

NEW YORK-PRESBYTERIAN Children's Health

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Spinal Muscular Atrophy Research Aims for Cure

A newly formed clinic and research network at Morgan Stanley Children's Hospital of NewYork-Presbyterian/Columbia University Medical Center is bringing physicians closer to finding a cure for spinal muscular atrophy (SMA). An autosomal-recessive disease that affects the spinal cord and nerves of children, SMA is the most common genetic killer of infants and toddlers. The National Institutes of Health (NIH) has identified SMA as the neurologic disease for which a treatment or cure is mostly likely to be found in the foreseeable future. Physicians at Morgan Stanley Children's Hospital recently received several grants to support research aimed at treating SMA.

The first grant was donated as a personal gift by the parents of a child with type III SMA. The purpose of the grant is to establish a clinic dedicated to children with SMA. "The grants allow us to provide state-of-the-art care to SMA children and create a venue to conduct clinical trials searching for a cure," said principal investigator Darryl C. De Vivo, MD.

In July 2004, the SMA Foundation gave a larger grant to establish a clinical trials network for SMA in the north-eastern region of the United States. The
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Treatment Advances in Pediatric Endoscopic Neurosurgery

When compared with conventional treatments for such disorders as hydrocephalus, intracranial cysts, and brain tumors, pediatric neuroendoscopy is a revolutionary development.

"Neuroendoscopy has been around for quite a while," said Neil A. Feldstein, MD, "but the equipment is finally reaching the point where it's delicate enough to be both safe and useful. It allows us to navigate with straw-sized or narrower tubes within the ventricles of the brain for such procedures as biopsying tumors, fenestrating a cyst, treating hydrocephalus internally, or just inspecting an area. Many endoscopic procedures take an hour or two, and the patient can go home the next day, their condition diagnosed or cured, whereas before we needed to do an open craniotomy, and recovery would take 3 to 5 days with a higher risk of complications."



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This issue highlights the pediatric neurologic care and related research programs at the Morgan Stanley Children's Hospital of NewYork-Presbyterian/Columbia University Medical Center and the Komansky Center for Children's Health, NewYork-Presbyterian/Weill Cornell Medical Center.

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Pediatric neurosurgeons at Morgan Stanley Children's Hospital of NewYork-Presbyterian/Columbia University Medical Center and the Komankys Center for Children's Health at NewYork-Presbyterian Hospital/ Weill Cornell Medical Center are providing children with a treatment alternative offering tremendous benefits.

The use of neuroendoscopy to treat hydrocephalus has already provided patients with a better treatment alternative. Before the advent of a technique called endoscopic third ventriculostomy (ETV), the insertion of a permanent shunt was the mainstay of hydrocephalus treatment. "Historically

normal circulatory pattern in and around the brain, avoiding dramatic changes in intracranial pressure. The process also takes less time. Whereas inserting a shunting device takes 30 minutes to an hour of surgery, the ETV surgical procedure takes 10 to 12 minutes. The most important selection criterion is that the patient has noncommunicating hydrocephalus, meaning that the CSF does not flow out of the ventricular compartment. Fortunately, among the pediatric population, most patients have noncommunicating hydrocephalus and are excellent candidates for the procedure.

The benefits of this technique are not limited to the newly diagnosed patient. "ETV works extremely well in patients previously shunted," Dr. Souweidane

to normalize. Before the advent of endoscopic cyst fenestration, treatment options meant either inserting a shunt or performing a craniotomy. A craniotomy takes 2 to 3 hours to perform, compared with the 20 to 30 minutes needed for an endoscopic cyst fenestration.

Patients with certain brain tumors located in the ventricular system also have greatly benefited from the minimally invasive nature of endoscopy. Cystic tumors such as colloid cysts, craniopharyngiomas, and epidermoid tumors are readily approached by an endoscope. The capsule of the tumor is coagulated, the contents are evacuated through aspiration, and the capsule is

"Neuroendoscopy has been around for quite a while, but the equipment is finally reaching the point where it's delicate enough to be both safe and useful."

Neil A. Feldstein, MD

that has worked very well. It saves lives and it is an easy procedure to do. However, there are a number of complications associated with shunting," observed Mark Souweidane, MD, including infection, obstruction and catheter disruption.

During ETV, an endoscope (Dr. Souweidane uses endoscopes that range from 1.1 mm to 6 mm in diameter) is used to create a fenestration in the third ventricle. Cerebrospinal fluid (CSF) then escapes from the ventricular compartment and enters the subarachnoid space, where it is normally absorbed. Amazingly, no shunt or indwelling device is required. The procedure not only obviates the need for a shunting device and all the inherent complications of shunting but also restores a

said. Shunted patients who undergo ETV are very appreciative, since they often have experienced repeated shunt malfunctions and multiple shunt-related surgeries or revisions. Studies indicate the risk of this procedure decreases dramatically as the surgeon gains more experience. Dr. Souweidane has been performing ETV since 1994. Although ETV has been associated with morbidity and even death, there has not been an instance of stroke or death during Dr. Souweidane's 11 years of surgical experience at NewYork-Presbyterian/Weill Cornell.

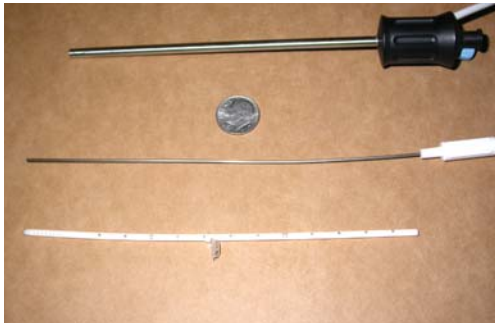
As with hydrocephalus, the treatment of intracranial cysts with endoscopy relies on the creation of a fenestration into a normal chamber of CSF flow. This fenestration allows CSF pressures

resected. The use of endoscopy in such a procedure has greatly reduced hospital stays. Instead of the customary 7- to 10-day hospitalization, patients commonly stay only 1 or 2 nights. There is also less morbidity and less cosmetic impact to the patient. Solid tumors pose more of a challenge because a solid component has to be resected with various instruments. "We are working with industry research and development firms to look at improving the types of technology offered to patients to take out solid tumors," said Dr. Souweidane.

Saadi Ghatan, MD, agreed that new technology such as the frameless neuronavigation system has changed the landscape of endoscopic neurosurgery. He compared the frameless neuronavigation system to a global positioning



Endoscopic third ventriculostomy eliminates placement of a permanent shunt.



Endoscopic instrumentation has shrunk, as have healing times.

system, but for the brain.

“Targets within the ventricles may be tiny or difficult to recognize, particularly in the setting of cysts, tumors, and scars,” said Dr. Ghatan. Instead of searching for landmarks and targets that may be difficult to find, the neuronavigation system allows the neurosurgeon to guide the endoscope directly to the target. “There is no doubt in your mind you are going to the right place,” he said.

Dr. Ghatan and colleagues at Morgan Stanley Children’s Hospital at NewYork-Presbyterian/Columbia have conducted research on the endoscopic management of cysts in lateral ventricular entrapment and 4th ventricular entrapment (in press).

Dr. Souweidane’s innovation in this field is expected to contribute to the safe application of endoscopy for patients who at the current time are not considered suitable. Strict and regimented selection criteria are used at NewYork-Presbyterian/Weill Cornell, and although endoscopic neurosurgery is not commonplace, it is gaining interest. The number of procedures performed at NewYork Presbyterian/Weill Cornell rises 10% to 15% each year. In addition, Dr. Souweidane annually leads courses on the topic and has shared his expertise in numerous publications. “Clearly, what we are doing here is recognized as being an advantage and a benefit to the patient,” said Dr. Souweidane. An international fellowship program mentored by Dr. Souweidane is expected to begin this year at the Weill Medical College of Cornell University.

Endoscopy isn’t the only area in which familiar procedures are being revisited and revised with excellent results. Explained Dr. Feldstein, “Chiari surgery is typically done through an opening in the skull base as well as an opening in the dural coverings of the brain, which adds up to more complications

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Ability To Diagnose Early Autism Improved Using High-Resolution Brain Imaging Technology

Parents are usually the first ones to notice the subtle signals that something is amiss with their children: a baby who doesn't babble or doesn't respond to people the way others do, or a toddler who suddenly becomes silent and withdrawn. Symptoms of autism are observed before 3 years of age, but tragically, the disorder often isn't diagnosed until much later. Yet the earlier diagnoses are made, the sooner families can get help for their children and better learn to cope.

The symptoms of autism didn't have a name until the middle of the 20th century, and even today, scientists remain uncertain about the precise etiology of the disorder—although they generally agree that both genetics and environment play a role.

For much of his career as a pediatric neurologist, the work of Barry Kosofsky, MD, PhD, has been broadly focused on the development and study of animal models of diseases that affect human brain development. This background serendipitously led him to his current emphasis: the early identification and diagnosis of autism, as well as treatments for the disorder.

Advances in imaging technology have given researchers new windows, allowing them to look inside the living brain to observe its structure and function. "For the first time we are able to see—with high resolution—how brain development proceeds normally and how it is altered by genetic and environmental factors," said Dr. Kosofsky. "This offers us tremendous power for improved diagnosis and a starting point to uncover new therapies." Using this technology with mouse models, Dr. Kosofsky and

his translational research team hope to expand our knowledge of complex diseases that affect human brain development, like autism.

"In the era of the human genome, it has become apparent that in addition to single-gene mutations, certain other diseases like asthma, obesity, and hypertension are polygenic, a consequence of multiple defective genes," said Dr. Kosofsky. He noted that developmental disorders like autism and Tourette's are increasingly being viewed this way. "They are highly genetic but not Mendelian, per se," he said.

In addition to the role of genes, environmental factors can either be protective or increase the risk of various diseases, Dr. Kosofsky noted. For example, we know that diet and exercise can lower the risk for hypertension and diabetes in adults. "We hope to develop a parallel set of insights on developmental disorders in general, and those affecting the brain in particular," he explained. "By combining our knowledge of genetics, genomics, and genetic diagnosis with screening, clinical assessments, and high-resolution imaging, we can get a picture of how one's individual genetic predisposition interacts with environmental factors to produce a phenotype with a certain brain-imaging signature." This will allow clinicians to better understand why one patient is different from another.

In the case of autism, Dr. Kosofsky and his group hope to track at-risk children (siblings of children with autism) between the ages of 1 and 3, before they show any signs of the disease. His team will watch for any brain changes that might serve as markers for those who would benefit from known

treatment modalities, such as applied behavioral analysis or Floortime. "This would advance our ability to sculpt and intelligently customize treatment for those who could benefit most," said Dr. Kosofsky.

Toward that end, Dr. Kosofsky works with a broad, multidisciplinary collaborative team that includes other faculty from Weill Medical College of Cornell University, and from other institutions (including Mass General Hospital, University of California at San Diego, and Oxford University), who are modifying the conventional hardware and software used in magnetic resonance imaging for kids. Dr. Kosofsky pointed out that scanners need to be specially adapted to image children who are younger as well as patients whose disease makes it too hard for them to stay still.

"Much of our expertise is in the area of post-image acquisition analysis," said Dr. Kosofsky. "A lot of brilliant people with backgrounds in engineering, computer science, radiology, and mathematics have revolutionized our analytic capabilities. Our team is refining methods to get more valid and precise morphometric data, measuring brain volume and white matter development. In mice, magnetic resonance spectroscopy and proton-weighted imaging are used; in humans, the focus is on T2-weighted and diffusion tensor imaging."

When he speaks of his hopes for the future for children and families with autism, Dr. Kosofsky's commitment, energy, and sense of urgency are palpable. "This work has to be done nationally, but if we can validate that our sophisticated brain imaging, acquisition, and analysis methods are sensitive and specific for 1- to 3-year-olds, we would be making a tremendous contribution," Dr. Kosofsky said.

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Early Signs of Autism Explored To Create Diagnostic Markers For Initiating Early Therapy

When the diagnosis is autism, both the medical community and the parents have more questions than answers. The symptoms of this disorder can range from mild to severe, and treatment options vary depending on the individual child.

An early, accurate diagnosis and appropriate early intervention are critical for better outcomes. Researchers at Weill Medical College of Cornell University will soon undertake

The study will aim to clarify what signs must be present to make a definitive diagnosis of autism early in life. “We have a sense of which behavioral symptoms are found in babies who are ultimately diagnosed with autistic spectrum disorder, but children with other developmental disorders may also have those very same symptoms,” noted Dr. Lipper.

In addition to diagnostic markers, various means of benefiting autistic children are being explored. A collaborative

special education, and occupational therapy, forms the backbone of good treatment for children with autism and other developmental problems.”

Work at the Komansky Center for Children’s Health at NewYork-Presbyterian/Weill Cornell is focused on a variety of aspects of neonatal brain development, including that in hospitalized premature babies. The staff at the neonatal intensive care unit (NICU) is examining the effect of stress on brain development, specifically the effect of noise and the environment on the sleep patterns of premature babies. As part of a study, recovering babies (particularly premature babies) hear single-instrument Mozart pieces for 2 hours a day during their stay in the unit. “It’s very soft, about 10 decibels higher than the background noise, which is at 55 decibels,” noted Jeff Perlman, MD, an expert on the neurologic problems of newborns. The longitudinal study is based on the concept that soft music is conducive to a more quiescent state, a more relaxed baby, and a lower heart rate. Data from animal experiments indicate that growth and development are stimulated in this tranquil state. Parents also seem to enjoy the music, Dr. Perlman noted.

As part of the unit’s overall strategy to reduce stress, those babies who are extremely ill during recovery will be placed in a newly constructed extra-quiet developmental room that has adjustable lighting and soft music. The NICU also plans to examine whether music that had a calming effect during pregnancy continues to exert the same effect postnatally.

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“One of the early signs of autism in infants is failure to point to objects in the way young children who are typically developing do.”

Evelyn Lipper, MD

research designed to determine if the early symptoms thought to be associated with autism are also prevalent in other developmental disorders. Babies ranging in age from 9 to 18 months who have a variety of developmental diagnoses and are exhibiting signs of atypical development will be included in the study.

“One of the early signs of autism in infants is failure to point to objects in the way young children who are typically developing do,” explained Evelyn Lipper, MD.

“But we know that children with other developmental problems, such as cerebral palsy and mental retardation, also may exhibit this communication delay. You can have a continuum from normal children to children with a whole range of developmental problems who exhibit the same symptom. To say, for example, that a child at 12 months who isn’t pointing has autism may be an overstatement, or it might not be.”

effort at both NewYork-Presbyterian Hospital medical centers is currently being considered, in which a central evaluation and diagnostic unit for children with autism and other developmental disorders would be established, said Dr. Lipper. Families with children exhibiting developmental abnormalities would be able to go to a central location for a comprehensive assessment.

When it comes to recommended treatments for children with developmental disabilities, the possibilities are just as varied as the symptoms. Most treatments are not based on science, and their efficacy has not been proved in large clinical trials, said Dr. Lipper. The success of treatments also varies from child to child. “The best treatment is delivered by professionals trained to work with young children,” said Dr. Lipper. “I believe a good combination of therapy, such as applied behavioral analysis, speech therapy,

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to the procedure. We found that we were able to do basically the same operation without opening up the dura. The operations are shorter, patients spend fewer days in the hospital, and recovery is much faster. I hesitate to say 'minimally invasive,' but it's much less invasive than conventional Chiari surgery."

Richard C.E. Anderson, MD, specializes in treating pediatric spasticity, and he said they are making big strides there as well. "The Morgan Stanley Children's Hospital is one of only 3 centers in the country that offer a minimally invasive selective dorsal rhizotomy to treat children with spasticity," he said. "The standard way of performing this operation is by removing 5 levels of

screws and rods internally in the pediatric population and stabilize the spine much more rigidly, so we don't have to use halo vests after surgery. Fortunately, the success rate for fusion approaches 100%. The youngest child I've performed this surgery on was about 18 falls, and he is doing well."

Other areas of investigation include immunologic treatment for brain tumors. "When children are diagnosed with malignant brain tumors before the age of 3, they can't have radiation therapy," explained Dr. Anderson. "Because malignant tumors in general cannot be cured with surgery, the only option is chemotherapy, which sometimes doesn't work. What we are trying to do is understand how the immune system interacts with these tumors, to see if it can be manipulated in a way that can work against the tumor."

"With the minimally invasive approach, only one level of bone is removed through about a 1 ½-inch incision. It allows patients to go home much sooner with much less postoperative pain."

Richard C.E. Anderson, MD

bone from the back of the spine through a 6-inch incision. With the minimally invasive approach, only 1 level of bone is removed through about a 1 ½-inch incision. It allows patients to go home much sooner with much less postoperative pain."

Dr. Anderson has also developed alternative methods of postsurgical cervical immobilization. "In the past," he explained, "when children needed surgery for congenital anomalies or traumatic instability of the upper cervical spine, afterward you would have to put them in a halo vest to keep the neck from moving. Halo vests are probably 1 of the most barbaric things we have in medicine. Even after wearing one for up to 3 falls, there's only about an 85% success rate. Now we have ways to place

Dr. Feldstein and colleagues are investigating new ways to apply cutting-edge technology. "Future directions include the evaluation of endoscopic techniques for craniofacial surgery," he noted. "It will allow for rather complicated operations to be done through a much smaller incision, with much more rapid recovery and much lower morbidity."

The group covers the full spectrum of pediatric neurologic surgery, and they take advantage of their association with NewYork-Presbyterian Hospital, teaming up with surgical colleagues in a variety of areas. "Craniofacial surgery is a collaborative effort," said Dr. Feldstein, "not done just by a neurosurgeon but by members of the craniofacial surgical team,



Standard rhizotomy technique involves a 6-inch incision rather than an incision <2 inches in length, as shown here.

which includes plastic surgery, neurosurgery, ENT, ophthalmological, and oromaxillofacial. Complex spine cases are managed jointly by a pediatric orthopedic surgeon and pediatric neurosurgeon. Certain nasal tumors are treated in procedures managed by both ENT surgery and neurosurgery."

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A Seizure-Free Life and World-Class Research Are Twin Goals of Pediatric Epilepsy Program

The pediatric epilepsy program at the Morgan Stanley Children's Hospital of NewYork-Presbyterian/Columbia University Medical Center enjoys a national reputation for excellence, performing cutting-edge research and developing optimal therapeutic strategies. The Comprehensive Epilepsy Center offers the chance of a seizure-free life for many children who have proved resistant to medication therapy.

But Frank Gilliam, MD, Director of the Center, is aiming to take the program to another level. His goal is to develop it into an independent, world-class research and treatment center. "Part of the passion we have for successfully completing this initiative is related to the dramatic need for centers to do research and provide optimal clinical care" for pediatric patients, Dr. Gilliam said. "Because, when you look at the numbers—whether it is delays in referrals or [inadequate] research funding—pediatric epilepsy is grossly underserved."

A case in point is the large discrepancy in public and private grants for childhood epilepsy compared to juvenile diabetes. While epilepsy is approximately 4 times more prevalent than diabetes in children under 18 and the standardized mortality rate is about 2 times higher, juvenile diabetes garners far more public and private support money.

The pediatric epilepsy center, with about 3,000 outpatients annually, is a collaboration among the Neurology Department of NewYork Presbyterian/Columbia, the Comprehensive Epilepsy

Center, and the Morgan Stanley Children's Hospital of NewYork-Presbyterian. Nearly 400 pediatric patients per year are admitted to the center's 4-bed video-electroencephalography (EEG) monitoring unit, most of whom are there to confirm a diagnosis and determine appropriate medical management. As much as 40% of the admitted pediatric epilepsy population arrive because their seizures remain uncontrolled after at least 3 trials of antiepileptic medications, according to Dr. Gilliam.

In an average 3-day stay, patients are monitored by video and EEG and also have a high-resolution magnetic resonance imaging scan in an effort to determine if a specific area of the brain is involved in seizure onset. They may undergo other imaging tests as part of the brain mapping process as well, including ictal single-photon emission computed tomography and positron emission tomography.

"We also use neuropsychological testing to look for possible memory changes and cognitive process changes that can help us point to a region of dysfunction consistent with seizure onset," Dr. Gilliam said.

He noted that if the focus of the seizures can be confirmed through multiple tests, there is a good chance that that portion can be resected, with a success rate of up to 75%, depending on the syndrome. Surgery carries a 1% to 2% risk of serious brain injury, Dr. Gilliam said, a fact that must be weighed against the estimated mortality rate for recurrent seizures, at 0.5% to 1.5% per year.

The epilepsy research program is pushing forward on a number of fronts, including trials of several new antiepileptic medications and experimental neural monitoring and stimulation technologies. One trial involves the use of an implantable device to stimulate the epileptogenic zone to determine "if we can increase the seizure threshold and decrease the chance of a seizure starting in that area of the brain," Dr. Gilliam explained. Another experimental device produces bilateral neurostimulation of the anterior nucleus of the thalamus in an effort to prevent seizures.

Investigators are also looking at the efficacy of a miniaturized monitoring system that records the abnormal electrical activity of individual neurons involved in epilepsy. The process entails pressing a chip containing 200 micro-electrodes into the cortex of the brain.

The outcome of all of this research won't be a single cure, Dr. Gilliam said. "From our perspective, we're going to chip away at specific cure after specific cure," until one day—"we're hoping in the next decade"—the great majority of pediatric epilepsy patients will be able to live seizure-free lives.

"But having said that," he added, "our cure rate overall for epilepsy surgery is between 60% and 70%, and for some syndromes it is 80%. I have a whole file of thank-you notes from parents whose children are living normal lives after a 2-hour procedure to safely resect a portion of the brain that was doing nothing other than causing seizures."

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Pediatric Neuromuscular Clinical Research (PNCR) network for SMA clinical trials is headquartered at Columbia University, with clinical sites

at Morgan Stanley Children's Hospital; Harvard University School of Medicine/Children's Hospital, Boston; and the University of Pennsylvania School of Medicine/Children's Hospital, Philadelphia. The center for managing the data is located at the University of

Rochester School of Medicine, Rochester, NY.

This new clinical research center "will be the first site in the United States that is totally dedicated to the conduct of clinical trials on SMA,"

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said Dr. De Vivo. Petra Kaufmann, MD, MPH, serves as Associate Program Director.

In addition, the Motor Neuron Center (MNC), also at Columbia University, interacts very closely with the SMA clinical research center. Dr. De Vivo codirects the MNC with Christopher Henderson, PhD, and Serge Przedborski, MD, PhD. At the MNC, basic and translational scientific studies are being conducted to improve the understanding of SMA and amyotrophic lateral sclerosis (ALS), which has many features in common with SMA. Inaugurated in November 2005, “the MNC now has several hundred investigators in 40 laboratories who are working on the biological role of survival motor neuron (SMN) protein and the pathological consequences of SMN deficiency,” said Dr. De Vivo.

SMA is currently diagnosed after the onset of symptoms and the performance of diagnostic testing. Each year in

the United States, approximately 16 new cases of SMA occur per 100,000 live births, which translates into an estimated prevalence of about 25,000 cases of SMA. Dr. De Vivo noted that in the last 5 or 6 years, there has been a movement toward recommending respiratory support for patients with type I SMA—the most severe form. This factor alone may be responsible for the increasing prevalence of SMA, as more patients with type I SMA are being kept alive with a respirator.

Many in the field feel strongly that SMA should be included in newborn screening efforts in the United States. However, there is currently no way to screen babies for SMA at birth. Recently, the NIH issued a grant to several investigators to develop assays.

“I think we are on the brink of a therapeutic breakthrough, and many of us feel very strongly that an assay should be developed that can be incorporated in the newborn screening procedures so we can identify a baby at birth. If we are ever going to get to the type I babies in time, we have to

treat them before they are symptomatic,” said Dr. De Vivo.

Currently, Dr. De Vivo’s group is in the process of conducting a 2-year natural history study of patients with SMA. The team at the PNCR network for SMA clinical trials includes Drs. De Vivo, Kaufmann, Wendy Chung, MD, and Jessica Rascoll, among others. Dr. Kaufmann spearheads the clinical trials initiative, and Dr. Chung directs the molecular core unit. “We have now accumulated scores of specimens that are banked in the tissue repository and are available to scientists at the MNC or other institutions.”

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