PROGRESSNOTES

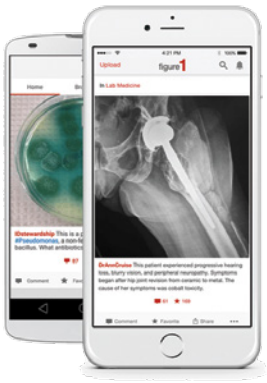
MUSC'S MEDICAL MAGAZINE // SPRING 2016

Introducing OR Notes
Take a front row seat
to complex surgeries

Introducing *OR Notes*

OR Notes is a new *Progressnotes* blog that will give health care professionals a front row seat to the complex and innovative surgeries offered at MUSC Health. New surgical cases will be posted regularly to the *OR Notes* blog (MUSChealth.org/or-notes) and to the @MUSCHealth profile on the free Figure 1 app (iOS and Android), which some have likened to an Instagram for physicians.

figure1



MUSC Health orthopaedic surgeon Dr. Vincent Pellegrini

MUSC Health virtual grand rounds on the Figure 1 app

MUSC Health transplant surgeon **Satish N. Nadig**, **M.D., Ph.D.** (below right) recently led a virtual grand rounds on Figure 1 (https://figure1.com/), a free case-sharing app for physicians. Thirteen surgical photos from a recent kidney transplant at MUSC Health were dropped one by one beginning at 8:00 pm on January 27, and Dr. Nadig was available during the event to answer questions. An abridged transcript of the event—"What a Kidney Transplant Looks Like"—can be found at http://bit.ly/1VmV7fv. The kidney transplant was part of a kidney chain. For more about kidney chains and about this series of operations, visit the *OR Notes* blog (MUSChealth.org/or-notes). All patients gave their consent.

Join **Vincent D. Pellegrini**, **M.D.** (above right), Chair of the Department of Orthopaedics, for a Figure 1 virtual grand rounds on revision hip replacement on April 26 at 8:00 pm. Ask him questions in real time about the case featured on page 14 of this issue.

MUSC Health transplant surgeon Dr. Satish Nadig

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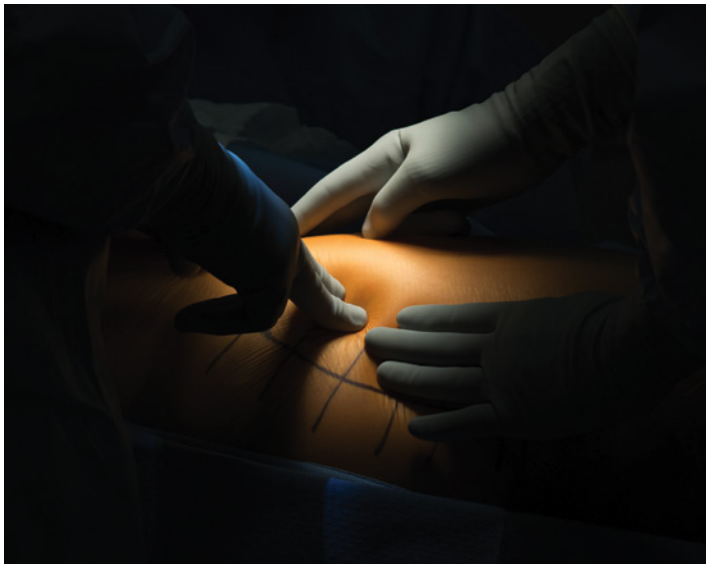


On the cover: Marking the incision site for revision hip replacement. Photograph by Brennan Wesley. See more surgical photographs under the folds on page 14.

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

LIFTOFF

MUSC Health recognized as a comprehensive stroke center

BY SVER AUNE

Photograph by Brennan Wesley

Advanced neuroimaging in MUSC Health's angiography suite guides cutting-edge stroke interventions.

In December 2015, the Joint Commission (JC) recognized MUSC Health as a comprehensive stroke center (CSC), its top certification. The new CSC certification is more than a badge of approval from the oldest and largest standards-setting body in health care. "It's really about lifting our quality of care to the highest level, from opening rapid communication channels with emergency first responders to performing neurosurgery for the most complex cases," says **Christine A. Holmstedt**, **D.O.**, Medical Director for Clinical Stroke Services and Co-Director of the MUSC Health Comprehensive Stroke & Cerebrovascular Center.

To qualify for CSC certification, the Center had to meet an additional eight measures beyond those of a primary stroke center (PSC), demonstrating that it had the expertise, experience, and infrastructure needed to provide the full range of care for patients with either an ischemic stroke (i.e., caused by a clot) or a hemorrhagic stroke (i.e., caused by a bleed). **Patricia E. Aysse**, **MSN**, Manager of MUSC Health's Stroke Program, had the job of making sure every paragraph of the commission's 346-page guide to certification was being followed. That required cooperation across the university. "We are so lucky in this organization to have stroke neurologists, interventionists, and emergency department physicians who are supportive of stroke care," says Aysse.

Essential to CSC certification was the availability of neuroendovascular surgeons with the expertise and experience to offer stroke patients advanced treatment options not typically available at PSCs. These include thrombectomy, carotid endarterectomy (i.e., removal of the inner lining of the carotid artery to improve blood flow), and carotid artery stenting (i.e., insertion of a metal mesh to hold the artery open) for ischemic stroke and endovascular coiling and surgical clipping procedures for hemorrhagic stroke, all of which are best performed at a high-volume CSC with advanced neuroimaging capabilities.

"For years, MUSC Health Neuroendovascular Surgery team members have been recognized worldwide as thought leaders in stroke and cerebrovascular disease, pioneering endovascular devices, surgical techniques, and outcomes research," says **Raymond D. Turner**, **M.D.**, Co-Director of the MUSC Health Comprehensive Stroke & Cerebrovascular Center. "CSC certification is another validation of the best-in-class care and clinical outcomes our program provides for patients in South Carolina and beyond."

As a CSC, MUSC Health is also able to provide round-the-clock neurocritical care for stroke patients, which is not typically available at a PSC. MUSC Health offers a 16-bed dedicated neurocritical care unit and the 24/7 availability of a consulting neurologist.

MUSC Health serves as a resource for the state, not only by treating the most complex cases but by partnering with other hospitals to coordinate stroke care so that patients are treated by facilities offering the level of care they require, as close to home as possible.

"We're helping empower our partners to treat stroke patients closer to home," says Holmstedt. "But when more advanced care is needed, as a CSC we have the education, training, physicians, and technology to treat and care for the most complex stroke patients."

For more about the MUSC Health Comprehensive Stroke & Cerebrovascular Center, visit MUSChealth.org/neurosciences/services/stroke. For more about types of stroke center certification, visit www.jointcommission.org.

PREVENTING STROKE

Trials establish an alternative to blood transfusions for some sickle cell patients

BY LINDY KEANE CARTER

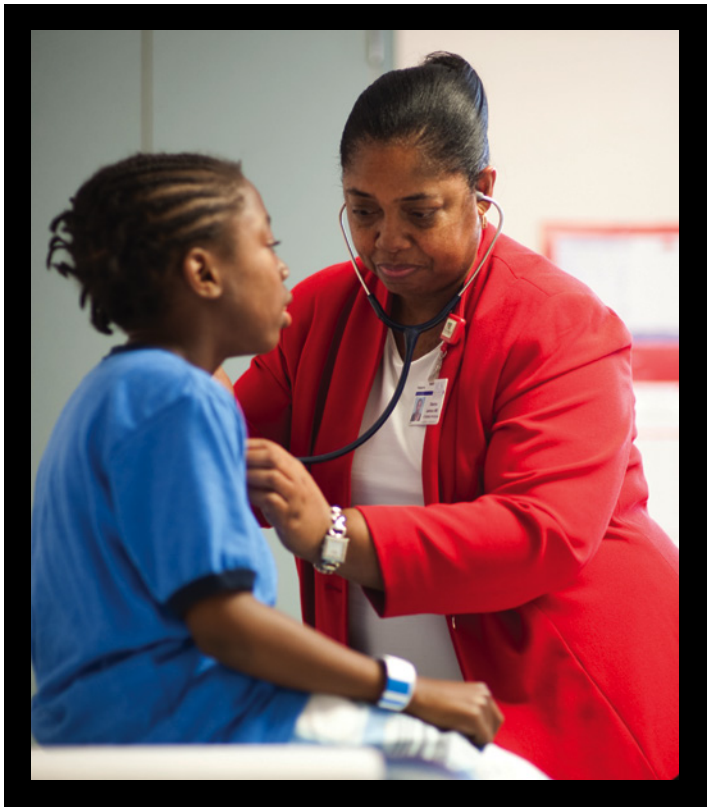
The drug hydroxycarbamide (hydroxyurea) has been proven to be as effective as blood transfusions in maintaining cranial blood flow velocities in some children with sickle cell disease (SCD) according to a national study. The TWiTCH trial (TCD With Transfusions Changing to Hydroxyurea), which included MUSC among its 26 trial centers, was designed to establish non-inferiority of the drug. The trial did so within four years, so TWiTCH was stopped one year early. The study's findings were reported in *The Lancet* (February 13, 2016).

Sherron M. Jackson, M.D., Associate Professor of Pediatrics, Division of Pediatric Hematology/Oncology, was the Principal Investigator at the MUSC site. "Now we have something better than transfusions to minimize the risk of stroke," she says. Chronic blood transfusions—the traditional therapy for preventing strokes—have significant negative side effects, including iron overload that can damage organs and lead to death. Hydroxyurea is easily administered in liquid or pill form.

Co-Principal Investigator of the national study was **Robert J. Adams, M.D.**, Professor of Neurology at MUSC Health. "The TWiTCH study is very significant," he says. "It gives us the second component of an effective protocol. The protocol of transcranial Doppler risk stratification of patients followed by regular red blood cell transfusion and then moving certain patients on to hydroxyurea should make long-term stroke prevention more practical. We hope this will lead to wider adoption of the protocol and bring us closer to the goal of a stroke-free generation of SCD patients."

Decades ago, Adams led a group of scientists and technicians in adapting the then-new technology transcranial Doppler (TCD) to use in SCD and they showed how it can help prevent stroke. TCD measures blood flow velocity in cranial vessels. A high-flow velocity indicates that the sickle cells have begun to occlude the vessels, eventually causing ischemic stroke. Today, TCD is the chief diagnostic tool for identifying children at risk for stroke.

Annual TCD screening is recommended for children with SCD and is performed at South Carolina's comprehensive sickle cell centers in Columbia, Greenville, and Charleston (MUSC Health). If the patient's cranial flow velocity is abnormal, hematologists will consider hydroxyurea as a treatment option. Hydroxyurea increases production of fetal hemoglobin and, as a result, fewer sickle cells are produced. Approximately 100 babies with SCD are born each year in South Carolina, says Jackson. The peak age for strokes is eight years of age.



Photograph by Brennan Wesley

Dr. Sherron M. Jackson examines a sickle cell patient in clinic.

To eliminate strokes altogether, there is much work to be done. Adams says that there are three problems yet to address: TCD does not completely predict all ischemic strokes in children; there is no way to identify those destined to experience intracranial hemorrhages so that physicians may intervene; and there is no good strategy for stroke prevention after childhood. Further research is needed to better understand how to move medicine closer to reducing stroke or even eliminating it in these young patients.

CREATING CELLS FOR SIGHT

Research offers hope for retinal disease

BY LINDY KEANE CARTER

Photo by Britta Kasholm-Tengve, iStock

Macular degeneration causes central vision loss (as shown above). Recent research at MUSC offers hope for restoration of sight.

Severe vision loss associated with retinal diseases such as age-related macular degeneration (AMD) is caused by dysfunction of the retinal pigment epithelium (RPE)—a layer of cells under the retina—and damage to the substrate under the RPE cells, Bruch's membrane (BM). Transplantation of RPE cells derived from induced pluripotent stem cells (iPSCs) is one therapeutic approach that researchers are exploring to treat this blinding disease.

Induced pluripotent stem cells are cells that have the potential to regenerate any cell or tissue in the body, as shown in a 2006 landmark paper published in *Cell*.[1] Clinical studies have demonstrated that RPE cells derived from other stem cells are safe and may be effective at improving vision, but life-long immune suppression drugs are necessary because the "mother" cells are derived from donors unrelated to the patient. To find an iPSC alternative that does not trigger transplant rejection, researchers at MUSC and elsewhere have used a patient's own skin cells to generate iPSCs, but the process uses viruses to introduce the desired reprogramming factors. Currently, the U.S. FDA does not allow clinical trials using virally generated iPSCs.

MUSC scientists led by **Lucian V. Del Priore**, **M.D.**, **Ph.D.**, Pierre Gautier Jenkins Professor in the Department of Ophthalmology, have demonstrated a successful alternative to viral induction: exposing skin cells to human proteins. "This works because ultimately the DNA creates a protein inside the cell, which then affects the cell's behavior," explains Del Priore. The efficiency is low; only about 1% of cells become transformed, he reports, but the research establishes that these cells can then be turned into RPE and that these cells function normally in the Petri dish. Specifically, the work demonstrated that the generated RPE can ingest outer segments from the retina, which is important in the normal maintenance of this delicate neural tissue. Work on this project involved a collaborative research team that included **Ernesto Moreira**, **M.D.**; **Jie Gong, M.D.**, **Ph.D.**; **Mark Fields**, **Ph.D.**, **MPH**; and **Zsolt Ablonczy**, **Ph.D.** Their primary findings were published November 25, 2015 in *PLoS ONE*.[2]

Successful transplantation of RPE cells will depend upon repair of the damaged BM beneath and Del Priore and investigators also have reported on the effects of doing a "chemical peel" of this substrate.[3] BM explants were dissected from young and old donor eyes. A combination of cleaning and then coating the explants with extracellular matrix ligands removed the abnormal protein deposits and rejuvenated the tissue. These results demonstrate that the detrimental effects of aging BM can be reversed by reengineering the BM surface with this approach.

The main application of this potential therapy is for treatment of the dry form of AMD. Ninety percent of AMD patients have the dry form, as opposed to the wet. Clinical trials for therapies that arise from this human protein–induced pluripotent stem cell research and BM reengineering are still several years away, says Del Priore. It is hoped that MUSC will be a principal site for these landmark studies.

References

[1] Takahashi K, Yamanaka S. *Cell* 2006 Aug 25;126(4):663-676.
[2] Gong J, et al. *PLoS One* 2015 Nov 25;10(11):e0143272
[3] Moreira EF, et al. *Translational Vision Science and Technology* 2015 Oct 30;4(5):10.

BEYOND THE GASTRIC BYPASS

Rare weight loss surgery for the extremely obese

BY LINDY KEANE CARTER

MUSC Health has become one of the few hospitals in the Southeast to offer biliopancreatic diversion duodenal switch (BPD/DS) surgery, a technically challenging but highly effective weight loss procedure. In December 2015, **Rana C. Pullatt, M.D., MS**, Associate Professor of Surgery, assisted by **T. Karl Byrne, M.D.**, Professor of Surgery, performed the laparoscopic surgery. Pullatt and Byrne are thought to be the only bariatric surgeons in South Carolina who perform this complicated procedure. Their patient was a woman who weighed more than 400 pounds and had a body mass index (BMI) of 65 kg/m^2. Four weeks after the surgery, she had lost 35 pounds. Pullatt's goal for her is a BMI of 40 kg/m^2.

Society places a huge amount of blame on the super-obese (BMI ≥ 50 kg/m^2), says Pullatt. "So I'm passionate about giving them a chance to regain control of their bodies. We know that 95% of patients will fail a diet. This surgery is the only solution that works long term." A 2006 study showed that for 350 super-obese patients, DS achieved successful weight loss (defined as Estimated Body Weight Loss >50%) in 84.2% of the patients after three years compared with gastric bypass (59.3% after three years). [1]

Bariatric surgery causes weight loss in one of three ways: by restriction (reducing the size of the stomach to limit food intake), malabsorption (bypassing a portion of the small intestine to limit absorption of calories and nutrients), or a combination of the two. In 2010, the most common bariatric surgical procedures were some form of gastric bypass (54.68%), some form of gastric banding (39.62%), and sleeve gastrectomy (2.29%). BPD/DS represented less than 1% of bariatric surgeries (.89%)[2] as it still does today, yet it is recognized as the most sustainable weight loss surgery because it bypasses more of the small intestine, allowing for more malabsorption.

DS is the combination of vertical sleeve gastrectomy (in which the stomach is stapled, reducing it by as much as 70%) and an intestinal bypass. In the latter, the first part of the small intestine (the duodenum) is divided, the last part of intestine is brought up and connected to the outlet of the newly created stomach, and thus about three-fourths of the small intestine no longer receives the food and calorie stream. DS done laparoscopically is technically difficult because of the potential for the surgeon's disorientation when rerouting the intestine. Furthermore, DS in general is difficult because it is reserved for the super-obese.

Photograph by Sarah Pack

Dietitian Dr. Nina Crowley (left) confers with Dr. Rana Pullatt about their patient's eating habits.

"DS, like all other bariatric procedures," says Byrne, "requires physicians to discuss risks vs. benefits with the patient. Complications with DS are higher, but it may be more beneficial than gastric bypass or sleeve gastrectomy." As is the case with any bariatric surgery, vitamin supplements will be required for the rest of the patient's life, and DS patients need higher doses of fat-soluble vitamins and proteins due to the more aggressive malabsorption resulting from the procedure. Other complications include the potential for bowel obstruction and leakage of the stomach or the new intestinal connections.

References

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2 DeMaria E, et al. *Surgery for Obesity and Related Diseases* 2010;6(4):347-355.

Tina Daigle (left), a clinical unit leader, sees the Magnet culture empowering nurses to drive their practice every day.

Photography by Brennan Wesley

The Highest Acknowledgement

MUSC Health nurses take the top prize in nursing excellence with Magnet® recognition

BY LINDY KEANE CARTER

The MUSC Medical Center has achieved the ultimate credential for high-quality nursing care. In September, the hospital received Magnet Recognition® from the American Nurses Credentialing Center (ANCC), a status held by only 7% of all U.S. hospitals.

"Achieving this designation is about the MUSC Medical Center's continual process to improve patient care," says **Marilyn Schaffner**, **Ph.D.**, **RN**, Chief Nursing Officer. "But it's also about recognizing and celebrating the excellent nurses at MUSC Health."

"From the very beginning of our Magnet journey, there has been full support from the Board of Trustees, administration, and the entire medical team," states **Patrick J. Cawley**, **M.D.**, **MHM**, **FACHE**, Chief Executive Officer, MUSC Health and Vice President for Health Affairs, MUSC. "What this designation means for our patients is that they will be cared for in an environment that attracts top-rate providers and promotes the most advanced nursing standards."

The Magnet® designation is not an award. It is a performance-driven recognition credential of quality patient care, nursing excellence, and innovations in professional nursing practice. The program's roots go back to the 1980's when the American Academy of Nursing appointed a task force to study the lack of nurses in the face of growing demand. Task force members noticed that certain hospitals attracted and retained excellent nurses while so many other hospitals faced severe shortages. They found strong cultural similarities among these hospitals, regardless of size or location, and isolated the variables that made them attractive to nurses. Those variables (entitled the "Forces of Magnetism") were quality of nursing leadership, quality improvement, autonomy, interdisciplinary relationships, and professional models of care. These are the basis of today's Magnet® program domains: transformational leadership, structural empowerment, exemplary professional practice, empirical quality outcomes, and new knowledge, innovations, and improvements.

Schaffner got the ANCC's phone call on September 14. She was surrounded by almost 100 people, many of whom were the nurses who had been preparing for the Magnet® review for more than ten years. Within seconds, the room erupted in celebration. Eventually, Schaffner was able to hear the highlights being shared by the Chair of ANCC's commission on Magnet® recognition. "She said the reviewers were most impressed by our professional practice model—that is, the core values defined within it—the autonomy of our nurses to participate in decisions about care, and our interprofessional collaboration, among other things," says Schaffner.

In 2002, hospital leadership began investing in the expensive and time-consuming Magnet® journey that requires publications, consultations, educational materials, application and site visit fees, and staff. The price tag is high—six figures in 2015—but research shows that Magnet® hospitals consistently provide the highest quality of care. The Magnet® credential is recognized by consumers as a quality indicator, by physicians and nurses as a measure of work environment, and by *U.S. News & World Report* as a factor in its annual ranking of the nation's best hospitals. Magnet® hospitals have 7.15% fewer

Kelly Curry (left) was a member of the committee that redesigned the nursing governance structure.

patient safety-related incidents, according to a Gallup study, and higher nursing retention. The drive was interrupted by external factors, but in 2011 a significant investment was made with the creation of a position solely dedicated to achieving Magnet®. **Andrea Coyle**, **MSN**, **MHA**, **RN**, was named Nursing Excellence Manager and charged with achieving the credential. Over the next four years, she and collaborators from many disciplines throughout the medical center laid the foundation for meeting the Magnet® application's 69 standards in its five domains. "To even be considered, we first had to outperform the national benchmarks in quality indicators, nurse engagement, and patient satisfaction," says Coyle.

While Schaffner and Coyle mapped out their plan for this complicated journey, they knew one thing had to be heard loud and clear every step of the way: the voice of the bedside nurse. Thus, in 2014 when the committee to redesign nursing's governance structure was being formed, 21 nurses from all levels (direct care and administration) were invited to contribute; 60% of them were bedside nurses. Their committee created a new structure that as of January 2016 gives every one of MUSC Health's 2,700 nurses a voice in how they deliver care to their patients in their units. The new MUSC Health Nursing Shared Governance promotes a culture that supports evidence-based systems and empowers all registered nurses to take ownership of nursing practice, processes, and outcomes.

In this new governance structure, every inpatient unit has a council of three to six elected nurses—and in some cases non-nurses—who participate in one or more of four hospital-wide councils based on Magnet® domains and a fifth that MUSC Health created: Healthy Work Environment. At these hospital-wide meetings, the communication is two-way. The representatives share best practices and solutions that have worked in their units and hear the same from others. They take these, as well as professional practice mandates from the hospital and state, back to the units. Outpatient units will begin participating in the shared governance structure in July.

Nurse autonomy

As a result, silos are dissolving, solutions are spreading, and nurses are seeing that they are empowered to directly change their practice and affect nurse-sensitive clinical indicators. Nurses now independently remove Foley catheters with a standing physician's order, which has lowered urinary tract infection rates. Likewise, nurses in the intermediate-care neurological unit who need to confirm by X-ray that a nasogastric tube has been accurately placed in the stomach now order the X-ray with a standing physician's order. In the past, according to **Tina Daigle**, **BSN**, **RN**, **CNRN**, **SCRN**, **CSRN**, clinical leader for the Neuro Intermediate Unit, "Time would go by while we waited for an order to be placed in Epic from the doctor for an X-ray, then waited for the X-ray to be taken, then waited for the interpretation." Meanwhile, nurses could not administer medications or nutrition. "Thanks to a process improvement project from a nurse in our unit, we can now place a standing order to expedite the X-ray," says Daigle. "It's usually done within 30 minutes. Then we page the doctor to read it. This practice has significantly reduced the time a patient must wait."

Innovation

The culture change includes stressing to all nurses, not just the seasoned, that innovation is important. New hires can expect to be asked to think about process improvement, to advance clinical inquiry, and to pursue professional development. "Now we start new graduates with a project to hardwire into their minds 'You can make a difference,'" says Daigle. It was a new graduate nurse in Daigle's unit who created a paging protocol as her process improvement assignment that has expedited communication in MUSC Health's three hospitals.

Nurses' pages now begin with "FYI", "Standard", or "Stat", followed by the relevant update. Physicians who are unable to respond in a given amount of time understand that the nurse who paged them will move on to another physician for an answer. The result: clarity of priority for the physicians, faster responses, and faster delivery of care.

Evidence-based practice

There has been a transition to implementing evidence-based practice and interdisciplinary collaboration. Nurses in the Surgical Trauma Intensive Care Unit (STICU) worked with physicians, respiratory therapists, and a pharmacist to review the literature and establish a protocol for the best time and way to remove a patient from sedation.

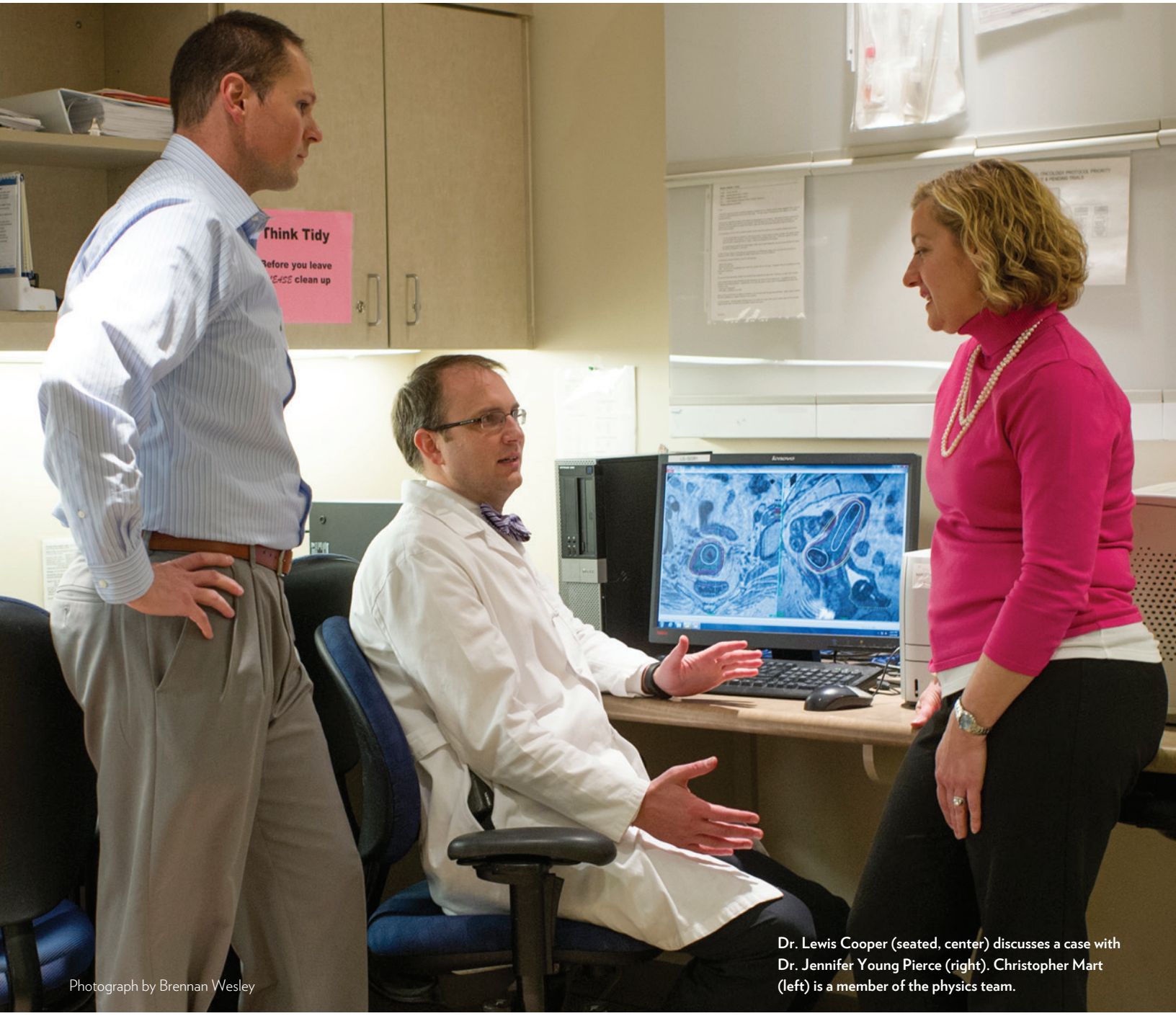
Christopher Hairfield, **BSN**, **RN**, **CMSRN**, a nurse in the Medical/Surgical ICU who chaired the Nurse Alliance (the previous governance council) and co-chaired the Shared Governance Design Committee, says this push to review what has been published and then apply it has changed his practice. "Talk about culture change," he says. "Once, I heard two providers disagree on the best approach for a patient and then heard the nurse say 'What does the literature say?' That's a powerful phrase to hear from nurses." Nurse-led research is supported by the medical center's Center for Evidence-Based Practice and Values Institute, which helps clinicians develop evidence-based guidelines and order sets and analyze best practice evidence for use in decision-making processes, such as time restriction of laboratory orders and integration of IV infusion pumps.

Christopher Hairfield (left) co-chaired the committee that designed the new nursing governance structure.

The road ahead

Nursing leadership is now working toward the next Magnet® milestone: redesignation in four years. The ANCC's standards won't change dramatically, explains Coyle. "But what they expect to see when you go for redesignation is more robust outcomes." Magnet® hospitals must outperform national benchmarks on nurse-sensitive indicators, such as patient falls, incorrect use of restraints, health care–acquired pressure ulcers, central line–associated blood stream infections, and ventilator-acquired pneumonia.

"As health care partners, we serve the community," says Coyle, "so it's our obligation to do so with the highest quality care so our patients have the greatest possible outcomes. I think we owe this to ourselves, but especially to the people we serve."



Photograph by Brennan Wesley

Dr. Lewis Cooper (seated, center) discusses a case with Dr. Jennifer Young Pierce (right). Christopher Mart (left) is a member of the physics team.

Tailor-made

Personalizing internal radiotherapy for locally advanced gynecologic cancers

BY KIMBERLY MCGHEE

A multidisciplinary team of clinicians at MUSC Hollings Cancer Center is offering women with locally advanced cervical cancer and other gynecologic cancers a cutting-edge version of a tried-and-true technique—image-guided, intracavity and interstitial high-dose-rate (HDR) brachytherapy. In 2014 Hollings began offering HDR brachytherapy for gynecologic cancer and in early 2015 joined leading medical centers such as Massachusetts General Hospital, Brigham and Women's Hospital, and UCLA Health in offering image-guided HDR. This state-of-the-art approach enables better ascertainment of tumor size and more precise treatment planning, in essence enabling the brachytherapy treatment to be tailored to fit the individual patient's anatomy. The Hollings team includes radiation oncologist **S. Lewis Cooper, M.D.**, and gynecologic oncologists **Jennifer Young Pierce, M.D., MPH**; **Whitney S. Graybill, M.D.**; and **Matthew F. Kohler, M.D.**, Director of the Division of Gynecologic Oncology.

Brachytherapy, or "internal radiotherapy," is the treatment of choice for women with locally advanced—International Federation of Gynecology and Obstetrics stage IB2 through IVA—cervical cancer because it is the only radiotherapy that delivers a high enough dose of radiation (>80 Gy) to effectively target the tumor with acceptable side effects.[1] It is typically performed after about five weeks of external-beam radiation.

Radiotherapy is often preferred to surgery for these patients because the pelvic bones and nearby blood vessels make it difficult for surgeons to obtain an adequate negative margin (i.e., no cancer cells seen at outer edge of removed tissue). Unlike external-beam radiotherapy, which is typically used not only to shrink the tumor but to eliminate microscopic disease in the surrounding lymph nodes and other tissues, brachytherapy targets the tumor directly with much higher doses of radiation than could be delivered with external-beam radiotherapy.

Hollings is a high-volume center, treating approximately 50 cervical cancer patients of all stages and 20 patients with locally advanced cervical cancer per year—about 25% of the cases in the state. Studies show that women with locally advanced cervical cancer are more likely to receive and complete recommended treatments and live longer when they receive care at high-volume centers (>9.4 locally advanced cervical cancer patients per year).[1] Five-year survival rates are significantly better when they receive brachytherapy from physicians with a high or medium vs. a low caseload.[2]

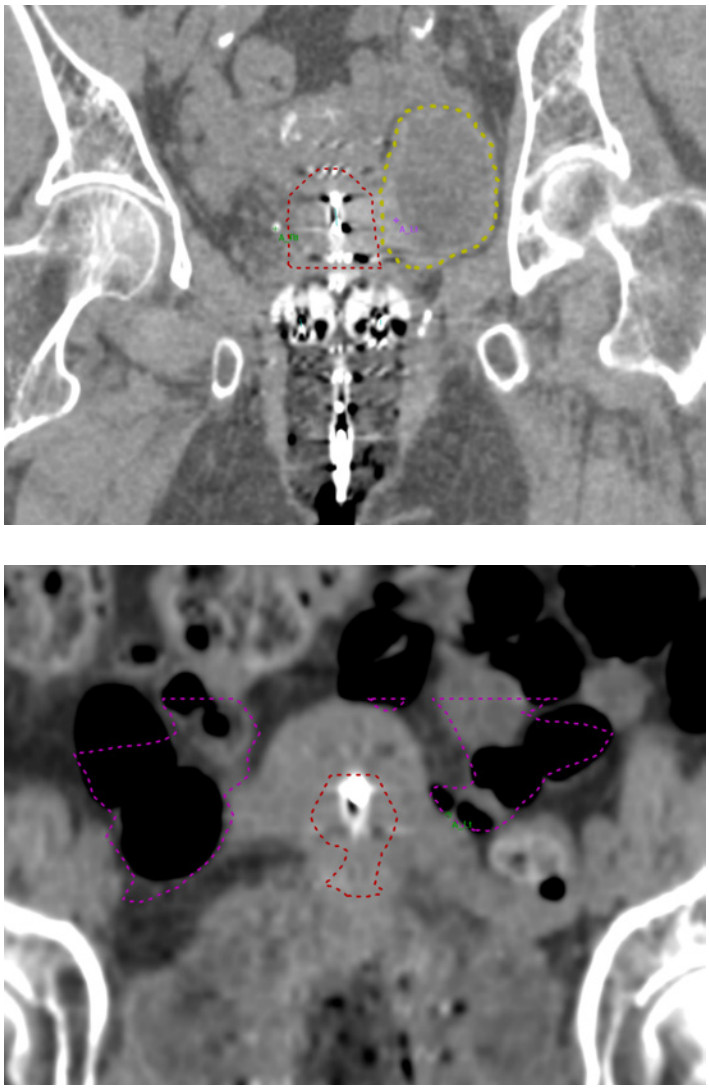


FIGURE 1. Brachytherapy has been traditionally prescribed to point A (top, indicated in green), a standard point 2 cm above and to the side of the ovoids. Prescribing to Point A can overestimate tumor size. For example, Point A is located in the bladder (top, yellow dotted line) and small bowel (bottom, purple dotted line) in these images. The red dotted line is the target volume.

LDR vs. HDR brachytherapy

Although low-dose-rate (LDR) brachytherapy has been standard of care for gynecologic cancers for many decades, HDR brachytherapy is growing in popularity because it has been shown to be as effective as LDR brachytherapy[3] while offering a number of key advantages, including shorter treatment times, reduced radiation exposure for health care workers, and greater convenience and comfort for the patient.

In LDR brachytherapy, applicators and radiation sources remain within the patient for 48-72 hours, during which time the patient must remain confined to a hospital bed, with special precautions taken to protect family members and staff against the radiation implanted in

the patient. In contrast, HDR brachytherapy typically requires four to five treatments over a one- to two-week period, with each visit lasting only a few hours and the treatment session requiring five to fifteen minutes. Applicators can be placed in the patient and removed after one or two treatment sessions, enabling the patient to return home and be with her family until time for the next treatment.

Image-guided HDR

Precision counts, however, when it comes to HDR brachytherapy, because the radiation source used is "hotter" than that used in LDR brachytherapy and so the treatment must be planned with great care to ensure delivery of the correct radiation dose to the intended target.

Traditionally, brachytherapy plans were prescribed to standard points, but doing so could underestimate or overestimate the tumor size (Figure 1). Instead, image-guided brachytherapy prescribes the dose to the actual tumor volume seen on imaging.

FIGURE 2. Axial T2 (left) and coronal T1 (right) slices of magnetic resonance planning images for high-dose-rate brachytherapy are provided for a single patient in each of the panels. The disease volume targeted for treatment is outlined in blue. For all images, the overlaid color wash represents the dose given during treatment, with the red area receiving the prescription dose.

Panel A. Tandem and ovoids for locally advanced cervical cancer. On the axial slice, the tandem is visible centrally in the target volume. On the coronal slice, the tandem can be seen centrally in the uterus with the ovoids placed on either side of the cervical os.

Panel B. Tandem and ovoids plus five needles for locally advanced cervical cancer. The needles are used to extend the dose asymmetrically beyond the central tandem and custom shape the dose distribution to the target volume.

Panel C. Interstitial implant with Syed applicator consisting of a vaginal obturator and 12 surrounding needles in and around the obturator for a uterine cancer vaginal recurrence. The central needles in the obturator provide a symmetric distribution of dose, while the needles in the tissue to the left of the obturator provide channels that are used to extend the dose asymmetrically and custom shape the dose distribution to the target volume.

We place needles and do very tumor-directed radiation so that the shape of the radiation fits the shape of the tumor. —Dr. Jennifer Young Pierce

Combined use of computed tomography (CT) and magnetic resonance imaging (MRI) yields the best results, as CT is useful for visualizing tissues and organs but can overestimate the size of the tumor, whereas MRI is the superior imaging tool for visualizing the tumor itself. In addition, a specialized hover bed, the Zephyr patient transfer system, is used to "hover" the patient between the operating room table as well as the CT and MR without having to lift her. This decreases the risk of applicator displacement and ensures treatment accuracy.

"MRI helps you see the tumor you are treating better so that you can be more confident and treat a smaller area, increase the dose to the tumor, and reduce the dose to surrounding tissues," says Cooper.

Once the parameters of the tumor are known from the MRI, radiation sources can be introduced using special applicators and needles that enable Cooper and other radiation oncologists to "tailor" or "sculpt" the dose of the radiation to match the contours of the tumor (Figure 2).

"We are designing a treatment that is not one size fits all," says Young Pierce. "We place needles and do very tumor-directed radiation so that the shape of the radiation fits the shape of the tumor."

Even women who were once thought to be poor candidates for brachytherapy—such as those who have undergone hysterectomy—can benefit. Many of the traditional brachytherapy applicators (i.e., tandem and ovoids, tandem and ring) are placed in the uterus and so are not good options for women whose uterus has been removed. These women can, however, benefit from interstitial brachytherapy, which uses hollow tubes and needles as applicators. "We can do a complex multi-needle implant in these women," says Cooper. Traditional applicators also do not work for women with bulky disease that extends down the vagina. However, they can still benefit from interstitial brachytherapy—needles are placed alongside the traditional applicators under ultrasound guidance in order to shape the radiation dose to match the tumor while minimizing exposure to surrounding organs.

Studies have shown that good local control can be achieved with image-guided HDR brachytherapy,[4] though distant metastases continue to be a problem. A definitive answer about the efficacy of the technique and its effect on survival awaits the results of the European study on MRI-guided Brachytherapy (EMBRACE, NCT00920920) trial, which has completed accrual and awaits final results.

For more information about the program or to refer a patient, contact gynecologic cancer nurse navigator Angela M. Raney, RN, MSN at 843-792-9877 or raneya@musc.edu.

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1 Lin JF, et al. *Gynecol Oncol.* 2014 Feb;132(2):416-422.
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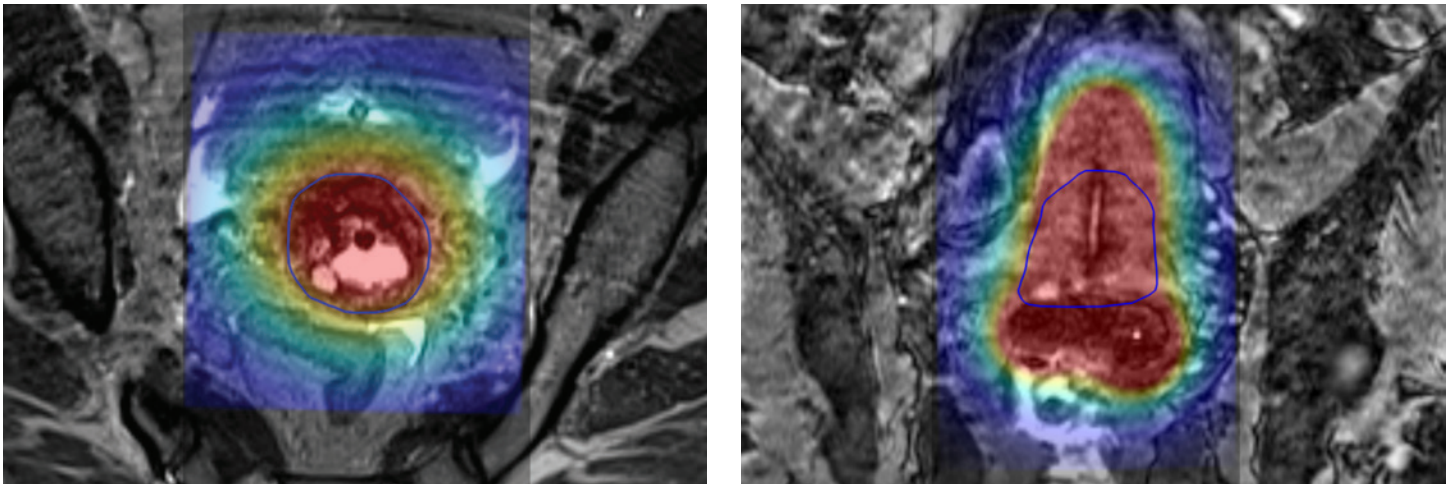
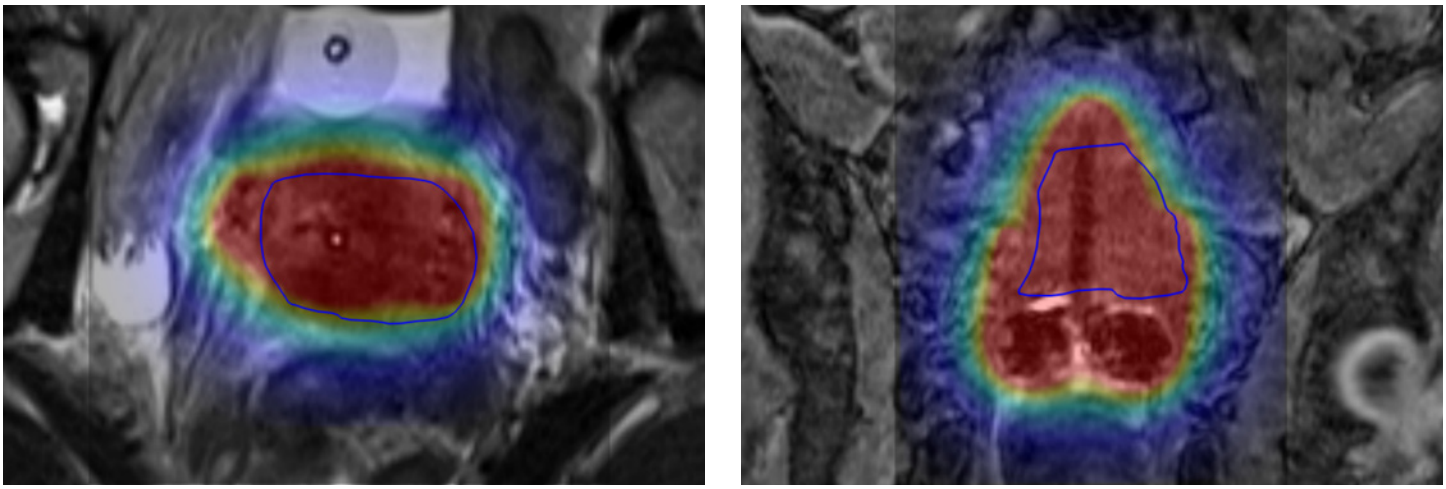
5 Tinkle CL, et al. *Int J Radiat Oncol Biol Phys.* 2015 Aug 1;92(5):1093-1100.

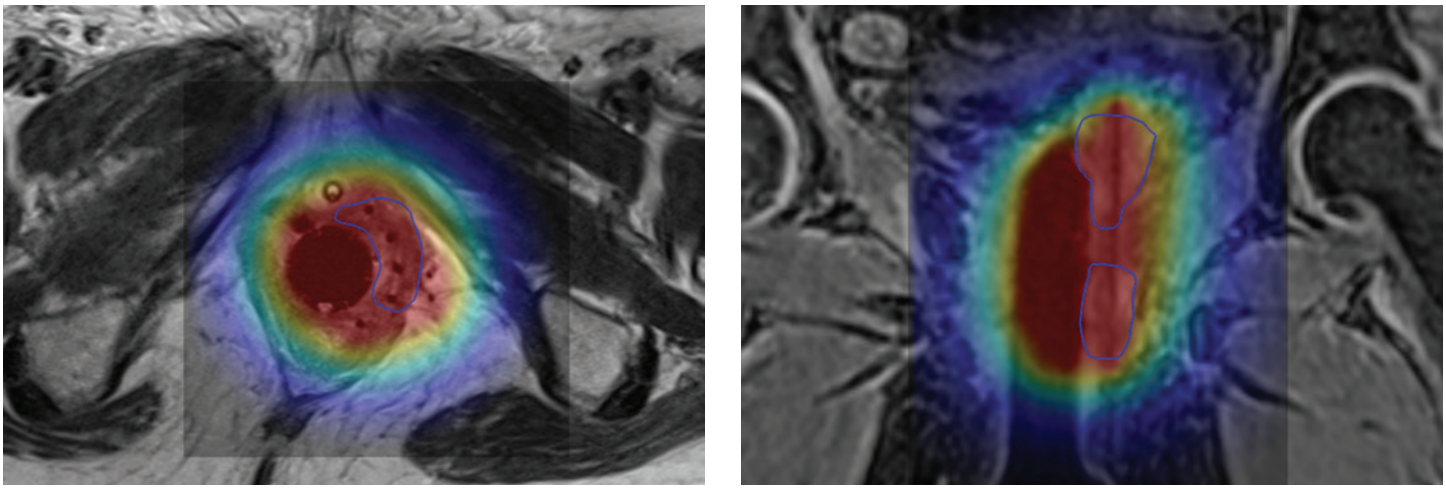
FIGURE 2. Magnetic Resonance Planning Images for High-Dose-Rate Brachytherapy



Panel A



Panel B



Panel C

OR NOTES

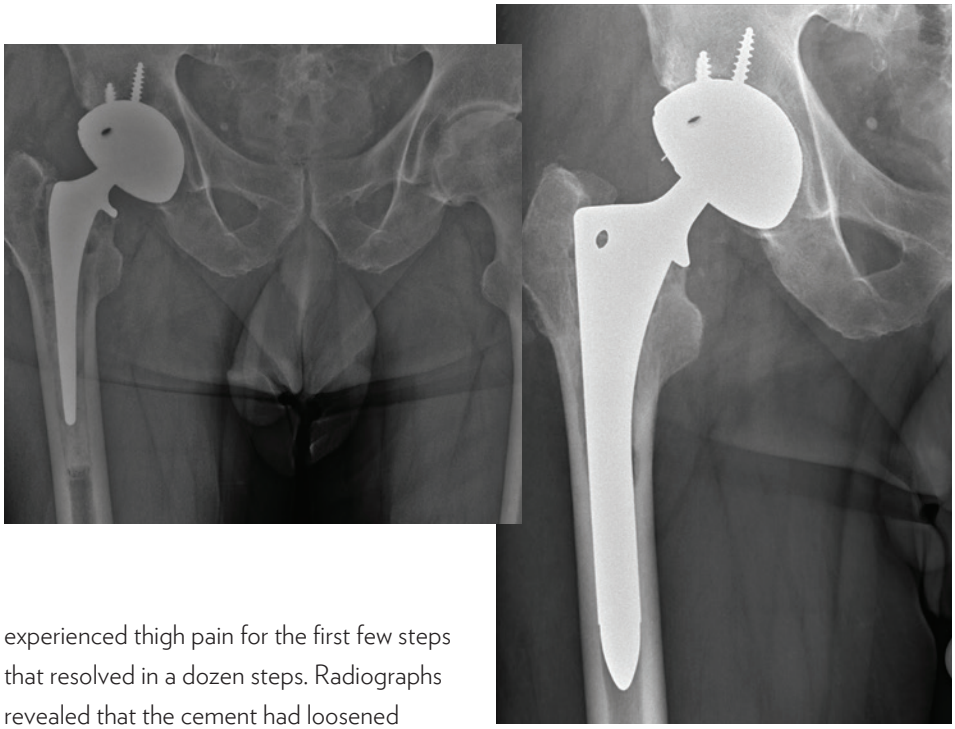
This article introduces a new blog—*OR Notes*—that will give readers a front row seat to complex surgeries. Open the folds to reveal surgical photographs highlighting key moments in a revision hip replacement. Then join us for a virtual grand rounds on the same topic on the free Figure 1 app at 8:00 pm on April 26.

Revision Hip Replacement

BY KIMBERLY MCGHEE

Dr. Vincent Pellegrini, Chair of the Department of Orthopaedics, specializes in revision joint replacements.

Photography by Brennan Wesley



Preoperative radiograph (left) shows a cemented femoral stem and cementless acetabular component, with evidence of demarcation at the bone-cement interface of the stem and an incomplete radiolucent line with evidence of osteolysis in zones 1, 5, and 7. This radiographic appearance is consistent with aseptic loosening of the femoral stem as well as the patient's symptoms.

Postoperative radiograph (right) shows that the cementless femoral stem fits tightly into the medullary canal with precision machining of the femur along the distal aspect of the stem.

Of the approximately 350,000 hip replacements performed each year in the U.S., about 10% will eventually require revision surgery—typically, 15-20 years after the original surgery—due to infection, wear, instability, or component loosening. Because revision hip replacements are more challenging and typically performed in an older population, they are best done at high-volume centers with robust critical care and advanced anesthesia services. At such centers, revision hip replacements are now commonly performed in patients older than 80 years of age, enhancing their mobility and enabling them to preserve an active lifestyle.

Vincent D. Pellegrini, **M.D.**, Chair of the Department of Orthopaedics at MUSC Health, and the other surgeons on the joint replacement team—**Harry A. Demos**, **M.D.**, **Jacob M. Drew**, **M.D.**, and **Richard J. Friedman**, **M.D.**—perform more than 650 hip and knee replacements annually, more than a quarter of which are revisions. In 2014, the program was awarded Joint Commission specialty certification for total hip, knee, and shoulder joint replacement.

Report of a Case

An 80-year-old man, who had undergone primary cemented hip replacement 16 years previously, presented with "start-up" thigh pain. Each time he stood or initiated gait, he experienced thigh pain for the first few steps that resolved in a dozen steps. Radiographs revealed that the cement had loosened from the femur, resulting in the cycle of pain that repeated every time the patient stood up and the femoral stem sank to a stable position in the bone. The cement loosened due to bone loss, resulting from a foreign body reaction to microscopic particles that were generated as the plastic liner of the replacement wore.

Revision hip replacement was advised and involved removal of the femoral component, the associated cement, and the plastic liner, with implantation of a new plastic liner and a cementless femoral component. Bone from which cement has been extracted tends to be smooth and does not provide reliable fixation for new cement; for this reason, cementless femoral stems, which have a roughened surface texture to which bone can attach, are preferred for hip revision surgery.

Often in hip revision surgery, the greater trochanter and the attached muscles must be cut to allow access to the femoral canal for cement removal. In this case, an anterolateral approach provided good femoral access without the need for trochanteric osteotomy and the patient was able to begin exercise immediately after surgery. He will use a walker or cane for only three to four weeks, much less than would have been required after trochanteric osteotomy.

A pathologist was on hand to analyze tissue samples for infection. Had infection been detected, all components would have been removed, the patient would have received several weeks of intravenous antibiotics, and a second surgery would have been scheduled to implant the new components.

Want to learn more about this case? Ask Dr. Pellegrini questions in real time during his virtual grand rounds (a live event) on April 26 at 8:00 pm on the free Figure 1 app (iOS and Android).

To consult with an MUSC Health joint replacement surgeon or to refer a patient, contact nurse navigator Kathleen Case at casek@musc.edu.

Follow more surgical cases on the *OR Notes* blog (http://www.muschealth.org/or-notes) and on the MUSC Health profile (@MUSChealth) on the free Figure 1 app (iOS and Android).

Click here to skip graphic content

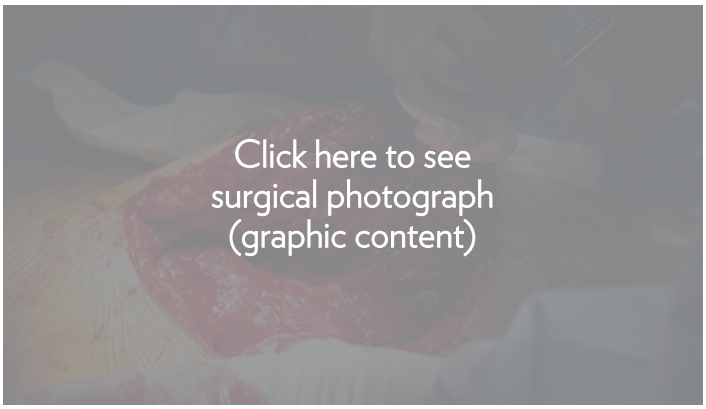


FIGURE 1. The patient is supine and the hip joint is accessed through a Watson-Jones approach, anterior to the gluteal abductor muscle mass, which contained repair sutures from the previous transgluteal exposure and a large bursal sac in the region of the repair.

FIGURE 2. After a radical anterior capsulectomy and complete circumferential posterior capsulotomy, the leg is placed in the figure 4 position to expose the femur. The femoral stem was grossly loose and rotationally unstable to light pressure with the suction tip.

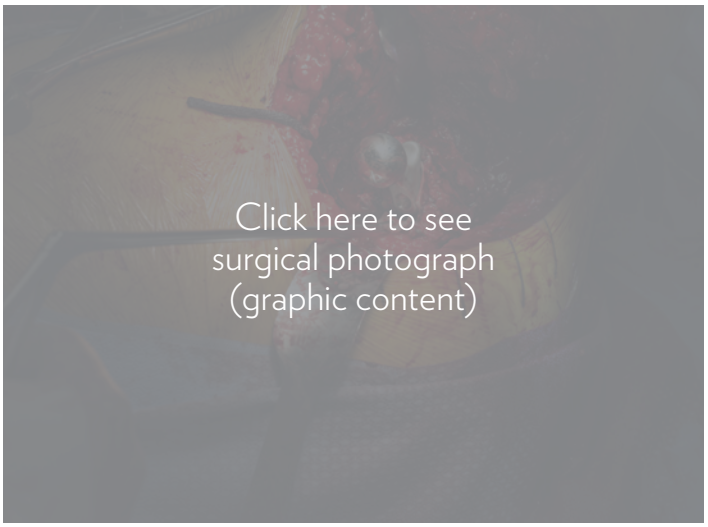


FIGURE 3. Safe extraction of a cemented stem, even when grossly loose, requires initial removal of the cement mantle at the lateral shoulder of the implant so that the greater trochanter is not fractured when the stem is backed out of the canal. This cement fragment is sectioned and deliberately removed prior to extraction of the stem.

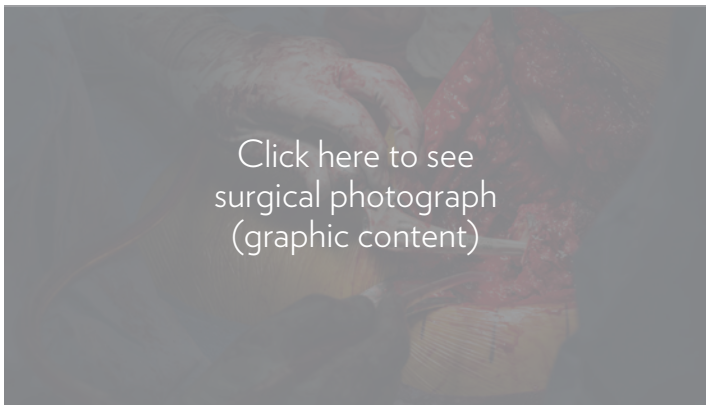


FIGURE 4. The stem is then easily and safely backed out of the canal.

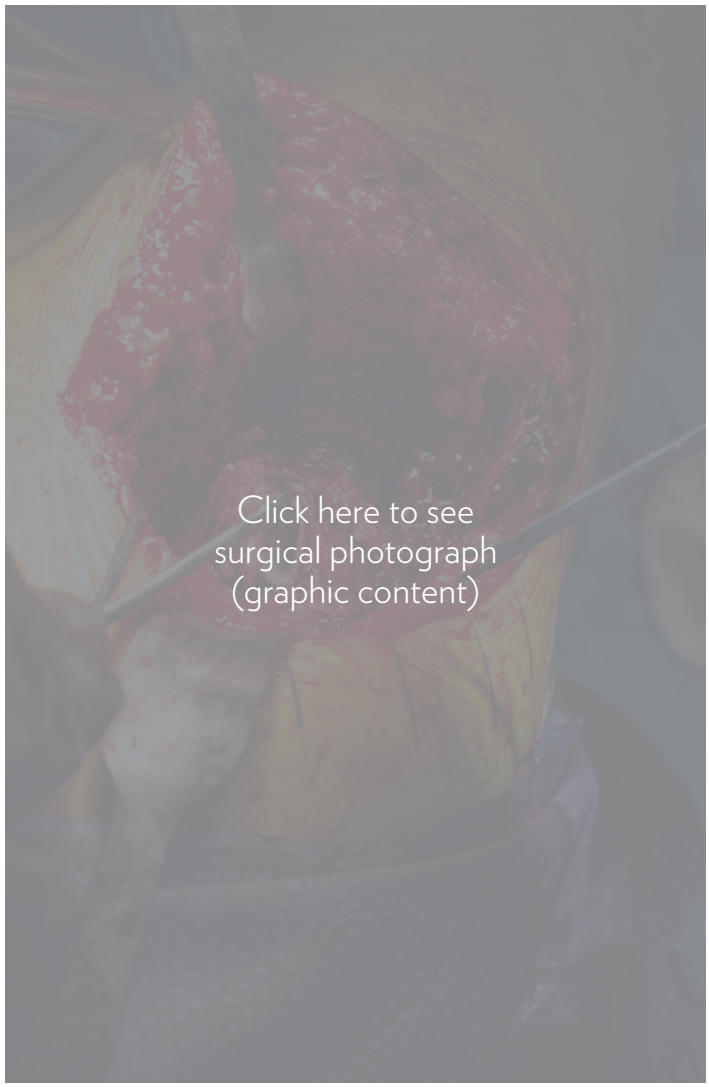


FIGURE 5. This leaves the remaining "empty" cement mantle attached to the inner surface of the femur. Long pituitary rongeurs, assorted straight and offset chisels, reverse hooks and curettes, and sharp narrow drills are essential instruments to facilitate the process of cement removal from deep within the canal.

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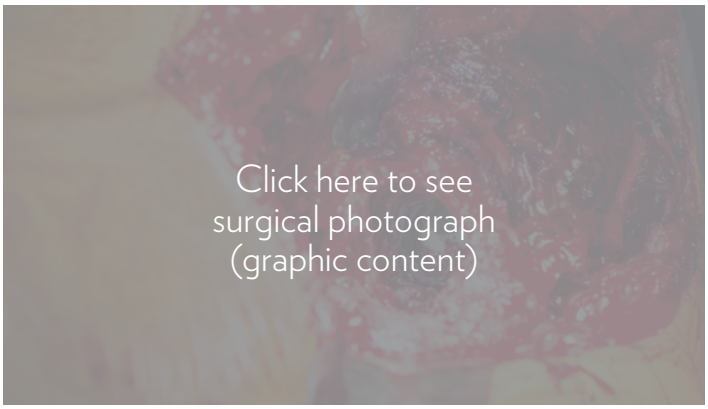


FIGURE 6. Cement is circumferentially removed in 2-3 cm segments from the inner side walls of the femur until the distal cement plug is reached and clearly visualized (direct line of sight). Once visualized, the cement plug is carefully drilled and extracted with a threaded tap.

FIGURE 7. The plastic liner of the acetabulum is removed and demonstrates wear along the superior aspect, which leaves a gap along the inferior margin of the femoral head, where debris can enter the interface between metal and plastic. The plastic liner is replaced.

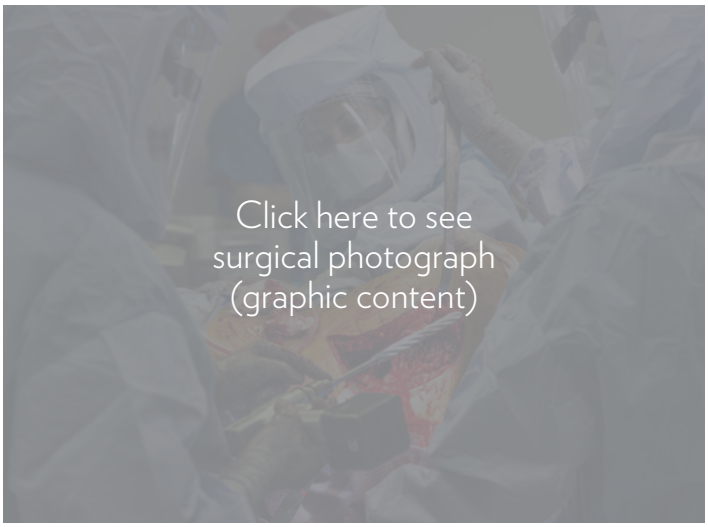


FIGURE 8. Alternating use of power reamers and hand broaches allows precise machining of the femoral canal to accept the new stem.

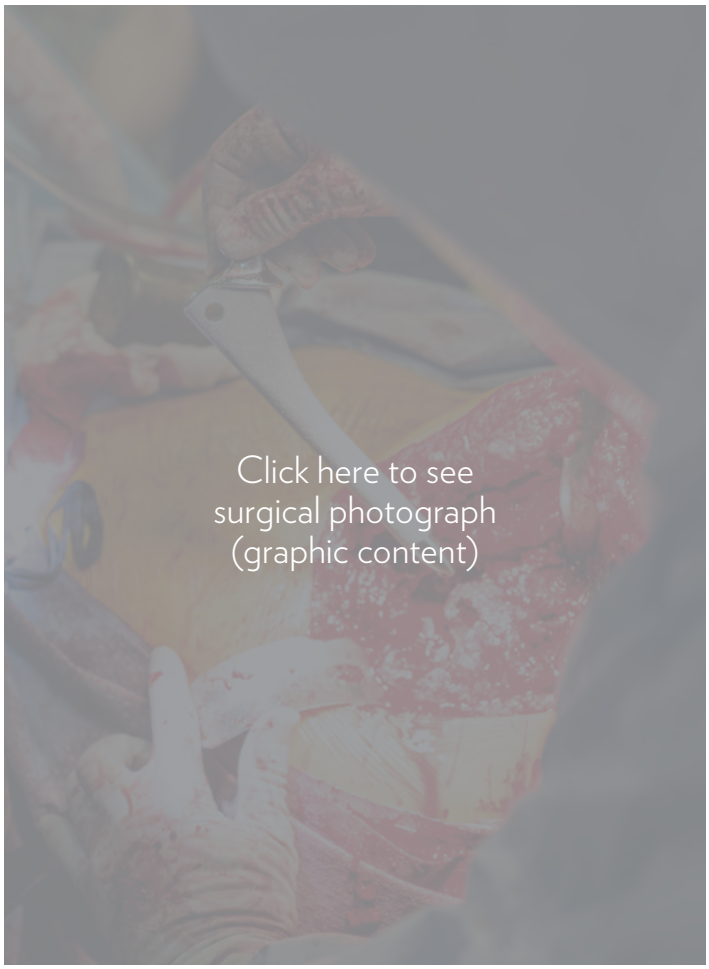


FIGURE 9. The final femoral stem has a roughened surface to encourage bone ingrowth for biologic fixation.

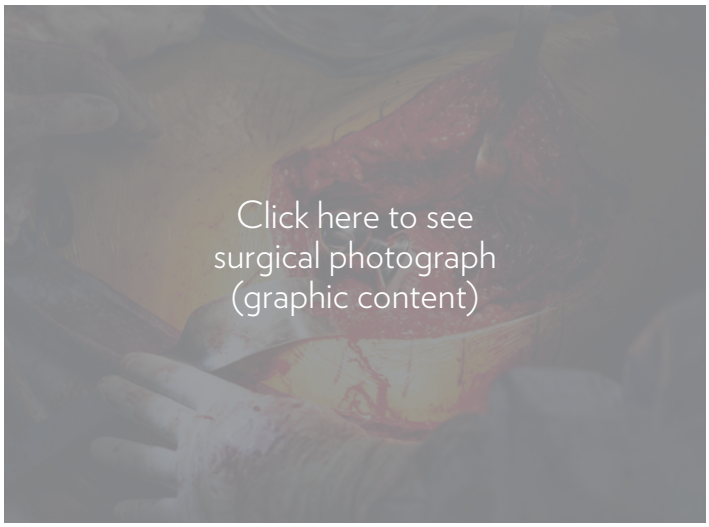
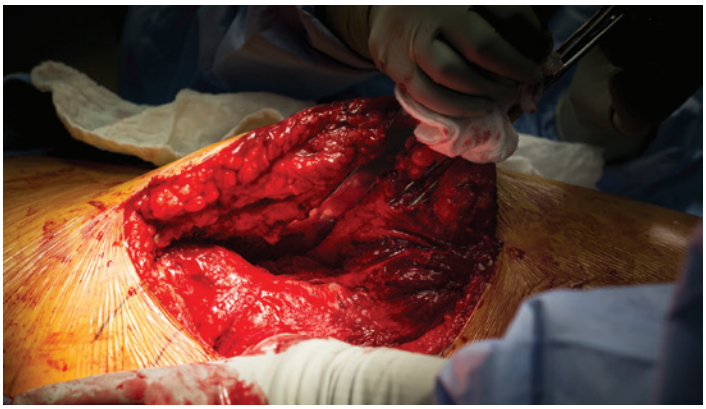


FIGURE 10. The stem is inserted into the canal with 75-100 short, firm blows. Rigid initial fixation is obtained because a stem size is selected that is 1 mm larger than the diameter of the last reamer.



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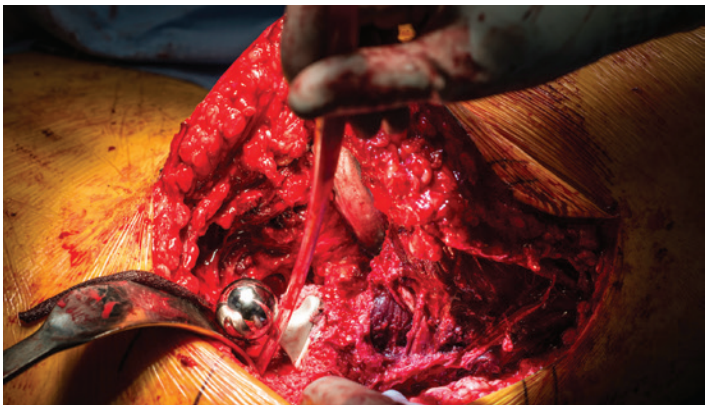

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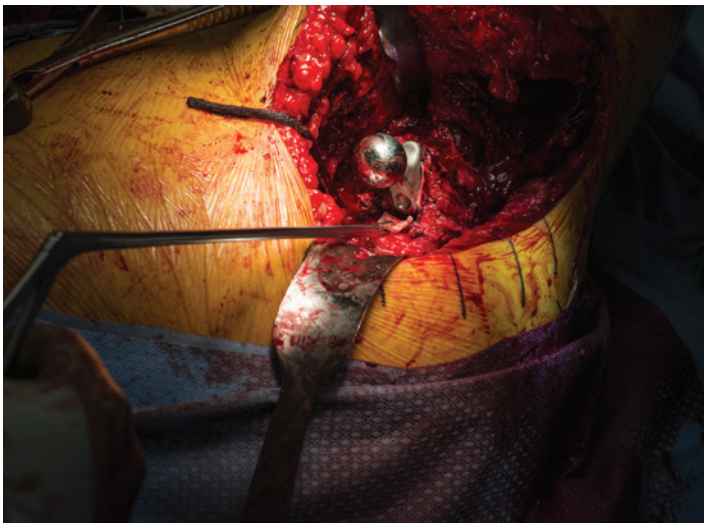

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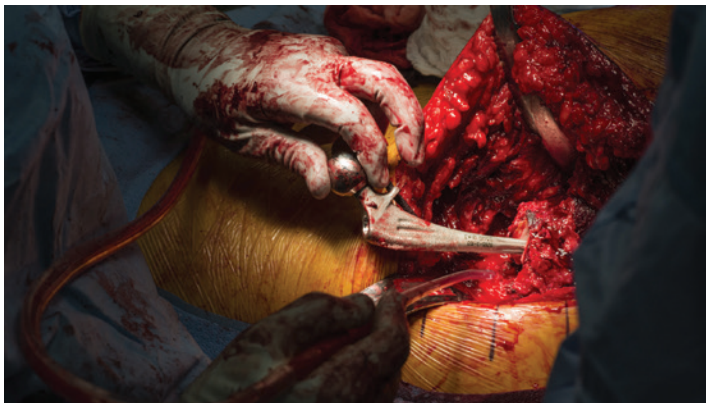

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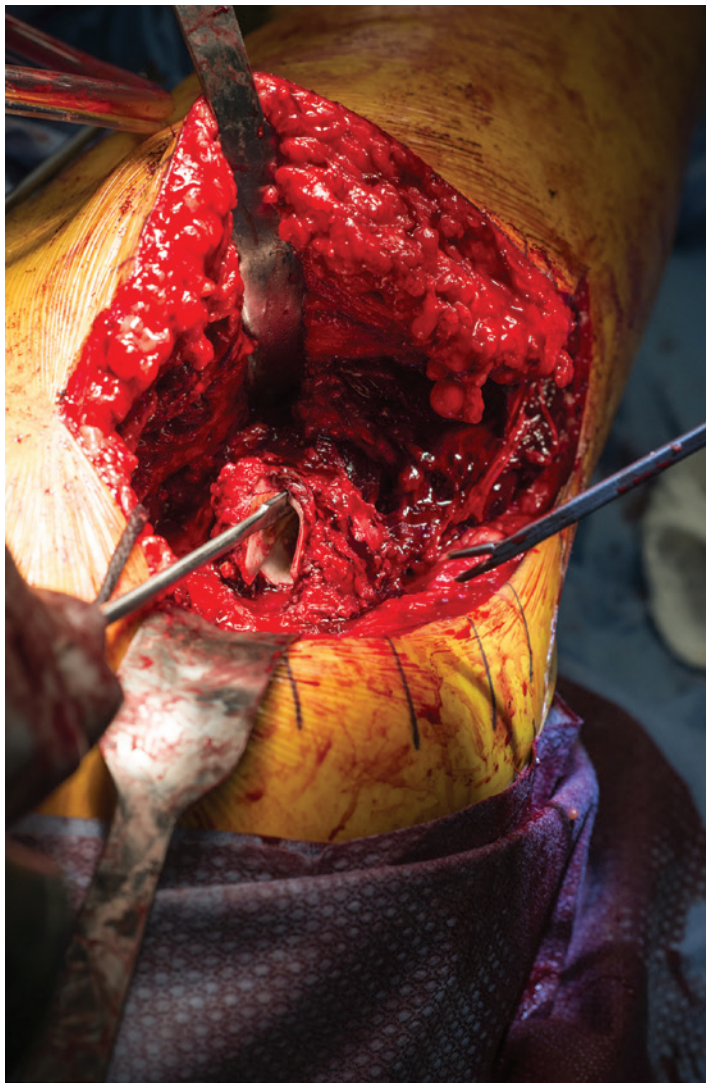

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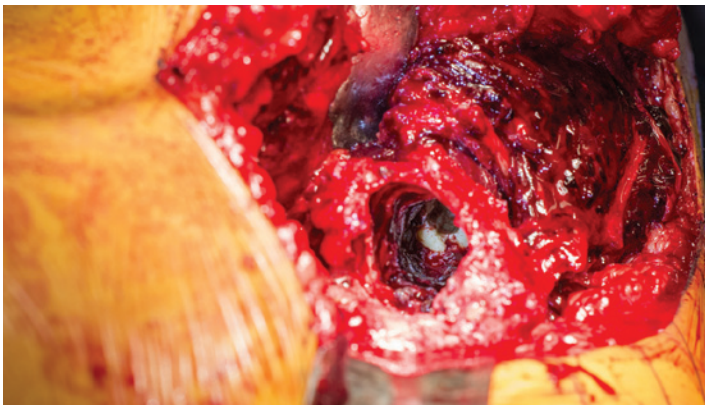

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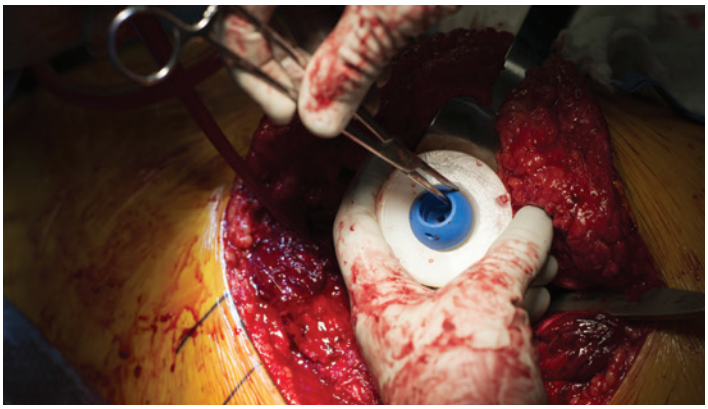

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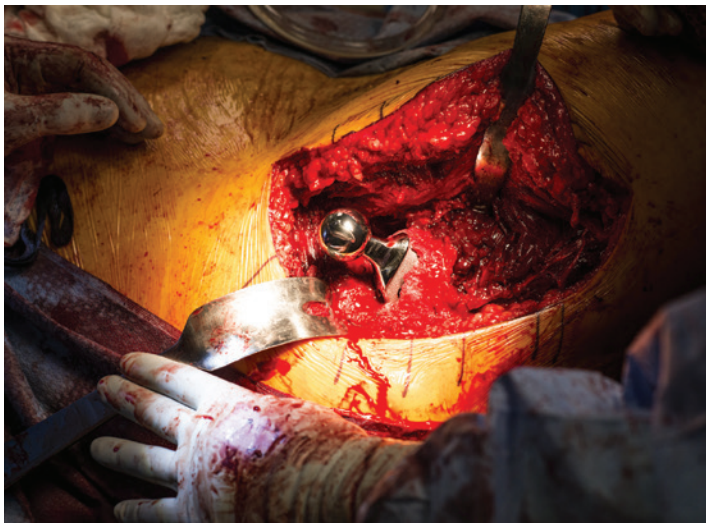

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The Better to Hear You

Otolaryngologists offer innovative therapies to improve hearing

BY LINDY KEANE CARTER

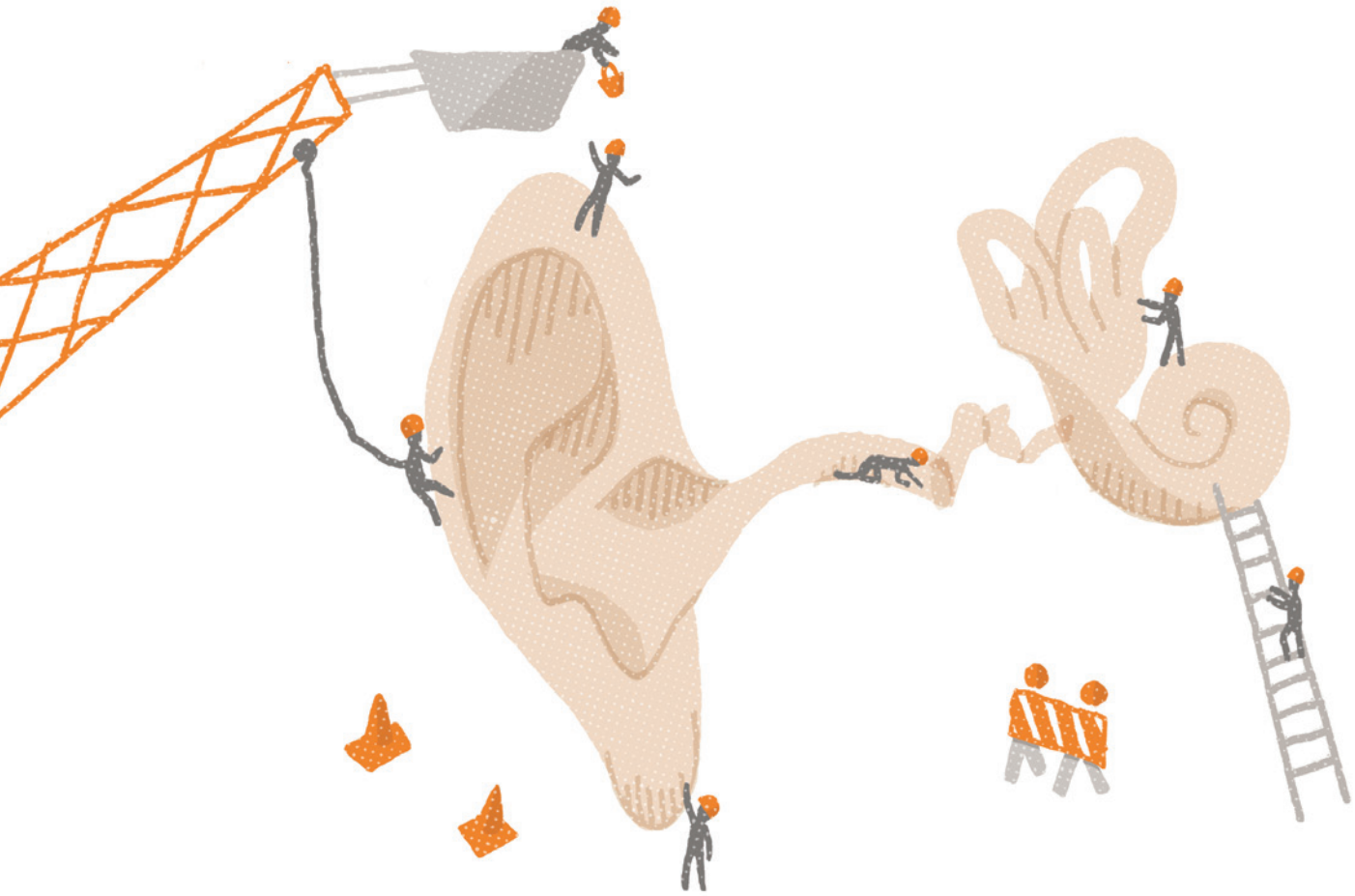

Illustration by Kristmar Muldrow

Approximately 15% of American adults ages 18 and over report some trouble hearing, according to the National Center for Health Statistics. Hearing loss has many causes—aging or noise-damaged nerves, problems with the ear bones, fluid in the ear space itself, for example—and many therapies, the most well-known being hearing aids and cochlear implants. MUSC Health otolaryngologists implant almost 150 adults and children with cochlear devices per year, says **Paul R. Lambert**, **M.D.**, Chair of the Department of Otolaryngology–Head & Neck Surgery, making MUSC Health one of the highest-volume cochlear implant centers in the southeast.

Less well-known, perhaps, are the updated devices and approaches that technological advancements have made possible. "We have so many more ways to restore hearing today compared to even five years ago," says Lambert. Four fellowship-trained surgeons at MUSC Health are making these innovative therapies available to patients in the clinic and through clinical trials. These specialists include Lambert, **Ted A. Meyer**, **M.D.**, **Ph.D**., Associate Professor of Otolaryngology and Director of the Cochlear Implant Center; **Theodore R. McRackan**, **M.D.**, Assistant Professor of Otolaryngology; and **Habib Rizk**, **M.D.**, **MSc**, Assistant Professor of Otolaryngology.

For example, for patients who have severe hearing loss in one ear, bone conduction implants (osteointegrated processing devices) are an effective option. The device is placed in the bone behind the deaf ear where it picks up sound and transmits it through the skull to the working ear. For the vast majority of patients, this device enhances hearing and thus safety and communication.

When damaged bones of the inner ear (the hammer, the anvil, or the stirrup) are the culprit, the implantation of titanium prostheses can achieve partial hearing restoration. This technology and procedure has existed for about ten years, but some patients' anatomical features have presented placement challenges to the surgeon. Lambert is working with a prosthesis manufacturer to develop new ways to use current implants and design new implants. The findings of one comparative study led by Lambert reported a novel use of total titanium prostheses in the journal *Otology Neurotology* (December 2015).

MUSC Health, one of the few academic medical centers in the country conducting clinical trials in Otolaryngology, is at the forefront of investigating new drugs and devices. Trials that are enrolling patients include:

- Phase 3 trial for tinnitus. The gel being studied in this trial (AM-101, Auris Medical, Inc., Chicago, IL) has the potential to be the first drug to gain approval treating acute inner ear tinnitus. It is administered in one treatment cycle, comprising three intratympanic injections into the middle ear over three to five days. The study started in 2013 and is ongoing with more than 300 patients enrolled worldwide.
- Phase 2 trial for Eustachian tube dysfunction (ETD). Dilation of the Eustachian tube is being studied for patients who have the symptoms of ETD, i.e., the feeling of blockage in the ear, earaches, and clicking, popping, or distorted sound. This study assesses the safety and efficacy of the ExprESS device (a balloon dilator developed by Entellus Medical, Inc., Plymouth, MN). MUSC Health is one of three sites in the nation that offer this procedure. The study began in 2015 and will end in the last quarter of 2016.
- Phase 3 trial of a steroid-containing thermosensitive gel (OTO-104, Otonomy, San Diego, CA) for Ménière's disease opened in February 2016. Initial findings of the phase 2b study were reported by Lambert in 2015 at a professional meeting in Rome, Italy. (For more information, see "Groundbreaking Clinical Trials" in the *Year in Review 2015* at www.muschealth.org/pn/yir-2015/index.html.)

For clinical trial enrollment information, contact clinical research coordinator Jack Muus at muus@musc.edu.

"I am incredibly proud of our physicians who are not only busy clinicians and surgeons who provide exceptional patient care, but also strive to advance the field through innovation and research. We have a wonderful history of collaboration with otolaryngologists in South Carolina and beyond and we look forward to advancing scientific discovery together in the future," says Lambert.

Charleston Alcohol Research Center TURNS 21

BY SVER AUNE

Photography by Sarah Pack.

Dr. Howard Becker, Director of the Charleston Alcohol Research Center

The Charleston Alcohol Research Center (ARC) at MUSC has received notification from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health (NIH) that it will receive funding ($7 million) for another five-year period beginning January 2016. The Charleston ARC, which is housed in the Addiction Sciences Division of the Department of Psychiatry and Behavioral Sciences at MUSC, has continually sustained this NIH support as a Center of Excellence for 21 years (since 1995). The renewed funding will sustain support for this important research for years 21-25.

The Charleston ARC, one of only a few NIH/NIAAA-funded "specialized" alcohol research centers, boasts a uniquely strong relationship between basic scientists and clinicians that places it at the leading edge among alcohol research facilities. The ARC combines basic research and clinical investigation in a comprehensive program that informs a robust outpatient treatment program—all under one roof. **Howard C. Becker**, **Ph.D.**, Professor in the MUSC Department of Psychiatry and Behavioral Sciences and Director of the Charleston ARC, praises this arrangement as highly advantageous to discovering new and better treatments for alcohol use disorders.

"I can't tell you how many times we meet around the coffee pot and discuss issues facing our patients, and then discuss how to bring that down to the laboratory level," says Becker. "Bringing everyone together and focusing on a common research problem from all these different perspectives really elevates the science we do at the ARC."

That common research problem is a serious one—more than half of all adults in the U.S. have a family history of alcoholism or problem

drinking. The economic, medical, and health care burden, not to mention personal tragedy, of alcohol use disorders in our society is enormous. Yet, while the negative health consequences of alcoholism are as familiar to us as those from hypertension or diabetes, less than 10% of people with alcohol dependency undergo treatment for the disorder. The mission of the ARC—to discover how alcohol affects health, with an emphasis on pharmacological intervention—relies on changing that statistic. It's a matter of changing perception about alcohol abuse. "The main thing the ARC allows us to do is bring information to medical professionals and the public that this is a brain disease, not an individual personal weakness," says Becker.

The renewed NIAAA funding provides support to continue basic and clinical research efforts that focus on complementary aspects of how alcohol alters normal functioning of the brain and how those changes in turn lead to heavy uncontrolled drinking and alcohol dependence. The basic research teams develop preclinical models to determine which brain regions and circuits change when exposed to alcohol and how those changes influence motivation to drink. The clinical research teams use neuroimaging (e.g., magnetic resonance imaging) approaches to see changes in the human brain. Working in a coordinated fashion, both groups use these results to learn which medications they should test that might best halt or reverse those changes.

As leaders in the field, ARC researchers are discovering how heavy alcohol drinking results in specific changes in the brain. Over time, the striatum, an inner region of the brain responsible for motivation and the pleasure response, becomes sensitized and highly reactive to visual and olfactory cues of alcohol. At the same time, long-term heavy alcohol use compromises the function of sub-regions of the cerebral cortex, reducing a person's ability to make responsible decisions about drinking. In particular, alcohol abuse can result in adaptations in the striatum and parts of the frontal cortex that increase impulsivity, enhance craving and vulnerability to relapse, and promote excessive and compulsive drinking. Changes in these regions and in the circuits connecting them appear to drive the transition from drinking for pleasure to drinking out of habit.

Understanding how changes in the brain underlie this transition from moderate, controlled drinking to uncontrolled, compulsive drinking is a major research focus within the ARC. For example, work in the research laboratories of ARC basic researchers **John J. Woodward**, **Ph.D.**, and **L. Judson Chandler**, **Ph.D.**, have shown that heavy alcohol exposure alters activity of brain cells and specific circuits in the cortex that are critical for executive (decision-making) function. Another project, led by **Raymond F. Anton**, **M.D.**, is testing whether people with a specific genetic makeup are more or less likely to respond to a medication that enhances behavioral control over drinking. The Center has also recruited a new clinical investigator to study a novel and exciting potential treatment option. Specifically, **Colleen A. Hanlon**, **Ph.D.**, is testing whether a new technique called transcranial magnetic stimulation (TMS)—a noninvasive tool to excite precise brain regions—can rescue "normal" communication between the cortex and striatum, thereby blunting brain activation to alcohol cues and strengthening behavioral control over drinking in alcohol-dependent study patients.

CAPTION: Dr. Colleen Hanlon (left) demonstrating transcranial magnetic stimulation.

Becker hopes that teasing apart the circuitry underlying drinking for pleasure and drinking out of habit will enable ARC researchers to develop pharmacotherapies and nonpharmacological approaches that may more effectively treat alcohol dependence. The five-year plan is to have a much better picture of which medications and therapies work in people with differing genetic and environmental backgrounds.

All of the effort within the ARC is helping define alcoholism as a true brain disease. "The more we learn about the neuroscience of alcohol addiction, the more we legitimize the fact that this is a medical problem that needs to be addressed and treated," says Becker.

Charleston ARC researchers collaborate with departments across MUSC and in the local and national community. To enhance the mission of the Center, encourage collaboration, and draw other investigators into the alcohol field, the ARC offers pilot funding to MUSC researchers and clinicians with pertinent questions about alcohol use disorders. Visit MUSC.edu/arc to learn more about alcohol use problems or for information about ARC research projects, collaborations, and community outreach activities.

Illustration by Steven Foley. Licensed from iStock.

Self Under Siege:

The Diagnosis and Management of Autoimmune Disease

BY MELISSA A. CUNNINGHAM, M.D., PH.D., PAULA S. RAMOS, PH.D.,
ERIC S. ZOLLARS, M.D., PH.D., AND KIMBERLY MCGHEE

Upon completion of this article, readers should be able to:

- *Recognize that systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) are appropriately diagnosed based on clinical signs and symptoms together with laboratory findings, but not on the basis of laboratory findings alone.*
- *Summarize why corticosteroid therapy is not advised long-term in SLE patients and should be avoided if possible in SSc patients.*
- *Explain the importance of early diagnosis/intervention and routine screening for cardiopulmonary and renal disease in SSc patients.*

Autoimmune diseases (ADs) are a family of more than 80 chronic, and often disabling, illnesses characterized by dysfunction of the immune system, activation of autoreactive lymphocytes, and development of immune responses to many self-antigens. The increased levels of autoantibodies can lead to chronic inflammation and organ damage. Patients often endure lifelong debilitating symptoms.

Most ADs exhibit sex and ethnic disparities. Nine out of ten people with systemic lupus erythematosus (SLE) are women, and people of African, Asian, and Native American ancestry are at higher risk for the disease than those of European descent. Those of African ancestry are also at greater risk for systemic sclerosis (SSc, scleroderma) and often develop SLE and SSc earlier in life and experience more severe disease than those of European descent.[1]

Sex Bias in Autoimmune Disease

Why are some ADs and female sex so closely entwined? Sex chromosomes and sex hormones are each thought to play a role.[2] The role of the X chromosome in SLE is supported by evidence showing that men with Klinefelter syndrome, who have at least one additional X chromosome (XXY), are much (14- to 18-fold) more likely to develop SLE than controls.[3,4] But the etiology of SLE cannot be explained by a surfeit of X chromosome alone. Women

Lupus, more formally known as systemic lupus erythematosus, is considered a prototypic autoimmune disease. It is thought to derive its name from the Latin word for wolf (*lupus*) because the characteristic facial rash was thought to be reminiscent of a wolf bite or distinctive markings on the faces of wolves.

of child-bearing age (ages 15-45) are nine times more likely than men to develop SLE, whereas premenopausal or postmenopausal women are only three times as likely to develop the disease, pointing to a role for sex hormones, especially estrogen.[2] SLE patients have higher serum levels of estrogen metabolites, suggesting dysfunctional estrogen metabolism, and lower levels of androgens. Administering estrogen to lupus-prone male or female mice worsens disease, whereas administering androgen slows disease progression.[5]

Although less likely to develop the disease, men and children with SLE are more likely to develop severe disease with organ damage and central nervous system involvement. "Estrogen receptor variants, estrogen, and other hormones may play a role in disease pathogenesis, but they may also be protective to some degree once you have the disease," says MUSC Health rheumatologist and SLE investigator **Melissa A. Cunningham, M.D., Ph.D.**

Genetic Etiology of Autoimmune Disease

Multiple lines of evidence suggest some degree of common genetic etiology in ADs, including clustering of multiple ADs in families and in individuals, and the number of confirmed genetic regions predisposing to several ADs. This genetic overlap is exemplified by the well-known associations of the Human Leukocyte Antigen (HLA) region with all ADs, as well as other loci associated with multiple ADs, such as *IL23R, TNFAIP3*, and *IL2RA*.[6] A recent review summarizes the ADs with published genome-wide association studies (GWAS) and the number of disease-associated loci uncovered from these GWAS.[7] It is the general consensus that there is a common genetic background predisposing to autoimmunity, and that further combinations of more disease-specific variations at HLA and non-HLA genes, in interaction with epigenetic (e.g., DNA methylation, histone modifications, non-coding RNA) and environmental factors, contribute to disease and its clinical manifestations.

Systemic Lupus Erythematosus

SLE is a chronic AD that can damage any part of the body, including the skin, joints, and organs. Repeated flares and remissions are common, with organ damage accumulating with each flare. About 80% of SLE patients develop arthritis, and 60% develop renal disease. In many SLE patients, autoantibodies attack the hematologic system, leading to thrombocytopenia, leukopenia, and anemia.

Date of Release:
April 1, 2016
Date of Expiration:
April 1, 2018

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Melissa A. Cunningham, M.D., Ph.D., Paula S. Ramos, Ph.D., Eric S. Zollars, M.D., Ph.D., and Kimberly McGhee have no relevant financial relationships to disclose.

Screening and diagnosis

It is vital that patients with suspected SLE who show signs of organ involvement be seen promptly by a rheumatologist; however, wait times for appointments can be long because of referrals based mainly on laboratory testing and generalized complaints of pain. A recent retrospective study showed that 90% of patients referred for a rheumatology consult based largely on a positive antinuclear antibody (ANA) test did not have an ANA-associated AD. The poor predictive value of ANA testing observed in this study was attributed to the fact that most tested patients had a low pre-test probability for ANA-associated rheumatic disease.[8]

Joint pain is indeed a symptom of SLE, but it is also associated with many other diagnoses, including osteoarthritis and rheumatoid arthritis. SLE most commonly occurs in women of child-bearing age

(15-45 years), especially women of African, Asian, or Native American ancestry, and thus clinical suspicion for SLE should be much lower in a 65-year-old woman with knee pain than, for example, a 25-year-old African American woman who is complaining of joint pain and may also have other associated SLE symptoms. The constellation of SLE symptoms include Raynaud's phenomenon, in which digital vasospasms impede blood flow, causing color changes to the skin (white/hypoxic, blue/cyanotic, and red/reperfused), extreme fatigue, alopecia, photosensitive malar/butterfly rashes on the nose and cheeks or discoid rashes, pleurisy or pericarditis, and evidence of organ damage, such as proteinuria, which is suggestive of renal involvement.

ANA testing should be ordered in a clinical context that is suggestive of AD. Positive results do not confirm an SLE diagnosis, as up to 15% to 20% of people can have a positive ANA without associated disease. Over-ordering ANA testing and referring based on those tests alone, without a strong clinical rationale, results in undue stress for patients who endure weeks to months of worry until the diagnosis is excluded by a rheumatologist. Better notation of clinical symptoms suggestive of SLE can help specialists better triage patients.

Management

Before the antimalarial hydroxychloroquine (Plaquenil®) became the accepted first-line treatment for SLE, physicians often relied on corticosteroids to control the inflammation associated with the disease. The anti-inflammatory effects of corticosteroids are seen quickly, whereas several months of hydroxychloroquine therapy may be necessary before a similar benefit is seen. However, hydroxychloroquine has few side effects, lowers cholesterol, and prolongs survival. Its long-term use is associated with a risk of retinal toxicity, making annual eye examinations mandatory. In contrast, long-term corticosteroid use can cause as many or more serious adverse effects than SLE itself, including osteoporosis, cataracts, hypertension, diabetes, metabolic syndrome, and avascular necrosis. Higher doses of corticosteroids are implicated in organ damage.

Physicians today should not rely on long-term corticosteroid treatment for SLE patients.[9] Hydroxychloroquine should be begun in all SLE patients, if there is no contraindication, and corticosteroids should be used only to control acute flares and for the shortest time possible at the lowest effective dosage.[9]

Other drugs used to treat SLE are immunosuppressants often prescribed for rheumatoid arthritis, such as methotrexate (Rheumatrex™), mycophenolate mofetil (CellCept®),and azathioprine (Imuran®). These medications help calm the overactive immune systems of SLE patients but can also leave them more vulnerable to infection. The only medication approved by the FDA specifically for SLE is the monoclonal antibody belimumab (Benlysta®), which has proven effective in a subset of SLE patients.

Treating to specified targets in SLE, as has been done in rheumatoid arthritis, is a topic of growing discussion. The T2T (Treat to Target)/SLE recommendations include early identification of lupus nephritis, targeting remission or the lowest disease activity possible to avoid long-term accrual of damage, reducing exposure to corticosteroids, and improving quality of life in SLE patients.[10]

Investigational therapies

MUSC is planning for the first U.S. trial of mesenchymal stem cells derived from umbilical cords as a treatment for refractory SLE (MscISLE; NCT02633163). Mesenchymal stem cells are stromal cells with substantial immunosuppressive properties that are not only pluripotent—capable, for example, of differentiating into bone, cartilage, muscle, marrow stroma, tendon-ligament, fat, and other connective tissues—but are thought to play a role in tissue regeneration and wound repair.[11] They have been shown to decrease SLE disease activity without serious side effects in uncontrolled trials in China.[12]

The planned multi-site, phase 2 trial led by MUSC Health rheumatologists **Gary S. Gilkeson**, **M.D.**, and **Diane L. Kamen**, **M.D.**,**MSCR**, will evaluate whether similar efficacy is shown in a placebo-controlled trial. Cells harvested from umbilical cords will be expanded in MUSC's Good Manufacturing Practice Quality Clean Cell Facility and infused into patients at MUSC or other study sites. The trial is planned to open in late spring or early summer 2016. For more information, contact Eden Gebre at gebre@musc.edu.

Systemic Sclerosis

SSc is a multisystem fibrosing disease that can involve the skin, heart, lungs, kidneys, and gastrointestinal tract, among other systems. Lung complications, particularly interstitial lung disease (ILD) and pulmonary hypertension, are associated with high morbidity and mortality.

Diagnosis

Quality of life can be improved and organ damage minimized if interventions begin early, before irreparable damage occurs. Early symptoms are subtle and can be missed, delaying referral to a rheumatologist.[13] The most characteristic symptom of SSc is hardening and tightening of the skin, but not all patients manifest this symptom, and in those who do, the symptom often manifests when much internal organ damage has already been done. The most important harbinger of SSc is Raynaud's phenomenon, and patients with this

condition, especially those with other early symptoms of SSc, including shortness of breath, extreme fatigue, or heartburn, and those with abnormal laboratory findings, should be referred to a rheumatologist.

Management

Corticosteroids, especially in higher doses, should be avoided if at all possible in SSc patients because they can precipitate acute renal crisis. Acute renal crisis, which is characterized by a sudden spike in blood pressure and rapid damage to the kidney, was the number one killer of these patients until the introduction of routine screening and treatment with angiotensin-converting enzyme (ACE) inhibitors.

It is important to recognize that blood pressures still in the normal range (<140/90 mm Hg) that are substantially higher than the patient's baseline blood pressure may be a signal of impending or ongoing renal crisis. Routine monitoring of blood pressure, prompt treatment with ACE inhibitors if a problem is found, and the avoidance of high doses of corticosteroids in these patients should ensure that gains against this killer are solidified. Due to the high risk of pulmonary hypertension and ILD in SSc, annual monitoring with echocardiography and pulmonary function tests is required.

Although there is no cure for SSc, early referral of patients to specialists to better manage their disease and prevent or minimize organ involvement can improve survival and quality of life. Patients under specialty care are also more likely to be enrolled in clinical trials.

Investigational therapies

Interest in drug therapy for SSc, which is considered a prototype of fibrosing disease, has never been greater. It has been estimated that 45% of all deaths in developed countries result from fibrosis (e.g., heart, lung, liver), and the pharmaceutical industry is very interested in developing drugs for SSc that could also be applied to more prevalent fibrosing diseases. Investigators in the Division of Rheumatology at MUSC are on the forefront of drug development for SSc. **Carol A. Feghali-Bostwick**, **Ph.D.**, received a Small Business Technology Transfer grant from the National Institutes of Health to partner with a biotech company to develop a drug from an anti-fibrotic molecule that she discovered. The laboratories of **Elena V. Tourkina**, **Ph.D.**, **Stanley R. Hoffman**, **Ph.D.**, **Galina S. Bogatkevich**, **M.D.**, **Ph.D.**, and **Richard M. Silver**, **M.D.**, are developing additional anti-fibrotic molecules.

MUSC investigators are also evaluating whether existing drugs could be repurposed to treat SSc. With funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Dr. Silver is investigating the safety of dabigatran (Pradaxa®), a thrombin inhibitor that is FDA-approved for atrial fibrillation, and plans to start a clinical trial of this agent in the first quarter of 2016. Industry-sponsored clinical trials evaluating whether two existing drugs (Riociguat® and Abatacept®) are effective in SSc are currently recruiting patients. For more information about clinical trials in SSc, contact Kelley Kajdasz at gibsonke@musc.edu or Dana Rosson at rosson@musc.edu.

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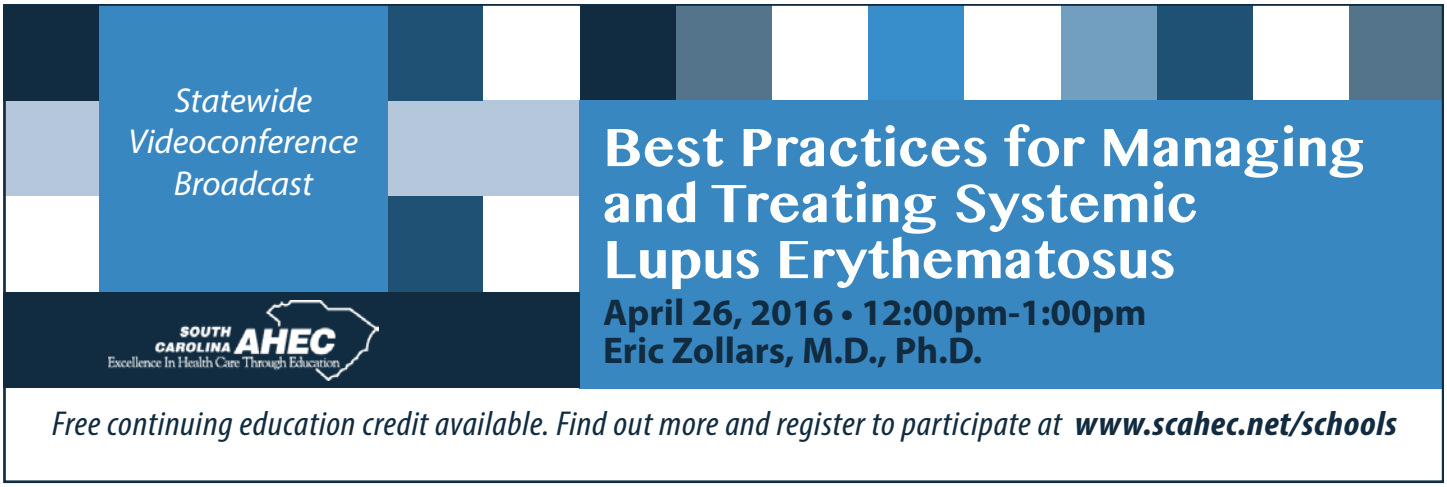


Interview

College of Medicine Announces New Dean

Raymond N. DuBois, M.D., Ph.D., Dean of the College of Medicine

On March 1, MUSC welcomed **Raymond N. DuBois**, **M.D.**, **Ph.D.**, as the new Dean of the College of Medicine. DuBois is a senior academic medical center administrator and physician-scientist internationally known for his groundbreaking work in cancer research. Previously, he was Executive Director of The Biodesign Institute at Arizona State University (ASU), which focuses on health solutions, sustainability, and biomedical science through 14 research centers. He was also a Professor of Medicine in the Mayo College of Medicine and directed an NCI Program Project Grant at the Mayo Clinic Cancer Center in Arizona. Prior to his ASU appointment, he served as Provost and Executive Vice President and Professor of Cancer Medicine and Cancer Biology at the University of Texas MD Anderson Cancer Center, where he oversaw all research, education, training, and faculty development, as well as the global academic programs. He began his research career at Vanderbilt University Medical Center in 1991 and eventually became the Director of the Vanderbilt-Ingram Cancer Center in 2005. He is Past President of the International Society for Gastrointestinal Cancer and Past President of the American Association for Cancer Research. He is also a founding scientific advisor for Stand Up to Cancer, a charitable foundation supporting translational cancer research, and currently serves as President and Chair of the American Association for Cancer Research Foundation.

The DuBois laboratory studies the molecular mechanisms by which inflammation affects the biology of cancer. This research led to the discovery of COX-2 as a target to selectively inhibit key pathways associated with inflammation and cancer.

PN: Can you tell us what attracted you to this position?

RD: This is my opportunity to make an imprint on an academic medical center. We're training the upcoming generations of doctors, biomedical scientists, and health care workers, and we need to make sure that we improve that process as much as possible. MUSC is already an incredible resource for the state, but we have only skimmed the surface of its potential impact. I feel lucky to be a part of its future growth and eminence. As for personal reasons, my wife was born and raised in the Greenville-Spartanburg area and has family here in Charleston.

PN: This is a time of dramatic change for medicine. How would you describe your charge from President Cole?

RD: Well, previous deans were directly responsible for overseeing the clinical operations as well as academic research and training. Now there's a CEO in place to oversee the entire health system, and though I'll be helping manage some aspects of clinical care from the academic side, I'll be focused on research, education, training, and other parts of the College of Medicine. I personally found this new structure very attractive because that's where my strengths are.

PN: Are you planning to teach?

RD: I would like to – as a guest lecturer, I hope. At ASU, I was a guest lecturer for an undergraduate biochemistry class. My favorite course to teach is the history of medicine. While at Vanderbilt I taught medical students in GI Physiology.

PN: And of course you'll continue your research here.

RD: I will. My role as the PI in a basic science cancer research lab is extremely important to me, which is why I'm pleased to have an appointment at the Hollings Cancer Center where we can continue our investigations into inflammation and cancer. I'm excited to begin collaborations with the outstanding oncology researchers at Hollings. Even though I've moved into an administrative position, I've found that maintaining a robust research presence helps me keep a finger on the pulse of research trends and breakthrough discoveries. In addition, when scientists come to me with issues and ideas, I often understand what they are describing, because I, too, am keeping an active lab going.

During the transition here, I spent a lot of time working with ASU senior scientist Dr. Dingzhi Wang, who will also be moving to MUSC and coordinating our lab move here, shipping our research equipment, moving the grants, and getting new protocols in place. By June 2016, we hope to be fully operational.

PN: Please describe the specific focus of your research.

RD: In the broadest sense, my research is focused on early detection and cancer prevention. I'm particularly interested in finding better ways to detect cancer earlier by understanding the molecular details required for normal cells to change into early stage colorectal cancer cells. I'm convinced that we can harness the power of the immune system and create approaches to prevent cancer (immuno-prevention), if we understand better how those early, premalignant lesions develop and how we can stop them before they have a chance to become full-blown cancer.

My lab is best known for our discovery of one of the key targets responsible for the progression of colorectal cancer, and, importantly, that this target is inhibited by aspirin and other nonsteroidal anti-inflammatory drugs. Our discoveries have led to the development of drugs now being examined to better treat colorectal and other cancers. We are very excited that recently the U.S. Preventive Services Task Force recommended aspirin for use in patients who have Lynch syndrome and are at high risk for colorectal cancer. Aspirin use has been shown to result in as much as a 50% decrease in overall cancer incidence in that population. So, our work was instrumental in helping understand the underlying basis for the target for the drug and how it affects the tumor microenvironment in the colon.

PN: What do you see as MUSC's research strengths?

RD: I'm really impressed by MUSC's interest in developing cancer as a clinical and research area. I would love to continue to help that develop, recruit new people, and mentor those already here. In terms of cancer biology and some of those areas, there's a group in lipid signaling that is outstanding. MUSC has also taken a leadership role in pulmonary fibrosis research; there's some interesting work in inflammation and joint disease; and there's a strong group here in addiction sciences and psychiatry. So, clearly those are wonderful areas to continue to enhance. There's not as much strength across the country in those areas, so I was particularly excited about that. Frankly, I need to learn more about what all of the faculty are doing and help contribute to the strategic plan going forward.

PN: Tell us a little about your family.

RD: My wife, Lisa, is a career freelance journalist and writer. We have been married for 35 years. Our daughter is a journalist working in Nashville and our son is studying law here at the Charleston School of Law and plans to establish a career in sports management.

New Director for the Division of Cardiology

The MUSC Department of Medicine welcomed **Thomas G. Di Salvo**, **M.D.**, **MPH**, **MBA**, on November 1, 2015 as the new Director of the Division of Cardiology. Previously, he was an Associate Professor of Medicine at Vanderbilt University Medical Center and Medical Director of the Vanderbilt Heart and Vascular Institute. He also served as an Assistant Professor of Medicine at Harvard Medical School and Massachusetts General Hospital, where he completed fellowships in Clinical Cardiology, Clinical Epidemiology, and Heart Failure/Cardiac Transplantation. His residency was completed at Johns Hopkins Hospital. Di Salvo is nationally known for his research in heart failure and is the author of numerous book chapters and more than 80 articles in medical journals. He succeeds **Michael R. Gold**, **M.D.**, **Ph.D.**, the Michael Assey Chair in Cardiology.

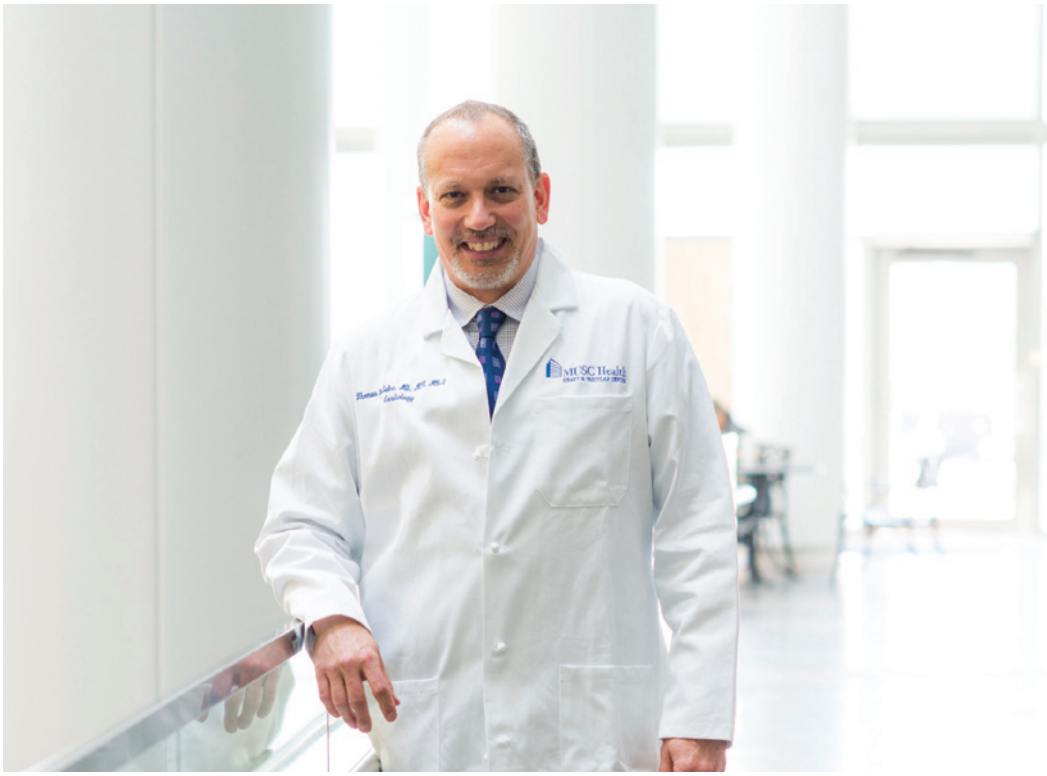
"Dr. Di Salvo has extensive experience in cardiology and academic medicine and it has been an absolute pleasure to work with him since his arrival," says **Don C. Rockey**, **M.D.**, Professor and Chair of the Department of Medicine. "He is fundamentally committed to excellence in our tripartite mission of patient care, education, and research, and we will all benefit from his energy and enthusiasm."

Di Salvo cites the division's robust clinical activities, its widely regarded clinical faculty, and MUSC's strong core research facilities as factors in his decision to accept the appointment. He has been charged with growing the clinical and research capacity of the division and will recruit many new clinicians, physician-scientists, and Ph.D. scientists. "The medical center also is committed to recruiting a surgeon dedicated to ventricular assist devices and heart transplant surgery," says Di Salvo. "As we are the only provider of heart transplants in the growing state of South Carolina, expansion of this program is vital."

As for research, Di Salvo says there has been strong support for many of the research endeavors that provide the platform for clinical and technological innovation and for discovery science. Thus, he has broad-ranging plans to develop areas of research that will link to MUSC Health's clinical mission. One example is the role of genomics in cardiovascular risk stratification, prevention, and diagnostic care for specific diseases. "We're committed to building a program in translational genomics that will serve patients across the state," he says.

Di Salvo's research has focused on the prognosis of advanced heart failure, clinical outcomes of heart failure, selected aspects of the clinical pathophysiology of heart failure (including a recent focus in epigenetics), cardiac transplantation, and cardiovascular health services.

Di Salvo and his wife, Sandra, an entrepreneur who is developing a business that administers on-site vaccinations, have a six-year-old daughter.



MUSC Welcomes New Communications Chief

On January 4, 2016, the Medical University of South Carolina (MUSC) welcomed **Sheila Champlin**, **M.A.**, as Chief Communications and Marketing Officer. In this new role, Champlin will develop a unified communications platform across all domains of MUSC. This realignment creates the opportunity to provide vision and direction for strategic communications to advance the reputation of MUSC for education, research, service, patient care, and economic development.

President **David J. Cole**, **M.D.**, has remarked that Champlin's eagerness to help take MUSC to the next level is palpable. "Sheila's communication expertise, paired with her talent for relationship-building, is just what we were seeking," he says. "I have every confidence that she will provide the inspiration and direction needed as we continue telling the great story that is MUSC."

Champlin comes to MUSC from the University of Tennessee Health Science Center in Memphis, TN, where she served as Assistant Vice Chancellor of Communications and Marketing since 2006. Previously, she was a communications consultant to corporations, small businesses, non-profit organizations, and individuals. She also served as Vice President of Communications at Scholastic, Inc., Director of Marketing Communications for AT&T Capital Corporation, Vice President and Director of Corporate Communications for Prudential Securities, Inc., and Vice President and Director of Business Development at Ogilvy Adams & Rinehart, Inc. She holds a master's degree in journalism from the University of Missouri-Columbia and a bachelor's degree in communications from St. Louis University. She is an active member of the Public Relations Society of America, Alpha Sigma Nu (the honor society of Jesuit colleges and universities), and Phi Beta Kappa National Honor Society.

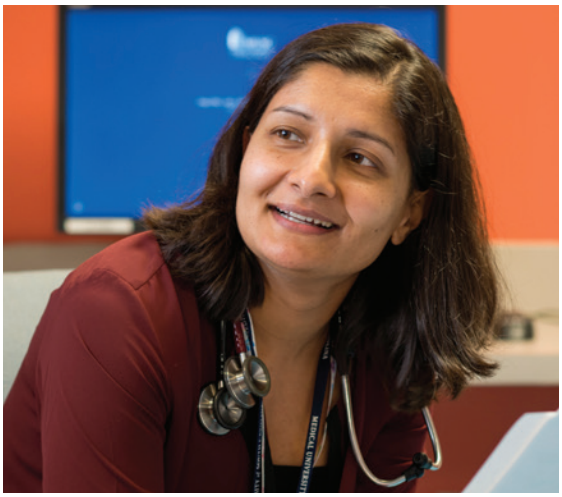
Champlin was chosen through a national search that yielded 15 qualified applicants who were reviewed by the search committee. **Jim Fisher**, Vice President for Development and Alumni Affairs, was the committee chair. "Three extraordinarily qualified finalists were invited to the MUSC campus and Sheila Champlin was unanimously recommended to Dr. Cole," he says.

This opportunity at MUSC attracted Champlin for many reasons, she says. "MUSC has a reputation that is so impressive and so extensive. It was fascinating to me that the leadership recognizes so clearly what the value of strategic communications can be to this organization. That really hooked me," she explains.

Champlin is married to Michael Champlin, a real estate attorney. They are the parents of a fifteen-year-old daughter.

New Physicians

Andrea M. Abbott, M.D.
Board Certification: American Board of Surgery // Specialty: Surgical oncology // Medical School: University of Missouri-Kansas City // Residency: University of Minnesota // Fellowship: Moffitt Cancer Center



Shean J. Aujla, M.D.
Chief, Division of Pediatric Pulmonology
Board Certification: Pediatrics, Pediatric Pulmonology // Specialty: Pediatric pulmonology // Medical School: Medical University of South Carolina // Residency: University of Connecticut // Fellowship: University of Pittsburgh

Clarice S. Clemmens, M.D.
Board Certification: Otolaryngology // Specialty: Pediatric Otolaryngology // Medical School: Medical University of South Carolina // Residency: Hospital of the University of Pennsylvania // Fellowship: Children's Hospital of Philadelphia

Virgilio V. George, M.D.
Head, Section of Colon and Rectal Surgery
Board Certification: Gastrointestinal Surgery: Colon & Rectal Surgery // Specialty: Colon and rectal surgery // Medical School: Universidad Centroccidental "Lisandro Alvarado" // Residency: Indiana University // Fellowship: Washington University, Barnes-Jewish Hospital

Christopher E. Gross, M.D.
Specialty: Orthopaedics // Medical School: Harvard Medical School // Residency: Rush University Medical Center // Fellowship: Duke University Medical Center

Robert F. Murphy, M.D.
Board Certification: Orthopaedic Surgery // Specialty: Pediatric orthopaedics // Medical School: Emory University // Residency: University of Tennessee-Campbell Clinic // Fellowship: Boston Children's Hospital-Harvard Medical School

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