Cleveland Clinic

Neurological Institute

2014 Year in Review

Contents

ON THE COVER — A glimpse inside Cleveland Clinic's new mobile stroke treatment unit, where patients with suspected stroke can begin to undergo assessment and treatment right at the spot of symptom onset. Specially trained emergency providers use the unit's broadband link to videoconference with stroke specialists on Cleveland Clinic's main campus, who direct assessment and management. The unit, one of the very first deployed in the U.S., is profiled starting on p. 6.

Cleveland Clinic Neurological Institute

A Distinctive Structure for Distinctive Caregiving

Cleveland Clinic's multidisciplinary Neurological Institute includes more than 300 medical, surgical and research specialists dedicated to the diagnosis, treatment and rehabilitation of adults and children with brain and CNS disorders.

The institute is structured into four departments — Neurology, Neurological Surgery, Physical Medicine and Rehabilitation, and Psychiatry and Psychology — that oversee training and coordinate activities across 14 subspecialized centers.

Patients access care through these centers (profiled beginning on p. 36), each of which incorporates a multidisciplinary approach to the diagnosis and management of a particular condition or group of conditions.

4
DEPARTMENTS

14
CENTERS

300+
PROFESSIONAL STAFF

NEUROLOGICAL INSTITUTE VITAL STATISTICS (2013)	
215,587	Annual outpatient visits
16,287	Annual admissions
93,454	Annual inpatient days
13,254	Annual surgical/interventional procedures
81,481	Annual neuroimaging studies
263	Staff physicians
150	Clinical residents and fellows
21	Research fellows

NEUROLOGICAL INSTITUTE RESEARCH FUNDING (2013)	
$15.71M	Total grant and contract research funding
61	Federal grants and contracts
190	Nonfederal grants and contracts
242	Active clinical research projects
93	New clinical research projects (initiated 2013)
75	Staff leading clinical research projects
5,933	Patients enrolled in clinical research projects

215,000+ PATIENT VISITS

16,000+ ADMISSIONS

13,250+ PROCEDURES

Across our more than 215,000 annual patient visits and over 16,250 annual admissions, the Neurological Institute manages the most common to the most complex disorders of the brain and CNS. For patients with challenging conditions in need of leading-edge diagnostics and treatment, our physicians and surgeons are regularly advancing innovations in areas including:

- Epilepsy surgery and monitoring
- Stereotactic radiosurgery
- Deep brain stimulation
- Telemedicine for stroke, multiple sclerosis and other conditions
- Concussion assessment and management
- Genomic profiling of brain tumor tissue
- Systems and processes for standardizing care around evidence-based practice

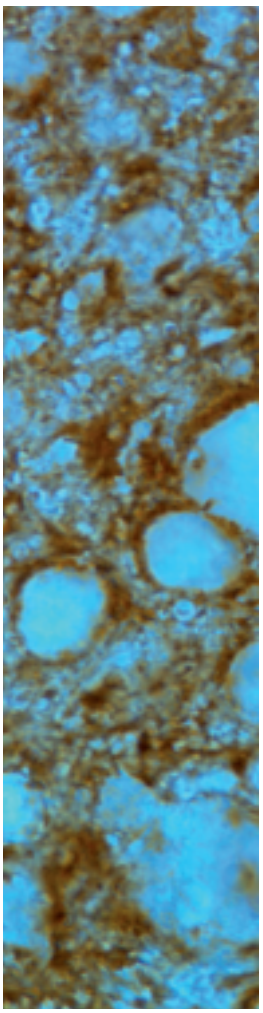
3-STATE PRESENCE = MORE PATIENT ACCESS

The Neurological Institute is committed to making access to the most advanced neurologic care convenient for all patients through a network with unique and strategic geographic reach:

- In Northeast Ohio, specialized Neurological Institute services are available at more than two dozen Cleveland Clinic community hospitals and family health centers throughout the region.
- Las Vegas is the home base of Cleveland Clinic Lou Ruvo Center for Brain Health, which offers expert care in neurocognitive disease and related brain disorders.
- Cleveland Clinic Florida's 155-bed hospital in Weston, Florida, offers extensive neurological specialty services, including a six-bed epilepsy monitoring unit.

These broadly dispersed locations put Neurological Institute expertise within a couple hours' flight of almost all mainland U.S. residents and provide a diverse patient base for clinical trials.

The institute's footprint in Florida will soon expand with construction of the Egil and Pauline Braathen Facility, which will house the expanded Pauline Braathen Neurological Center (architect's rendering below). The 143,000-square-foot building, which will also house oncology services, will include a neurointerventional suite, advanced radiosurgery equipment for brain and CNS tumors, and other leading-edge technology. The facility, supported by a $30 million gift from Mrs. Braathen, is scheduled to open on the Weston campus in 2015.



$15.7M
IN RESEARCH GRANTS

242
CLINICAL RESEARCH PROJECTS

Our clinical care is complemented by a robust research program that fosters collaboration and innovation. Neurological Institute physicians and scientists team with colleagues in the Lerner Research Institute, Cleveland Clinic's basic science research arm, to pursue lab-based and translational studies in addition to our hundreds of ongoing clinical trials. We recently enhanced our neuroimaging research capabilities across multiple conditions with acquisition of a 7-tesla MRI scanner. Other standout aspects of our research program include:

- One of the largest U.S. clinical trial programs for neurocognitive diseases
- Leadership in studying deep brain stimulation for treatment of neuropsychiatric disorders and chronic pain
- The nation's only nonmilitary installation of the CAREN virtual reality treadmill for studying mobility in realistic but protected settings
- Pioneering investigations in the use of mesenchymal stem cell therapy for multiple sclerosis
- High-impact investigations into the molecular, genetic and cellular mechanisms of epilepsy

DATA CAPTURE = TRANSFORMED CARE

The Neurological Institute is dedicated to data-informed clinical practice. Our Knowledge Program interactive data collection platform, now in its eighth year, has captured health status measure (HSM) data from well over 1 million patient visits. At every outpatient visit, HSMs are administered to patients electronically, while providers report outcomes as part of usual medical documentation.

We aggregate these patient- and provider-generated data with information from other sources — such as our growing number of EMR-embedded care paths and our collection of condition-specific mobile apps — to optimize clinical decision-making, quality improvement and research opportunities. The result is better care for populations and individuals alike. This forward-looking data strategy has put the Neurological Institute well on its way to the use of predictive analytics to improve individual patient outcomes, reduce costs and enhance healthcare value.

MICHAEL T. MODIC, MD, FACR
CHAIRMAN, CLEVELAND CLINIC NEUROLOGICAL INSTITUTE

WELCOME FROM THE CHAIRMAN

Dear Colleagues,

Who, where and how? As Cleveland Clinic's Neurological Institute continues the never-ending quest for greater healthcare value, those are the questions we've repeatedly been asking ourselves throughout 2014 and into the new year.

Value in healthcare centers on doing the right thing for patients at the right cost, which requires a relentless focus on delivering care in the right way. Identifying the right way typically boils down to answering three questions:

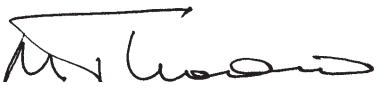
Who does it? The Neurological Institute is increasingly addressing this question through our more than two dozen condition-specific care paths for standardizing care around evidence-based practice. One key objective of these care paths is to better match patients with the type of provider most appropriate to their differing needs at various stages of an episode of care. The payoffs are many — patients get more face time with providers, providers practice at the top of their training and the cost of care is often reduced.

Where do they do it? More and more, we are delivering care closer to patients' homes, thanks to the efforts of our Center for Regional Neurosciences to bring highly subspecialized care into the community to a degree that's rare for academic medical centers. We also increasingly bring care directly *to* patients' homes, through our burgeoning telemedicine initiatives — most notably with the new mobile stroke treatment unit spotlighted in our cover story (p. 6) — and growing numbers of Cleveland Clinic mobile apps that allow patients to monitor their health more closely than ever.

How do they do it? We are increasingly delivering care in ways that are thoroughly informed by data. Data-driven practice is a key goal of our institute's Orchard of Neurological Apps initiative profiled on p. 14. As we develop more and more clinical mobile apps using shared modules applied across common functional domains for various neurologic conditions, we will build the big databases that can make predictive care models possible to better individualize care and drive value.

These three questions are the leading paths to innovation in today's healthcare landscape. The following pages spotlight a few of the innovations the Neurological Institute has rolled out over the past year. In addition to our five feature stories, we introduce our first year-end photo essay (p. 26) and briefly profile selected 2014 highlights from each of our clinical centers (p. 36). I invite your feedback on anything you see here, and we welcome the opportunity to work together on patient care and research in the year ahead.

Respectfully,



Michael T. Modic, MD, FACR

Chairman, Cleveland Clinic Neurological Institute
modicm1@ccf.org

PHOTO — Inside the mobile stroke treatment unit: A broadband video link enables a neurologist on Cleveland Clinic's main campus to evaluate a stroke patient at the site of symptom onset.

< 2014 SNAPSHOT >

Acute Stroke Management: Taking It to the Streets

Not long ago, Cleveland Clinic's Cerebrovascular Center faced a challenge that vexes stroke centers nationwide. Despite years of efforts to trim the time it takes to deliver potentially lifesaving tissue plasminogen activator (tPA) to ischemic stroke patients, rates of tPA delivery in the ER within the optimal three-hour window after symptom onset had plateaued at 17 percent.

"We're essentially bringing the emergency room to the patient."

— PETER RASMUSSEN, MD

While that compares favorably with national rates (see sidebar), it wasn't good enough for Cerebrovascular Center Director Peter Rasmussen, MD. "We felt we weren't making enough of a difference in treating our patients in a timely fashion," he says. "We needed to change the system."

Dr. Rasmussen and colleagues had heard of a novel ambulance-like "mobile stroke unit" being used by a teaching hospital in Homburg, Germany, to shorten the time between stroke symptom onset and management, so they visited Germany in 2013 to check it out.

They were so impressed that the Cerebrovascular Center developed plans for Cleveland Clinic's own mobile stroke treatment unit (MSTU), which they were able to realize when dedicated donor funding became available in 2014. When it began operations in July 2014, Cleveland Clinic's MSTU became one of the first such units in the United States.

An ER on Wheels

The MSTU looks like an ambulance on the outside, but inside it's equipped and staffed like a virtual ER dedicated to stroke diagnosis and management:

- It houses a portable CT scanner and a briefcase-sized telemedicine unit that enables — via a 4G broadband link — rapid transfer of brain scans and videoconferencing with a neuroradiologist and a stroke specialist on Cleveland Clinic's main campus.
- An onboard mobile lab allows testing of blood samples and immediate administration of tPA to those patients for whom it's indicated (based on the CT findings and videoconference).
- The MSTU is staffed by a paramedic, a critical care nurse (who administers treatment), a CT technologist and an EMS driver, all specially trained in acute stroke care delivery.

The approach allows the specialist physicians on the other end of the broadband video link to determine whether the patient is indeed having a stroke — and, critically, whether it is an ischemic or hemorrhagic event, which determines whether or not tPA is indicated. As a result, crucial steps in stroke diagnosis and treatment can be accomplished at the site of stroke onset or while the patient is en route to the hospital, slashing intervention times for a condition where time equals brain.

The MSTU is based at Cleveland Clinic's main campus and dispatched (along with a standard ambulance) via the city of Cleveland's 9-1-1 system in cases of suspected stroke. When a stroke is diagnosed, the MSTU will transport the patient to the nearest Primary Stroke Center or Comprehensive Stroke Center.

"We're essentially bringing the emergency room to the patient," says Dr. Rasmussen. He notes that the use of telemedicine to allow the neurologists to manage the case remotely, rather than on board the MSTU, was a Cleveland Clinic adaptation of the initial German model of the mobile unit.

Trimming Treatment Times Down to a New Standard

In its first four months of operation, the MSTU transported more than 100 stroke patients to a total of 12 healthcare facilities across the greater Cleveland area. None of these patients had to be transferred to another facility, reducing unnecessary and expensive hospital transfers.

But the biggest benefit has clearly been more timely patient management. "The usual aim is to administer tPA to ischemic stroke patients within 60 minutes of their arrival at the hospital door," says M. Shazam Hussain, MD, Head, Cleveland Clinic Stroke Program. "But only half of U.S. patients get treatment within that time frame. The MSTU has enabled us to treat patients within a mean of 19 minutes after their entry into the mobile unit. That is sooner than they would typically even show up at the hospital door in the standard care model."

He cites one case in September in which a patient was successfully treated with tPA within 11 minutes of entering the MSTU. "That's one of the fastest times any stroke patient has ever been diagnosed and treated in this country," Dr. Hussain notes.

A pilot study of the German mobile unit found that it cut the median time from emergency call to thrombolytic delivery by 34 minutes compared with optimized conventional hospital treatment. Cleveland Clinic's MSTU team will be assembling data from its initial experience to publish its own outcomes, which will inform decisions about whether to add a second mobile unit.

A Compelling Cost Case Too

Although the initiative requires substantial investment — the MSTU itself cost nearly $1 million, and it takes about $1 million a year to staff — Dr. Rasmussen anticipates it will save between $2 million and $4 million in its first year of operation, through savings in rehabilitation, long-term care and other aspects of post-acute stroke therapy. "The beauty of this approach," he says, "is that in addition to reducing patient injury and suffering, it should reduce overall healthcare costs."

Numbers of Note

on the Mobile Stroke Treatment Unit (MSTU) …

19 MINUTES

Average time from patient entry into the MSTU to tPA administration

11 MINUTES

MSTU's average response time to the scene of stroke-like symptom onset

6 TIMES

Increase in the frequency of tPA delivery within allowable time window with MSTU vs. national average for ischemic stroke patients

1 TO **2**

Average daily number of stroke patients treated by the MSTU

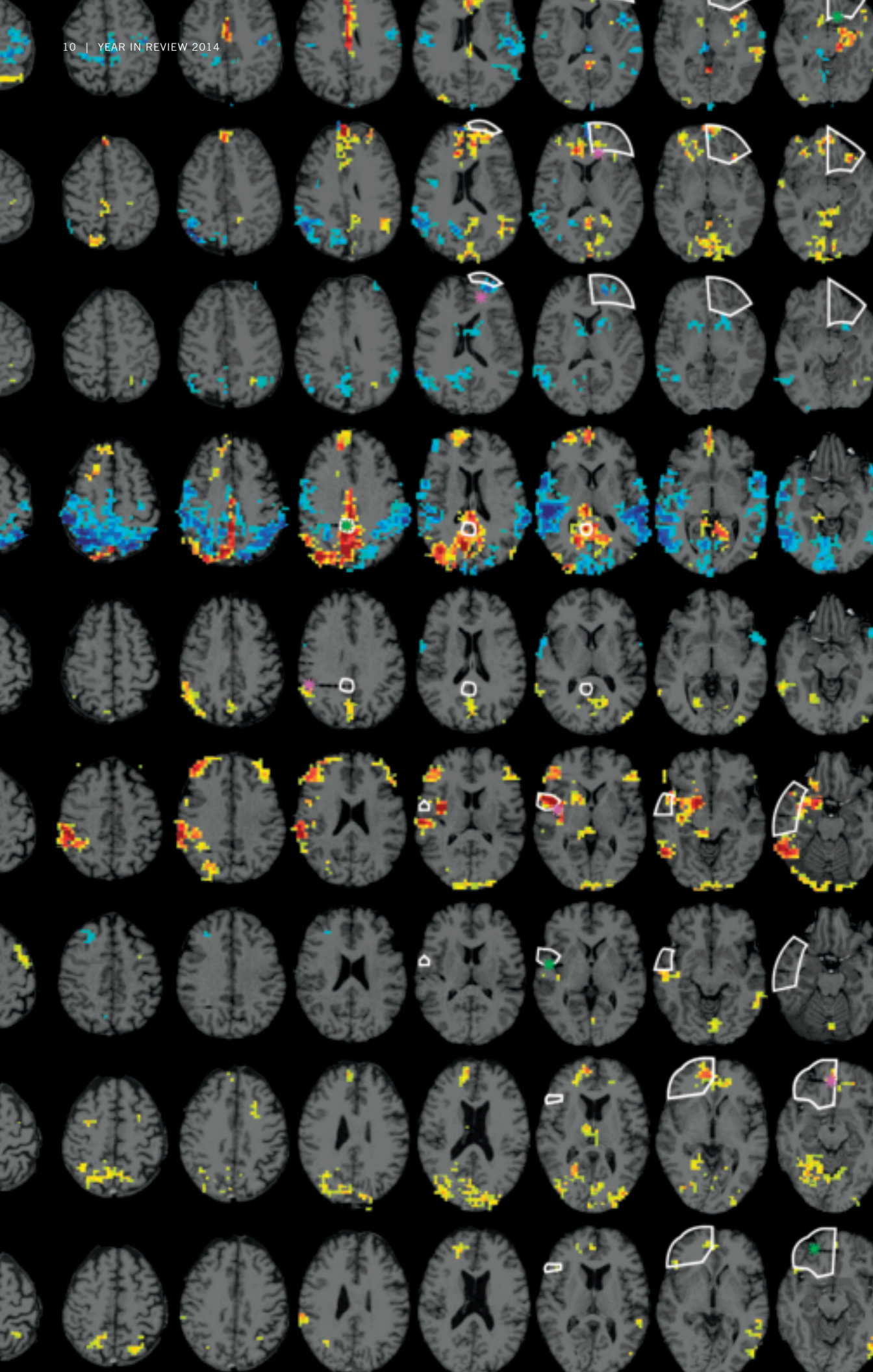
… and Why They Matter

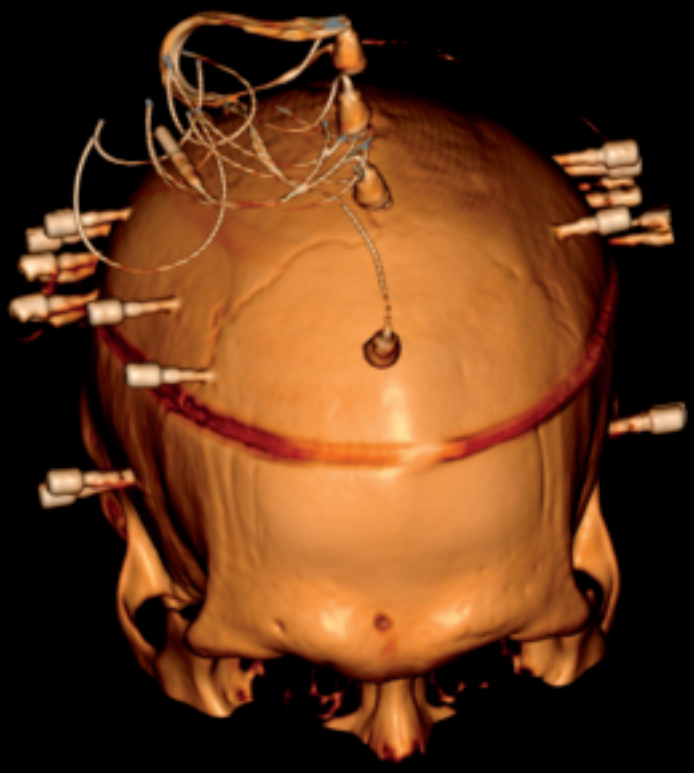
2 TIMES

Increase in the likelihood of recovery with good function when an ischemic stroke patient receives tPA within 1 hour vs. 6 hours

≈ 5%

Share of potentially eligible stroke patients who actually receive tPA under the standard ER model (based on literature reports)





〈 2014 SNAPSHOT 〉

Pairing fMRI with Intracranial Stimulation to Pinpoint the Epileptogenic Zone

At first blush, the cure for pharmacoresistant focal epilepsies — surgical removal of the brain's epileptogenic zone (EZ) — can seem deceptively straightforward. The trick, however, is ensuring sufficient identification of the EZ and related epileptic network. Several techniques have been proposed, but none has offered adequate spatial coverage and sufficiently precise localization of source signals. Until now.

> "We were able to stimulate the electrodes during simultaneous fMRI imaging and see in real time how the entire brain — four-dimensionally — reacted to the stimulation."
>
> — STEPHEN E. JONES, MD, PhD

A Novel Combination: fMRI and Intracranial Stimulation

In May 2014, a Cleveland Clinic team led by neuroradiologist Stephen E. Jones, MD, PhD, and neurosurgeon Jorge Gonzalez-Martinez, MD, PhD, published preliminary clinical data *(Brain Connect.* 2014;4[4]:286-298) introducing a new technique for studying brain connectivity that promises to enhance preoperative identification of epileptic areas in the human brain.

Their technique arises from the earlier observation that the blood-oxygen-level-dependent (BOLD) response on fMRI can be used to demonstrate localized networks of activity across the entire brain, usually through task-related activation or while the patient is at rest. Working from this premise, the investigators decided to combine direct intracranial electrical stimulation of the brain with simultaneous fMRI (DES-fMRI) to assess the BOLD response to intracranial stimulation near the hypothesized EZ. They then compared the response to evoked electrical recordings from other intracranial electrodes.

The team reported results from the first five patients with pharmacoresistant seizures who underwent the DES-fMRI technique at adequate stimulation frequencies and voltages. All patients were already undergoing invasive evaluation for presurgical planning using the stereoelectroencephalographic (SEEG) methodology.

Correlations Between BOLD Response and Epileptic Regions

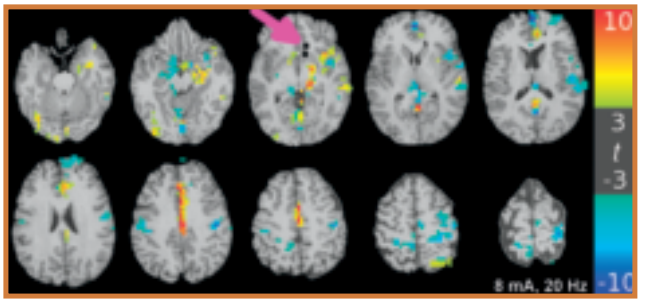
Robust fMRI maps of activation networks were easily produced, and they showed a significant but weak positive correlation between quantitative measures of BOLD activity and measures of electrical activity in response to direct stimulation.

Among the four patients with outcomes data at six months after surgery, successful surgical outcome was consistent with the resection of brain regions that had high local fMRI activity.

"We were able to stimulate the electrodes during simultaneous fMRI imaging and see in real time how the entire brain — four-dimensionally — reacted to the stimulation," says Dr. Jones. "This allows us to localize the site of hyperactivity that causes the patient's seizures."

Wide-Ranging Implications

The results suggest a role for DES-fMRI in evaluation of full-brain volume in studies of brain connectivity, including in surgical planning for patients with medically intractable epilepsy. Since the BOLD response was found to be consistent with electrical recordings, the investigators note that the complete coverage and precise localization offered by fMRI could complement invasive evaluation, extending the range of corticocortical evoked potential assessment to the whole brain.



fMRI activation maps during high-current stimulation trials in a patient. The site of bipolar stimulation is marked by the two asterisks denoted by the large magenta arrow. The overlaid colored regions indicate portions of the brain that significantly react to the stimulation, as denoted by the color bar (red indicates increased reactivity; blue indicates reduced activity). Note how the brain can react to stimulation both close to and far away from the electrodes — even on the opposite side of the brain. Most interestingly, the pattern of activation conforms to segments of known functional anatomy (e.g., the cingulate gyrus).

The technique might also improve the yield of invasive evaluations by identifying brain regions with high activity levels that merit sampling via a SEEG electrode. Such a procedure could be done intraoperatively and interactively, with the DES-fMRI data from each electrode guiding the placement of the subsequent electrode.

"Sometimes we need to perform two or three surgical procedures to control the seizures in a patient with refractory focal epilepsy," says Dr. Gonzalez-Martinez. "This technique promises to better define the seizure area so we can cure these patients with a single procedure."

In Pursuit of Follow-On Research Questions

As in most biomedical advancements, the team's investigation prompted at least as many questions as it answered. Among the questions to be addressed by their ongoing and future studies:

- How do activation patterns compare when stimulation is applied to the EZ vs. non-EZ regions?
- How should stimulation and fMRI acquisition parameters be optimized?
- How will the DES-fMRI technique affect long-term clinical outcomes as well as pathology and activation maps?

Regardless of exactly what these future investigations yield, Dr. Jones suspects their team has come across an important real-time combination of technologies. "If you can help identify the one piece of tissue implicated in refractory seizures," he notes, "you can have a tremendous impact on a patient's life."

"Sometimes we need to perform two or three surgical procedures to control the seizures in a patient with refractory focal epilepsy. This technique promises to better define the seizure area so we can cure these patients with a single procedure."

— JORGE GONZALEZ-MARTINEZ, MD, PhD

〈 2014 SNAPSHOT 〉

Seeing an Orchard Rather Than Trees:

A Bold Approach to Healthcare App Development

By various measures, 2014 was a good year for the Cleveland Clinic Concussion (C3) App:

- Fast-growing numbers of U.S. universities and high schools adopted the app for concussion assessment in their student athletes.
- Studies validating the app's ability to precisely quantify postural stability were published in peer-reviewed journals.
- Apple even highlighted the C3 App in its popular "What will your verse be?" campaign for the iPad® (apple.com/your-verse/concussion-game-plan/).

But the most enduring legacy of the C3 App is likely to be the collection of mobile healthcare apps that Cleveland Clinic's Neurological Institute has been developing in its wake using selected modules from the C3 App and insights from its initial use. These efforts accelerated in 2014 and were formalized into a coordinated strategy — dubbed the "Orchard of Neurological Apps" — to efficiently leverage digital health technology and common data elements across a range of neurologic conditions.

"Instead of using new digital health technologies to create one-off apps, which leads to multiple fragmented approaches to care, we're looking at mobile apps as modules to be applied across common functional domains for various conditions," says Cleveland Clinic Concussion Center Director Jay Alberts, PhD, the primary force behind the C3 App, which debuted in 2011.

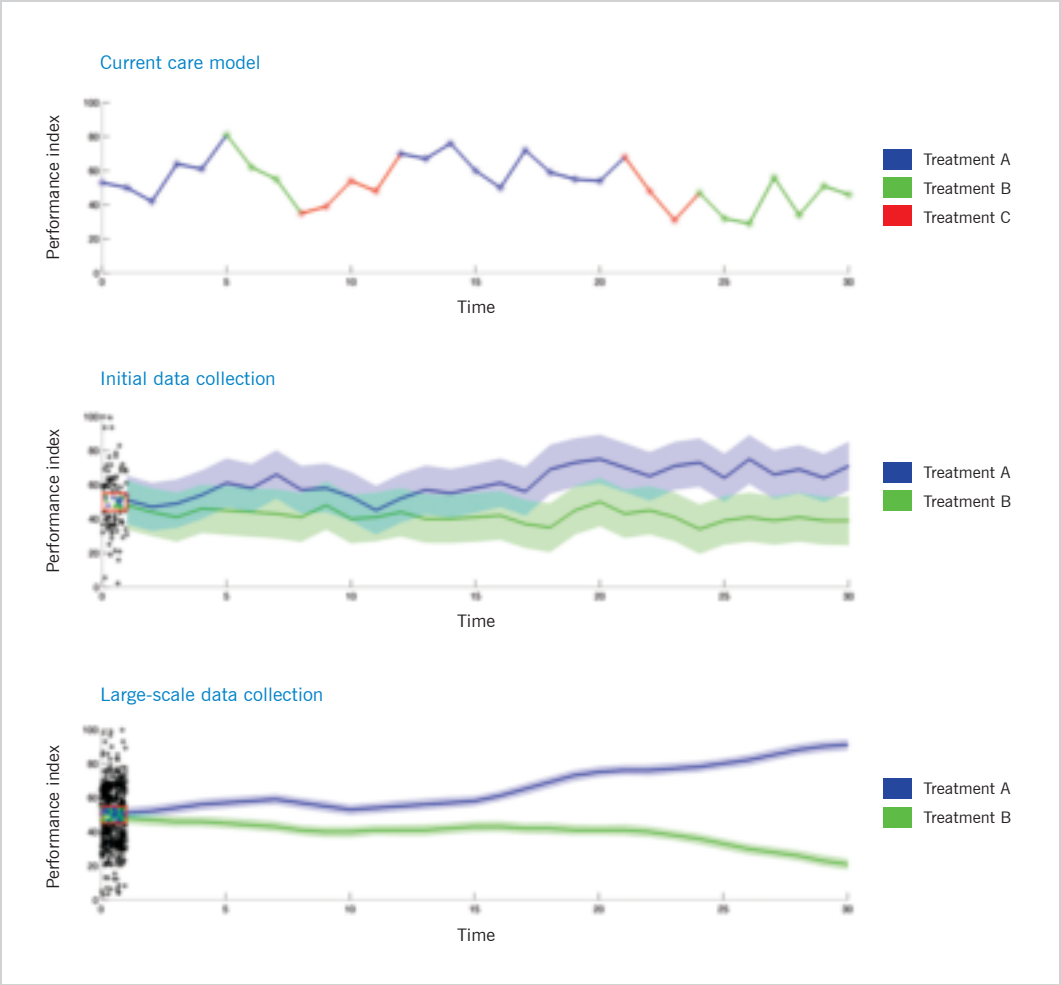
Dr. Alberts took on an additional title in 2014 — Institute Vice Chair for Health Technology Enablement — and was charged with overseeing the Orchard of Neurological Apps strategy.

Leveraging Big Data

The essence of the strategy is to use related mobile healthcare apps to develop, implement and test predictive treatment models by collecting objective, quantitative outcomes among populations of patients with various neurologic conditions. By building "big data" outcomes repositories through collection of common data elements across these associated apps, the institute aims to guide refinement of care paths and enable predictive models of care.

"Mobile apps provide an unprecedented means to collect objective and truly mineable outcomes throughout the treatment process," says Dr. Alberts. They also offer singular opportunities for data visualization (see diagram on p. 17).

LEFT — A high-tech version of the 9-Hole Peg Test developed for several Neurological Institute mobile apps that assess manual dexterity, including those for multiple sclerosis and Parkinson disease. Integration of the well-established test with the iPad enables highly precise and nuanced assessment of response times and related measures. Its use across several different apps embodies the philosophy behind the Orchard of Neurological Apps.

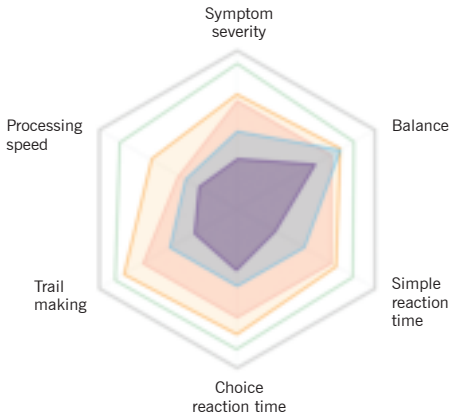


Plots depicting how care may be transformed through predictive analytics for individual patients made possible by the Orchard of Neurological Apps. **The top plot** represents the current model of care for many neurological patients, with variable outcomes (shown on the y-axis) as different treatments and doses are tried based on response to subjective clinical assessments of cognitive or motor function. The result is time-consuming and costly care that does not optimally serve the patient. **The middle plot** illustrates the initial value of collecting objective functional outcomes in combination with treatment protocols in a relatively large set of patients (e.g., 1,000). Variability in outcomes over time has been reduced, but the overlap in confidence fields around the plots for Treatments A and B shows some remaining uncertainty about which treatment is best for a patient presenting at a given functional level. **The bottom plot** shows how clearly distinct outcomes between Treatments A and B might be predicted for a given patient early in management once predictive treatment models are well-populated through large-scale collection (e.g., tens of thousands of patients) of objective outcomes from mobile apps. As the size of the database grows, the predictive modeling has less variability and becomes more patient-specific.

The Trees of the Orchard

A Sampling of Conditions with Apps in Development or Testing

- Concussion
- Mild traumatic brain injury in the military
- Multiple sclerosis
- Parkinson disease/essential tremor
- Fall risk in inpatients and outpatients
- Low back pain
- Sleep disorders
- Chronic pain
- Brain tumor



LEFT — Example (from the multiple sclerosis app) of the data visualization that's possible across multiple domains of function under the Neurological Institute's model of mobile app development.

Shared Assessment Modules

Central to the strategy is the development of a series of assessment modules that quantify domains of functional impairment common to various neurologic conditions. Dr. Alberts cites the example of postural stability. "Patients with multiple sclerosis, Parkinson disease, stroke or concussion all may have balance problems. So there's no reason to create separate balance tests for each and have fragmented approaches to assessment." Accordingly, the C3 App's balance module has been integrated into Neurological Institute apps for multiple sclerosis, Parkinson disease/essential tremor and fall risk assessment. Similar approaches have been taken with other cognitive and motor domains.

Three Phases of Orchard Cultivation

Dr. Alberts foresees the Orchard of Neurological Apps strategy being rolled out in three overlapping phases over the next several years:

Phase I involves completing an emerging suite of Neurological Institute care paths with defined goals and care outcomes and integrating them with complementary mobile apps to collect objective outcomes data across the Cleveland Clinic health system. These data (both clinical and patient-reported) will be used to refine care paths and gather foundational data to build predictive care models.

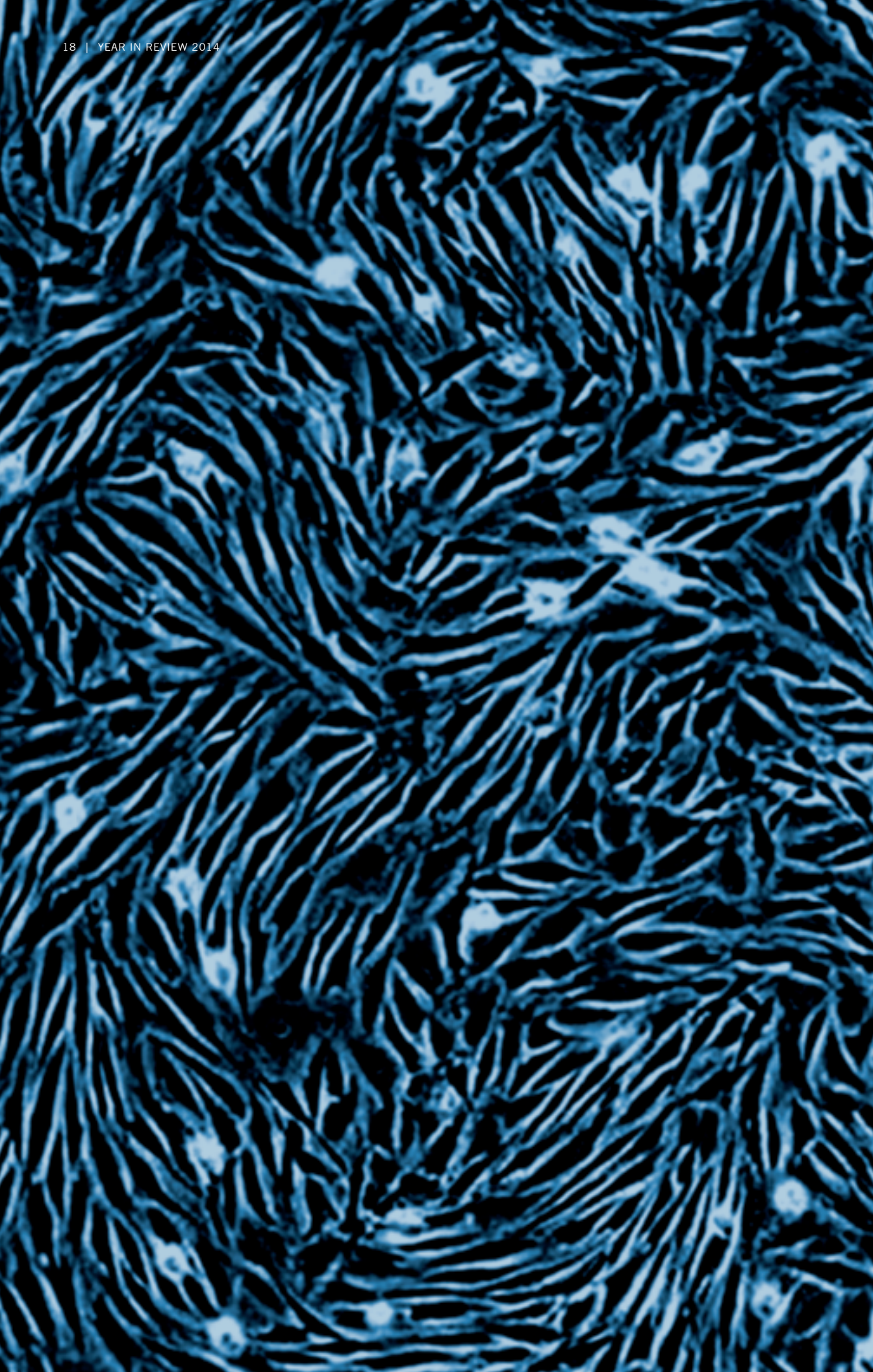
Phase II will see deployment of the care paths and mobile apps to affiliate hospitals across the U.S. Such efforts are already underway with the C3 App and the multiple sclerosis app. During this phase, tools for real-time predictive analytics will be included within the apps and care paths to promote rapid achievement of patient-specific ideal outcomes.

Phase III will consist of identifying the true cost of current patient care scenarios and the cost of delivering care as recommended by the care path. Another goal is to provide the project's tools for objective assessment, coupled with predictive modeling, to address care delivery gaps in rural and underserved areas.

Toward Anticipatory Medicine

Operationally, data from the collection of mobile apps will be used to build an ever-evolving database that will allow providers at Cleveland Clinic and beyond to evaluate patients with these apps and identify the clinical state of their patients relative to others presenting with similar symptoms and dysfunction. The provider can then determine how their patient may respond to various interventions (see figure, opposite page), the rate of disease progression and other fundamental aspects of management.

"Coordinated application of these tools can move us from an episodic care model to a patient-specific model in which clinical decisions are driven by outcomes from large data sets rather than clinical dogma or the treating physician's experience base," says Dr. Alberts. "Our aim is to turn mobile devices from expensive electronic notebooks into data collection systems that can transform the quality and cost of medicine."



〈 2014 SNAPSHOT 〉

Stem Cell Therapy for MS Gets Green Light in First U.S. Clinical Trial

Mesenchymal stem cell (MSC) therapy for multiple sclerosis (MS) has cleared its first major clinical development hurdle in a phase 1 study conducted at Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research.

"The goal was to demonstrate safety, feasibility and tolerability, and this was shown," says lead investigator and Mellen Center Director Jeffrey Cohen, MD, who presented the study results in September at MS Boston 2014, the joint Americas and European Committees for Treatment and Research in Multiple Sclerosis (ACTRIMS/ECTRIMS) meeting.

The study, the first phase 1 investigation of MSCs for MS completed in North America, paves the way for larger human studies that will look more directly at potential benefits from the therapy, which Dr. Cohen says is based on a strategy — repair of damaged tissues in MS — wholly distinct from the mechanisms of MS therapies developed to date.

No Safety Issues or Signs of Disease Activation

The phase 1 study involved 24 patients — 14 with secondary progressive MS and 10 with relapsing-remitting MS — who had scores between 3 and 6.5 on the Expanded Disability Status Scale (mean, 5.2), active disease within the prior two years and optic nerve involvement.

Patients underwent treatment with autologous adult MSCs derived from the bone marrow. The cells were expanded in culture, cryopreserved and thawed for administration by IV infusion as a single dose. The mean dosage was 1.9×10^6 cells/kg (range, 1.3 to 2.0).

Cell infusion was well-tolerated, and over six months of serial follow-up, no treatment-related severe or serious adverse events were observed. Additionally, no disease activation was observed on MRI assessment for gadolinium-enhancing lesions, which was reassuring since investigational MS therapies can sometimes trigger relapses.

Phase 2 Testing to Explore Encouraging Hints of Benefit

The study was not designed to assess efficacy, but patients underwent clinical and MRI

LEFT — Image showing the characteristic morphology of mesenchymal stem cells in culture.

> "Stem cells are directed at repair [of demyelination]. This is a totally different strategy."
>
> — JEFFREY COHEN, MD

monitoring for six months after their infusion. Dr. Cohen says there were no dramatic changes in any patients, but he noted some "encouraging trends" across the results as a whole and "enticing hints of benefits" in individual patients.

Any such benefits will be explored in two studies Dr. Cohen and his team will launch in 2015:

- A larger phase 2 trial to further examine the safety of MSC infusion and more directly evaluate efficacy
- A study to label and track MSCs by MRI following infusion to address unanswered questions about exactly where the cells migrate within the body and how long they survive

"The theory is that MSCs will seek out where they are needed and migrate to damaged tissues," Dr. Cohen notes.

For these future studies, Dr. Cohen plans to use fresh stem cells, as recent studies have suggested that stem cells may be in shock after thawing. His team will also consider using higher doses of stem cells and/or several doses rather than the single infusion used in this initial study.

The Underlying Rationale

Investigation of MSCs is one of several avenues being pursued to thwart MS by promoting the activity of oligodendrocytes, a class of cells that serve to maintain the myelin sheaths that protect nerve axons. In MS, oligodendrocytes stop functioning or are killed off. The hope is that if their activity could be restarted, thereby promoting remyelination, disability progression in MS might be prevented or even reversed.

Ongoing research by Dr. Cohen and his collaborators is aimed at producing other types of therapeutic stem cells with the ability to mature into myelin-forming oligodendrocytes, with the goal of spurring repair of the demyelination implicated in MS disability. It represents a wholly different approach from all approved MS therapies, which are aimed at reducing relapses and slowing disease progression. "Stem cells are directed at repair," he explains. "This is a totally different strategy."

MSCs of patients with MS are believed not to be affected by the disease, but this premise is being evaluated. "One element of our research is to compare the MSCs from MS patients with those from matched controls," Dr. Cohen says. "Although they resemble each other, there may be nuanced differences that aren't easily detectable."

Still a Long — Albeit Promising — Road Ahead

Dr. Cohen notes that while these encouraging phase 1 findings build on equally promising data from MSC studies in animal models of MS, much work remains before cell therapies' potential role in MS can be more fully gauged.

"Beyond needing to determine and quantify potential efficacy against the disease, we still need to understand the manipulations the cells undergo before implantation and then optimize cell types, administration routes, numbers of cells to infuse and other factors," he says. "But this work is off to a strong start."

The phase 1 study was funded by the U.S. Department of Defense and the National Institutes of Health. Dr. Cohen's research team includes co-investigators from the Mellen Center plus colleagues from Case Western Reserve University and University Hospitals Seidman Cancer Center, both in Cleveland.

Opening a GATE to More-Affordable MS Therapy

Dr. Cohen with a patient.

In addition to his early-stage data on a potentially groundbreaking MS therapy (see main story), Dr. Cohen also presented results at the ACTRIMS/ECTRIMS meeting that could broadly expand access to a well-established MS therapy, glatiramer acetate (Copaxone®).

He served as lead investigator of the international GATE trial, a randomized study comparing Copaxone with a generic version of glatiramer acetate from Synthon Pharmaceuticals and with placebo in 735 ambulatory patients with relapsing-remitting MS. All treatments were given by daily subcutaneous injection for nine months.

Copaxone was approved by the FDA in 1997, but no generic versions are currently available for it or other leading MS therapies.

"Some of the first MS medications are going off patent, which creates an opportunity for generic versions to be approved, which could bring patients significant savings in medication costs," Dr. Cohen says. Many MS medications cost patients between $40,000 and $50,000 a year.

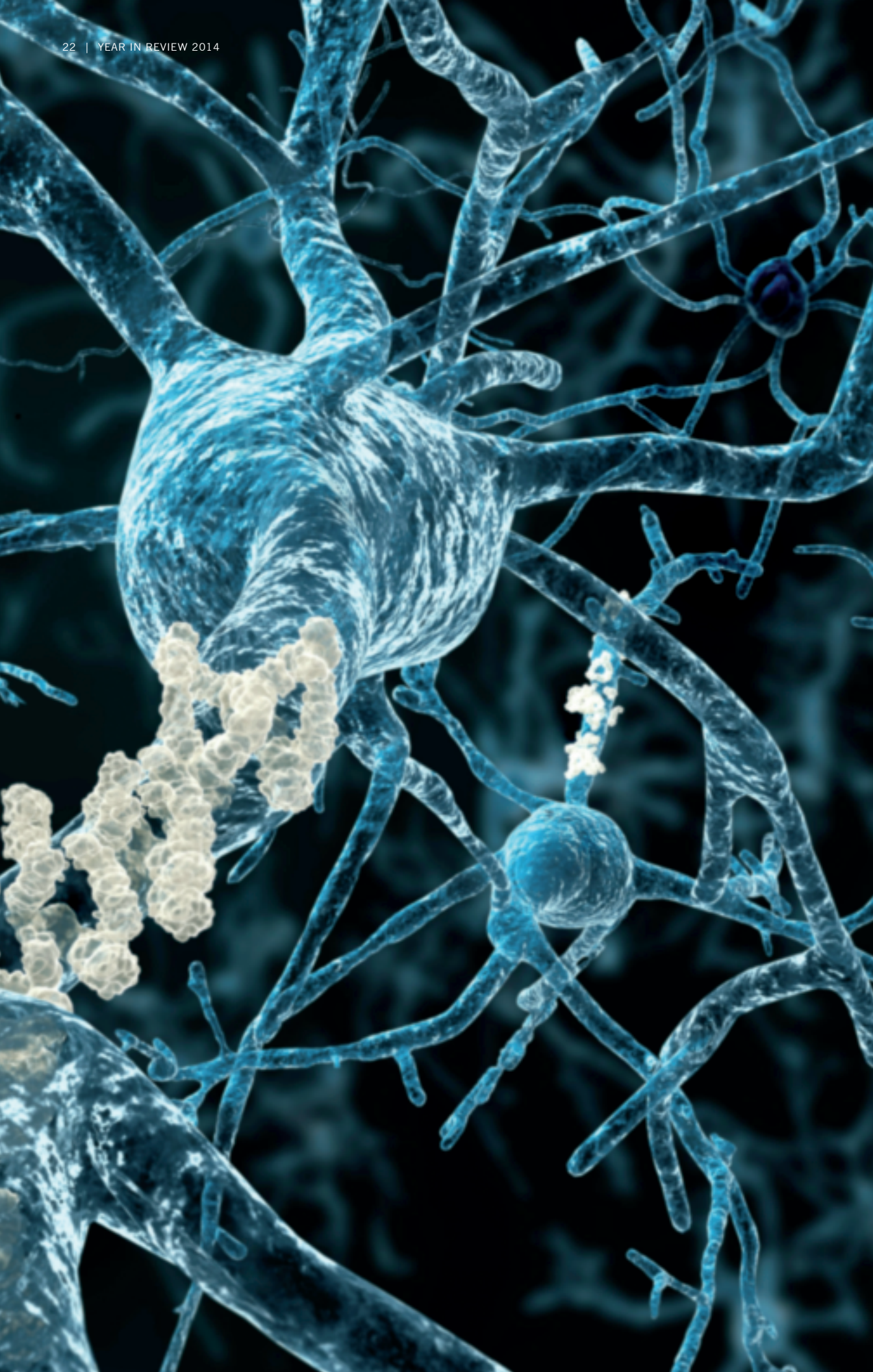
Yet because glatiramer acetate is a complex polypeptide mixture, the standard pharmacokinetic comparisons used in generic equivalence studies are not possible. "This complexity means that small differences in how a generic version is manufactured could produce significant changes in the safety or efficacy of the compound," Dr. Cohen explains.

The GATE study found no such changes between Copaxone and the compound's generic version. Among the key study findings reported by Dr. Cohen:

- The numbers of gadolinium-enhancing MRI lesions were the same over months 7 to 9 (the study's primary endpoint) in patients treated with Copaxone and its generic version, and both groups showed superiority over placebo.
- Rates, types and severity of adverse effects were similar with Copaxone and the generic version.

The fate of Synthon's generic version of the compound now rests in the FDA's hands. Although the GATE results bode well for its eventual approval, Dr. Cohen suspects the compound's complexity may result in a longer-than-typical review time.

Still, the tide may be turning on generic versions of MS therapies — and patients stand to benefit in the pocketbook.



〈 2014 SNAPSHOT 〉

From Wrong Turns to the Right Stuff:

A Strategy for Clinical Trial Success in Alzheimer Disease

There's no sugarcoating it: Alzheimer disease (AD) researchers have been unsuccessful in the quest for new therapies to prevent the disease or delay its onset, slow its progression or improve its symptoms.

That's the inescapable conclusion of a comprehensive review published in July 2014 by researchers at Cleveland Clinic Lou Ruvo Center for Brain Health. The analysis (*Alzheimers Res Ther.* 2014;6[4]:37) found that between 2002 and 2012, 99.6 percent of AD drugs that entered the clinical trial pipeline failed.

"Traditionally, most clinical trials have studied drugs to treat AD once an individual has signs of dementia," says the study's lead author, Jeffrey L. Cummings, MD, ScD, Director of the Lou Ruvo Center for Brain Health. "By that point, it may be too late to make a significant impact."

Focusing on the 'Right Stuff'

Armed with that insight, Dr. Cummings and his colleagues are shaping the Lou Ruvo Center for Brain Health's clinical trial program for AD — one of the largest programs in the nation — to help change the trajectory of success in AD trials.

The multisite program (with four locations — in Las Vegas; Weston, Florida; and Cleveland and Lakewood, Ohio) is pursuing a bold three-pronged mission of developing strategies to transform the clinical trial process, improve the quality of trials and develop new therapies for AD.

Central to the program is a commitment to improve the track record of investigational therapies for AD by doggedly focusing on the "right" things, including:

- The right patients
- The right drugs (or other interventions)
- The right outcomes and biology

The Right Patients — at the Right Time

Although AD trials historically have focused on patients with Alzheimer dementia, researchers have come to realize that AD has a long existence in the brain before signs of dementia manifest. "We now believe that treating patients in the dementia phase is too late because the neuropathological changes are already well-established," Dr. Cummings explains.

LEFT — Neurons with amyloid plaques, one of the targets of ongoing trials in patients with Alzheimer disease.

Table. Selected Cleveland Clinic AD Trials Focused on Prevention or Early Intervention

Study name / descriptor	Study location(s)	Subject profile	Subject age (yr)	Intervention	Duration
TOMMORROW	Las Vegas and Weston, Fla.	Normal cognition	65-83	Daily dose of pioglitazone	5 yr
A4	Las Vegas	Normal cognition but has evidence of amyloid plaque	65-85	Monthly infusion of solanezumab (monoclonal antibody)	3 yr
Donepezil	Cleveland	Normal cognition but has first-degree relative with AD diagnosis	60-75	Donepezil (cholinesterase inhibitor) 5 mg/d for 4 wk, then 10 mg/d	9 visits over 7-8 mo
Rasagiline	Las Vegas; Cleveland and Lakewood, Ohio	Mild to moderate AD	50-90	Rasagiline (MAO inhibitor) 1 mg/d	28 wk
NeuroAD	Las Vegas and Lakewood, Ohio	Mild to moderate AD	60-90	Transcranial magnetic stimulation	15 wk

A complete list of AD clinical trials offered by the Lou Ruvo Center for Brain Health is at clevelandclinic.org/BrainHealthTrials.

Therefore, much of the center's current AD research is focused on:

- **Prevention** in individuals who are overtly normal but at high risk of developing AD
- **Earlier intervention** in patients who are symptomatic for mild disease but do not yet meet the criteria for Alzheimer dementia

The table profiles a sampling of prevention and early-intervention studies now underway at the center. Two of the major prevention studies are outlined below.

TOMMORROW. The largest worldwide AD prevention study to date, TOMMORROW focuses on age and genetics to determine AD risk among 65- to 83-year-olds who are still cognitively normal. It is recruiting more than 5,000 healthy participants across three continents. Individuals at high risk for AD are randomized to placebo or pioglitazone (currently FDA-approved to treat type 2 diabetes) to determine whether the latter therapy can delay or prevent AD.

The study is also investigating whether gene-based biomarkers can determine the risk of developing mild cognitive impairment due to AD within five years. One of the genetic biomarkers being studied is TOMM40, a protein encoded by the *TOMM40* gene, which inspired the study name.

Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study. In this three-year investigation, cognitively normal 65- to 85-year-olds with evidence of amyloid plaque in the brain are receiving placebo or the experimental monoclonal antibody solanezumab, which attacks the abnormal protein. The center is participating in the trial through the Alzheimer's Disease Cooperative Study, a cohort of 40 top U.S. academic medical centers. "This is the most advanced neuroscience trial in AD currently being conducted," Dr. Cummings notes.

Along with the priority given to prevention, other studies in patients with diagnosed AD are trending toward an increased focus on mild to moderate disease, where early interventions may have a more significant impact. For example, a randomized trial is evaluating transcranial magnetic stimulation to improve cognitive functioning in patients with early-stage disease (see table and photo). The therapy stimulates targeted brain areas affected by AD to make them more receptive to cognitive training.

The Right Drugs

Current treatments for AD, which include cholinesterase inhibitors and memantine, do not modify the underlying disease process. There is an urgent need to identify therapies that slow disease progression as well as drugs that further improve AD symptoms.

The Lou Ruvo Center for Brain Health is studying novel drug therapies, including antibodies given intravenously or subcutaneously, oral medications to improve mitochondrial function and other agents that impact AD pathology.

The center's researchers also are embracing a "multiple shots on goal" strategy. For example, a rasagiline study is testing this multifunctional molecule (currently FDA-approved for Parkinson disease) to determine its potential to affect several aspects of neurobiology in AD. "This approach promises to be very important in identifying therapies that eventually will be effective," Dr. Cummings says.

Additionally, immunotherapy studies at the center are looking at ways in which the body's immune response can be stimulated or antibodies can be developed artificially to potentially reduce AD's effects on the brain.

A patient with mild AD undergoes transcranial magnetic stimulation in a clinical trial of the therapy at Lou Ruvo Center for Brain Health in Las Vegas.

The Right Outcomes and Biology

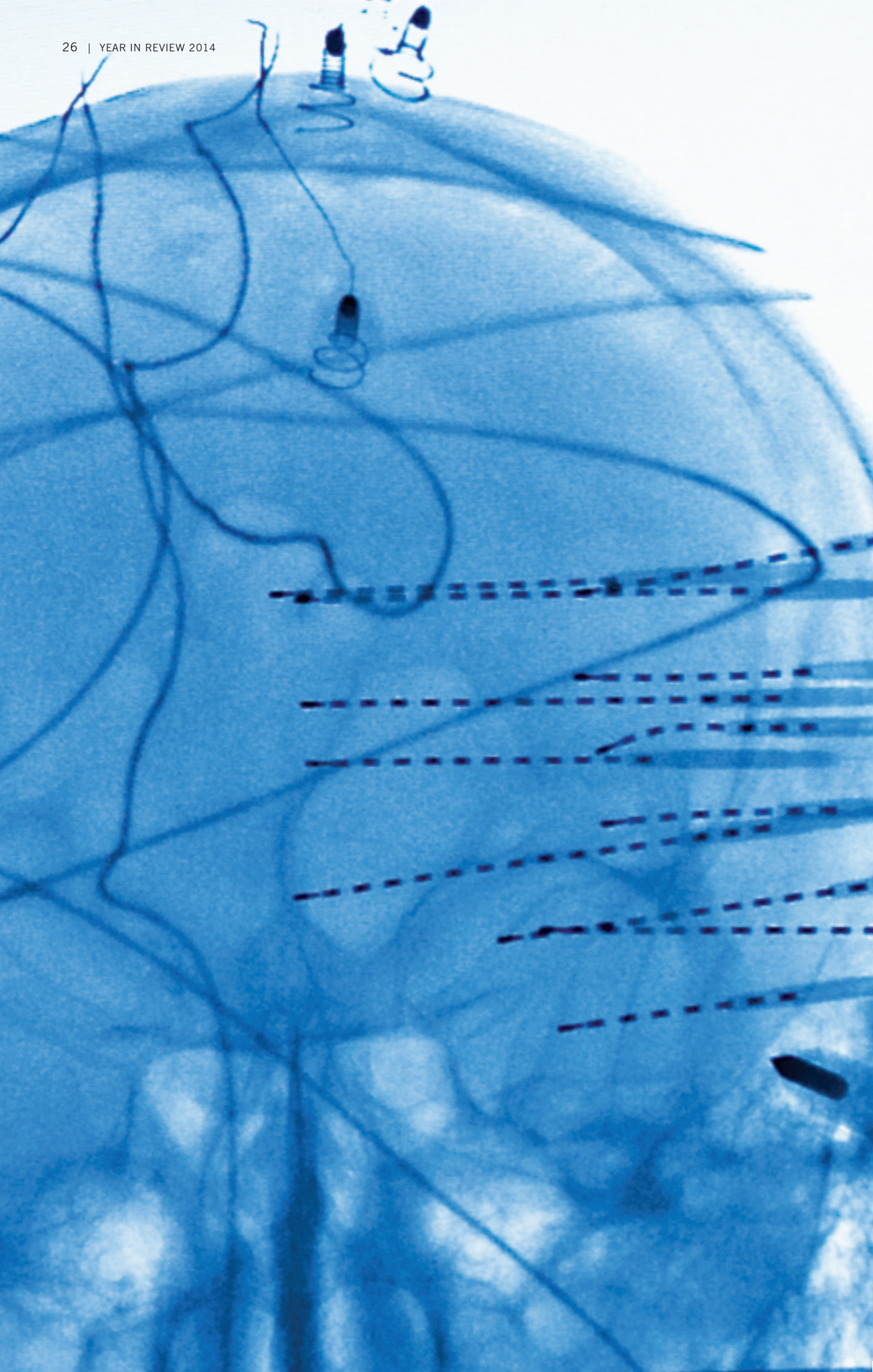
Measuring the success of therapies hinges on measuring the right clinical outcomes, including cognitive-behavioral assessments and biomarkers.

Lou Ruvo Center for Brain Health researchers are collaborating with the FDA's Coalition Against Major Diseases to develop new cognitive-behavioral assessments to measure outcomes in patients with very mild AD. "Just as we need to move to studying and treating patients with more mild disease, we also need to adjust the instrumentation so we can capture changes induced by the drugs," Dr. Cummings says. "If the FDA accepts the recommendations, they could become new standard outcome assessments for clinical trials."

Thinking is also evolving around which biomarkers provide the most useful information in AD research. For the first time, two studies at the center are focusing on pathologies reflected by tangles of tau protein on brain scans, rather than plaques shown by amyloid imaging. "We are finding that tau may be more closely related to cognition than plaques are," Dr. Cummings notes.

Hope for a New Era

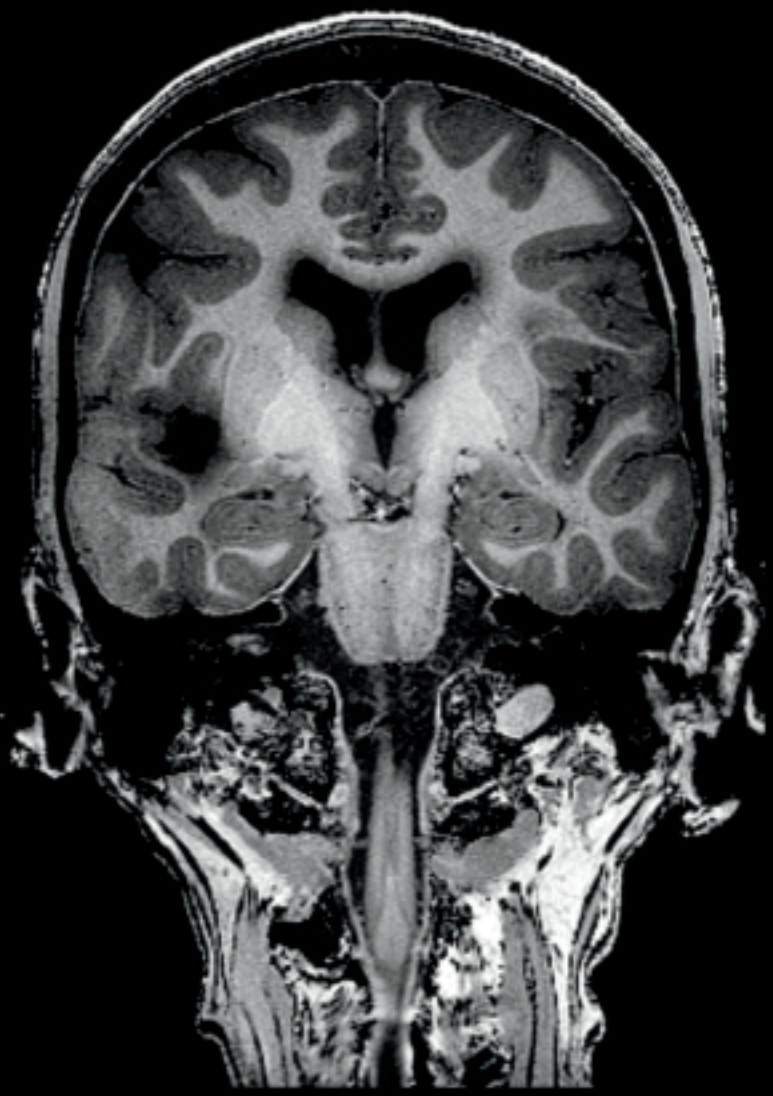
"Collectively, these clinical trials and studies represent an exciting new era in AD research," Dr. Cummings observes. "We are helping transform the approach to clinical trials through innovation, with an ultimate goal of finding more — and more-effective — options for patients with AD."



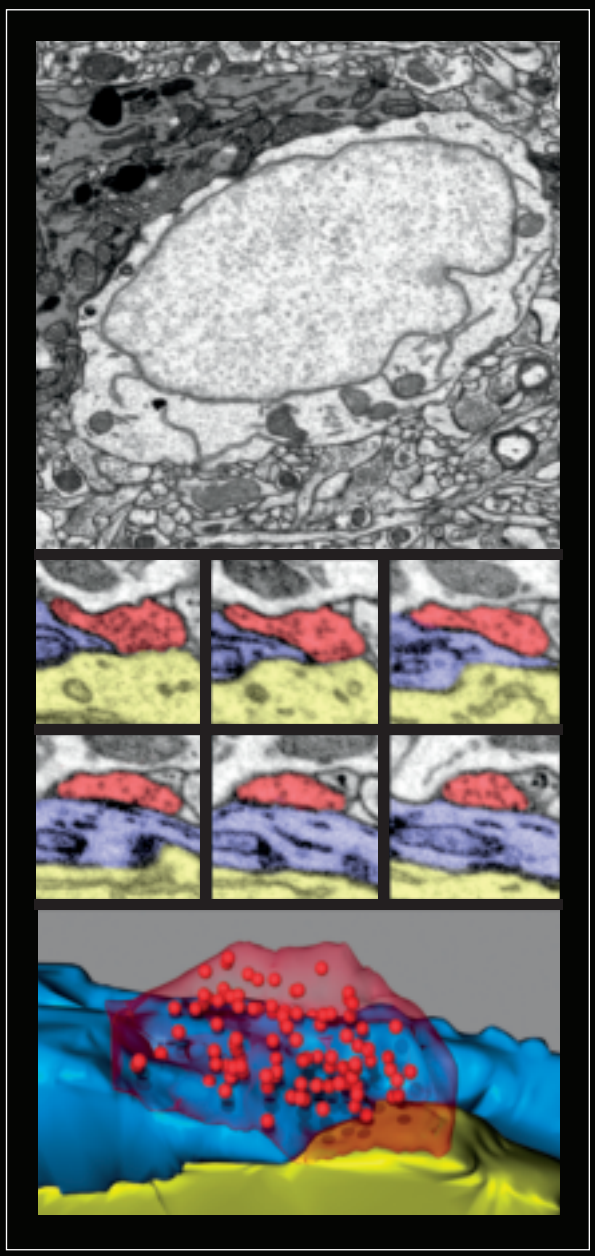
2014 Images of the Year

The clarity of technical advances, the spark of collaborative engagement and the intimacy of caregiving are often expressed far better in images than in words. The Neurological Institute's hundreds of caregivers share a fundamental recognition that the care of brain and nervous system disorders demands equal parts technical and interpersonal expertise. We conclude our 2014 features with a collection of images capturing some choice clinical and scientific achievements from the year along with a few snapshots of the collaborative, patient-focused caregiving we strive to deliver every day of every year.

LEFT — Image of a brain following stereoelectroencephalography (SEEG). Recent advances in SEEG pioneered in Cleveland Clinic's Epilepsy Center are being applied in novel ways by investigators in the Epilepsy Center and the Center for Behavioral Health to unravel pathophysiologic mechanisms in psychiatry. In 2014, neurosurgeon Jorge Gonzalez-Martinez, MD, PhD, and neuroscientist John Gale, PhD, generated initial findings from their promising use of SEEG to probe processes of decision-making and reward encoding, two brain functions that may be involved in conditions such as major depression and obsessive-compulsive disorder.



Coronal section of a 3-D T1-weighted high-resolution MRI taken at 7-tesla (7T) field strength. The spatial resolution of this image, which is not possible at clinical field strengths, permits excellent tissue contrast in important structures such as the hippocampus — the seahorse-shaped structure visible here on either side of the brainstem. Cleveland Clinic acquired a 7T MRI scanner in mid-2013, and 2014 marked the first full calendar year that Neurological Institute researchers were able to take advantage of its magnificent capabilities.



While some researchers believe activated microglia cause harmful inflammation that destroys healthy brain cells, other studies suggest a more beneficial, neuroprotective role. In July 2014, Department of Neurosciences Chair Bruce Trapp, PhD, and his research team demonstrated for the first time that when microglia are activated (top panel above), they migrate to and dislodge inhibitory synapses, the connections between brain cells that slow the firing of impulses. This "synaptic stripping" (shown in the middle panels above [serial electron micrograph sections] and the bottom panel [3-D reconstruction of the serial images]) increases neuronal firing and leads to a cascade of events that enhance brain cell survival. Images are from the team's paper, published in *Nature Communications* (2014 Jul 22;5:4486).

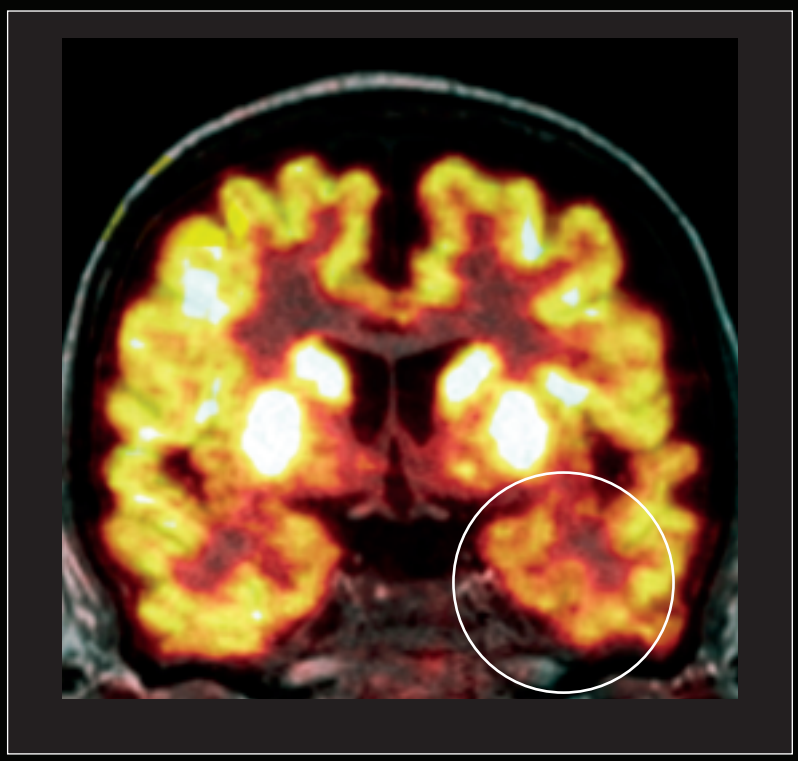
Cross-disciplinary collaboration is a touchstone of caregiving in the Neurological Institute. Two examples are shown here.

ABOVE — Center for Neurological Restoration Director Andre Machado, MD, PhD (left), confers with biomedical engineer and Concussion Center Director Jay Alberts, PhD, while a Parkinson disease patient undergoes assessment in the foreground with a new Cleveland Clinic iPad app for Parkinson disease assessment. The app is being developed by a team led by Drs. Machado and Alberts using selected components of the successful Cleveland Clinic Concussion App that Dr. Alberts introduced in 2011.

RIGHT — Neurosurgeon Pablo Recinos, MD (left), and otolaryngologic surgeon Raj Sindwani, MD, partner on a complex endoscopic skull base surgery that relies on a "two surgeons, four hands" simultaneous approach rather than the tag-team approach of traditional endonasal surgery. These procedures proliferated in 2014 with the launch of Cleveland Clinic's Minimally Invasive Cranial Base and Pituitary Surgery Program, a multidisciplinary collaboration between the Neurological Institute's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and Cleveland Clinic's Head & Neck Institute.

Physiatrists, researchers and therapists in the Department of Physical Medicine and Rehabilitation evaluated a bionic exoskeleton in a patient for the first time in 2014, as shown here. Exoskeleton devices allow paralyzed individuals to stand and take steps with assistance. Patients trigger the computer-controlled exoskeleton to step by shifting their weight, enabling participation in weight-bearing exercises and gait training. These devices are licensed in the U.S. for rehabilitation training under medical supervision but are not approved for nonhospital use.

Epilepsy specialist Stephen Hantus, MD (standing), and EEG technologist David Carr keep an eye on the monitors in the epilepsy/EEG central monitoring unit (eCMU) on Cleveland Clinic's main campus. The eCMU allowed distant monitoring of more than 7,200 patient-days in 2014 at the main campus, other Cleveland Clinic health system hospitals in Northeast Ohio and the Epilepsy Unit at Cleveland Clinic Florida in Weston. The eCMU serves as a live integrated control center with the ability to monitor EEGs and video 24 hours a day, 365 days a year, and give immediate feedback to clinicians at the various hospital units to aid in acute management of the monitored patients.



Cleveland Clinic's pediatric neurosciences program recognizes the special need to marry high-touch sensibilities with high-tech capabilities in the management of neurologic disorders in the youngest patients.

LEFT — Pediatric neurologist Neil Friedman, MBChB, evaluates a young patient in Cleveland Clinic's Neurocardiac Clinic. The clinic is one of only a handful of U.S. clinics dedicated to the multidisciplinary management of the neurodevelopmental disabilities common in children with congenital heart disease — and one of fewer still that are housed within a neurology staff infrastructure. By the end of 2014, the clinic had seen approximately 400 patients since its 2011 launch.

ABOVE — The first pediatric PET-MRI brain examination conducted following Cleveland Clinic's recent acquisition of a leading-edge PET-MRI unit. A colorized PET image overlays a colocalized grayscale anatomic T1-weighted coronal MRI of a 6-year-old with intractable epilepsy. The white circle designates a region of significant hypometabolism. Combined PET-MRI scanning blends MRI's superior spatial resolution with PET's ability to detect hyper- or hypometabolism in selected brain subregions. Simultaneous capture of the two types of imaging allows for a single sedation session, which is especially advantageous for children.

Our Centers at a Glance

Profiles and 2014 Highlights

The Neurological Institute is structured into four departments — Neurology, Neurological Surgery, Physical Medicine and Rehabilitation, and Psychiatry and Psychology — that oversee education/training and coordinate activities across 14 condition-based centers. Patients access care through these subspecialized centers, which are profiled here.

Center for Behavioral Health

The Center for Behavioral Health combines the expertise of over 90 psychiatrists, psychologists and neuropsychiatric researchers to manage common to complex behavioral health disorders and enhance the care and quality of life of patients throughout Cleveland Clinic. These staff care for patients across more than 50,000 outpatient visits and nearly 10,000 inpatient admissions annually. They draw on the latest technology, such as 7-tesla MRI for research and combined PET-MRI for clinical assessment, as well as innovative practice approaches, such as shared medical appointments for selected conditions and a hybrid abstinence/medication-assisted treatment approach to opiate dependence. Interdisciplinary collaboration is at the center's core, through consultation services as well as pacesetting research. The latter ranges from novel uses of magnetoencephalography to study brain connectivity in psychiatric disease to studies of deep brain stimulation for major depression and other psychiatric disorders. Among the center's distinctive offerings are the MEDALS Program for coordinated care and research of mood disorders from childhood through end of life, as well as an interdisciplinary program integrating cognitive behavioral therapy into refractory headache management.

2014 Developments & Highlights

- Applied Cleveland Clinic's new 7T MRI scanner to growing numbers of neuropsychiatric research uses
- Introduced a transcranial magnetic stimulation clinic for patients with medication-resistant depression
- Launched a new fellowship in behavioral neurology and neuropsychiatry
- Reported unprecedented clinical study findings on the potential role of serum S100B as a biomarker for blood-brain barrier disruption related to childhood emotional trauma (*J Psychiatr Res.* In press.)
- Generated first data from innovative use of SEEG to study the pathophysiology of psychiatric functions (e.g., decision-making, reward encoding) in epilepsy patients

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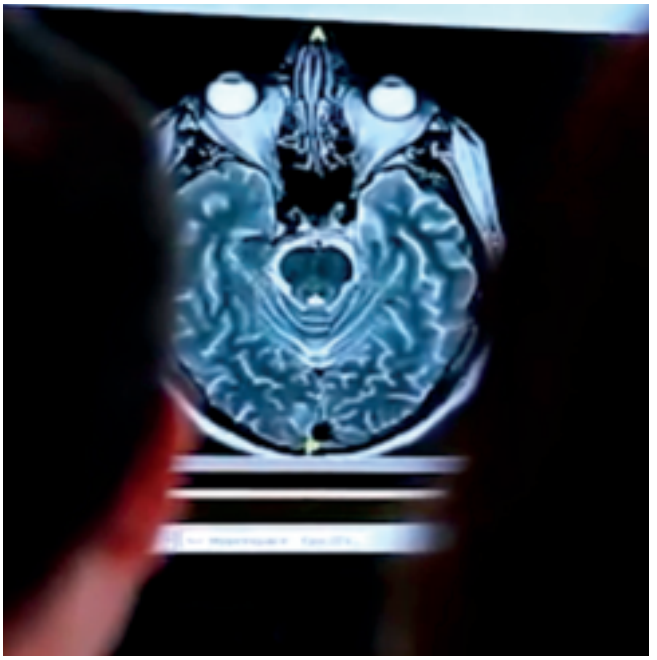

PROGRAM OF

30+

ACTIVE BRAIN HEALTH TRIALS

Lou Ruvo Center for Brain Health

Cleveland Clinic Lou Ruvo Center for Brain Health provides diagnosis and ongoing treatment for patients with a variety of neurocognitive disorders at four sites across the U.S. — in Las Vegas; in Weston, Florida; and at Cleveland Clinic's main campus and another community hospital in Northeast Ohio. The center combines a team of neurocognitive specialists with neuropsychologists, psychiatrists, movement disorder specialists and experts in demyelinating disease to offer highly comprehensive brain health expertise. The center is also a research powerhouse, operating a program of more than 30 clinical trials that draw patients from all four of the above clinical sites to give its studies a unique geographic reach.

2014 Developments & Highlights

- Established the Center for Brain Health Biobank to make well-characterized biospecimens rapidly available for research on neurodegenerative and aging-associated brain diseases
- Led a multicenter phase 3 trial showing benefit and safety of pimavanserin for Parkinson disease psychosis; the study, which featured a novel run-in design, was published in *The Lancet* (2014;383:533-540)
- Launched multicenter study of rasagiline using new trial technology to improve patient adherence and allow at-home patient monitoring, and continued two major Alzheimer disease prevention trials (see p. 22)
- Continued enrollment of over 450 professional fighters in the unprecedented Professional Fighters Brain Health Study of the longitudinal impact of head trauma

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Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center

The Burkhardt Brain Tumor Center is one of the nation's largest, most comprehensive programs for primary and metastatic tumors of the brain, nerves and spine and their effects on the CNS. In 2014, the center performed over 1,100 surgeries and saw adult and pediatric patients at over 10,800 outpatient visits. Its team of neurosurgeons, neuro-oncologists, medical and radiation oncologists, and behavioral health specialists offers a diversity of treatment options in collaboration with Cleveland Clinic's Taussig Cancer Institute. These include leading-edge approaches such as intraoperative MRI, stereotactic radiosurgery, new-generation laser interstitial thermal therapy, convection-enhanced delivery and genomic profiling of tumor tissue. The center's extensive research program ranges from studies of the molecular motors behind glioma cells to dozens of active multicenter clinical trials.

2014 Developments & Highlights

- Established a Minimally Invasive Cranial Base and Pituitary Surgery Program for complex endoscopic skull base surgeries in conjunction with Cleveland Clinic's Head & Neck Institute
- Participated in major clinical trials of therapies including the imaging agent 5-ALA to enhance tumor visualization during resection, the retroviral replicating vector Toca 511 for recurrent glioma and combined use of tumor treating fields therapy with bevacizumab
- Performed 100th NeuroBlate® MRI-guided laser ablation procedure to date
- Continued national leadership in Gamma Knife Perfexion® instruction, training hundreds of clinicians to date

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Concussion Center

The Concussion Center is one of the world's premier programs for advancing the evaluation and management of concussed patients and related research. The center brings together a diverse team, including primary care sports medicine physicians, neurologists, neurosurgeons, neuropsychologists, biomedical engineers, certified athletic trainers, neuro-ophthalmologists, vestibular therapists and radiologists. This team has codified recommended management into a Cleveland Clinic Concussion Care Path, which is continuously refined through data collection via the innovative Cleveland Clinic Concussion (C3) App for mobile devices. Concussion Center staff cared for over 1,500 patients in 2014.

2014 Developments & Highlights

- Continued expansion of C3 App use by high schools and universities across the U.S.; > 12,000 baseline assessments performed on student athletes in 2013-2014 season
- Published validation studies of the C3 App's ability to quantify postural stability in *Journal of Athletic Training* and *Experimental Brain Research*
- Received Department of Defense grant to adapt the C3 App for assessing mild traumatic brain injury in military personnel
- Launched The Trust, a collaboration with the NFL Players Association and other top medical centers, to provide comprehensive brain-body assessments and longitudinal monitoring for retired football players; > 240 participating athletes by year's end

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>3,200

STROKE DISCHARGES ANNUALLY

Cerebrovascular Center

The Cerebrovascular Center, including the Joint Commission-certified Comprehensive Stroke Center at Cleveland Clinic's main campus and a network of eight Primary Stroke Centers and six Stroke Ready Centers, manages one of North America's highest stroke-related patient volumes, with over 3,200 stroke discharges and 1,100 surgical/interventional procedures annually. Center staff also manage the care of patients in 106 neurological care specialty beds, including 22 neurological ICU beds. These cerebrovascular specialists and neurointensivists offer the full continuum of care, from neurologic evaluation to rehabilitation, for patients with all cerebrovascular conditions, from carotid stenosis to intracerebral hemorrhage. Points of distinction include prehospital stroke care with a 24/7 telestroke network and one of only two mobile stroke treatment units in the nation. The center also houses dedicated programs for rare cerebrovascular disorders such as moyamoya disease.

2014 Developments & Highlights

- Launched one of the nation's first mobile stroke treatment units, enabling evaluation and treatment of stroke patients at their home or the site of their stroke (see p. 6)
- Published large study *(Stroke.* 2014;45:467-472) showing that a hyperacute MRI protocol reduces acute endovascular interventions by half while improving outcomes of the overall stroke population, supporting the center's innovative method of using MRI for patient selection to promote safety and cost reduction
- Expanded use of My**Care** Online, a new virtual visit option for follow-up appointments offering the look and feel of an outpatient clinic visit via remote computer or device connection
- Initiated pilot studies of the Cleveland Clinic Stroke Care Path (for ischemic and hemorrhagic strokes plus TIA) at two sites in advance of planned systemwide rollout in 2015
- 30 active research projects underway, including two clinical trials of alternative treatments for wide-neck aneurysms: the Pivotal Study of the LVIS and the SCENT trial
- Joint Commission Comprehensive Stroke Center certification received for Cleveland Clinic's main campus, and Cleveland Clinic Florida (Weston) designated a State of Florida Comprehensive Stroke Center

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>390

EPILEPSY SURGERIES ANNUALLY

Epilepsy Center

Cleveland Clinic's Epilepsy Center is one of the world's largest, most comprehensive programs for the evaluation and treatment of epileptic disorders across the life span. Each year the center's epileptologists and neurosurgeons manage adult and pediatric patients at more than 8,500 outpatient visits, perform over 390 epilepsy surgeries and provide 7,200+ patient-days of real-time seizure tracking in its monitoring units. The center combines this vast experience base with a wealth of innovative technologies ranging from EEG/fMRI to combined PET-MRI to magnetoencephalography. This marriage of clinical expertise and leading-edge equipment has made Cleveland Clinic a pioneer in the development and use of many clinical practices, including stereoelectroencephalography (SEEG), continuous EEG monitoring, laser ablation for intractable epilepsy and more. These forward-leaning practices are bolstered by the center's robust program of basic, translational and clinical research.

2014 Developments & Highlights

- Published first report of a novel technique combining intracranial stimulation with fMRI to define the epileptogenic zone to guide epilepsy surgery (see p. 10)
- Reported provocative findings suggesting that growth-associated protein 43 may be a pathology-specific biomarker for epileptogenicity and epilepsy progression in cortical dysplasia (*Ann Clin Transl Neurol.* 2014;1:453-461)
- Began pioneering use of robotics to implant the NeuroPace® RNS® neurostimulator for faster, more precise and less invasive implantation
- Published first single-center U.S. series on use of the SEEG methodology for extraoperative mapping of refractory focal epilepsy in pediatric patients (*Neurosurgery*. 2014;75:258-268)
- Additional research projects underway in areas ranging from genetic and cellular mechanisms of epilepsy development to advanced signal-processing and imaging techniques for detecting and understanding abnormal EEG/MEG discharges

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Mellen Center for Multiple Sclerosis Treatment and Research

Mellen Center specialists provide ongoing care for approximately 8,000 patients with multiple sclerosis (MS) annually as well as consultative services for neurologists and patients worldwide. They also have made major contributions to the development of therapies to curb MS disease activity and progression. The Mellen Center combines a team of neurologists specializing in demyelinating diseases with physiatrists, psychiatrists, psychologists, and neurocognitive and neuroimaging specialists to address the physical, emotional, cognitive and rehabilitation needs of MS patients and their families. A broad research program in experimental therapeutics, neuroimaging, neurorehabilitation, neurobiology, genetics and immunology offers patients significant clinical research opportunities.

2014 Developments & Highlights

- Played a lead role in organizing 2014 joint ACTRIMS-ECTRIMS meeting, the largest international meeting of MS clinicians and investigators to date
- Presented encouraging findings from first North American clinical trial (a phase 1 study) of mesenchymal stem cell therapy for MS (see p. 18)
- Published overview of Cleveland Clinic's Multiple Sclerosis Performance Test suite of mobile apps for the iPad in *Journal of Visualized Experiments* (2014 Jun 30:e51318), and presented positive validation results of its Processing Speed Test component
- Introduced My**Care** Online for MS patients, a new virtual visit option for follow-up appointments via remote connection by computer or mobile device
- First research patients scanned using the 7-tesla MRI machine recently installed at the Mellen Center, enabling exposure and identification of previously invisible disease components

- Integrated Cleveland Clinic's new, leading-edge CAREN virtual reality treadmill into the neurorehabilitation program for selected MS patients
- Launched first-ever multicenter NIH-funded clinical trial for progressive MS (SPRINT-MS)
- Received five-year institutional fellowship grant from the National MS Society
- Jeffrey Cohen, MD, appointed new Mellen Center Director

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1ST NIH-FUNDED MULTICENTER CLINICAL TRIAL LAUNCHED FOR PROGRESSIVE MS

Center for Neuroimaging

The Center for Neuroimaging's 26 physicians and researchers include diagnostic neuroradiologists, neurointerventionalists, interventional neurosurgeons and physicists whose specialized expertise in brain disorders draws patients from around the world. They work with colleagues across the Neurological Institute's many other centers to bring subspecialized diagnostic and interventional acumen to highly complex cases. The center houses the best available imaging equipment, including a fully equipped intraoperative MRI suite, a leading-edge combined PET-MRI unit designed primarly for clinical use and one of the nation's few 7-tesla MRI scanners. Center staff use these tools to advance neuroimaging research projects ranging from whole-brain 3-D MR spectroscopy studies of the neurochemistry of psychiatric disease to novel applications of diffusion tensor imaging in pediatric epilepsy.

2014 Developments & Highlights

- Integrated use of Cleveland Clinic's new 7T MRI scanner in research studies for a wide spectrum of neurologic conditions
- Exceeded 2,000 quantitative MRI studies performed to date for differentiating between normal and abnormal cognitive decline
- Broadened use of a new combined PET-MRI scanner to pediatric patients, where its technical benefits and single sedation session are especially useful (see p. 35)
- Published first examples of direct electrical stimulation during fMRI in epilepsy (see p. 10)
- Demonstrated a neural basis for distinguishing blast-related from mechanical concussion (*J Neurotrauma.* 2014;31:169-179), identifying an enduring "neural signature" of concussion

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Neuromuscular Center

The Neuromuscular Center is dedicated to the diagnosis, treatment and research of neuromuscular disorders such as ALS, peripheral neuropathy, myasthenia gravis and myopathies. The center's neurologists regularly collaborate with diverse specialists from across Cleveland Clinic to offer the comprehensive, coordinated management often required by these diagnostically challenging conditions. Its high-volume EMG laboratory is accredited with exemplary status by the American Association of Neuromuscular and Electrodiagnostic Medicine. The center also houses one of the nation's few cutaneous nerve laboratories, dedicated to improving diagnosis and research in small fiber sensory neuropathy, and a comprehensive autonomic testing center, including thermoregulatory sweat testing, for patients with autonomic disorders.

2014 Developments & Highlights

- Contributed to an international study in *Nature Neuroscience* (2014;17:664-666) identifying mutations of the *MATR3* gene as a rare cause of familial ALS
- Initiated an EMG procedure quality assurance program across the entire Cleveland Clinic health system
- Published descriptive electrodiagnostic findings from the largest cohort of patients with true neurogenic thoracic outlet syndrome to date (*Muscle Nerve.* 2014;49:724-727)
- Continued national leadership in neuromuscular ultrasound training, including at the second Cleveland Clinic Musculoskeletal Ultrasound Workshop in June 2014

clevelandclinic.org/neuromuscular

Center for Neurological Restoration

The Center for Neurological Restoration brings together diverse specialist physicians and researchers for the comprehensive management and study of movement disorders, chronic pain and headache. The center is nationally recognized for innovations in the treatment of movement disorders and a world leader in deep brain stimulation (DBS), which is routinely used for Parkinson disease, essential tremor and some forms of dystonia. Center staff are also studying how DBS may alleviate other conditions, including obsessive-compulsive disorder, major depression, some forms of chronic pain, and weakness following stroke. The center's unique structure, which fosters cross-pollination among multiple disciplines, also helps advance understanding and treatment of processes underlying pain chronification. Other points of distinction include a Huntington's Disease Comprehensive Care Clinic, a program for performing DBS under general anesthesia with intraoperative MRI, a comprehensive Chronic Pain Rehabilitation Program and the distinctive IMATCH Program for multimodal management of chronic headache. The center also offers deep experience in spinal cord stimulation for refractory pain syndromes, including revision surgery. All these activities are supported by a broad research portfolio comprising diverse clinical trials and multiple laboratory investigations.

2014 Developments & Highlights

- Merged with Cleveland Clinic's Neurological Center for Pain to allow for greater integration of patient care combining medical, behavioral and surgical therapies
- Conducted first study evaluating an innovative Cleveland Clinic iPad app for assessing Parkinson disease and essential tremor patients using modules from the Cleveland Clinic Concussion App and a novel stylus (see p. 30)
- Conducted a magnetoencephalography study (*J Neurophysiol.* 2014;112:276-286) demonstrating for the first time that neural processing of visually cued pain anticipation involves the primary visual cortex, yielding insights into maladaptive pain conditioning
- Led first-ever controlled clinical trial (still ongoing) of DBS targeting the ventral striatal region for post-stroke pain syndrome
- Demonstrated in a preclinical model that a Cleveland Clinic-developed approach to chronic deep cerebellar stimulation promotes cortical plasticity and recovery of motor function after stroke (*J Neurosci.* 2014;34:9040-9050)

- Developed a model (*Neuroscientist.* 2014 Jun 20 Epub) describing how chronically stimulating ipsilesional premotor areas may strongly affect key mechanisms of stroke motor recovery as an alternative to primary motor cortex stimulation
- Integrated Cleveland Clinic's leading-edge CAREN virtual reality treadmill into the neurorehabilitation program for selected movement disorder patients

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Pediatric Neurosciences

Cleveland Clinic's pediatric neurosciences program comprises over 40 physicians and psychologists specializing in child and adolescent neurology, neurosurgery, epilepsy, brain tumors, psychiatry and other CNS-related disciplines. They direct a multitude of specialized clinical programs, many of them interdisciplinary, for challenging brain and spine disorders. Points of distinction include a Neurocardiac Clinic for managing neurodevelopmental disabilities in children with congenital heart disease, 24/7 continuous EEG monitoring, and one of the nation's few pediatric syncope and dysautonomia programs with a fully equipped pediatric autonomic lab. The program's robust research efforts range from breakthrough investigations in autism to novel studies of the pathophysiology of Chiari malformation.

2014 Developments & Highlights

- Started the nation's third center of excellence for *CDKL5*-related disease as designated by the International Foundation for CDKL5 Research
- Serving as lead national site for a study of the natural history of Pearson syndrome
- Published largest-ever studies of twins with autism (*J Autism Dev Disord.* 2014;44:2013-2015) and females with autism (*J Am Acad Child Adolesc Psychiatry.* 2014;53:329-340), demonstrating a strong genetic component and identifying a specific female autism phenotype
- Identified unique pattern of brain abnormalities and cognitive deficits in a subgroup of autism (children with *PTEN* mutations) that may help individualize therapy (*Mol Psychiatry.* 2014 Oct 7 Epub)
- Convened major CME symposium, "Epilepsy Surgery in Children," the first of its size and caliber in over a decade, with dozens of national and international expert faculty
- Neil Friedman, MBChB, appointed Director of the Center for Pediatric Neurology

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Center for Regional Neurosciences

Beyond the centers profiled here, an additional Neurological Institute center is designed expressly to increase patient access to the expertise of all the others.

The Center for Regional Neurosciences supports the coordinated extension of highly subspecialized neurologic and neurosurgical services beyond Cleveland Clinic's main campus to multiple Cleveland Clinic community hospitals and family health centers throughout Northeast Ohio. The result is convenient access to world-class neurologic expertise for almost all Northeast Ohio residents.

Many patients can visit their nearby community hospital or family health center to see specialists in movement disorders, multiple sclerosis, cerebrovascular disease, neurocognitive disorders and other complex conditions. Additionally, surgical procedures not typically offered in the community by other academic medical centers — such as many spine and cerebrovascular operations — are provided at community hospitals in addition to the main campus. Even patients whose procedures are restricted to the main campus, such as deep brain stimulator implantation, can receive preparatory and follow-up care at community locations.

Department of Physical Medicine and Rehabilitation

The Department of Physical Medicine and Rehabilitation offers full cross-disciplinary services for patients with physical, psychosocial, cognitive and vocational impairments. Care is coordinated across a continuum that spans the acute hospital as well as inpatient rehabilitation, skilled nursing and outpatient therapy at facilities throughout Northeast Ohio. Three Cleveland Clinic Rehabilitation Hospitals and Cleveland Clinic Children's Hospital for Rehabilitation offer acute inpatient rehab care across 114 beds. Over 40 staff physiatrists and collaborative clinical staff work with 700+ specialty-trained physical, occupational and speech therapists to care for patients at nearly 400,000 outpatient and over 325,000 inpatient visits annually. Department staff develop the rehabilitation components of numerous care paths and innovative mobile apps to ensure quality-driven care for patients across the enterprise. Sponsored researchers pursue investigations ranging from nerve regrowth in spinal cord injury to analyses of distance-learning interventions and outcomes measurement.

2014 Developments & Highlights

- Published multiple validation studies confirming reliability of 6 Clicks, a set of electronically administered questions assessing mobility and basic function developed by Cleveland Clinic and Boston University, used to rationalize rehab resource use and acute hospital discharge planning
- Fully integrated the use of two new virtual-reality treadmill systems — the Computer Assisted Rehabilitation Environment (CAREN) and C-Mill — to assess, train and study patients' mobility in realistic but protected settings
- Continued investigations funded by $5 million in federal grants, including an evaluation of the utility of transcranial direct current stimulation and its impact on neuroplasticity
- Sponsored and directed the Spinal Cord Injury Board Review Course in collaboration with the Academy of Spinal Cord Injury Professionals — now in its 15th successful year

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New Joint Venture with Select Medical

In August 2014, Cleveland Clinic and national rehabilitation services provider Select Medical formed a joint venture to enhance inpatient rehab services in Northeast Ohio and improve access for patients with complex rehab needs.

As part of the venture, the two organizations are building a 60-bed adult inpatient rehab hospital in Avon, Ohio, west of Cleveland, expected to open in late 2015. They also have completed a management agreement to enhance operations at existing Cleveland Clinic rehab facilities. The venture also includes plans to establish a residency program for physicians in physical medicine and rehabilitation.

"This represents collaboration on the best rehabilitation research, the latest clinical protocols, and the finest educational resources and programs for our staff and patients," says Frederick S. Frost, MD, Chairman of the Department of Physical Medicine and Rehabilitation and Executive Director of Cleveland Clinic Rehabilitation and Sports Therapy. "Cleveland Clinic intends to grow exceptional rehabilitation services regionally, nationally and internationally."

Sleep Disorders Center

Cleveland Clinic's Sleep Disorders Center was among the nation's first programs dedicated to the diagnosis and treatment of sleep disorders in patients of all ages. Accredited by the American Academy of Sleep Medicine, the comprehensive center is staffed by physicians from disciplines including neurology, psychiatry/psychology, pulmonary and critical care medicine, otolaryngology, pediatrics, internal medicine and family medicine. They bring particular expertise to management of sleep problems in the setting of comorbidities such as epilepsy, stroke, hypertension, cardiac disease and depression. The center is a national leader in sleep research, with NIH- and industry-sponsored trials ranging from use of positive airway pressure (PAP) in paroxysmal atrial fibrillation, investigation of a novel phrenic nerve stimulation technique to treat central sleep apnea, and assessment of PAP therapy in stroke patients. Points of distinction include development of the online GO! To Sleep program to facilitate home self-management for short-term insomnia and a growing volume of adult and pediatric sleep studies (> 10,000 a year) performed across the center's multiple sleep labs.

2014 Developments & Highlights

- Participated in an NIH-funded trial (*N Engl J Med.* 2014;370:2276-2285) showing significant blood pressure reductions with continuous PAP therapy, but not with supplemental oxygen therapy, in patients with obstructive sleep apnea (OSA) and elevated cardiovascular risk
- Participated in the NIH-funded HeartBEAT study (*J Clin Sleep Med.* 2014;10:835-843) and led an analysis showing an association between severe untreated OSA and elevated blood pressure in patients with increased cardiovascular risk despite intensive antihypertensive therapy
- Expanded availability of home sleep testing as a qualifying test for patients with high pretest probability of moderate to severe OSA
- Published large clinic-based analysis (*Epilepsy Behav.* 2014;37:270-275) finding that PAP therapy produces beneficial effects on seizures in adults with epilepsy and OSA
- Initiated development of a sophisticated mobile app for sleep disorders assessment adapted from the successful Cleveland Clinic Concussion App profiled on p. 14

- Expanded sleep apnea management clinics across the enterprise, providing service for > 500 patients in a group setting
- Fully integrated sleep program at Cleveland Clinic Florida, a developing multidisciplinary program modeled on the Cleveland program

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Center for Spine Health

The 18 spine surgeons and 17 medical/interventional spine specialists in the Center for Spine Health care for the full spectrum of spine disorders, from low back pain to complex spine deformities and tumors. The center's comprehensive offerings include medical management, physical therapy, surgical interventions, minimally invasive injection procedures, specialized exercise programs, acupuncture, osteopathic manipulation and an in-house functional restoration program. Points of distinction include its dedicated Spine Research Laboratory, one of the nation's largest and most experienced spine tumor review boards, and one of the best-established spine radiosurgery programs. The center employs leading-edge technology ranging from the O-arm® Surgical Imaging System to a MySpine smartphone app that aids in patient self-management of acute back pain.

2014 Developments & Highlights

- Implemented (with EMR integration) the acute-care phase of the Cleveland Clinic Spine Care Path across the health system following pilot studies demonstrating reductions in inappropriate imaging and opioid use plus substantial cost reductions
- Began pilot studies of the subacute-care phase of the Spine Care Path (for back pain of six to 12 weeks' duration)
- Instituted novel online program allowing spine surgeons to review costs of their surgeries in near real time for greater cost awareness and more cost-effective practice
- Published largest-ever study of concurrent MS and cervical stenosis (*Spine J.* 2014;14:331-337), yielding insights on prognosis and outcomes by MS subtype
- Two new center Co-Directors, Thomas Mroz, MD, and Michael Steinmetz, MD, assuming leadership in Jan. 2015 to replace retiring Director Gordon Bell, MD

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60%

REDUCTION IN SURGICAL SITE INFECTIONS VS. PRIOR YEAR (3.7% TO 1.5%)

A New Standard for U.S. Spine Care

January 2014 saw the launch of the National Orthopaedic & Spine Alliance (NOSA), an unprecedented clinically integrated physician-hospital organization for orthopaedic and spine care founded by Cleveland Clinic and four other leading U.S. institutions.

NOSA is designed to create a new quality-driven model for orthopaedic and spine care delivery through coordinated development of standardized care protocols and consistent measurement of outcomes and cost. The alliance is organized so that participating provider organizations collectively contract with large employers to deliver care reimbursed through bundled payments for entire episodes of care. NOSA members then share the financial rewards and risks.

NOSA's aim is to add best-in-class provider organizations in 10 metropolitan areas where employees of the 500 largest U.S. companies are highly aggregated. For more, visit *nationalorthospine.com*.

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By Toby Cosgrove, MD,
CEO and President, Cleveland Clinic

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About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), 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 2014, Cleveland Clinic was ranked one of America's top four hospitals in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 20th consecutive year) and urologic care.

Cleveland Clinic

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