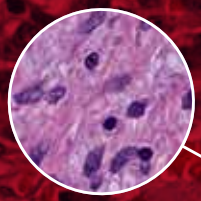
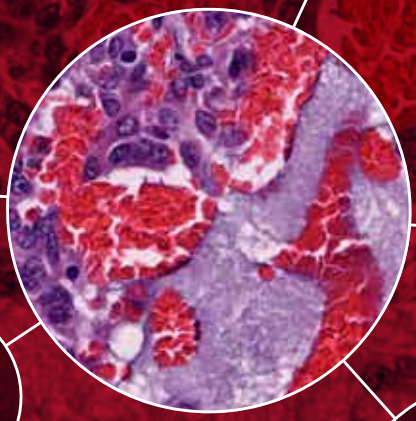
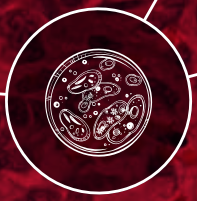
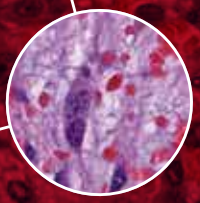
MAGNIFY

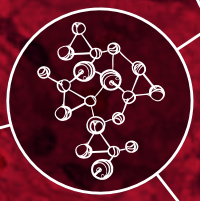
the art & science of diagnostic medicine

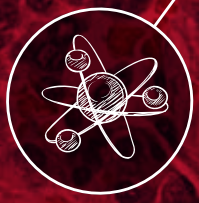


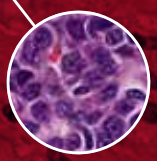












ARUP® LABORATORIES

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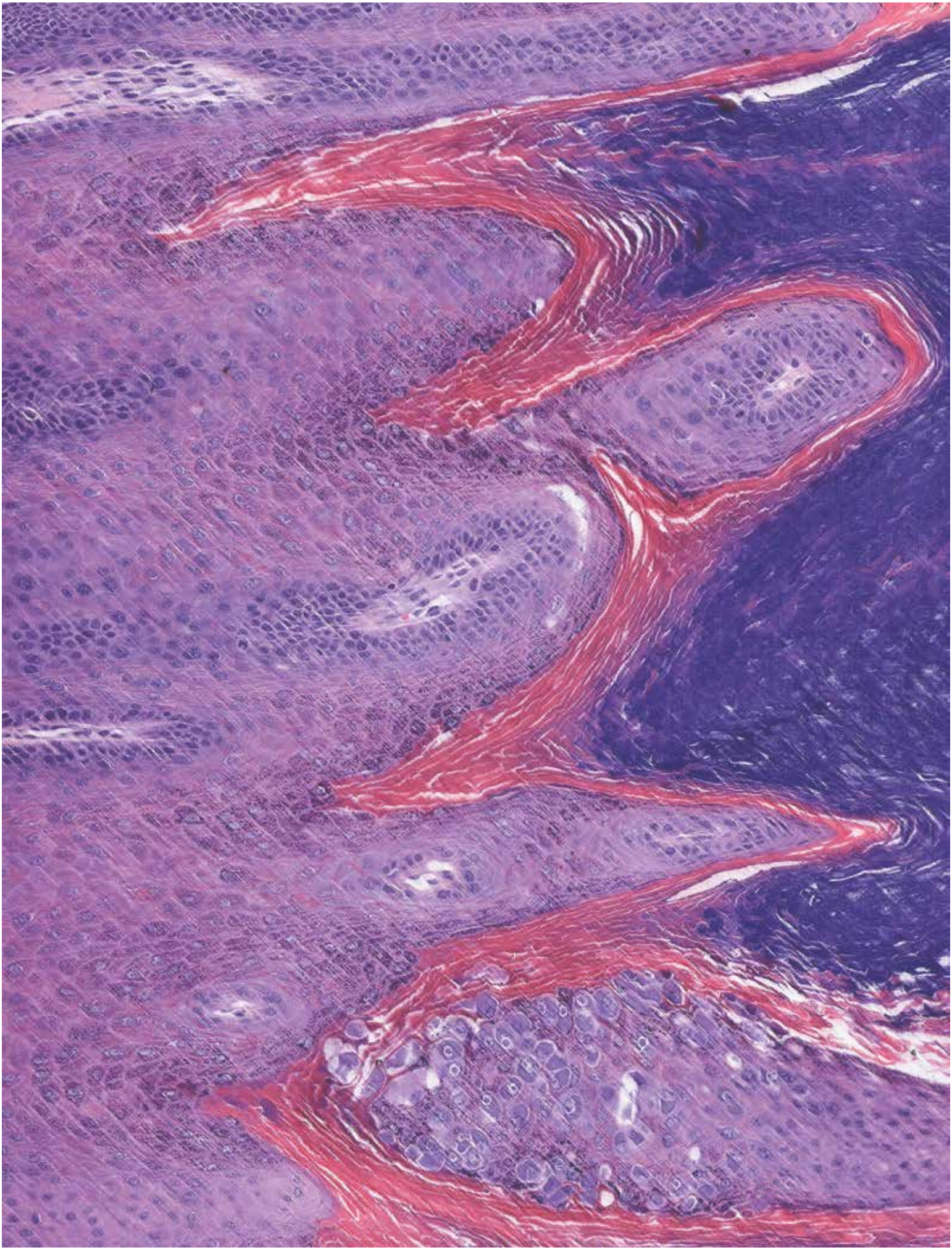


Magnify

The Art and Science of Diagnostic Medicine

Have you ever approached a Claude Monet painting, stopping only when you are inches from the canvas? The whole becomes the sum of its parts: a brush stroke, minuscule touches of color, the interplay of shapes. Not unlike this, in medical diagnostic medicine, pathologists approach the patient in a similar way, zooming in and magnifying the infinitesimal details that make up the patient—a blood cell, the spiral of a DNA strand, a gene variant, a foreign bacteria or a virus.

Through these microscopic clues, pathology experts assist in the detection, diagnosis, treatment, and management of human diseases and conditions. Approximately 70 percent of patient-care decisions are based on in vitro diagnostic test results produced by a clinical laboratory.

Magnify focuses in on ARUP Laboratories' current role in diagnostic medicine, as well as its drive for pushing knowledge and discoveries forward. As one of the country's two largest nonprofit, national reference laboratories, ARUP has entrepreneurial roots and strong ties to academic medicine that guide its unique business approach. (It is a nonprofit enterprise of the University of Utah and its Department of Pathology.)

This approach includes emphasis on education, strict adherence to evidence-based knowledge, and an environment that promotes collaborations and thus accelerates innovations. The stories among these pages will allow readers to see for themselves, zooming in and back out, ARUP's patient-focused and market-facing dynamics at work.

inside

His parents were stunned when he announced his plans to be a doctor.

His parents were stunned when he announced his plans to be a doctor. "Have you even been inside a hospital? Have you ever seen blood beyond a simple cut or scrape?" they stammered.

At 18, Edgar Braendle was graduating from high school soon and needed to declare his vocation before starting university, as is customary in Germany.

"They did prefer my choice of medicine over philosophy," Braendle, ARUP's new CEO, recalls with a wry smile. The three agreed he would first get a job in a hospital before committing to medicine.

Within a week, Braendle, who now holds an MD and a PhD, had a job at a local hospital assisting a group of nurses as needed. Before long, a surgeon, noticing his youth, asked him why he was there. He then asked Braendle if he played tennis (yes); the surgeon was in need of a tennis partner. "Okay, here's the deal," the surgeon said. "You meet me at 6 a.m. each morning for a tennis match and at 8 a.m. you assist me with my operations."

"Two months later, I could see myself in medicine," recalls Braendle, who doesn't play tennis anymore but is an avid skier and road cyclist. He went on to specialize in oncology, and then after burning out from the emotional toll of working with very sick cancer patients, he moved on to specialize in urology and pharmacology. (His PhD is in cardiology.)

ARUP LABORATORIES WELCOMES A NEW CEO

While Braendle had always been interested in science—as a teenager he was fascinated with electronics, building radios and amplifiers—the breadth of sciences to be found in medicine and the prospect of applying this knowledge to make a remarkable and tangible difference drew him in. "It was about using science to save lives. I didn't want to do something that was entrenched in theories and equations. I wanted to do something that, at the end of the day, helped people," said Braendle, who grew up with one sister.

His got his first taste of science at the dinner table. His dad, an engineer for a coal-mining company in Homberg, often talked about his work overseeing the mines' ventilation systems, some descending 300 feet into the earth. At the time, the city of some 15,000 was entrenched in the coal- and steel-manufacturing industries, attracting laborers from all over Europe and beyond. "It was a society and culture of hard-working, blue-collar types, and many who didn't speak German," recalls Braendle.

They were his coworkers. His first job as a teenager was laboring in the coal mines and, with experience, he eventually ended up supervising a crew of 10. He recalls that the differences among the men didn't matter. What mattered was trusting one another to do the job right, getting it done, and staying safe. "There was only one way in and one way out; we relied on each other to not make any mistakes," Braendle recalls. "It was dark, dirty, and dangerous work."

Watching a management style surface that promotes an interdisciplinary team-driven focus—a reliance on diverse expertise—and accountability, one wonders if Braendle's style took root in these early days among his crew in the coal mines.

A Powerful Mentor and Memory

Research has been a constant thread throughout Braendle's career, initially fitting it in around his schedule caring for patients with cancer. Around this time, while presenting his research work at a conference, a man with thick-rimmed glasses and a wave of white hair came up to study his poster—a display of his research on kidney mechanisms in relation to kidney stones. He turned to the 28-year-old Braendle and told him, "This is fine but it's not the best," and challenged Braendle on several of his points. Then, he suggested Braendle come do basic research in his lab.

Six-year-old Edgar Braendle's first day of school; with time, he would naturally take to math and the sciences.

While studying medicine at the University of Ulm, Edgar Braendle (second row, second from left) also played guitar in a folk-jazz band. He received training in oncology, urology, and pharmacology.

The inquisitor was Karl Ullrich, MD, the director of the Max Planck Institute of Biophysics in Frankfurt. His work in kidney research was world renowned, as was the institute—science-wise, this series of institutes is on par with the top academic-medical centers in the United States.

It was a no-brainer; Braendle accepted. He was ready to move on from oncology, and immersed himself in basic research, eventually becoming a professor of pharmacology and urology at the University of Ulm. As a urologist, he began seeing patients again while continuing with his clinical research. Over the years, Braendle's research focused primarily on translational medicine and the development of new diagnostics. During this period of his career, he received seven national and international awards, including the Maximilian Nitze Award, the highest scientific award of the German Society of Urology.

While Ullrich was a powerful mentor in respect to being a great scientist and teacher, one memory in particular has stayed with Braendle throughout his life. Arriving at work one morning in Ullrich's lab, Braendle encountered an absorbed and a bit disheveled-looking Ullrich; he had been there since 2 a.m. "Why?" wondered Braendle. Who or what would make this celebrity of science come to work in the middle of the night? This is a man who could have chosen to spend the rest of his career traveling and speaking at conferences. Ullrich explained that he couldn't sleep because he was obsessively puzzling over some research and finally left his bed for the lab to figure it out more.

"I was dumbfounded; he didn't have to be working that hard," recalls Braendle. "And then I realized, it wasn't about Ullrich at all; it was about what he was trying to accomplish. He was driven to make a difference, to make an impact; in Ullrich's mind, it had very little to do with him personally."

Coming to America

America made a strong impression on Braendle, twice. The first time was when, at 17 years old, he came to live with a farming family in North Carolina. The second time was when he arrived not long after 9/11 to begin work at the pharmaceutical company, Schering AG/Berlex, in New Jersey. He was transferred from the German offices to oversee the company's clinical development of drugs. He, his wife, and two young daughters found an America shaken by the terrorist attacks, suspicious of foreigners, more restricted in personal freedoms, and intensely patriotic. "My prior view of America was from my North Carolina experience, completely different than what I found this time around," recalls Braendle.

His year-long stint living with a farming family in North Carolina was a substantial cultural shift for Braendle. He recalls the long flight to New York City, the bus ride to the town of Wilmington, disembarking to meet—for the first time—the host family, and the monthly phone calls to his parents. "My parents had this idea that this would be a good way for me to improve my English. And I was game."

> "There was this belief and freedom here that people could really go after and achieve their dreams and pursue new ideas; the mind-set was if you had an idea, go for it."
>
> Edgar Braendle, MD, PhD,
> CEO and President

> At the end of the day, it was about impacting patients' lives."

Braendle searches for ways to describe just how different it all seemed to him—it was the American way, layered on the Southern way, layered on the farming way, layered on being a teenager. "I had to figure it all out and be okay with such different ways of doing and approaching things," remembers Braendle.

He relinquished his discomfort and absorbed the perspectives gained by new exposure and attitudes. "There was this belief and freedom here that people could really go after and achieve their dreams and pursue new ideas; the mind-set was if you had an idea, go for it."

To his parents' dismay, Braendle didn't return speaking fluent and stellar English. "I came back knowing plenty of southern and English slang, not the fine English my parents were hoping to hear," says Braendle, with a hint of mischief in his smile.

At the End of the Day

Braendle left the academic-medical arena when the Berlin-based pharmaceutical company Schering AG/ Berlex recruited him to build up its translational-medicine capabilities, which, among other responsibilities, involved overseeing clinical trials. Braendle viewed his move to Novartis, a larger pharmaceutical company, as an opportunity to make a bigger difference. "If [you are] successful in delivering a drug, you can impact thousands if not millions of lives versus one life at a time," says Braendle. Over a decade, he went from focusing on the clinical development of new cancer medications to global-development positions of all oncology and molecular diagnostics, and finally overseeing the company's companion-diagnostics unit, which was responsible for the development and worldwide regulatory approval of all diagnostics for Novartis. "At the end of the day, it was about impacting patients' lives."

As Braendle talks about his career and the pharmaceutical and now laboratory industries, his examples pulling consistently from patient scenarios, patient care seems to be his home plate. The patient is the starting and ending place for all efforts, an ingrained perspective no doubt stemming from his earlier years as a physician caring for patients.

In a steady German accent, the phrase, "At the end of the day," peppers Braendle's explanations and stories. Soft-spoken and a keen listener, he uses this phrase to exude both the practicality and mindfulness with which he approaches his work and engages those working with him. It's about taking stock of what has been accomplished, and recognizing that tomorrow—yet another day—there is more to be done. With his track record of overseeing large challenges requiring expansive efforts, such a phrase suggests a manageable approach—a step-by-step, day-by-day approach in leading others forward. ■

Q & A WITH DR. BRAENDLE

You are considered an "outsider" within the world of pathology. How do you think this may be a strength and/or influence what you bring to the job?

I want to know how diagnostics influence patient outcome. I look at how diagnostics fit into the patient flow and into the decisions being made regarding treatment. My background as a physician involved in the care of patients has provided me with a thorough understanding of what the patient is going through in order to get to the diagnosis. At the end of the day, this means knowing the points at which diagnostics are needed in treatment, how they may be used throughout the care of the patient, and getting to the right treatment as soon as possible.

In Germany, I worked a lot with clinical pathologists. Pathologists have a good understanding of the methods involved. Through my work at Novartis, I gained a good understanding of the technologies used by pathologists—by no means am I an expert, but I do have an understanding.

You come from working for companies that are of the for-profit, publicly traded mind-set—a different culture than what is found at ARUP. How are you going to support the culture and value system unique to ARUP?

One of the reasons I was so attracted and excited to take this job is that it allowed me to combine my previous two experiences: my academic career, an area that is driven by patient care and cutting-edge innovation, doing science; and my career in business, which has taught me the principles of business.

These principles are not just about the bottom line. They are about how to lead an organization and do the right thing. In business, there is the challenge of aligning people to work toward a common goal, requiring skill and accountability, as well as motivation. You have to know how to motivate people to work toward that end. People come to work to earn a salary, but, I believe, they also want to come to work to make a difference—especially in healthcare.

At Novartis, I worked with an impressive leader, David Epstein [CEO], who was always telling us that if we focused on doing the right thing for the patient, it would turn out to be the right thing for the company, too.

I saw this play out a number of times in decisions that did not make sense financially for the company but did for patient care. For example, when Novartis was developing Gleevac [a medication for treating chronic myelogenous leukemia (CML)], the initial thought was that there wasn't a big enough ROI [return on investment] for the small group of people with this rare disease, and the medication would only extend their life expectancy to 10 months. Instead, these patients on Gleevac were living far beyond this, and CML was increasingly being treated as a chronic disease. Business-wise, this was a success story, and it was driven by doing the right thing for the patient.

Under this exceptional leader, I learned the importance of creating an environment that supported doing the right thing for patients and trusting that there is good business behind this approach.

Many new therapies come out of the pharmaceutical industry so they do make a significant contribution to patients' lives. It is also a high-risk business, where out of hundreds of compounds that are being tested, only one may make it to market. And, yes, there are stakeholders; yes, earning money is a target, but based on my experience, it is not so black and white.

One of ARUP's differentiators is that it is part of an academic-medical system and mentality. You have an academic-medical background too. How will you view this aspect in moving forward?

There's a lot to appreciate in what academic medicine drives, including cutting-edge approaches and generally being at the forefront of innovation. It doesn't necessarily look at things from a profit perspective, and often the primary focus is based on what will benefit the patient.

ARUP has an abundance of opportunities to collaborate with the [University of Utah] Health Sciences and to continue driving this innovative aspect. It can do this while also focusing on the business aspects, which drive financial success, and in turn fund research and collaborative efforts.

The real challenge is to figure out the right balance between academic freedom and innovation and driving a business, which in turns fuels the innovation part of it. It's really full circle when everything is balanced and flowing.

What have you learned from your experience working at pharmaceutical companies that can benefit you in your new positon?

I've learned a lot about organizations, leadership, and business practices in the companies I've worked within. I've also seen how certain approaches can or cannot work. Working in these environments, I've gained perspectives that I did not have when I worked in an academic-medical setting.

A team approach was key to success at these companies. It wasn't about individual achievement and self-promotion, but rather about everyone working in the same direction. You were measured by how you contributed to the success of the team; territorial approaches didn't work.

I think the biggest contribution I can bring to ARUP is to encourage this team approach. Medicine and science is becoming increasingly more complex, making collaboration that much more necessary within ARUP, with the [U of U] Health Sciences, and with external companies. This is one of the most important things I've learned in the pharmaceutical industry.

You've had great success with precision medicine and companion diagnostics initiatives with Novartis. Will these two areas influence your objectives here?

Precision medicine is a big part of what we do. It is a part of why I'm here and what I believe in. It essentially means everyone is different, and approaching medicine this way is driving innovation and new developments in treatment. While it has come a long way, there is still great progress ahead.

ARUP can help others drive precision medicine. It is not something we can do on our own. No one can. It means collaboration. An area where we are making a big difference, and will continue to do so, is through our UM [utilization management] program, which is about making sure the right diagnostic is being used at the right time in order to lead to the right therapy.

Precision medicine is the combination of a therapeutic with a diagnostic tool. This might be imaging, but in most cases, it involves clinical or AP [anatomic pathology] laboratory testing. It is precision medicine at its best, not only identifying the disease, but subdividing it by certain mutations or biomarkers, and then determining the right diagnostic tools with the right therapeutics.

Do you see an expanded role for companion diagnostics?

With advancements in genomic research—as well as in proteogenomics, microbiome, and informatics—the role of precision medicine is accelerating. The excitement around its potential is growing, consider the Cancer Moonshot Initiative or the Precision Medicine Initiative. Such medicine will not only make a big difference in individual lives but will also make a difference overall in healthcare as we identify more effective treatments, avoid unnecessary treatments, and, by doing so, reduce healthcare costs.

In many cases precision medicine is the combination of diagnostics aiming to identify the best subset of patients with a treatment. This is the basic concept of companion diagnostics. Over the past few years, we have seen more drug/diagnostic combinations, and I believe this will continue to shape the future of medicine. The diagnostics medical community will be developing not only to identify the patient populations responding to certain types of drugs, but it will also include pharmacogenetic tests and drug monitoring to individualize dosage.

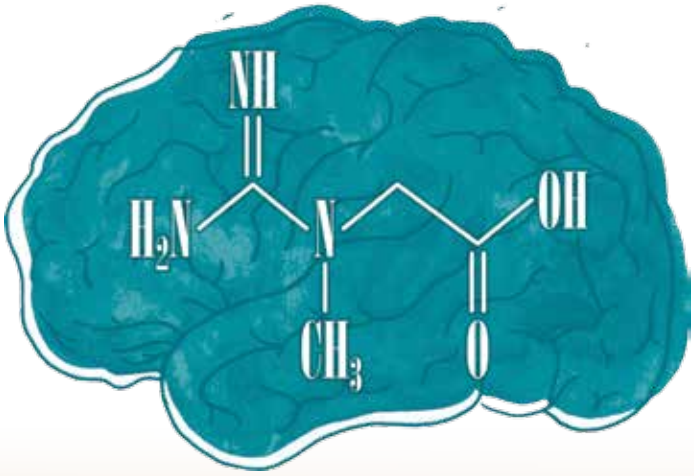
What are some of the key challenges and opportunities you see ahead facing the diagnostics industry?

This is one of the most exciting times in medicine and in the lab industry. Do we have pressures? Yes. This pressure is on the entire healthcare system. There is pressure to find new models, provide more transparency, maintain high quality, and keep a cost-savings mindset. This could affect labs, although laboratory testing accounts for only 3 percent of healthcare costs while influencing 60 to 80 percent of the medical decisions being made.

We may see many current technologies used in testing be replaced by NGS [next-generation sequencing]. This, of course, impacts how we need to think about our business. We do anticipate new technologies happening in other areas, such as proteogenomics [the analysis of proteins in cells] and microbiome.

While disruptive technologies and changes in the healthcare system introduce challenges, they also provide new opportunities to focus and grow. At the end of the day, agility and strategic thinking are key in taking advantage of inevitable change. ■

One Got It, One Didn't



A Newborn Test Determines Different Trajectories in the Lives of Two Siblings

"She smiled a lot, crawled at a year, walked at 18 months—this was slow but not alarming. It wasn't enough to make a pediatrician seek out testing," recalls Heidi Wallis about her oldest child, Samantha (affectionately known as Sam). At two, she "had no words." "I kept saying to myself, 'she is going to be fine. She is just moving at her own pace.' Everyone else said not to worry, that I was just being a nervous first-time mom."

But things didn't get better. Sam became increasingly more delayed. Wallis spent the first five years of her daughter's life desperately trying to figure out why Sam was struggling and what would help.

She had been tested for autism at 3, yet she barely registered on the autism spectrum.

Despite the long stretches of working daily with Sam at home on behavioral and cognitive exercises—hours of prompting communication through picture cards—and attending ongoing speech and occupational therapy appointments, progress was slow.

It was the seizures that ultimately led the Wallis family to a test that provided some answers. For several months, Heidi noticed Sam's eyes occasionally rolling back; she videotaped it for their pediatrician, who then referred them to a neurologist at Primary Children's Hospital.

Suspecting seizures, the neurologist ordered a series of tests, including a magnetic resonance spectroscopy that measures biochemical changes in the brain. It showed a lack of creatine in Sam's brain—an essential nutrient created in the body that provides energy to all our cells.

A biochemical genetics test followed by a DNA test confirmed that Sam had a mutation in her *GAMT* gene, which makes the enzyme that creates creatine. It was a broken process. (GAMT stands for guanidinoacetate methyltransferase.) This disorder was only discovered in 1994, nine years before Sam's arrival on a hot July morning. The disorder is rare; at the moment, Sam is only one of about 110 people worldwide with a documented diagnosis of GAMT deficiency.

Additional DNA tests confirmed that Heidi and her husband, Trey, were both carriers. "The mutation from my husband was novel; my mutation they had seen before," says Heidi. To manifest, a child must inherit a mutation from each parent to trigger the disorder. Some mutations have not been identified yet, and will only be discovered with continued research.

GAMT deficiency is one of three known disorders affecting the metabolism of creatine. These disorders primarily affect the brain and muscles and usually result in severe intellectual disability and limit speech development to a few words. Most affected people experience recurrent seizures and develop autistic behaviors. They also have weak muscle tone and delayed motor skills development.

What If Sam's Treatment Had Begun at Birth Instead?

When Sam's tests came back showing no creatine, her care team turned to Nicola Longo, MD, PhD, a soft-spoken, Italian-born physician well known for his research and expertise in caring for patients with GAMT deficiency. At his University of Utah-based clinic, he guides the care of six patients in Utah and a dozen nationally.

While the effects of a creatine metabolism disorder are severe, the "cure" is relatively simple and inexpensive: a mix of several supplements. Longo fine-tuned the treatment by monitoring his patients' progress over the years. In addition to replacing the missing creatine, he added ornithine and sodium benzoate to prevent the buildup of toxins in the brain that cause seizures. "We measured and monitored everything biochemically and adjusted it until we saw clinically it was making a difference."

Longo suspects many more parents roaming around in the developmentally delayed, mental retardation, cerebral palsy, and seizure disorder world have children who may actually have a creatine deficiency.

"Because the symptoms are so non-specific, it means there's a lot of room for misdiagnosis. It may not be as rare as we think," says Longo, who is chief of the Division of Medical Genetics, and co-director of the Biochemical Genetics and Newborn Screening laboratories at ARUP.

When these supplements are taken, families see dramatic changes. "I'll get a call 24 hours later saying my child seems completely different," says Longo, noting that some children start walking within a month of starting therapy.

Almost immediately, Sam's speech improved. "Ba, ma, da" became "ball, mommy, duck." Within nine months, she was stringing together five or six words at a time, excitedly sharing what she wanted to eat, where she wanted to go. "She was so excited to finally be heard and understood," says Wallis.

What if Sam's treatment had started as a newborn instead of at 5 years old? She would likely be navigating middle school like any other 13-year-old girl. Wallis knows, because her son, Louis, born eight years after Sam, was tested for the disorder as a newborn. He tested positive and was started on the supplements immediately.

Today, Louis is a rambunctious preschooler with no signs of slowing down. "I'll never stop watching him super close looking for any hints or signs of delays," confides Wallis. "He's going to grow up like other kids, whereas Sam will need me for the rest of her life."

> "We measured and monitored everything biochemically and adjusted it until we saw clinically it was making a difference."

A Spoonful of Sugar Does NOT Help This Go Down!

"If your child has been telling you about his/her friend named Sam who 'doesn't' talk' and you've been wondering what that means, we thought we would tell you a little about this week's Super Star, Sam."

So began a letter from Heidi Wallis, Sam's mom, to her daughter's kindergarten class. Six months earlier, Sam had been diagnosed with GAMT deficiency, providing some long sought-after answers and introducing a whole new routine into the Wallis' lives.

Now 13 years old, Sam's routine is structured around the mix of "nasty tasting" supplements that she must take four times a day to counter her creatine deficiency and deter seizures. Each day starts with a tap on the shoulder at 6:30 a.m. to wake up Sam for breakfast and her first dose of creatine—a 30 ml syringe-full.

Each Sunday, Wallis spends an hour and a half preparing 28 syringes for the week ahead—five of these doses Sam will take at school. "It looks like a drug bust scene in our kitchen," admits Wallis with a laugh.

There's no super-secret ingredient in this mix of supplements (creatine monohydrate, L-ornithine, and sodium benzoate). "You can buy them on Amazon," quips Wallis. Body builders are drawn to creatine for its muscle-building trait.

The Taste Challenge

Early on, enticing Sam to swallow the powder was difficult at an age when most kids were pushing away their broccoli. However, refusing wasn't an option; this powdered mix—or lack of it—was why Sam was developmentally delayed. "It will make you strong and smart," coaxed Wallis. She experimented by masking the bitter flavor with Kool-Aid, apple juice, apple sauce, and in smoothies. "She hated it all, sometimes throwing it up."

By the time Sam was 8, they figured it out. "She loves Caffeine-Free Diet Coke, so I would set one in front of her, crack it open and then say, 'alright let's do this,'" says Wallis, who would use a syringe to squirt the supplements toward the back of Sam's throat. Then Sam would grab the Coke and start guzzling it down to wash away the flavor.

When Sam's little brother, Louis, was born, his creatine deficiency was diagnosed right away. He was swallowing the supplements as a newborn, desensitizing him to the taste and preventing the disorder from taking root. "Although he still grimaces every time," says Wallis.

Wallis keeps Sam and Louis' diets low in arginine (an amino acid)—a low protein diet. Arginine can lead to the build-up of a neurotoxin leading to seizures; both Sam and Louis are missing a key enzyme that prevents this.

To help with Sam's seizures, she has been taking cannabis oil. "She is a sweetheart when she is feeling like herself. But for days leading up to a seizure she can be like Dr. Jekyll and Mr. Hyde," confides Wallis. A seizure leaves Sam feeling exhausted and frustrated for the rest of the day.

"When she's spiraling out of control, the best way for me to bring Sam back down to earth is with hugs," says Wallis. "It is literally her reset button." ■

Your Baby's First Step? Newborn Screening

For a baby, modern medicine's prick on the heel and speedy shuttling of bloodwork to a lab can utterly change a life to be led. In the case of children like Sam and Louis, one will lead an independent life, while the other will always be dependent on care—all because of the age at which a condition was found and treated. (See accompanying story.)

To try to avoid such scenarios, each state has a department of health that screens for disorders. For example, the Utah Department of Health (UDOH) screens for 39 primary conditions (44 conditions in total). Thirty-four of those are part of the national Recommended Uniform Screening Panel (RUSP) set by the Secretary of the U.S. Department of Health and Human Services and the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). Because ARUP is based in Salt Lake City, it partners with the UDOH, conducting tests for all but nine of Utah's 39 screened conditions.

After the infant's heel is quickly pricked and the blood arrives at ARUP, specialized laboratory technicians in the Biochemical Genetics (BCG) and Newborn Screening laboratories start looking for any red flags. "We're looking for metabolites [substances that are intermediates or final products of metabolism]—characteristics of the disorders screened—they are mainly amino acids and acylcarnitines and are present in abnormal concentration in patients with a metabolic disorder. An abnormal screen result is followed up by confirmatory testing," says Rebecca Guymon, supervisor for BCG and Newborn Screening.

Some of the conditions ARUP screens for include PKU (phenylketonuria), a metabolic disorder that can cause a build-up of phenylalanine and related metabolites in the blood, resulting in severe developmental delays and other metabolic conditions that can shorten or drastically hinder a life if left undetected and untreated.

Newborn screens can vary greatly by state—from the conditions tested to the screening method and the algorithms used to evaluate whether a result is "abnormal" or "normal." Certain conditions are listed on the federal government's RUSP, and their screening has been implemented in most states. These include PKU, cystic fibrosis, and congenital hypothyroidism, which can lead to intellectual slowdown and delayed growth if not discovered in the first two weeks of a child's life.

When many states screen for a certain disease, looking at their pooled populations provides more information for research. For example, GAMT deficiency occurs with an incidence of 1 in 120,000. With a Utah birthrate of about 50,000 a year, researchers wait longer to find a case they can prospectively identify and treat. "1 in 120,000 does not mean that one baby with this disease will be born exactly after 120,000 babies are born. If more states screened for GAMT deficiency, the potential to identify at least one case of GAMT deficiency every year will increase," says Dr. Marzia Pasquali, medical director and section chief of BCG and Newborn Screening at ARUP.

ARUP's collaboration with the Utah Department of Health has improved the department, says Kim Hart, the DOH's Newborn Screening Program manager. "ARUP is able to provide some excellent medical interpretation of results. Having a truly passionate partner to work with is important—Dr. Pasquali sleeps and breathes newborn screening." ■

For children with a creatine deficiency, there are no specific outward symptoms at birth; developmental delays between 6 to 12 months are the first signs that something is awry. Catching the disorder at 5, the age at which Sam was diagnosed, cannot turn back the clock; the developmental damage will already have been done.

What If Every Child Could Be Tested as a Newborn?

One day in 2008, Longo went home and shared with his wife that he had seen his first patient with GAMT deficiency in clinic and felt there was something more that could be done to prevent this from happening to other families.

The conversation may have ended there, but the topic hit close to home (actually, work); his wife, U of U Pathology Professor Marzia Pasquali, PhD, was instrumental in developing the newborn testing program in Utah and is the head of the Biochemical Genetics and Newborn Screening section at ARUP Laboratories. She too felt there was more they could do.

"We saw how we could include this into our other newborn screening test analysis with minimal changes," recalls Pasquali. Such screening was already being done in a Canadian province and in Australia. She began developing a test that could accurately diagnose GAMT deficiency.

She tested 10,000 archived bloodspots and was able to identify the three known GAMT deficiency samples mixed in. In 2015, the test was added to Utah's newborn screening panel—the first and only state to offer it so far. With more than 50,000 births a year in Utah, it is just a matter of time before a child is identified with a creatine deficiency. Pasquali is now working on the implementation of this screening nationally.

"With this screening, as time passes, we may learn more about the frequency of this disorder," says Pasquali, who estimates that 1 in 120,000 children will test positive for it. Based on current U.S. birth rates, that is about 33 babies a year.

Right Now, Diagnosis Is One Hundred Percent Luck

Witnessing the dramatic differences developmentally between Sam and Louis further motivated Longo and Pasquali to push for screening nationally, with the Wallises leading the charge. They've become a cadre of advocates; Longo serves on the medical advisory board of the Association for Creatine Deficiencies, of which Wallis is the administrative director and a board member. They all travel to meetings in Washington D.C. to join with families to lobby for screening.

"We've always tried to do the best we can for families, but now we're taking it to a different level," says Pasquali. "We have the chance to give these kids a normal life. It's a terrible waste to do nothing."

"Diagnosis for a GAMT kid is 100 percent luck right now. A full life or a life of misery is currently left to chance," says Wallis. She accepts that there was no testing available when Sam was born; she cannot accept the fact that there are children being born today whose families will end up on the same diagnostic odyssey she was on, asking repeatedly, "What is wrong with my child?"

"There is a sense of urgency," stresses Wallis. "It may be a rare condition, but the impact on the individual, their families, and communities is dramatic. And it just doesn't have to happen." ■

"We've always tried to do the best we can for families, but now we're taking it to a different level. We have the chance to give these kids a normal life. It's a terrible waste to do nothing."

A Real Page Turner

Extracting Vital Clues from the Stories within Our Genes

What if our bodies were libraries? And the thousands of books, instead of sitting on the shelves, were circulating through our bodies? Each book a gene; each gene, a story. Written into these stories are vital, personal clues for identifying and treating disease.

Delving into these discoveries requires the use of sophisticated technology and the bio-computing prowess to go with it. Next-generation sequencing (NGS) is one such technology that breaks open stories so sequence analysts and ARUP medical directors can begin looking for mutations or variants in a patient who may desperately need answers. NGS delves into the DNA found in the patient's saliva, a cheek swab, blood or—more invasively—the DNA found in a tumor via biopsy or surgery.

Patients who receive NGS testing may have a suspected inherited disease (that could also involve testing their family members), or they could have cancer and need the improved information that NGS cancer testing can provide to better select and manage their chemotherapy.

"Once the sequences of DNA building blocks are deciphered from a patient's DNA, highly developed and complex computerized analysis known as bioinformatics must occur next, to decipher the millions of data points and unravel whether genetic abnormalities are present in a patient's sample," explains Mary Bronner, MD, division chief of Anatomic and Molecular Oncologic Pathology at ARUP.

Finding the answers is no small task. Keeping with the book analogy, medical director Todd Kelley, MD, says, "Imagine all the sentences from all these books [genes] are jumbled up. Now reconstruct them and put them back into the right place in each book." Sequence analysists must then "read each book and look for potential errors."

These analysts look closely at these "errors" or aberrations, some of which may be typical gene variants (i.e., a variant determining your eye color). It is the variants that may express pathogenic or disease-causing changes—mutations in a gene—that they are most interested in further analyzing.

Increasingly, the use of NGS in laboratory testing is actively driving patient care. While NGS has a strong track record in research, ARUP has been using it to deliver NGS-based results to clinicians since 2012. Bioinformatics at ARUP spans five areas of clinical focus: molecular genetics, immunology, hematopathology, solid tumor pathology, and, soon, infectious diseases. Application of NGS technology to these areas has resulted in massively complex data needs.

"Bioinformatics is truly at the heart of the successful application of NGS technology in medicine," says Frederick Strathmann, PhD, interim scientific director, Biocomputing, and medical director, Toxicology. "Without the bioinformatics aspect, the sequencing sits in limbo and cannot be fully appreciated. It is an integrated process that involves numerous technologies and highly skilled people to provide actionable information to physicians." ■

"Imagine all the sentences from all these books [genes] are jumbled up. Now reconstruct them and put them back into the right place in each book." Sequence analysists must then "read each book and look for potential errors."

Todd Kelley, MD, Medical Director, Molecular Hematopathology and Hematopathology

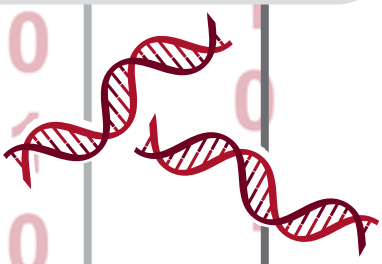
NGS Testing: Pipeline from Patient to Diagnosis

Ashley developed easy bruising and had frequent nose bleeds and infections over the last few weeks. An analysis of her blood revealed anemia and a low platelet count. Her doctor extracted some bone marrow to send to ARUP for analysis.

Charlie passed out on the basketball court. Because he's an avid athlete and only 17, this was surprising. His doctor ran some cardiology tests and then sent a blood sample to ARUP for analysis. The doctor suspected aortopathy, a disease that can cause the aorta (the heart's main artery) to rupture. It can run in families or not.

In each lab, using NGS instrumentation, laboratory staff extract DNA from areas of interest and prep it for sequencing. This process replicates the DNA millions of times. Such amplification of the DNA allows scientists to home in on targeted areas and see DNA reactions happening simultaneously. In contrast, the Sangar method, an older technology, can only look at one specific area/ reaction at a time.

Genomics Lab



Bioinformatics Mining

Both labs send this NGS raw data to their team of bioinformatics experts. Remember the jumbled-up sentences from millions of books? This is it. Their job is to organize this raw data. Essentially the DNA is cut up into lots of little pieces then reassembled so it is sensible and can be interpreted more easily and accurately.

Sequence Analysis

Sequence analysts generate reports that contain changes, or variants, that are found in the patient's DNA and information related to those variants. They begin by interpreting the data and comparing findings to gene-specific databases and medical literature. They are looking for whether this variant has been reported previously. If so, is it connected to a disease? Or is it a variant found in a large segment of the population and therefore likely benign?

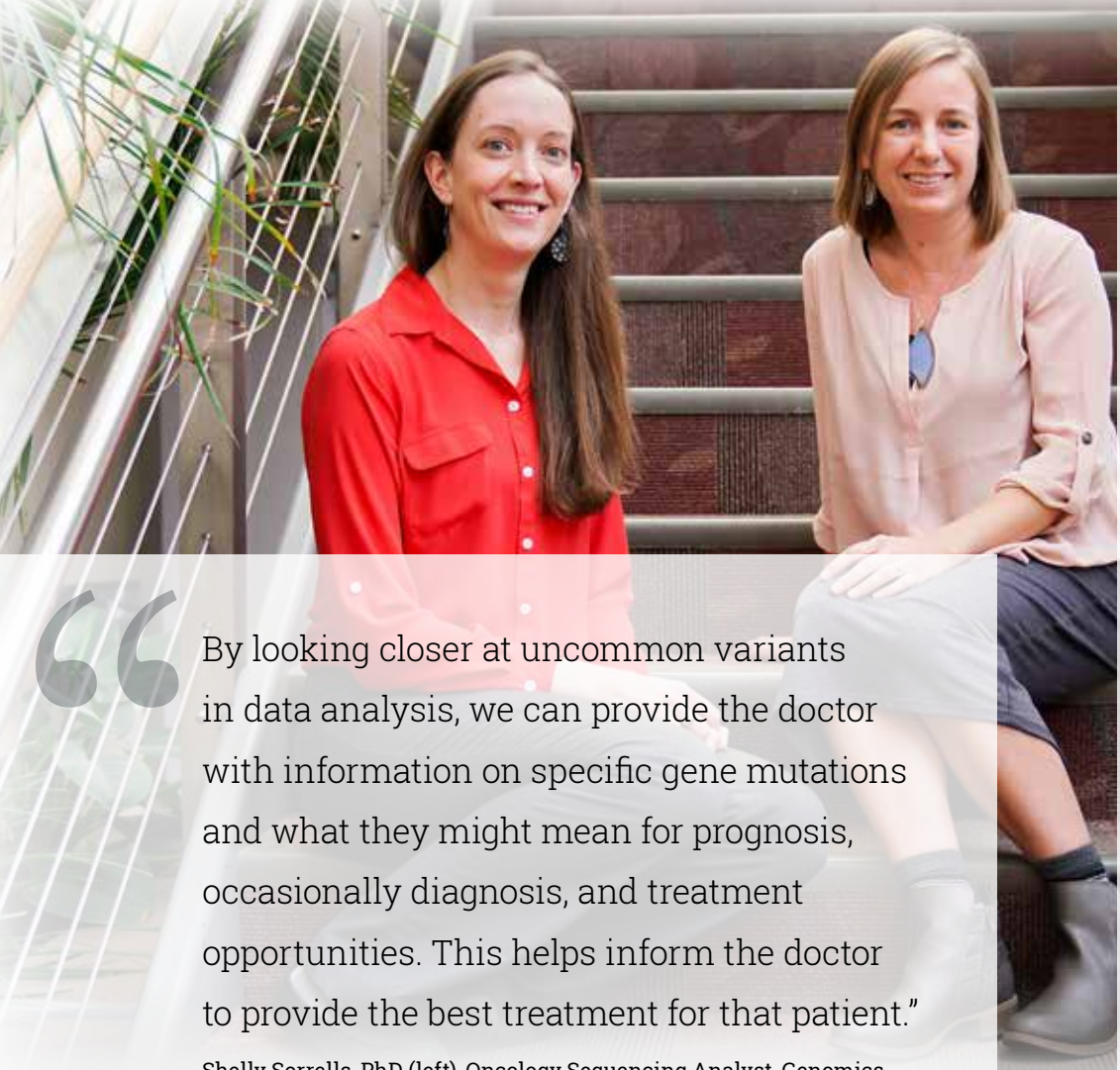
Medical Director Analysis

Nearly 30 of ARUP's medical directors are involved in NGS testing and in this final stage of analysis, they are providing a secondary review and ensuring that all clinical aspects have been considered. This means providing clinicians with an accurate and comprehensive report of their patients' results.

To further ensure accuracy, a medical director may pick out the variants of interest and send them in for Sanger evaluation to confirm their role in diagnosis. Sanger is an earlier method used in DNA sequencing and, while slower, it is still considered the gold standard, but that may change as NGS evolves.

Ashley and her family learned that she had acute myeloid leukemia, a type of blood cancer. The NGS results helped her doctor determine that a bone marrow transplant would be her best chance for a long-term cure.

Charlie and his family found out that he tested positive for a mutation that causes Marfan syndrome, a type of aortopathy. Based on this information, his doctor prescribed medication and discussed the lifestyle changes Charlie needed to make and the need for on-going screenings throughout his life. Charlie also learned that his children would have a 50 percent risk of inheriting the disease.



"By looking closer at uncommon variants in data analysis, we can provide the doctor with information on specific gene mutations and what they might mean for prognosis, occasionally diagnosis, and treatment opportunities. This helps inform the doctor to provide the best treatment for that patient."

Shelly Sorrells, PhD (left), Oncology Sequencing Analyst, Genomics

"Ultimately, what we are interested in are the variants identified in the regions, or genes, potentially associated with the patient's symptoms. Are they likely to cause the disease or are they benign?"

Hunter Best, PhD, ARUP Medical Director, Molecular Genetics & Genomics

"Using NGS.Web platform as a key analysis tool, we're able to interface with our own evolving database of variants and annotated information. We can then identify what we're seeing and its significance—for example, is it disease causing or not?—and pull all this information into the patient's report."

Erica Cuttitta, ARUP NGS Informatics Supervisor

Bioinformaticians build pipelines to convert data derived from genes buried within the 3 billion base pairs of DNA sequence into human interpretable data through three major steps: sequence alignment and polishing, variant calling, and variant annotation."

Elaine Gee, PhD, ARUP Director of Bioinformatics

The DNA of a tumor holds the keys to diagnosing inherited disorders and gene targets for cancer therapy. Extracting the DNA for NGS testing requires a biopsy, although more recently blood samples are also being used. NGS testing also requires specialized pathologists to identify the proper tumor cells for NGS testing."

Mary Bronner, MD, Division Chief of Anatomic and Molecular Oncologic Pathology

Dancing Through the Pain

Advancements in Immunogenicity Testing Deliver Relief to Patients with Autoimmune Diseases

In order to keep dancing, she kept pushing through the joint pain. Then one morning, she couldn't even walk; her body was not allowing her to put any pressure on her feet. Looking back, Lisa Foley recalls this moment vividly because it halted her plans to move to L.A. and give professional dancing a shot. And it was the beginning of her life with rheumatoid arthritis. She was 22.

Rheumatoid arthritis (RA) is an autoimmune disease, more specifically a non-infectious inflammatory disease. Other diseases in this category include inflammatory bowel disease, lupus, and psoriasis, to name a few. Inflammation results from the overproduction of several proteins in the body, including one known as tumor necrosis factor (TNF).

TNF's primary role is regulating immune cells (white blood cells) that protect your body against infectious disease and foreign invaders. To manage the overproduction of TNF seen in rheumatoid arthritis, patients are prescribed TNF blockers, medications that suppress the response to TNF and decrease inflammation.

These medications, referred to as biologicals, are made of naturally occurring molecules. TNF-blocking drugs don't always work because the body may see them as foreign invaders, producing antibodies against them that make the drugs ineffective.

Testing for drug levels of biologicals helps clinicians figure out if the drug is still working for the patient and if it is being administered at the right dose. "This can lead to a more personalized approach to treating patients with autoimmune diseases who aren't responding to treatment,

which of course improves patient care and saves time and money," explains Julio Delgado, MD, MS, ARUP's chief medical officer and formerly medical director of Immunology. He recently coauthored an article on this topic in the journal *Clinical Chemistry* with ARUP colleague Eszter Lázár-Molnár, PhD, medical director, Immunology. Both hold faculty positions at the University of Utah School of Medicine.

When Foley was diagnosed, TNF blockers were not yet available. "They first started me on steroids, then some other pretty potent medications," she recalls. To have children, Foley had to go off the medications. Three months before her second child was born in 1998, the first TNF blocker came on the market. Since then, she has been on three different TNF blockers. "It works for a number of years, then my body starts rejecting it. At first you think it's the be-all, end-all drug; then, the body plateaus," says Foley, who kept on dancing whenever she could.

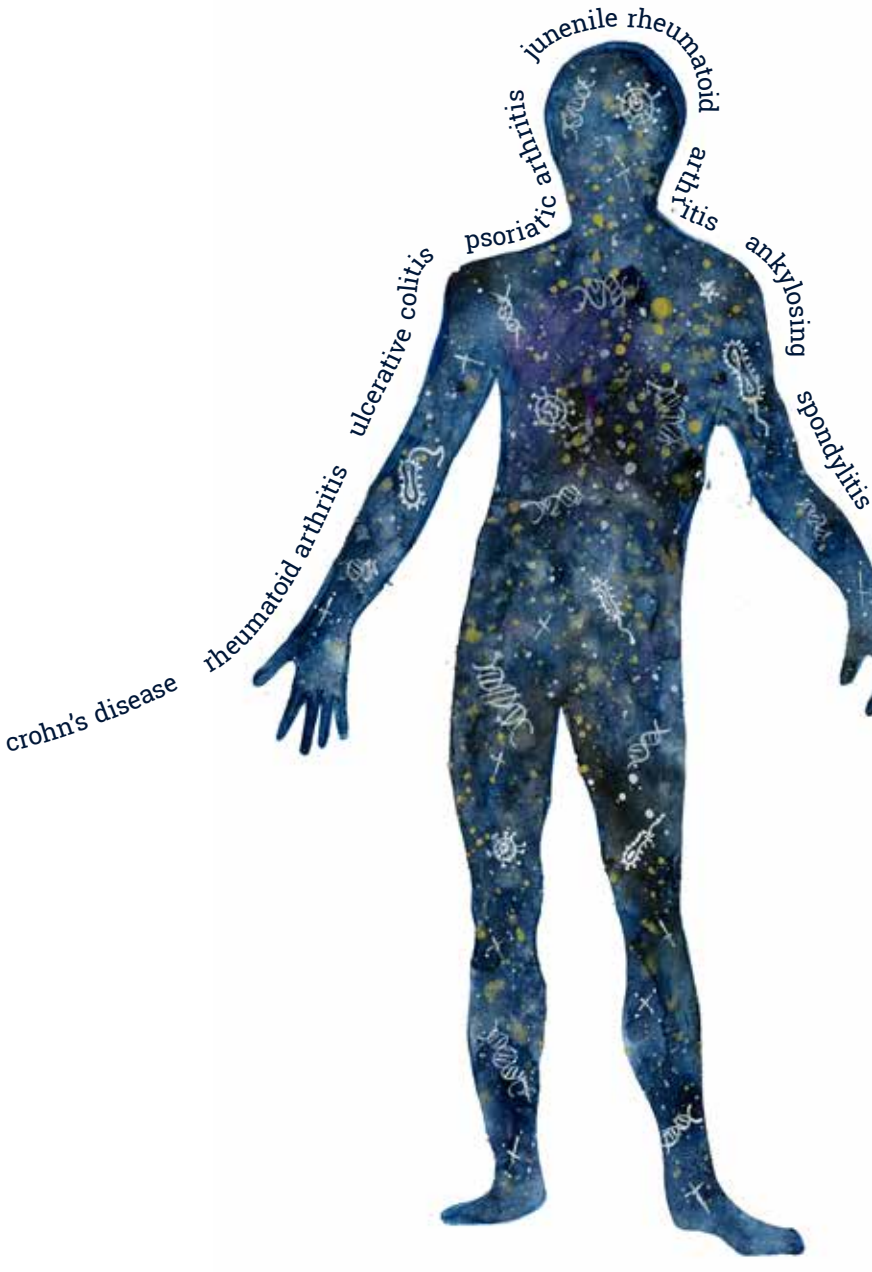
"What happens is the body starts seeing the medication as a foreign element, triggering the immune system to create antibodies to eliminate it. This is called immunogenicity," explains Delgado. "This happens in about half of the patients." He explains that when a patient has been responding to a drug, then stops all of sudden, the physician wants to know why.

If the patient has developed antibodies against the drug, the physician may switch them over to another type of TNF-blocking drug. There are five of them available in the United States, with one biosimilar recently approved. When the patient develops antibodies against the TNF blocker, it is important to switch to another drug, as the patient could end up with an immune-complex disease that threatens the organs.

Immunogenicity testing may also reveal that there are no drug antibodies present, indicating that the patient may require a higher dosage. "We are the only lab that offers a test that specifically identifies the production of neutralizing antibodies against TNF blockers, a situation in which TNF blockers become functionally ineffective," says Delgado. There are antibodies produced against TNF blockers that are non-neutralizing, but these antibodies can disappear over time, which doesn't require the need to switch to another TNF blocker.

"What happens is the body starts seeing the medication as a foreign element, triggering the immune system to create antibodies to eliminate it. This is called immunogenicity. This happens in about half of the patients."

Julio Delgado, ARUP Chief Medical Officer



Drs. Delgado and Lázár-Molnár developed a test that helps clinicians figure out if the prescribed medication is still working for a patient with autoimmune diseases and if it is being administered at the right dose. Such precision medicine improves patient care and saves everyone involved time and money.

Lázár-Molnár explains that the most commonly used tests measure the presence of any antibody that can bind to the drug molecule, regardless of whether or not they interfere with drug activity. The ARUP test only detects the presence of those antibodies that inhibit the function of the drug, which makes it more specific for identifying the cause as to why the drug treatment is not working.

ARUP developed immunogenicity testing after being approached again and again by clinicians and hospitals looking for a method that was as good or better than what was already being offered by other laboratories but less costly. Patients were being hit with expensive testing bills, some thousands of dollars, on top of already expensive medications.

"So far when doctors have not seen an improvement in the patient, they have increased the dose or frequency or switched to another drug," says Lázár-Molnár. This approach can be time consuming. "This more personalized approach using laboratory testing is likely to be more cost effective and reduce delays in finding the right treatment, which is important considering TNF antagonists are among the most expensive prescription drugs."

It's been 17 years since Foley first started taking TNF blockers, and she continues to live her life on her terms. "I make my choices based on quality of life—I want to live life as normally and fully as possible," expresses Foley. "I've always believed in making the best of what I have right now." ■

plaque psoriasis

uveitis

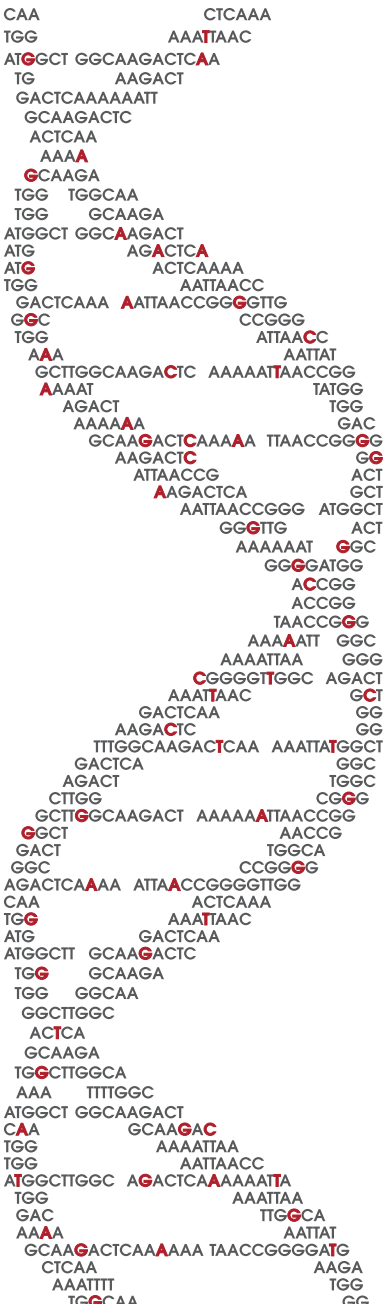
sarcoidosis

> "It works for a number of years, then my body starts rejecting it. At first you think it's the be-all, end-all drug; then, the body plateaus."
>
> **Lisa Foley, mother and dancer**

The Wow Factor

Since 1984, ARUP has worked quietly behind the scenes to support patient care—so quietly, in fact, that people don't realize the extensive role ARUP plays in diagnostic medicine. So we've decided to speak up and share some extraordinary facts with you.

Since 2012, ARUP has been using next-generation sequencing (NGS), a laboratory testing technology that delves into one's DNA, to look for disease-causing aberrations. A rapidly evolving area, NGS now spans five areas of clinical focus at ARUP: molecular genetics, immunology, hematopathology, solid tumor pathology, and soon infectious diseases.



We cultivate a culture of caring—and not just for patients. Every year, ARUP employees donate money—nearly $50,000 in 2016 alone—to selected nonprofits that help people and animals.

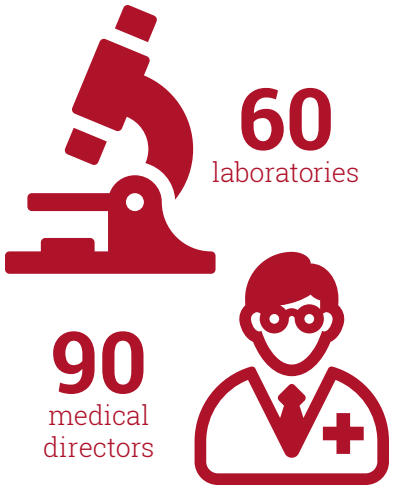
Every year, ARUP runs more than 3,000 different tests on 10 million biological samples from across the country; many of these tests rely on tools at the leading edge of precision medicine, including screens for hereditary cancers, molecular profiling panels for tumors, and next-generation sequencing.

3,000 tests

10M samples

Some 5,000 to 6,000 yellow shipping boxes destined for ARUP Laboratories arrive in Salt Lake City on Delta Air Lines flights each month. These boxes protect some of the 50,000 specimens arriving daily for testing and analysis by ARUP pathology experts.

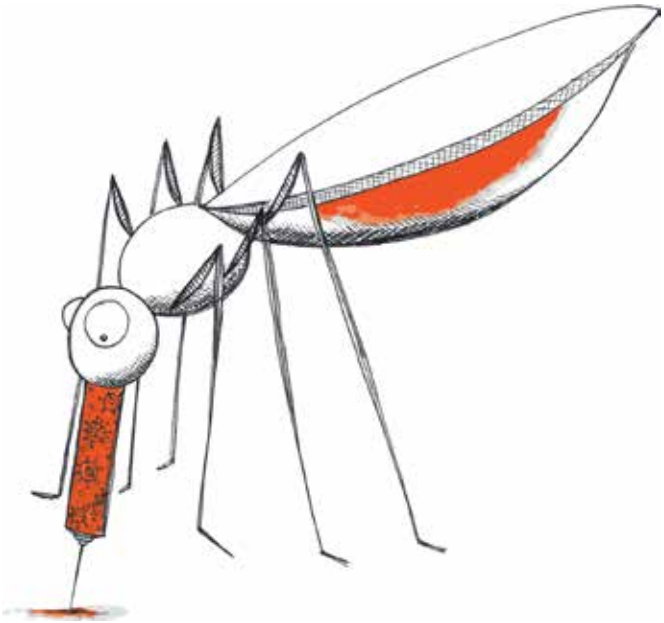
More than 30 years ago, ARUP sprang from the University of Utah's Pathology Department, experiencing all the trials and tribulations of a startup. Today, it provides laboratory testing for patients from every state and includes 60 laboratories and more than 90 medical directors, most of whom are faculty at the U of U.



60 laboratories

90 medical directors

A Rare *NEJM* Case Study Raises Questions about Zika Transmission



The first Zika virus-related death in the continental U.S. occurred in June of this past year, but even now, months later, two aspects of this case continue to puzzle health experts. First, why did this patient die? It is quite rare for a Zika infection to cause severe illness in adults, much less death. Second, how did another individual, who visited the first while in the hospital, become ill from Zika? This second patient did not do anything that was known at the time to put people at risk for contracting the virus.

Researchers at ARUP Laboratories and the University of Utah School of Medicine in Salt Lake City begin to unravel the mystery in *The New England Journal of Medicine*. Details from the two cases point to an unusually high concentration of virus in the first patient's blood as being responsible for his death. The phenomenon may also explain how the second patient may have contracted the virus through casual contact with the primary patient, the first such documented case.

Patient 1 was initially identified as being potentially infected with Zika virus during validation of a real- time PCR test for Zika virus, now offered by ARUP Laboratories (see sidebar), and was subsequently confirmed as positive by both the Utah Department of Health and the Centers for Disease Control and Prevention.

"From a clinical perspective, an important finding was that the virus can be transmitted person-to-person by routes other than mosquito bites or through sexual contact," says coauthor Kimberly Hanson, MD, MHS, a medical director at ARUP. "This was the first recognized case, and a very rare one, of a secondary Zika virus infection acquired by contact with a sick person."

"From a clinical perspective, an important finding was that the virus can be transmitted person-to-person by routes other than mosquito bites or through sexual contact. This was the first recognized case, and a very rare one, of a secondary Zika virus infection acquired by contact with a sick person."

Kimberly Hanson, MD, MHS, Medical Director, Mycology; Section Chief, Clinical Microbiology

This case emphasizes the need to further understand how Zika spreads and what precautions may need to be taken to prevent spreading. "We may never see another case like this one," says corresponding author Sankar Swaminathan, MD, chief of Infectious Disease and professor of internal medicine at the University of Utah School of Medicine. "But one thing this case shows us is that we still have a lot to learn about Zika."

The narrative unfolds in the *NEJM* case study. Last May, Patient 1 (a 73-year-old man) traveled to southwest Mexico, a Zika-endemic area. Eight days after returning, he started having abdominal pain and fever, and by the time he was admitted to the University of Utah hospital he also had inflamed, watery eyes, dangerously low blood pressure, and a rapid heart rate. Despite the medical staff's best efforts to stabilize him, his condition declined rapidly. During this time, Patient 2 came to visit and reported wiping away Patient 1's tears and helping to reposition him in the hospital bed. It wasn't long before Patient 1 slipped into septic shock, and his kidneys, lungs, and other organs started to shut down. He died shortly thereafter.

Even though it's well known that Zika can cause severe brain damage in unborn babies, symptoms are typically mild in adults. At the time of Patient 1's death, only nine other Zika-related deaths have been reported worldwide, says Swaminathan. Despite the odds, tests performed after Patient 1's death revealed that he had Zika.

Further research using Taxonomer, a tool developed by scientists at University of Utah and ARUP Laboratories that rapidly analyzes all genetic material from infectious agents in a patient's sample, suggested that there were no other obvious infections in the blood that explained his illness. "There was a question of whether this may be a more pathogenic strain. The viral genome sequence didn't support this, which put more weight on the high viral load," explains ARUP Medical Director Robert Schlaberg, MD, MPH. Taxonomer also found that the Zika virus that infected the patient was 99.8 percent identical to that carried by a mosquito collected from southwest Mexico, the same region that Patient 1 had visited a few weeks prior.

Seven days after Patient 1's death, Patient 2 developed red, watery eyes, a common Zika symptom. Tests suggested that Patient 2 had also developed a Zika infection, but in contrast to Patient 1, this patient only had mild symptoms that resolved within the following week.

Like Patient 1's death, Patient 2's diagnosis was unexpected. The species of mosquito that carries Zika had not been found in Utah, and Patient 2 had not traveled to a Zika-endemic area. A reconstruction of events ruled out other known means of catching the virus. An unprecedented transmission by casual contact between the two patients was found to be the most likely explanation.

"This and any future cases will force the medical community to critically re-evaluate established triage processes for determining which patients receive Zika testing and which do not," says ARUP Medical Director Marc Couturier, PhD.

The authors believe that the reason behind the unusual nature of the case lies in yet another anomaly. Patient 1's blood had a very high concentration of virus, at 200 million particles per milliliter. This equals roughly 10 million viral particles per drop of blood. "I couldn't believe it," says Swaminathan.

"The viral load was 100,000 times higher than what had been reported in other Zika cases [at this point in time], and was an unusually high amount for any infection." The observation opens up the possibility that the extraordinary amount of virus overwhelmed the patient's system, making him extremely infectious.

Still, what led to the unusually severe infection in the first place remains unknown. Was there something about Patient 1's biology or health history that made him particularly susceptible? There were small differences in the virus' genetic material compared to other samples of Zika virus; did they cause the virus to be exceptionally aggressive?

Swaminathan says, "This type of information could help us improve treatments for Zika as the virus continues to spread across the world and within our country." ■

> "This type of information could help us improve treatments for Zika as the virus continues to spread across the world and within our country."
>
> Sankar Swaminathan, MD, Chief of Infectious Disease, Professor of Internal Medicine, University of Utah School of Medicine

“Our test is reliable, robust, and reproducible to run—meaning that it produces the same results in multiple tries. We can also test more patients, more rapidly, with this test. A patient may get a faster result from us, and know sooner that they’re off the hook.”

Marc Couturier, PhD, D(ABMM), Medical Director, Microbial Immunology, Parasitology and Fecal Testing, and Infectious Disease Rapid Testing

Sincere thanks to our neighbor, the beautiful University of Utah Red Butte Garden, for a stunning photo backdrop.

The *NEJM* case study's authors included (left to right): Marc Couturier, PhD, Kimberly Hanson, MD, MHS, and Robert Schlaberg, MD, MPH, all medical directors from ARUP Laboratories and faculty at the University of Utah Department of Pathology; as well as Sankar Swaminathan, MD, chief of Infectious Disease and professor of internal medicine at the University of Utah School of Medicine and Julia Lewis, DO, from the University of Utah School of Medicine. The work was supported by the National Institutes of Health and published as *Fatal virus infection with secondary nonsexual transmission* in *The New England Journal of Medicine* on September 28.

What You Don't Know About Zika

Can any mosquito carry Zika?
No. Zika virus is transmitted primarily through the bite of an infected Aedes species mosquito (*Aedes aegypti* and *Aedes albopictus*). These mosquitoes also spread dengue and chikungunya viruses in overlapping regions.

What is the range of transmitting mosquitoes?
In the United States, Aedes mosquitos can be found in southern California and extending just north of San Francisco, across the Southern states, across the Midwest into southern Minnesota, and into New York, southern Connecticut, and sometimes into other New England states.

What is the best prevention for Zika?
Avoid mosquito bites.

Should you avoid mosquitoes only during the day?
No. Mosquitoes that spread Zika bite during the day and night.

What are the symptoms of Zika?
Patients may experience any combination of fever, rash, joint pain, conjunctivitis, muscle pain, and headache. Conjunctivitis is one of the more unique symptoms of Zika that helps to distinguish it from other cocirculating viruses.

Are there always symptoms?
No. Many people infected with Zika won't have symptoms or will have only mild symptoms.

When do symptoms develop?
Usually within a week, if symptoms occur. They usually last several days to a week.

What is the typical clinical outcome of Zika infections?
People rarely die of Zika, and many people might not realize they have been infected. However, Zika can be passed from a pregnant woman to her fetus. Infection during pregnancy can cause certain birth defects, such as microcephaly. In that case, the infant is born with a smaller head than expected for its sex and age. An infected person can also pass Zika to a sexual partner.

Which areas of the United States have reported Zika transmission risk?
Local mosquito-borne Zika virus transmission has been reported in Brownsville, Texas and in South Florida.

Once you have been infected with Zika virus, can you get it again?
Once a person has been infected, they are likely to be protected from future infections; however, it is not known how long the protection lasts.

Please note that guidelines can change quickly; consult the most current information on the CDC website (www.cdc.gov/zika). ■

Taking It to the Next Level

ARUP Attains Hard-Earned ISO Accreditation

Earning this standard gives ARUP the opportunity "not only to 'study for the exam,' but also to 'learn for life,'" said Frank Schneider, MD, FCAP, and chair of the College of American Pathologists (CAP) 15189 Committee. Two years of work in examining and sharpening processes at ARUP—performed closely with CAP advisors—resulted in this internationally recognized standard for laboratories.

The accreditation essentially recognizes that ARUP is extremely competent and has operational systems in place that back up that competency. "In clinical lab accreditation, this is a fairly new program [since 2008 from CAP]—on the cutting edge—and we're one of the largest labs to reach this stage," said Janice Pinterics, ARUP quality manager. "Before this, the accreditation had not gone to a laboratory of our size and high level of complexity."

This is a significant achievement, setting ARUP apart from other large organizations. Pinterics, along with Jonathan Carr, director of Compliance, Quality, Privacy and Risk, and an ISO Steering Committee of 15 or so individuals from multiple departments (including Technical Operations, Compliance & Quality Systems, Finance, Purchasing, Medical Directorship, Human Services) spearheaded several months of coordinated changes that earned the lab this honor.

The serious work began in August 2014, when ISO assessors performed a "gap assessment" at ARUP to find areas where the laboratory would need to make changes and integrate systems to achieve ISO 15189 accreditation.

Hammering things into place as an organization, bringing six laboratory divisions together to communicate about best practices, and integrating a new system took perseverance and dedication. "We were always good at identifying problems," notes Carr, "But now we can be more effective at stopping them from repeating. Now our processes require us to prove to ourselves that the same mistake won't happen again."

ISO 15189
CAP
ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

> Achieving this status just further validates the value that everyone here places on the work that they do for patients. They want to do it with the highest quality possible."
>
> Dr. Ron Weiss, ISO Steering Committee member and ARUP former Chief Operating Officer

"It's a culture of identifying process improvements. We're getting better at sharing best practices and identifying where multiple labs may be struggling with the same types of issues," says Jonathan Carr (left), who worked closely with ARUP colleagues Janice Pinterics (center), Dr. Ron Weiss (right), and others on the ISO Steering Committee in attaining ISO 15189 accreditation.

Four Different Perspectives on the ISO Accreditation Process

Perspective

Jonathan Carr,
ARUP's Director of Quality, Privacy, and Risk

What does ISO 15189 accreditation mean for ARUP?
The accreditation not only shows our commitment to quality and identifying errors, but also to assuring we've corrected them effectively (closed the loop), identified a problem, its cause, and its corrective action, and then evaluated whether the corrective action is effective. We are also improving ways for our various lab sections to learn from each other as corrective actions are implemented.

What's an example of something that has changed with ISO accreditation?
We have made an effort to enhance the culture of identifying process improvements, not just reacting to human error. If we find that someone is not following every step of the official written process, our ISO 15189 processes force us to ask why a step was omitted. But in the process established by ISO accreditation, we ask why it happened, and there is room for communication—for learning how to make the system better. The organization takes appropriate responsibility for the error and identifies how the system should be improved, in addition to any individual accountability.

Implementing ISO 15189 helps us continue to learn why things happen, and make appropriate changes as a result.

> "We have made an effort to enhance the culture of identifying process improvements, not just reacting to human error."

Perspective

Janice Pinterics,
ARUP Quality Manager

> “ISO really wants to give technologists a voice, to empower them to take a part in redesigning our process with the shared goal of improving patient care.”

What was one of the major changes?
Previously, we used a database to write up any problems and what actions we took to fix them, then cases were closed without review. For ISO accreditation, we significantly reconfigured the system to harmonize our method of investigating problems, and there was training for everyone using it. The change required buy-in from multiple areas that were previously relatively independent—all six lab divisions worked with the CRM Salesforce team, IT, and CQS. We had to work out any issues in the new system and agree upon a harmonized approach for investigations and reviews.

How did ISO accreditation sharpen ARUP’s already existing high quality?
I think the accreditation presents an advantage for ARUP in a few different ways: it promotes standardization and harmonization as an organization. Additionally, ISO really wants to give technologists a voice to empower them to take a part in redesigning our process with the shared goal of improving patient care. Reaching a consensus for the required changes within a large organization and empowering our employees is a very unifying event.

What has changed?
In the past, ARUP was good at containing problems—we have always been very responsive and able to correct and contain the immediate issues; frequently, this would involve retraining an individual on a procedure that wasn’t followed. But because doing so takes a lot of time and our labs are extremely busy, we didn’t consistently go back to find and address the true underlying root cause. ISO is saying don’t just retrain a person on a procedure; we want to hear back on whether the procedure was clear, whether the training was adequate, and whether our process is flawed. When we ask these more difficult questions and get to the real root causes and fix them, it allows us to continually improve processes.

“To ensure consistency of work, communication needs to be fostered. It’s important that staff be heard and truly listened to, and that action is taken. It has been truly striking to me, professionally, to see the ways that ARUP has made it possible for the staff to be heard.”

Perspective

Amy Pennock, MS,
ISO 15189 Lead Assessor, College of American Pathologists (CAP)

What catches your eye about ARUP since it achieved ISO 15189 status?
ARUP is now truly empowering the staff at all levels. As an employee, that means changing the way you think about doing your job every day. Instead of thinking, “I’ll come in and do my work and leave at the end of the day,” ARUP employees are now taking a broader view of their work area and the surrounding areas, then vocalizing their ideas and getting involved in driving improvement. It’s important that staff be heard and truly listened to, and that action is taken. That’s now taking place at ARUP.

How is ARUP unique in achieving this new status?
Given the test menu that ARUP offers, it is among the largest organizations to achieve ISO 15189-accredited status. It’s impressive that an organization with so many labs has been able to unify those sections with best practices and effective ways of sharing information. From an assessor’s perspective, I see greater communication throughout the organization—across departments, and across leadership at local and across executive management.

What’s the significance of ARUP having achieved the status?
Seeing ARUP and the journey it has been on to achieve accreditation—the dedication of staff at all levels, from management to bench-level—demonstrates a commitment to quality testing, and, most importantly, to patient care. It has been exciting to observe the evolution of ARUP’s quality management system.

A member of the ISO Steering Committee at ARUP and professor of pathology at University of Utah, Ron Weiss, MD, MBA, is ARUP's former president/chief operating officer and is now a senior hematopathology consultant.

What does ISO 15189 accreditation mean to you?
I think ARUP's history has always been focused on service quality and a commitment to excellence in healthcare. Achieving this status just further validates the value that everyone here places on the work that they do for patients. They want to do it with the highest quality possible.

You were a member of the ISO Steering Committee, which numbered about 15 individuals who contributed from various departments to the two-year process of making adjustments at ARUP to achieve ISO 15189 accreditation. What brought you to the committee?
I was asked to join, in part to represent the medical directors' group with Dr. Chris Lehman [comedical director, University Hospitals and Clinics Clinical Laboratory], who has experience through the College of American Pathologists with the ISO process. The goal was to determine how best to message to our fellow medical directors how their lives would be impacted, and to encourage them and be a resource as they activated those standards. Given my long history at ARUP and experience in the quality program, I was interested in the opportunity to participate.

What else is exciting about the accreditation?
It was gratifying to see this process play itself out, and to see the commitment not only of the Steering Committee, but everyone at ARUP. In a sense, I was not surprised that we ended up with ISO accreditation. As with any process, there were points of adjustment, but there was always commitment from the staff at ARUP to make this happen.

Perspective

Ronald L. Weiss, MD, MBA,
ARUP ISO Steering Committee

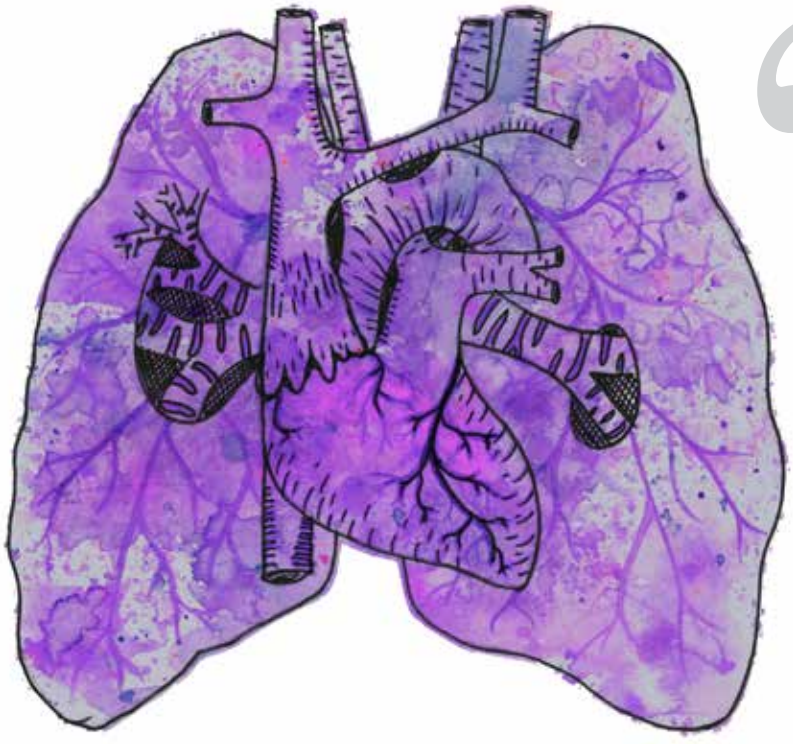
> "Achieving this status just further validates the value that everyone here places on the work that they do for patients. They want to do it with the highest quality possible."

New Genetic Test Identifies Rarer Forms of Pulmonary Hypertension, Improving Treatment and Deterring Need for Biopsy

If you are the patient, the difference between a blood sample and a lung tissue sample is significant; the latter is invasive and can present risks. Until recently, this was not a choice for patients suspected of having a rare form of pulmonary hypertension.

Now a simple blood sample can provide diagnostic information and allow for earlier intervention and, ultimately, more targeted, life-saving treatment. Pulmonary hypertension occurs when the pressure in the blood vessels leading from the heart to the lungs is too high.

A collaboration between Intermountain Medical Center and ARUP Laboratories led to the discovery of a new genetic cause of pulmonary hypertension in 2013 and, more recently, the development of a new genetic test for identifying these mutations.



Mutations in the identified gene (*EIF2AK4*) cause a rarer form of pulmonary hypertension, known as pulmonary capillary hemangiomatosis (PCH) and pulmonary venoocclusive disease (PVOD). Both are different manifestations of the same disease caused by mutations in the same gene. PCH is defined by uncontrolled growth of capillaries in the lungs. PVOD is defined by the widespread obstruction of the pulmonary veins.

"Traditionally, patients who have this condition [PCH/PVOD] have to undergo a lung biopsy to confirm the diagnosis," says ARUP's molecular genetics scientist Hunter Best, PhD, who collaborated with pulmonologist Greg Elliott, MD, at Intermountain Medical Center.

"Now, we can simply take a blood sample and confirm the diagnosis through genetic testing. If you have causative mutations in that gene, the patient will no longer need a biopsy, which can be risky and invasive," adds Best, medical director of ARUP's Molecular Genetics Lab and an expert on next-generation sequencing (a method used for analyzing DNA).

Not everyone who has *EIF2AK4* gene mutations will present with identical disease manifestations, but mutations running in a family are a good predictor of developing symptoms of the disease, which has a high mortality rate. About half of all patients diagnosed with this condition die within two years. "This discovery will eventually lead to improved care, and, believe it or not, lower costs for patients," says Elliott. "The biggest savings will come from accurate diagnoses, which will reduce the use of ineffective and potentially harmful interventions."

> If you look at the fact that someone has pulmonary hypertension and then go through the testing to determine if they have these rarer forms caused by genetic mutations, the treatment will change based on each disorder."
>
> Hunter Best, Medical Director, Molecular Genetics, Director, High Complexity Platforms—NGS, ARUP Laboratories

What Led to the Gene Discovery?

When Elliott was caring for two brothers, both diagnosed with PCH, he suspected a genetic cause and reached out to Best to set up a gene discovery study. By analyzing the DNA of the brothers, additional siblings, and the parents, they were able to identify not one but two causative mutations in the *EIF2AK4* gene. Family members who carried only one mutation were unaffected by the disease; those carrying two mutations—passed down from each parent—had the disease. The study also included DNA analysis from other families.

Often a patient is diagnosed with pulmonary arterial hypertension (PAH), but the rarer form of disease (PCH/PVOD) is not confirmed until an autopsy is conducted. Yet the treatment for PAH is often not effective in treating PCH or PVOD. Symptoms associated with these are the same as regular pulmonary hypertension, including both heritable and idiopathic types, which are relatively common.

"I think the disease [PCH and PVOD] is understudied and underdiagnosed," says Best.

Doctors often treat patients for pulmonary hypertension, but when they actually have the rarer disease, the conventional treatment methods result in poor outcomes.

"The new testing methodology is a model of how genomic testing can and will ultimately provide better outcomes for many disorders, decrease the cost of healthcare delivery, and lower risks to patients," says Elliott. "It involves a rare disease, but this theme will be repeated again and again in many ways." ■

Pulmonary Hypertension Symptoms

Shortness of breath, initially while exercising and eventually while at rest

Fatigue

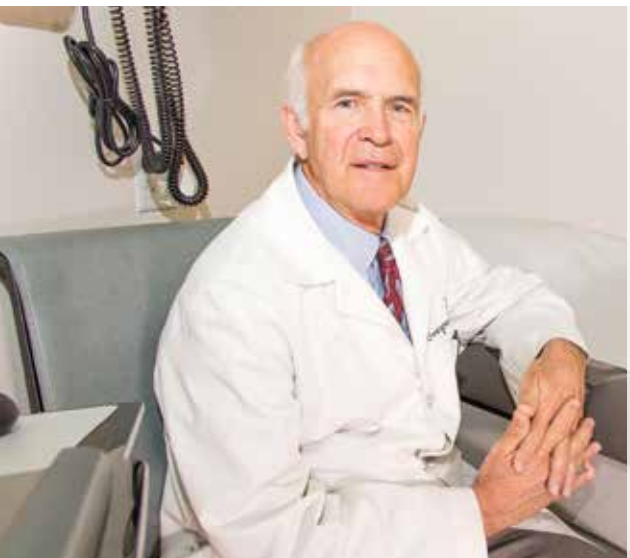
Dizziness or fainting spells

Chest pressure or pain

Swelling in ankles, legs, and eventually abdomen

Bluish color to lips and skin

Racing pulse or heart palpitations



ARUP molecular genetic scientist Hunter Best, PhD (right), teamed up with pulmonologist Greg Elliott, MD (left), of Intermountain Medical Center, to home in on disease-causing genetic mutations.

Questions of Clinical Utility | Thiopurine Drug Toxicity Testing

Thiopurine S-methyltransferase (TPMT) is an enzyme encoded by the *TPMT* gene that inactivates thiopurine drugs, which suppress the body's immune system and are used to treat patients with autoimmune disorders, inflammatory bowel disease, and organ transplants.

Changes in the *TPMT* gene cause TPMT deficiency; without enough of the TPMT enzyme, the body can't metabolize (turn off) thiopurine drugs. TPMT and xanthine oxidase, an enzyme involved in purine metabolism, work together to inactivate 90 percent of a drug dose, while only 10 percent of the dose is converted to metabolites that stop inflammation and T-cell proliferation.

Because xanthine oxidase does not exist in bone marrow, the risk for life-threatening bone marrow toxicity depends on TPMT enzyme activity. Patients with low TPMT activity are at increased risk for thiopurine drug-induced toxicity when treated with a standard drug dose. Patients with high TPMT activity, however, may be undertreated.

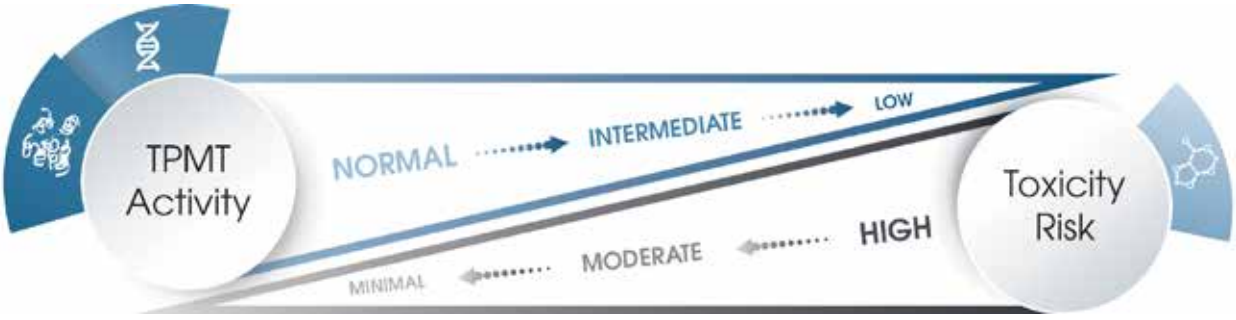
Due to single nucleotide polymorphisms (SNPs; pronounced "snips") in the *TPMT* gene, TPMT enzyme activity varies within a population. SNPs occur at a specific position in a gene and are the most common genetic variations within a population.

Altering the function of genes encoding drug-metabolizing enzymes can impact how an individual responds to a given drug. For example, there are more than 30 alleles on the *TPMT* genes, but four of them—*2, *3A, *3B, and *3C—account for approximately 95 percent of low enzyme activity in a specific population.

Patients who inherit two nonfunctional alleles on their opposite chromosomes have an increased risk for severe bone marrow toxicity from conventional doses of thiopurine drugs. The most common functional allele found in the Caucasian population is *TPMT**3A. The most common allele variant found in the Asian and African populations is *TPMT**3C.

People of Caucasian race follow a tri-modal—low, intermediate, and high—distribution pattern of TPMT enzyme activity. About 89 percent of Caucasians with high TPMT enzyme activity have the homozygous (two of the same allele) wide-type genotype, while 11 percent of those with intermediate enzyme activity have one wild-type and one variant allele. However, one out of every 300 individuals with low enzyme activity has two low TPMT activity alleles or is homozygous for the deficient alleles.

> "The phenotype (enzyme assay) or genotype tests should be performed prior to thiopurine drug therapy to identify patients with abnormal TPMT enzyme activity. Dose adjustments may be required to minimize the risk for toxicity and to optimize therapy."
>
> Kamisha Johnson-Davis, PhD, DABCC



ARUP Medical Directors Yuan Ji, PhD, DABCP, FACMG, and Kamisha Johnson-Davis, PhD, DABCC, specialize in pharmacogenetics and toxicology (respectfully) and address questions of clinical utility regarding thiopurine drug testing and TPMT pharmacogenetics testing.

What is the best way to utilize *TPMT* genotyping or phenotyping tests?
TPMT genotyping or phenotyping should be performed **prior** to thiopurine administration to predict the risk of developing severe bone marrow toxicity. For the phenotype (enzyme) assay, patients should currently not be on thiopurine therapy, as the substrate for the enzyme assay is 6-mercaptopurine.

If a patient is on thiopurine therapy, the thiopurine drug metabolite assay can be ordered to assess TPMT activity by measuring levels of 6-methyl mercaptopurine (6-MMP) and 6-thioguanine nucleotides (6-TG) nucleotides to determine if the patient has normal metabolism (i.e., metabolites are within the therapeutic reference range).

The genotype assay can also be ordered post thiopurine drug therapy. If a patient is identified as having low or intermediate TPMT activity, dose adjustments should be made to minimize the risk for bone marrow toxicity and optimize therapy.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines for TPMT and thiopurine dosing to guide clinicians in proper dose adjustment based on *TPMT* genotype and likely phenotype.

What are the limitations of genotype and phenotype testing?
Several drugs can alter or inhibit TPMT enzyme activity, which may lead to falsely low results (e.g., TPMT activity in red blood cells can be masked if the patient has received a recent blood transfusion). Saliva genotype assays have been proposed to overcome this limitation. Conventional *TPMT* genotyping assays are designed to target the most common *TPMT* SNPs but don't allow for the detection of rare alleles. Testing both TPMT enzyme activity and *TPMT* genotyping can help minimize effects of these limitations, thus greatly enhancing clinical utility.

Several recent studies have reported that individuals who carry low functional alleles for the *NUDT15* gene encoding the Nudix hydrolase 15 cannot tolerate standard doses of thiopurine drugs.

Clinicians should keep in mind that *TPMT* genotype and phenotype tests do not replace the need for careful clinical monitoring.

What is the evidence that genotype and phenotype testing improves patient outcomes?
TPMT pharmacogenetics is one of the first examples that demonstrated the clinical utility of pharmacogenetic testing. Genetically low TPMT activity was first linked to thiopurine drug-associated, life-threatening toxicities in 1989; since then, multiple studies have confirmed this association in a variety of disease settings.

Based on strong and consistent clinical evidences, CPIC has issued guidelines with strong recommendations for considering alternative agents or drastically reducing doses for patients carrying low or deficient *TPMT* alleles prior to drug therapy.

TPMT gene and related thiopurines drugs (i.e., thioguanine, mercaptopurine, and azathioprine) were also listed in the table of pharmacogenetic biomarkers in drug labeling by the U.S. Food & Drug Administration. ■

People Proud

Knowledge fuels the engines here at ARUP. And it is our dynamic cadre of research scientists who provide the know-how and expertise. Each year, they publish hundreds of articles in leading journals, present at conferences around the world, and contribute to professional organizations. We are proud that they are being recognized for their hard work and expertise.

Marc Couturier, PhD, D(ABMM), medical director, Microbial Immunology and other areas, won the 2017 Diagnostics Young Investigator Award from the American Society for Microbiology (ASM). According to ASM, the Diagnostics Young Investigator Award recognizes research excellence and potential to further the educational or research objectives of an outstanding young clinical scientist. Dr. Couturier will be presented with the award in June at the ASM Microbe 2017 conference in New Orleans.

Georgios Deftereos, MD, medical director, was named to the American Society for Clinical Pathology's (ASCP) prestigious 40 Under Forty list for 2016 in recognition of his achievements in the medical laboratory field. The pool of applicants was the largest ever, making the selection process very competitive within a group of pathology and laboratory medicine professionals.

Julio C. Delgado, MD, MS, was appointed chief medical officer (CMO), director of laboratories, and co-chief of the Clinical Pathology Division, effective January 1. He joined ARUP in 2006 as a medical director in the Department of Immunology and was coexecutive director of the ARUP Institute for Clinical and Experimental Pathology® from 2013 to 2015.

Thomas Haven, PhD, R&D ARUP investigator, received the Doctoral Award from the Association of Medical Laboratory Immunologists (AMLI) for his presentation entitled *Retrospective analysis of autoantibody diversity in pediatric patients undergoing evaluation for autoimmune encephalitis*.

R&D principal investigator **Sonia La'ulu, BS** received the Outstanding Abstract Award from the American Association of Clinical Chemistry (AACC), Endocrinology Division, for her abstract entitled *Free thyroid hormone measurements in pregnancy: comparisons of immunoassays and mass spectrometry.*

A group including medical directors **Eszter Lázár-Molnár, PhD, D(ABMLI)**; **Erica F. Andersen, PhD**; **Julio C. Delgado, MD, MS**; and R&D scientist II **Tracie Profaizer** (not pictured) won the Best Case Study Award from the American Society for Histocompatibility and Immunogenetics (ASHI) for their presentation entitled *Resolution of conflicting HLA assignment due to loss of heterozygosity in the HLA region by NGS typing*.

Elaine Lyon, PhD, FACMG, medical director, was elected as a Molecular Genetics Director to the Board of Directors of the American College of Medical Genetics and Genomics. Her term is April 1, 2017, through March 31, 2023.

Kristi J. Smock, MD, medical director, was also named to the American Society for Clinical Pathology's (ASCP) prestigious 40 Under Forty list for 2016, in recognition of her achievements in the medical laboratory field. Considering the largest pool of applicants ever, the selection process was very competitive within a talented group of pathology and laboratory medicine professionals.

Lacy Taylor, MS, R&D toxicology specialist, won the Leo Dal Cortivo/ Young Forensic Toxicologist Award from the Society of Forensic Toxicologists (SOFT) for her poster entitled *Use of an internal hydrolysis indicator for monitoring β-glucuronidase activity*.

Karl V. Voelkerding, MD, FCAP, received the CAP Distinguished Service Award from the College of American Pathologists (CAP)—the only one of its kind awarded this year. For the past five years, Voelkerding, ARUP director, Molecular Pathology Fellowship and medical director, Genomics and Bioinformatics, has led a team developing accreditation requirements and proficiency testing for next-generation sequencing (NGS) for CAP.

Whitney Wooderchak-Donahue, PhD, R&D principal investigator, received the Top Poster Award from the American College of Medical Genetics (ACMG) for her poster entitled *Identification of novel* SMAD3 *mutations in families with variable Marfan-like clinical findings featuring aortopathy*.

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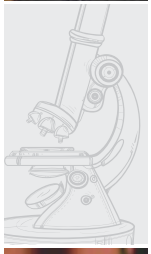

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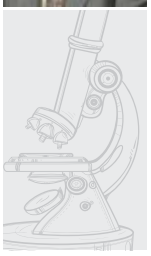

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