

Neurological Institute

2015 Year in Review

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The Neurological Institute:

A Care Model for Transformative Practice

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 nervous system disorders.

The 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 subspecialty centers. (2015 news briefs from each of these centers begin on page 28.)

Patients access care through these subspecialty centers, which bring together medical, surgical and rehabilitative experts in a model organized around patients’ diagnostic and management needs rather than a traditional departmental or discipline-based structure.

1 INTEGRATED INSTITUTE



4 ORGANIZATIONAL DEPARTMENTS

14 SUBSPECIALTY CENTERS FOR CARE

300+ PROFESSIONAL STAFF

NEUROLOGICAL INSTITUTE VITAL STATISTICS (2014)

224,567 Annual outpatient visits

15,932 Annual admissions

90,447 Annual inpatient days

13,473 Annual surgical/interventional procedures

78,398 Annual neuroimaging studies

257 Staff physicians

155 Clinical residents and fellows

25 Research fellows

NEUROLOGICAL INSTITUTE RESEARCH FUNDING (2014)

\$16.8M Total grant and contract research funding

52 Federal grants and contracts

224 Nonfederal grants and contracts

276 Active clinical research projects

75 New clinical research projects (initiated 2014)

78 Staff leading clinical research projects

7,123 Patients enrolled in clinical research projects

225,000
PATIENT VISITS

16,000
ADMISSIONS

13,500
PROCEDURES

Across its nearly 225,000 annual patient visits and 16,000 annual admissions, the Neurological Institute manages the full spectrum of brain and CNS disorders. For patients in need of leading-edge diagnostics and treatment, Neurological Institute physicians and surgeons frequently advance innovations in areas including:

- > Epilepsy surgery and monitoring
- > Stereotactic radiosurgery
- > Deep brain stimulation
- > Brain tumor therapeutics
- > Concussion assessment and therapy
- > Use of telemedicine and mobile devices to enhance patient access and experience

ACCESS IN 3 STATES
AND BEYOND

Access is an increasingly critical element of U.S. healthcare value, and Cleveland Clinic recognizes its particular importance in complex brain and spine diseases. Neurological Institute services are available at more than two dozen Cleveland Clinic locations across Northeast Ohio, as well as in Weston, Florida, and Las Vegas. This network enables patients to access the institute's specialists within a couple of hours' flight time from almost any spot in the continental U.S. And the Neurological Institute is aggressively adopting distance health initiatives to expand patient access beyond geographic boundaries and boost patient empowerment in the process (see page 8).



\$16.8M
IN RESEARCH GRANTS
276
RESEARCH PROJECTS

The Neurological Institute's clinical caregiving is complemented by a robust research program that prioritizes collaboration and innovation. In addition to conducting 276 clinical research projects, the institute's experts team with scientists in Cleveland Clinic's Lerner Research Institute to pursue lab-based and translational investigations. Program highlights include one of the largest U.S. clinical trial programs for neurocognitive diseases, leadership in studying deep brain stimulation for novel applications, and pioneering work in the simultaneous use of neural stimulation and fMRI to study, diagnose and manipulate diseased brain networks.

DATA CAPTURE = TRANSFORMED CARE

The Neurological Institute is committed to data-informed practice. Its pioneering Knowledge Program interactive data collection platform electronically collects and tracks discrete patient-reported outcomes within existing clinical workflows. It can be customized for specific conditions and is accessible across the Cleveland Clinic enterprise, capturing data from millions of patient visits to date.

The institute has extended this ethic of data-driven care to the development of EMR-embedded care paths and to its growing collection of integrated mobile apps for neurological conditions, all of which aim to optimize clinical decision-making while informing quality initiatives and identifying 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 patient outcomes, reduce costs and enhance healthcare value.

2015 A YEAR OF TRANSITIONS & >>> TRANSFORMATION

ANDRE MACHADO, MD, PhD, was appointed Chair of the Neurological Institute in October 2015. Dr. Machado has been a neurosurgeon at Cleveland Clinic since 2006, most recently serving as Director of the Center for Neurological Restoration. He has received numerous patents and earned international acclaim for his clinical work in deep brain stimulation and neuromodulation. An active laboratory researcher and leader of several clinical trials, Dr. Machado was a recipient of the 2009 NIH Director's New Innovator Award to support his ongoing research in deep brain stimulation for chronic pain. He lectures and publishes widely and holds leadership roles in the Congress of Neurological Surgeons and the American Society of Stereotactic and Functional Neurosurgery.

MICHAEL T. MODIC, MD, FACR, stepped away from his role as founding Neurological Institute Chair (a title he held since 2007) to take on a key new role in Cleveland Clinic's leadership: Chief Clinical Transformation Officer. In this new position, Dr. Modic is leading enterprise-wide efforts to evolve Cleveland Clinic's care delivery systems to stay ahead of changes in where and how U.S. healthcare is delivered and how it is reimbursed. His appointment stemmed directly from innovative changes he implemented as Neurological Institute Chair, including early support of the Knowledge Program data platform and launching Cleveland Clinic's care path initiative. Dr. Modic continues his practice as a neuroradiologist in the Neurological Institute.



ANDRE MACHADO, MD, PhD
CHAIRMAN, CLEVELAND CLINIC NEUROLOGICAL INSTITUTE

WELCOME FROM THE CHAIRMAN

Dear Colleagues,

Neurological disorders — Alzheimer and Parkinson diseases, stroke and others — are the leading cause of disability in the developed world. The burden these disorders pose in terms of individual suffering and healthcare costs is already enormous, and it will only grow with the aging of the population. To address this burden, neurologists, neurosurgeons and the broader healthcare community need to do three fundamental things:

- Identify the populations at risk.
- Develop strategies to reduce the risk of those populations.
- Manage those populations more effectively than we do today.

The third objective will of course require new and better therapies, but all three objectives require something equally important: a transformation of how, when and where healthcare is delivered.

As I have taken on my new role of Neurological Institute Chair in the closing months of 2015, I am privileged to inherit the many forward-looking initiatives implemented by my predecessor, Michael T. Modic, MD, FACR, to transform care along these lines in the Neurological Institute. Under his leadership since 2007, our institute has been in the vanguard of Cleveland Clinic's adoption of patient-reported outcomes collection (via our Knowledge Program data platform), electronic medical record-integrated care paths, distance health initiatives and coordinated healthcare app development. In fact, these initiatives were a primary reason for Dr. Modic's recent appointment as Cleveland Clinic's first Chief Clinical Transformation Officer.

The fruits of those initiatives fill many pages of this review of the past year in the Neurological Institute, from the report on page 8 outlining our diverse telemedicine offerings to the page 16 feature profiling our leadership in the innovative MS PATHS "learning health system" initiative in multiple sclerosis. Additionally, the story on page 24 reflects how Cleveland Clinic focused its 13th Annual Medical Innovation Summit, held here in October, specifically on promoting efforts to transform care and technology in the neurosciences.

Mixed in with these features are reports on our 2015 efforts to advance healthcare in the more traditional sense — through research on novel treatment approaches for disorders ranging from glioblastoma to stroke-related disability. Indeed, progress in today's healthcare environment requires transformation in both the therapies we use and the ways we deliver care to patients. I'm proud to report that the Neurological Institute is on task in both regards.

Respectfully,



Andre Machado, MD, PhD

Chairman, Cleveland Clinic Neurological Institute
machada@ccf.org



2015 HIGHLIGHT

Going the Distance with Virtual Medicine for Better Access, Outcomes and Experience

Cleveland Clinic is pioneering remote delivery of care through multiple distance health initiatives (see sidebar, page 10), and its Neurological Institute has been at the forefront of those efforts throughout 2015.

The Case for Distance Health

“We are responding to patients’ needs for better care, greater convenience and improved access to our services,” says Peter Rasmussen, MD, Cleveland Clinic’s Medical Director of Distance Health and Director of the Cerebrovascular Center in the Neurological Institute. He adds that using distance health technologies for the right patients in the right place at the right time can maintain or enhance the quality of care while reducing healthcare costs, such as by curbing unnecessary ER visits.

“Virtualizing the practice of medicine drives value where it makes clinical and economic sense,” Dr. Rasmussen notes. He points out that telemedicine-enabled virtual visits can increase providers’ efficiency in the era of bundled payments while providing a lower-cost care option for many patients, especially if they have to travel to see a provider.

“Virtualizing the practice of medicine drives value where it makes clinical and economic sense.”

PETER RASMUSSEN, MD

Making a Difference in Acute Stroke

Beyond efficiencies and convenience, Neurological Institute caregivers are finding that distance health can be a lifesaver in acute stroke care. In addition to Cleveland Clinic’s pioneering use of its mobile stroke treatment unit (see sidebar, page 11), Cerebrovascular Center specialists now provide consults via videoconference to many patients with suspected stroke who arrive in the ER of a Cleveland Clinic regional hospital or an outside hospital participating in Cleveland Clinic’s Telestroke Network.

Such patients receive specialist consults in an average of less than five minutes. “That’s faster than most neurologists can walk to the ER,” Dr. Rasmussen says. “Having a stroke neurologist present virtually with a patient is 98 percent as accurate as having a stroke specialist there in person, and diagnosis is 30 percent more accurate than if the patient were assessed by an emergency physician or general neurologist.”

Expanding the Use of Teleconsults

The stroke experience has shown that distance is not a deterrent to diagnosis. In 2015, Neurological Institute physicians began providing

Sampling of Cleveland Clinic Distance Health Initiatives

MyCare Online, a HIPAA-compliant Skype®-like app that connects patients directly with Cleveland Clinic providers for face-to-face visits

MyConsult Online, a secure web platform that allows patients to obtain a written second opinion from a Cleveland Clinic specialist

Remote Image Upload, which enables digital transfer of images from multiple vendor sources into a patient's EMR and subsequent access from any point of care

A coordinated collection of neurological apps (the "Orchard of Neurological Apps") and related remote management tools that allow monitoring of patient data in real time and/or interaction with patients to monitor their condition

Telestroke Network, which provides outside hospitals 24/7 access to enhanced stroke consultation services from specialists in Cleveland Clinic's Cerebrovascular Center via a mobile two-way videoconferencing system and linked imaging systems

A mobile stroke treatment unit that brings the essential tools of stroke diagnosis and treatment right to the site of stroke onset via a specially equipped and staffed ambulance

general neurology consults to one Cleveland Clinic regional hospital with no neurologist on staff. Similarly, they offer neurocritical care consultation services via telemedicine at Cleveland Clinic Florida's hospital in Weston, Florida. "This can be a valuable superspecialty augmentation to the bedside intensive care team," Dr. Rasmussen notes.

Similar expansion is being seen in online second opinions. Whereas 106 patients sought second opinions from Neurological Institute staff via Cleveland Clinic's MyConsult Online platform in 2014, that number was on track to be substantially higher in 2015 (as of press time). And Cleveland Clinic will soon expand options to include a video appointment with the specialist who provides the second opinion.

Popular with Patients Everywhere...

In noncritical situations, teleconsults and virtual visits have become a convenient way of conducting outpatient visits for patients in various subspecialty areas, such as pediatric neurology, sleep disorders, neuromuscular disease, behavioral health and post-acute stroke care.

"It works very well for routine follow-ups, including postop checkups, medication checks, screenings and general issues," Dr. Rasmussen says. "Patients love the system because it's so convenient. And the interactions are generally shorter for providers, which increases efficiency."

The MyCare Online app helps make these interactions happen. Patients simply open the app on their Apple or Android device, log in and enter an electronic waiting room. After reviewing the patient's chart or test results, the physician "enters" the room and chats face to face with the patient through a secure connection with Skype®-like access.

... Including Rural Nevada

The same principles are used by Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas to bring neurological expertise to remote areas of Nevada with few or no neurologists. In a teleconference room located in Elko, Nevada, a nurse coordinator helps Cleveland Clinic neurologists in Las Vegas follow outpatients with chronic neurological conditions.

“We’re able to provide the same exam we offer in Las Vegas,” says Lou Ruvo Center for Brain Health neurologist Charles Bernick, MD, MPH.

... and the NFL Players Association

Perhaps the most intriguing use of virtual visits involves longitudinal monitoring of retired NFL players through The Trust, a collaborative program with the NFL Players Association designed to help address these players’ elevated risk of neurological disease. Retired players’ brain health is assessed at Cleveland Clinic to obtain baseline measures, after which follow-up can be conducted via virtual visits. The goal is to identify changes likely to lead to cognitive impairment, decreased motor function, intractable pain, depression, suicide or other potentially predictable outcomes of repeated brain trauma.

“The program allows us to facilitate personalized guidance for proper follow-up care,” says Jay Alberts, PhD, the Neurological Institute’s Vice Chair for Health Technology Enablement and Director of the Concussion Center.

App-Enabled Patient Empowerment

Neurological Institute specialists have similarly tapped into the public’s mobile device fascination to develop interactive apps promoting greater self-management of stroke recovery, spinal conditions, epilepsy and multiple sclerosis (MS).

“Most of the apps we’ve developed enhance self-management by patient participation in remote assessments that allow more frequent monitoring,” says Matt Stanton, Senior Director of Distance Health. “This lets us track patients’ health more closely and know, for example, whether they are following medication instructions.”

The crown jewel is the Cleveland Clinic Concussion (C3) App. Developed by Dr. Alberts’ team to facilitate concussion assessment in student athletes, the app is now used by over 150 schools in 32 states. It uses the iPad’s built-in functionality to collect data on postural stability and to assess cognitive and motor function versus an athlete’s pre-injury baseline. In Alaska, the C3

App has reduced the need for specialized medical personnel to visit remote schools by bush plane in cases where assessment can be handled by iPad-equipped providers.

Only the Beginning

As the benefits of distance health become apparent, the Neurological Institute is working to find new ways to exploit relevant technologies. Among the efforts underway:

- › Integrating data from the C3 App and a similar app for MS into the patient’s EMR
- › Installing telemedicine monitoring stations at skilled nursing facilities to increase communication with patients’ providers
- › Developing an aggregator that collects data obtained through various consumer apps into a common format that can be entered in MyCare Online and the patient’s EMR

“Pooling data into large data sets will make it possible to do powerful predictive analyses around elements of cognitive and motor function in various neurologic diseases,” Dr. Alberts notes.

Distance Health on Wheels: The Mobile Stroke Treatment Unit

In July 2014, Cleveland Clinic deployed the nation’s second mobile stroke treatment unit (MSTU) — and the first to use telemedicine to connect the unit’s emergency team to a hospital-based vascular neurologist to direct management. That effort continued making headlines in 2015. An analysis of the first 100 patients with acute stroke-like symptoms transported in the MSTU was published in *JAMA Neurology* in December, and it found that the MSTU significantly reduced times from door to CT completion and from door to tPA administration compared with a control group taken to the ER. Ninety-nine of the 100 patients were evaluated successfully, with just one connection failure due to crew error. Results from a clinical outcomes study of the MSTU are expected in 2016.



2015 HIGHLIGHT

Exploring the Potential of Deep Brain Stimulation in Post-Stroke Recovery

Post-stroke physical rehabilitation holds promise as the next frontier for deep brain stimulation (DBS). So suggest pioneering animal investigations conducted at Cleveland Clinic that show strong translational potential.

Promising Effects in Preclinical Models

The recent research involved in vivo studies of DBS of the cerebello-thalamo-cortical pathway in a rodent model of stroke. The objective was to evaluate whether the stimulation could promote or modulate neurogenesis and angiogenesis after cerebral injury.

The study findings, presented in June 2015 at the World Congress of the International Neuromodulation Society by Andre Machado, MD, PhD, showed that DBS of this pathway promoted motor recovery along with neurogenesis and angiogenesis in the thalamus and perilesional cortex. Notably, excitatory glutamatergic neurogenesis was promoted while GABAergic neurons were inhibited.

“Our findings suggest that DBS of the cerebello-thalamo-cortical pathway may enhance the brain’s plasticity and ability to form new neural connections during recovery from stroke,” says Dr. Machado, Chairman of Cleveland Clinic’s Neurological Institute and Director of its Center for Neurological Restoration. “The expectation is that stimulation may augment the effects of physical rehabilitation for stroke.”

He notes that the cerebellum was the region targeted for stimulation in the hope of re-establishing flow of neurological input to the brain hemisphere affected by stroke.

The new findings build on earlier work from Dr. Machado’s team, funded by the National Institutes of Health and published in *Neurosurgery* in 2013 and the *Journal of Neuroscience* in 2014, showing that DBS enhanced motor recovery after stroke in the rodent model and promoted perilesional plasticity and formation of new synapses compared with a control sham intervention.

Dr. Machado believes DBS fosters selective neurogenesis after focal injury. “The implications for the neurorestorative potential of this therapy are strong,” he says, “but these findings are of course preliminary.”

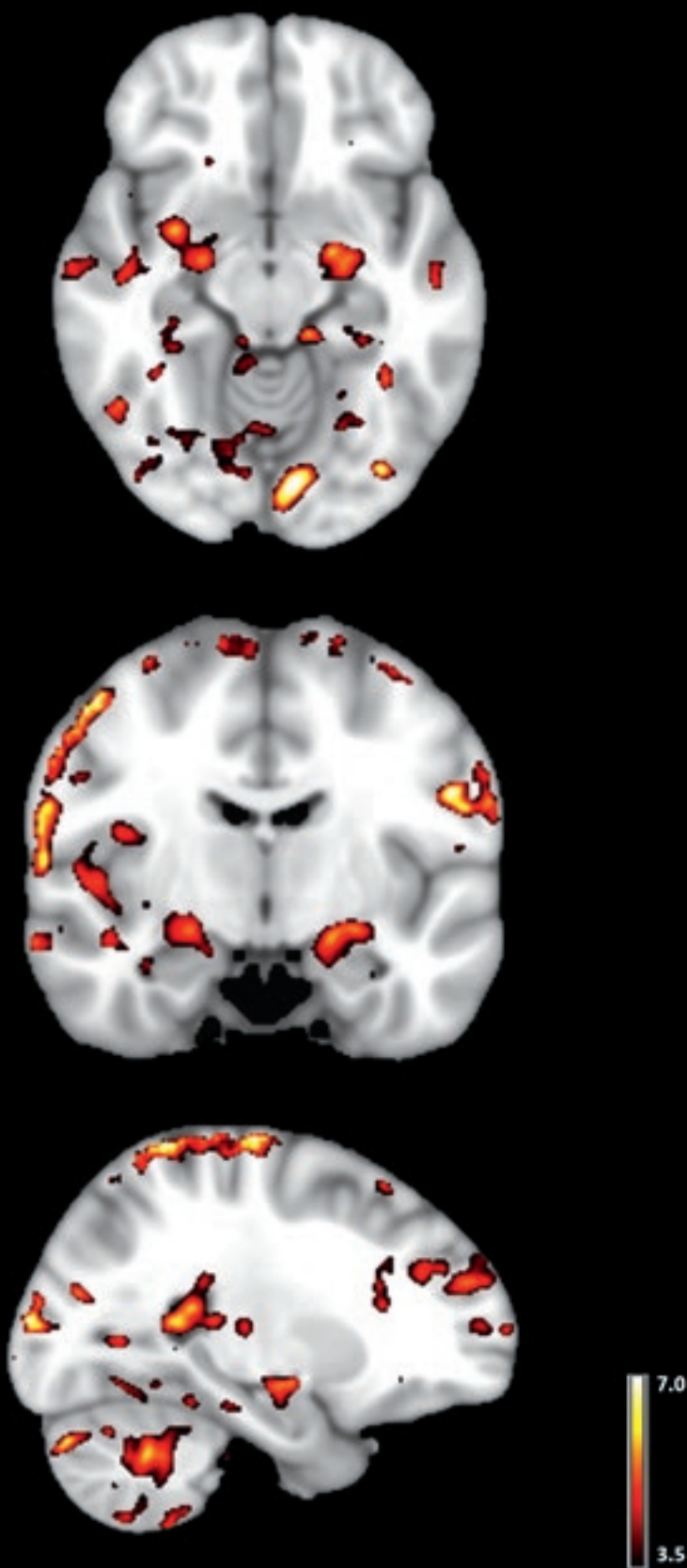
Preparation for Human Testing Underway

No direct evidence exists that DBS of the cerebellum can promote new neuron formation in humans, but Dr. Machado’s team is applying to the FDA for permission to start testing their approach in patients affected by hemiparesis after stroke. Key questions they will seek to address include:

- › Given the heterogeneity of stroke survivors, who would be the best candidates?
- › At what point in post-stroke recovery would DBS be most beneficial?
- › Is continuous DBS needed, or do benefits endure without ongoing stimulation?

“Deep brain stimulation is now a routine procedure for managing symptoms of Parkinson disease and essential tremor,” Dr. Machado notes. “This research at Cleveland Clinic indicates it may hold promise for post-stroke recovery as well.”

LEFT — Dr. Machado during surgery. Cleveland Clinic is pursuing FDA approval to test deep brain stimulation for post-stroke recovery in humans.



2015 HIGHLIGHT

Decoding Spatial Memory Functions of Hippocampal Subregions

The hippocampus and nearby medial temporal lobe (MTL) cortex are critical to the formation of episodic memories. Although high-resolution fMRI provides valuable insight into specific MTL subregions involved in episodic memory, few studies have been completed, which leaves unclear the precise nature of the function of hippocampal subfields and the adjacent MTL cortical subregions.

In 2015, researchers from Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas presented results from a National Institutes of Health-funded research project that obtained high-resolution fMRI data in subregions of the human hippocampus and segmented them using three-dimensional T1 structural images to identify activation in hippocampal subfields at 3 tesla. A repetition suppression task was performed to examine differences in pattern separation and completion tendencies of hippocampal subfields. This enabled hippocampal subfield-specific memory activations to be determined as a function of pattern separation distance.

“We found that hippocampal activation generally increases as a function of changes in distance of the objects that were presented as stimuli,” notes lead researcher Dietmar Cordes, PhD, of the Lou Ruvo Center for Brain Health.

The researchers plan to develop a simpler version of their spatial memory task with clinical applications such as monitoring treatment effects of human memory disorders.

“The innovation of our study stems primarily from the advanced data analysis techniques we’ve used to obtain more specific activation maps than standard univariate methods are able to achieve,” Dr. Cordes explains. “We adapted a locally constrained multivariate analysis to reduce artifacts. Notably, this method can be transformed into a mathematically equivalent form of a constrained, multivariate multiple regression problem for which any linear contrast of interest can be readily computed.”

For a more detailed version of this article, including references, visit consultqd.org/spatialmemory.

Toning Down TREM2 May Curb Neurodegeneration in AD

Another important 2015 study led by Lou Ruvo Center for Brain Health researchers suggests that macrophages expressing the protein TREM2 play a functionally important role in Alzheimer disease (AD) pathogenesis. The study, published in *Journal of Experimental Medicine* (2015;212:287-295), showed that TREM2 deficiency reduced plaque formation and brain inflammation and improved neuron survival in a mouse model of AD. The results may have direct implications for development of TREM2-targeted therapies.

LEFT — Functional MRI images showing whole brain activation during a memory-related task in the novel Lou Ruvo Center for Brain Health research project. Note that activations are primarily in the gray matter.

2015 HIGHLIGHT

MS PATHS: Harnessing Real-Time Patient Data to Reshape MS Care and Research

When the Institute of Medicine recently called on healthcare institutions to share data from routine care to create “learning health systems,” it had a few principles in mind:

- Align science, informatics, incentives and culture for continuous improvement
- Embed best practices into the care process
- Empower patients to take part in their care
- Systematically capture new knowledge as a byproduct of caregiving

“This sounds great in theory, but it’s been relatively uncommon in practice,” says Robert Bermel, MD, Medical Director of Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research. The stumbling blocks, he notes, have been mostly logistical and technological.

But in 2015 Dr. Bermel collaborated with colleagues from other healthcare institutions and Biogen on a planned initiative to overcome those barriers in multiple sclerosis (MS). The project, sponsored by Biogen, is known as MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions).

“MS PATHS is a one-of-a-kind collaboration between academic institutions and industry to create an integrated, efficient data collection system to conduct research and potentially improve clinical care,” he explains. “We aim to leverage data in aggregate and collaborate across centers to learn more about MS through standardized neuroperformance testing, patient-reported data and imaging.”

Efforts are focused on information-sharing via a learning health system to which Cleveland

Clinic’s Mellen Center and other leading healthcare institutions in the U.S. and Europe will contribute standardized patient-reported data.

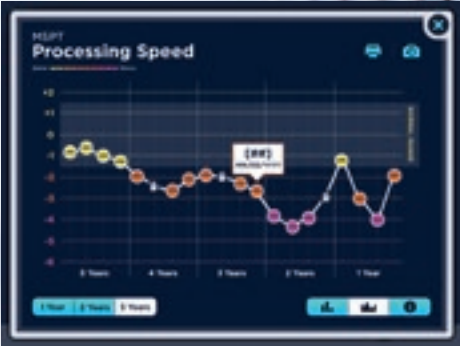
“Through research, this network of technology-enabled MS centers intends to create a way to learn from clinical practice and generate insights to one day inform point-of-care decision-making, with the goal of improving outcomes,” Dr. Bermel says.

At the heart of MS PATHS is the Multiple Sclerosis Performance Test (MSPT), a suite of iPad-based assessments originally developed at Cleveland Clinic that is now being shared by Biogen with all MS PATHS centers. Self-administered by patients before routine appointments, the MSPT comprises a structured patient history, the Neuro-QoL outcome instrument and electronic adaptations of the Multiple Sclerosis Functional Composite to provide quantitative assessments of motor, visual and cognitive performance.

MS PATHS will combine assessments from the MSPT with standardized MRI acquisition sequences and a biobanking protocol. Shared data will be aggregated in an informatics infrastructure that provides a platform for conducting research to expedite discoveries in MS and support development of personalized treatment options.

“MS PATHS will take the strengths of clinical trials — standardized data collection and imaging, rigorous data collection — and apply them to large numbers of patients in clinical care,” Dr. Bermel explains.

RIGHT — Dr. Bermel explains the MSPT app to a patient. Inset shows how the app displays measures over time.





2015 HIGHLIGHT

Safely Bringing Early Mobilization to the Neurological ICU

The many studies that established the benefits of early mobilization for ICU patients all had at least one thing in common: They failed to include patients in neurological ICUs.

“Studies of early mobilization in the ICU have traditionally excluded patients with acute brain injuries,” says Kate Klein, ACNP-BC, CCRN, noting that such patients raise particular concern about the potential for safety compromises during mobilization. As a result, early mobilization of patients with neurological injury has been infrequently tried, and its potential benefits are poorly understood.

In this context, Klein and colleagues developed and implemented a nurse-designed and -driven early progressive mobility protocol for Cleveland Clinic’s 22-bed neurological ICU. To evaluate its impact, they then conducted a prospective comparative analysis that included data collection in the neurological ICU over four-month periods before ($n = 260$) and after ($n = 377$) protocol implementation.

Results were published in the April 2015 issue of *Critical Care Medicine* and showed that, compared with the pre-intervention group, patients managed in the neurological ICU after protocol implementation had:

- Greater maximum mobility ($P < .001$)
- Shorter length of stay in both the hospital and the neurological ICU ($P < .001$ for both)
- Greater likelihood of being discharged home ($P = .002$)

These advantages were maintained at statistically significant levels after multivariate analysis.

Patients in the early mobility group also felt better, with significantly reduced scores for depression and anxiety relative to the pre-intervention group.

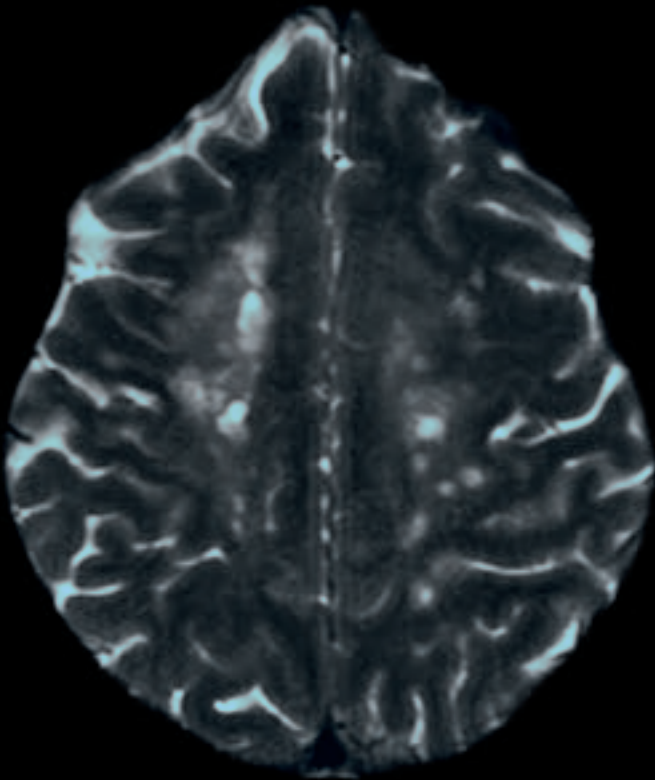
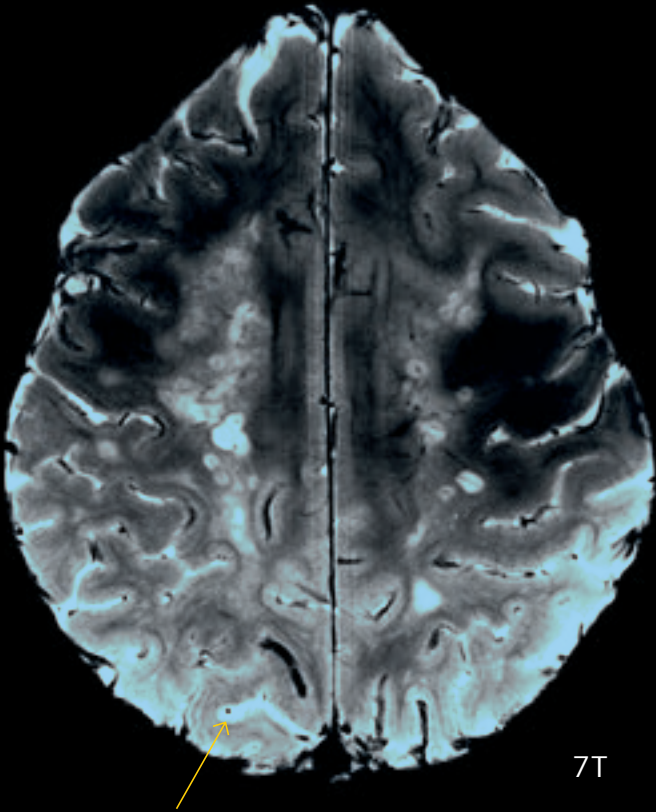
“Not only did we reduce hospital complications across the board,” says Klein, “but patients spent 36 percent less time in the neurological ICU after protocol implementation. Overall hospital stay was reduced by 33 percent, ventilator days by 70 percent (for patients who needed ventilator therapy) and overall cost by 30 percent. All these results tell us that getting patients out of bed sooner is best practice.”

Klein has since teamed with colleagues to develop Cleveland Clinic’s Mobility with Safe Patient Handling Care Path, a novel nurse-led early mobility program that emphasizes keeping caregivers safe while promoting patient mobilization. The care path — which can be applied only in units that contain safe patient handling equipment, such as slings and ceiling lifts — has been piloted in the Neurological Institute to assist in the care of neurological patients throughout their hospital stay.

“Units across the full continuum of neurological care have been outfitted with safe patient handling equipment,” Klein notes. “That speaks to the Neurological Institute’s commitment to the safety of both patients and caregivers.”

For a more detailed version of this article, visit consultqd.org/earlymobilization.

LEFT — Kate Klein, ACNP-BC, CCRN (foreground), and a nurse colleague help a patient get out of bed using a ceiling lift and sling in Cleveland Clinic’s neurological ICU.



2015 HIGHLIGHT

Expanding the Clinical Utility of Ultra-High-Field MRI

Cleveland Clinic is one of about 50 institutions worldwide with a 7-tesla (7T) MRI scanner — and one of a select few that use it in close relation with an active hospital. An IRB-approved protocol is used to image patients with neurological disease for strict comparison of findings at lower magnetic fields versus 7T.

A Formidable Patient Experience Base

Over the past 18 months, Cleveland Clinic has used 7T to image 77 patients with diagnoses ranging from epilepsy (n = 37) to traumatic brain injury (n = 14), amyotrophic lateral sclerosis (n = 11), multiple sclerosis (MS; n = 8), brain tumor (n = 4), vasculitis (n = 1), mild cognitive impairment (n = 1) and cavernous malformation (n = 1). This collective experience of patients imaged at 7T is one of the world's largest, and it is serving to help investigate the clinical utility of ultra-high-field MRI.

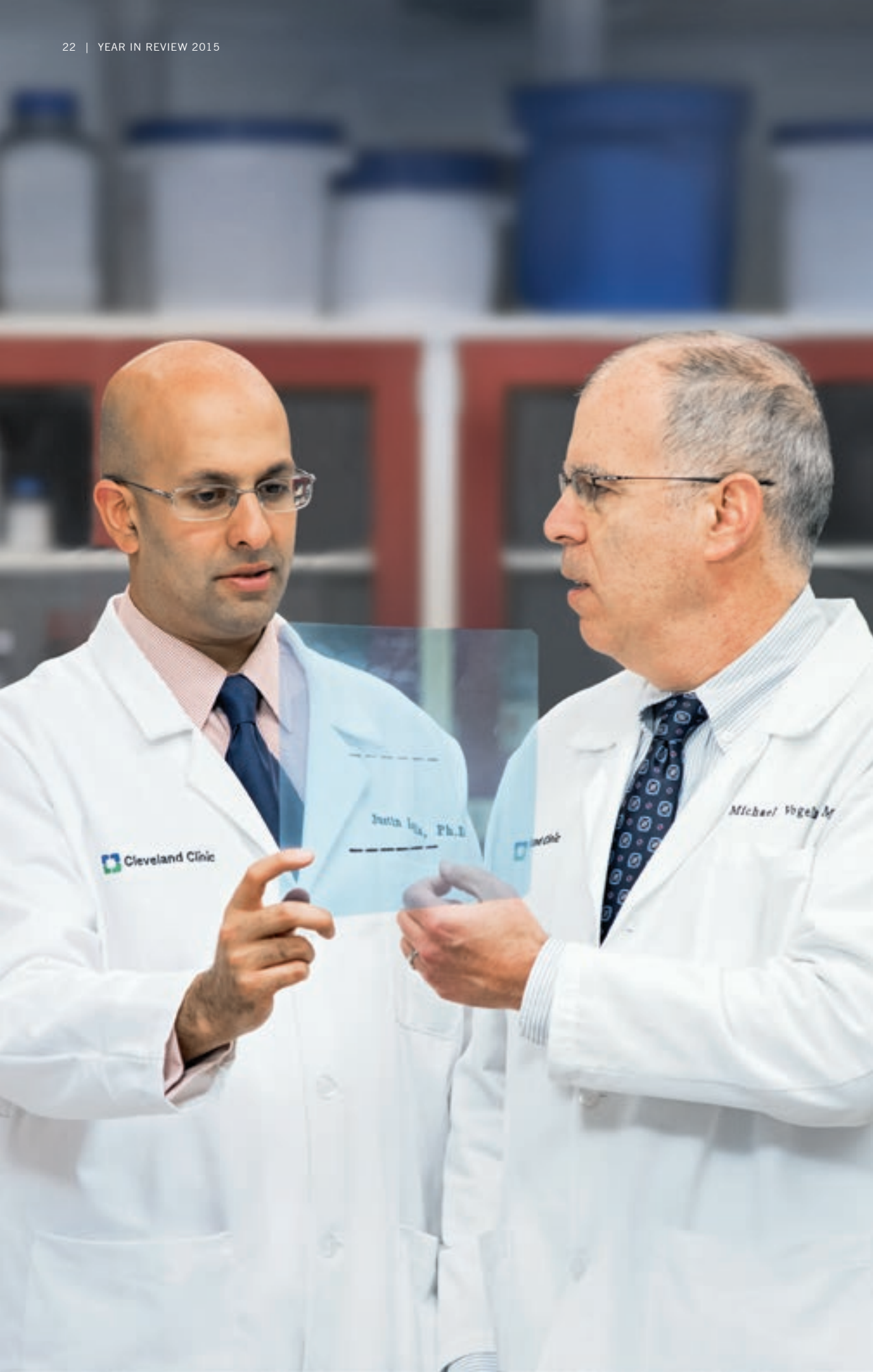
The principal clinical advantage of 7T imaging stems from increased spatial resolution, including both in-plane voxel spacing and slice thickness. Initial experience suggests that although few lesions are seen at 7T that are not visible at a lower magnetic field, those seen at a higher field are seen with higher resolution and greater neuropathology detail — sometimes leading to an altered diagnosis not appreciated at lower fields. For example, 7T is superior for visualization of microhemorrhages, and it can reveal an increased extent of traumatic brain injury than is seen at lower fields.

The Value Added in an MS Case

Another example is provided by the images on the facing page, which show the white matter in a patient with advanced MS. The lower-field (1.5T) image at the bottom shows a uniform field of signal hyperintensity (brightness), but the 7T image at the top allows details within the disease to be appreciated with greater resolution. Note the myriad rounded lesions that appear superimposed at 7T but appear coalesced at lower field. Moreover, 7T reveals a central black dot at the center of nearly all lesions (arrow in upper image shows one example), which represents the effects of blood flow in a central vein. This association is well established from microscopic pathology, and it can now be demonstrated on MRI with the advent of 7T. In the future, observation of this feature may help determine an MS diagnosis by distinguishing it from numerous look-alikes at lower magnetic field.

Another fascinating advantage of 7T involves resting-state functional imaging, in which brain networks can be revealed with the patient doing nothing in the scanner for a period of six to 10 minutes. The resting-state technique improves visualization as a result of smaller voxels as well as increased blood-oxygen-level-dependent (BOLD) response that scales favorably with magnetic field strength. Recent research with this technique could enhance targeting of intracranial electrodes for deep brain stimulation, for which identification of networks may be essential.

LEFT — MRIs of white matter in a patient with advanced multiple sclerosis taken at 7T (top) and at 1.5T (bottom). See text for a detailed comparison.



2015 HIGHLIGHT

Applying Immunologic Insights to Chart a New Course in Glioblastoma Therapy

Cleveland Clinic researchers are hopeful that discoveries they've advanced in 2015 regarding the role of myeloid-derived suppressor cells (MDSCs) in glioblastoma will open a path to novel immunotherapies for this uniformly fatal brain tumor. A clinical trial is being planned.

"The only effective treatments for cancers arising in the brain are surgery, radiation and a few conventional chemotherapies," says neurosurgeon Michael A. Vogelbaum, MD, PhD, Associate Director of Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. "There is enormous focus now on understanding the immune system's function in the context of cancer. Immunotherapies are showing promise for a variety of cancers, including brain tumors."

MDSCs in Glioblastoma

MDSCs are immature immunosuppressive cells found in various tumors and at sites of inflammation and infection. In cancer, they suppress beneficial cytotoxic immune cell function, contributing to tumor growth and metastasis.

Building on Cleveland Clinic research into the role of MDSCs in renal cell carcinoma, Dr. Vogelbaum and colleagues discovered several years ago that these cells are upregulated in the peripheral blood of glioblastoma patients as well. He is now partnering with Justin D. Lathia, PhD, of the Department of Cellular and Molecular Medicine, whose lab recently showed that MDSCs find their way into the brain, where they communicate with self-renewing cancer stem cells (CSCs) present in many advanced tumors.

"CSCs activate MDSCs, which alter the immune system and promote tumor growth. This appears to be an important mechanism in glioblastoma immune evasion," Dr. Lathia explains.

Translating to Therapeutics

Drs. Vogelbaum and Lathia have developed a novel chemotherapeutic strategy aimed at reducing MDSC levels in the blood to reverse immunosuppression and activate the patient's immune system against glioblastoma progression. Cleveland Clinic medical oncologist David Peereboom, MD, will be primary investigator for a clinical trial of the strategy, with enrollment projected to begin within six months.

"Our trial will use FDA-approved agents that activate the immune system and directly eliminate MDSCs from the bloodstream and bone marrow — before they reach the brain tumor," Dr. Lathia says. This approach doesn't depend on crossing the blood-brain barrier, Dr. Vogelbaum adds. Instead, MDSCs will be targeted in the peripheral blood with 5-fluorouracil, which has demonstrated effectiveness in killing MDSCs in mouse studies. The team is evaluating other agents too.

"We believe some form of immunotherapy or immunostimulation, alone or with conventional treatments, has the potential to help people with malignant brain tumors live longer," Dr. Vogelbaum concludes.

For a more detailed version of this article, visit consultqd.org/MDSC.

LEFT — Drs. Lathia (left) and Vogelbaum are collaborating on research to determine whether the role of myeloid-derived suppressor cells in glioblastoma can be translated to successful immunotherapeutic strategies.



2015 HIGHLIGHT

Focusing Global Attention on How to Advance Neuroscience Innovation

The emerging role of biomarkers and big data in brain health. The neuroscience R&D profiles of top device and pharma firms. How to shrink the costs and timelines of neuropsychiatric drug trials. When Cleveland Clinic convened its 13th Annual Medical Innovation Summit in October 2015, neuroscience took center stage — and topics like these filled the agenda.

More than 1,700 healthcare leaders from around the nation and the globe came to Cleveland for the three-and-a-half-day event, which featured thought-provoking expert panel discussions, one-on-one exchanges with influential healthcare CEOs and glimpses of innovations that promise to disrupt the healthcare landscape. This year's focus was neuroscience, as reflected in the summit's subtitle, "Memory. Mood. Movement."

The mix of speakers and attendees was broad, ranging from senior executives from the healthcare industry's provider, payer and drug/device manufacturer sectors to investors, government officials, entrepreneurs and leading clinicians.

The diversity was deliberate, says Cleveland Clinic Neurological Institute Chair Andre Machado, who participated in several summit sessions. "Researchers don't bring a concept from bench to bedside by themselves," he notes. "It requires a village to do this work, and the summit brought together the many players in that village who can help transform a drug, device or other technology from concept to clinical reality."

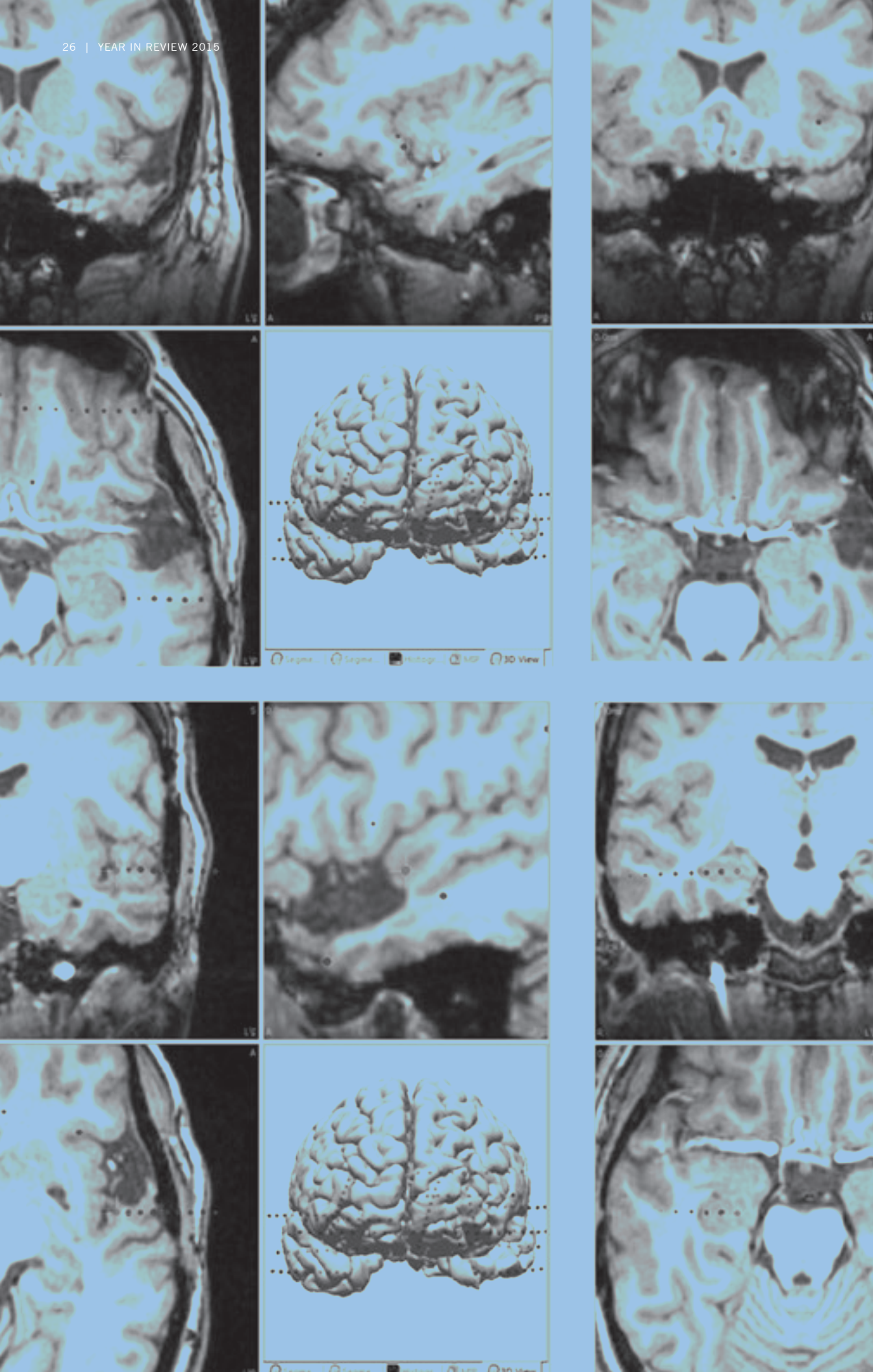
In addition to sharing case lessons from how Cleveland Clinic innovators have navigated that transformation in areas from wearable devices to telemedicine, the summit deeply explored what innovation involves from diverse perspectives — those of clinicians, investors, basic scientists, industry, regulators, IT developers and more — and how these players can work together to be more effective. It also aimed to share ideas for fostering innovation within an organization, most notably via the full-day Innovation Base Camp that kicked off the summit.

The summit closed with the unveiling of the annual Top 10 Medical Innovations, which has become a staple of the event. The list recognizes innovations that a panel of 75 Cleveland Clinic physicians and scientists believe will most shape healthcare over the coming year. Two neuroscience-related innovations figured in this year's Top 10: naturally controlled artificial limbs (No. 7) and neurovascular stent retrievers (No. 10).

Notably, the list's innovations included a few novel methods of healthcare delivery or research approaches in addition to the standard new therapeutics and diagnostics, echoing a theme of the overall summit. "Innovation today is about more than discovering new therapies," Dr. Machado said during one session. "It's also about finding new and better ways to deliver care for common problems."

Videos of all summit sessions are available at clevelandclinic.org/innovationvideos.

LEFT — Despite its focus on neuroscience, the 2015 Medical Innovation Summit was multidisciplinary and collaborative in every aspect. Here, Cleveland Clinic anesthesiologist Joseph Foss, MD, speaks during a session titled "Ground Waves" focused on technologies shaking up the status quo in brain/CNS care and beyond.



2015 CASE HIGHLIGHT

Overcoming Refractory, Difficult-to-Localize Epilepsy with SEEG-Guided Laser Ablation

In 2015, 31-year-old Amelia (a pseudonym) experienced her first seizure-free year since her long-standing case of focal epilepsy began at age 6 soon after she tripped and struck her head on a desk.

Her case illustrates the challenges of seizure localization in the setting of medically intractable focal epilepsy with no evidence of an underlying lesion on MRI. It also illustrates the potential of stereoelectroencephalography (SEEG) to shed light on the most complex epileptogenic networks — even when distributed over several lobes or sublobar structures — and to guide laser ablation to achieve dramatic seizure control in the most refractory cases.

Amelia first underwent video-EEG monitoring at Cleveland Clinic's Epilepsy Center in 2002 and was diagnosed with temporal lobe epilepsy. Since half the recorded seizures were not clearly lateralized, she had depth electrodes placed, and then underwent subdural grid evaluation in early 2003. Seizure onset was recorded from the lateral left temporal lobe structures, coinciding with language function, and Amelia underwent partial anterior resection of the left anterior superior temporal gyrus (resection was limited due to proximity to the eloquent cortex).

Unfortunately, seizures recurred in March 2003, and Amelia continued trying various anticonvulsive medications over several years, with no effective seizure control.

After initial reluctance to undergo recommended SEEG evaluation, Amelia and her family decided to pursue it in 2013, and it revealed results

similar to those obtained by the earlier subdural grid evaluation.

After intense multidisciplinary discussion, Epilepsy Center physicians designed a new SEEG implantation to confirm a three-part hypothesis:

- › The seizure onset pattern from the subdural grid evaluation may represent the “exit pattern” of a deep epileptogenic region.
- › Based on seizure semiology and previous noninvasive data, the insular-opercular region and the anterior cingulate region could be responsible for the patient's epilepsy.
- › There was also a possibility that both temporal regions were epileptogenic.

Meticulous analysis of this invasive evaluation revealed evidence of high epileptogenicity at multiple foci: in the left superior temporal gyrus/temporal operculum, the left posterior orbitofrontal and left anterior insular regions, and the right hippocampus.

Based on all these evaluations, in January 2014 Amelia underwent SEEG-guided laser ablation in two areas of high epileptogenicity: the left orbitofrontal region and left anterior insula. She reported reduced frequency and severity of seizures during immediate postoperative follow-up, with no side effects.

Amelia has been seizure-free since December 2014 and has been able to resume driving.

[For a detailed version of this case report with multiple figures and images, visit \[consultqd.org/seeglaser\]\(https://consultqd.org/seeglaser\).](https://consultqd.org/seeglaser)

LEFT — MRIs and 3-D reconstructions used in planning the patient's SEEG-guided laser ablation. The blue dots indicate the electrode trajectories, and the red dots indicate the location of contacts with high epileptogenicity.

2015 Achievements from Our Centers

A sampling of other notable developments
across Cleveland Clinic’s Neurological Institute over the past year —
one from each of its 14 subspecialty centers and departments

Center for Behavioral Health

➤ *Specialized program launched for psychogenic nonepileptic seizures*

Approximately 30 percent of patients who undergo video-EEG monitoring after referral to Cleveland Clinic’s Epilepsy Center are diagnosed with psychogenic nonepileptic seizures (PNES). Although this condition is not caused by epileptiform discharges in the brain, signs and symptoms of PNES can closely resemble those of epileptic seizures. Many affected patients are trauma survivors with multiple psychiatric comorbidities. In response to the prevalence of PNES and the special needs of affected patients, Cleveland Clinic’s Center for Behavioral Health recently partnered with Epilepsy Center clinicians to establish a specialized PNES program. The program’s full-time clinical psychologist plays a key role in helping reluctant patients accept the PNES diagnosis and pursue treatment, which can involve individual psychotherapy, group and/or family therapy, and potential referral to a psychiatrist for pharmacotherapy. Treatment aims to confer effective coping skills to help patients control their PNES and restore quality of life.

Lou Ruvo Center for Brain Health

➤ *COBRE grant from NIH will fuel Alzheimer, Parkinson research*

In September, Cleveland Clinic Lou Ruvo Center for Brain Health and the University of Nevada, Las Vegas, were awarded an \$11.1 million grant from the NIH’s National Institute of General Medical Sciences to create a Center of Biomedical Research Excellence (COBRE) to advance understanding of Alzheimer and Parkinson diseases. The five-year grant will fund three research initiatives. One will determine the brain imaging correlates of cognitive decline in Parkinson disease. Another will combine leading-edge neuroimaging with neuropsychological measures to define commonalities between Alzheimer and Parkinson diseases. The third will assess novel models of Alzheimer disease, with special focus on the immune system. “This work extends from the preclinical to the clinical science level,” says principal investigator Jeffrey Cummings, MD, ScD, Director of the Lou Ruvo Center for Brain Health. “We will capitalize on our facility’s tremendous brain imaging capacity.”

\$11.1M
COBRE GRANT

FOR 3 RESEARCH
PROJECTS IN AD & PD
OVER 5 YEARS

Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center

➤ *Pioneering staged Gamma Knife radiosurgery in the U.S.*

In 2015, Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center became the first known facility outside Japan to use staged Gamma Knife® radiosurgery for patients with large or radioresistant brain tumors that respond poorly to standard Gamma Knife radiosurgery. This novel approach involves two Gamma Knife treatment sessions one month apart, each with a medium-high dose of radiation that intensifies delivery without injuring the brain. The aim is to protect the surrounding normal brain tissue from excessive radiation while enabling a higher-than-normal radiation dose. Cleveland Clinic has found staged Gamma Knife surgery to be feasible, safe and effective for large brain metastases, with preliminary results showing significant reductions in tumor size after the second treatment and a 90 percent response rate to date. Data are being prepared for publication in 2016.



Cerebrovascular Center

➤ *Mobile stroke treatment unit makes its mark*

2015 marked the first full year of operation for Cleveland Clinic’s mobile stroke treatment unit (MSTU), one of only two of its kind in the U.S. and the first to allow stroke neurologists to manage cases remotely via two-way telemedicine. The purpose-designed ambulance is equipped and staffed to bring essential diagnostic and management tools of the ER to the prehospital site of symptom onset for patients with suspected stroke. A case-control analysis of early experience with the MSTU was presented at the 2015 International Stroke Conference and showed statistically significant reductions in time to patient evaluation and time to tPA administration relative to traditional acute stroke management. At least 280 patients were managed in the MSTU in the first 11 months of 2015, and its operation is now being expanded to a 24/7 basis.

Concussion Center

➤ *Leveraging data to improve brain health follow-up of retired athletes*

The Concussion Center is directing Cleveland Clinic’s participation in The Trust, a collaboration with the NFL Players Association and two other top medical centers to provide comprehensive brain-body health assessments and longitudinal monitoring for retired football players. Cleveland Clinic had screened over 300 former players by late 2015, making it the collaboration’s top center for participant volume. It is now analyzing and preparing data from these screenings for publication, with a focus on changes in brain MRIs and how they relate to neurocognitive test results. These analyses can be used to help The Trust improve follow-up care and monitoring of participants, including via telemedicine, and to flag candidates for trials of early interventions against mild cognitive impairment. They also can help inform research efforts around very low hippocampal volumes and other frequent imaging findings in this population.

Epilepsy Center

➤ *Nomograms yield proof of concept for epilepsy surgery outcome prediction*

Surgical treatment of epilepsy remains one of the most underused accepted therapy interventions in medicine — in part because of inadequate tools for predicting which patients are most likely to benefit. In response, Cleveland Clinic Epilepsy Center clinicians developed a pair of nomograms that use six clinical characteristics to predict surgical outcome based on data gathered from 846 patients who had resective surgery at Cleveland Clinic over a 15-year period. They then validated the nomograms in an external retrospective cohort of 604 patients who underwent resection at four epilepsy centers in Europe, Latin America and the U.S. Their findings, published in *Lancet Neurology* in March, showed that the nomograms performed reasonably well and provided the first proof of concept that individualized outcome prediction is possible in epilepsy surgery. Prospective validation studies are in the works.

2 NOMOGRAMS
USE <<<
6 CLINICAL FACTORS
FROM 15 YEARS OF
EXPERIENCE

TO PROVIDE **1ST PROOF OF CONCEPT** FOR SURGERY OUTCOME PREDICTION



Mellen Center for Multiple Sclerosis Treatment and Research

➤ *MS Performance Test introduced to routine clinical use*

Summer 2015 saw significant clinical rollout of a novel suite of Cleveland Clinic-developed iPad® apps within the Mellen Center for Multiple Sclerosis Treatment and Research. Known as the Multiple Sclerosis Performance Test (MSPT), these five apps provide quantitative assessment of motor, visual and cognitive performance in MS. Patients self-administer the MSPT during the initial portion of their clinic appointments, yielding real-time quantitative neuroperformance test results they can discuss with providers at their visit. The aim is to foster patient engagement, inform decision-making with current data and ensure more consistent completion of clinically relevant assessment tools. The MSPT will figure prominently in the multicenter MS PATHS research collaboration that the Mellen Center is leading, as detailed on page 16.

Center for Neuroimaging

➤ *Outlining the network topology preceding Huntington disease onset*

Clinical trials of strategies to prevent Huntington disease (HD) are hindered by a shortage of measures to serve as surrogate outcomes. Building on recent interest in measures of functional connectivity from resting-state fMRI, Cleveland Clinic led a multicenter investigation using two complementary analytic approaches to compare whole-brain resting fMRI connectivity between individuals with prodromal HD and gene-negative controls. All subjects were from the larger PREDICT-HD study. The results revealed, for the first time, abnormalities in whole-brain intrinsic functional connectivity in prodromal HD that increased with disease burden. “Both analytic approaches provided a unique window into brain reorganization that was not related to brain atrophy or motor symptoms,” says Cleveland Clinic’s Stephen Rao, PhD, primary author of the research, which was published in *Brain* in 2015. Longitudinal studies are now underway to chart the course of functional changes to pinpoint the most sensitive markers of HD progression.

Neuromuscular Center

➤ *Matching MRI findings with pathology to illuminate ALS*

Staff from Cleveland Clinic’s Neuromuscular Center and Department of Neurosciences continued a novel interdisciplinary research effort in 2015 designed to illuminate the pathogenesis of amyotrophic lateral sclerosis (ALS) and identify new therapeutic targets for the condition. Under the program, ALS patients undergo brain MRI soon after diagnosis and approximately one year later. They may also provide advance consent for postmortem MRI and rapid autopsy of the brain and spinal cord. The objective is to find MRI biomarkers of in vivo ALS pathogenesis by mapping tissue pathology onto all MRIs, allowing retrospective identification of the earliest imaging abnormalities that ultimately evolve into the postmortem pathology. As of mid-2015, 12 patients were being monitored via brain MRI and 13 patients had undergone postmortem MRI and rapid autopsy.

Center for Neurological Restoration

➤ *First human study of DBS for chronic neuropathic pain*

In addition to reporting pioneering work in deep brain stimulation (DBS) for post-stroke rehabilitation (see page 12), Center for Neurological Restoration researchers advanced another novel application of DBS in 2015 — for treatment of thalamic pain syndrome (TPS). The researchers, led by Andre Machado, MD, PhD, completed the first human clinical trial of DBS for refractory TPS, which was also the first prospective randomized study of DBS in any chronic neuropathic pain condition. The study involved stimulation of the ventral striatum/ anterior limb of the internal capsule, which represents emotional and affective behavior. “Our results show that intervening in the emotional networks of the brain in chronic pain is safe and can be effective in some patients with TPS,” says Dr. Machado, who is preparing the findings for peer-reviewed publication.

Pediatric Neurosciences

➤ *Helping shape the care of rare pediatric diseases*

Even while treating thousands of young patients each year with more common CNS diseases, Cleveland Clinic’s pediatric neurosciences program finds opportunities to advance care and understanding of rare disorders in children. Two examples emerged in 2015. The Cleveland Clinic Pediatric MS Center was selected by the National Multiple Sclerosis Society to join its Network of Pediatric MS Centers (NPMSC), making it one of only 12 centers nationwide to earn this distinction. Membership in the NPMSC enables Cleveland Clinic to build on its existing collaborative research into pediatric MS and other demyelinating diseases in children. Additionally, in September a Mitochondrial Medicine Society writing group led by Cleveland Clinic’s Sumit Parikh, MD, published the first North American consensus statement on the diagnosis and management of mitochondrial disease to help standardize management of this congenital condition. The statement appeared in *Genetics in Medicine* (2015;17:689-701).

Department of Physical Medicine and Rehabilitation

➤ *PM&R residency to launch in 2016*

To meet increasing national demand for physiatrists, Cleveland Clinic’s Department of Physical Medicine and Rehabilitation announced in 2015 that it is launching a physical medicine and rehabilitation (PM&R) residency program. Recruitment is underway, with the first two residents in the new three-year program expected to start in July 2016. As a large-volume tertiary referral center, Cleveland Clinic will offer PM&R residents exposure to a diverse mix of complex patients in a variety of acute care and outpatient settings, including many with challenging neurological conditions. “Our residency program will mirror our unique clinical environment,” says Department of Physical Medicine and Rehabilitation Chair Frederick S. Frost, MD. “We’re building a curriculum to shape the next generation of PM&R clinicians, researchers and teachers.”

2 RESIDENTS START THE
3-YEAR PROGRAM IN 2016

Services Expanded in Florida and Ohio

With the support of its unique Center for Regional Neurosciences, the Neurological Institute is committed to increasing patient access to subspecialized neuroscience expertise beyond Cleveland Clinic’s main campus. Two developments advanced that mission in a big way in 2015. Early in the year, the Pauline Braathen Neurological Center was opened in a large new building on Cleveland Clinic Florida’s campus in Weston, Florida. It features more than 15 integrated service lines, including advanced interventional facilities and a comprehensive brain health program with electroneurodiagnostic capabilities. Later in the year, neurology and neurosurgery services were expanded significantly at Fairview Hospital, a regional hospital serving Cleveland’s west side and nearby suburbs. Chief among the many enhancements there was the opening of a four-bed epilepsy monitoring unit staffed 24/7 and connected to the leading-edge epilepsy/EEG central monitoring unit on Cleveland Clinic’s main campus.

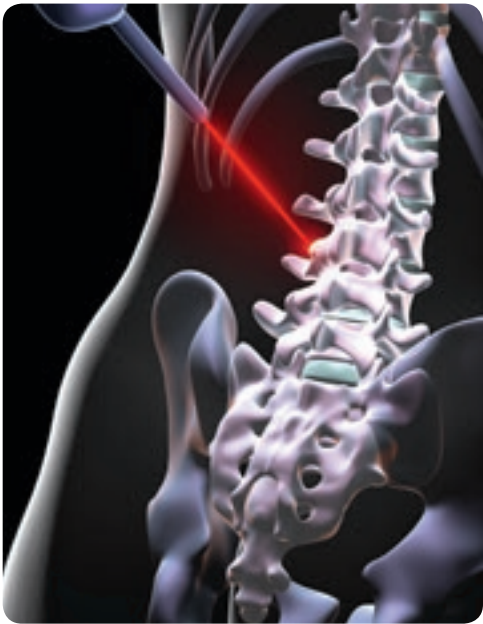
Sleep Disorders Center

› *Shedding light on CPAP's real-world effects on blood pressure*

Clinical studies suggest an association between sleep-disordered breathing (SDB) and resistant hypertension (HTN), but few have examined the real-world practice effect of continuous positive airway pressure (CPAP) on blood pressure in patients with SDB and resistant HTN. Researchers from Cleveland Clinic's Sleep Disorders Center changed that by leveraging electronic medical records (EMR) and the Knowledge Program, an innovative and powerful Cleveland Clinic EMR-integrated resource. The effect of CPAP on blood pressure was examined in a large cohort of 894 SDB patients with either resistant or nonresistant HTN presenting to a tertiary care sleep clinic. Their results, published in *Chest* in 2015, showed significant blood pressure reductions (strongest for systolic pressure) over one year in response to CPAP in the overall cohort, with similar reductions in resistant and nonresistant HTN. "Given the intimate connection between SDB and HTN, these findings have important population health implications by providing guidance on anticipated blood pressure response from CPAP therapy in a real-world setting," says study co-author and Sleep Disorders Center Director Nancy Foldvary-Schaefer, DO, MS.

NO DIFFERENCE

IN POST-CPAP BLOOD
PRESSURE REDUCTIONS
BETWEEN RESISTANT &
NONRESISTANT HTN



Center for Spine Health

› *Helping the National Orthopaedic & Spine Alliance stand tall*

2015 witnessed important growth in the National Orthopaedic & Spine Alliance (NOSA), the unprecedented clinically integrated physician-hospital organization that Cleveland Clinic co-founded with four other top institutions in early 2014. Center for Spine Health staff play key roles in NOSA's work to create a new model for orthopaedic and spine care delivery through development of uniform guidelines on clinical care and consistent measurement of outcomes and cost. NOSA contracts with large employer groups to deliver care via a Centers of Excellence model involving reimbursement in the form of bundled payments or similar risk-sharing methods. Over 40 provider organizations have asked to join NOSA to date, and five more provider groups were added to the alliance in 2015, bringing total NOSA membership to 10 across diverse U.S. locations. In 2015 NOSA also completed contracts with two national plan sponsors covering over 1 million beneficiaries.

Cleveland Clinic Neurological Institute Staff

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Chairman, Neurological Institute

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Institute Vice Chairman, Health Technology Enablement

William Bingaman, MD
Institute Vice Chairman, Clinical Areas

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Institute Vice Chairman, Research and Development

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Institute Vice Chairman, Regional Neurosciences

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Chairman, Department of Neurology

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Chairman, Department of Diagnostic Radiology

Bruce Trapp, PhD
Chairman, Department of Neurosciences

Jocelyn Bautista, MD
Institute Quality Improvement Officer

Adrienne Boissy, MD
Institute Patient Experience Officer

CENTERS AND DEPARTMENTS

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Director

Veena Ahuja, MD

Susan Albers-Bowling, PsyD

Murat Altinay, MD

Amit Anand, MD

Kathleen Ashton, PhD

Joseph M. Austerman, DO

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Lou Ruvo Center for Brain Health

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Director

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Director, Cleveland

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Stephen Rao, PhD, ABPP/CN
Director, Schey Center for Cognitive Neuroimaging

Kasia Rothenberg, MD, PhD

Rawan Tarawneh, MD

Babak Tousi, MD

Po Heng Tsai, MD

[†] Deceased

Ryan Walsh, MD, PhD
Dylan Wint, MD
Xue (Kate) Zhong, MD, MSc

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Brain Tumor and Neuro-
Oncology Center

Gene Barnett, MD, MBA,
FACS
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Institute Vice Chairman,
Regional Neurosciences
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Mellen Center for
Multiple Sclerosis Treatment
and Research

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Sciences
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Esben Vogelius, MD

Center for Neurological Restoration

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Neuromuscular Center

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Director

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Editorial and Art Staff

Managing Editor
Glenn R. Campbell
Art Director
Chip Valleriano
Photography/Illustration
Don Gerda
Russell Lee
Mark Sabo
Steve Travarca
For address changes:
Cleveland Clinic
9500 Euclid Ave. / AC311
Cleveland, OH 44195
216.448.1022
CCNI@ccf.org
clevelandclinic.org/neuroscience

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[†] Deceased

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The Cleveland Clinic Foundation
9500 Euclid Ave. / AC311
Cleveland, OH 44195