RACING TOWARD AN ANSWER

U-M research moves closer to demystifying fibromuscular dysplasia

INSIDE:

Brain tumor gene therapy study recruits patients

New drug relieves opioid-induced constipation

Alternatives to warfarin

Guidelines for sepsis care needed
**Walk it off**

**Peripheral arterial disease research study recruits patients**

UM cardiologist Elizabeth Jackson, M.D., is recruiting patients with peripheral arterial disease (PAD) to take part in a year-long study that will look at two different approaches to walking regimens.

“Previous research in the past several decades has shown that walking is the best treatment for PAD,” says Jackson. “Many patients have difficulty adhering to walking programs because their disease causes pain in the lower limbs — at first. If we can encourage people to stop and rest when the pain begins, then resume their walking, over time the pain will lessen.”

The study will compare participants assigned to two different groups: One group will walk in a structured program offered through a cardiac rehab facility, and the other group will walk following an Internet-based program. Those in the second group will have fitness monitors, such as a FitBit, and will be more self-directed. They will also have access to online support from the study staff as well as other programs such as virtual walking groups.

Both groups will be closely examined for the first four months with follow up to occur eight months later in order to gauge adherence to their walking regimens.

**STUDY**

This study is actively recruiting participants. If you have patients who might be interested, please direct them to activitydaily.org for details on how to be considered.

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**ALL HEART**

The University of Michigan C.S. Mott Children’s Hospital Congenital Heart Center is pleased to announce that Donald Malcolm, M.D., has joined Ronald Grifka, M.D., at our pediatric cardiology practice in Grand Rapids. Together, these long-time Grand Rapids community members offer a full range of pediatric heart care to children with congenital and acquired heart conditions, further fulfilling our commitment to serve patients and their families in West Michigan.

The Grand Rapids clinic accepts referrals for the evaluation and treatment of all pediatric cardiology concerns including:

- Congenital heart defects including septal defects, valve abnormalities and pulmonary artery and aorta abnormalities
- Arrhythmias
- Palpitations, syncope and chest pain
- Acquired pediatric cardiac conditions
- Cardiomyopathy

Services offered include newborn referrals, murmur evaluations, EKG, pediatric echocardiography, pacemaker care, exercise testing and athlete screening follow-up.

**REFER**

The clinic is located in the Metro Heart and Vascular building in Grand Rapids. To make a referral or learn more about the Grand Rapids clinic contact M-LINE at 800-962-3555.

**SUMMER STUDY OPPORTUNITIES**

UM offers a variety of self-study and in-person education opportunities for community primary care providers, such as these summer updates and reviews:

- Updates in Nephrology for the Primary Care Provider: May 16 at The Inn at St. John’s in Plymouth, Mich.
- Internal Medicine Spring Review: May 29–30 at The Inn at St. John’s in Plymouth, Mich.
- 33rd Annual Internal Medicine Update: July 31–Aug. 2 at The Grand Hotel on Mackinac Island, Mich.

**STUDY** Visit ocpd.med.umich.edu/cme/course-calendar to see a complete calendar and to register.
MOTT ASKS …

Most parents agree their children should be ready to move out of the pediatrician’s office into adult-focused care by age 18, but just 30 percent actually make that transition by that age, according to the University of Michigan C.S. Mott Children’s Hospital National Poll on Children’s Health. The poll found that about two-thirds of parents (69%) believe adolescents should stop seeing their child-focused provider and begin seeing an adult-focused provider for primary care at age 18 or even younger. Parents’ confidence in their children’s abilities to handle other aspects of their own health care is reported in the graphic at right.

GET MORE Learn more about the poll and browse other reports at mottpch.org.

Table: Parent’s perception of their adolescent’s/young adult’s ability to manage health care needs

<table>
<thead>
<tr>
<th>Age of Adolescent/Young Adult</th>
<th>16-17</th>
<th>18-19</th>
<th>20-21</th>
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<tr>
<td>Takes medications correctly</td>
<td>80%</td>
<td>85%</td>
<td>90%</td>
</tr>
<tr>
<td>Knows when to go to the ER</td>
<td>55%</td>
<td>70%</td>
<td>88%</td>
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<td>Could fill out a medical history form, including medications</td>
<td>41%</td>
<td>54%</td>
<td>81%</td>
</tr>
<tr>
<td>Knows how to make doctor’s appointment</td>
<td>22%</td>
<td>47%</td>
<td>79%</td>
</tr>
<tr>
<td>Knows what their insurance covers</td>
<td>16%</td>
<td>28%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Source: C.S. Mott Children Hospital National Poll on Children’s Health, 2014

After the fact

New Sarcoma Survivorship Clinic addresses late effects of treatment

The majority of patients diagnosed with sarcoma will be cured of their disease and live cancer-free. But as they age, these patients — who are diagnosed as children, teens or young adults — are at great risk of developing a severe or life-threatening chronic medical condition related to their sarcoma treatment.

A first-of-its-kind clinic at the University of Michigan Health System puts medical oncologist Laurence Baker, D.O., and cardio-oncologist Monika Leja, M.D., side by side to help sarcoma survivors. In addition, the multidisciplinary clinic includes specialists in kidney disease, endocrinology, physical medicine and rehabilitation, and psychiatry to help manage the conditions most often seen in sarcoma survivors.

Chemotherapy and radiation put sarcoma survivors at risk for developing lifelong chronic or life-threatening illnesses including:
- Heart disease
- Type 2 diabetes
- High blood pressure
- Lipid disorders
- Kidney failure
- Anxiety, depression and other mental health problems
- Sarcoma recurrence
- New cancers

Many of these conditions are issues more commonly seen in older adults and, as a result, are often overlooked in sarcoma survivors. The clinic emphasizes early detection with a focus on standard interventions to prevent or treat these conditions. Survivors receive a personalized plan with recommendations for further treatment if necessary and a program of follow-up visits.

The clinic is open to bone sarcoma and soft tissue sarcoma survivors 18 and older who have been off all therapy for at least two years. Patients are eligible even if they received their sarcoma treatment outside of the University of Michigan.

REFER To refer a patient to the Sarcoma Survivorship Clinic call M-LINE at 800-962-3555.
EMERGENCY CRITICAL CARE CENTER NOW OPEN

A hub for the most critical emergency patients

For decades, physicians around Michigan and beyond have sent the most critically ill and injured adults to the U-M emergency department. With the opening of the 7,800-square-foot Emergency Critical Care Center (EC3), such patients can now receive higher level care throughout the first crucial hours.

Among the first of its kind in the nation, the EC3 ensures patients a smoother transition to the next phase of care, whether that be in an operating room or an intensive care unit. It may even allow some patients to avoid ICU-level hospitalization altogether — an important goal given the high demand for U-M ICU care.

The EC3 includes five resuscitation/trauma bays and nine patient rooms with an ICU-level environment for initial care. Designed in partnership with UMHS critical care medical directors and the Michigan Center for Integrative Research in Critical Care, the EC3 makes it easier for teams to test new diagnostics, devices, monitoring equipment and treatment strategies. It also serves as the training ground for a new breed of emergency critical care physicians.

Kyle Gunnerson, M.D., the U-M emergency physician and critical care specialist leading the EC3, says, “We have a window of a few minutes to a few hours to diagnose and treat these patients, so having a cutting-edge ICU infrastructure with critical care expertise in the ED preserves precious time and perhaps shortens overall hospital or ICU stays. As we seek to push this type of care forward through innovative approaches and technologies, the EC3 will act as a test bed of new ideas.”

Collected evidence

First clear guidelines issued on use of complementary therapies for breast cancer

Nearly 80 percent of breast cancer patients in the United States use complementary therapies following a breast cancer diagnosis, but there has been little science-based guidance to inform clinicians and patients about their safety and effectiveness.

Researchers from the Society for Integrative Oncology recently released evidence-based guidelines to indicate which integrative treatments appear to be most effective and safe for patients. The researchers analyzed more than 4,900 articles covering various practices such as acupuncture, dietary supplements, massage and meditation. The guidelines are outlined by symptoms — pain, sleep disorders, nausea and quality of life. All trials examined focused on symptom control and quality of life, not treating cancer. Recommendations were graded using the U.S. Preventive Services Task Force grading system.

Results appear online in the Journal of the National Cancer Institute Monograph.

“Most breast cancer patients have experimented with integrative therapies to manage symptoms and improve quality of life. But of the dozens of products and practices marketed to patients, we found evidence that only a handful currently have a strong evidence base. The key is that complementary therapies are integrated with conventional treatments and that all care decisions are based on evidence,” says Suzanna M. Zick, N.D., M.P.H., associate professor of Family Medicine and Environmental Health Sciences at the University of Michigan. Zick is also president of the Society for Integrative Oncology.

Read

Get linked to the guidelines at Colleagues in Care Online at med.umich.edu/cic.
AN EARLY START

Prenatal consultations available for cleft lip and palate

When Toni Enstep was 20 weeks pregnant, a routine ultrasound revealed that her baby would be born with a cleft lip and likely a cleft palate. Her obstetrician referred her to the University of Michigan C.S. Mott Children’s Hospital Craniofacial Anomalies Program for a prenatal consult.

“While there are no fetal interventions for a cleft lip and palate approved at this time, there are a number of things we can do with families to help them prepare for the unique needs a baby with a cleft will have,” says Steven Buchman, M.D., pediatric plastic surgeon and director of the Craniofacial Anomalies Program.

For example, families should anticipate that babies with a cleft often experience feeding problems. The baby will want to suck, but can have difficulties making an airtight seal around a nipple.

“Our prenatal consults allow us to go over special bottle types that work well with infants with cleft lips, as well as review what the child's treatment will likely consist of,” says Carolyn Walborn, nurse practitioner, who works with the program.

“My husband and I were scared. We did not understand what cleft was or how we would care for our son. Meeting with Carolyn before Dominic was born greatly eased our stress and we could start to prepare for what was ahead, and how to care for him,” says Enstep.

Shortly after Enstep’s baby, Dominic, was born, he was seen at the Craniofacial Anomalies clinic, where Enstep and her husband learned to tape Dominic’s lip to provide for better alignment. Taping also aims to bring the lip segments closer together in preparation for surgery, in order to achieve a more effective repair. Dominic was also seen by pediatric otolaryngologists to be evaluated for hearing and possible drainage tubes, and by pediatric geneticists to determine any potential syndromic cause for his condition.

At 4 months old Dominic underwent surgery to repair his cleft lip, and again at 13 months to repair his palate.

“The benefit of our integrated program here is that a family has access to all the various subspecialists who may be involved in the care of a child with a craniofacial anomaly,” says Buchman. “A multidisciplinary team approach is the most beneficial to the child born with a cleft, because these children have a broad range of treatment needs that no one specialist can fulfill. We all work together to provide unparalleled care for each and every child we treat.”

Patients are usually seen periodically for routine follow-up by their plastic surgeon until around age 3, at which point they are seen by the full multidisciplinary craniofacial team, including pediatric dentistry, speech pathology, orthodontia, oral surgery and neuropsychology, to evaluate any additional needs that may have developed.

“It is comforting to know we are not in this alone, and that we have a full team of specialists helping Dominic, to ensure he continues to progress and to evaluate his needs as he gets older and develops,” says David Wietecha, Dominic’s father.

“Today, Dominic is an outgoing, social little boy. He is like all the other little boys in his class,” says Enstep. “We’re so grateful to the team at Mott for helping him.”

ONLINE Check out our cleft lip and cleft palate family resources, including a video about preparing for cleft palate surgery and our downloadable patient guide, at mottchildren.org/craniofacial.
Pamela Mace loves to run. Whether training for a marathon or jogging for the joy of it, the 52-year-old is always ready to hit the pavement. She is forever looking forward.

Mace is particularly looking forward to a day when the world better understands fibromuscular dysplasia (FMD), a rare blood vessel disease that presents no unique symptoms, which explains why doctors rarely look for it and often misdiagnose it.

To speed up the race toward FMD recognition, Mace took the reins as executive director of the Fibromuscular Dysplasia Society of America (FMDSA), a nonprofit organization dedicated to building FMD awareness, education and research. Mace’s devotion to FMD comes from her heart, since she herself has the disease — and she’s determined to make life better for tomorrow’s FMD patients.

**RACE AGAINST TIME**

Mace’s story began in 2000, when the then-37-year-old woke up with a nasty headache. As the day progressed she sensed that something was seriously wrong, and by the time she was admitted to the emergency room, her fears were confirmed. She’d suffered a transient ischemic attack.

She eventually learned that she’d suffered dissections in the lining of the arteries that supply blood to her brain. The reason for the dissections remained a mystery for

As of today, there is no known cause or cure for FMD and no protocol to screen for it or evaluate and treat patients already diagnosed with the disease.
another year, until finally she was officially diagnosed with FMD. Mace eventually had stents implanted in her carotid arteries and restarted anticoagulation therapy.

**BRIDGING RESEARCH AND CARE**

As of today, there is no known cause or cure for FMD and no protocol to screen for it or evaluate and treat patients already diagnosed with the disease. However, there’s been some progress in our understanding of the condition. FMD causes one or more arteries — most commonly the renal, carotid or vertebral arteries, although it can occur in the abdomen and extremities — to have abnormal cell development in the artery wall. In more than one-half of FMD patients there will be evidence of FMD in more than one artery. The most common form of FMD presents a characteristic “string of beads” in images of the affected arteries.

“The causes of FMD are not yet understood,” stresses Santhi K. Ganesh, M.D., assistant professor of Cardiovascular Medicine at U-M and FMDSA Medical Advisory Board member. However, Ganesh and a team of U-M scientists are in pursuit of FMD’s molecular and genetic basis, as well as disease triggers. She has engaged several international collaborating centers with clinical experts in FMD to facilitate the research. In addition, Ganesh leads an FMD specialty clinic that provides patient care as well as a bridge to emerging research.

Ganesh and her research team — whom she refers to as “some of the world’s best genetic experts” — are currently investigating a hypothesis that FMD is a systemic disease with a genetic predisposition in at least some families. However, even with similar genetics, a relative may have different artery involvement, different disease severity or not develop FMD at all.

**SO MANY PEOPLE ON BOARD**

In addition to Ganesh’s research, U-M’s Michigan Cardiovascular Outcomes Research and Reporting Program supports an FMD clinical registry, initiated by James Froehlich, M.D., M.P.H. (See sidebar.) Interest in FMD at University of Michigan goes back to the 1970s when vascular surgeon James Stanley, M.D., first described characteristics of the disease. Throughout his career, Stanley has consulted on surgical management of FMD.

There are no guidelines to screen for FMD, but it is recommended that those previously diagnosed have a one-time brain-to-pelvis screening of the arterial tree. Mace sees more recommendations on the horizon, saying, “FMDSA is motivated, patients are motivated, and researchers are motivated. There are so many people on board all over the world helping us to find answers!”

* FMD presents a characteristic “string of beads” in images of the affected arteries.

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**What we have learned**

In 2008, the Fibromuscular Dysplasia Society of America established the U.S. Registry for Fibromuscular Dysplasia. This marked the first effort to identify characteristics associated with FMD, potential disease markers and commonly used imaging and treatment modalities. “It’s our hope that the registry will identify patterns and help set guidelines for disease therapies — or better still, a cure,” says Pamela Mace, executive director of FMDSA.

Today, 14 participating registry centers have collected clinical and imaging data for more than 1,100 FMD patients. Several centers, including the U-M FMD specialty clinic, are actively participating in research to isolate the gene(s) associated with FMD and ultimately identify the disease’s cause. The FMDSA registry is distinct but complementary to the research Santhi Ganesh, M.D., and her colleagues are conducting.

Here are several findings from the registry:

- Ninety percent of patients with FMD are women, although it does occur in men and children. Data shows that women have more cerebrovascular symptoms and men are more likely to have aneurysm or dissection.
- Seven percent of patients in the registry have a family member diagnosed with FMD. However, among first- and second-degree relatives of patients with FMD, stroke occurred in half, aneurysm in a quarter and sudden death in 20 percent.
- FMD occurs in the renal, carotid or vertebral arteries approximately 70 to 75 percent of the time.
- The most common presenting symptoms are hypertension, headache, pulsatile tinnitus and dizziness.
- Less than 7 percent of patients suffer from a stroke on initial presentation. However, about one in five FMD patients has an arterial aneurysm, and one in five has experienced an arterial dissection.

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**REFER** U-M operates a multidisciplinary clinic for patients diagnosed with or suspected of having fibromuscular dysplasia (FMD). Call M-LINE at 800-962-3555 to refer a patient.

**LINK** Get linked to more information about FMD at Colleagues in Care Online at med.umich.edu/cic.
Pedro Lowenstein, M.D., Ph.D., and Maria Castro, Ph.D., are leaders in a quest to find effective treatments for brain tumors, and are in the midst of several promising research studies.
Gene therapy for brain tumors gets first test in human patients

A unique new approach to fighting brain tumors that delivers a one-two punch designed to knock out one of the most aggressive neurological malignancies. The Phase I clinical trial of the approach, based on U-M research, delivers two different genes directly into the peritumoral region of the brain immediately following primary tumor resection. The idea is to trigger immune activity within the brain itself to kill remaining tumor cells — the ones neurosurgeons can’t resect and which lead to almost certain recurrence. It’s the first time this gene therapy approach is being tried in humans, after more than a decade of research in experimental models.

A COMBINATION OF THERAPIES

One of the genes is designed to kill tumor cells directly and is activated by an oral drug, valacyclovir. The other gene spurs the body’s own immune system to attack remaining cancer cells. Both are delivered into the peritumoral region via an adenovirus vector. Patients also receive the current standard of care, which includes temozolomide and radiotherapy.

The use of two vectors, Ad-hCMV-TK and Ad-hCMV-Flt3L, allows the trial to combine direct tumor cell killing (TK) and immune-mediated stimulation of anti-tumor immune responses (Flt3L).

The Phase I clinical trial has already enrolled several newly diagnosed, untreated adult patients who have tolerated the gene delivery without complications. More patients will be able to enroll at a pace of about one every three weeks, through a careful selection process. In addition to surgery and gene therapy at U-M, each will receive standard chemotherapy and radiation therapy as well as follow-up assessments for up to two years.

All patients in the study must have a presumptive diagnosis of WHO grade 3 or 4 malignant primary glioma, such as glioblastoma multiforme; patients must not have been treated yet by any therapy. They must also have a Karnovsky score greater than or equal to 70, be between the ages of 18 and 75, and not be pregnant. Other hematologic, renal and liver function criteria apply.

THE OBJECTIVES

The primary study objective is to determine the safety of the approach by measuring toxicity and autoimmune responses. Secondary objectives will

Flying under the radar

Brain tumors fly under the radar of the body’s defense forces by coating their cells with extra amounts of a specific protein, new U-M research shows. Like a stealth fighter jet, the coating means the cells evade detection by the early warning immune system that should spot and kill them.

But as researchers and clinicians try new immune-based approaches to treat brain tumors, other new U-M research suggests that adding a drug usually taken by organ transplant recipients may aid response.

The “stealth” research, performed in mice and rats, shows the key role of a protein called galectin-1 in the ability of high-grade malignant gliomas to evade immune detection. Published in Cancer Research by Pedro Lowenstein, M.D., Ph.D., and Maria Castro, Ph.D., with their team, the findings stem from a case of scientific serendipity: The team discovered the effect while studying other aspects of galectin-1.

When they blocked cancer cells from making galectin-1, the tumors were eradicated by the immune system’s natural killer or NK cells. But when the tumor cells made their usual amounts of galectin-1, the immune cells couldn’t recognize them as dangerous.

The findings open the door to research on the effect of blocking galectin-1 in patients with gliomas.

At the same time, the U-M team is already planning to move forward with another approach to boost the tumor-specific immune response of glioma patients: giving a drug called rapamycin during immunotherapy.

Normally given to transplant patients to stave off the immune responses that lead to organ rejection, rapamycin combined with gene therapy enhanced animals’ ability to summon immune cells called CD8+ T cells to kill tumor cells directly. Due to this cytotoxic effect, the tumors shrank and the animals lived longer.

The drug also increased the immune system’s “memory” cells so that they could attack the tumor if it ever reared its head again. The mice and rats in the study that received rapamycin lived longer than those that didn’t.

Rapamycin is an FDA-approved drug that produces few side effects in transplant patients and others who take it to modify their immune response. The U-M team hopes to add rapamycin to their ongoing gene therapy clinical trial (see main story).
evaluate functional status, progression-free survival and overall survival.

“We’re very pleased to see our years of research lead to a clinical trial, because based on our prior work we believe this combination of cell-killing and immune-stimulating approaches holds important promise,” says principal investigator Pedro Lowenstein, M.D., Ph.D., the U-M Department of Neurosurgery professor who has co-led the basic research effort to develop and test the strategy.

Co-leader Maria Castro, Ph.D., notes that the patients who agree to take part in the Phase I trial will be the first in the world to help establish the safety of the approach in humans. “Without them, and without our partners on the U-M Neurosurgery team and donors to the Phase One Foundation who support our work, we wouldn’t be able to take this important step in testing this novel therapeutic approach.”

In addition to surgery by Drs. Oren Sagher, Daniel Orringer, Shawn Hervey-Jumper or Jason Heth, patients will undergo 24 months of follow-up. The U-M team will keep referring physicians updated regularly on patients’ progress.

**Hijacking blood supply**

Brain tumors grow by hijacking the brain’s existing blood supply throughout their progression and occupying narrow potential spaces between and along brain blood vessels, new U-M research shows. The findings contradict the concept that brain tumors need to grow their own blood vessels to keep themselves growing — and help explain why drugs that aim to stop growth of new blood vessels have failed in clinical trials to extend the lives of patients with the worst brain tumors.

In fact, trying to block the growth of new blood vessels in the brain actually spurs gliomas to grow faster and further, research by a team led by Pedro Lowenstein, M.D., Ph.D., and Maria Castro, Ph.D., shows. On the hopeful side, the research suggests a new avenue for finding better pharmaceutical approaches to stem glioma growth.

The discoveries come from a U-M team studying tumors in rodents and humans, and advanced computer models. The report was chosen as the cover article of a recent issue of *Neoplasia*.

The new findings show that tumor cells grow exclusively within the spaces around the brain’s own blood vessels, close enough to draw their own energy and fuel their growth in the same way typical brain tissue does. Instead of spawning their own offshoots of these vessels as the tumor cells divide, they simply crowd out the normal cells in the immediate area and continue to fill the spaces between neighboring vessels.

This continued “autovascular” growth, as the researchers call it, was detected from the very beginning to the final stages of tumor progression. It runs directly counter to the theory of neoangiogenesis, or new blood vessel formation, that has driven the use of certain drugs to treat brain tumors such as glioblastoma multiforme and other cancers.

Earlier, two clinical trials showed that glioblastoma patients taking an anti-angiogenic drug as part of treatment had similar survival as patients who didn’t receive the medication. Patients whose glioblastoma has returned after treatment also use the drug to reduce swelling.

The researchers note that physicians should not base medical decisions on their findings. But further research is exploring how therapies affect tumor cells growing along blood vessels.
Naloxegol now approved for the treatment of adults with opioid-induced constipation

Research led by gastroenterologist William D. Chey, M.D., professor of Internal Medicine at U-M, recently resulted in the U.S. Food and Drug Administration’s approval of naloxegol (Movantik, AstraZeneca Pharmaceuticals). The peripherally acting opioid receptor antagonist for the treatment of opioid-induced constipation in adults is on track for spring 2015 availability.

In the United States alone, more than 240 million opioid prescriptions are written annually. Of those on long-term opioid therapy, an estimated 40 to 90 percent of patients suffer opioid-induced constipation (OIC).

“Symptoms can range from a little nuisance to significant disability that makes functioning difficult — and may even cause some patients to discontinue their opioid therapy,” Chey stresses. “For many patients, that makes naloxegol an important advancement, since it does not interfere with the narcotic’s analgesic properties, but it does inhibit the gastrointestinal tract side effects.”

Opioids work by binding to mu-receptors in the brain, blocking the brain’s ability to perceive pain. However, opioids also bind to mu-receptors in the bowel, which is what causes OIC. Naloxegol limits the effects of opioids on the gastrointestinal tract without impacting the opioid receptors in the brain.

Naloxegol’s safety and effectiveness was determined in two Phase III studies, both funded by AstraZeneca Pharmaceuticals and designed, executed and interpreted with the assistance of Chey and his team. The studies included 1,352 adult participants who had taken opioids for at least four weeks for non-cancer-related pain and had OIC. Participants were randomly assigned to receive 12.5 mg or 25 mg of naloxegol or placebo daily for 12 weeks.

In the first trial, 44 percent of participants receiving 25 mg of naloxegol and 41 percent of those receiving 12.5 mg of naloxegol experienced an increase in the number of bowel movements per week, compared with 29 percent of participants receiving placebo. The second trial showed similar results. Naloxegol’s most commonly reported side effects were abdominal pain, diarrhea, nausea, vomiting and flatulence, all of which appear to be dose-related, as side effects occurred more commonly in the 25 mg group.

Chey offers a word of caution concerning naloxegol. “Constipation is a generic symptom for which there are many causes. So it’s important to get a patient’s medical history. If someone did not have constipation before starting prescription opioid pain medicines, then naloxegol is an excellent place to start. If, however, the patient has a history of constipation, you may not be looking at true opioid-induced constipation and naloxegol may not be the solution.”
Thinning Out the Options

New FDA-approved anticoagulants being evaluated by U-M physicians

For more than 60 years, warfarin was the sole prescription anticoagulant approved for use in the United States. Finally, there are more options: In the past five years, the U.S. Food and Drug Administration has approved four new oral anticoagulants as alternatives to warfarin:

- Dabigatran (brand name Pradaxa)
- Rivaroxaban (brand name Xarelto)
- Apixaban (brand name Eliquis)
- Edoxaban (brand name Savaysa)

The U-M Anticoagulation Management System is participating in the Michigan Anticoagulation Quality Improvement Initiative (MAQI²) — a multicenter, regional collaborative registry investigating the safety, quality and outcomes of anticoagulation treatment.

“As part of this collaboration, we now manage patients on warfarin and the new agents,” says James Froehlich, M.D., M.P.H., medical director of the University of Michigan Anticoagulation Service and professor of Internal Medicine. “There’s no doubt that the new anticoagulants are less problematic than warfarin in some ways, but they also introduce new issues. We’re looking at the data to determine each drug’s pros and cons.”

We’re looking at the data to determine each drug’s pros and cons.

James Froehlich, M.D., M.P.H.

Warfarin has a long history as an effective, safe and inexpensive medication, although the drug does come with “tricky challenges that the new anticoagulants don’t have,” stresses Geoff Barnes, M.D., clinical lecturer in Cardiovascular Medicine at U-M. “Warfarin’s biggest challenges involve frequent blood tests, monitoring and dosage adjustments to avoid bleeding problems. The new anticoagulants require no blood draws and minimal management.”

There are also dangerous food and drug interactions associated with warfarin, of which there are far fewer with the new anticoagulants. In addition, warfarin requires several days to take effect or completely leave the body, while the new anticoagulants need only hours at both ends. “It’s not safe to be on a blood thinner during certain procedures,” Barnes stresses. “So for those on warfarin, that means a lot of extra monitoring and management before and after procedures. It’s just not an issue with the newer anticoagulants.”

The dominant known disadvantage to the new anticoagulant agents is cost. U-M research suggests that the overall health care cost of anticoagulation therapy using the expensive new drugs could potentially be mitigated by fewer doctor visits, blood draws and complications. However, insurers currently consider these drugs second-line therapy and impose higher coinsurance or copay burdens on patients. Froehlich is hopeful that once insurers realize the savings these drugs will bring them down the line, they will re-evaluate coverage decisions.

“I see the cost issue disappearing soon — for at least some of these new agents,” Froehlich concludes. “These medications offer too many advantages to be relegated to second class status.”

ONLINE The U-M Anticoagulation Management System helped MAQI² create an online resource for patients and physicians at anticoagulation toolkit.org. Information includes pros and cons of approved anticoagulants, how to choose, how to switch between medications, provider education and patient instructions.
Slow to Mature, Quick to Distract

ADHD study reveals brain differences

A new study of brain activity in 750 children and teens reveals a key difference in brain architecture between those with attention-deficit/hyperactivity disorder (ADHD) and those without.

Those with ADHD lag behind others of the same age in how quickly their brains form connections within, and between, key brain networks, the study suggests. The result: less-mature connections between a brain network that controls internally directed thought (such as daydreaming) and networks that allow a person to focus on externally directed tasks.

That lag in connection development may help explain why patients with ADHD become easily distracted or struggle to stay focused. The new findings, and the methods used to make them, may lead to a neuroimaging “biomarker” for better diagnosis and treatment tracking in ADHD. The same approach could also be used for other behavioral and psychiatric conditions.

The research, performed by a U-M team led by Chandra Sripada, M.D., Ph.D., used advanced computing techniques to analyze detailed functional MRI scans from 275 children and adolescents with ADHD, and 481 others without the condition. Using “connectomic” methods that can map interconnectivity between networks in the brain, the team could see how a number of different brain networks, each specialized for certain types of functions, were “talking” within and amongst themselves.

The findings are relevant to thinking about the longitudinal course of ADHD from childhood to adulthood, as some patients “grow out” of the disorder, while others face it throughout adulthood.

“We and others are interested in understanding the neural mechanisms of ADHD in hopes that we can contribute to better diagnosis and treatment,” says Sripada. “But without the database of fMRI images, and the spirit of collaboration that allowed them to be compiled and shared, we would never have reached this point.”

Their results were published in the Proceedings of the National Academy of Sciences.
New technology improves prostate cancer biopsies

The University of Michigan is the first center in the region to offer targeted prostate biopsies. UroNav, a new technology that combines highly specialized MRI and real-time ultrasound, helps guide a biopsy needle to the most suspicious areas of the prostate gland, helping urologists identify higher-risk prostate cancers.

In addition, the system can store the biopsy needle trajectory so that future biopsies can sample the same areas. U-M specialists have been using a similar system for research studies for nearly two years.

“The more information we can learn about a tumor — through better biopsies and better diagnostic tests — the more we will be able to personalize therapy. Our goal is to offer individualized treatment plans based upon patient-specific information,” says Ganesh Palapattu, M.D., associate professor of Urology and chief of Urologic Oncology at the University of Michigan Comprehensive Cancer Center.

The technology is most useful for men with a concerning prostate MRI or an elevated PSA, or men considering or currently under active surveillance for prostate cancer.

Prostate MRI is primarily used to identify potential sites of prostate cancer when the standard workup does not identify disease — for example, a negative biopsy but a rising PSA. Modern MRI is sensitive enough to identify intermediate- and high-risk prostate cancers while minimizing the identification of non-aggressive prostate cancers.

“MRI has only become useful in stratifying prostate cancer risk over the last several years. Advanced MRI technique allows us to identify and target clinically significant prostate cancers. One of the nice side effects is that modern MRI tends to minimize the appearance of non-aggressive prostate cancers. So it really refines our ability to find the kind of cancer we want to find,” says Matthew Davenport, M.D., assistant professor of Radiology at the U-M Medical School.

In addition to using MRI to help visualize the prostate, newer markers combined with PSA allow urologists to better gauge the risk of aggressive prostate cancer. A new test developed at the University of Michigan called Mi-Prostate Score combines PSA, PCA3 and the gene fusion TMFRSS2-ERG.

“PSA has been criticized as a poor marker for prostate cancer. We’re developing advances that go beyond just an elevated PSA. A PSA test may be part of the picture, but it’s no longer all we have available,” says Jeffrey Montgomery, M.D., associate professor of Urology at the U-M Medical School.

“Refer To speak with a urologist or radiologist about UroNav or multiparametric prostate MRI, or to refer a patient call M-LINE at 800-962-3555.

Read more about Mi-Prostate Score at Colleagues in Care Online at med.umich.edu/cic.
It’s been done for acute myocardial infarction. It’s been done for congestive heart failure. It’s been done for pneumonia. Now it’s time to do it for sepsis, say U-M experts. It’s time, they say, to harness the power of research and data to ensure consistent, high-quality care for every patient.

Sepsis now affects more hospital patients, and leads to more hospital costs, than any other diagnosis. It kills one in every six people diagnosed with it. More die from sepsis than from prostate cancer, breast cancer and AIDS combined.

In the Journal of the American Medical Association, U-M intensivists Colin Cooke, M.D., M.Sc., M.S., and Theodore Iwashyna, M.D., Ph.D., lay out the case for a national system that would hold hospitals and care teams accountable for sepsis diagnosis and care.

Just as it has done for other diseases, the federal government should set clear standards and targets for the kind of care that gives sepsis patients the best odds of surviving, they say. But unlike in previous efforts, the approach should incentivize better detection, start with regional collaboration to determine the best approaches, and respond to new evidence from rapidly evolving sepsis research.

The authors note that currently, only about one-third of sepsis patients nationwide receive the best possible care — despite national guidelines to help hospitals and doctors recognize and treat it. Late and missed diagnoses are common.

Says Cooke, “We believe that by creating a framework for quality improvement in sepsis care that takes into account evolving knowledge of this condition, we can improve patients’ odds of survival and reduce variation in care.”

Adds Iwashyna, “Excellent sepsis care requires careful clinical judgment and good teamwork, but at the same time it has to happen fast. This is not easy. But we have to improve our quality of care even when it is not easy.”

**Does obesity protect sepsis patients?**

Obese patients are more likely to survive sepsis than those of normal weight, U-M research finds — bringing to light interesting questions about how obesity impacts the body’s response to infection. The study of 1,404 Medicare beneficiaries was published in Critical Care Medicine.

“Physicians expect obese patients to do poorly, and this belief can affect the care and counseling they provide to patients and their families,” says Hallie Prescott, M.D., a U-M critical care physician. “Our study indicates obese sepsis patients actually have lower mortality and similar functional outcomes as normal weight patients.”

A better understanding of this difference may improve care for all patients with sepsis and other critical illnesses.

Only about one-third of sepsis patients nationwide receive the best possible care.

**READ** Get linked to the JAMA paper at Colleagues in Care Online at med.umich.edu/cic.
FIVE MINUTES WITH MARSCHALL RUNGE, M.D., Ph.D.

New executive vice president for medical affairs

What three characteristics describe your leadership style?

1. Empowering: Success for our academic health system depends upon my working very closely with, and empowering, highly effective leaders. UMHS has outstanding leaders in place and in the pipeline, as well as exceptional partners across the state. I look forward to developing a leadership structure that promotes excellence and accelerates decision-making.

2. Engaged: Although my new position has many demands, I want to remain engaged in all aspects of the UMHS mission — clinical care, research and teaching — so that I stay connected to the challenges facing faculty. To this end, I will see patients (which includes clinical teaching) and my research lab will move to Michigan this summer.

3. Fiscally disciplined: What I mean here is the need to be disciplined and strategic in prioritizing capital. For faculty and staff to excel, we need state-of-the-art resources (space, technology and equipment). But, just as important, we need to invest in our faculty and staff — our human capital. This will be of critical importance for future successes.

What are the main challenges you anticipate as EVPMA?

These are exciting yet challenging times in medicine. We will have to deal with the need to reduce health care costs, the challenge of educating medical professionals to practice in tomorrow’s environment, and the increasing complexity of bridging medical discovery to practices that improve the human condition.

While there is no single road map for success, I am convinced that no state is better positioned to tackle these challenges than Michigan. What attracted me most to the University of Michigan is its deep, long-standing commitment to excellence and innovation, especially in health care.

You’ve spent most of your time in the south. Are you ready for Michigan winters?

That’s a good question! I was in Baltimore for medical school and residency, and then in Boston for my fellowship. So, I’m looking at Michigan winters as similar to Boston winters. Recently, one of my sons introduced me to “hot yoga,” so when I need a fix of heat and humidity, I’ll visit the nearest Bikram studio. I’m not very flexible, but the heat in those rooms makes the outside feel pretty good!

Though I never lived in Michigan, my maternal grandfather was a first generation American who earned his undergraduate degree, M.D. and Ph.D. at U-M, and served on the faculty before heading south. My mother was born in Ann Arbor and several family members attended U-M. So, this is a very special opportunity for me.