

PROGRESS NOTES

MUSC'S MEDICAL MAGAZINE // FALL 2019



MUSC Ranked State's No. 1 Hospital Fifth Year in a Row

U.S. News & World Report releases annual national rankings

MUSC Health was named the No. 1 hospital in South Carolina by *U.S. News & World Report* for the fifth year in a row, with three of MUSC Health's specialty areas ranking among the best in the entire country: rheumatology, cancer, and ear, nose and throat. Four other MUSC Health programs are considered "high performing" in the 2019-20 rankings: nephrology, neurology and neurosurgery, orthopaedics, and urology.

"For five years in a row now, MUSC Health has been recognized for the high-quality care and tremendous value that we provide our state," said **Patrick J. Cawley, M.D.**, MUSC Health CEO and MUSC Vice President for Health Affairs, University. "Our industry has a lot going on within it right now, so this achievement demonstrates not just our commitment to putting our patients and their families first, but a real and enduring commitment to changing what's possible in how we deliver care through innovation, transformation and growth."

U.S. News & World Report recently unveiled the 30th edition of the Best Hospitals rankings. Designed to help patients with life-threatening or rare conditions identify hospitals that excel in treating the most difficult cases, Best Hospitals 2019-20 includes consumer-friendly data and information on 4,500 medical centers nationwide for 25 specialties, procedures and conditions.

"We're looking at things differently. We're tearing down barriers to care, successfully training the health care leaders of tomorrow and integrating our research discoveries in real time whenever possible. The citizens of our state can take great pride and comfort in the knowledge that their only public statewide hospital system is consistently cited as one of the best in the country," Cawley said.



**MUSC Health
Medical Video Center**
MUSCHealth.org/medical-video

A sampling of current videos:

Bolstering Damaged Rotator Cuff Through Bioinductive Tissue Grafting

Dr. Shane Woolf discusses a new twist on a procedure to treat rotator cuff disease with partial-thickness tearing and degenerative tendinopathy.

Hyperthermic Intraperitoneal Chemotherapy for Abdominal Cancers

MUSC surgeon Dr. Ramsay Camp discusses HIPEC for patients with cancer within the peritoneum, which is hard to treat with intravenous chemotherapy.

Knee Replacement Surgery Optimization

Dr. Lee Leddy, an orthopaedic surgeon at MUSC, discusses the steps taken before, during and after a knee replacement in order to improve a patient's quality of life.

Heart Transplant Procedure To Treat Heart Failure

Dr. Lucian Lozonschi, a surgical heart failure and cardiac transplantation physician at MUSC, describes each step of a heart transplant procedure when used to treat a patient with heart failure.

Deep Brain Stimulation Using a Frameless Platform

Dr. Nathan Rowland, a neurosurgeon and assistant professor at MUSC, utilizes a novel, customized frameless platform to perform deep brain stimulation on a patient with essential tremor.

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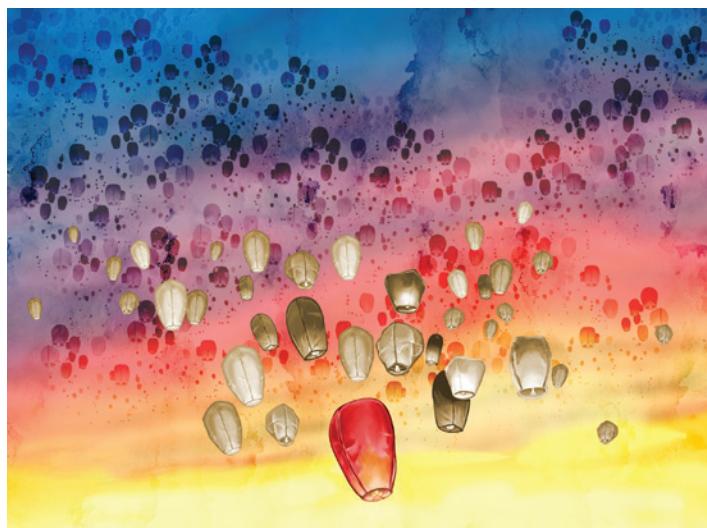
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On the cover: Progressnotes celebrates the spirit of hope embodied by the new MUSC Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion with an issue dedicated to pediatric and maternal health.
Illustration by Michael Mattocks.



NEWS

The Next Level

Kids' trauma center hits important new high

BY HELEN ADAMS

The trauma center at MUSC Children's Health has become the only kids' trauma center in the state to achieve Level I verification from the American College of Surgeons (ACS). That's the highest possible level.

Surgeon **Chris Streck, M.D.**, directs the pediatric trauma medical program at MUSC. "The main factors that distinguish Level I pediatric trauma centers are volume and quality of patient care. That includes 24/7 coverage by specialists such as pediatric trauma surgeons, neurosurgeons, orthopaedic surgeons, emergency medicine providers, anesthesiologists, child abuse treatment experts and intensive care unit providers. Injury prevention outreach and quality and volume of research are also major factors."

Nurse **Madeline Gehrig, MSN, RN**, manages the pediatric trauma program at MUSC. "What this verification means to our

patients and their families is the assurance that they are receiving safe, innovative and high-quality care from some of the most knowledgeable and skilled medical providers in the industry."

Streck said the trauma center team cares for kids hurt in major accidents or events. "The most common severe mechanisms of trauma that we care for are motor vehicle collisions, pedestrians and bicyclists struck by automobiles, falls from a height, bicycle- and golf cart-related injuries, gun- and knife-related trauma, burns and child abuse."

MUSC Children's Health was first named a pediatric Level I trauma center several years ago by the South Carolina Department of Health and Environmental Control. Then, DHEC started requiring hospitals to meet even higher standards set by the ACS, which MUSC Children's Health has now

done. This makes it one of just 59 Level I pediatric trauma centers in the country.

Streck said that, unfortunately, more than 90% of children hurt in the United States aren't taken to trauma centers, at least not initially. "In trauma care, we refer to the golden hour, where early intervention can really make a difference."

In other words, the earlier a trauma patient gets expert care, the better the chance of survival. "The pediatric trauma center at MUSC Children's Health benefits children across the Lowcountry. We also get transfers of severely injured children from across the eastern half of South Carolina," Streck said. "Having a high-level trauma center is like having good community amenities like parks, roads, schools and libraries where you may not inherently recognize their daily value until you need the resource, and then it's very meaningful."

The MUSC Shawn Jenkins Children's Hospital & Pearl Tourville Women's Pavilion, opening soon, will offer more state-of-the-art options for trauma patients and their families. "Our new facility's infrastructure will match the high level of care that we provide to kids. This is a win for everyone in the community."

DISCOVERY

Defining Risk of Preeclampsia

MUSC researchers aim to understand and potentially predict preeclampsia

BY CELIA SPELL

The force of blood traveling through your arteries and veins determines much of your heart health. High blood pressure can lead to heart disease, heart failure, heart attack, stroke and chronic kidney disease, and when it's coupled with type 1 diabetes and pregnancy, it can put both the mother and the baby at risk.

In a recent paper in *The Journal of Clinical Endocrinology & Metabolism*, researchers at the Medical University of South Carolina look at preeclampsia, a combination of high blood pressure and pregnancy, when it coincides with type 1 diabetes.

The general female population has a 5% chance of developing preeclampsia during pregnancy, but that chance increases to 20% for diabetic women. "By studying these patients, we have identified different markers that could help predict the complication before its onset," said **Clare Kelly, Ph.D.**, an endocrine researcher who worked with MUSC endocrinologist **Timothy Lyons, M.D.** on the paper.

According to the Centers for Disease Control and Prevention, preeclampsia can lead to a baby being born early and can put the mother at risk of a seizure or stroke during delivery. It can also lead to damage in the kidneys, liver, lungs, heart or eyes and can increase a patient's risk for cardiovascular disease in the future.

Some current treatments for pre-eclampsia include taking aspirin or remaining on bed rest, and the only cure is delivering the baby. But by monitoring someone at high risk for preeclampsia,

physicians can work closely with these patients and take proactive measures to keep their blood pressure down.

Each patient in the study could be categorized as having one of three haptoglobin phenotypes: 1-1, 1-2 and 2-2. Phenotypes describe the way a person expresses their genetic makeup and can be determined using a simple, one-time blood test. By looking at the three groups and their lipoproteins, the compounds that transport fat throughout their bodies, the researchers were able to determine that the diabetic patients with a 2-2 phenotype who also had elevated lipoproteins were at greater risk for preeclampsia.

Previous studies have examined lipoprotein levels and diabetes, but this one concluded that these markers were indicative of risk only for patients with the specific haptoglobin phenotype. Otherwise, looking at the biomarkers was not useful. "Currently, we're taking the more reactive approach when it comes to preeclampsia," said Kelly. "But if we know a patient is diabetic and has the 2-2 phenotype, we can monitor her more closely throughout her pregnancy and treat it proactively."

While high lipoprotein levels in conjunction with the 2-2 phenotype were associated with an increased risk of preeclampsia, this scenario is not yet proven to be causative. Currently, there are various hypotheses about what contributes to preeclampsia, like insufficient blood flow to the uterus or poor nutrition, but the root cause of the disease is not known.



Clare Kelly, Ph.D., an endocrine researcher at MUSC, studies preeclampsia during pregnancy.

By looking at the genetics and conditions associated with preeclampsia, researchers are moving one step closer to understanding what causes it and potentially how to prevent it.

"While we were looking at pregnant women with type 1 diabetes specifically," said Kelly, "we're hoping to extend some of our findings to women with type 2 diabetes and gestational diabetes as well as the general population of diabetics when identifying people at risk for hypertension."

PHOTO: SARAH PACK
PHOTO: ANNE THOMPSON



PHOTO: SARAH PACK

Patients of female physicians have lower hospital readmission rates and lower mortality than patients of male physicians, but the profession is losing many female physicians due to gender disparities.

DISCOVERY

Sticker Shock

In medicine, young women continue to pay a higher price for family

BY HELEN ADAMS

Forty percent of female doctors in a recent study stopped working or moved to working part time within a few years of finishing their medical training. In contrast, all of the male doctors kept working full time.

The researchers, including senior author and MUSC psychiatrist **Constance Guille, M.D.**, say this is important for a few reasons. First, there's a growing shortage of doctors in the U.S. Losing doctors early in their careers is making it worse. And losing female doctors may be particularly problematic.

"We know that patients of female physicians have lower hospital readmission rates and lower mortality in comparison to patients of male physicians. Further, when we lose women in medicine, we lose the potential for them as leaders in health care. This is

really important given that gender diversity in leadership is highly associated with better profits and decision-making."

Elena Frank, director of the Intern Health Study at the University of Michigan and lead author on this study, said she and Guille wanted to know why there was such a clear difference when it came to male and female doctors' schedules.

The difference was evident from their participants' responses. "For men, the big words that jump out are financial — need money, loans. I don't think you could even find the word 'child' on the male ones," said Frank.

Guille said for women the major factor was childcare responsibilities — balancing work and family.

The researchers said women and men should be free to choose how much they work or whether they stay home for family reasons. But it should be a genuine choice, not something forced on them by circumstances.

"It's very common for people to see this and say some women are just choosing to put family first," said Frank. "Which is wonderful and a great choice for anyone who wants to make that. But in reality, what we're seeing is that often there isn't choice."

Guille said that if the differences weren't so striking, they wouldn't be speaking out so strongly. "But the major gap between these two groups is suggesting that we don't have systems in place to support physicians as parents."

Frank agreed. She said the U.S. lags behind much of the world when it comes to supporting work/family balance. Having programs in place to support people juggling work with childcare and other family responsibilities could change things.

"Resources like on-site day care, flexibility in work hours and paid maternity leave would be helpful," said Guille.

Federal law guarantees 12 weeks of unpaid leave, but not everyone is able to actually take the time. Frank would like to see change not just in policies but also in the culture surrounding them. "Men often have access to leave, but the institutional culture pushes against them actually taking it," she said.

The study reported here included 344 doctors. About half are women, half are men. They work in a range of specialties.

Frank said it's important to see the gender difference in medical work hours as something that can stack the deck against women and that labeling it as a disparity will help people see that it has to do with power and underlying structures and history.

"We're not going to see the kind of changes we need without first acknowledging that," she said.

NEWS

Maestro and Mentor

MUSC's Patrick M. Woster joins Medicinal Chemistry Hall of Fame

BY BRANDON YOUNG

Patrick M. Woster, Ph.D., SmartState Endowed Chair in Drug Discovery and chair of the Department of Drug Discovery and Biomedical Sciences at the MUSC College of Pharmacy, was inducted into the Medicinal Chemistry Hall of Fame at the 2019 National Meeting of the American Chemical Society in San Diego, California. Woster was one of only four researchers worldwide inducted this year. He joins an elite group of fewer than 100 scientists, three of them Nobel laureates, previously honored with Hall of Fame membership for their contributions to the field of medicinal chemistry and training of future medicinal chemists. Medicinal chemistry uses a combination of chemistry and biology techniques to discover new pharmaceuticals to better human health.

"It's a great honor to be inducted into this group of eminent scientists, many of whom have been mentors and researchers that I have admired throughout the years," said Woster.

Induction into the Medicinal Chemistry Hall of Fame requires nomination by two ACS division members and selection by the executive committee. Receipt of this award validates a successful career for Woster, who came to MUSC in 2011. Woster has remained committed to the field of chemistry, as evidenced by his 25 years on the executive committee of the ACS Division of Medicinal Chemistry.

The work of medicinal chemists is crucial to the development of new drugs, according to Woster.

"Medicinal chemists begin the drug discovery pipeline," explained Woster. "They

optimize chemical structure to maximize potency and efficacy, but also make compounds orally active and ensure they reach their target within a patient."

Woster acknowledges that great science cannot be done in isolation. He has benefitted from a 30-year collaboration with Robert Casero, Ph.D., at Johns Hopkins University. They were the first to produce small-molecule inhibitors of lysine-specific demethylase 1 and to show that they help to reexpress tumor suppression factors.

"I've enjoyed the collaborative nature of research, and science cannot be done alone," said Woster. "You must have great collaborators like Bob to be successful."

Woster has also been an inspirational

mentor for the next generation of medicinal chemists.

"I've really enjoyed working with graduate students," said Woster. "They are kind of like your kids in a way, and it's extremely gratifying to see them do well."

Woster's commitment to science and training are also held in high esteem at MUSC.

"Pat is an outstanding role model in the College of Pharmacy," said **Phillip D. Hall, Pharm.D.**, dean of the MUSC College of Pharmacy. "His tremendous success as a scientist illustrates the pairing of hard work with a profound and curious mind, which is an inspiration for his students and the faculty he mentors. His wit and warmth brighten the lab and the classroom, and we are blessed to have him as a leader. We're very gratified he is getting this richly deserved recognition."

Induction into the ACS Medicinal Chemistry Hall of Fame acknowledges Woster on the national stage for an outstanding career not only as a scientist but as a colleague, collaborator and mentor.



Patrick M. Woster, Ph.D., 2019 inductee into the Medicinal Chemistry Hall of Fame.

PHOTO: SARAH PACK

Someone To Watch Over Them

MUSC Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion is a healing place built *for* families, conceived and designed by families and care team members

BY SHAWN OBERRATH



All children deserve the chance to grow up — and the new MUSC Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion aims to deliver just that chance for children in South Carolina and beyond.

The hospital was created with utmost consideration of the family's experience. In a dedication ceremony held in August, MUSC Health CEO **Patrick J. Cawley, M.D.**, stated, "When this facility opens its doors to patients, it will be the most patient- and family-centered and technologically advanced children's hospital in the nation. What a blessing for the children and mothers of this state and a beacon of hope and progress for our counterparts as we lead the way in raising all standards of excellence for patient care."

The family-centric features include an innovative floor for amenities, such as indoor and outdoor dining with magnificent views of the Ashley River, a large indoor atrium, and a 10,000-square-foot outdoor garden and play area that showcases a large movie screen and stage for community events. There is also a quiet zone outdoors and a chapel indoors for those seeking a contemplative atmosphere.

In addition to the amenity level, families requiring extended stays will have access to kitchens, showers and other conveniences, and there are play spaces and quiet areas on each patient floor.

The medical care offered at the children's hospital extends to the state's only level 1 pediatric trauma center and only level 4 NICU; the cardiology, surgical, and cancer expertise of MUSC Health specialists; and cutting-edge obstetrical teams for all facets of labor, delivery and postpartum care.

In the NICU, single-patient rooms replace the more traditional open bay design to allow for greater privacy and bonding for mothers and babies. Additionally, there are couplet care rooms with the infrastructure to support critical care of mothers and babies together.

The top level of the children's hospital is designated for patients with cancer and blood disorders. Children with these illnesses often must spend weeks or months in the hospital; with that in mind, the

rooms are larger, play spaces are steps away, and there are expansive, calming views to soothe both parents and children.

To round out the forethought that went into the design of the hospital, the rooftop is equipped with an advanced helipad — connected directly to the emergency department via express elevator — that can accommodate the Coast Guard's Jayhawk

Transforming how pediatric and maternal health care is delivered...on all levels

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| 2 | <ul style="list-style-type: none"> ■ Pediatric Intensive Care Unit ■ Burn Clinic |
| 3 | <ul style="list-style-type: none"> ■ Heart Care Center |
| 4 | <ul style="list-style-type: none"> ■ Pearl Tourville Women's Pavilion <ul style="list-style-type: none"> • 29 mother-baby postpartum rooms • 7 couplet care rooms • 2 obstetrical ORs |
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| 7 | <ul style="list-style-type: none"> ■ Boeing Outdoor Play Space ■ Jerry and Anita Zucker Family Atrium |
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helicopter to allow emergency and disaster responses.

Finally, smart room technology is integrated into all patient rooms, allowing for seamless communication between patient families and care team members. This technology and MUSC's participation within the robust South Carolina Telehealth Alliance will continue and deepen the commitment to collaboration with pediatricians and other children's hospitals throughout the state.

Ultimately, the care, innovation and coordination that led to the creation of the children's hospital and women's pavilion all serve the goals of success, health and opportunity to grow for all children in South Carolina. To learn more, visit musckids.org.



ON-RAMP TO REMISSION

CAR-T therapy at MUSC Health offers high-octane hope for previously incurable blood cancers

BY VITRIA ADISETIYO

Last spring, MUSC Health became the only center in South Carolina and one of a handful of medical centers in the Southeast certified to offer chimeric antigen receptor T-cell (CAR-T) therapy, the first FDA-approved gene transfer-based immunotherapy for refractory or relapsed B-cell acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL).

B-cell ALL and NHL are blood cancers affecting B lymphocytes, a type of white blood cell that marks foreign invaders for destruction by T cells. ALL originates in the bone marrow and is the most common childhood cancer, while NHL originates in the lymphatic system and is the seventh most common cancer in adults.^{1,2} Both cancers have high cure rates with traditional treatments, such as

chemotherapy, radiation and bone marrow transplant (80-90% for ALL, 71% for NHL). However, for patients with refractory cancers that do not respond to traditional therapies or who relapse after receiving these therapies, there have been no further treatment options, making the advent of CAR-T therapy an important step.

"CAR-T therapy is a way of harnessing someone's own immune system and reprogramming it to fight against the cancer," explains **Michelle P. Hudspeth, M.D.**, associate professor of pediatrics and director of the Blood & Marrow Transplant (BMT) Program at the MUSC Hollings Cancer Center.

To do this, T cells are collected from the patient and sent to a laboratory, where the cells are engineered to carry a chimeric antigen

receptor (CAR) gene. This gene reprograms the T cells to make CARs that bind a specific B-cell marker, CD19, thereby enabling the patient's own T cells to recognize and kill B cells. The T cells are then infused back into the patient and act as a "living drug." In clinical trials, CAR-T therapy demonstrated complete remission rates of over 50%.^{3,4}

At MUSC, turning the science fiction-like promise of CAR-T therapy into a treatment reality involved monumental efforts in collaboration. Once CAR-T therapy received FDA approval, MUSC's BMT team successfully completed onboarding of the treatment for children and young adults (up to 25 years old) with refractory or relapsed B-cell ALL.

"It really speaks to resources across the university, from the clinical trials office, pharmacy, nurses, finance and emergency departments, inpatient and outpatient units, to the intensive care unit (ICU) and cancer staff," says Hudspeth. "This level of engagement shows one of MUSC's main strengths, and that's collaboration and the willingness to push things forward to provide the best therapies for patients."

From the patient's standpoint, receiving CAR-T therapy involves typical outpatient and inpatient stays and consists of a leukapheresis procedure to collect white blood cells, chemotherapy to prepare the body for CAR-T therapy, and infusion of CAR-T cells. The routine nature of the treatment experience underscores the BMT team's expert choreography behind the scenes.

According to Hudspeth, "there are a million and one safety checks involving two very specialized teams: the hemapheresis team that collects the patient's T cells and the cryopreservation team that handles the CAR-T cells for infusing back into the patient."

After receiving CAR-T therapy, patients remain in the hospital for monitoring of both the treatment response and potential side effects, such as the loss of healthy B cells and a dangerous inflammatory condition called cytokine release syndrome (CRS). Fortunately, standby treatments are in place, including anticytokine therapy for CRS.

"There are very precise CRS treatment algorithms," says Hudspeth. "At any point a patient may have their first encounter, our staff has been trained to recognize, communicate, understand and follow the treatment protocols. So far, we've treated our first patient, and we're pleased that he didn't have toxicity, side effects or require ICU care."

As part of the Children's Oncology Group, MUSC has also been selected as a site for a clinical trial that will test CAR-T therapy as a frontline treatment for B-cell ALL patients at high risk for relapse with traditional therapy. In this trial, patients undergoing chemotherapy

who show signs of cancer after just two treatment cycles will be switched to CAR-T therapy, with the medication provided at no cost to patients.

"We are excited to offer this less toxic treatment earlier in therapy," says **Jennifer J. Jaroszak, M.D.**, an associate professor of pediatric hematology and oncology at MUSC. "Treating high-risk B-cell ALL up front with CAR-T therapy has the potential to significantly reduce the length of treatment for patients, from the standard two and a half years down to four months."

Because of the personalized and engineered nature of CAR-T therapy, one challenge that the U.S. health care system must overcome is the prohibitive cost — the latest estimates suggest a hefty price tag of \$475,000.⁵

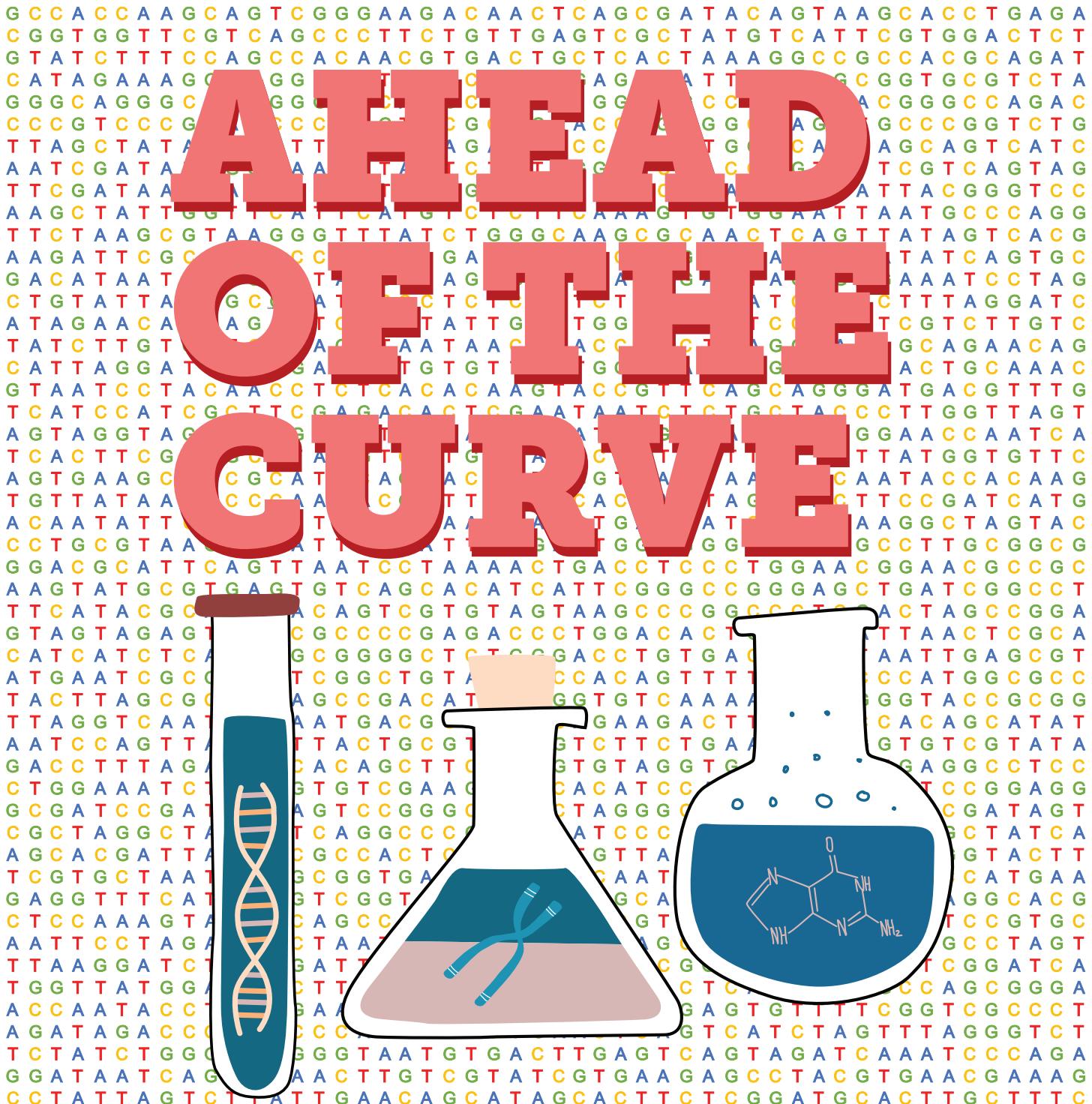
"Just like any other significant therapy, medical as well as financial eligibility must be determined," cautions Hudspeth. "It takes extensive effort from our financial group to work out a case-by-case negotiation agreement with insurance companies and Medicaid to offer these new therapies in a responsible way."

Despite the financial hurdles, the possibilities for CAR-T therapies seem endless. At MUSC, under the lead of **Brian Hess, M.D.**, assistant professor of medicine, onboarding of CAR-T therapy for adults with NHL is well under way, and recruitment for the CAR-T therapy clinical trial for high-risk B-cell ALL will begin this fall. On a larger scale, the frontiers of CAR-T technology are also expanding. Scientists are testing this technology on solid cancers, which are more prevalent than blood cancers, and developing second-generation CAR-T cells that attack more than just the CD19 marker to prevent relapse.^{6,7}

"It's been a lot to work through, but we're excited," says Hudspeth. "CAR-T therapy represents a revolutionary way to be able to potentially cure patients who were once incurable."

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Researchers at MUSC use CRISPR/Cas9 technology to
advance genetic research locally and regionally

BY CELIA SPELL

Genetic engineering is a modern buzzword whose roots date back thousands of years, to the advent of selective breeding. What began as domesticating wolves and leapt to cultivating crops has now grown into CRISPR-based genome editing technology.

CRISPR, or clustered regularly interspaced short palindromic repeats, describes short and repetitive segments of DNA that are part of the bacterial defense system against foreign invaders. By guiding CRISPR-associated nucleases like Cas9, bacterial RNA can target a specific and precise site in the invading DNA and use the nuclease to destroy it. Scientists have recently harnessed this ancient process to pinpoint the roles of specific genes throughout the human genome by way of animal models.

By slicing DNA with Cas9, which is akin to using exact molecular scissors, scientists are able to more easily and efficiently remove or change a particular gene from a mouse or rat in order to understand its functionality. Instead of having to breed mice over many generations to obtain only a few models with the knocked-out gene, researchers can use CRISPR/Cas9 technology to quickly and reliably engineer animal models with their intended modifications, and they can do it at MUSC by using the services of the Transgenic and Genomic Editing Core, also known as the TGE Core.

The TGE Core's scientific director, **Alexander Awgulewitsch, Ph.D.**, and research specialist **Jan Guz** work with researchers both affiliated and not affiliated with MUSC to create animal models. "CRISPR technology came into being back in 2013," he said. "And in that time, we have adopted this new methodology at MUSC."

By partnering with the TGE Core, which is the only one in South Carolina, researchers can make advancements more quickly than they could in the past.

The difference for MUSC Regenerative Medicine and Cell Biologist **Russell Norris, Ph.D.**, was speed. "We went from sitting down and saying we are looking at this mutation to actually having a mouse in just a few months," he said. Working with five independent lines provided the opportunity for supertargeted research. Knocking out a gene can have unintended side effects, but using the Core's technology and researching multiple lines of an animal model gives the team more confidence in their results.

"All five of those lines had the exact same phenotype," said Norris. "So, we were completely confident that our mouse was the right mouse and was truly representative of our study." It made for a seamless and streamlined analysis of his research on mitral valve prolapse (MVP).

As one of the first studies to use MUSC's new TGE Core, Norris' recent paper in *Science Translational Medicine* (also highlighted in

Nature) examined the defects in primary cilia that lead to MVP later in life. MVP is one of the common causes of heart murmurs; it affects 1 in 40 people and is the most common indication for mitral valve surgery. While its origins are poorly understood, MVP occurs when the two valve flaps in the mitral valve do not close properly and instead swell into the left atrium, and severe cases can cause arrhythmias, heart failure or sudden cardiac death.

By studying the slow advancement of this genetic disease in animal models, Norris and his team hope to one day keep patients from needing mitral valve surgery.

Another MUSC research team used the TGE Core to create animal models that shed light on breast cancer risk. As reported recently in *PLOS Genetics*, these researchers used rat models to study breast cell proliferation and the role of the *Cdkn1b* gene, which encodes the protein p27. As a key regulator of the cell cycle, p27 may contribute to breast cancer risk and tumor growth regulation.

In people, there is a separate subpopulation of luminal epithelial progenitor cells that has been associated with breast cancer risk. By using CRISPR/Cas9 technology to delete the *Cdkn1b* gene in an animal model susceptible to estrogen-induced mammary tumors, researchers found a smaller pool of these cells, which points to p27's role in regulating this population.

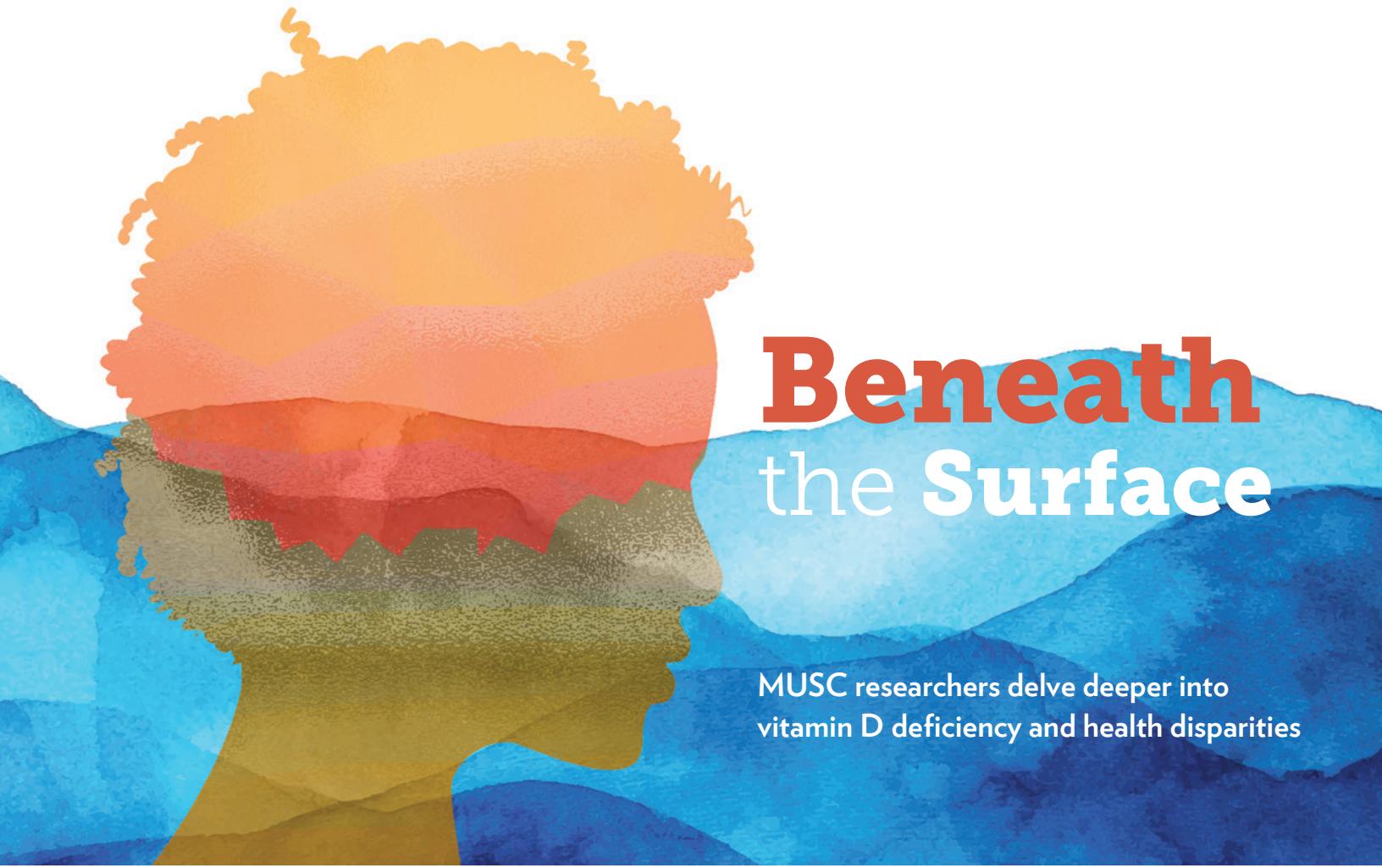
"This study also found that cells with and without *Cdkn1b* reacted differently to progesterone receptor signaling, which could indicate this gene may affect many different cancer pathways," said Awgulewitsch. "I think that would be an exciting next step, to look into that."

These two papers are the first of many in the pipeline that are using the TGE Core's genome editing capabilities to make speedier advancements in the study of genetically linked diseases at MUSC. The Core can be used to knock out a specific gene in animal models unconditionally or to introduce conditional knockout alleles as a way of monitoring how certain genes are expressed.

Researchers can also study function by using a "safe harbor" for gene expression, where a gene is overexpressed in an animal model at a specific genomic location where other genes are known not to affect expression. And these are just a few ways of using this technology.

Awgulewitsch is hoping the local presence of this rapidly changing genome editing technology can make a difference to researchers throughout the Southeast. "We have to continuously monitor the scientific literature in the CRISPR field, as it progresses almost daily," said Awgulewitsch. And that's just part of what makes this new methodology so inviting and so important.

"CRISPR is hot," said Guz. "And it's just going to get hotter."



Beneath the Surface

MUSC researchers delve deeper into
vitamin D deficiency and health disparities

BY RYAN BARRS

Historically, daily sun exposure fulfilled the vitamin D needs of humans. Modern living, however, has made it challenging to get enough vitamin D since we spend much of our time indoors and eat few vitamin D-rich foods (e.g., oily fish). Fortified foods have helped increase our daily intake, but vitamin D deficiency is still very common.

Vitamin D insufficiency and deficiency affect 1 billion people worldwide.¹ The National Health and Nutrition Examination Survey (NHANES) found that from 2001 to 2010, 28.9% of American adults were deficient in vitamin D. Non-Hispanic black American adults were the most deficient, at 71.9%, four times higher than the rate for non-Hispanic white Americans and almost twice that for Hispanics.²

Coincidentally, African Americans also have higher disease rates and mortality rates than white Americans, according to the Centers for Disease Control and Prevention.³ Socioeconomic factors are a major contributor to these health disparities, but the role of vitamin D is often ignored.

"I think it has been overlooked for a long time," says **Carol Wagner, M.D.**, a neonatologist at MUSC Children's Health who studies the effects of vitamin D supplementation on human health, particularly in women and children.

Dark skin has more melanin, which reduces the amount of UVB radiation available for vitamin D conversion in the skin, and therefore needs longer sun exposure than fairer skin to produce the same amount of vitamin D.

Low vitamin D related to skin color has been associated with the severity and prevalence of multiple diseases, and new studies support recognizing vitamin D status as a biological determinant of health disparities.^{4,5}

Maternal and pediatric health

Vitamin D is classically known for its role in skeletal health, but it modulates many different systems in the body, including the immune

system. "It certainly affects calcium and bone metabolism," explains Wagner. "But it has also been shown to affect your innate and adaptive immunity."

Wagner recently led a study examining the relationship between vitamin D status and the vaginal microbiome during pregnancy. The study found that lower levels of circulating vitamin D in pregnant women of African descent were associated with a greater abundance of *Megasphaera* — a type of bacteria linked to bacterial vaginosis, an infection of the vaginal canal that can increase the risk of preterm birth.⁶ Women of African ancestry are twice as likely to be diagnosed with bacterial vaginosis and are more than twice as likely to give birth early preterm (<34 weeks).^{7,8}

Early intervention between the first and second trimesters may be key to suppressing vaginal microflora associated with preterm birth.⁹ "It appears that vitamin D is far more important early in pregnancy than later," said Wagner. "We now screen all pregnant women at their first prenatal visit for vitamin D deficiency."

Wagner advocates for vitamin D supplementation during pregnancy. "A pregnant woman should take a prenatal vitamin but should also discuss her vitamin D level with her doctor," Wagner says. "We really want women to have a level around 40 ng/mL."

Beyond environmental impacts, genetics also contributes to differences in vitamin D status among racial groups. **Dan Newton, Ph.D.**, a scientist in the Department of Pediatrics at MUSC, found that differences in the gene encoding vitamin D-binding protein (VDBP) affect vitamin D status in children. "Vitamin D-binding protein is one of the most abundant proteins in the blood, and it carries about 85% of vitamin D metabolites," explains Newton.

Newton found that most African American children had VDBP gene variants associated with low vitamin D.⁸ Even when these children received the recommended daily allowance (RDA) of vitamin D, which is 600 IU for children older than 1 year, they did not reach sufficiency. Genotypic differences can affect responses to vitamin D supplementation, and that should be taken into consideration when creating a treatment plan.

Men's health

The Transdisciplinary Collaborative Center (TCC) in Precision Medicine and Minority Men's Health was established at MUSC in 2016 to tackle disparities in health outcomes among minority men.

Stephen Savage, M.D., director of minimally invasive urology, is leading a project to investigate the effects of vitamin D supplementation on prostate cancer.

Savage recently found that there are biological differences in the

prostate tissue between African Americans and European Americans. African Americans had a higher expression of inflammatory genes in their prostate, which may contribute to more aggressive disease progression.¹⁰ "We're seeing inflammatory changes which appear to be related to heredity and vitamin D," said Savage.

In a collaboration with the Department of Veterans Affairs, Savage and his colleagues showed that, compared to historical controls, supplementation at 4,000 IU/day for a year reduced tumor progression in low-risk patients undergoing active surveillance.¹¹ Vitamin D sufficiency may therefore be beneficial for low-risk prostate cancer patients.

Savage and his collaborators in the MUSC TCC hope to unify social, environmental, and biological determinants of prostate cancer to enable more personalized treatment.

Vitamin D is not a wonder drug, but it is a foundational nutrient with complex functions in human health and disease. Establishing an effective RDA for diverse populations is important for public health. The current RDA, which is 600-800 IU for adults, may be too low for many Americans to reliably reach sufficiency (>30 ng/mL), especially with limited sun exposure.¹²

A dose of around 4,000 IU/day has been shown to consistently raise the vitamin D status of women and men effectively, regardless of race, without negative side effects. "Out of tens of thousands of people who have been in these trials, we are still waiting on our first adverse event," says **Bruce Hollis, Ph.D.**, professor emeritus in the Department of Pediatrics and a long-time vitamin D researcher at MUSC.

Future studies at MUSC and beyond will guide the understanding of vitamin D's multifarious roles in human physiology and lead the development of more inclusive policies for vitamin D supplementation.

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Long-Distance Medicine 2.0

PART 2 IN A SERIES

MUSC offers broad array of pediatric telemedicine services that are improving the health of children across the state

BY MATTHEW GRESETH

Telemedicine has enabled physicians to reach their patients at home. This is especially important here in South Carolina, one of the more rural states in the country. The legislature has invested heavily in the development of telemedicine across the state, and MUSC's Center for Telehealth coordinates and facilitates access to specialized expert care for people in remote rural areas of South Carolina that don't have a large hospital nearby.

Targeting pediatric and maternal health care

MUSC's telehealth program has seen exponential growth, going from 12 programs to more than 70, and has identified several innovative strategies for delivering health care.

"One of the ways in which MUSC has really distinguished ourselves is we have one of the broadest varieties of pediatric telehealth services either in operation or in development anywhere in the country," says **S. David McSwain, M.D., MPH, FAAP**, MUSC's chief medical information officer and medical director for the South Carolina Children's Telehealth Collaborative.

MUSC has more than 20 different services that utilize telemedicine to improve pediatric and maternal health care. Some of the programs focused on children include behavioral health, psychological advice, nutritional advice, school-based telehealth and pediatric critical care. For maternal medicine, MUSC offers obstetric help for maternal fetal medicine, genetic counseling, diabetes management and behavioral health — MUSC has the only specialist in the state that works with addiction in pregnant women.

MUSC continues to grow its presence across the state and maintains a network of partnerships, especially with children's hospitals. One of the near-term goals is to strengthen the internal connections of these partnerships. This is particularly true of the new MUSC Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion. Most of the rooms are equipped with cameras so that specialists can link in to talk with patients. The emergency room

and neonatal intensive care unit (NICU) will be equipped with carts that enable specialists to see their patients from distant locations. Furthermore, video conferencing will allow families who are unable to visit to be part of the case discussions, especially for babies who must spend long periods in the NICU.

Reducing emergency room admissions for asthma

The school-based health program is one of the founding telemedicine programs at MUSC. It began in three schools (in Charleston, Kingstree and Hemingway) and has grown to more than 100 across the state as legislators, with public support from their communities, funded and built the infrastructure needed to expand the program.

"What's wonderful about the program is that it is designed to be a partnership with local communities," says **James T. McElligott, M.D., MSCR**, telehealth executive medical director and founder of the school-based telehealth program, now led by **Kathryn K. Cristaldi, M.D., MHS**, assistant professor of pediatrics in the College of Medicine at MUSC. "In some ways, that's done by us delivering the care here at MUSC, in other ways we can have local practitioners do it."

The school-based system functions like Uber. The school nurse activates the system, which alerts one of the local providers to get on the platform and see the child. If the first call goes unanswered, a second local physician is contacted. If the call still remains unanswered, MUSC takes the call. This system allows MUSC to partner with local physicians and be a critical resource for the state.

Each school is provided with a cart that is capable of video conferencing for visual examination of the student. The cart is also equipped with a stethoscope and a camera with various lenses to examine the skin, ears and teeth. With these capabilities, 90% of consultations, ranging from acute conditions such as a rash or earache to chronic conditions like asthma or ADHD, can be managed in partnership with local physicians.

"We have been doing this program for a while, and we believe in it," says McElligott. "Anecdotally, kid by kid, we can see the success of it, but until recently we didn't have true empiric data to support it. In Williamsburg County, where I started the program and where we have 100% school coverage, we saw, over a three-year period, a steady decline — more than 20% — in the use of the emergency room for kids with asthma."

These data were recently published in *JAMA Pediatrics* and highlight the success of telehealth when it is fully integrated into the community. Coverage of the entire county increases utilization of the program and avoids any stigma associated with it. Over the next few years, McElligott and Cristaldi want to replicate the success of Williamsburg County in other counties across the state.

Consulting for pediatric critical care

Another one of the earliest telehealth programs at MUSC focuses on pediatric critical care. Pediatric ICUs specialize in the care of critically ill infants, children and teenagers. Children who visit the PICU often require complex care. Many hospitals lack the technical expertise for these complex cases, so pediatric telemedicine allows physicians at MUSC to share their knowledge and expertise across the state.

MUSC has active relationships with five different community hospitals that have telehealth capabilities in their emergency departments and pediatric floors, and the South Carolina Children's Telehealth Collaborative supports the development of pediatric critical care programs at children's hospitals across the state.

"The community hospitals we currently partner with do not have PICUs, so we are their only resource for that type of care," says

Whitney E. Marvin, M.D., assistant professor of pediatric critical care at MUSC Children's Hospital and medical director for pediatric critical care telemedicine. "A few hospitals have small pediatric wards with pediatricians on staff, but they are not as well versed on managing critical care cases as our training allows us to be."

Oftentimes, MUSC plays a consultative role, providing 24-hour access to experienced physicians. MUSC physicians can visually monitor patients remotely through video conferencing, and a stethoscope attachment allows them to examine the heart and lungs. In some cases, MUSC physicians may assist in acutely managing certain traumas, septic patients or patients with obstructed airways. Thanks to these interactions, there has been a noticeable impact on the health of children.

"We did a study on the pediatric critical care program a couple of years ago that demonstrated that kids who get a pediatric critical care telemedicine consult are 2.6 times less likely to be admitted to the

intensive care unit than kids who get the traditional telephone consultation," explains McSwain. "That's a huge outcome and something that we didn't really expect."

This improvement likely comes from intervention in acute conditions, having relationships with patients and knowing the health status of the children well enough to feel comfortable admitting them less often or admitting them to lower intensive centers.

One of the major goals of the pediatric telehealth program is to see and treat patients at home as much as possible, and remote patient monitoring is helping make this a reality. Not only does this save families time and money, but it allows physicians to monitor patients over time and have a better sense of their history. To facilitate at-home monitoring, families can use the mobile, patient-facing software Epic MyChart to set up a video conference appointment, access their medical records and upload data; however, these features do require a smartphone.

"One of the key barriers is the simple fact that broadband network access might be difficult to come by for patients in rural areas," says McSwain. "That's a challenge that still needs to be addressed."

Interestingly, telemedicine offers the unique ability to help with disaster preparedness, and MUSC is looking to pioneer a program focused on responding to a disaster quickly and efficiently.

"We already have many established relationships with other emergency departments," says Marvin. "In the event of a major disaster or some type of infectious pandemic outbreak, I think there is a potential use for telehealth to help triage patient care across large areas."

In the future, McSwain and Marvin hope to expand the improvement they've seen in South Carolina throughout the country.

"This is one of the premier pediatric critical care telemedicine programs in the country, and in fact, our program was used as a model for the development of a pediatric critical care telemedicine service in British Columbia, Canada," says McSwain. "So we've had an international impact as well."

Growing pediatric health care safely

Telemedicine is improving the lives of patients across South Carolina and the nation. Concurrently, pediatric telehealth is growing rapidly, and it is imperative that doctors assess their progress to ensure that children are receiving the best care. One of the biggest challenges facing pediatric telehealth is identifying which practices offer the best care for children and which practices can be improved upon. This is a critical part of developing and growing programs that will have the greatest impact on improving our health care system, and over the past few years, MUSC has been tackling this challenge.



PHOTO: SARAH PACK

In counties with 100% telehealth school coverage, MUSC physicians have seen a 20% decline in the use of the emergency room for kids with asthma.

“One of the areas where we are leading nationally in pediatrics is in research around telehealth,” says McSwain, who is also a cofounder of the SPROUT Pediatric Telehealth Research Collaborative.

The SPROUT (Supporting Pediatric Research on Outcomes and Utilization of Telehealth) initiative has several goals. One goal focuses on identifying and addressing barriers to telehealth access through multicenter research. Another important goal centers on evaluating state and federal telehealth policies and linking those to research priorities and best practices. Ultimately, SPROUT aims to demonstrate how telehealth fits into value-based health care across the country.

MUSC is the main investigative site for the NIH-funded SPROUT-CTSA (Clinical and Translational Science Awards) Collaborative Telehealth Research Network. This collaborative partners with health systems across the country and allows McSwain and his colleagues to centralize data collection and research. The findings are then disseminated to other institutions to improve their telehealth programs and help them develop their own research strategies.

The telehealth programs at MUSC are generously supported by the state, and McSwain feels strongly that we should help other states, providers and communities that don’t have that support. SPROUT has helped implement best practices for vulnerable

populations such as children, but McSwain sees the success of pediatric telehealth research expanding.

“SPROUT is growing rapidly,” says McSwain. “The goal is to establish a model for the approach to telehealth research that can be expanded beyond pediatrics. We want to be the standard bearer for telehealth research across all disciplines.”

Realizing the promise of telehealth

Many doctors are still hesitant about utilizing telehealth services; however, as more data accumulates, it will become harder to ignore the benefits of these unique programs, especially in more rural areas. One of the big advantages of telemedicine services is that the families are really engaged in their health care. Each engagement centered around an immediate concern, like a runny nose, can become a broader conversation — reminding parents about vaccination schedules, informing parents about other health concerns, and prompting parents to look after their own health.

The many telehealth programs at MUSC have laid the foundation across South Carolina and the country to deliver on the promise of improving health care administration.

Read part 1 of the *Progressnotes* series on telehealth, published in Summer 2019, at MUSCHealth.org/pn/telehealthpart1.



HIGH RISK

High Reward

Physicians at MUSC prepare for the rise in high-risk pregnancies through a team-oriented approach

BY CELIA SPELL

The national birthrate is at a historical low. Almost 60 of every 1,000 women in the United States gave birth in 2018, which is down 2% from 2017 and is now the lowest it has been in 32 years, according to the Centers for Disease Control and Prevention.

Potential reasons for this decline range from changes in the nation's economic health to society's increased access to birth control.

But while the national overall birthrate and fertility rate have been declining, the number of women having children in their thirties has increased. As maternal age is one of the most common contributing factors to a high-risk pregnancy, physicians across the state as well as the country are changing the way they approach treatment.

In the past, new parents wouldn't know about a congenital anomaly or risks associated with their delivery until they went into labor or soon after. By incorporating improved methods of imaging and collaboration among hospitals throughout South Carolina, physicians at MUSC are diagnosing issues earlier and treating patients proactively, which improves outcomes for the mother and her baby.

The Advanced Fetal Care Center, the Center for Placenta Accreta Spectrum and the Simulation Center are just a few ways MUSC physicians of different specialties and disciplines are collaborating to better treat their pregnant patients.

High risk brings specialties together

When assessing a woman for potential pregnancy risks, physicians look at a patient's age, weight and blood pressure as well as any accompanying medical conditions that existed before pregnancy, such as diabetes or heart or kidney problems. They also look at any family history of genetic disorders and monitor for any issues with previous pregnancies. Other conditions can also develop during pregnancy, like gestational diabetes or preeclampsia, which is one reason routine prenatal appointments are important.

Maternal age, especially when a woman is over 40 years old, is a risk factor for pregnancy complications, but it is not necessarily the most significant contributing factor to a high-risk pregnancy. It's what



PHOTO: SARAH PACK

An ultrasound can show some markers for placenta accreta, but the addition of other imaging techniques – for example, fetal MRI – helps physician teams at MUSC prepare to receive these patients.

can accompany age. “It’s the fact that as you get older, your chances of developing conditions like diabetes and high blood pressure go up,” said **Eugene Chang, M.D.**, a maternal fetal medicine specialist at MUSC. “Age can change the risk profile of the average pregnant patient in multiple ways.”

The Advanced Fetal Care Center has been part of the plan for the new MUSC Shawn Jenkins Children’s Hospital and Pearl Tourville Women’s Pavilion for years, but after successful collaboration between maternal fetal medicine specialists and fetal cardiologists at MUSC, Chang and Fetal Cardiology Director **Sinai Zyblewski, M.D.**, partnered to create the center a few years before the opening of the new hospital.

Since its inception in 2015, more subspecialties have joined the group, and the program will continue to grow with its dedicated home in the new children’s hospital. Physicians throughout South Carolina and even further afield should look for potential fetal abnormalities at the patient’s 20-week ultrasound appointment; women with risk factors can then be referred proactively to the Advanced Fetal Care Center and will work with multiple specialists to create a pregnancy plan that addresses all aspects of their care.

The ability to detect any potential complications early on has only grown in recent years, as have potential treatments both in the womb and soon after birth. These advancements have also created the need to counsel families not only on the most up-to-date treatment options available but on those that are currently being investigated.

The Center offers an integrated approach to prenatal and postnatal care. Patients receive comprehensive counsel and care from a multidisciplinary team at the Advanced Fetal Care Center that may

have started with pediatric cardiology and maternal fetal medicine specialists but will now include neonatology, urology, neurosurgery, general pediatric surgery and otolaryngology.

Physicians who specialize in treating these various conditions in nonpregnant adults don’t always want to treat the same condition in someone who is pregnant. “It can be almost like a scarlet letter,” said Chang. “Which is why having physicians with dedicated interests in pregnancy in one location is so unique.”

Having the Advanced Fetal Care Center also provides patients with a point of contact. Because MUSC acts as the regional provider for fetal anomalies and high-risk pregnancies, many patients arrive from hundreds of miles away.

“Having a centralized contact provides a nice complement to the physician team and helps families coordinate multiple subspecialties and make decisions about their child’s care,” said **Chris Goodier, M.D.**, a maternal fetal medicine specialist at MUSC who works with Chang at the Advanced Fetal Care Center.

Placenta accreta on the rise

Another way that MUSC is tackling high-risk pregnancies is through the Center for Placenta Accreta Spectrum (CPAS). Usually the placenta rests atop the uterus and detaches during delivery, but in placenta accreta, the placenta attaches firmly into the uterine wall and instead can cause severe bleeding issues and can lead to the need for a hysterectomy. The spectrum is made up of three grades, which are defined by the depth of attachment into the muscular layer of the uterus: accreta, increta and percreta.

The most critical factor when dealing with a patient with placenta accreta is early detection and diagnosis. With the CPAS, MUSC is working with physicians across the state to catch the warning signs early. In a recent study, Chang and Goodier worked with other doctors in the state to validate the Placenta Accreta Index, which uses 2-D and color Doppler sonographic exams to calculate a patient’s risk.

An ultrasound can show some markers for placenta accreta, but the addition of other imaging techniques – for example, fetal MRI – helps physician teams to prepare to receive these patients. If a physician in the community sees anything suspicious on a patient’s ultrasound, they can refer the patient to the MUSC Prenatal Wellness Center for further imaging and care coordination.

Once a placenta accreta diagnosis has been made, a multispecialty team at the CPAS focuses on the planning needed for the patient’s care and the surgical and medical management of her placenta accreta. Each case requires multiple specialists including maternal fetal medicine, gynecologic oncology, anesthesia,

neonatology, urology, trauma surgery and nursing.

With a comprehensive team like this, Chang has seen more positive results in his patients' care. "The good news is the morbidity has definitely gone down and taking care of those patients has been a lot more successful."

Although improved care is available, rates of placenta accreta have been increasing over time: the American College of Obstetricians and Gynecologists estimates that 1 in 272 pregnancies are affected each year. Risk factors for placenta accreta include accreta in a previous pregnancy and prior caesarian section during delivery as well as other uterine surgeries. The rise in placenta accreta in the U.S. correlates with the rise in C-sections.

"It's a scary time for a family to discover their baby has something that requires intervention. We follow them from start to finish, and I think that's comforting."

— Dr. Eugene Chang

In a systematic review in *Obstetrics and Gynecology*, researchers found that the rate of placenta accreta rose from 0.3% after one previous C-section to almost 7% for women with five or more previous C-sections.

"When I started my residency 20-25 years ago, I saw maybe one case of placenta accreta in those four years," said Chang. "But now we probably see one a month."

But while rates of C-section deliveries and the rates of placenta accreta have been rising, it's unclear if C-sections are completely to blame. According to Goodier, placenta accreta typically occurs in a thin or poorly formed tissue in an area of scarring which allows the placenta to invade or directly attach to the uterine muscle. Other factors, such as a mother's age, uterine fibroids and infertility can be associated with a risk for accreta, which is one of the reasons he set out to validate the Placenta Accreta Index.

Preparation is key when treating placenta accreta, and that is the main goal of the Center for Placenta Accreta Spectrum at MUSC.

Planning for the unexpected with simulation

South Carolina is divided into four different perinatal regions – Charleston, Florence, Columbia and Greenville – with MUSC

staffing both Charleston and Florence. Using these divisions, most patients don't need to travel too far for their care, unless they have an unusual anomaly that sends them to Charleston.

As part of the state's Birth Outcome Initiative, there is a mobile simulation training lab called SimCoach that travels throughout the perinatal regions allowing health care providers to gain hands-on practice managing the complications of labor and delivery. Goodier describes it as, "A way for these health care teams to enhance communication, identify obstacles and prepare for all types of obstetric emergencies."

A few examples of these complications include dystocia, which is when a baby gets stuck in the birth canal during delivery; postpartum hemorrhage, when a new mother bleeds excessively after birth; eclampsia, which is when a pregnant woman experiences seizures; and maternal cardiac arrest, which also allows the team to practice perinatal resuscitation.

In addition to traveling throughout the state working with physician teams, Goodier also works with resident and medical student teams on campus at the MUSC Health Care Simulation Center. He helps to provide exposure to unstable pregnant patients through the use of immersive and procedural scenarios.

These programmed scenarios take place throughout the year in the simulation center and on the labor and delivery floor of the hospital.

"It's all about exposure, communication and ensuring workflows are in place," says Goodier. "It's not meant for you to study; it's about practicing for patients, especially for rare events."

Through the development of the Advanced Fetal Care Center as well as the Center for Placenta Accreta Spectrum and the MUSC Health Care Simulation Center, MUSC works with physicians to form a patient-centric process for tackling high-risk pregnancies to improve outcomes for both mothers and babies. Through early diagnosis and intervention, physicians can guide patients through a smoother pregnancy, labor and delivery.

"It's a scary time for a family to discover their baby has something that requires intervention," said Chang. "We follow them from start to finish, and I think that's comforting."

To learn more about the Advanced Fetal Care Center, visit <https://musckids.org/our-services/advanced-fetal-care>.

Tracking CAKUTT





How to monitor patients with congenital anomalies of the kidneys and urinary tract

SUBJECT MATTER EXPERT: DR. SHUMYLE ALAM

BY SHAWN OBERRATH

At the end of this article, the reader should be able to:

- Define the spectrum of CAKUT manifestations and recognize the potential impact of seemingly benign cases of CAKUT
- Monitor CAKUT patients for progression to chronic kidney disease or end-stage renal disease

Water — mother and sustainer of life — can also destroy if not kept in check. A critical balance is needed to maintain homeostasis. In the human body, the kidneys and urinary tract perform this essential function by cleaning and filtering the blood, eliminating waste, maintaining the water volume and solute concentrations, and influencing blood pressure.

The physical plumbing system is deceptively simple: two filtration units are linked by ducts to a collecting reservoir that must be routinely emptied. Yet the intricacies of the developmental process require perfect coordination of tubule, duct, and bladder formation, not to mention the complex process of kidney development itself. The kidneys are the filtration units, and they contain millions of nephrons that cleanse the blood, reabsorb essential solutes and remove any remaining waste. Any hiccup during the developmental process can spell disaster for the filtration and fluid regulation system, but the system does include a few redundancies that make it resilient in the face of disruption, meaning that some anomalies can be benign, or at least may seem that way.

Hence the spectrum of congenital anomalies of the kidneys and urinary tract (CAKUT), which encompasses a wide variety of diseases that in many cases were previously considered individual entities. These disorders fall into three main classes: hydronephrosis, kidney malformations, and disorders involving renal migration or collecting system anomalies. The first class includes vesicoureteral reflux and obstruction of the ureteropelvic junction (the most commonly seen CAKUT, comprising about 20% of cases) or the lower urinary tract; malformations of the renal parenchyma can include kidney agenesis and kidney dysplasia; and problems of renal migration or collecting system formation can include ectopic kidneys, horseshoe kidney, posterior urethral valves, and duplications of ureters and/or kidneys.^{1,2}

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The overall burden of chronic kidney disease (CKD) is on the rise among both children and adults, and almost 50% of the pediatric CKD burden can be attributed to CAKUT. CAKUT can be confined to the affected structure and its functions or can be part of a multiorgan syndrome with far-reaching consequences. For example, VACTERL syndrome affects both renal and extrarenal systems in a predictable pattern of vertebral, anal, cardiovascular, tracheo-esophageal, renal, and limb defects. CAKUT may be an important cause of pediatric hypertension, and while supportive data are not yet available, it is certainly likely that a percentage of adults who develop essential hypertension have an underlying, potentially undiagnosed CAKUT. Most compellingly, decreased glomerular filtration rates (GFR) have been shown to correspond to reductions in the expected life span, mostly because

of cardiovascular effects, but careful monitoring of GFR throughout childhood and adolescence can help with appropriate detection and treatment.^{1,5}

Primary care providers may see and manage patients with various CAKUT manifestations without necessarily recognizing their place on the CAKUT spectrum. CAKUT can range from relatively benign and self-limiting anomalies to life-threatening disease requiring immediate intervention. It is crucial for awareness of the spectrum to increase among both pediatricians and doctors who treat adults, as even seemingly benign disease in childhood may progress to end-stage renal disease (ESRD) later in life and because CAKUT patients require lifelong care and monitoring.

Normal kidney development and etiology of CAKUT

CAKUT can occur at any time during fetal development, and the timing of developmental disturbance determines the exact physical and functional manifestations.

The structures comprising the urinary and reproductive systems arise from the intermediate mesoderm, one of the embryonic germ layers. Kidney development occurs in three stages, from anterior to posterior: pronephros, mesonephros and metanephros. The pronephros consists of tubules and a duct and is nonfunctional; it degenerates over time, but the caudal part of the duct remains and becomes the mesonephric duct, or Wolffian duct. The mesonephros consists of tubules and the mesonephric duct and is functional but temporary; mesonephric nephrons form but later degenerate as the metanephros takes over functionality. Outbranching from the mesonephric duct forms the ureteric bud, which grows into the metanephric mesenchyme and contributes to formation of the nephrons, renal pelvis, calyces, ureters and collecting tubules. The metanephric mesenchyme eventually differentiates into the functioning kidneys.^{1,4}

The cells of the metanephric mesenchyme produce and secrete glial cell line-derived neurotrophic factor (GDNF). This chemical signal orchestrates the proper formation of nephrons via mesenchymal-to-epithelial transformation, regulated by numerous transcription factors and other molecules. The process is intricate and complex and is influenced by genetic as well as epigenetic factors.⁴

A wide variety of genetic studies have identified more than 50 single-gene disorders that can include CAKUT alone or as part of a syndrome. Some of these genes are part of the GDNF pathway, such as *WT1*, *EYA1* and *PAX2*. Other well-known players include *HNF1B*, *DSTYK* and *BMP4*. *PAX2* and *HNF1B* are known to explain a significant proportion of CAKUT cases and are thus used for diagnostic screening. Additionally, many patients with CAKUT carry copy number

variations (CNVs) known to be associated with defined syndromes or that are extremely large or rare. However, only about 10% of CAKUT cases can be attributed to a known genetic disorder, and another 16% to CNVs. Thus, there is much room for progress in defining the genetic underpinnings of the remainder of cases and eventually mapping how genotypic architectures relate to prognosis, specifically the risk of renal failure for patients with CAKUT.^{5,6}

While genetics certainly seems to play a role in CAKUT, epigenetic influences and environmental factors also have impacts. For example, high glucose levels due to maternal diabetes or stresses induced by maternal malnutrition, obesity, depression or other factors can influence the DNA and histone methylation patterns and other histone modifications during development, and the effects on gene silencing or expression can persist in the developing fetus. Exposure to teratogenic drugs, such as ACE inhibitors, can also disrupt normal kidney development.^{2,6}

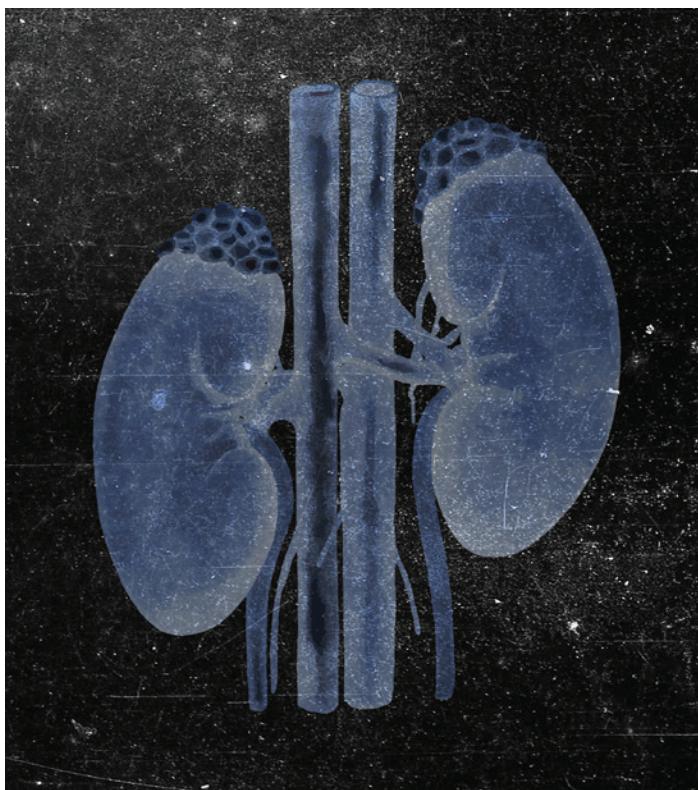
Diagnosis and treatment

Most cases of CAKUT can be seen upon fetal ultrasonography of the kidney and urinary structures during pregnancy. Amniocentesis can also be performed where warranted to analyze the fetal urine as an indicator of fetal renal function. If prenatal detection does not occur, diagnosis in infants or children can be performed by blood testing, urinalysis, ultrasonography, voiding cystourethrography and CT or MRI scanning, particularly for children with frequent urinary tract infections.^{1,2}

In recent years, advances in prenatal interventions have provided options that, while potentially subject to life-threatening complications, may be able to increase the chance of survival for fetuses with severe disorders. For example, vesicoamniotic shunting and fetal cystoscopy may be able to clear or circumnavigate obstructions in the urinary system, and amniotic fluid infusions can keep the fluid level optimal for proper lung development.

In newborns with CAKUT, surgery to remove obstructions can be performed in the hope of preserving the kidney function on the affected side. Even with any prenatal interventions and postnatal surgical treatment, the kidney function may be deficient or absent. Severe CAKUT can lead to ESRD during infancy, but even formerly mild cases may progress to ESRD by adolescence.

Renal replacement therapy is required to support patients with ESRD. Dialysis in infants is expensive and difficult, but it is generally agreed that transplantation is not an option until the child reaches a weight of 10 kg. Thus, dialysis and nutritional therapy often serve as a bridge until the child can receive a transplant. In a recent risk



assessment of a large birth cohort, children who received transplantation preemptively, without prior dialysis, had higher survival and growth rates than those who received dialysis first. Conservative management via nutritional support and growth hormone supplementation may therefore provide the safest bridge to transplantation. Overall, transplantation is the most successful intervention for children with CAKUT who progress to ESRD.¹⁷

Monitoring by primary care providers

Primary care providers are the linchpins of successful patient management for those with CAKUT. Because of the spectrum of possible manifestations and the risk of less severe conditions developing later into high-risk ones, patients should be monitored carefully throughout life.

Cystatin C (CysC) is an important indicator of the GFR in adults and children and was recently studied as a marker of renal function in neonates as well, since the CysC level in neonates is not influenced by the maternal CysC level. In a prospective risk assessment study of infants with severe CAKUT, neonatal CysC levels of 3.0 mg/L or higher and nadir serum creatinine levels of 0.6 mg/dL or higher were the most significant predictors of early progression to CKD or ESRD. The presence of comorbidities and a gestational age

of less than 36 weeks were also strong predictors of progression to advanced CKD.^{7,8}

Renal disease in children with CAKUT can be progressive, so it is important to monitor GFR, CysC and serum creatinine throughout childhood. Decreases in life expectancy can begin when the GFR falls below 60 mL/min/1.73 m². In addition, growth and physical development should be measured, as there is a relationship between CKD and growth stunting. CAKUT disorders often present in a bimodal pattern, so even those who remain relatively unscathed during infancy and early childhood must still be monitored for progression during adolescence by examining growth, renal, and cardiovascular markers. Moreover, holistic factors such as cognitive development and nutritional status should be assessed for satisfactory progress.^{7,8}

Further studies to define which CAKUT cases evolve into CKD will help us to understand and develop different treatment modalities to help stop progression. Our ability to innovate the current treatment arsenal will benefit from standardized follow-up and measurement of GFR. This is especially important given the opportunity to avoid a reduction in life expectancy in this population.^{3,9}

Need for CAKUT centers

CAKUT is complex and multifaceted, and research into best practices for its management is still under way. The team at the Medical University of South Carolina (MUSC) has seen positive results by taking a holistic, collaborative approach to CAKUT and modeling care around the concept of a medical home, with nephrologists, transplant surgeons, developmental pediatricians, genetic experts, dietitians, social workers, nurses and others working together to treat and monitor each patient. Validated data from evidence-based studies are still required, but in many cases the progression of renal disease has been delayed or halted. The development of CAKUT centers devoted to these patients is a critical step toward efficient and comprehensive care that offers hope and the highest-quality lifestyle possible. In the meantime, primary care providers are charged with supporting and monitoring CAKUT patients and collaborating with proper specialists as required for each case.

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of the Musculoskeletal Integrated Center of Clinical Excellence and currently serves as director of the MUSC Sarcoma Tumor Board. He also served on the executive committee of the Musculoskeletal Tumor Society and is the program chair for the Council of Orthopaedic Residency Directors.

Raymond N. DuBois, M.D., Ph.D., dean of the MUSC College of Medicine, says “Leddy brings an excellent combination of leadership, clinical, education, research and administrative skills to this position, and I am confident that he will devote his energy and effort to the continued development and success of the department.”

The culture of care at MUSC inspired Leddy’s enthusiasm for the department’s growth. “The current faculty and staff have created an organization that is high performing and maintains a strong conviction of its mission to provide exemplary and compassionate musculoskeletal care,” he said. “These values guide the commitments of the faculty to patient care, education, research and humanitarian endeavors. We are proud to recruit and develop faculty who are content experts and who make a national impact.”

Leddy also envisions a strong emphasis on successful training and research. “Growth in clinical care is dependent upon recruitment of new faculty who share the same values and commitment to excellence in all domains,” he said. Currently, the department offers a robust and successful training program for learners at all levels, which will continue to be a primary focus for the department as it expands its teaching efforts and refines its curriculum to include novel methods like advanced surgical simulation.

PHOTO: SON NGUYEN

MUSC Appoints New Chair of Orthopaedics

As **Lee Leddy, M.D.**, the newly appointed chair of the MUSC Department of Orthopaedics and Physical Medicine, steps into his new role, he aims to embrace growth.

Leddy wants to work with providers to extend MUSC’s high level of care across the state and throughout the region. “With new buildings and strategic alliances, advanced and routine musculoskeletal care is more convenient and efficient for both our patients and referring providers,” he said. “And that

will help us grow. Furthermore, there are new opportunities through both the [MUSC] Regional Health Network and in telehealth that will allow MUSC to provide access and care across a larger geographic area.”

Leddy is a well-known orthopaedic surgical oncologist with expertise in limb salvage. He joined the MUSC faculty in 2009 as an assistant professor and has served as the orthopaedics residency director for the past five years. In 2018, he was named the chief

New Physicians



Dane Daley, M.D.

Specialty: Hand Surgery // **Clinical Interests:** Peripheral nerve surgery, targeted muscle reinnervation, amputees, brachial plexus injuries and birth palsies, hand, wrist and forearm surgery // **Medical School:** East Tennessee State University Quillen College of Medicine // **Residency:** Medical University of South Carolina // **Fellowship:** The OrthoCarolina Hand Center



Steve Kahn, M.D.

Board Certifications: General Surgery and Surgical Critical Care // **Specialties:** General & Acute Care Surgery, Critical Care, Burn Surgery and Burn Surgery – Pediatrics // **Clinical Interests:** Burn – adult and pediatric, critical care medicine, skin and soft tissue infections, scar revision // **Medical School:** East Tennessee State University College of Medicine // **Residency:** University of Rochester // **Fellowship:** Vanderbilt University Medical Center and University of Rochester



Kimberly Kicielinski, M.D., MSPH

Specialties: Neurosurgery, Neuroendovascular Surgery // **Clinical Interests:** Aneurysms, AVMs, carotid stenosis, ischemic and hemorrhagic strokes, cavernous malformations, moyamoya disease, nonvascular interests in brain tumors, pituitary tumors, trigeminal neuralgia, hydrocephalus, degenerative spine disease // **Medical School:** Pennsylvania State College of Medicine // **Residency:** University of Alabama Birmingham // **Fellowship:** Beth Israel Deaconess Medical Center and Harvard Medical School

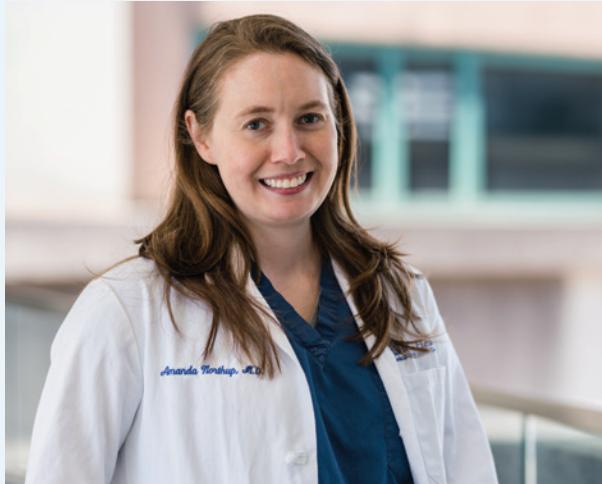


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Clinical Interests: Chronic disease management, cancer screening, preventative medicine //

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Residency: Trident/MUSC Family Medicine Residency Program

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// Residency: Roswell Park Comprehensive Cancer Center



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for benign prostatic hyperplasia, treatment of pelvic congestion syndrome,

HHT, uterine artery embolization, placenta accreta, venous disease, cancer

treatment, peripheral vascular disease // Medical School: Medical University of

South Carolina // Residency: University of Virginia //

Fellowship: University of Virginia



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