

# The Fetal Center

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# Twin Anemia Polycythemia Sequence: Solving the Diagnostic and Treatment Dilemma

Monochorionic twins (identical twins sharing one placenta) are susceptible to complications during pregnancy that include twin-twin transfusion syndrome (TTTS) and, more rarely, twin anemia polycythemia sequence (TAPS), a slow-developing, chronic form of TTTS.

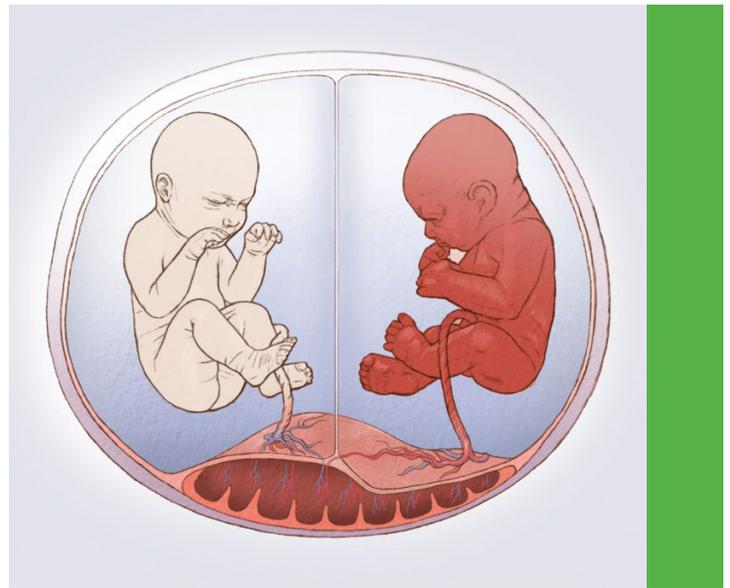
Monochorionic twins usually share blood vessel connections. In about 15 percent of these pregnancies, twin-twin transfusion occurs when the blood vessels produce an uneven sharing of blood, with blood from one twin—the donor twin—is pumped to the other twin—the recipient twin.

“TAPS occurs when this unbalanced fetofetal transfusion results in slowly developing anemia in the donor twin and polycythemia in the recipient twin,” says Ramesha Papanna, MD, MPH, a maternal-fetal medicine specialist affiliated with The Fetal Center at Children’s Memorial Hermann Hospital and an associate professor in the division of Maternal-Fetal Medicine at McGovern Medical School at UTHealth. “The sequence occurs spontaneously in 3 to 5 percent of monochorionic twins, or can develop in 2 to 16 percent of twin-twin transfusion cases treated with laser surgery.”

With TAPS, blood moves between the twins at a slower rate than in TTTS, resulting in unequal blood counts in the two babies. The donor twin has fewer red blood cells, and does not receive the oxygen needed for development of its organs. The donor twin’s heart works harder to support vital organs, such as the brain and heart. The

recipient polycythemic twin’s heart works harder as well, pumping thicker blood. TAPS is associated with high morbidity and mortality.

“Because the connections between the two TAPS babies in the placenta are few and small, the blood from one twin moves into the other gradually, creating a chronic transfusion from one twin to the other,” Dr. Papanna says. “The baby losing blood becomes pale and anemic,



and the one gaining blood becomes polycythemic, with an increase in red blood cell mass that causes turgescence and a reddish complexion.”

## Detecting TAPS

Twin anemia polycythemia sequence is difficult to detect, as there is no direct and accurate way to measure anemia or polycythemia in the fetuses. Often TAPS is suspected only when one of the twins has very fast-moving blood in the middle cerebral artery (MCA) on ultrasound readings and the classic



Anthony Johnson, DO, co-director of The Fetal Center, performs an ultrasound scan for a patient of The Fetal Center.

signs of TTTS are missing, such as polyhydramnios and oligohydramnios. There are no patient symptoms in TAPS, unlike TTTS, in which patients may experience a sensation of rapid growth of the uterus, a uterus that is large for the stage of pregnancy or a sudden increase in the mother's bodyweight as well as abdominal pain, tightness or contractions.

"Because of the rarity of the condition, reliable information about the natural history of TAPS remains scarce, and is mostly based on small cohort studies," says Dr. Papanna, who is internationally recognized for his research on improving outcomes following fetal intervention and investigating methods for the prevention of preterm delivery. "Studies have shown that TAPS can develop within a wide range of time in a monochorionic pregnancy, from 15 to 35 weeks of gestation. Currently, there is no consensus on when to start routine fetal MCA Doppler assessments to check for the presence of TAPS, but based on mounting evidence of the serious consequences associated with the disorder, we believe that MCA Doppler should be included in the standard biweekly workup for twins, starting early in the second trimester."

MCA Doppler is an indirect way to diagnose TAPS by measuring peak systolic velocity in the middle cerebral artery. While researchers have proposed certain thresholds in velocities to diagnose TAPS, these have not been verified systematically. "We may suspect TAPS, but the only way to diagnose it with 100 percent certainty is with sample blood from both fetuses before or after birth," Dr. Papanna says.

### Fetoscopic Laser Surgery for TAPS at The Fetal Center

At The Fetal Center at Children's Memorial Hermann Hospital, the typical care process for babies sharing a placenta includes a MCA Doppler assessment at 16 weeks, followed by a Doppler every two weeks until delivery. In pregnancies earlier than 38 weeks, the Center offers fetoscopy and laser ablation of the blood vessel connections for TAPS, the same procedure offered for TTTS.

"From 28 to 32 weeks, we can perform an intrauterine transfusion for the fetus with anemia, who is at greater risk of brain damage or death from anemia," Dr. Papanna says. "Most tertiary centers offering transfusion do it every two weeks, but this is not a well-established guideline. After 32 weeks, we deliver. However, the optimal prenatal treatment for TAPS has yet to be determined."

Options offered to parents include expectant management, preterm delivery, intrauterine transfusion with or without a partial exchange transfusion, fetoscopic laser surgery and selective reduction. Due to the low incidence of TAPS, studies investigating perinatal outcome are scarce and the research results available combine outcomes of spontaneous and post-laser TAPS twins. "To improve our knowledge of TAPS, we are collaborating with an international group of researchers that set up the TAPS Registry, a large collaboration aimed at collecting data on diagnosis, treatment and outcome in TAPS twins," Dr. Papanna says. "We've learned quite a lot in the last four or five years, and studies are underway to learn more about the natural history of the disease, and when and how to treat it. Without knowledge of optimal management, it's difficult to advise parents in ways in which they can make informed decisions."

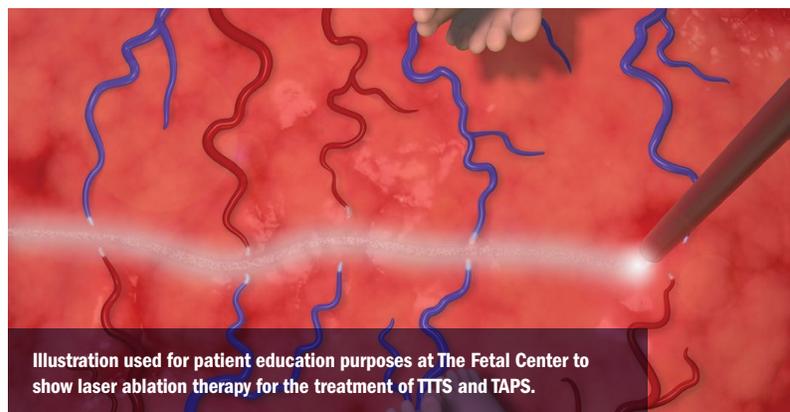


Illustration used for patient education purposes at The Fetal Center to show laser ablation therapy for the treatment of TTTS and TAPS.

### The TAPS Registry and Ongoing Research

The TAPS Registry was established in 2013 as a web-based registry for anonymous data collection; international fetal therapy centers were invited to participate. Between 2014 and 2019, 17 specialized fetal therapy centers, including The Fetal Center at Children’s Memorial Hermann Hospital, contributed data to the registry via [tapsregistry.org](http://tapsregistry.org).

Leiden University Medical Center in the Netherlands is leading the international collaboration that produced the largest long-term management and outcome study available of solely spontaneous TAPS twins. “By pooling data from our patient populations, we are gaining more understanding of the big picture about outcomes,” Dr. Papanna says.

The research group conducted multiple analyses using the database to uncover knowledge gaps in diagnosis and treatment. They found that TAPS can develop at 15 weeks—and possibly earlier—and up to 35 weeks of gestation. Management of the disorder in all 17 centers submitting data was found to vary considerably, with fetoscopic laser surgery being the most frequent intervention.

“In this study of 249 cases of spontaneous TAPS, the perinatal outcome was poor, with a high rate of mortality in donor twins,” he says. “These findings remind us of the need for increased awareness on the part of clinicians about the severity of TAPS. We need guidelines to ensure early diagnosis, and we also need more clinical studies to determine the optimal management strategy.”

The researchers presented their findings at the 38th Annual Meeting of the International Fetal Medicine and Surgery Society, held in Sils, Switzerland, in October 2019. “Our collaborative study is the first to show significant differences between donor and recipient perinatal mortality,” he says. “We found that donor twins had a higher risk of spontaneous fetal demise, which suggests that fetal anemia is a more direct threat to intrauterine survival than fetal polycythemia. In addition, donors were more frequently chosen for selective reduction than recipients, perhaps because progressive worsening of fetal anemia is easier to monitor than fetal polycythemia. Almost half the donor twins in our study were severely growth restricted, in contrast to 12 percent of recipient twins, which confirms findings from previous studies.”

Dr. Papanna also notes that anecdotal information and what is reported in studies is only the tip of the iceberg. “There is an urgent need for more systematic studies to improve the diagnosis of TAPS and increase our knowledge of treatment options. Until these studies are conducted and produce answers to the questions, there will be twin pregnancies lost due to missed diagnosis or incorrect diagnosis,” he says. “What we’re trying to do now is understand and define the knowledge gap systematically, work on the questions we can answer and eventually go to clinical trials at a future date.”

Leiden University Medical Center currently is leading The TAPS Trial: Fetoscopic Laser Surgery for Twin Anemia Polycythemia Sequence, A



L-R: Loverpreet Mann, MBBS; Ramesha Papanna, MD; and Jong Hak Won, PhD, collaborate on research in The Fetal Center research lab.

Multicenter Open-label Randomized Controlled Trial for twins diagnosed with TAPS between 20 and 28 weeks. Participants will be randomized to fetoscopic laser surgery versus each participating center’s standard of care, consisting of expectant management, intrauterine transfusion, preterm delivery or selective feticide. The researchers hypothesize that fetoscopic laser therapy will improve neonatal outcome by prolonging pregnancy.

“We need this large randomized, controlled trial evaluating the possible beneficial effect of fetoscopic laser surgery to determine the optimal treatment option for TAPS,” he says. “We hope to learn that fetoscopic laser surgery improves outcomes for TAPS twins. In the meantime, our research is focused on learning more about the natural history of the disease and improving surveillance to detect TAPS as early as possible. We still have many questions without answers.”

# To Grief and Back: Joy, Heartbreak and Gratitude in the Dugger Family

Christine and Blake Dugger learned they were pregnant with twins in December, 2017. “The entire pregnancy was a surprise,” Christine Dugger says. “We have two older daughters, who were six and three at the time, and we were very much not planning on having more children, but when we found out, we were excited.”

Christine Dugger’s first maternal-fetal medicine appointment in Sacramento, California, went well. “The second appointment, at about 13 weeks of pregnancy, was a complete shift,” she says. “We had the ultrasound done before the physician came in, and the tech was quiet. When the doctor came in, she did a rescan. She said she wasn’t visualizing Baby B’s bladder or kidneys, but then she said maybe it’s too early. That didn’t feel right to me based on my experience with prior pregnancies, and also because she could

visualize those organs on our other twin. We knew the diagnosis of renal agenesis was likely to be fatal, but it was early in the pregnancy and we still held out hope that his kidneys were too small to be visualized on ultrasound. We hoped that this was something that could be treated either in utero or after his birth.”

Babies without kidneys do not produce amniotic fluid, which has a serious impact on lung development. Lack of amniotic fluid is a symptom of twin-twin transfusion syndrome (TTTS). Identical twins that share a common placenta usually have blood vessel connections between the two fetuses. In about 15 percent of these pregnancies, twin-twin transfusion occurs when the blood vessels produce an uneven sharing of blood, with blood from one twin (the donor twin) pumped to the other (recipient) twin. When this occurs, the heart of the donor twin does extra work to support the recipient twin, who gets too much blood. The donor twin doesn’t get enough.

With treatment, TTTS can resolve and amniotic fluid levels can regulate. “In our case we had two possible causes for Rand’s (Baby B’s) lack of amniotic fluid: renal agenesis or TTTS,” Dugger says. “The first was automatically fatal; the other potentially fatal for both twins, but treatable with the right intervention. We asked for an immediate referral to a tertiary care center.”

## Referral to San Francisco

At Christine Dugger’s request, her maternal-fetal medicine specialist in Sacramento referred her to the University of California, San Francisco Medical Center, an hour-and-a-half drive away. After the first appointment, doctors there confirmed that Rand suffered from renal agenesis and not TTTS. “It was devastating,” she says. “I remember driving home across the San Francisco Bay, looking out at the water and thinking I’d never felt more alone.”

After the first appointment, Christine was seen

Christine and Blake Dugger with their son and two daughters.



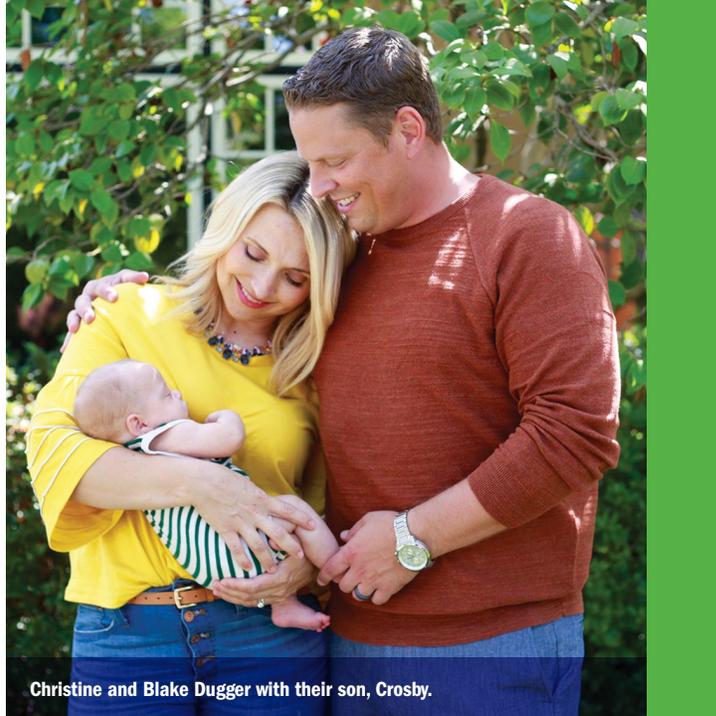
twice a week to monitor other issues with her twins. While Crosby (Baby A) appeared to be developing normally, Dugger's physician team said that there was a high probability that Rand would die in utero, given his diagnosis and other issues that were appearing. When one twin dies in utero, the shared blood immediately goes to the other twin, creating a stroke-like effect that can lead to neurodevelopmental problems for the surviving twin—or death.

"We were in this state of constant monitoring and never knew what was going to happen from one day to the next," she recalls. "One of my coping mechanisms for processing what we were going through was research. I needed to educate myself, but more than anything, I was willing to fly anywhere in the world if someone could help Rand."

Dugger went into full research mode. She emailed and called researchers in Japan, South Korea and Belgium as well as the top maternal-fetal medicine centers in the United States. "I found their names through ResearchGate, and asked them to share their research with me because I couldn't get access without medical credentials," she says. "I was collecting a body of research so I could understand the big picture, as well as be informed about all treatments available—not just the ones offered to me. The primary issue I researched was exploratory treatments for Rand's lack of amniotic fluid. I thought if we could find a way to mimic the amniotic fluid a baby normally produces, it would be possible for his lungs to develop. If we could do that, Rand might be a candidate for peritoneal dialysis at birth until he could receive a kidney transplant. It was a pie-in-the-sky hope that wasn't to be."

At the same time, Dugger was coming across research describing a different type of transfusion syndrome affecting identical twins. Twin anemia polycythemia sequence (TAPS) is a rare form of twin-twin transfusion syndrome caused by chronic blood loss between the fetuses through tiny vessels in the placenta. She compared the research she was collecting with Rand and Crosby's twice-weekly ultrasound reports.

"I came across it almost by accident," she recalls. "As I read the TAPS papers, I kept coming back to the term 'middle cerebral artery Doppler (MCA),' and in the back of my mind recalled there being a discrepancy between Rand and Crosby's



Christine and Blake Dugger with their son, Crosby.

MCA readings on their ultrasounds. I'm a data-driven person, and I put a lot of weight in science, so I started plotting the twins' MCA results in an Excel spreadsheet to see if I could recognize any patterns."

As she plotted data over eight weeks, she saw that Rand and Crosby's MCA Doppler readings continued to trend apart. MCA blood flow can be measured during an ultrasound, and anemia is suspected if the blood flow in one of the MCA fetal vessels of the brain is increased by a certain level.

Based on the MCA Doppler readings, Rand was severely anemic. As he became more anemic, new issues showed up in the ultrasound reports. "One week he had fluid around his heart. The next week he was suspected of selective intrauterine growth restriction. Another week the doctors were concerned that he had an enlarged vessel in his brain," she says. "All the while, the MCA readings continued to be alarmingly discordant, and gradually it became clear to me that our twins had TAPS."

"It was like we had been struck by lightning twice. By then we knew that Rand would not live after birth. In addition to Rand's fatal anomaly, Crosby was now faced with a life-threatening situation," she says. "My otherwise healthy baby was severely polycythemic, with too much blood, and his life was now at risk without immediate intervention."

The interventions for TAPS are the same as for TTTS—fetoscopic laser ablation, an intrauterine surgery that stops the blood flow between

the problematic blood vessels in the placenta, or selective termination of one twin. “My doctors told me they did not perform laser ablation for TAPS, but could offer selective termination. To us, selective reduction was the imposition of guaranteed risk—death for Rand and risk of death for Crosby. We were not willing to impose guaranteed risk on either baby, so I asked them to refer me elsewhere.”

### The Search for a Physician Who Could Intervene

Dugger knew she wanted fetoscopic laser ablation of the communicating vessels between Crosby and Rand, a minimally invasive procedure that would stop the abnormal fluid exchange by cauterizing blood vessel connections. “Successful laser ablation would be curative for the TAPS that was threatening both of their lives and ensure that each baby had his own blood supply. Should Rand pass away before birth from his other complications, his death would no longer pose the same threat to Crosby,” she says.

An internet search led Dugger to physician-scientist Ramesha Papanna, MD, MPH, an associate professor in the division of Maternal-Fetal Medicine at McGovern Medical School at UTHealth. Dr. Papanna, who is affiliated with The Fetal Center at Children’s Memorial Hermann Hospital, is internationally recognized for his research on improving outcomes following fetal intervention and investigating methods for the prevention of preterm delivery. He is actively involved in fetal intervention for twin-twin transfusion syndrome, fetal spina bifida and other fetoscopic and needle-guided in utero procedures.

“I was on the phone with one of the nurses at The Fetal Center right away, and they called me the next day and asked us to come to Houston. I talked with Dr. Papanna after he had reviewed my medical records. He said, ‘Yes, this is serious and there is an intervention. How soon can you get here?’”



Ramesha Papanna, MD

### Fetoscopic Laser Ablation for TAPS in Houston

On Friday morning, Dugger called her mother and asked her to fly to Houston, while her husband remained at home with their daughters. “Although Blake wanted to be with me, we decided that our kids needed normalcy. I told the girls I was going on a work trip, packed some yoga pants and a sweatshirt, and left for the airport,” she says.

On the way to the airport, she called her OB/GYN to ask for an urgent referral to Dr. Papanna and Children’s Memorial Hermann Hospital. “When I got insurance approval, I understood how privileged and lucky I am, and that other mothers’ inability to make the choices I was making is rooted in inequality. It saddened me that women have to make life or death decisions based on financial concerns,” she says.

In Houston, they met Dr. Papanna and one of his ultrasound techs. “At that point, TAPS had progressed since my last ultrasound in California a day or two before. In TAPS Stage 2, one twin is clearly polycythemic and the other is anemic,” Dugger says. “By Stage 4, the anemic twin is hydropic, with extreme swelling of organs caused by the buildup of fluids in tissues. That’s what we had the day we got to Texas.”

“TAPS is a rare and misunderstood condition that puts the lives of both twins at risk,” Dr. Papanna says. “We had to act quickly to save Crosby’s life.”

He gave her two options: selective termination or laser ablation. The following morning he performed a minimally invasive fetoscopic laser ablation to close the blood vessels connecting Crosby and Rand, safeguarding Crosby until delivery.

“Dr. Papanna treated me with such respect, and he was genuinely approachable, yet I was in awe of him,” Dugger says. “Here is this world-class physician who is changing the lives of so many families, and he’s with me in a hospital room at 9 p.m. on a Friday night. The next day we’re in surgery receiving the intervention I had sought so desperately.”

During the procedure Dr. Papanna took photos that provide a stunning visual representation of TAPS. “Rand, the anemic twin, was almost iridescent. You could see beneath his skin. He was transfusing all his blood to his brother. Crosby was deep maroon because of the thickness and volume of blood. Dr. Papanna said we were within days of losing Rand and possibly both babies,” she says.



Children's Memorial Hermann Hospital

After surgery, an ultrasound showed that both babies were living, and that Rand was no longer anemic and Crosby was not polycythemic. “In a perfect world, I wanted to spend the rest of my pregnancy in Houston, where I felt like I would receive the best care, but intellectually, I understood that now, post intervention, it was a waiting game.”

Dugger flew back to California Sunday night. “I was only 22 weeks pregnant at this point, yet with everything our twins had gone through, it felt like a lifetime,” she says.

### **Giving Back and Paying It Forward**

Dugger transferred her care back to Sacramento and went into labor at 31 weeks. She was hospitalized for eight days after her water broke. When her maternal-fetal medicine team was unable to delay labor any longer, she delivered Rand and Crosby by C-section.

“Crosby was born first and Rand a minute later,” she says. “We had been operating under the notion that Crosby was the healthy baby and Rand, the sick baby, but to our surprise and horror, Crosby was born pale and mottled and didn’t cry. They had to resuscitate him and immediately transfer him to the NICU. We knew Rand would not live long after birth due to his renal agenesis and the resulting lack of lung development. After hours of consultation with various care providers, we had decided in advance to offer comfort care to Rand. The nurses gave him to me right away while they finished surgery. Rand lay on my chest the entire time, except for when my husband held him. I’ve never said as many ‘I love you’s as I did in those 58 minutes.”

As he lay on his mother’s chest, the hospital chaplain baptized him before he passed away. “I wanted to be certain that Rand never experienced pain. Palliative care for terminal infants ensured that,” Dugger says. “After his death, Rand stayed with us for the next 48 hours, and I held him the entire time. Those hours, the only ones I have with Rand, are permanently burned into my memory. Our girls came to the hospital the morning after his birth to meet their

brothers. We all went to the NICU where Crosby was, and that is our only photo of all six of us.”

After Dugger was discharged and the family said goodbye to Rand, she spent the next six weeks in the NICU with Crosby. Those six weeks gave her perspective and clarity on what to do next.

“After experiencing the NICU myself and seeing what other parents were going through, we wanted to do something for Rand and at the same time ensure that the moms who come after me have access to research and interventions,” she says. “Waiting for an intervention can be, and very often is, deadly. We also wanted to make sure the research Dr. Papanna is doing is continued. We were stunned not only by his resume but also by his human kindness. He treats people like people, not subjects or opportunities. My husband and I will do anything to keep TAPS at the forefront of medical research, and supporting Dr. Papanna is one way we can ensure that.”

A few days after the twins were born, the Duggers created the Rand Francis Dugger TAPS Research Memorial Fund at McGovern Medical School to raise funds to further Dr. Papanna’s work. In 2019, they founded the Rand Francis Dugger Foundation with the goal of raising money for Dr. Papanna’s research and funds to support families going through complicated twin pregnancies.

“We’re not limiting support to TAPS, but plan to offer it to anyone experiencing a complicated twin pregnancy who needs a higher level of care and for whatever reason can’t access it,” she says. “The foundation is an important part of our recovery process. I don’t want to say heal because I don’t think you ever heal from the loss of a child. Rand is a part of our world and is with us every day.”

The Duggers incorporate Rand into their lives every day through photos, bedtime prayers and conversation. “My five-year-old daughter will say this: ‘I have three brothers and sisters but only two are here. Rand is with us too, but in heaven.’ We don’t hide our grief. This experience has given us an opportunity to explore our feelings and discover that you can feel happy and sad at the same time. We take advantage of every opportunity to honor Rand. I’m so proud of how our kids have taken on such big adult issues and are figuring out really beautiful ways to process and live with them. It’s important to us that our kids and the world know that Rand was real and Rand was magic.”

## The Fetal Center and NICU Patient and Family Reunion

In April 2019, Children's Memorial Hermann Hospital hosted a combined reunion event for patients and families of The Fetal Center and Neonatal Intensive Care Unit (NICU). Families, friends, physicians and staff members gathered at the Toyota Center in Houston to enjoy a morning full of fun activities together. The event included over 300 guests, who were reunited with members of The Fetal Center care team. Now held on an annual basis, the next reunion event will take place in Spring 2020.



The Fetal Center and NICU Patient & Family Reunion 2019

## Two Pediatric and Congenital Heart Surgeons Join Children's Heart Center

Two subspecialists have joined the medical staff at Children's Memorial Hermann Hospital and the faculty of McGovern Medical School at UTHealth. They are pediatric and congenital heart surgeons Peter C. Chen, MD, and Christopher E. Greenleaf, MD, MBA.

Dr. Peter Chen received his bachelor's degree in biology in the Honors Program at the University of North Carolina at Chapel Hill and his medical degree at Wake Forest University School of Medicine in Winston-Salem, North Carolina. He completed general surgery residency training at the University of Rochester in Rochester, New York. During residency, he completed a two-year research fellowship at Boston Children's Hospital/Harvard Medical School, focused on the development of tissue-engineered heart valves and clinical outcomes after congenital heart surgery. He went on to complete a cardiothoracic surgery fellowship at the Texas Heart Institute/Baylor College of Medicine in Houston and a congenital cardiac surgery fellowship at the Children's Hospital of Philadelphia. Dr. Chen has served in national leadership roles: as president of the Thoracic Surgery Residents Association and as a member of the Society of Thoracic Surgeons Health Policy and Relationships Council Operating Board. He is board certified in thoracic surgery by the American Board of Thoracic Surgery.

Dr. Chen's clinical interests include complex neonatal heart disease, single ventricle palliation, pediatric and adult congenital heart disease, pediatric heart failure and minimally invasive approaches to congenital heart surgery. His research interests include tissue-engineered heart valves, regenerative medicine, cerebral and myocardial protection, surgical outcomes after congenital heart surgery and the development of innovative surgical techniques. He is actively involved in medical student and resident mentorship and the continued improvement of surgical education. Dr. Chen is an assistant professor in the division of Pediatric and Congenital Heart Surgery at McGovern Medical School at UTHealth.

Dr. Chris Greenleaf is certified by the American Board of Surgery in general surgery and by the American Board of Thoracic Surgery in thoracic surgery. A Pennsylvania native, Dr. Greenleaf grew



Peter Chen, MD, Pediatric and Congenital Heart Surgeon at Children's Memorial Hermann Hospital

up in the Philadelphia area and received his undergraduate degree from the University of Pennsylvania. A former rower, Dr. Greenleaf represented the United States on the men's national team in 2004.

He received his medical degree and Master of Business Administration at Jefferson Medical College and Widener

University in Philadelphia, respectively, and completed his general surgery residency at Lankenau Medical Center in Wynnewood, Penn. During his surgical training, he received a resident teaching award and was chief surgical resident. He completed fellowship training in cardiothoracic surgery at the University of Mississippi Medical Center, and finished his fellowship and clinical instructorship in congenital cardiac surgery at Texas Children's Hospital in Houston. During his time there he was awarded the 2018 John A. Hawkins Top Scoring Abstract Award by the Congenital Heart Surgeons' Society. He is an assistant professor of pediatric and congenital heart surgery at McGovern Medical School.



Chris Greenleaf, MD,  
Pediatric and Congenital  
Heart Surgeon at  
Children's Memorial  
Hermann Hospital

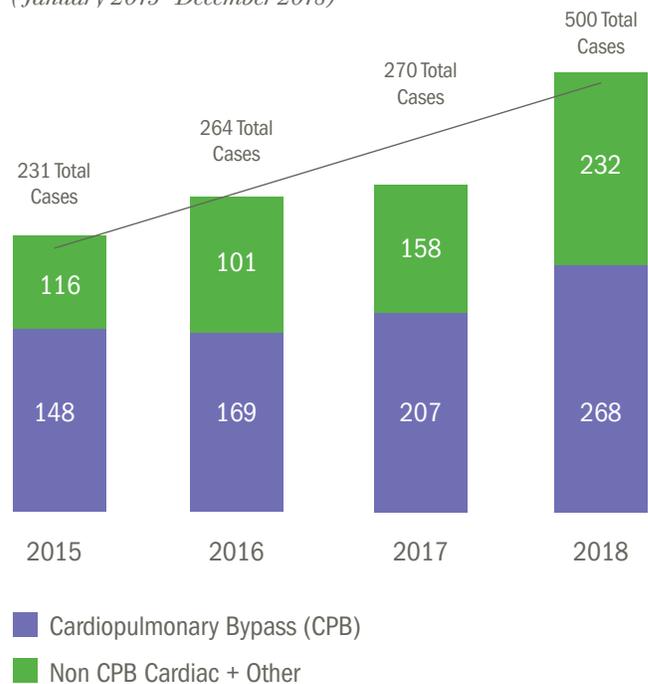
## Children's Heart Center – Nationally Top Ranked Surgical Outcomes

The Children's Heart Center<sup>1</sup> at Children's Memorial Hermann Hospital, in collaboration with pediatric sub-specialists at McGovern Medical School at UTHealth, is dedicated to pioneering innovative solutions that offer patients with even the most complex problems the greatest opportunity for a normal life. The affiliated team strives to be transparent and provide the community with up-to-date information on patient outcomes data. The data is intended to serve as a helpful resource when making informed decisions regarding patient care.

According to The Society of Thoracic Surgeons (STS), the Children's Heart Center ranks among the leaders in the United States and Canada for patient care and outcomes in congenital heart surgery. Overall, the Children's Heart Center's unadjusted mortality rate is 2.9 percent, which is over 40 percent better than the expected mortality rate the STS designated for the program, due to the high complexity of patient cases (4.8 percent expected mortality rate). An overview of the Children's Heart Center's surgical outcomes data is available on the Children's Memorial Hermann Hospital website.

### Children's Heart Center Surgical Volume

(January 2015 - December 2018)



\*Note: All cases reported, not just index cases.  
Source: Internal Data and STS Database, Table 1

To view the Children's Heart Center outcomes data, visit: [childrens.memorialhermann.org/chc/outcomes](http://childrens.memorialhermann.org/chc/outcomes)

<sup>1</sup> The Children's Heart Center at Children's Memorial Hermann Hospital is affiliated with the physicians at McGovern Medical School at UTHealth and the UT Physicians Pediatric Outpatient Clinics across Greater Houston. Affiliated physicians evaluate patients at UT Physicians clinic locations and perform all inpatient procedures and treatments at Children's Memorial Hermann Hospital.

## Open In-utero Repair of Severe Spina Bifida Using a Human Umbilical Cord Patch

Ramesha Papanna, MD, MPH, is the clinical lead principal investigator in a multicenter study of open in-utero repair for severe spina bifida using a patch made of cryopreserved human umbilical cord (HUC). The patch is widely used for ocular surface repair and chronic skin ulcers because its innate



Affiliated physicians at The Fetal Center, Kenneth Moise, Jr., MD; Anthony Johnson, DO; and Kuolen Tsao, MD, perform open fetal surgery for spina bifida repair on a patient of The Fetal Center.

regenerative properties facilitate faster healing with minimal scarring.

Dr. Papanna and his research team have used the HUC patch successfully with three patients through the FDA's Expanded Access program, a pathway for people with life-threatening conditions or serious diseases to gain access to investigational medical products for treatment outside of clinical trials, when no satisfactory alternative therapy options are available.

"Cryopreserved human umbilical cord has anti-scarring, anti-inflammatory and regenerative properties that makes it an effective substrate for wound healing," Dr. Papanna says. "These unique properties may eliminate the scar formation

associated with traditional spina bifida repair methods and reduce the need for future surgeries for tethered spinal cord, a complication of the disorder. Preclinical data have shown that the patch promotes organized cell growth, resulting in a spinal cord repair that appears more normal with better function."

Spina bifida is the most common neural tube defect in the United States, affecting about 1,500 to 2,000 of the more than 4 million babies born in the country each year, according to the National Institute of Neurological Disorders and Stroke. Associated disorders include hydrocephalus and learning disability. An estimated 166,000 individuals with spina bifida live in the U.S.

In addition to McGovern Medical School and The Fetal Center at Children's Memorial Hermann Hospital, other participating centers include the University of Colorado Denver; Children's Hospitals and Clinics of Minnesota; Fetal Care Center Dallas in Medical City Dallas Hospital; University of California, San Francisco; and Cincinnati Children's Hospital Medical Center.

The company that develops the patch will pay for all participant hospital expenses related to research, including the patch itself, travel expenses and a follow-up MRI at 12 months. Although the study concludes at 12 months, the primary outcome date required for the FDA to approve the patch for clinical indications, data will continue to be collected on participating patients for 30 months.

The study is the culmination of 10 years of research conducted by Dr. Papanna, an associate professor of maternal-fetal medicine at McGovern Medical School and Lovepreet K. Mann, MBBS, an assistant professor of maternal-fetal medicine, along with their team. The researchers found that using a graft of the human umbilical cord (HUC) after surgery for spina bifida could promote regeneration of the protective layers around the spinal cord and improve neurological function in animal models.

"HUC could be a game changer for spina bifida repair," Dr. Papanna says. "Our ultimate goal is to ensure that babies born with the disorder can walk and lead normal lives. We also think HUC will lead to new paradigms in fetal wound healing for other spinal defects and repairs."

# Fetoscopic Spina Bifida Repair for Small Defects Using a Human Umbilical Cord Patch

Researchers at McGovern Medical School at UTHealth affiliated with Children’s Memorial Hermann Hospital, are now enrolling patients in a study to determine the feasibility of fetoscopic surgery to repair spina bifida and facilitate vaginal delivery. The single-center study is led by Ramesha Papanna, MD, MPH, an associate professor of maternal-fetal medicine who is internationally recognized for his research on improving outcomes following fetal intervention and investigating methods for the prevention of preterm delivery.

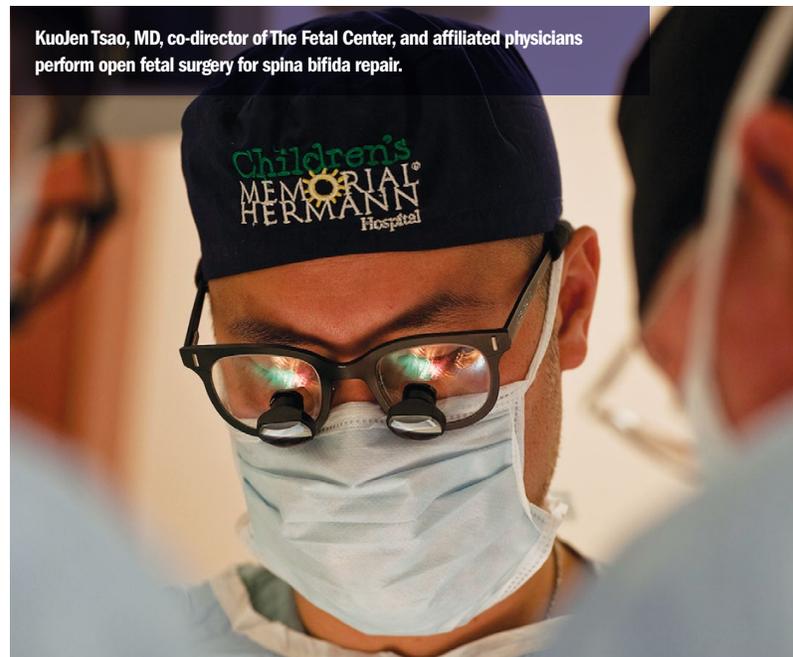
“Our primary outcome measure for the study is successful surgical closure of the spina bifida defect with a watertight patch that approximates native tissue and allows for the natural growth of the spinal cord,” Dr. Papanna says. “The procedure differs from in-utero repair, which requires a large incision on the uterus and delivery by cesarean section. Instead, we will repair the spina bifida defect in two layers through three small incisions in the uterus using fetoscopes and tiny surgical tools. The first layer will be closed using a NEOX®Cord 1K patch as a meningeal patch placed over the spinal cord, followed by a second layer of primary closure of the skin. Mothers will undergo vaginal delivery, unless there is an obstetrical indication for delivery by C-section.”

The NEOX Cord 1K patch is made of cryopreserved umbilical cord and amniotic membrane. Extensive laboratory and clinical research on an ocular wound surface has shown that placental tissues help manage inflammation in wounds, facilitate cell proliferation and create an environment for tissue regeneration. NEOX Cord 1K has demonstrated consistently high closure rates in real-world experiences.

The study, the first to use a meningeal patch to

cover the spina bifida defect, will enroll 15 patients, age 18 and older with a singleton pregnancy, a spina bifida defect of 4 centimeters or less and no preterm birth risk factors. Participants also must meet other study qualifications.

A digital image of the fetal repair site will be captured immediately after the repair, and efficacy of the fetoscopic repair will be assessed after birth by three blinded reviewers. Reviewing neurosurgeons are Arthur Day, MD, McGovern Medical School and UTHealth Neurosciences in Houston; Bradley Edward Weprin, MD, UT Southwestern Medical Center in Dallas; and John Honeycutt, MD, Cook Children’s Hospital in Dallas.



Kuolen Tsao, MD, co-director of The Fetal Center, and affiliated physicians perform open fetal surgery for spina bifida repair.

Patients referred to The Fetal Center at Children’s Memorial Hermann Hospital who intend to undergo open in-utero spina bifida repair will be offered and screened for the alternative minimally invasive approach. Women who participate in the study must agree to deliver at Children’s Memorial Hermann Hospital.

“We have published promising preclinical data and have rigorously tested our techniques before taking fetoscopic repair to humans,” Dr. Papanna says. “Our research is changing the way we approach spina bifida to improve closure, reduce scar tissue formation, reduce neurological deficits and improve function. With this trial we hope to show that the NEOX Cord 1K patch optimizes long-term outcomes for these kids.”

# Contact Us

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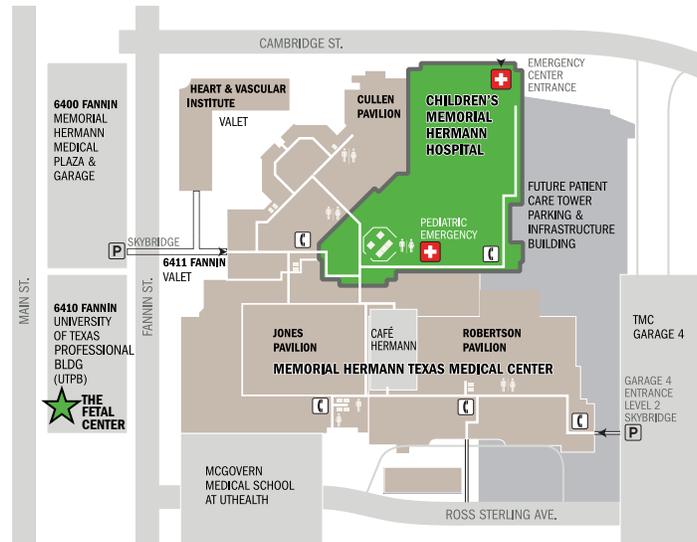
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Located within the Texas Medical Center, The Fetal Center is affiliated with Children's Memorial Hermann Hospital, McGovern Medical School at UTHealth, and UT Physicians.

To view The Fetal Center's online resources, visit [Childrens.memorialhermann.org/fetal-journal](http://Childrens.memorialhermann.org/fetal-journal).





  
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