PET Tracers Are Revolutionizing Cancer Treatment

MALLINCKRODT INSTITUTE OF RADIOLOGY // WASHINGTON UNIVERSITY // ST. LOUIS
Three PET tracers, now available at MIR, are having a big impact on how certain cancers are detected and ultimately treated.
A massive national study involving MIR researchers may provide the groundwork for understanding how autism develops.

MIR researchers participated in a national study that predicted with 80% accuracy the likelihood of autism in babies who have an older sibling with the disease.

Interventional radiologist Raja Ramaswamy, MD, provided Vinita Woods with pain relief from peripheral arterial disease that got the 69-year-old back on her feet.
A Change Would Do You Good

Mallinckrodt Institute of Radiology continues to “define how radiology is practiced” as it ushers in its next generation of leaders.

Robert McKinstry, MD, PhD, likes to reinvent himself about every seven years.

So when current MIR director and radiology department chair Richard L. Wahl, MD, came on board in 2015, McKinstry approached him about his desire for a job change. It was well past his self-imposed deadline: he had been chief of pediatric imaging for nine years. But he was also director of the Center for Clinical Imaging Research and the Division Chief of Research Facilities. He didn’t want more responsibilities; he wanted different ones.

McKinstry’s conversation set into motion a series of events that would eventually lead to a different job for him, as well as a new one for Daniel Picus, MD, also a professor of radiology and then Senior Vice Chair and Division Chief of Diagnostic Imaging. The timing was serendipitous.

“Dr. Picus was looking to change what he was doing — he had been doing his job for quite some time — and I was looking for a change,” McKinstry says. In March, Picus became MIR’s first Senior Vice Chair for Special Projects and McKinstry took over Picus’s former position.

“I’m fortunate to have this opportunity, and we’re fortunate that Dan was such a strong leader for so many years.”

Currently McKinstry is working with Barnes-Jewish Hospital on capital improvements to modernize its fleet of radiology equipment. “We want to define how radiology is practiced. And in order to do that, we need to have the imaging equipment that allows us to push the practice forward, to push the envelope, to innovate."

Mentoring is a sweet spot for McKinstry and one he intends to champion moving forward.

“I’m very interested in helping to mentor faculty, in setting clear guidelines and expectations, and making sure the process is transparent so that the people know what they need to do to be promoted, and that they feel like the process has been fair and open.”

For Pamela K. Woodard, MD, professor of radiology and biomedical engineering, success has been a balancing act. Since 2012, she has directed the Center for Clinical Imaging Research (CCIR), helping the research facility grow and making it fiscally sound.

During her tenure, Woodard led the CCIR through a major construction project, developed a strategic equipment refreshment plan, and balanced the CCIR budget on a cash basis. As an addendum to her financial acumen, she has brought in nearly $10 million of NIH and industry funding since she has been at Washington University.

In March, Woodard was officially named Senior Vice Chair and Division Chief of Radiology Research Facilities at MIR, stepping into the position previously held by colleague Bob McKinstry, MD, PhD.

“Pam is ideally qualified to assume this important position and has learned the job with gusto,” says MIR director and head of the Department of Radiology, Richard L. Wahl, MD, who appointed her to the post.

Woodard, who now has nine radiology research facilities at MIR under her purview, is determined to provide excellent service to everyone who uses the imaging research facilities. “These facilities serve the entire university,” she says, referring to the over 70% of users who are not radiology faculty.

“Researchers throughout the Washington University School of Medicine, Danforth Campus [at Washington University], and researchers and students from Saint Louis University use our imaging facilities,” among others, she adds.

“We’ve refined the business model over several fiscal years to the point where the facility is now consistently breaking even,” says Woodard, the first woman to hold a senior vice chair position at Mallinckrodt Institute of Radiology.

Woodard will continue to serve in her clinical administrative role as head of cardiac CT/MRI moving forward and in her current research administrative capacities until suitable replacements are identified.
New PET Tracer Detects Alzheimer’s Earlier

Mallinkrodt Institute of Radiology researchers have developed a new PET tracer that potentially detects Alzheimer’s disease better and earlier than the other imaging compounds currently available.

“I think we’ll be able to detect Alzheimer’s maybe 10 to 15 years sooner, especially in people who might be at risk for developing the disease,” says Vijay Sharma, PhD, professor of radiology, neurology and biomedical engineering.

Called Fluselenamyl, the new chemical compound can identify smaller clumps of amyloid beta, which is a sticky protein found in the brains of people with Alzheimer’s disease. By the time patients exhibit signs of cognitive decline and memory loss from the disease, their brains are riddled with amyloid plaques.

The MIR-produced tracer binds to amyloid beta three-to-10 times better than the three other FDA-approved imaging agents designed to detect Alzheimer’s. It also detects diffuse plaque — something that none of the other compounds can do, Sharma says. Amyloid plaques can either be “compact” or “diffuse.” Compact forms of amyloid plaque appear after significant brain damage has occurred. Formerly thought to be benign because it’s found in the brains of the elderly with and without Alzheimer’s, diffuse plaque is now believed to be an indicator of pre-clinical disease.

People begin to acquire diffuse plaque around 50 years of age. Most people who develop Alzheimer’s, except those with the inherited form of the disease, typically first experience symptoms during their 60s. “Fluselenamyl will be able to detect Alzheimer’s before symptoms and brain damage occur,” Sharma says. “It will also better quantify the efficacy of existing state-of-the-art drugs and new therapies under development for either reducing or excreting plaques from the brain of AD (Alzheimer’s disease) patients.” Because of its ability to detect diffuse plaques, application of Fluselenamyl could extend well beyond Alzheimer’s.

So far, Fluselenamyl has been used in animal studies only. Human testing is next, and Sharma has submitted an application to the National Institutes of Health for a Phase 0 trial. Results of pre-clinical tests conducted by Sharma and his associates were published in the journal *Scientific Reports*.

“Since it was published, Fluselenamyl has been widely discussed at Alzheimer’s disease forums and listed by major societies, including World Molecular Imaging and the Radiological Society of North America,” he says. “It’s listed as a ‘discovery of the month.’”

Avoid Breast Biopsy Surgery With New System

A new breast biopsy system that’s compatible with digital breast tomosynthesis — also known as 3D mammography — is now available at the Breast Health Center. Prior to the acquisition of this new piece of equipment, women with certain suspicious breast findings detected through tomosynthesis had to undergo a surgical biopsy.

“We couldn’t use our existing biopsy needle techniques for certain findings,” explains Catherine Appleton, MD, chief of breast imaging at Mallinckrodt Institute of Radiology and at Siteman Cancer Center. More specifically, they couldn’t perform a stereotactic breast biopsy because they couldn’t see the findings that 3D mammography could. “Consequently, women with these findings were sent off to the operating room,” Appleton says. “This required the radiologist to place a small guidewire in the breast to help the surgeon locate and remove the suspicious area.” The new biopsy system, called Affirm® by Hologic, addresses that issue and more.

Above: Women can be seated during their breast biopsy with the new system.

“The Affirm biopsy system permits accurate pre-operative diagnosis. It has also proven to be faster in some cases, as well,” says Appleton. Because the new system allows patients to be seated during the procedure rather than prone, it can better accommodate the very elderly and those with back problems. The system snaps onto the mammography unit and the patient is seated in a chair with her breast compressed by the technologist, just as she would with a mammogram.
Close to 200 faculty, staff and postdoctoral research associates turned out for the Mallinckrodt Institute of Radiology 2017 Research Symposium and poster session held in the Farrell Learning and Teaching Center on March 28. The annual event included more than 60 posters showcasing an array of ongoing basic and clinical research conducted by MIR investigators. Lectures were also presented by Beau Ances, MD, PhD, professor of neurology and radiology; Vijay Sharma, PhD, professor of radiology, neurology and biomedical engineering; and Suresh Vendantham, MD, professor of radiology and surgery.

Paul Thompson, PhD, professor of radiology, neurology, psychiatry and engineering at the University of Southern California, gave the keynote lecture “The ENIGMA Consortium: Mapping Human Brain Disease with Imaging and Genomics in 50,000 Individuals from 35 Countries.”

A Graduate research assistant Inema Orukari (left) listens to graduate fellow Dov Lerman-Sinkoff.

B The 2017 MIR Research Symposium and poster session was held in the Farrell Learning and Teaching Center, located on the Washington University School of Medicine campus.

C Robert J. Gropler, MD, professor of radiology, and Sally J. Schwarz, MS, RPH, BCNP, professor of radiology

D Keynote speaker Paul Thompson, PhD, specializes in the field of human brain mapping.

E MIR director and head of radiology, Richard L. Wahl, MD, addresses attendees.

F Beau Ances, MD, PhD, professor of neurology and radiology, gives the opening lecture.
SCANNING THE HORIZON

New PET Tracers Detect Cancers Sooner

Above: A laminar flow hot cell where patient doses are drawn
Three new radiotracers now available for clinical use at Mallinckrodt Institute of Radiology are revolutionizing the way certain cancers are detected and ultimately treated. When paired with a PET/CT scanner, the new tracers—C-11 choline, F-18-fluciclovine (FACBC) and Ga-68 dotatate—provide essential information previously unattainable.

According to Richard L. Wahl, MD, director of MIR and head of the Department of Radiology, the new oncologic PET examinations are highly sensitive. “It’s about knowing if there’s cancer, where it’s located, if it’s localized or disseminated, and then using that information to more precisely inform and guide treatment,” says Wahl. “We’re talking about precision cancer imaging.”

**Early Detection for Prostate Cancer**

C-11 choline and FACBC are used to detect suspected, biochemically recurrent prostate cancer as indicated by rising PSA levels after prior treatment. Of the two radiopharmaceuticals, C-11 choline is produced on site at MIR.

“We’re one of a handful of institutions across the nation with FDA (U.S. Food and Drug Administration) approval to manufacture C-11 choline,” says Barry Siegel, MD, professor of radiology and of medicine, Senior Vice Chair and director of the MIR’s Division of Nuclear Medicine.

Access to C-11 choline is limited to facilities that have an on-site cyclotron and FDA approval to produce the radiopharmaceutical. MIR has four cyclotrons in use.

“The application is expensive, the approval process is stringent, and the tracer is short lived,” Siegel says. C-11 choline loses half of its radioactivity every 20 minutes. Because it decays so quickly it must be produced on site, he adds.

C-11 choline PET is so sensitive it can detect tiny pockets of cancer before a tumor becomes visible through conventional imaging. Men diagnosed with a biochemical recurrence at this early stage have more options for curative treatment.

Both oncologic tracers are used with a PET scanner, which tracks the localization of the radiopharmaceutical throughout the body. Because cancer cells accumulate the C-11 choline or FACBC, the increased uptake appears as “hotspots” on the scan.

“Of all the men who have curative therapy for prostate cancer, at least 30% of them will experience biochemically recurrent disease,” Siegel says.

Not only can the exam detect if there is a recurrence of prostate cancer, it can pinpoint the exact location of the relapse. However, a biopsy is still typically needed to confirm cancer.

Although the molecular mechanism behind each radiopharmaceutical is different, C-11 choline PET and FACBC PET exams have largely similar detection rates. FACBC has a longer half-life (110 minutes) but is made offsite and is currently available at MIR once a week. C-11 choline is offered five days a week.

**Candidates for C-11 Choline & FACBC**

“In general, we’re selecting men whose bone scans and CT/MRI scans are either negative or equivocal (non-informative) for disease,” says Siegel, “then using the new PET studies to define the active disease and its location so the referring physician can make a treatment decision.”
While the purpose of either scan is to map out the full extent of the disease, the broader goal is to see if a cure can be achieved without resorting to systemic therapy, which has multiple side effects and usually leads to the tumor ultimately becoming resistant to treatment.

**How Low Can You Go?**

Mallinckrodt will consider imaging patients with PSAs as low as 0.2 after a prostatectomy, Siegel says. But the scans perform better with men who have higher levels, he adds.

Ralph Erickson, 72, from Kirkwood, MO, has had two relapses. He's also had C-11 choline and FACBC PET examinations. The former test was performed in 2013 at the Mayo Clinic in Rochester, MN, (the only site at the time with C-11 choline) and the latter at Mallinckrodt in 2017. Both exams found a cancerous lymph node.

“PSA level is a surrogate for how much tumor volume is likely to be present. Therefore, the sensitivity of the tracers increases as the PSA level increases,” Siegel says.

Erickson’s PSA levels reached 1.7 ng/mL when his C-11 choline PET exam was performed, and 1.3 ng/mL when his FACBC PET exam was performed. Both detected early stage cancer.

In the past, patients like Erickson would have been followed until their PSAs were higher. But the game is changing, says Siegel.

**Finding the NETs**

Ga-68 dotatate, the third new oncologic PET tracer, is used for localizing neuroendocrine tumors, or NETs, expressing somatostatin receptors (SSTRs) in adults and children. Made daily at Mallinckrodt, the tracer is dramatically changing how these tumors are found.

NETs develop in the hormone-producing cells of the body’s neuroendocrine system and most often occur in the lungs, appendix, small intestine and pancreas. According to Farrokh Dehdashti, MD, a professor of radiology in the Division of Nuclear Medicine, they are rare and “very difficult to detect.”

Left: Reproduction image of Ga-68 dotatate PET with multiple metastatic foci
Conventional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) scans often miss them, and the imaging agent (indium-111 pentetreotide or Octreoscan) that’s been used for years to detect NETs has a low detection rate.

With this agent, we see so many very small lesions, even those you wouldn’t consider as disease by conventional imaging.

NETs have receptors for somatostatin, a hormone that regulates the endocrine system. Ga-68 dotatate works by binding to these receptors, which sit on the surface of cancerous cells. The result is superior images and vastly better detection.

**Better, Faster, Costs the Same**

“Ga-68 dotatate is a huge improvement in our ability to diagnose and detect the presence and extent of neuroendocrine disease,” Dehdashti says. “With this agent, we see so many very small lesions, even those you wouldn’t consider as disease by conventional imaging.”

Information from the exams also helps with selecting the most appropriate therapy, as well as with follow-up evaluation of that therapy. In addition to being far more effective than the previous standard diagnostic agent, imaging with Ga-68 dotatate is also quicker than that with indium-111 pentetreotide. The latter is performed over a two-day period with an injection on day one and a scan on day two. With Ga-68 dotatate PET, patients are scanned in a single session lasting less than two hours. And it turns out Ga-68 dotatate doesn’t cost any more, says Wahl.

**The Next Best Thing**

Nuclear imaging is evolving at a rapid clip with new tracers replacing older ones all the time. The ability to make the oncologic radiopharmaceuticals on-site is increasingly important, especially for those tracers with shorter half-lives.

C-11 choline, FACBC and Ga-68 dotatate with PET/CT and PET/MRI are approved by the U.S. Food and Drug Administration for clinical use and covered by Medicare for the aforementioned indications. All tests can be ordered via Allscripts or by calling (314) 362-8275.
Left: An infant’s or toddler’s ability to engage others, such as by pointing at something that grabs their attention, is a behavior that children with autism spectrum disorder don’t often or ever initiate.
Detecting Autism Earlier

A key developmental behavior occurring around the first year of life—one that most parents or caregivers give barely a thought to—is the event called initiation of joint attention. This is where a toddler will see something of interest and point at it or otherwise acknowledge its existence by a shifting eye gaze or a non-linguistic babble in the presence of another toddler or person.

It’s a non-verbal action that implies: ‘Hey, isn’t this neat?’ And it draws others into the joy of discovery. However, those who a) don’t often or ever initiate joint attention, b) keep focus on a restricted set of interests and activities, and c) exhibit repetitive behaviors (like arm flapping) may be considered at risk for developing autism spectrum disorder (ASD). The severity of ASD, a neurological disorder most commonly diagnosed between the ages of two and four, can vary greatly. At its more extreme levels it can make social engagement difficult and achievement challenging.
The Sooner the Better

Researchers studying autism and related neurological disorders agree that diagnosis at a younger age provides an opportunity for an earlier introduction of helpful treatment therapies, which can lead to a better outcome for the autistic child. Now those researchers are encouraged by the findings from a massive, multi-institutional study that features the analysis of functional magnetic resonance imaging data by the Mallinckrodt Institute of Radiology.

Published in the journal *Cerebral Cortex*, the data gathered in the study from the brains of 177 children, ages 12- and 24-months, reveals a fingerprint of brain function that highlights two sets of interacting functional networks. The brain function was imaged with MRI as the children slept quietly, and the tendency to initiate joint attention was assessed in a laboratory setting the day following their scans.

In the brain fingerprint of the initiators, there was a very strong positive coupling between the visual network and the posterior cingulate areas of the default mode network. The default mode network is active during quiet rest or daydreaming but tends to shut down while a person focuses on a challenging task. In those less likely to initiate, there was a strong connection between the brain’s visual and dorsal networks. The dorsal attention network helps one to maintain focus on something while allowing the brain to respond to other potentially important sensory information.

May I Have Your Attention?

Linking this functional connectivity data out of a pool of 26,000 functional connections in the brain was an enormous undertaking.

“We were interested in understanding the associations between this behavior and the way the brain is wired together using this model of functional connectivity,” says Adam T. Eggebrecht, PhD, instructor in radiology, and the paper’s first author. They used the Communication and Social Symbolic Behavior Scale to assess how much kids were spontaneously initiating joint attention.

“Initiation of joint attention is such a fundamental stepping stone to get to extraneous high-level and dynamic social interaction behaviors. This is an absolutely unique and amazing data set as far as having clean, functional connectivity MRI data,” says Eggebrecht. “Also, having the behavioral MRI data in this age group is a very special thing.

You can apply these analyses that we’ve developed to a wide range of behaviors to better understand typical and altered early childhood development relating to autism spectrum disorder and neurodevelopmental disorders in general.”

Above: Limited interests and repetitive activities in a very young child can be a symptom of autism, whereas the joy of discovery is not.

It’s a non-verbal action that implies: ‘Hey, isn’t this neat?’ And it draws others into the joy of discovery.
The study involved dozens of researchers from other institutions in the multicenter Infant Brain Imaging Study (IBIS).

A Team Effort

John R. Pruett, Jr., MD, PhD, associate professor of child psychiatry at Washington University, is co-senior author on the paper. “We think this is the first demonstration of brain-based correlates for initiation of joint attention using MRI, and we’re very excited about that,” says Pruett. “Our hope is that we can identify brain-based changes that are predictive of autism outcome before behavioral symptoms manifest, and then we can get children into treatment earlier, which could mean great improvements in managing autism.”

In addition to Eggebrecht, Pruett and their MIR colleagues, who are funded by National Institute of Mental Health programs, the study involved dozens of researchers from other institutions in the multicenter Infant Brain Imaging Study (IBIS). IBIS is funded by the National Institutes of Health and headquartered at the University of North Carolina, Chapel Hill. The IBIS network principal investigator is Joseph Piven, MD, co-senior author on the paper, and a professor of psychiatry, pediatrics and psychology at the University of North Carolina. Piven is the principal investigator of a National Institute of Child Health and Human Development grant called Autism Centers of Excellence.
ASD is now defined by two categories of disruption. The first is disruption of social communication, including language and non-verbal communication. The second is repetitive and restricted behaviors. For instance, according to NINDS, some early suspicious childhood behaviors that might require an expert’s evaluation include no babbling or pointing by age one, no response to name, no single words by 16 months or two-word phrases by age two, poor eye contact, no smiling, and excessive lining up of toys or objects. For children beyond age two, indicators include an inability to make friends, impaired ability to initiate or sustain a conversation, repetitive or unusual use of language, and abnormally intense or focused interest.

“There is no known specific biological basis for autism today,” says Eggebrecht. “Moreover, with few exceptions, a person’s genetic predisposition is not a ‘smoking gun’ for developing autism at a certain severity level.”

This research lays the groundwork for understanding how fundamentally aberrant processes develop in the brain as autism is first emerging in infants,” says Piven. “Future work relating signatures of brain function to brain structure and behavior as children progress to school age may help illuminate the neurobiology underlying autism, and help us design more effective therapies.”

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorders not otherwise specified (PDD-NOS) all fall under the autism umbrella. And the National Institute of Neurological Disorders and Stroke (NINDS) says ASD occurs in every racial and ethnic group, and across every socioeconomic level. It’s estimated that one out of every 100 babies born in the U.S. develops autism. Furthermore, the risk may be as high as 20 out of every 100 births for infants with older siblings who have the disorder. (See sidebar.)

Above: “You can apply these analyses that we’ve developed to a wide range of behaviors to better understand typical and altered early childhood development relating to autism spectrum disorder and neurodevelopmental disorders in general,” says Adam Eggebrecht, PhD.
Evaluating Familial Risk

Researchers evaluated 116 young children at 12 months of age and 98 children at 24 months. Some kids were imaged at both time frames and about 75% of all subjects had an older sibling with ASD. The latter makes the child high-risk, which the researchers knew going into the study.

“One of the fundamental characteristics of the study is to try to understand what effect this familial risk has on exhibition of behaviors, as well as receiving a full-blown diagnosis,” Eggebrecht says. “Kids with an older sibling who has autism have a much higher likelihood of either developing autism or going on to exhibit disrupted behaviors, generally associated with autism, but at a level too low for a full-blown diagnosis.”

Children the age of the study participants are notoriously restive, adding to the difficulty of the study. The preference is to bring them into laboratories at night and “train” them so that they can sleep with the noise of the MRI machine, which can reach 120 decibels.

“You basically bundle them up, so they’re very cozy and snug, and put on noise-cancelling earphones and headphones to deaden the sound,” Eggebrecht says. “Many kids will sleep comfortably for at least two hours.”

Next Generation of Diffuse Optical Tomography (DOT)

Eggebrecht and MIR colleagues are striving hard to develop the next generation of DOT, an optical imaging alternative to f-MRI. They are making improvements on the DOT hardware, which is literally a cap a patient wears. The cap holds dozens of wires that are optical fibers that shine infrared light to measure a host of brain responses. The researchers are making the hardware lighter, more wearable and more portable, enabling them to use this technology on infants in the first few weeks of life. They’re more compliant than 12- and 24-month-olds because they sleep most of the time.

“The data set we’ve gathered in this study is very informative to the optical tools we are developing,” Eggebrecht says. “The regions and connections of the brain we’ve found vital in this study can help us optimize the design of our DOT caps for these kids.”

A Second Study

Can Breakthrough Research Predict Autism in Siblings of Children with Autism?

Mallinckrodt Institute of Radiology researchers participated in a national study that predicted, with 80% accuracy, the likelihood of autism in babies who have an older sibling with the disorder. It’s estimated that one out of every 100 babies born in the U.S. develops autism. The risk may be as high as 20 out of every 100 births for infants with older siblings with the disorder.

Researchers conducted MRI scans of sleeping infants at six, 12 and 24 months of age. A special computer program known as a “machine learning algorithm” was subsequently used to predict which babies would develop autism by two years of age. Typically, autism is diagnosed later, i.e., between two and three years of age. An earlier diagnosis would allow health care professionals to intervene pre-symptomatically, when the brain is still pliable.

Mallinckrodt was one of five clinical sites participating in the first-of-its-kind study. “Over 100 high risk and control infants longitudinally were scanned as part of this project,” says Kelly Botteron, MD, professor of psychiatry and radiology. Botteron’s MIR colleagues, Robert McKinstry, MD, PhD, professor of radiology, and John Pruett, MD, PhD, associate professor of psychiatry and radiology, also participated in the study. “I’m not sure how many of the subjects are ours, except we tend to have the most in any publication,” adds Botteron.

The breakthrough study grabbed the attention of local and national media, including the NBC Nightly News, the “Today” show and St. Louis CBS-affiliate KMOV-TV.
In the NICK of Time

Left: A normal angiogram of the bilateral lower extremities.
Tiny nicks in the skin and arteries help deliver minimally invasive treatments that diminish leg pain caused by peripheral arterial disease.

Vinita Woods noticed the pain in her right leg about 12 years ago when she was a delivery driver for the local Meals on Wheels program. “Jumping off and on the truck, that’s when I noticed it,” says Woods, a resident of The Grove, a St. Louis neighborhood near Washington University Medical Center. That’s also when Woods suspects her peripheral arterial disease (PAD) began.

Initially her pain was intermittent and she tried to self-remedy for years. “I would rub it,” says Woods, bending over as if she were going to stroke her right leg. “I would rub it with alcohol, with anything.”

But her leg pain progressively worsened and by February 2016, Woods could barely walk. That’s when her doctor’s office referred her to Mallinckrodt Institute of Radiology (MIR).
Blocked Blood Flow Increases Risk of PAD

“PAD is caused by atherosclerosis that narrows and blocks arteries in various critical regions of the body,” says Raja Ramaswamy, MD, an interventional radiologist at MIR. It usually occurs after age 50, and is most often seen in the legs.

“Blocked blood flow raises the risk of getting an infection in the affected limbs,” Ramaswamy says. In very serious cases it can lead to leg amputation.

Because other conditions share similar symptoms (with PAD) many healthcare professionals underdiagnose it.

Woods was diagnosed with multiple blockages in her superficial femoral artery — the main artery that runs alongside the thigh. Inadequate blood flow caused her leg to ache.

“The most common symptoms of PAD involving the lower extremities are cramping, pain or fatigue in the affected leg or hip muscles when walking or climbing stairs,” continues Ramaswamy. “The pain goes away with rest, but returns when you resume walking.” This is called claudication and most patients who come to see Ramaswamy and his MIR colleagues present with it. So did Woods.

“Her blood flow was so bad that her leg wasn’t perfusing adequately,” he says. It wasn’t flowing down into her leg or foot. “That’s why she was having issues with walking.”

Underdiagnosed and Undertreated

Many people mistake PAD for something else. What’s worse, because other conditions share similar symptoms many healthcare professionals underdiagnose it.

“The most common test for PAD is the ankle-brachial index (ABI), a painless exam in which ultrasound is used to measure the ratio of blood pressure in the feet and arms,” says Ramaswamy. ABI exam results, together with one’s symptoms and risk factors, help determine the diagnosis.
Above: Raja Ramaswamy, MD, in one of the MIR interventional suites at the Center for Advanced Medicine.
PAD risk factors include a history of smoking, diabetes, high blood pressure or high cholesterol, and advanced age. Woods had three of these risk factors: she was 69, and had diabetes and high blood pressure. Peripheral arterial disease can also be diagnosed with a magnetic resonance angiogram (MRA) or computed tomography angiogram (CTA), says Ramaswamy. An MRA or CTA is also a noninvasive study that produces detailed images of the blood vessels, and can be performed in areas of concern.

Although Ramaswamy strongly suspected an arterial problem upon examining Woods, a CTA confirmed it. “He told me ‘I’m going to fix that leg for you,’” says Woods. “He was so nice. He made all the difference.” Relieved, Woods nonetheless still had reservations. “She asked me if I was going to ‘cut her open,’” says Ramaswamy. “I told her ‘No,’ and that everything we do here is through minimally invasive techniques.”

Woods’ life dramatically improved when she underwent a new type of balloon angioplasty to open the blocked artery, followed by a stent insertion to keep the artery open.

**First-Line Treatment for Arterial Occlusions**

Interventional radiology and its minimally invasive imaged-guided procedures are gaining momentum as the treatment of choice for many conditions — including peripheral arterial disease.

“Early randomized trials have shown interventional therapy to be as effective, and with less complications, when compared to surgery for arterial occlusions,” says Ramaswamy.

There currently are three options for a minimally invasive image-guided procedure, each with specific patient parameters.

“In an atherectomy, a tiny catheter is inserted into the artery at the site of blockage to ‘shave’ or ‘cut’ the plaque from the inside of the artery and remove it,” says Ramaswamy. “A stent-graft is a tiny scaffold-like device covered with synthetic fabric that’s inserted into the blood vessels to bypass diseased arteries.”
Ramaswamy performed the third option on Woods — an angioplasty and stenting.

“Balloon angioplasty and stenting have generally replaced invasive surgery as the first-line treatment for PAD,” says Ramaswamy. Using imaging for guidance, the interventional radiologist threads a catheter through a tiny nick in the femoral artery in the groin to the blocked artery in the legs, then inflates the balloon to open the blood vessel where it is narrowed or blocked.

To Stent or Not to Stent

The decision to stent or not depends upon the case. Woods’ peripheral arterial disease was compounded by other conditions and severe enough to still warrant a stent. “We put Ms. Woods under moderate sedation with pain and anti-anxiety medication through an IV,” says Ramaswamy. “We rarely perform these procedures under general anesthesia.”

They accessed the blocked vessel with a catheter through skin and arterial nicks the size of a pencil point. Contrast dye was injected to highlight the targeted vessel. Then the drug-coated balloon was inserted, inflated and removed.

Dye was injected again, immediately after the balloon angioplasty, allowing Ramaswamy to see in real time how the vessels reacted. Within an hour, Woods’ artery was re-opened and all blockages were gone, says Ramaswamy. A precautionary stent was inserted, however.

“The best thing about this (case) is that Ms. Woods is able to walk and do her normal activities again,” he says. “We brought her here to one of our interventional suites, did the procedure in an hour, watched her for two hours after the procedure, and then let her go home the same day. It’s a very streamlined process as opposed to open surgery, and the patient recovers much quicker.”

There currently are three options for a minimally invasive image-guided procedure.

Ramaswamy used a new drug-coated balloon on Woods. “Once you inflate it, the drug penetrates the walls of the artery and helps the walls of the vessel stay open. It’s a relatively new technology and the whole point to it is so that you don’t have to put a metal stent inside the vessel,” he says. Metal stents can ‘catch’ debris, such as fatty deposits of plaque in the bloodstream, and occlude.
Howard Forman, MD, MBA, is a professor of diagnostic radiology (and vice chair of finance), public health (health policy), economics and management at Yale University. His interest in health policy was sparked during his residency at Mallinckrodt Institute of Radiology and his expertise in the field has taken him to the halls of the U.S. Senate and the White House.

Why did you choose Mallinckrodt for your residency training?

It was obvious from the moment I walked in that Mallinckrodt was not like any other radiology department. They had a very well organized interview day, where I got to meet several faculty members and the chief residents. The most influential person that day was D. Claire Anderson. She was incredibly enthusiastic about the program and explained to me why St. Louis is such a great city. Stuart Sagel was also inspirational in his passion and belief that Mallinckrodt was the best program in the country. In talking to the residents, it was clear that there was no place I could go to get better training than at Mallinckrodt.

Which instructors at Mallinckrodt made the greatest impression upon you?

The instructors in the abdominal imaging section—Bruce McClennan, Jay Heiken, Bill Middleton, Jim Brink, Dennis Balfe—were very strongly committed to my professional development from the very beginning. In 1992, while I was at Mallinckrodt, there was a very important presidential race that brought health care front and center for the first time. I developed my own personal ideas about what I thought could be a positive direction for the country in terms of health care and I had conversations with many of the faculty. I became very passionate about what positive change could look like. I briefly considered working on Bill Clinton's campaign, or doing a policy career alongside radiology, with perhaps a fellowship in the middle of my residency.

The abdominal team and their desire to support me under any circumstance were very important to my ultimate decision to do a post-residency fellowship in health policy at the University of Pennsylvania. I cannot overstate how much they helped me at that time. When I left in 1994, I did so with their support and promotion.

Tell us about the many roles you perform at Yale.

I was recruited as vice chair of finance and administration at Yale in 1996, nine months after Bruce McClennan arrived at Yale as the chairman of radiology. In 1998, I was invited by the economics department to start teaching to undergraduates, which I still do today. I worked with a team to create our MD/MBA program, something we’re very proud of here. We’ve graduated 14 classes from that program. I’ve had a faculty appointment in the School of Management since 2001. I’m the faculty director of the healthcare management program in the School of Public Health, which is now one of the two biggest educational programs at Yale. I’m the faculty director of the healthcare focus area in the School of Management’s MBA for Executives program. And I still practice diagnostic radiology an average of two to three days per week.
What brought you to the U.S. Senate in 2001-2002?
I was a Robert Wood Johnson health policy fellow working with Sen. Bob Graham of Florida. There was an expectation that health care would be a high priority on the Senate’s agenda and that medical prescription benefits would pass. But after 9/11 happened, Sen. Graham was pulled to work on those issues, so I worked more closely with Sen. Edward Kennedy and his staff. It was an incredible opportunity and experience. Kennedy truly cared about the physicians who worked on his staff, and on the policy and agenda he had set. The experience taught me about the legislative process and forged connections to the executive and legislative branches that are still very strong, on both sides of the aisle.

You were among the health economists who participated in an Affordable Care Act roundtable at the White House in 2009. What did you take away from that?
It was validating to know that the feelings I had about the issue were shared by other people. It also informed my ability to teach these issues. I gained a clearer understanding of how the process works and how well-informed thought leaders can make the process work better. I now bring guest speakers to campus 20 times a year, largely to speak on this topic. All of that happens because of my experience in the Senate and with health care reform.

What examples from your education at Mallinckrodt do you draw on in your positions at Yale?
Bruce McClennan and Jay Heiken always looked out for me and sought to promote me without having any interest in promoting themselves. They were always willing to connect me with people who would help inform my decisions about my career. The single greatest praise I receive from people, the thing I am most proud of in my teaching, is that I am an effective mentor. I have helped promote the careers of dozens, if not hundreds, of people over the past two decades at Yale. That is, in no small part, due to those individuals at Mallinckrodt who put themselves out for me. I don’t forget that at all.

Above: Forman with then U.S. Surgeon General and Vice Admiral Vivek H. Murthy, MD, and (current) acting Surgeon General and Rear Admiral Sylvia Trent-Adams, Ph.D., R.N.
MIR faculty William H. McAlister, MD, Sheng-Kwei Song, PhD, and Farrokh Dehdashti, MD, were honored recently at Washington University School of Medicine’s 2017 Distinguished Faculty Awards ceremony. The annual event, held February 15 at the medical school’s Eric P. Newman Education Center, recognizes physicians from across the university for their achievements in clinical care, community service, research and teaching.

McAlister, professor of radiology and pediatrics, was honored with the Distinguished Clinician Award for his tireless dedication in caring for patients and mentoring fellows at Washington University in St. Louis. He is an expert in skeletal dysplasias and metabolic bone disease in children and his career has spanned more than 60 years.

Song, professor of radiology, was honored with the Distinguished Investigator Award for his innovative contributions focusing on new techniques for imaging the central nervous system (CNS). Song is a world renowned imaging scientist whose work is widely applicable to many CNS diseases, as well as some cancers.

Dehdashti, professor of radiology, received the Daniel P. Schuster Award for Distinguished Work in Clinical and Translational Science. Dehdashti, an innovative translational researcher, was honored for her seminal efforts in identifying and expanding the role of positron emission tomography (PET) in the field of oncology.

Robert C. McKinstry, MD, PhD, professor of radiology and Senior Vice Chair for the Division of Diagnostic Imaging, is the recipient of the William R. Orthwein, Jr. and Laura Rand Orthwein Chair in Radiology and Pediatrics at MIR. McKinstry’s installation was followed by his inaugural lecture “Advanced MR Imaging of the Developing Brain” on March 29, 2016.

Dennis M. Balfe, MD, professor of radiology, received the Walter B. Cannon Medal Award during the annual meeting of the Society of Abdominal Radiology on March 29, 2017, in Hollywood, Florida. The award is given to a distinguished radiologist who has made an outstanding contribution to the field of gastrointestinal radiology and to the society. Balfe is the former chief of abdominal imaging at MIR.

Samuel I. Achilefu, PhD, Michel M. Ter-Pogossian Professor of Radiology and chief of optical radiology, received an Excellence in Health Care Award from the St. Louis American for his work using ultraviolet light to fight cancer. Achilefu was one of seven recipients honored by the newspaper’s foundation on April 28, 2017.

Grants

Joseph Ippolito, MD, PhD, an instructor in radiology, received a one-year, $50,000 grant for “Hybrid MR/MALDI Imaging of Prostate Cancer: A Feasibility Study” from the Prostate Cancer Foundation. The grant is effective through October 2017.

Joseph J.H. Ackerman, PhD, professor of radiology and professor of chemistry, received a $2 million grant from the National Institutes of Health to purchase a GE SPINlab™ dissolution DNP (dynamic nuclear polarization) instrument. SPINlab™-enabled HP MR is a promising and powerful technology for metabolic assessment and pathway analysis. The GE SPINlab™ is currently the only commercially available hyperpolarization device. Delivery of the instrument is expected in the first quarter of 2018.

Jennifer Nicholas, MD, MHA, assistant professor of pediatric radiology, received a $74,000 resident Education Scholar Grant from the Radiological Society of North America (RSNA). The one-year grant for “Facilitating a Radiology Curriculum for Radiology Residents in Haiti Using Tablet Computers” is effective through June 30, 2018.
Lectures

Pamela K. Woodard, MD, professor of radiology and biomedical engineering, was selected to give the Charles T. Dotter Memorial Lecture at the 2016 American Heart Association Scientific Sessions in New Orleans. The lecture, presented on November 25, 2016, was titled “Precision Plaque Imaging: Are We There Yet?” Woodard also presented “Cardiac PET/MRI: Tool or Toy?” at the Society for Cardiovascular Magnetic Resonance on February 3, 2017, in Washington D.C.

Marilyn Siegel, MD, professor of radiology, presented on multiple topics during the Computed Tomography 2016: National Symposium in Las Vegas on November 3-5, 2016, and again at the National Diagnostic Imaging Symposium in Orlando on December 8, 2016. She also spoke at the Radiologic Society of Saudi Arabia & American Institute for Radiologic Pathology in Jeddah, Saudi Arabia, on October 24-27, 2016.

Akash P. Kansagra, MD, MS, assistant professor of radiology, neurological surgery and neurology, presented: “Endovascular Stroke Therapy: New Treatments for an Old Disease” at the Midwest Stroke Symposium in St. Louis on November 4, 2016; “Variations in Workflow Practices Before Mechanical Thrombectomy” at a Stroke Center Workshop for the Society of Vascular and Interventional Neurology in Brooklyn, New York, on November 16, 2016; and “Endovascular Treatment of Acute Ischemic Stroke: An Evidence Based Approach” for the Department of Radiology and Biomedical Imaging at the University of California in San Francisco on December 12, 2016.

Joseph Ippolito, MD, PhD, an instructor in radiology, presented “Identification of a Sexual Dimorphism in Glioma Glycolysis” at the 21st annual meeting of the Society of Neuro Oncology in Scottsdale, AZ, on November 18, 2016.

Michael D. Darcy, MD, professor of radiology and chief of interventional radiology, presented the 33rd annual Dr. Charles T. Dotter Lecture for the Society of Radiology (SIR) on March 5, 2017, in Washington, D.C. Darcy was selected to present the lecture based on his contributions to the field, his service to the society, and his distinguished career achievements. He is a past president of SIR and has been involved with the society for nearly 30 years.

Dehdashti Named Senior Vice Chair for Nuclear Medicine

Following a national and international search, Farrokh Dehdashti, MD, has been appointed Senior Vice Chair and Division Director for Nuclear Medicine effective July 1, 2017. She replaces Barry A. Siegel, MD, who has served in the position since 1973. An MIR faculty member since 1990, Dehdashti is a professor of radiology and noted translational scientist. Her clinical interests include oncologic applications of PET, such as receptor imaging in breast and prostate cancers, hypoxia imaging in various cancers, and imaging tumor proliferation. She is also co-director of the Cancer Imaging Program at Siteman Cancer Center.
Dr. O. Clark West Returns to Alma Mater

Alumnus O. Clark West, MD, FASER, FACR, returned to Mallinckrodt Institute of Radiology to deliver the 23rd annual Hyman R. Senturia Memorial Lecture on April 7, 2017.

West, a professor of diagnostic and interventional imaging, and vice chair of clinical operation and informatics at the University of Texas McGovern Medical School in Houston, presented “Modern Approach to Analyzing Spinal Trauma.”

As a member of the American Society of Emergency Radiology (ASER) since 1992, he’s held multiple positions within the organization. In 2006, West was named the society’s president and three years later was given its highest honor, the Gold Medal.

“We chose Dr. West because he is a national leader in emergency radiology and a phenomenal speaker,” says Vincent Mellnick, MD, assistant professor of radiology and chief of MIR’s abdominal imaging section. “His perspective on trauma imaging is even more helpful since he knows our program so well.”

West has been involved in developing the emergency radiology curriculum for the ASER, the Radiological Society of North American (RSNA) and the American Roentgen Ray Society (AARS).

An expert in emergency and trauma imaging, he has co-authored over 25 abstracts, 34 peer-reviewed articles, and five book chapters. West has made more than 100 presentations throughout the U.S. and across the globe.

Wippold Steps Down as Chief of Neuroradiology

Franz J. “Jay” Wippold, MD, announced his decision to step down as chief of neuroradiology effective July 1, 2017. He joined Mallinckrodt Institute of Radiology in 1989 as an assistant professor. “Jay and I met at MIR as trainees in 1982,” says MIR director Richard L. Wahl, MD. “His multidimensional skills were apparent then and have grown over the decades.”

Wippold earned his medical degree from Saint Louis University, finished residencies at Walter Reed Army Medical Center and, in 1983, completed his neuroradiology fellowship at MIR.

“He has served as an outstanding neuroradiologist and is thoroughly respected by our residents and referring physicians for his expertise in neuro and head and neck imaging,” Wahl says.

In 2000, following a national search, Wippold was appointed section chief. In addition to being a multiple recipient of MIR’s teaching award, in 2008 he received the Washington University School of Medicine Distinguished Clinician Award. Wippold became a Fellow of the American College of Radiology in 1997 and has served as President for the Center of Bioethics and Culture of Missouri from 2012 to 2013. He is credited for developing an ambitious curriculum for neuroradiology training. Under his leadership, MIR’s endovascular neuroradiology program was the first in the country to be accredited.

“Jay will be leaving an outstanding section for the next chief to build upon,” Wahl says. “Fortunately, he will remain engaged with the clinical, research and teaching missions of the section.”

Kostakoglu’s active research includes multiple multicenter PET/CT studies in oncology, particularly in defining the role of PET/CT as a response marker. In addition, she has been involved in oncological applications of positron emission tomography imaging.

“Dr. Kostakoglu has been engaged with national and international groups in the development of new response criteria for lymphomas that are heavily based on PET,” says Barry A. Siegel, MD, professor of radiology and medicine, and director of the Division of Nuclear Medicine with MIR. “It was very relevant to both radiology and oncology communities at Washington University to have an expert review of lymphoma response criteria and of response-adapted approaches to managing lymphoma patients.”

Sally Schwarz, professor of radiology at MIR, gave Kostakoglu a tour of Mallinckrodt’s cyclotron facility during her visit. The cutting-edge facility includes two laboratories that produce PET radiopharmaceuticals used for clinical and PET imaging.

A sought-after national and global lecturer, Kostakoglu’s ultimate goal is to develop management strategies integrating molecular imaging techniques to individualize cancer therapy by early assessment of chemosensitivity.

Dr. Ippolito Goes to Washington

Joseph Ippolito, MD, PhD, instructor in radiology, was selected as a 2017 recipient of a travel award from the Academy for Radiology & Biomedical Imaging Research. The award allowed Ippolito and 14 other young investigators to participate in the 8th Annual Medical Imaging Technology Showcase in Washington D.C. on March 27, 2017.

As an awardee, Ippolito became part of the Academy Council of Early Career Investigators in Imaging (CECF). CECF members prepared and presented a research poster depicting research in the pipeline at their Institution that was displayed on Capitol Hill during the annual technology showcase.

Ippolito’s poster topic addressed “Imaging Tools to Identify Men with Aggressive Urinary and Prostate Disease Using PET and MRI.” The award creates a unique opportunity for investigators like Ippolito to learn first-hand how to advocate for imaging research, discuss research with policy makers, and visit the National Institutes of Health.

“Dr. Ippolito has been engaged with national and international groups in the development of new response criteria for lymphomas that are heavily based on PET,” says Barry A. Siegel, MD, professor of radiology and medicine, and director of the Division of Nuclear Medicine with MIR. “It was very relevant to both radiology and oncology communities at Washington University to have an expert review of lymphoma response criteria and of response-adapted approaches to managing lymphoma patients.”

Above: Joseph Ippolito, MD, PhD, is one of 15 new members of the Academy Council of Early Career Investigators in Imaging (CECF).
A LOOK BACK

WHAT A DIFFERENCE A DECADE MAKES

In 2008, Mallinckrodt Institute of Radiology was the site of seminal research into autism, and the pioneering subjects were just six months old. Nearly a decade later, at least three of the same researchers participated in a breakthrough national study that predicted with 80% accuracy the likelihood of autism in babies who have an older sibling with the disorder. To learn more about the first-of-its-kind study that grabbed the attention of local and national media, turn to page 8.

A Focal Spot 2008
The front cover of the summer issue features one of the study’s adorable subjects.

B The Comforts of Home
A baby relaxes in her mother’s lap before she falls asleep and is scanned for the study.

C Not Your Typical Nursery
Robert C. McKinstry, MD, stands in an MRI suite that contains a crib, rocking chair and blankets for his young study subjects.

D Principal Investigator
Kelly Botteron, MD, principal investigator for the St. Louis arm of a national study about autism, believes early intervention is instrumental in treatment of the disorder.

E Doing What Comes Naturally
A sleeping infant caught sucking his thumb while an MRI scan is performed.

F Sweet Dreams
Bundled up and already asleep, this baby is about to be scanned.

G Can You Hear Me Now?
A baby is prepped with tiny earplugs and noise-muffling headphones before falling asleep inside the bore of the scanner.

Images courtesy of Mallinckrodt Institute of Radiology Archives
Below: The Center for Multiple Myeloma Nanotherapy (CMMN) held its second National Cancer Institute Alliance for Nanotechnology in Cancer site visit on April 12, 2017. Attendees included (from left) Timothy Eberlein, MD, director of Siteman Cancer Center, Samuel I. Achilefu, professor of radiology and a CMMN principal investigator, Richard L. Wahl, MD, director of MIR and head of radiology, and Jennifer K. Lodge, vice chancellor for research at Washington University in St. Louis.