

Neurological Institute

2016 Year in Review

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THE NEUROLOGICAL INSTITUTE: A Care Model for Transformative Practice

Cleveland Clinic’s multidisciplinary Neurological Institute includes over 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:

- > Center for Behavioral Health
- > Lou Ruvo Center for Brain Health
- > Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center
- > Cerebrovascular Center
- > Concussion Center
- > Epilepsy Center
- > Mellen Center for MS Treatment and Research
- > Center for Neuroimaging
- > Center for Neurological Restoration
- > Neuromuscular Center
- > Center for Pediatric Neurosciences
- > Center for Regional Neurosciences
- > Sleep Disorders Center
- > Center for Spine Health

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.

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1 INTEGRATED INSTITUTE

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4 ORGANIZATIONAL DEPARTMENTS

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14 SUBSPECIALTY CENTERS FOR CARE

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300+ PROFESSIONAL STAFF

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NEUROLOGICAL INSTITUTE VITAL STATISTICS (2015)	
230,874	Annual outpatient visits
16,434	Annual admissions
94,829	Annual inpatient days
14,064	Annual surgical/interventional procedures
85,198	Annual neuroimaging studies
240	Staff physicians
151	Clinical residents and fellows
30	Research fellows

NEUROLOGICAL INSTITUTE RESEARCH FUNDING (2015)	
\$20.5M	Total grant and contract research funding
59	Federal grants/contracts
236	Nonfederal grants/contracts
343	Active clinical research projects
75	New clinical research projects (initiated 2015)
102	Staff leading clinical research projects
7,859	Patients enrolled in clinical research projects

230,800
PATIENT VISITS

16,400
ADMISSIONS

14,000
PROCEDURES

Across its more than 230,800 annual patient visits and 16,400 annual admissions, the Neurological Institute manages the full spectrum of brain and central nervous system disorders. For patients in need of advanced diagnostics and treatment, Neurological Institute physicians and surgeons are at the forefront of practice innovation in areas including:

- › Epilepsy surgery and monitoring
- › Stereotactic radiosurgery
- › Deep brain stimulation for movement disorders and emerging applications
- › Brain tumor therapeutics
- › Multiple sclerosis therapeutics and disease monitoring
- › Use of telemedicine and mobile devices to enhance patient access and experience

A MULTIREGIONAL U.S. PRESENCE

Access has become a critical component of U.S. healthcare value, and Cleveland Clinic recognizes its special 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, Nevada. This network enables patients to access the institute's specialists within a couple hours' flight time from almost any site in the continental U.S.



\$20.5M
IN RESEARCH GRANTS

343
RESEARCH PROJECTS

The Neurological Institute's clinical caregiving is complemented by a robust research program prioritizing collaboration and innovation. In addition to operating 343 clinical research projects, its clinicians 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, pathbreaking translational research in multiple sclerosis and other demyelinating diseases, 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® platform electronically collects and tracks patient-reported outcomes for real-time integration into clinical workflows. The Knowledge Program is customized for a diversity of conditions, leveraging data from millions of patient visits to guide clinical decisions at the point of care.

The institute has applied this ethic of data-driven care to the creation of EMR-embedded care paths and a growing collection of integrated mobile apps for neurological conditions. The aim is to optimize clinical decision-making while informing quality initiatives and identifying key research questions. The result is improved care for populations and individuals alike. This data strategy has put the Neurological Institute on a path toward use of predictive analytics to improve patient outcomes, reduce costs and enhance healthcare value.

EXTREME ACCESS: LEADING THE WAY IN VIRTUAL CARE

The Neurological Institute's commitment to patient access increasingly extends beyond geographic boundaries through its expanding collection of virtual healthcare offerings and other pacesetting distance health initiatives. These include:



- › **A mature and expanding telestroke network** providing remote, two-way-video-enabled consultation services out of Cleveland Clinic's main campus for patients with acute stroke at 15 facilities in three states.



- › **A growing teleneurology program** offering two-way-video-enabled virtual visits with a Cleveland Clinic neurologist for hospitalized patients at external hospitals that lack 24/7 neurologist coverage. Conditions managed by the program range from seizure disorders to cranial neuropathy to nontraumatic spine conditions and many others.



- › **One of the nation's very first mobile stroke treatment units** for management of suspected acute stroke at the site of symptom onset. Since its launch in July 2014, the unit has been dispatched over 2,600 times, transported more than 660 patients and delivered IV tPA to over 90 stroke patients.



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

WELCOME FROM THE CHAIRMAN

Dear Colleagues,

If there's one thing the past year has made clear, it's this: Healthcare is changing and will continue to change.

In Cleveland Clinic's Neurological Institute, we strive to navigate this change by relying on our mantra of "Excellence, Discovery and Innovation." Yet in these times when change increasingly comes in the form of tightening reimbursements, it can be tempting to shift greater focus to excellence at the expense of discovery and innovation. After all, the rise of healthcare consumerism and hospital rating systems has made high-volume delivery of excellent care — in terms of both outcomes and patient experience — more critical to success than ever. Who can blame patients or staff for wondering whether a day spent advancing discovery or innovation — perhaps in the lab or writing a grant — might not be better spent seeing a few more patients and perhaps impacting more lives?

It's an interesting argument, but it's ultimately a false choice. For one, neglecting discovery and innovation would amount to abandoning the founding mission of Cleveland Clinic. And it would shortchange our children and grandchildren by undercutting development of the therapies of tomorrow. If our predecessors had adopted this mindset, how many treatments that we take for granted today would have never materialized?

But the strongest argument for not neglecting discovery and innovation is that they are so often linked inextricably to excellence in care. This

Year in Review publication from our Neurological Institute is filled with examples:

- › Our novel two-stage approach to Gamma Knife® therapy discussed on page 12 may represent innovation, but it's innovation born of a bold, uncompromising commitment to providing the best possible therapy option to patients with large brain metastases.
- › The multiple sclerosis (MS) rapid autopsy program detailed on page 16 may be primarily about discovery, but the story also notes how our clinicians are leveraging this translational initiative to develop new MRI sequences to better manage today's MS patients.
- › The population health pilot program featured on page 14 is more than a trial run of an innovative model for managing chronic back pain; it's also a patient-empowering initiative to deliver better pain outcomes than patients typically achieve with riskier, costlier procedure-driven care.

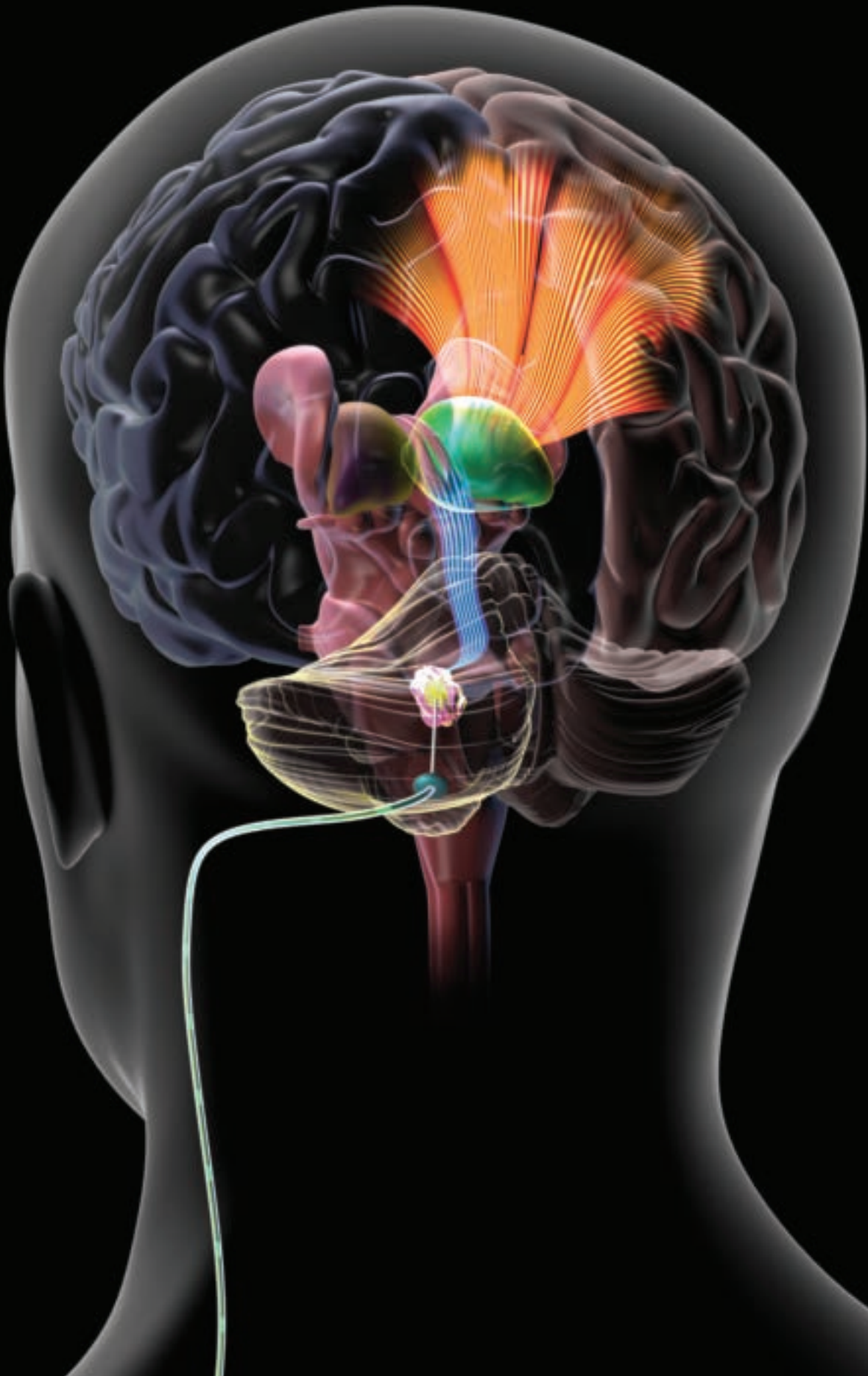
The latter example is a helpful reminder that innovation itself can and should extend beyond new therapies and technologies to encompass *care delivery* as well. You'll find additional examples throughout these pages, which I hope you'll find useful and of interest.

Respectfully,



Andre Machado, MD, PhD

Chairman, Cleveland Clinic Neurological Institute
machada@ccf.org



2016 HIGHLIGHT

First-in-Human Trial of DBS for Stroke Recovery Launched with NIH BRAIN Support

Can neuromodulation be used effectively to recover neurological function, such as in paralysis?

That's among the key research questions being explored in a Cleveland Clinic *first*: a new clinical trial testing deep brain stimulation (DBS) as rehabilitative therapy for stroke survivors. The trial, launched in 2016, was awarded nearly \$5 million in funding from the NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative.

"When we use DBS for a movement disorder, we're attempting to suppress a positive symptom, such as tremor or rigidity, that's overlaid on top of normal function," explains lead investigator Andre Machado, MD, PhD. "In contrast, in this trial we're attempting for the first time to use DBS to help recover a function that's been lost — i.e., motor function on the paretic side of a stroke survivor's body."

The study will examine a novel strategy — stimulation of the dentatothalamocortical pathway to enhance excitability and plasticity in spared cerebral cortical regions — with the aim of promoting recovery of motor function.

"Our primary hypothesis is that by applying DBS to the connections between the cerebellum and cerebral cortex, we can facilitate the plasticity that occurs in the cortex around the stroke and thereby promote recovery of function beyond what physical therapy alone can do," Dr. Machado notes.

The study builds on more than a decade of Cleveland Clinic preclinical research. "We know that deep cerebellar stimulation promotes motor recovery in a preclinical model of cortical stroke," says Kenneth Baker, PhD, of Cleveland Clinic's Department of Neurosciences. "Our goal is to advance this therapy to promote recovery of motor function in humans. This has the potential to be a significant advancement for the field."

Trial enrollment is underway. Candidates are patients with severe residual hemiparesis from an ischemic stroke 12 to 24 months previously despite physical therapy. Primary aims include:

- › Establishing safety and proof-of-concept data for dentate nucleus DBS in this population and defining optimal metrics for further trials
- › Characterizing acute and chronic effects of dentate nucleus DBS on cerebral cortex excitability
- › Characterizing movement-related local field potential changes in the area of the cerebellar dentate nucleus in patients whose leads are temporarily externalized
- › Characterizing changes in perilesional cortical maps in response to chronic dentate nucleus DBS

"We need more and better options to help the many patients who remain chronically disabled after a stroke," says Dr. Machado. "The opportunity here is to explore a new avenue that may improve their long-term rehabilitative outcomes."

LEFT — Illustration showing a DBS lead implanted in the cerebellar dentate nucleus for treatment of post-stroke motor deficits. Low-frequency stimulation is predicted to enhance neural activity across the ascending, excitatory dentatothalamic pathways (blue) and, in turn, thalamocortical pathways (red/yellow), thereby increasing cerebral cortical excitability and enhancing functional reorganization across spared perilesional cortex.



2016 HIGHLIGHT

Sizing Up Ketamine vs. ECT for Treatment-Resistant Depression

Use of the anesthetic agent ketamine as an alternative to electroconvulsive therapy (ECT) for treatment-resistant depression has surged over the past decade and a half. The problem is, no large-scale trials of ketamine's safety and efficacy in treatment-resistant depression have been conducted, so its use in this setting hasn't been covered by insurers. And patients and clinicians have no direct evidence of how ketamine and ECT stack up in terms of efficacy, side effects and patient quality of life.

A key partner of the federal government is now intent on changing that, by way of an \$11.8 million award to fund a Cleveland Clinic-led study comparing ketamine and ECT for patients with treatment-resistant depression. The award comes from the Patient-Centered Outcomes Research Institute (PCORI), which is authorized by Congress to fund comparative effectiveness research. The study was one of just three research projects to win PCORI funding in its July 2016 round of awards.

"This study will fill the evidence gap around ketamine versus ECT for treatment-resistant depression," says the study's principal investigator, Amit Anand, MD, Vice Chair for Research in Cleveland Clinic's Center for Behavioral Health. Dr. Anand was a member of the 1990s Yale University team that first discovered that ketamine could effectively treat severe depression.

The PCORI-funded study is a five-year investigation in which 400 patients with severe treatment-resistant depression at Cleveland Clinic and three

other U.S. sites are being randomized to receive one of the following for three weeks:

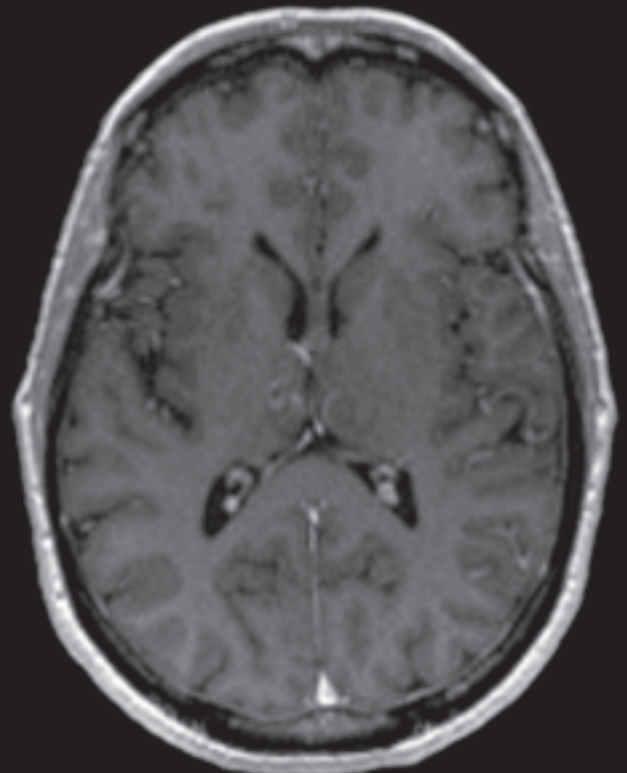
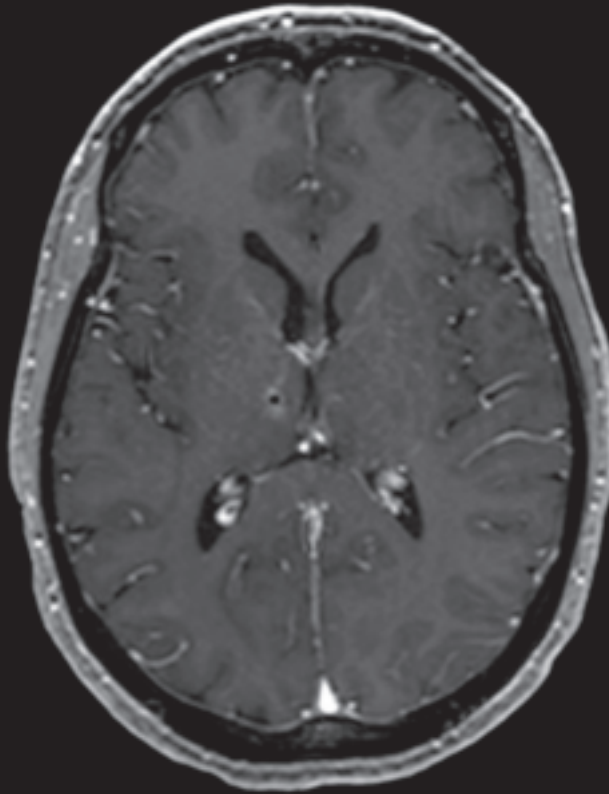
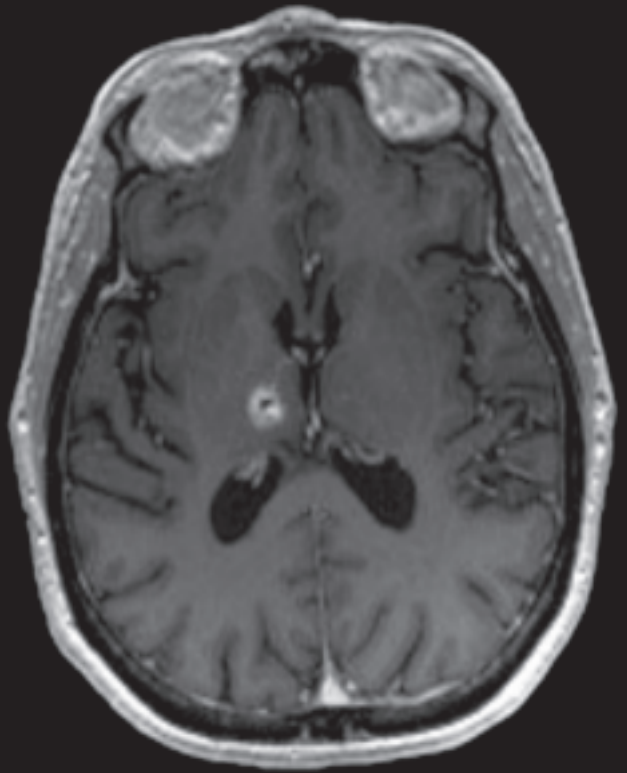
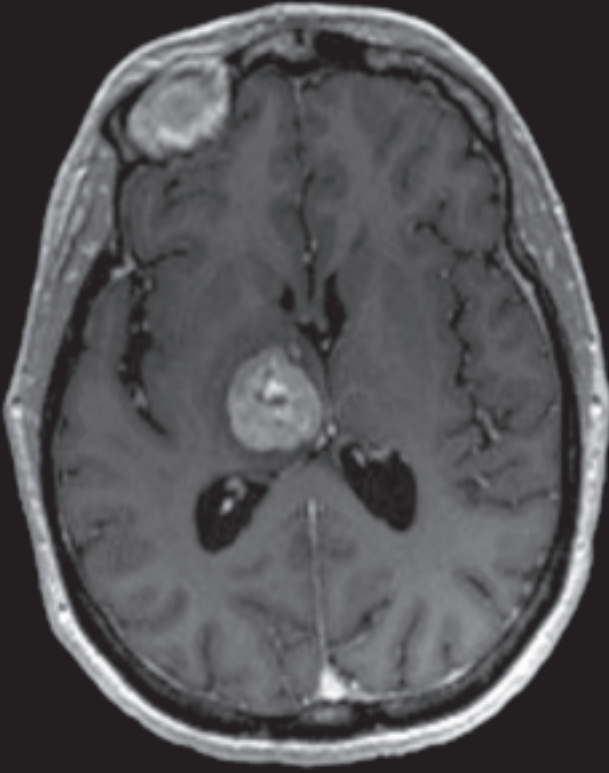
- › Multiple infusions of ketamine (at a subanesthetic dose) twice a week
- › ECT three times a week

Changes in depressive symptoms, memory function and quality of life will be assessed through patient self-reports and clinician ratings. Following the acute phase of treatment, responders to each therapy will be followed up by their usual providers to measure differences in long-term outcomes.

Quality of life and relief from depression without significant side effects are key outcomes of interest. Although ECT is highly effective for treatment-resistant depression, many patients find it unsatisfactory because ECT is often associated with memory deficits, is difficult and costly to administer, and tends to carry a lingering social stigma.

"If ketamine is found to be as effective as ECT, it is likely to be rapidly adopted by patients, providers and payers for the acute reversal of treatment-resistant depression," says Dr. Anand, who notes that ketamine has potentially fewer side effects, is easier to administer and will likely be less expensive than ECT.

For a more detailed version of this article, see consultqd.clevelandclinic.org/ketamine.



2016 HIGHLIGHT

Pioneering Staged Gamma Knife for Large Brain Metastases: Two Smaller Sequential Doses May Be Better Than One

A novel two-stage approach to Gamma Knife® stereotactic radiosurgery is showing improved outcomes for treating large brain metastases, and Cleveland Clinic has become the first center outside Japan to embrace it. By allowing for delivery of an overall higher dose of radiation with minimal toxicity, the strategy represents a potential new standard of care for large brain metastases.

The Challenge of Large Tumors

Although standard Gamma Knife radiosurgery has gained favor in recent years as monotherapy for brain metastases, its success has been limited in patients with metastases larger than 2 cm.

“The question is how to get a large dose to a large tumor so patients don’t fail therapy,” explains Cleveland Clinic neurosurgeon Lilyana Angelov, MD.

Two Medium-High Doses a Month Apart

In recent years, she and colleagues in Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center have begun using a novel approach that could dramatically improve the odds of a good outcome with large metastases.

Instead of a single radiation dose limited by the toxicity resulting from treating large tumors, Gamma Knife therapy for large tumors is now delivered in medium-high doses over two stages about a month apart.

“This allows us, in most cases, to spare the patient the risks of open surgery and the toxicity of whole-brain radiation therapy that would be standard of care,” Dr. Angelov explains. “It’s a game-changer.”

Encouraging Numbers to Date

Among Cleveland Clinic’s first 54 patients — with a total of 63 brain metastases ≥ 2 cm — treated this way, the local control rate at six months has been 88 percent, up from only 49 percent for similar-sized metastases previously managed with single-stage (standard) Gamma Knife therapy at Cleveland Clinic. Moreover, the treatment is well tolerated, with only seven instances of adverse radiation effects, which were mostly mild and transient.

Since these initial results, which were submitted for publication in 2016, Dr. Angelov’s team has used the staged approach for about 150 more cases, with continued positive outcomes.

She expects the approach to ultimately become the standard of care across the country for large brain metastases: “I see it as a primary modality for treating these patients in a minimally invasive manner. I think many patients will be well-served.”

For a more detailed version of this article, see consultqd.clevelandclinic.org/stagedgamma.

LEFT — MRIs from a patient who underwent staged Gamma Knife therapy. Top images were taken before the first treatment (left) and immediately before the second (staged) treatment (right). Bottom images are from six months (left) and four years (right) after the second treatment, showing significant reduction in the size of the metastases.



2016 HIGHLIGHT

Remaking the Management of Chronic Low Back Pain

Value-based care and the opioid epidemic don't usually come up in the same sentence, but they have at least one thing in common: Both ranked high among 2016's healthcare headlines.

Over the past year, Cleveland Clinic's Neurological Institute has given these issues another point of intersection with a bold new initiative to promote value-based care for patients with chronic pain while also preventing inappropriate opioid use.

The initiative, launched in August 2016, is a population health pilot program to treat more than 1,000 patients with chronic low back and leg pain by prioritizing functional outcomes over opioid- or procedure-based care. If successful, the model can be applied to other chronic pain conditions and perhaps replicated at other institutions.

Eligible patients are those with low back or leg pain for more than three months. All undergo combined physical and behavioral pain rehabilitation as the first line of care.

The aim is to promote pain rehabilitation by managing the sensory, cognitive and affective domains of pain. The key outcome metric is restoration of function. "It's about delivering real value to patients, with a meaningful transformation of their lives, rather than hoping for a quick fix," says Neurological Institute Chair Andre Machado, MD, PhD.

Spine medicine physicians and spine surgeons are available throughout patients' longitudinal care. They manage medications, order tests and provide surgical evaluations when appropriate.

"Patients will not be denied surgery, procedures or pain medications if the diagnosis calls for such,"

explains spine neurosurgeon Edward Benzel, MD, founder of Cleveland Clinic's Center for Spine Health. "We emphasize that surgery is deemed appropriate only after all other relevant and safer treatment strategies have been considered or tried."

The program is expected to achieve its primary goal of helping patients recover function and become active again, while also achieving:

- › Avoidance of opioid prescriptions for chronic pain
- › Greater prudence in prescribing
- › Greater patient empowerment to self-manage and control pain

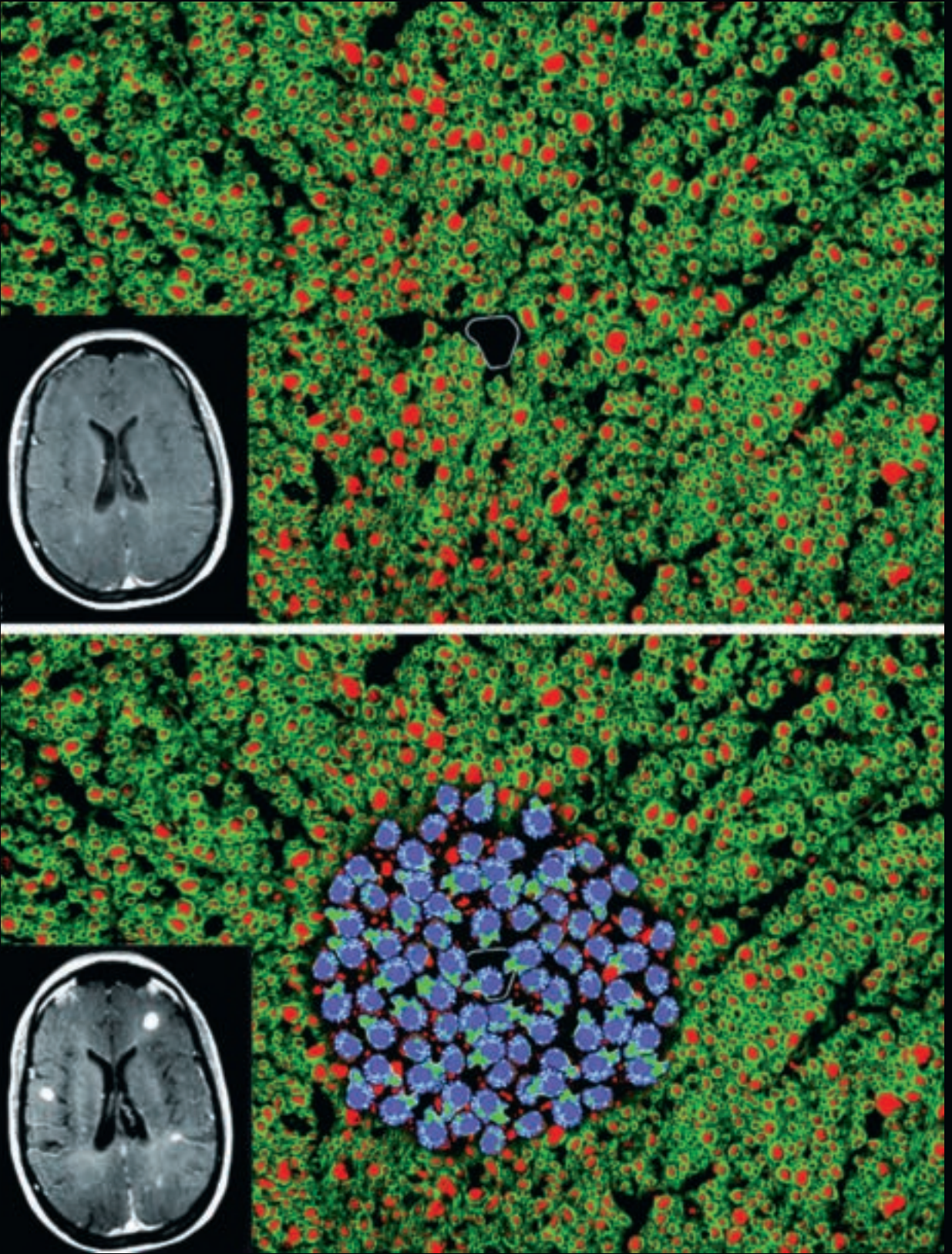
The program is highly interdisciplinary, with leadership from the Neurological Institute's Center for Spine Health, Department of Physical Medicine and Rehabilitation, Center for Neurological Restoration and Center for Behavioral Health.

"The literature supports a collaborative approach to these patients," says Mary Stilphen, PT, DPT, Senior Director of Rehabilitation and Sports Therapy. "Single approaches, used in isolation, are often unsuccessful."

"Pain is a multifaceted experience that demands interdisciplinary collaboration," adds Sara Davin, PsyD, MPH. "Our program differs from others in its interdisciplinary approach to care."

"This project is made possible by the Neurological Institute's distinctive organizational structure, which breaks down departmental barriers to promote collaboration across subspecialties," notes Dr. Machado. "Pulling this off in a traditional model would be difficult."

LEFT — A patient undergoes physical therapy as part of Cleveland Clinic's pilot program for chronic low back pain, which combines physical therapy with behavioral pain rehabilitation as the first line of care.



2016 HIGHLIGHT

Rapid Autopsy Program Speeds Research Progress in Multiple Sclerosis

When Cleveland Clinic's Bruce Trapp, PhD, created one of the first rapid autopsy programs for multiple sclerosis (MS) back in 1994, he was pioneering a novel concept — to collect a pre-consented patient's body shortly after death (ideally within a few hours) for advanced MRI studies followed by removal of the brain and spinal cord for pathological analysis. The aim was to study the effects of MS on the brain in a way impossible with animal models or standard imaging.

Now, more than two decades later, the program is the largest of its kind in the world, with over 160 specimens collected, and it's been central to Cleveland Clinic's mounting grant funding to advance understanding of how MS develops and progresses in the human brain. Three grants were awarded in 2015-2016 for research that draws on the autopsy program:

- › \$6.97 million from the National Institute of Neurological Disorders and Stroke (NINDS) to identify new therapeutic targets causing axonal and neuronal degeneration
- › \$1.7 million from the NINDS to support work to further reveal factors influencing remyelination
- › \$460,000 from the National MS Society to investigate differences between primary progressive and secondary progressive MS, with the goal of aiding therapy development

"One of our program's aims is to correlate MRI changes with pathological changes," explains Dr. Trapp, now Chairman of Cleveland Clinic's Department of Neurosciences. "We've uncovered

surprises — some MRI changes have been shown to not be what we historically thought they were."

Those surprises included the groundbreaking 1998 discovery that transected axons are common in MS lesions and may underlie the disease's irreversible neurological impairment, as well as the 2002 insight that cells capable of producing myelin are present in chronic lesions of MS.

In parallel with Dr. Trapp's work, neurologists in Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research are using the rapid autopsy program in ways that promise more immediate impact for patients: testing new MRI sequences and technologies in MS.

By applying newly developed MRI sequences to cadavers, Mellen Center researchers get an immediate reading on whether the MRI changes observed are suggestive of the underlying brain and spinal cord pathology. Once validated in the postmortem program, the sequences can be applied as outcome measures in selected clinical trials, with the hope that some can ultimately be brought into clinical practice.

"The postmortem program is the perfect place for incorporating new MRI technologies in MS," says the rapid autopsy program's medical director, Daniel Ontaneda, MD. "We're directly translating MRI research to pathology, and it accelerates MRI development."

For a more detailed version of this article, see consultqd.clevelandclinic.org/rapidautopsy.

LEFT — Pathology images from normal white matter (top) and white matter with an active MS lesion (bottom), with corresponding MRI findings in the insets. Such pathology-MRI correlation is a central objective of Cleveland Clinic's rapid autopsy program for MS.



2016 HIGHLIGHT

Dual-Task mTBI Assessment: Out of the Biomechanics Lab, Onto the Battlefield

Dual-tasking — simultaneous performance of cognitive and motor tasks — is something we all do hundreds of times daily: Checking the time while running out the door. Reading while sipping coffee. Chatting while crossing the street.

So why shouldn't neurological disorders — including mild traumatic brain injury (mTBI) — be evaluated in a way that reflects that reality, rather than assessing each function individually?

Currently, dual-task neurological evaluation is available only at centers with biomechanics labs. Cleveland Clinic researchers hope to change that by bringing dual-task evaluation to the patient — or, in military contexts, the soldier. They're doing so with help from a three-year, \$1.3 million grant from the U.S. Department of Defense to develop and validate a dual-task mTBI assessment for the military.

Dual-task capability can be a matter of life and death for military personnel, who may be monitoring data or interpreting radio transmissions while performing strenuous activities. The job is even more perilous for personnel with or recovering from mTBI.

“Studies demonstrate that following mTBI, soldiers often experience declines in postural stability and oculomotor and visual function,” says Jay Alberts, PhD, Director of Cleveland Clinic's Concussion Center and Vice Chair for Health Technology Enablement in the Neurological Institute. These declines are more pronounced under dual-task conditions, he notes.

Accurate assessment of a soldier's mTBI is vital but not always clear-cut. Corps-level medical

personnel lack a cohesive system and standard tools. “We hope to come up with simple dual-tasking and vision assessments and standards to use across their system — to put more science into the art of evaluating and monitoring mTBI,” says Dr. Alberts.

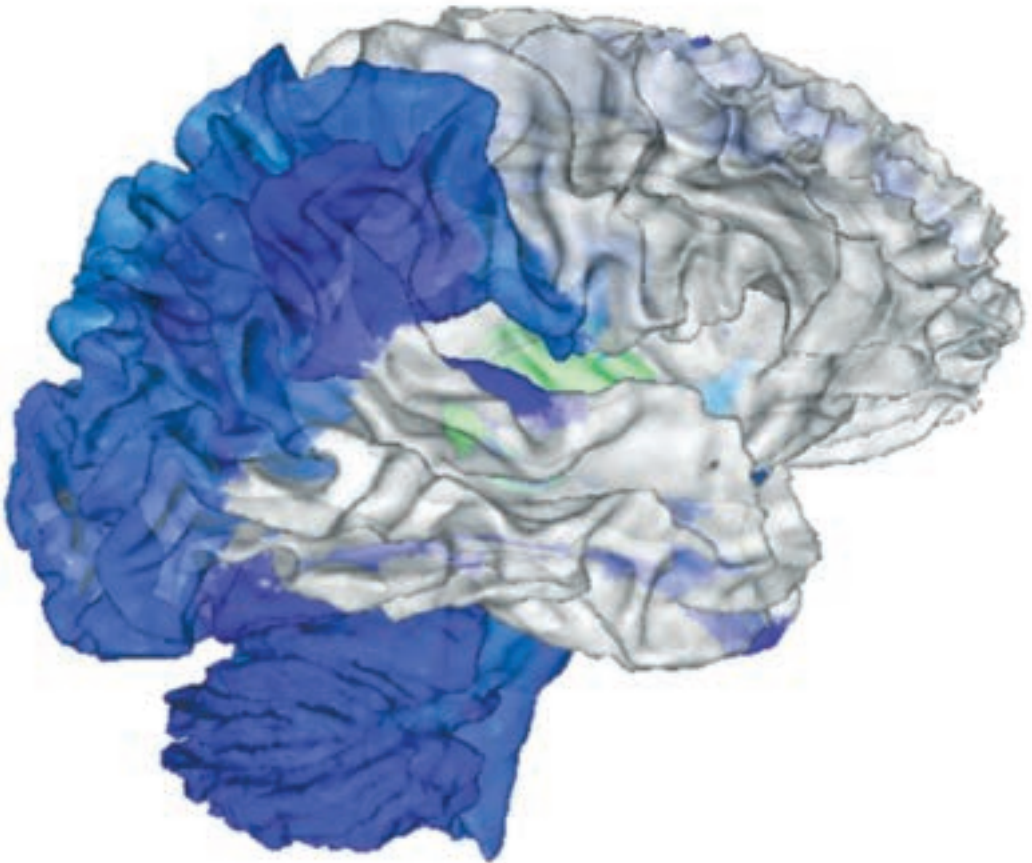
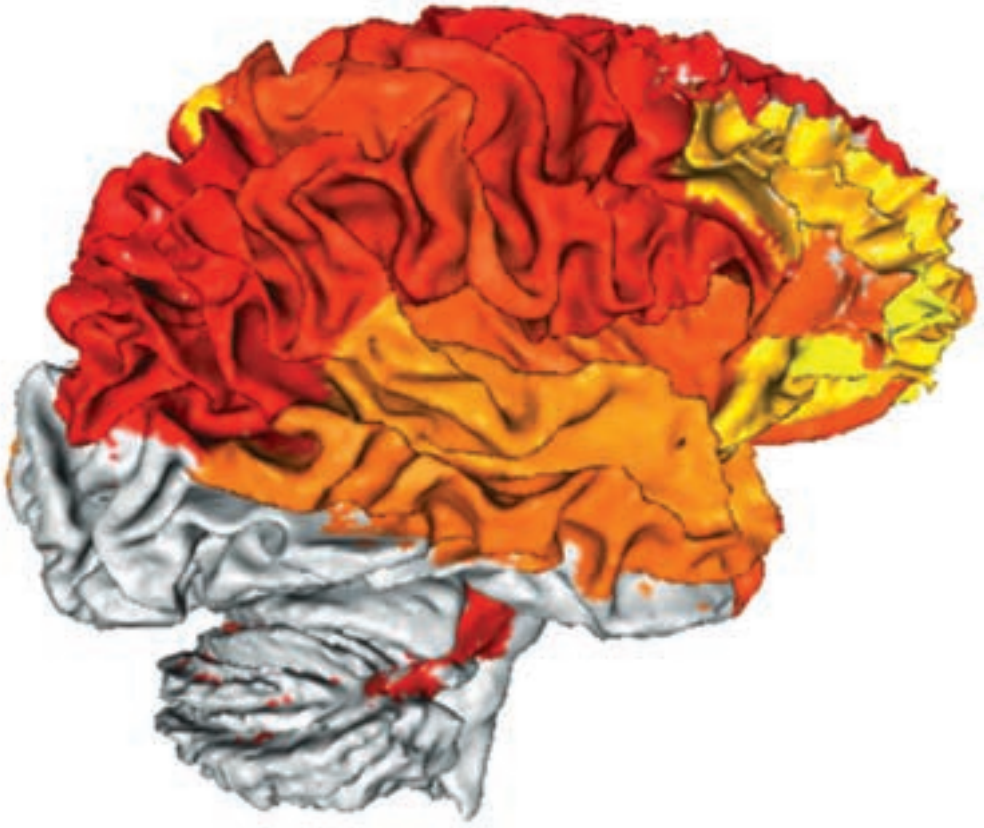
The basis for his team's mTBI assessment is the Cleveland Clinic-developed C3Logix™ mobile app, which is widely used to assess concussion among student athletes. With their new grant, the team is combining the C3Logix app's motor and cognitive functions into a dual-task assessment and establishing military-specific norms for it. They also will develop a multicomponent vision assessment.

Phase 1 of the project includes developing dual-task assessment software and validating it for civilians. The C3Logix app will be calibrated with the industry's leading biomechanical assessment tool, the CAREN (Computer Assisted Rehabilitation Environment) system (photo). “We'll test gait and Stroop tasks on CAREN to determine which cognitive challenges have the most valuable effect on biomechanics, such as postural stability,” Dr. Alberts explains. “Then we'll collect data from CAREN and the mobile app simultaneously to ensure the app produces accurate data.”

Phase 2 involves validating dual-task and vision assessments for military personnel, to set military norms. “We expect initial results in early 2017,” says Dr. Alberts.

[For a more detailed version of this article, see \[consultqd.clevelandclinic.org/dualtask\]\(https://consultqd.clevelandclinic.org/dualtask\).](https://consultqd.clevelandclinic.org/dualtask)

LEFT — A subject undergoes testing on the CAREN system being used in the dual-task mTBI research.



2016 HIGHLIGHT

2016 Look-Back in Brain Health: Two Studies with Potential Long-Term Impact

When a center runs one of the nation's largest neurocognitive disease clinical trial programs, any year may yield notable developments. For Cleveland Clinic Lou Ruvo Center for Brain Health, 2016 saw at least two such examples, recapped below.

Bexarotene in BEAT-AD

Ever since reports that the cancer therapy bexarotene reduced brain amyloid- β , plaque load and behavioral deficits in mouse models of Alzheimer's disease (AD), interest in the agent has been keen. That interest led to BEAT-AD, a phase 2a trial conducted at the Lou Ruvo Center for Brain Health among 20 patients with AD (confirmed by florbetapir scan) randomized in a double-blind fashion to four weeks of placebo or bexarotene 300 mg/day.

While the trial was negative for one of its primary outcomes — amyloid burden reduction across the overall sample — it found that bexarotene significantly reduced amyloid burden in the subset of patients who were noncarriers of the *ApoE4* allele for AD, another primary prespecified outcome.

Lou Ruvo Center for Brain Health Director Jeffrey Cummings, MD, ScD, says the study, published in *Alzheimer's Research & Therapy* (2016;8:4), is the first time a small-molecule agent has lowered amyloid in a subset of patients in a double-blind, placebo-controlled setting. "This biomarker-based proof-of-concept trial supports a mechanism-based biological effect of bexarotene on targets relevant to AD pathogenesis," notes Dr. Cummings. He plans a longer phase 2/3 trial of bexarotene in carriers and noncarriers of the *ApoE4* allele with mild to moderate AD.

Detecting CTE In Vivo

Despite the headlines surrounding chronic traumatic encephalopathy (CTE) in athletes, research on the condition has been hampered by the fact that CTE currently can be diagnosed only after death.

But a multicenter study launched in 2016 aims to change that. The NIH-funded, \$16 million DIAGNOSE CTE trial is the largest study to date of living former athletes designed to help enable in vivo detection of CTE. "There's an urgent need to develop accurate methods for detecting and diagnosing CTE during life," notes Dr. Cummings, one of the trial's four lead investigators.

DIAGNOSE CTE will seek those methods by studying 240 men aged 45 to 74 with differing exposures to repetitive head impacts (RHI):

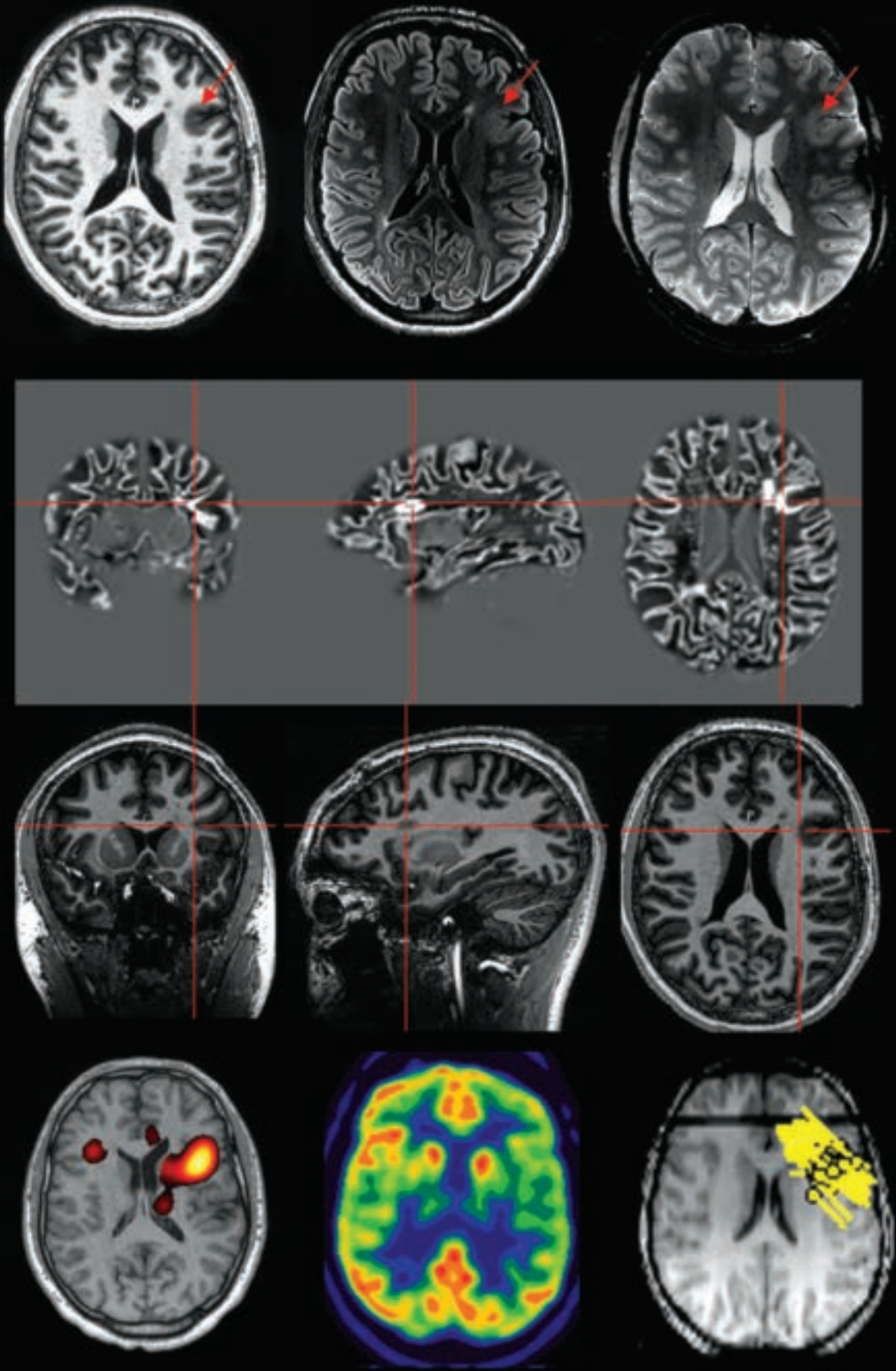
- › 120 former NFL players with and without CTE symptoms (high RHI exposure)
- › 60 former college football players with and without CTE symptoms (medium RHI exposure)
- › 60 controls with no history of RHI exposure

Participants will be monitored for three years via neuroimaging studies (PET, MRI and MR spectroscopy), biofluid analyses, neurological examinations and neuropsychiatric tests.

"We hope to be able to detect CTE before brain damage occurs and discover means of preventing it," says Dr. Cummings.

For a more detailed version of this article, see consultqd.clevelandclinic.org/lookback.

LEFT — Images showing mean change in amyloid burden from baseline to week 4 among noncarriers of *ApoE4* in the BEAT-AD trial's bexarotene group (top) and placebo group (bottom). The red end of the color spectrum indicates reduced amyloid burden, whereas the blue end indicates increased amyloid burden.



2016 CASE HIGHLIGHT

Advanced MRI Complements Intracranial EEG for Surgical Treatment of a Youth with Epilepsy

Eighteen-year-old “Randy” (not his real name) had experienced seizures since age 5 and tried many antiepileptic medications, without relief. At age 12, he underwent extensive testing at an outside center, which indicated that the seizure onset zone was overlapping with language function. His family declined resective surgery, concerned that it would result in a speech deficit.

Randy’s seizures increased over time, prompting him to come to Cleveland Clinic’s Epilepsy Center in 2016 for consultation and possible epilepsy surgery. He underwent standard presurgical noninvasive evaluation, including repeat MRI, PET, SPECT and MEG. He also participated in an IRB-approved research protocol allowing him to undergo 7T MRI scanning for comparison with the standard 3T MRI obtained in clinical practice.

The 7T MRI results were impactful, revealing a subtle but clear malformation of cortical development in the depth of the left inferior frontal sulcus, with thickened cortex and indistinct gray-white junction. The lesion was confirmed by postprocessing of the 7T MRI using a quantitative voxel-based morphometry approach — and also confirmed with repeat 3T MRI.

Results from video-EEG, PET, MEG and ictal SPECT showed convergent findings, suggesting his seizures arose from the region of the malformation in the depth of the left inferior frontal sulcus. Yet the concern about language deficit remained, as the lesion was near the usual location of Broca’s area, which is critical for speech.

After intense multidisciplinary discussion, Epilepsy Center staff designed a combination evaluation with stereotactic depth and subdural electrodes. Meticulous analysis of this invasive evaluation revealed evidence of high epileptogenicity restricted to the dysplastic cortex in the depth of the left inferior frontal sulcus. Functional speech cortex was mapped on surface cortex posterior to abnormal sulcus that was not primarily epileptogenic, delineating a resective surgical approach expected to be both effective and safe.

Randy underwent focal resection of the lesion with intraoperative electrocorticography (ECOG) guidance under awake conditions. Language function was intact postoperatively, and the active intraoperative ECOG normalized after resection, showing absence of pathological patterns. Four months after surgery, he had a single cluster of five seizures on one day, with no further seizures after medication adjustment. While long-term follow-up will be definitive, Randy’s epilepsy appears to have been positively impacted.

This case illustrates the benefits of advanced neuroimaging with 7T MRI and postprocessing. By rendering lesions more detectable, these techniques can enable precise implantation of depth and subdural electrodes and then development of a strategy for surgery, even after “nonlesional” findings on standard MRI.

For a more detailed version of this case, see consultqd.clevelandclinic.org/7Tcase.

LEFT — Images from Randy’s evaluation, including 7T MRIs in the top row and postprocessing studies of the 7T MRIs in the second and third rows (crosshairs show lesion location). Bottom row contains SPECT, PET and MEG images showing convergent lesion findings.

2016 Clinical and Research Achievements

A sampling of notable developments from across Cleveland Clinic's Neurological Institute

New Use for Cortico-Cortical Evoked Potentials

Cortico-cortical evoked potentials (CCEPs) offer distinct advantages for invasive monitoring of epilepsy surgery patients. Now Cleveland Clinic's Epilepsy Center is spearheading an NIH-funded project to expand this tool's utility by developing a brain atlas of CCEP responses from across hundreds of patients who have undergone epilepsy surgery using stereoelectroencephalography.

The research aims to elucidate the complex interactions of brain regions that can be elicited using CCEP studies. Its goal is to find noninvasive strategies to identify the cortico-cortical pathways that underlie the pathophysiology of intractable epilepsy — and perhaps of other neurological conditions.

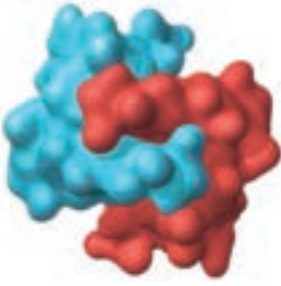
This project to map brain connectivity was awarded a five-year R01 grant from the National Institute of Neurological Disorders and Stroke. Cleveland Clinic serves as a principal investigative site along with the University of Southern California.

For more, see consultqd.clevelandclinic.org/ccep.



20 PLACEMENTS | IN | **10** PATIENTS

That's the cumulative count through November 2016 for successful placements of the Cleveland Multiport Catheter (CMC), a novel convection-enhanced delivery device for direct administration of high volumes of chemotherapy to the brain in patients with high-grade gliomas. The device (shown above) was developed by Cleveland Clinic experts, and all CMC placements to date have been done at Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. Multicenter efficacy trials of the promising CMC device are being planned.



Adolescent Suicide: Search Is On for Objective Risk Marker

Objective measures for suicide risk are scarce, but a Cleveland Clinic team hopes to change that with a study launched in 2016. Supported by a \$400,000 National Institute of Mental Health grant, the study is exploring whether blood levels of the astrocytic protein S100B (molecular model above) and five other peripheral inflammatory markers can predict suicidal ideation in adolescents following hospital discharge after a prior suicide attempt.

The study, the first longitudinal investigation of its kind, will enroll 120 patients and 40 controls. Patients are adolescents admitted to Cleveland Clinic's psychiatric unit after a suicide attempt. All will have blood samples taken at admission, at discharge and at any time they may make another suicide attempt in the year following discharge. Serum biomarker levels will be matched with suicide screening test results to assess for correlations.

"About 30 percent of adolescents who attempt suicide will have a relapse of suicidal ideation," says lead investigator Tatiana Falcone, MD, of the Center for Behavioral Health. "So we want to see if their levels of these inflammatory markers correspond with whether and when they may have suicidal thoughts again." An ultimate goal is a blood test to help predict which patients are at greatest risk of relapse so interventions can be better targeted.

For more, see
consultqd.clevelandclinic.org/S100B.

Milestones in Data-Informed MS Care

Data-informed care for patients with MS. That's the *raison d'être* for two recent initiatives by Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research that grew by leaps and bounds in 2016.

As of early November, more than 1,600 unique patients had undergone over 2,100 assessments with the Multiple Sclerosis Performance Test (MSPT) suite of iPad® app modules developed at Cleveland Clinic. By enabling patients to efficiently self-report MS signs and symptoms as a routine part of each office visit, the MSPT allows providers to focus on interpreting and acting on data rather than collecting and entering it.

The MSPT is now being rolled out to other MS centers around the U.S. as part of the pioneering MS PATHS collaborative led by Biogen and Cleveland Clinic. MS PATHS is a multicenter initiative to use clinical and imaging data from routine office visits to develop better outcome measures and improve care for patients with MS. To date, over 1,300 patients have authorized use of their clinical data for the initiative at Cleveland Clinic alone.

For more on MS PATHS, see
consultqd.clevelandclinic.org/mspaths.

> 2,100 MSPT
ASSESSMENTS

> 1,300 CLEVELAND
CLINIC
MS PATHS
PARTICIPANTS



A Growing Inpatient Rehab Footprint

The past year has seen Cleveland Clinic's Department of Physical Medicine and Rehabilitation expand its joint venture with rehabilitation services provider Select Medical. First there was the December 2015 opening of a new 60-bed rehabilitation hospital 20 miles west of Cleveland that is operated under the joint venture. Then construction began in 2016 on two similar hospitals at sites east and south of Cleveland, with completion expected by the end of 2017. The result will be a system of state-of-the-art inpatient rehabilitation hospitals across Northeast Ohio operated under the venture.

Pursuing the Promise of Coordinated Reset DBS

Researchers in Cleveland Clinic's Center for Neurological Restoration and Department of Neurosciences are investigating a novel deep brain stimulation (DBS) paradigm that holds promise for mitigating the risk of stimulation-induced side effects. The therapeutic potential of the paradigm — known as coordinated reset DBS — is supported by various theoretical models and now by experimental data from a preclinical parkinsonian model.

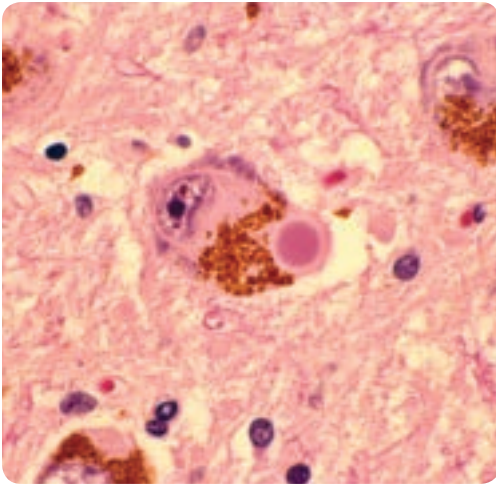
Researcher Kenneth Baker, PhD, published data from that model in *Brain Stimulation* (2016;9:609-617) showing that benefits from coordinated reset DBS accumulated over five days of intermittent therapy and persisted for more than a week after therapy cessation, in contrast to limited carryover effects with traditional DBS. "Our ongoing work aims to realize the translational potential of coordinated reset DBS while also elucidating the link between changes in motor circuit neural activity and motor sign manifestation in Parkinson's disease," says Dr. Baker.

For more, see consultqd.clevelandclinic.org/dbsreset.

Going Mobile for Acute Stroke

Since its launch in July 2014, Cleveland Clinic's mobile stroke treatment unit (MSTU) has remade the management of acute stroke for thousands of patients in Northeast Ohio, with over 2,680 dispatches to date through October 2016. Here's a sampling of stats from 2016 alone (annualized based on YTD data through September):

- 1,264** MSTU dispatches
- 299** Patient transports
- 32** IV tPA administrations
- 8** Endovascular therapy interventions
- 52** Minutes, on average, from 911 call to IV tPA administration
- 10** Municipalities now served, with > 575,000 population in total



Spearheading the First Dementia with Lewy Bodies Consortium

Research into dementia with Lewy bodies (DLB) has been hampered by a shortage of biomarkers and a lack of research consortia to leverage resources and patient volumes across multiple centers. But now DLB, the second most common dementia in the elderly, is getting its due with formation of the Dementia with Lewy Bodies Consortium, funded by a \$6 million, five-year NIH grant awarded in 2016.

Cleveland Clinic has been designated the coordinating site for the consortium, which consists of nine U.S. centers with expertise in Lewy body disorders. “This consortium brings together a group of investigators who have collaborated extensively on DLB for many years,” says the project’s principal investigator, James Leverenz, MD, Director of Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland.

The project aims to emulate consortia for Alzheimer’s and Parkinson’s diseases by creating a foundation for biomarker development through enrollment of large numbers of subjects, systematic assessment of patients, collection of biofluid samples and imaging data, and ultimately collection of autopsy specimens. Creation of a sample of patients for translational and therapeutic studies is an expected ancillary benefit.

Defining the Demographics of Sports-Related Concussion

Portable yet systematic characterization of sports-related concussion. That’s the impetus behind the five-year-old Cleveland Clinic-developed C3Logix™ mobile app. Now Cleveland Clinic Concussion Center researchers have leveraged the app to characterize triage for suspected concussion in one of the largest observational samples of young athletes reported to date.

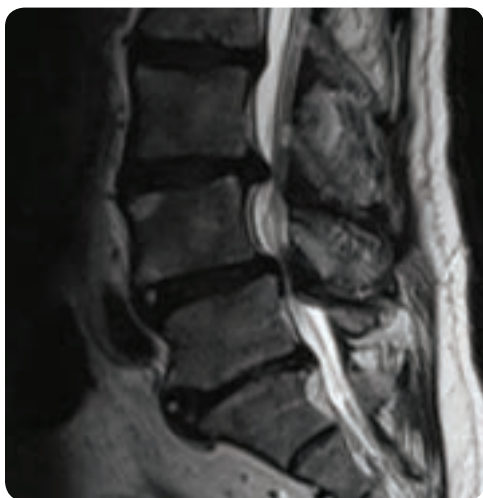
Their study, presented at the International Consensus Conference on Concussion in Sport, held in Berlin in October 2016, reviewed electronic incident reports completed with the app for suspected concussion among athletes in the care of Concussion Center clinicians over a recent 19-month period. The sample included youth ($n = 110$), high school ($n = 1,175$) and college ($n = 309$) athletes.

Among key findings:

- › Injuries were most frequent in football for males and soccer for females.
- › Youth athletes were sent to emergency departments following injury at a fourfold higher rate (22 percent) compared with high school and college athletes (5 percent) despite having significantly fewer red-flag findings.
- › The incidence of injury as a function of sport and setting (practice vs. competition) remained constant across the various age cohorts of athletes.

4-fold

Increase in the rate of ED referrals following suspected concussion among youth athletes compared with high school and college athletes



Taking on Confusion Around Spine Fusion

Should we add spinal fusion for patients undergoing laminectomy for lumbar spinal stenosis? That was the question tackled by a pair of studies published in the *New England Journal of Medicine* in April — the first major randomized, prospective trials on this question.

The studies were from the U.S. and Sweden, and Cleveland Clinic was one of the lead centers in the U.S. study, known as the SLIP trial, which involved patients with stenosis and spondylolisthesis. This study found that adding lumbar spinal fusion to laminectomy was associated with slightly greater but clinically meaningful improvement in overall health-related quality of life compared with laminectomy alone. In contrast, the Swedish study found no difference in outcomes.

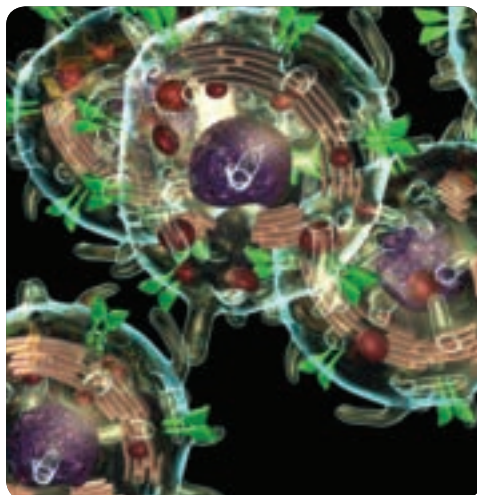
“This is a very common operation in the U.S.,” says SLIP trial co-author Edward Benzel, MD, a neurosurgeon in Cleveland Clinic’s Center for Spine Health. “The message to glean from our study is that fusion is appropriate in selected cases. The decision depends on symptoms and the imaging findings. This is not yet the final word.”

For more, see consultqd.clevelandclinic.org/fusion.

Viral Immunotherapy Shows Promise in High-Grade Glioma

For the first time, clinical data have shown that treatment with the retroviral replicating vector Toca 511, when used in combination with an antifungal agent, kills high-grade glioma cells and appears to activate the immune system against them while sparing healthy cells. So demonstrated a phase 1 multicenter study of the therapy co-directed by Cleveland Clinic and published in June 2016 in *Science Translational Medicine*.

The study assessed the combination of Toca 511 plus Toca FC (flucytosine) among 45 patients with recurrent or progressive high-grade glioma. Median overall survival was 13.6 months and was statistically improved relative to an external control group. Tolerability was excellent. “These encouraging survival and safety results support the ongoing randomized phase 2/3 trial of this immunotherapy and offer hope for a new treatment option in brain cancer,” says senior author Michael Vogelbaum, MD, PhD, of Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. Cleveland Clinic is participating in the phase 2/3 trial, known as Toca 5.



Getting to the Core of PD Progression

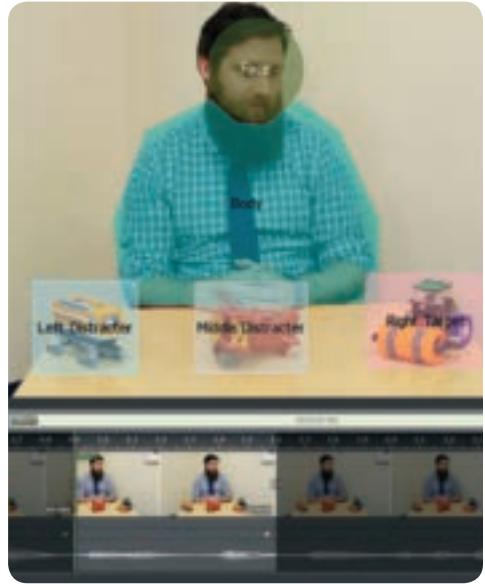
In February 2016, the Michael J. Fox Foundation selected Cleveland Clinic Lou Ruvo Center for Brain Health to serve as the pathology core for the Parkinson's Progression Marker Initiative (PPMI). PPMI is a large multinational clinical research study that aims to identify and develop disease biomarkers (blood or spinal fluid tests) in people with Parkinson's disease (PD) and those at risk for developing it.

The pathology core is creating a brain and tissue bank to collect and store postmortem brain tissue donated by PPMI participants. The goal is to help researchers correlate the brain changes that take place in PD with the motor, cognitive and behavioral changes observed throughout participation in the PPMI study and with the blood and spinal fluid biomarkers developed during the study.

>400

That's the number of former pro football players who've been assessed by Cleveland Clinic to date as part of its participation in The Trust collaboration with the NFL Players Association — more than for any other participating center. Under The Trust, former players undergo a comprehensive brain-body health evaluation to characterize their neurocognitive health status and identify opportunities for early intervention, if indicated.

In 2016, Cleveland Clinic also integrated screening for sleep disorders into its evaluations for The Trust. Former players who screen positive undergo sleep studies and are offered specialized treatment as needed.



On the Trail of Autism's First Objective Diagnostic Tool

The first objective tool for use in diagnosing autism may be at hand, thanks to work reported by Cleveland Clinic autism specialists and pediatric neurologists in the *Journal of the American Academy of Child and Adolescent Psychiatry* (2016;55:301-309). The team developed an autism risk index (ARI) based on a composite of measurements of remote eye gaze tracking in response to established social and nonsocial visual stimuli (example shown above). Initial and replication testing of the ARI found it to be highly accurate in distinguishing children with autism spectrum disorder (ASD) from those with non-ASD developmental disorders, as detailed in the above paper.

Although further replication of the findings in larger samples is warranted, the ARI holds promise as an objective tool to supplement clinical observation for ASD symptom assessment — and potentially to help measure treatment response.

For more, see consultqd.clevelandclinic.org/ari.

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