI-related neural changes long after the injured individual’s cognitive function has returned to normal.

Clinic researchers are using similar imaging techniques in longitudinal studies to identify imaging biomarkers in people genetically at risk for Alzheimer disease and to study patients in the preclinical stages of Huntington disease.

Study Charts New Territory in Profiling Predictors of Obstructive Sleep Apnea in Epilepsy

Early diagnosis of obstructive sleep apnea (OSA) is a focus of Cleveland Clinic’s Sleep Disorders Center, but the diagnosis of OSA can be fraught with complexities in populations with neurologic disease. Since OSA is a contributor to poor seizure control in epilepsy patients, early OSA diagnosis and treatment can yield clear payoffs in this population.

To better understand the predictors of OSA in epilepsy, researchers from the Sleep Disorders Center and the Epilepsy Center recently teamed to assess cross-sectional OSA prevalence and predictors in 130 consecutive adults with epilepsy using polysomnography, structured interviews and subjective assessments. Their study, the first to explore OSA predictors using polysomnography in patients unselected for epilepsy severity or sleep disorder symptoms, was published in Epilepsy & Behavior (2012;25:363-367).

A full 30 percent of study participants had OSA (apnea-hypopnea index [AHI] ≥ 10) and 16 percent had severe OSA (AHI ≥ 15), rates that are markedly higher than those in the general population. The risk for OSA increased with age and higher doses of anti-epileptic drugs regardless of gender, body mass index and seizure frequency. Some traditional OSA risk factors, such as male gender and higher body mass index, were found to be stronger predictors of the severity of OSA than of the presence of OSA.

While noting that their observational study requires confirmation in longitudinal trials, the Cleveland Clinic researchers concluded that these findings support implementation of routine OSA screening in adult epilepsy clinics.

A New Tool for Alzheimer Evaluation — And Counseling to Support It

When the FDA approved the radiopharmaceutical Amyvid™ in April, it became possible for the first time to determine the brain’s density of the neuritic plaques implicated in Alzheimer disease (AD) without brain biopsy or autopsy exam. Cleveland Clinic Lou Ruvo Center for Brain Health is one of a limited number of centers across the country using Amyvid, and it’s setting itself apart even more by the counseling it offers patients after they undergo Amyvid testing.

Amyvid is approved for use with PET imaging of the brain’s density of the neuritic plaques implicated in Alzheimer disease (AD) without brain biopsy or autopsy exam. Cleveland Clinic Lou Ruvo Center for Brain Health is one of a limited number of centers across the country using Amyvid, and it’s setting itself apart even more by the counseling it offers patients after they undergo Amyvid testing.

PET imaging with Amyvid in a healthy brain (left) and an Alzheimer disease brain (right).
CLEVELAND CLINIC

Integrating Singular Care Across Multiple Sites

Cleveland Clinic’s Neurological Institute has locations throughout Northeast Ohio as well as in Weston, Fla., and Las Vegas, Nev.

In Northeast Ohio, the Center for Regional Neurosciences brings together physicians and other healthcare providers at more than 30 locations across the region to care for adults and children with the most common to the rarest and most complex neurological conditions:

- Cleveland Clinic’s main hospital campus
- Eight community hospitals, including comprehensive neurological services at Lakewood Hospital and Hillcrest Hospital
- A children’s hospital for rehabilitation
- Multiple family health centers

In Las Vegas, Cleveland Clinic Lou Ruvo Center for Brain Health offers highly specialized services in the diagnosis, treatment and research of Alzheimer disease and other neurocognitive disorders and collaborates with expert centers in our Cleveland location in the management of multiple sclerosis and movement disorders.

At Cleveland Clinic Florida, epileptologists diagnose patients in a dedicated four-bed adult epilepsy monitoring unit and collaborate with their colleagues in Cleveland when surgical treatment is indicated. Programs for the treatment of brain tumors, Alzheimer disease and dementia are similarly linked.

In Las Vegas, Cleveland Clinic Lou Ruvo Center for Brain Health brings together physicians and other healthcare providers at more than 30 locations across the region to care for adults and children with the most common to the rarest and most complex neurological conditions:

- Cleveland Clinic’s main hospital campus
- Eight community hospitals, including comprehensive neurological services at Lakewood Hospital and Hillcrest Hospital
- A children’s hospital for rehabilitation
- Multiple family health centers

Cleveland Clinic Information

About Cleveland Clinic

Cleveland Clinic is an integrated health-care delivery system with local, national and international reach. At Cleveland Clinic, 2,800 physicians represent 120 medical specialties and subspecialties. We are a main campus, 18 family health centers, eight community hospitals, Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City, and Cleveland Clinic Abu Dhabi.

In 2012, Cleveland Clinic was ranked one of America’s top 4 hospitals in U.S. News & World Report’s annual “America’s Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 14 specialty areas, and the top hospital in three of those areas.

Resources for Physicians

Referring Physician Center and Hotline

Cleveland Clinic’s Referring Physician Center has established a 24/7 hotline — 855.REFER.123 (855.733.3712) — to streamline access to our array of medical services. Contact the Referring Physician Hotline for information on our clinical specialties and services, to schedule and confirm patient appointments, for assistance in resolving service-related issues, and to connect with Cleveland Clinic specialists.

Physician Directory

View all Cleveland Clinic staff online at clevelandclinic.org/staff.

Track Your Patient’s Care Online

DrConnect is a secure online service providing real-time information about the treatment your patient receives at Cleveland Clinic. Establish a DrConnect account at clevelandclinic.org/drconnect.

Critical Care Transport Worldwide

Cleveland Clinic’s critical care transport teams and fleet of vehicles are available to serve patients across the globe.

- To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467 (see clevelandclinic.org/criticalcare-transport).

Outcomes Data

View clinical Outcomes Books from all Cleveland Clinic institutes at clevelandclinic.org/outcomes.

Clinical Trials

We offer thousands of clinical trials for qualifying patients. Visit clevelandclinic.org/clinicaltrials.

CME Opportunities: Live and Online

The Cleveland Clinic Center for Continuing Education’s website offers convenient, complimentary learning opportunities. Visit ccfme.org to learn more, and use Cleveland Clinic’s myCME portal (available on the site) to manage your CME credits.

Executive Education

Cleveland Clinic has two education programs for healthcare executive leaders — the Executive Visitors’ Program and the two-week Samson Global Leadership Academy immersion program. Visit clevelandclinic.org/executiveducation.

Same-Day Appointments

Cleveland Clinic offers same-day appointments to help your patients get the care they need, right away. Have your patients call our same-day appointment line, 216.444.CARE (2273) or 800.223.CARE (2273).

Stay connected with us on:

Edition: Glenn Campbell
Designer: Amy Ruskay-Wood
Contributing writers: Wayne Kuznar
Photographers: Don Gerda, Stephen Travacca, Tori Merce, Russell Lee, Al Fuchs, Tom Greaves

24/7 Referrals

Referring Physician Hotline

855.REFER.123 (855.733.3712)

Hospital Transfers

800.553.5056

On the Web at clevelandclinic.org/refer123

Stay connected with us on:
Go green with Cleveland Clinic today!

Use your device to connect to our medical professionals page and sign up to receive publications electronically from Cleveland Clinic Neurological Institute.

To read the QR code with your device, find and download a reader from http://ccf.org/QRCodes.