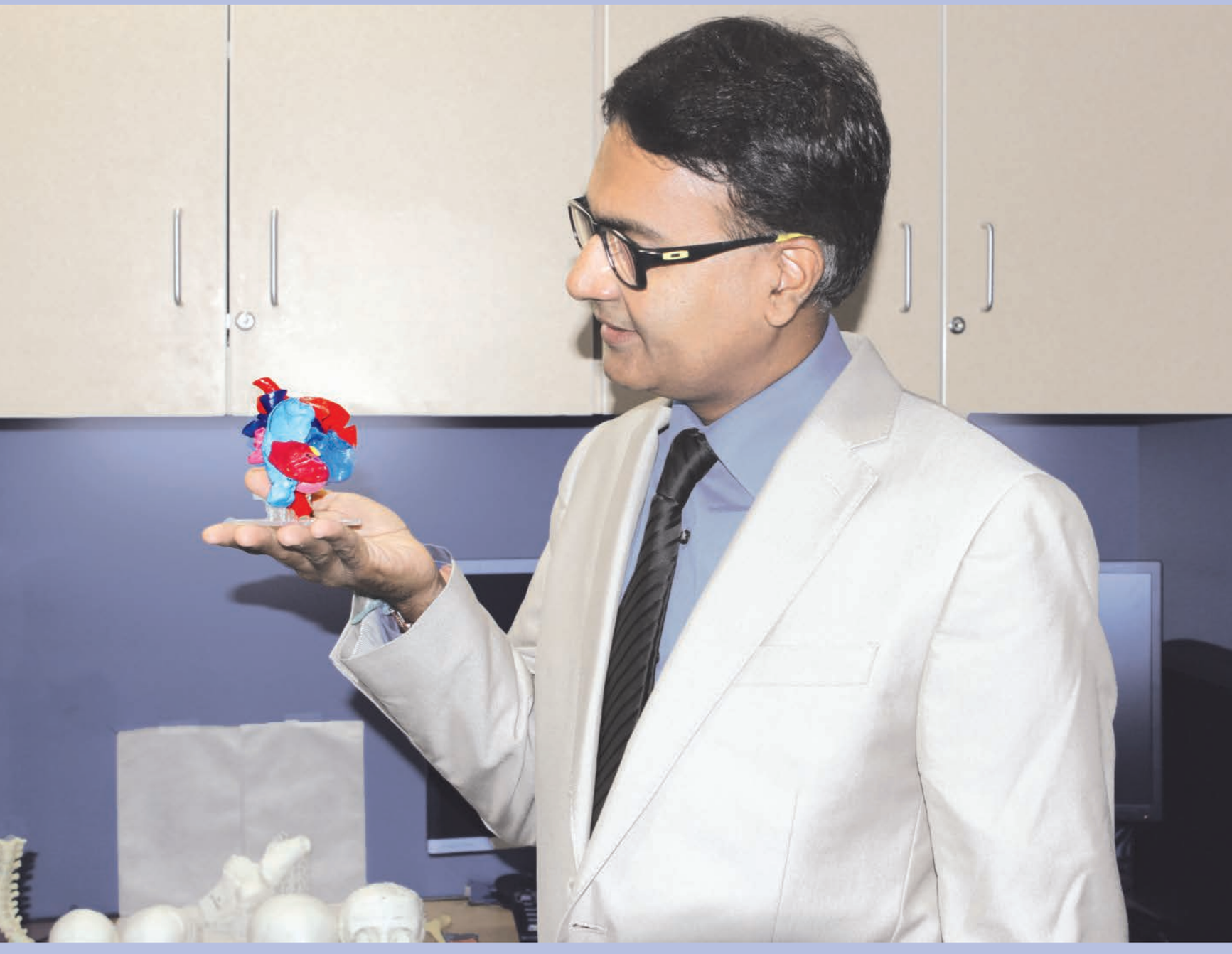
Explorations and revelations taking place in the medical school



Three-dimensional printed models of tissues, bones and organs are helping reduce the operative time at Children's, thanks to Darshit Thakrar's team.

MODEL SOLUTION

3D RADIOLOGY HELPS KIDS

BY KATY RANK LEV

Darshit Thakrar holds up a red-and-blue plastic model about the size of a bell pepper. It's a life-size replica of a 3-year-old patient's rare anomaly known as criss-cross heart. "Seeing and touching these models can change a surgeon's perspective," Thakrar says, pointing to brightly dyed atria emptying into the wrong ventricles. In a laboratory within the radiology department at UPMC Children's Hospital of Pittsburgh, Thakrar used a 3D printer to render the organ's likeness so the patient's cardiac surgeon could study it. The typical approach for this condition, Thakrar explains, is to create a tunnel to redirect the blood. "Our surgeon studied the model and found a more efficient fix—a bypass that took the blood in a more direct path."

Thakrar, assistant professor of radiology at Pitt, benefited from 3D imaging technology himself when engineers constructed the socket of his prosthetic limb. He lost a leg in a car accident shortly after moving to Pittsburgh in 2015. Thakrar spent months at home recovering, undergoing rehabilitation and learning to use his prosthesis, which was built based on 3D images of his leg.

While recovering and still in a wheelchair, he was eager to learn something new and keep his mind active. "I needed sanity," he says. He read voraciously about 3D visualization and printing in his field and how to apply the principles of 3D printing to help his patients.

Thakrar had an idea: start a 3D printing program at Children's. Colleagues at UPMC Presbyterian helped him get started; and Thakrar taught himself to use drafting software. With the support of his division chief, Ashok Panigrahy, who holds the John F. Caffey Chair in Pediatric Radiology, Thakrar was able to secure a 3D printer and start the program in 2016. Initially working nights and weekends, Thakrar printed the first few models. Seeing the benefits, the administration added April Krivoniak, a biomedical engineer, to the lab to perfect these models. On this day, she's snipping excess residue off of a model of a child's enlarged heart. The sound is like cracking pistachios.

Across from a row of computers interpreting X-rays, MRIs and CT scans, another bank of machines churns away at turning flat digital slices into multidimensional models. In the middle of the room, a 3D printer constantly whirs.

The models have aided medical teams at Children's in planning operations, practicing techniques and constructing medical implants. They've also helped boost morale for the children. For example, a model can help a child with cancer understand what her tumor looks like and how important it is to stick with her therapy, Thakrar says. Some kids like to crush their model as they go through the therapy—a process that makes them feel empowered over the disease.

Anyone can order models of healthy bones online. The ability to print pathology has been a game-changer from a teaching standpoint, Thakrar says, gesturing at his cabinet of curiosities: gleaming ribs, distorted lungs, congenital conditions in all shades of dyed resin.

> **"Our surgeon studied the model and found a more efficient fix—a bypass that took the blood in a more direct path."**

Now, students and surgeons are no longer limited by the decomposition rate of preserved tissue. They can pass around a model of the same diseased kidney for years.

Thakrar, a father of two, jokes that he really should print a brand new leg for himself using actual human tissue: He imagines building one from scratch with stem cells from his child's umbilical cord. "We never can imagine the wonders science can create. I will wait for the science to get there in my lifetime," says Thakrar.

He's already checked off one item on his bucket list. With his new blade-type sprinter's leg, he ran a 5K. ■

COURTESY D. THAKRAR

BENJAVISA/GETTY IMAGES

NOT THE MAMA

FERTILITY TREATMENTS, NOT MATERNAL AGE, MAY DRIVE RISK OF IMPRINTING ERRORS

BY ALLA KATSNELSON

Last November, a woman in central India reportedly gave birth to twin girls at the age of 74, making her the oldest-ever new mom.

Advanced maternal age isn't just the stuff of record books, of course. Routinely, women are having babies much older than in the past—well into their 40s and beyond—often with the help of assisted reproductive technology (ART).

Researchers know that babies born to mothers who undergo fertility treatments have an elevated risk of some diseases caused by glitches in the genome. They also have an elevated risk of certain diseases caused by errors in how genes are expressed, such as the neurological disorder Angelman syndrome.

Mellissa Mann, associate professor of obstetrics, gynecology and reproductive sciences at Pitt, wondered what might be driving this increased risk.

"Because assisted reproduction is often used with increasing maternal age," she explains, "we wanted to ask whether the age of mothers themselves could cause the problem."

Mann studies a process called genomic imprinting, which occurs during the development of eggs and sperm. When chromosomes from each parent join forces in a fertilized egg, certain genes are expressed only from the maternal chromosomes and others only from the paternal ones. Chemical tags called methyl groups are attached to the DNA at the nonimprinted copies of these genes, silencing them.

In earlier studies, Mann and her colleagues had found that genomic imprinting was perturbed in mouse embryos that were generated using a process similar to what doctors use for human ART: treating a prospective mouse mom with hormones, removing fertilized embryos from her uterus, and then growing them for several days in a dish. The team found that the hormone treatments scrambled genomic imprinting, as did the process of growing the embryos in the dish.

Her team focused on a handful of genes that, when imprinted incorrectly, cause neurological and other diseases in childhood. The researchers tracked these genes in embryos from four different age groups of female mice ranging from the equivalent of 15 years old to more than 45 years old in human years. And surprisingly, across these age groups, they saw no difference in how the genes were imprinted.

Next, Mann and her colleagues tested whether ART procedures such as injecting females with hormones combined with growing the embryos in a dish affected imprinting. The team ultimately found that indeed they did—but equally so across all four age groups.

The results, published in Clinical Epigenetics in November 2019, were "promising," says Mann. "We thought we would see changes in DNA methylation with advanced maternal age, because we know there are biological pressures on the system," she says. "It was good to see that age was not a problem."

Mann notes that there's at least one caveat to the study: The oldest mice her team tested were just 14 months of age, and although that is an advanced maternal age for mice, the human equivalent of 45-plus years leaves more time for molecular damage to accrue. Researchers must test the finding in eggs from humans of different ages to be sure, she says.

Still, the findings hint that while some factors affect genomic imprinting in the embryo, others do not. "Now we can focus on narrowing in on those biological factors," she says. Her group is trying to tease out exactly how hormone treatments and other aspects of ART affect gene expression in early embryos. They also plan to perform a similar study in older fathers, Mann says. "The literature is now suggesting that there may be biological effects with advanced paternal age." ■

SERGEI DUBROVSKII/GETTY IMAGES

OUT IN THE COLD

NEARLY HALF OF TRANSGENDER YOUTH AVOID DISCLOSING TO THEIR DOCS

BY HEATHER BOERNER

Gina Sequeira (Fel '20) remembers what it was like to be a young person visiting doctors who assumed she was straight—and how that made her doubt that those clinicians were safe to come out to as a queer person.

So when an adolescent patient of hers at UPMC Children's Hospital of Pittsburgh's Gender and Sexual Development Program told her that a previous provider had refused to treat them after the patient explained that they were transgender, Sequeira wondered how many other patients in the program had avoided talking to their physicians about their gender identities.

The answer, it turned out, was more than Sequeira could have imagined.

According to her paper, published in the Journal of Adolescent Health in February, almost half—46%—of the young people surveyed (204 of the clinic's patients, ages 12–26) had purposefully avoided disclosing their gender identity to their provider, even when it was important to their health. A quarter hadn't disclosed their gender identity to any provider outside of the gender clinic.

"It really opened my eyes to how much work there still is to do as health care providers and health care systems" to make clinics welcoming to all young people, Sequeira says.

The findings are especially important because data have shown that parental support and access to gender-affirming care in adolescence and adulthood is associated with lower rates of depression and anxiety, and fewer suicide attempts—all of which are far more prevalent in transgender people than in the general population.

Nondisclosures can have wide-ranging health consequences, says Gerald Montano, medical director of the Gender and Sexual Development Program at Children's, Pitt assistant professor of pediatrics and Sequeira's mentor.

Montano recalls an adolescent transgender girl who had wanted to start hormones as part of medical transition, but her parents weren't ready. So the teen went to another clinic.

"She passed really well, so [physicians] didn't know she was assigned male at birth, and they started her on hormonal contraception," he says. "That's not … the right medication to help affirm someone's gender identity."

Or in another example: Imagine a young man in the emergency department complaining of abdominal pain, but failing to disclose that he has ovaries.

"That's critical information to make sure that I'm working up that patient … in the most appropriate way," Sequeira says.

The onus to encourage disclosure is on providers, not patients, she says. In the survey, 47% of participants said they'd like the provider to initiate a conversation on gender, preferably during the confidential portion of the exam. "We are not creating a space that is welcoming or safe for young people to talk about their identities," Sequeira says.

She notes that it's "very likely" that her survey respondents—all of whom were patients in UPMC's multidisciplinary gender clinic—are not representative of the scope of the problem in the broader population of transgender youth. A vast majority of the respondents have "pretty significant parental support," she says, and almost 90% of those patients are white.

Sequeira—a Pitt alum now at the University of Washington—is pursuing a follow-up study via social media to include a more diverse and representative sample of trans youth.

Before her study, Sequeira was already routinely asking her patients about their support networks. Now, she says, she also asks patients which health care providers they are out to, so she can communicate effectively with the team without unintentionally outing the patient.

She wants more insight. "How can we provide better education for everyone in the health care delivery system, from the front desk staff to the nursing staff to the physicians? These data highlight the continued need."

To patients considering disclosing their identity to a provider, Sequeira says that the "when" and the "how" of this decision are extremely personal. There is no one right way.

"Just because disclosure looks a certain way for one person does not mean it has to look the same for someone else. It really should be up to each individual person to decide what feels right for them." ■