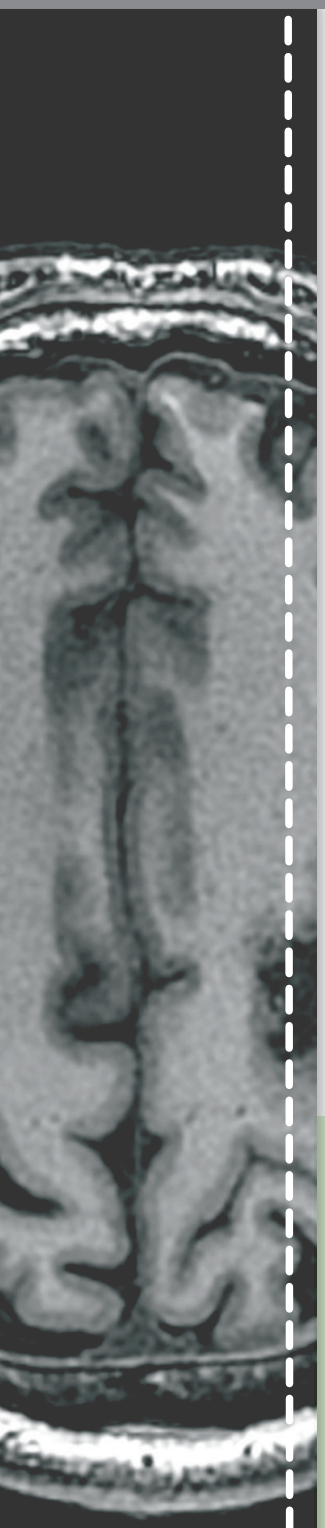
Le Bonheur Children's Hospital
Memphis, Tennessee

Brain Waves

Neuroscience Institute

Spring 2020

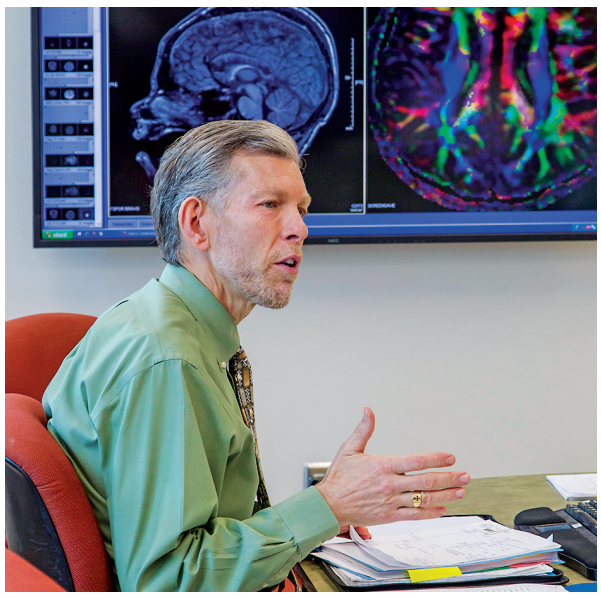


Le Bonheur named a Dravet Syndrome Comprehensive Care Center

The Le Bonheur Neuroscience Institute's Dravet syndrome program was recently named a Dravet Comprehensive Care Center by the Dravet Syndrome Foundation.

Le Bonheur's program is one of only 13 in the country certified by the Foundation as a facility with a high level of expertise and resources offering multidisciplinary care for children with this type of epilepsy.

"This designation reflects our continued commitment to providing the best care for children with rare epilepsies," says Chief Pediatric Neurologist and Co-director of the Neuroscience Institute James Wheless, MD. "Our clinicians have an excellent track record of diagnosing and treating every aspect of a child with Dravet syndrome."



Neuroscience Institute Co-director James Wheless, MD

Dravet syndrome is a rare form of epilepsy that typically begins in the first year of life and is diagnosed before the pre-school years. It has a genetic cause — mutations in the SCN1A gene.

Le Bonheur's Neuroscience Institute offers a variety of medications for seizures caused by Dravet syndrome as well as multidisciplinary care for cognition, behavior and sleep. The Center is actively engaged in research protocols and clinical trials for seizures, their causes and new treatments.

Le Bonheur is expanding the neuroscience partnership with St. Jude Children's Research Hospital with the launch of a translational neuroscience institute. Research will focus on untreatable epilepsies with genetic causes, such as Dravet syndrome.

Dravet on Trial: *One family's journey with drug trials for Dravet syndrome*

"I'm the type of mom that if there's a cure for my son and I have to go to Antarctica to get it, I'm going tomorrow," says Crystal Byrd, mother to 11-year-old Charlie who was diagnosed with Dravet syndrome at 2 years old.

So now Crystal and Eric Byrd of West Liberty, Ky., gladly make the nine-hour journey to Le Bonheur so that Charlie can participate in the Fenfluramine trial for Dravet syndrome – the only medication that successfully keeps his seizures under control.

Charlie began to have seizures after his first round of childhood vaccinations. Thinking they were febrile seizures, the Byrds weren't concerned until his seizures started again just a few months later. This time, they were referred to a local epileptologist for diagnosis and treatment.

The symptoms were clear and a genetic test confirmed – Charlie had Dravet syndrome.

But standard epilepsy treatments weren't controlling Charlie's seizures. After three years on various medications, Crystal and Eric knew their son needed more specialized care. Researching online, Crystal found eight hospitals recommended by the Dravet Foundation – the Byrds chose Le Bonheur.

"It was perfect," says Crystal of their first experience. "Le Bonheur was such a different and more welcoming atmosphere. We wanted to stay forever!"

The Byrd family makes a nine-hour journey in order for 11-year-old Charlie to participate in a trial for Dravet syndrome. This has been the only medication to successfully reduce his seizures.

Neurologist Stephen Fulton, MD, worked steadily to get Charlie the treatment that would be most effective. His seizures stabilized, and he was able to avoid hospitalization. However, as he grew older, his seizure pattern changed, and the increasing medication dose was no longer effective in seizure control.

So in 2013, Charlie underwent surgery for a vagus nerve stimulation

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ZOGENIX CLINICAL TRIALS

- **ZX008-1501:** two fixed doses of ZX008 oral solution as adjunctive therapy in children and young adults with Dravet syndrome
- **ZX008-1503:** an open-label extension trial to assess the long-term safety of ZX008 oral solution in children and young adults with Dravet syndrome
- **ZX008-1800:** expanded access program for ZX008 oral solution as adjunctive therapy in patients with Dravet syndrome
- **ZX008-1900:** an open-label extension trial to assess the long-term safety of ZX008 oral solution as an adjunctive therapy for seizures in patients with rare seizure disorders such as epileptic encephalopathies including Dravet syndrome and Lennox-Gastaut Syndrome
- Preparation is underway for a **Phase I/II study** as to whether the drug can help safely prevent seizures from happening with fewer side effects.

Referrals: 866-870-5570
www.lebonheur.org/neuroscience

A pediatric partner with The University of Tennessee Health Science Center/College of Medicine and St. Jude Children's Research Hospital

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT NEUROLOGY & NEUROSURGERY 2019-20

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(VNS) implant. He responded well – his mood improved, but he was still having nocturnal seizures, which pose the highest risk of death for someone like Charlie.

So Fulton decided that it was time to get Charlie into a brand new drug trial – ZX-008 (fenfluramine hydrochloride) oral solution.

"Charlie's seizures were extremely difficult to control and quite dangerous," says Fulton. "It was an easy decision to talk to his family about the current trials for Dravet syndrome as they had so much potential for better seizure control than previous therapies."

Tracee Ridley-Pryor, DNP, APRN, PMHNP-BC (far right), oversees the trials for Dravet syndrome ensuring that Le Bonheur's epilepsy patients can participate in the latest therapies available.

At first, the Byrds came to Le Bonheur twice a month in order to initiate participation in the trial. Various tests, including blood work, EKGs, ECHOs and more, determined if Charlie qualified and established a baseline for his health and seizure patterns. Crystal also had to track everything for the drug trial – when he had seizures, what kind of seizures he had, when he received medication and any other health concerns.

Tracee Ridley-Pryor, DNP, APRN, PMHNP-BC, is director of Research for the University of Tennessee Health Science Center Pediatric Neurology and oversees the current trials for Dravet syndrome while also investigating new trials for current and future patient participation.

"Every clinical trial requires a review of inclusion and exclusion criteria to evaluate which patients would be best suited for a clinical drug trial," says Ridley-Pryor. "The most rewarding part is seeing patients make strides that parents weren't even sure were attainable."

Beginning at the lowest dose, Charlie has slowly increased his medication so that he now takes the maximum dosage permitted. He has not experienced any side effects during his three years on the trial and had a 90% reduction in his seizures – where he use to have 24 to 30 seizures a month, he now has one or two.

"We are so thankful for Dr. Fulton," says Crystal. "At first the trial was overwhelming, but we know we have a knowledgeable health care team with Charlie's best interest at heart, who will be on top of all the details of the trial."

But Crystal is holding out hope for one more drug for Charlie – a DNA therapy drug that could potentially address his Dravet syndrome at the genetic level. This drug would correct the genetic mutation that leads to seizures and other symptoms Charlie and children like him have to wrestle with.

"Someday his disease may not affect anybody, but we'll never get there if we don't have people actively engaging in trials like these," says Crystal. "I wouldn't recommend a drug trial just anywhere, but at Le Bonheur the communication and support are incredible. Sometimes you get scared, but I know that I have somebody who I can talk to who will return my calls and concerns within minutes."

One in Ten Thousand

Neurologists perform Le Bonheur's first gene therapy infusion for spinal muscular atrophy

As the state of Tennessee finalized the newborn screening process for spinal muscular atrophy (SMA), 10,000 random samples were pulled for quality assurance testing. Charleigh Jones's sample was one of them. Diagnosed through the screening with SMA type 1 – a genetic condition characterized by increasing muscle weakness and early morbidity – Le Bonheur neurologists worked with Charleigh's pediatrician to intervene with a brand-new gene therapy, Zolgensma, to save Charleigh's life.

In December 2019 at 8 weeks old, Charleigh was the first Le Bonheur patient to receive this infusion delivering the gene that Charleigh is missing. This stops SMA in its tracks by preserving motor neuron cells, improving motor function and allowing her to reach childhood milestones like sitting without support.

Charleigh is one of many children who have entered Le Bonheur's Muscular Dystrophy Association (MDA) Clinic for comprehensive care. Thanks to a multidisciplinary approach, children with neuromuscular conditions have access to a variety of specialists and support services.

A Grim Diagnosis

Prior to the screening, no one suspected Charleigh's SMA diagnosis. The state lab contacted Le Bonheur Neurologist Elena Caron, MD, and her team who alerted Charleigh's pediatrician with the screening results and scheduled an appointment for her at the MDA Clinic two days later.

Charleigh Jones was the first Le Bonheur patient to receive the newly-approved drug Zolgensma for spinal muscular atrophy.

SMA type 1 is a genetic disease caused by a missing or nonworking SMN 1 gene responsible for making SMN protein. If left untreated SMA type 1 leads to death or the need for permanent ventilation by the age of 2 in more than 90% of cases.[1]

Zolgensma protocol calls for a one-time, one-hour intravenous infusion followed by a 24-hour inpatient observation period. Candidates must meet multifaceted criteria to be eligible for the drug. Zolgensma delivers a new copy of the deleted SMN gene through a viral vector, AAV serotype 9, providing a functional copy of the SMN gene to instruct cells to produce the protein needed to keep anterior horn cells of the spinal cord alive.

Neurologist Elena Caron, MD, examines Charleigh Jones during her appointment at the Muscular Dystrophy (MDA) Clinic.

Nine days after her diagnosis, Charleigh was at Le Bonheur Children's for her infusion.

"I'm thrilled we were able to accomplish this so quickly," said Caron. "It felt like a race against the clock – every day mattered. We had to act as quickly as possible to help achieve the best outcome for Charleigh."

While the infusion will not cure Charleigh of the disease, it will halt her symptoms so that she is able to continue to achieve childhood milestones and preserve her muscle function. Clinical data from the trial of Zolgensma showed unprecedented rates of survival, rapid motor function improvement and milestone achievement.

A Multi-Disciplinary Approach

All children who receive the Zolgensma infusion, including Charleigh, are followed in Le Bonheur's MDA Clinic where children with neuromuscular diseases, like

Treating Neuromuscular Disease

Le Bonheur's Muscular Dystrophy Association Clinic offers a variety of treatments for neuromuscular diseases striving to offer the most current medications and identify drug trials from which patients can benefit.

Current Treatments:

- **Exondys 51:** for Duchenne muscular dystrophy with mutation in the DMD gene that is amenable to exon 51 skipping
- **Vyondys 53:** for Duchenne muscular dystrophy with confirmed mutation of the dystrophin gene that is amenable to exon 53 skipping
- **Spinraza:** for treatment of spinal muscular atrophy types 1, 2 and 3 allowing the body to produce more SMN protein
- **Zolgensma:** for treatment of spinal muscular atrophy in patients younger than two years old delivering new, working copy of SMN gene

Future Treatments:

- Medications to reduce inflammation caused by muscle breakdown in patients with Duchenne muscular dystrophy
- Partner with and provide data to MDA Neuromuscular Disease Registry which collects data on children with neuromuscular disease and follows the impact of care on patient outcomes
- Treatments and trials are constantly in development for all neuromuscular diseases. The MDA Clinic follows these closely to match patients with treatments from which they might benefit.

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Beard joins Le Bonheur as psychologist

Gwen Beard, PsyD

Gwen Beard, PsyD, joined the Neuroscience Institute at Le Bonheur as a psychologist. She completed her residency at the University of Tennessee Professional Psychology Internship Consortium and her fellowship at the University of Tennessee Health Science Center, Center of Excellence for Children in State Custody.

Beard offers short-term therapy for neurology patients with a variety of psychological concerns, including Tourette's, tics, anxiety, depression, adjustment difficulties, behavior problems and psychogenic non-epileptic events. Her primary treatment modalities are behavioral therapy and cognitive behavioral therapy (CBT).

14th Annual Pediatric Neurology Symposium Rescheduled for July 2020

Due to the COVID-19 pandemic, the Pediatric Neurology Symposium has been moved to July 24-25, 2020. If you are already registered for the conference, your registration is valid for the new dates. If you would like to cancel your registration and be refunded, contact cme@mlh.org.

The Symposium will still be held at The Westin Memphis Beale Street. To register, **www.methodistmd.org/cme** or call **(901) 516-8933** for the program.

— New Date —

14th Annual

Pediatric Neurology Symposium

July 24-25, 2020

Guest Speakers:

Gregory L. Holmes, MD
Professor and Chair, Department of Neurological Sciences
University of Vermont Larner College of Medicine
Recipient of this year's Kayden R. Vinson Distinguished Scholar Award and Lecture, Holmes' talks will include "Epileptic Encephalopathy: The Perfect Storm" and "Epilepsy and Co-Morbidities (or Seizures are the Least of My Child's Problems)."

Jeffrey Waugh, MD, PhD
Assistant Professor of Pediatric Neurology
University of Texas Southwestern Medical Center
Dallas, Texas
Director of the Pediatric Movement Disorders Program
Co-director of the Pediatric Functional Neurological Disorders Clinic
Waugh's talks will include "Dystonia: From Phonotype to Genotype" and "Recognizing Abnormal Movements in Children."

One in Ten Thousand, continued from page 2

SMA, receive supportive care. While a plethora of treatment options are available to children, no cures exist for these neuromuscular diseases. While drug treatments do provide a drastically improved prognosis, good preventative care is required to sustain these benefits.

"The goal of our MDA Clinic is to care for medically complex kids, giving them the resources and support they need to live their life to the fullest," said Caron. "We are committed to a preventative and mindful approach to provide meticulous care for our patients to get the maximum benefit from drug treatments."

The clinic provides all specialties needed for neuromuscular disease patients in one place and during one appointment. This includes specialties of neurology, pulmonology, cardiology and orthopedics as well as additional resources such as physical and occupational therapy, nutrition, social work, palliative care and orthotics and equipment.

The structure of the clinic also allows providers to collaborate with one another, hearing concerns from other specialties and enacting preventative measures for these medically complex children.

"Studies show that children do better with multidisciplinary care," said Caron. "This approach allows us to provide the best outcomes for children and prevent complications that can arise from their neuromuscular disease."

In addition to the clinical aspects, Caron and her MDA team are actively involved in going beyond the walls of the clinic to support the places where their patients live. This includes educating the school system on what accommodations children with neuromuscular disease need in order to participate on the same level as their peers.

Strides in Neuromuscular Treatment

While current treatments are not cures for neuromuscular diseases such as Charleigh's SMA type 1, certain FDA-approved treatments can mitigate the morbidity associated with a wide variety of conditions. In addition, studies are ongoing across the country that address neuromuscular disease causes at a genetic level.

"Our goal is to be preventative and mindful in the treatment of our neuromuscular patients," said Caron. "We constantly push our patients' care to get their treatment to the place where they can participate in their age-appropriate activities and do all that is possible for them to do."

Future care for neuromuscular disease takes many forms. MDA clinic patients are eligible for enrollment in the MDA Neuromuscular Registry as well as other large patient registries for specific neuromuscular diseases that study long-term outcomes. These registries allow Caron and her team to have a database of patients and their gene defects so that the team can reach out immediately when new treatments are approved or trials become available for which they are eligible.

The Future of SMA Treatment

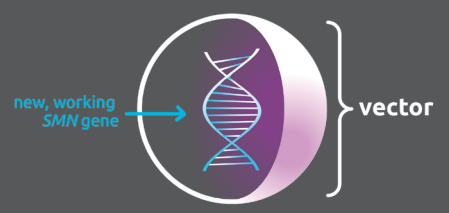
SMA is one of the neuromuscular diseases to benefit from recent drug advances such as the Zolgensma infusion. The state of Tennessee added SMA testing to newborn screenings in February 2020. Le Bonheur is a designated treatment site in West Tennessee for children diagnosed with SMA by their newborn screening.

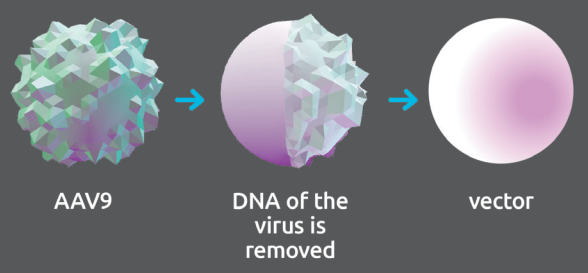
"We anticipate more patients being identified and referred to us through newborn screening," said Caron. "We will continue to follow infants with SMA and other neuromuscular diseases and provide excellent multidisciplinary care to provide the best outcomes."

[1]Finkel RS, McDermott MP, Kaufmann P. et al. Observational study of spinal muscular atrophy type 1 and implications for clinical trials. Neurology. 2014;83(9); 810-7.

How Zolgensma Works

- *Zolgensma is made of a functional copy of a human SMN gene placed inside a viral vector. The virus used is adeno-associated virus 9, or AAV9, which can travel throughout the body and across the blood-brain barrier to deliver the working gene to the cells where it is needed.*





- *DNA of the virus is removed, and the new SMN gene is put inside.*

- *The vector takes the new, working SMN gene to the motor neuron cells in the body.*

- *When the new gene reaches the motor neuron cells, it tells them to start making SMN protein. This takes place throughout the body.*

- *Motor neuron cells are now able to make SMN protein. Motor neuron cells that have not died may survive, function and be maintained.*

Source: https://www.zolgensma.com/how-zolgensma-works

Le Bonheur Children's Hospital

Brain Waves is a quarterly publication of the Neuroscience Institute at Le Bonheur Children's Hospital. The institute is a nationally recognized center for evaluation and treatment of nervous system disorders in children and adolescents, ranging from birth defects and learning and behavioral disorders to brain tumors, epilepsy and traumatic injuries.

Scan to learn more about our Neuroscience Institute.

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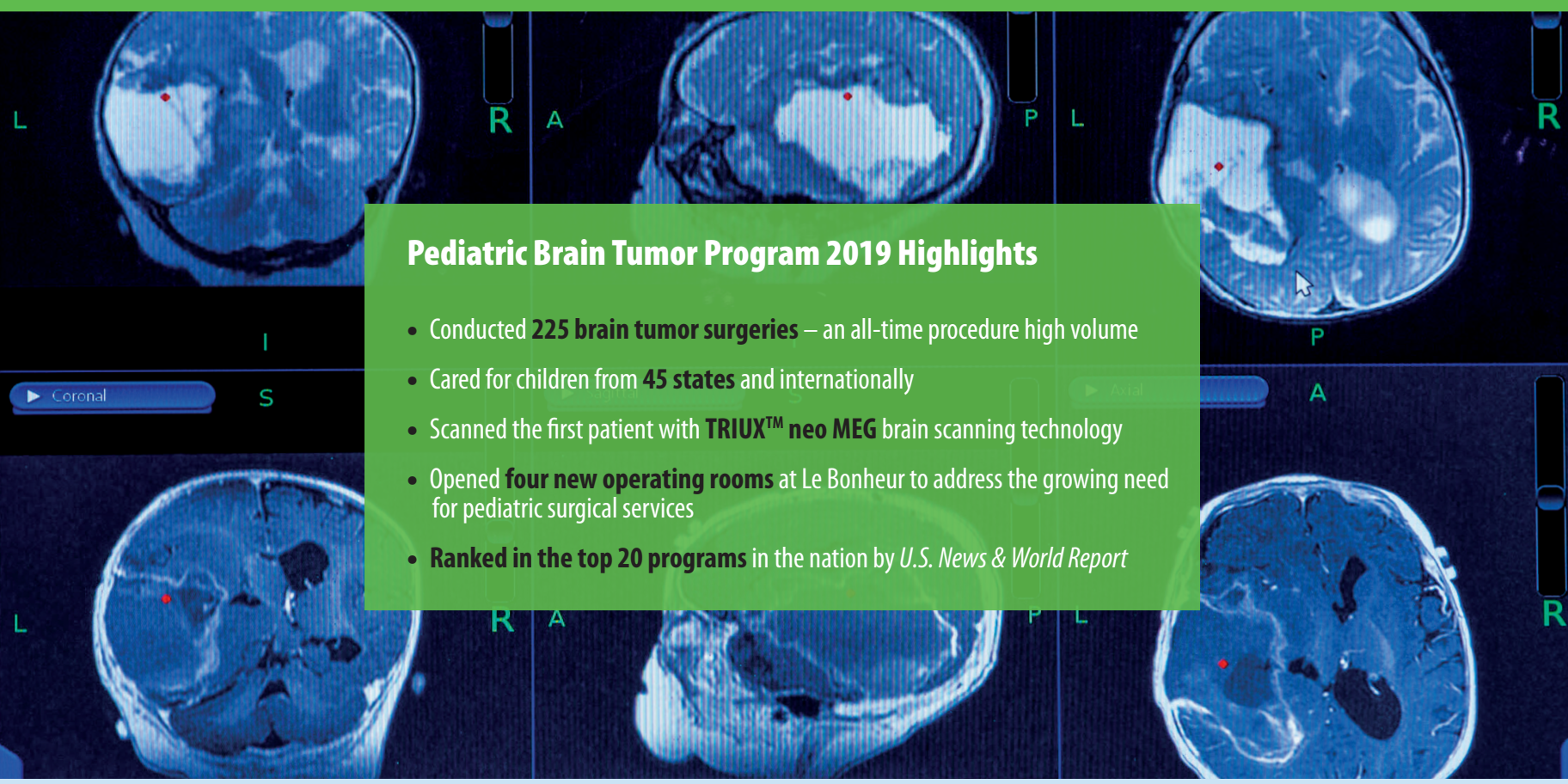

Pediatric Brain Tumor Program 2019 Highlights

- Conducted **225 brain tumor surgeries** – an all-time procedure high volume
- Cared for children from **45 states** and internationally
- Scanned the first patient with **TRIUX™ neo MEG** brain scanning technology
- Opened **four new operating rooms** at Le Bonheur to address the growing need for pediatric surgical services
- **Ranked in the top 20 programs** in the nation by *U.S. News & World Report*

Le Bonheur continues to grow Pediatric Brain Tumor Program

Le Bonheur's Pediatric Brain Tumor Program remains one of the largest surgical brain tumor programs in the nation, continuing to partner with St. Jude Children's Research Hospital to provide the best care for children with brain tumors.

"We are aggressive in treating brain tumors in the children that we see," said Neurosurgeon Frederick Boop, MD, co-director of the Neuroscience Institute. "Our patients have some of the highest one-year survival rates, and we are dedicated to determining the best treatment plan and the best outcomes for each child."

The partnership with St. Jude allows for a complete treatment plan for children with brain tumors. While most are treated with surgery, radiation and chemotherapy can also be part of the treatment plan. Through the partnership with St. Jude, children with brain tumors have access to promising new treatments not yet available at other hospitals.

Neurosurgeon Frederick Boop, MD, co-director of the Neuroscience Institute