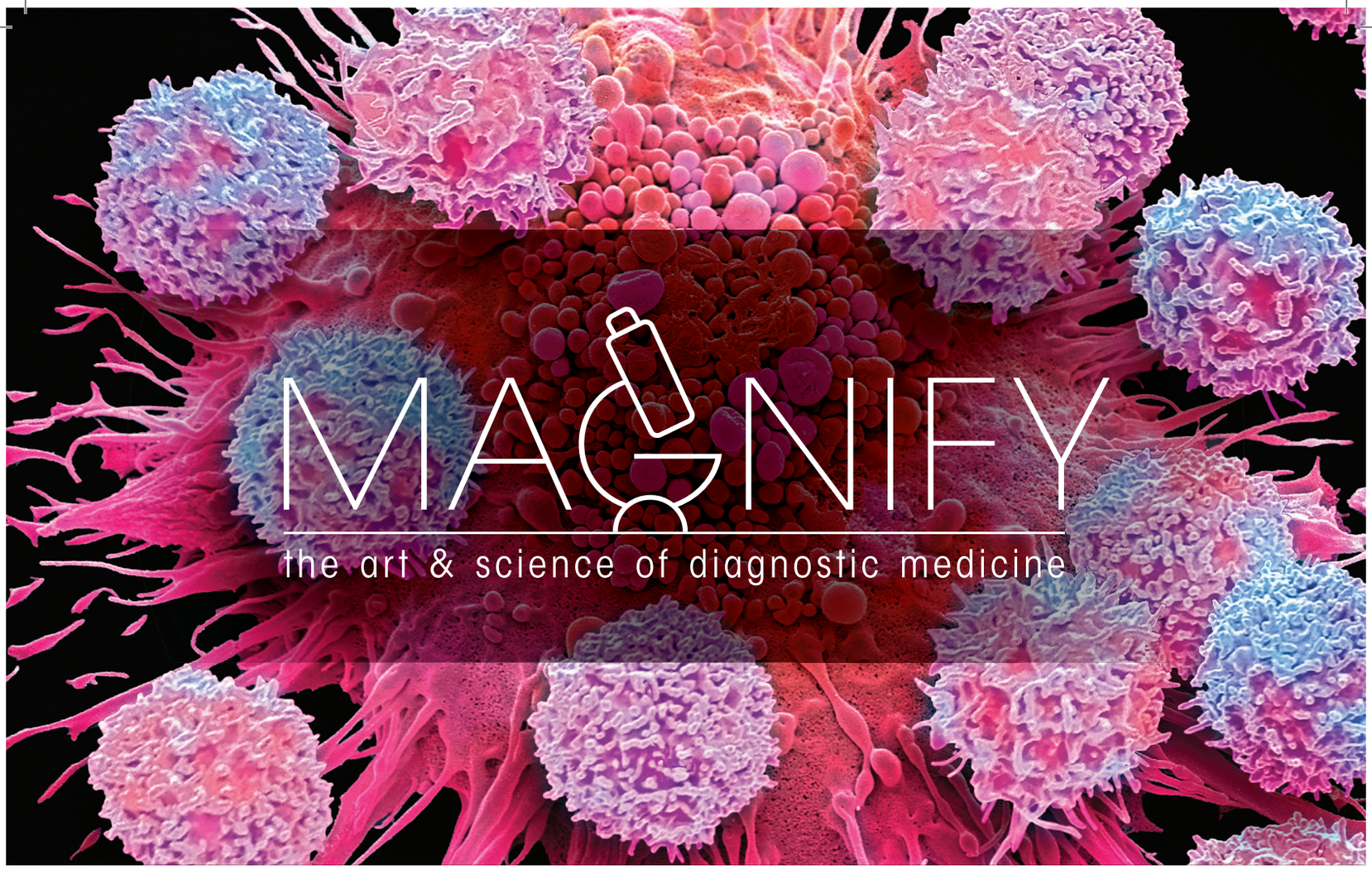

Fall 2023

A Focus on Drug Testing

ARUP Pioneers New Approaches to Deliver Answers Patients Can Trust

Also in this issue: ARUP Expands Capacity for Cytogenetics Testing

ARUP LABORATORIES

MAGNIFY

the art & science of diagnostic medicine

Contents

In Magnify, we share stories that bring laboratory medicine to life.

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A Message From the CEO

Ten years ago, Gwen McMillin, PhD, DABCC (CC, TC), FAACC, first implemented what was then considered an unorthodox approach to drug testing. By eliminating the standard drug screening test and going straight to more sensitive, more accurate mass spectrometry testing when it made sense clinically, the ARUP medical director of Clinical Toxicology pioneered a way to provide faster, more accurate results while eliminating unnecessary tests and decreasing testing costs for hospital and health system clients nationwide.

McMillin's innovative strategy is now part of laboratory drug testing guidelines she helped write, and many laboratories have adopted the approach, despite their initial skepticism.

She, like all ARUP medical directors, cares deeply about the good lab stewardship that is embodied in the new approach to drug testing that she championed. McMillin and her peers work tirelessly to identify and implement changes that translate to more efficient and effective patient care, even as testing needs continually evolve. Clients can count on ARUP to meet changing needs without ever losing sight of lab stewardship as a guiding principle.

The work of Erica Andersen, PhD, FACMG, ARUP's section chief of Cytogenetics and Genomic Microarray, also demonstrates ARUP's commitment to provide high-quality testing efficiently and effectively. With careful forethought and planning, Andersen has led ARUP's effort to invest in instruments and space and build the expertise necessary to increase testing capacity and boost volumes in her labs by 20% a year through 2026.

Growth is taking place even as Andersen's labs continue to ensure that clinicians order the right tests in the right order to obtain rapid, accurate results that inform essential clinical care.

Read more about these two innovative leaders in this edition of Magnify. You will understand why they make me proud.

Andy Theurer
CEO

ARUP Continues to Pioneer Improved Drug Testing to Support Patient Care

Almost a decade ago, ARUP Laboratories launched a new drug panel that countered all known and accepted approaches to drug detection. The approach, pioneered by a visionary clinical toxicologist and ARUP medical director, Gwen McMillin, PhD, DABCC (CC, TC), FAACC, eliminated the traditional screening test that was followed by a confirmatory test.

Instead, McMillin proposed a new philosophy that would provide more accurate results in less time, reduce unnecessary testing, and decrease testing costs. The philosophy was simple: Use the test that best fits the clinical need, even if that means skipping the standard screening test.

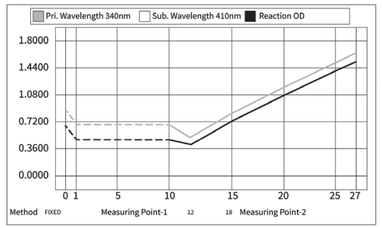
"If you know that a screening test isn't going to give an accurate result, doesn't perform well, or doesn't meet your clinical needs, then why do it at all?" McMillin said. "I knew that, in many cases, it would be better to bypass the screening test and go straight to the more sensitive, more accurate test."

According to McMillin, immunoassays are often used as an initial screen because they can provide results quickly, they are inexpensive, and the equipment used to perform them is more readily accessible to clinical laboratories. Immunoassays are also known to cross-react with multiple compounds and therefore provide ambiguous results that require confirmation. By contrast, mass spectrometry testing can yield a very specific and accurate result.

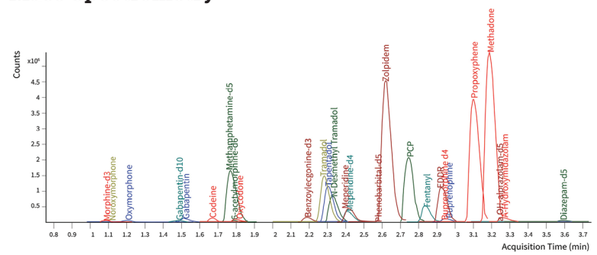
"The team has built a lean, targeted panel that provides the information clinicians need and reduces confusion regarding results," said Jessica Boyd, PhD, FCACB, DABCC (TC), the medical director of Clinical Toxicology who now oversees the drug panel.

The new panel, the first for which this mass spectrometry-first approach was used, initially met with resistance. McMillin fielded call after call from other laboratorians and clinicians who found the strategy baffling.

Immunoassay Screen



Mass Spectrometry



Mass spectrometry provides a more specific result and is more sensitive than an immunoassay drug screen. The immunoassay screen (left) detects the presence of a compound or similar compound by the light that is emitted when the compound(s) react with specially formulated reagents. In contrast, mass spectrometry (right) identifies each compound that is present based on its mass-to-charge ratio.

Jessica Boyd, PhD, FCACB, DABCC (TC), medical director of Clinical Toxicology, who recently joined ARUP from Canada, oversees urine drug testing.

Gordon Nelson, Chemistry operations director, and Warren Hunt, Chemistry group manager, showcase the new Mass Spectrometry Laboratory in ARUP's state-of-the-art facility.

> *"We've tried to evolve in concert with our clients' needs, and what patients and clinicians need, so that we can respond, even if that's breaking down traditional approaches and models."*
>
> **Gwen McMillin, PhD, DABCC (CC, TC), FAACC, ARUP Scientific Director for the Mass Spectrometry Platform and Medical Director of Clinical Toxicology**

"The approach was originally seen as somewhat clinically unorthodox," said Gordon Nelson, the Chemistry operations director who participated in the initial launch. "Clinicians were so dialed in to the idea that you needed to confirm every single drug test that they didn't understand the logic."

Confident in the soundness of her philosophy, McMillin persevered, devoting significant effort to educating colleagues and clinicians and establishing the beneficial outcomes.

"We have centered our efforts around innovation and what makes sense for the patient," McMillin said. "Many other labs have followed in our footsteps in trying to focus on what's needed for clinical lab management."

Now, 10 years later, many other laboratories have adopted McMillin's once unconventional method, and McMillin has since helped to write new laboratory guidelines for drug testing based on this strategy to promote more efficient, effective clinical outcomes.

That determination to continuously drive change that leads to better patient outcomes is a characteristic common to all of the team members in ARUP's Clinical Toxicology Department. Their efforts have transformed a single, small clinical laboratory with about 20 employees into a thriving, robust department—with five clinical laboratories and more than 200 employees—that delivers quality results for tens of thousands of patients each month.

"We've tried to evolve in concert with our clients' needs, and what patients and clinicians need, so that we can respond, even if that's breaking down traditional approaches and models," McMillin said.

This month, ARUP's Clinical Toxicology Labs will complete their move into ARUP's new state-of-the-art facility. The move marks the culmination of more than six years of effort to design a laboratory uniquely suited to mass spectrometry testing.

"We've carefully considered every aspect of this space—from how to limit the noise to make the lab staff more comfortable to using the excess heat the machines generate as a heat source for the building," said Warren Hunt, Chemistry group manager, who has played a key role in designing the new space and making it operational.

The new lab will group testing into two categories, quantitative and qualitative mass spectrometry, and increase both operational capacity and efficiency.

"We've consolidated our processes to streamline tests that are performed on the same types of instrumentation and that generate the same types of results, aligning inputs to outputs," McMillin said.

This isn't the first time the Clinical Toxicology Labs have successfully combined testing in such a way that it resulted in big wins. Several years ago, as Clinical Toxicology shifted its focus to mass spectrometry testing on the heels of McMillin's revolutionary approach, the lab moved all immunoassay testing to ARUP's Automated Core Lab.

"That consolidation really allowed the Automated Core Lab to focus on what they do best, and the Clinical Toxicology Labs to focus on our strength, which is mass spectrometry," Nelson said.

As a result, the turnaround time for immunoassays decreased by 30%, and the capacity for mass spectrometry tests more than doubled. The team hopes the current consolidation will further increase efficiency and capacity.

"In toxicology, whether you're screening for drugs of abuse or drugs that are prescribed, speed and accuracy are the two keys that drive operations, because there's always someone who is waiting on a dosing adjustment or a treatment plan," Hunt said.

Building Tests That Support Patient Care

Building efficient testing processes has lasting effects well beyond the laboratory. For clinicians who need information, sometimes urgently, to begin effective treatment, efficient testing can mean the difference between successful treatment and failure.

In 2022, Kamisha Johnson-Davis, PhD, DABCC (CC, TC), medical director of Clinical Toxicology, launched a new expanded drug profile that supports emergency departments across the nation in cases of unknown drug exposure. The profile detects an impressive 127 drugs and drug metabolites,

Kamisha Johnson-Davis, PhD, DABCC (CC, TC), medical director of Clinical Toxicology, launched a test in 2022 that detects 127 drugs and drug metabolites with a single injection and supports emergency departments with rapid, accurate results in cases of unknown drug exposure.

including prescription, over-the-counter, and illicit drugs. For patients who are experiencing adverse reactions to an unknown drug, identifying the cause quickly and accurately is critical to starting effective treatment.

"You can imagine the scenario of a pediatric patient who has unknowingly gotten into the medicine cabinet and is experiencing an adverse reaction to that exposure," Johnson-Davis said. "It's critical that we determine quickly what that drug is so that the patient can begin receiving a potentially lifesaving treatment."

As part of her efforts, Johnson-Davis consolidated the test onto one platform, which makes it possible for the test to detect all 127 drugs with a single injection. According to Johnson-Davis, consolidating testing onto one platform not only increases efficiency, it has also enabled better testing of pediatric samples.

"We no longer have to split a sample between multiple platforms, which has significantly reduced the amount of sample required," Johnson-Davis said. "It is often difficult to collect sufficient quantities from pediatric patients. With the single injection, we can run the test from even just 1 milliliter of sample."

Johnson-Davis carefully selected which drugs to include in the panel based on data from the American Association of Poison Control Centers on the most common accidental exposures.

"It's impossible to include everything because there are hundreds and hundreds of drugs," Johnson-Davis said. "I wanted to build a test that would support the top clinical needs. We designed the test to pick up routine medications that could be found at home."

"We were one of the first laboratories to go live with a broad-spectrum screen by mass spectrometry; now we have a mass spectrometry test that covers 127 different compounds with a single injection," said Hunt, the Chemistry group manager. "It's truly remarkable when you think about the amount of progress that has occurred in a relatively short time span."

Individual, Precise Diagnostic Medicine

Pharmacogenomics (PGx), an emerging medical specialty, leverages genetic testing to predict how patients are likely to respond to certain medications. PGx testing aims to select the most appropriate drug options and doses for individual patients and avoid adverse drug effects.

"Drug manufacturers base their dosing on what is most appropriate for the vast majority of the population," said Ryan Nelson, PharmD, medical director of Precision Medicine. "The challenge with that approach is that not everybody is the same, and we all have slight variations in how we react to or metabolize drugs."

According to Nelson, a recent study involving members of the Kentucky Teachers Retirement System found that using

Ryan Nelson, PharmD, medical director of Precision Medicine, is spearheading the development of an open-source database that will allow clinicians to access relevant information regarding how genes affect drug metabolism to inform treatment plans.

Sherin Shaaban, MD, PhD, FACMG, medical director of Pharmacogenomics and Molecular Genetics, has led the development of pharmacogenomics testing to provide more precise, personalized guidance on effective medications.

> ***"It's important that we offer testing for genes and variants that are actionable and have the highest levels of evidence of their role in drug metabolization."***
>
> **Sherin Shaaban, MD, PhD, FACMG, ARUP Medical Director of Pharmacogenomics and Molecular Genetics**

PGx resulted in a 15% reduction in inpatient visits, a 6.8% reduction in emergency department visits, and a cumulative savings of $37 million during a 32-month period.

One issue hindering the implementation of PGx in the clinic is a lack of consensus between regulatory and guideline-producing authorities on when and how PGx should be used.

Nelson is currently working to build an open-source database, MetaCensus, using blockchain technology, that will make relevant clinical information on PGx free for anyone to access. Additional scientific domains will be added to MetaCensus as it continues to grow.

"Most clinicians cannot afford to access the most recent data published on PGx," Nelson said. "This hinders clinicians worldwide from accessing reliable information promptly and, in turn, hinders them from providing the best care based on the most recent information in the field."

Nelson hopes this open-source database will enable clinicians to access up-to-date information in a concise format so that they can make better-informed clinical decisions, and that it will change how meta-analyses are performed. He has gathered a team of topic experts in precision medicine and data science to volunteer their time to build MetaCensus.

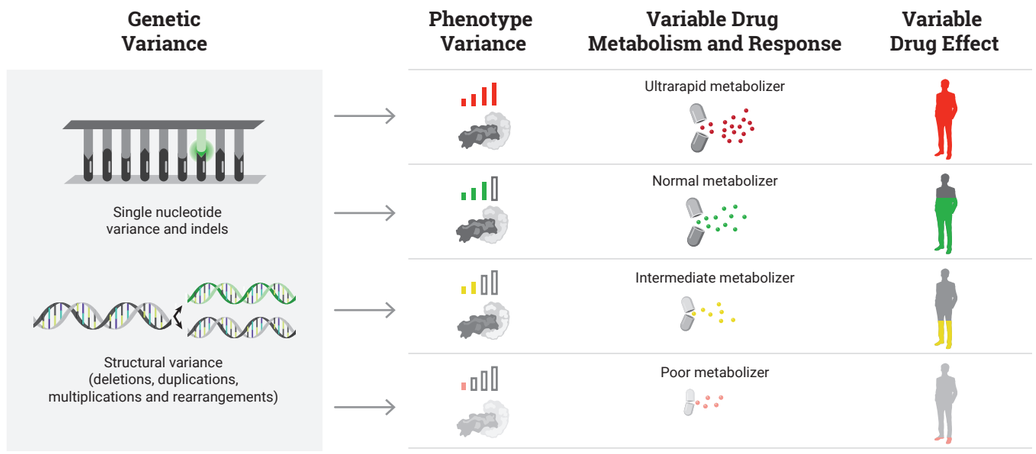
"We've seen significant enthusiasm from the PGx community members, who are volunteering their time to build MetaCensus to accelerate scientific consensus and produce more robust meta-analyses," Nelson said.

MetaCensus will function as a central resource for industry and medical experts to review and assess the same data, then determine how to interpret and apply the evidence.

Sherin Shaaban, MD, PhD, FACMG, medical director of Pharmacogenomics and Molecular Genetics, has led the development of PGx testing. Shaaban has carefully curated the genes included in ARUP's PGx panels based on research that has demonstrated the clinical relevance of those genes to drug metabolism.

"It's important that we offer testing for genes and variants that are actionable and have the highest levels of evidence of their role in drug metabolization," Shaaban said.

According to Shaaban, many healthcare providers may still be reluctant to order PGx testing because they do not feel comfortable choosing the test and interpreting the results. Shaaban and her colleagues are available to consult with clinicians on test ordering and results interpretation.



> *"We've seen significant enthusiasm from the PGx community members, who are volunteering their time to build MetaCensus to accelerate scientific consensus and produce more robust meta-analyses."*
>
> **Ryan Nelson, PharmD, ARUP Medical Director of Precision Medicine**

"The interpretation, especially for the two larger panels, can become complicated," Shaaban said. "We want to help physicians navigate the complex world of pharmacogenomics."

Recently, Shaaban consulted with a physician who had contacted ARUP about one of his patients, a child with autism who had been on a treatment plan that effectively managed his condition for a long time, but whose condition then started to deteriorate. Shaaban recommended the physician order a psychotropic panel.

"The physician reported back a few months later that they had needed to change a lot of dosing and drug choices, but the new treatment plans—based on the patient's genetic ability to metabolize drugs—had helped to stabilize the patient's symptoms," Shaaban said.

"I'm proud of the quality of testing we offer. It's an additional layer of patient care that makes it possible to individualize the management of patients from drug choice to proper dosing," Shaaban said. "We've focused our strategy on providing results that will actually be useful to clinicians as they make decisions for their patients."

Kellie Carrigan, kellie.carrigan@aruplab.com

The Many Uses of Drug Testing: **Examples of Clinical Scenarios**

Therapeutic Drug Monitoring

Meet Chris. He received a kidney transplant a year ago and is now taking immunosuppressant drugs to ensure that his body doesn't reject the new organ. Therapeutic drug monitoring by mass spectrometry enables his physician to walk the fine line between effective treatment and harmful side effects such as infection.

Meet Denzel. He is waiting for a pancreas transplant, and one of the requirements to be eligible for a donor organ is that he abstain from alcohol use. A test that detects an alcohol biomarker, phosphatidylethanol, which only forms in the presence of ethanol, can determine whether an individual has consumed alcohol. The test has nearly 100% specificity and can confirm Denzel's continued eligibility for the transplant.

Trace Element Testing

Meet Sarah. She recently explored an old gold mine with a group of her friends. While exploring, Sarah unknowingly came across residual mercury from mining practices in which mercury was used to extract gold from ore. Sarah's clinician can use trace element testing to identify whether she experienced toxic exposure, and, if so, the level of contamination.

Meet Isaac. He has had symptoms such as abdominal pain, diarrhea, nausea, and weakness since fighting an industrial fire. He may have been exposed to heavy metals during the fire. Isaac's physician orders a trace element test to identify what he's been exposed to, and the results will inform his treatment.

Pharmacogenetics

Meet Carlos. He has been diagnosed with colon cancer and is receiving a form of chemotherapy called irinotecan hydrochloride. Irinotecan is metabolized to its active form (SN-38) in the liver, and the amount of SN-38 that circulates in Carlos's bloodstream determines the effectiveness of the treatment. However, too much SN-38 increases his risk for toxicity because SN-38 also reduces white blood cell count. Pharmacogenetic testing can determine how well Carlos metabolizes irinotecan and better guide appropriate dosing.

Meet Akira. There is a possibility that she lacks the *DPYD* gene that is responsible for producing DPD, an enzyme necessary to metabolize a type of chemotherapy medication called 5-fluorouracil (5-FU). Without the enzyme, she could have a harmful and potentially fatal reaction to the chemotherapy. By taking a genetic test, Akira can find out whether she can safely receive treatment with 5-FU.

Meet Jared. He experiences depression, and recently his treatments stopped helping to manage his condition, even though he has worked with his physician for many months on medication and dose adjustment. A pharmacogenetic test helps determine how Jared uniquely processes drugs, and which drugs might be most effective for him. Using those test results, Jared's physician is able to readjust his treatment plan, and his condition becomes more manageable.

***All scenarios are examples of possible clinical uses for clinical toxicology testing and are not based on real patient data.**

Visionary Clinical Toxicologist Gwen McMillin Has Transformed Drug Testing to Better Support Clinical Needs

Colleagues describe Gwen McMillin, PhD, DABCC (CC, TC), FAACC, scientific director for the mass spectrometry platform and medical director of Clinical Toxicology at ARUP Laboratories, as someone who has a vast and intricate knowledge of everything related to clinical toxicology but who never loses sight of the goal of testing: to empower clinicians with knowledge to aid their patients.

"She's always thinking about how these test results will be used at the end of the day. The nitty-gritty details of the testing, the processes, the reporting are important, but she never forgets to consider the clinical impact," said Joely Straseski, PhD, MS, MT(ASCP), DABCC, FAACC, section chief of Chemistry and medical director of Endocrinology at ARUP.

That unique awareness is evident in the various ways McMillin has transformed the field of clinical toxicology, pushing testing to become more relevant and more efficient and finding new solutions to challenging problems.

McMillin was instrumental in shifting the field from a standard drug testing model that used both a screening and a confirmatory test for every drug test. The standard screening test, an immunoassay, often fails to adequately identify compounds. McMillin advocated instead for an approach that would skip the screening immunoassay and go straight to the more accurate testing method when indicated by clinical situation. The new approach reduces unnecessary testing, yields faster results, and provides more useful information to better inform treatment decisions.

> *"She's always thinking about how these test results will be used at the end of the day. The nitty-gritty details of the testing, the processes, the reporting are important, but she never forgets to consider the clinical impact."*
>
> **Joely Straseski, PhD, MS, MT(ASCP), DABCC, FAACC, ARUP Section Chief of Chemistry and Medical Director of Endocrinology**

"We have been leaders in the philosophy that you don't need to follow the traditional 'screen with reflex to confirmation' approach for clinical toxicology. It makes more sense to align the test with the clinical purpose and receive the result you need up front, rather than going through a series of tests," McMillin said.

Although McMillin's approach initially met with resistance, her extensive efforts to educate clinicians and advocate for more effective testing have eventually led many to adopt her approach and to a worldwide recognition of McMillin's expertise.

She has since contributed to the development of guidelines for the Clinical and Laboratory Standards Institute (CLSI), an organization that publishes recommendations and standards for laboratory testing.

McMillin's expertise is respected not only within the laboratory community—she's also frequently called upon as an expert witness in court proceedings. Recently, McMillin was asked to provide her expertise in a case in which a woman had been accused of resuming meth use based on the results of an immunoassay screen.

"Women who are pregnant are often treated with a medication called labetalol due to their high blood pressure during pregnancy," McMillin said. "Labetalol will cause a false positive for methamphetamine because of its chemistry, which is similar to that of methamphetamine."

McMillin's testimony clarified the limitations of immunoassay screening and its potential to provide false-positive results and demonstrated that an immunoassay alone was insufficient evidence to prove the patient had returned to meth use.

"Gwen's expertise in test interpretation has had a profound impact in so many aspects of clinical care. She's a shining example of being able to align a clinical focus with research and test development, and she's had a strong influence on our Clinical Toxicology Laboratory," said Jonathan R. Genzen, MD, PhD, ARUP chief medical officer.

The Road to Renown

McMillin's interest in clinical toxicology stems from a personal experience in which she was able to closely observe the differing effects of a variety of medications.

As a teenager, McMillin watched her youngest brother suffer with a seizure disorder. More than ten years his senior, she took an active role in his care, helping to administer medications and record his seizure types.

"It was horrific to witness his suffering, but also fascinating to me to observe how the different medications affected him—which ones worked, which ones didn't, and how they interacted with each other," McMillin said.

Fortunately, her brother eventually outgrew the condition, but the experience spurred McMillin to study neuropharmacology during her undergraduate education at Grinnell College.

During graduate school, McMillin studied pharmacology and focused her efforts on anticonvulsant drug development and mechanistic studies. As part of her first faculty position in the College of Pharmacy at the University of Utah, McMillin led the mechanistic studies for the U's Anticonvulsant Drug Development Program. The project evaluated drugs for their efficacy in preventing convulsions and developed new antiepileptic agents.

During her studies, McMillin witnessed the harmful effects of the opioid epidemic as a volunteer at the University of Utah Hospital. There, she saw many drug overdoses and drug-related adverse events.

"People were struggling with the very drugs that were supposed to help them, and they didn't help them. I witnessed therapeutic failure, which I very much considered to be an adverse drug reaction," McMillin said.

Her experience at the hospital deepened her interest in drug testing. In November 1996, McMillin joined ARUP Laboratories, initially securing a position as a research scientist in the Research Institute. At the time, former ARUP President and CEO Edward Ashwood, MD, recognized her talents and capabilities and encouraged her to pursue becoming a medical director. McMillin returned to the University of Utah to complete a postdoctoral fellowship at the University of Utah School of Medicine.

Focus on Maternal and Pediatric Health

Since joining ARUP, McMillin has continued to drive innovation in clinical toxicology to find better testing solutions that improve patient outcomes.

"My mantra is to take what I've learned and turn it into something that is hopefully helpful to everyone," McMillin said.

McMillin has focused much of her work on supporting maternal and pediatric health needs. As a result of the opioid epidemic, an increase in newborns experiencing neonatal abstinence syndrome generated a need for methods to assess in utero exposure to drugs. McMillin spent five years helping to develop and validate a panel of mass spectrometry newborn drug tests using meconium, a newborn's first stool.

"I tried to optimize the testing to align better with our clients' needs by understanding how results were being used, both clinically and in court, and whether that leads us to provide better resources for the mother and family, or to find a better circumstance for the baby," McMillin said.

Eventually, she recognized the logistical difficulties of using meconium and explored the possibility of using a sample of umbilical cord tissue instead. As a result of McMillin's extensive research on the results of umbilical cord tissue testing, she has led ARUP in developing a mass spectrometry test, using umbilical cord tissue as the specimen type, that detects almost 50 different compounds.

"It's imperative that we have testing to assess in utero drug exposure, as individuals who are pregnant are also vulnerable to substance use disorders," said Kamisha Johnson-Davis, PhD, DABCC (CC, TC), medical director of Clinical Toxicology. "Gwen has been instrumental in bringing on testing that supports the needs of newborns."

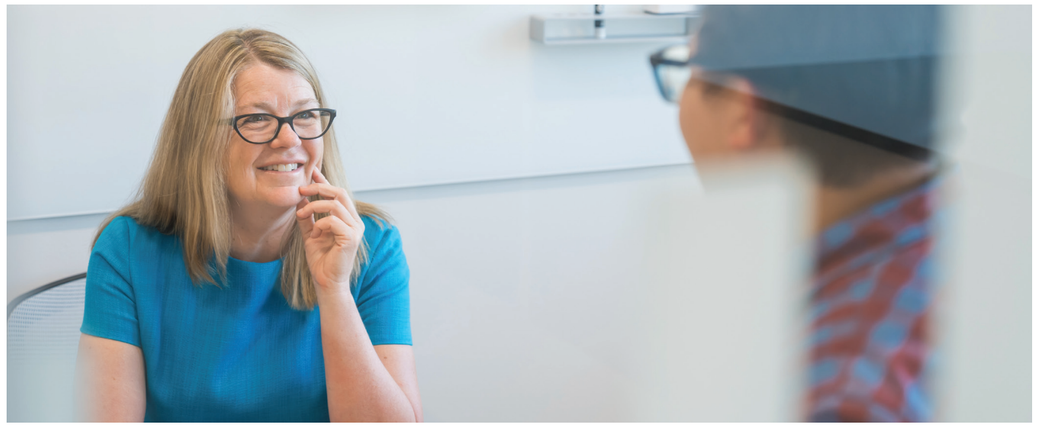
As part of one of her many research projects, McMillin has collaborated with Torri Metz, MD, MS, an associate professor of Obstetrics and Gynecology and vice chair of research of Obstetrics and Gynecology at the University of Utah, to determine the prevalence of drug use in Utah.

"The data from the cord sampling project have enabled us to help patients in regions that have very high rates of substance use during pregnancy," Metz said. "The data we collected were used to apply for a grant to establish an entire center for reduction of morbidity and mortality from substance use disorders in pregnancy in Utah."

The University of Utah has received a $14 million dollar grant to establish the ELEVATE Center: Reduction of Maternal Morbidity from Substance Use Disorder in Utah, which will provide interventions to patients affected by substance use disorders. These interventions include community engagement, clinician and patient education, and ongoing surveillance of the prevalence of the disorders.

"Personally, I find it very satisfying that we can help families get the resources they need; we want to identify newborns exposed to drugs so they can get treated appropriately, but it's about the downstream effects to make sure that families are put on the best path forward," McMillin said.

According to Metz, "McMillin has expertise across the entire spectrum, both clinical and research, and her perspective is valuable not only as an expert in lab science, but she also has a sense of what our work means for patients outside of the lab, and how it will trickle down to public health and broader outcomes."



McMillin regularly consults with clinicians and caretakers to learn how testing can be improved.

> *"With Gwen's leadership in that area and institutional support, ARUP is ready to take on the challenge of the next generation of toxicology testing."*
>
> **Vrajesh K. Pandya, PhD, DABCC, Medical Director of Clinical Chemistry and Toxicology at the University of Utah Hospital Lab**

A Supportive Colleague

McMillin's near colleagues value her renowned expertise and describe her as incredibly supportive.

"She knows so much and has had such an impact on everything in all of the toxicology labs, and she's a very supportive colleague," said Jessica Boyd, PhD, FCACB, DABCC (TC), a fellow medical director of Clinical Toxicology at ARUP.

Vrajesh K. Pandya, PhD, DABCC, medical director of Clinical Chemistry and Toxicology at the University of Utah Hospital Lab, completed a fellowship at ARUP Laboratories during which he collaborated with McMillin on further studies to compare meconium and umbilical cord test results. Pandya described McMillin as a "very proactive and engaged mentor who always roots for your success."

After Pandya's transition from fellow to medical director, McMillin was the first person to reach out to acknowledge him as a fellow colleague.

"She's truly the pioneer of toxicology testing at ARUP. She's a leading authority in the world on neonatal drug testing as well as pharmacogenetic testing, which is clearly reflected in her publications over the years," Pandya said. "With Gwen's leadership in that area and institutional support, ARUP is ready to take on the challenge of the next generation of toxicology testing."

Kellie Carrigan, kellie.carrigan@aruplab.com

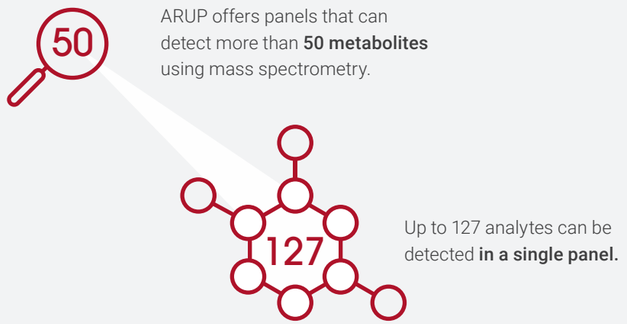
The Benefits of Mass Spectrometry

Mass spectrometers can detect a wide array of drugs and analytes by measuring the mass-to-charge ratio of molecules in a sample. Mass spectrometry is used in many laboratory medicine specialties, including:

- Clinical toxicology
- Chemistry
- Biochemical genetics

Scientists can use mass spectrometers to rapidly design laboratory-developed tests.

Mass spectrometry can yield results with higher specificity than alternate methods, which translates to a low risk of false-positive results.



NEW Mass Spectrometry Lab

During the construction of ARUP's most recently added facility, a 220,000-square-foot, state-of-the-art building, ARUP's Facilities team and contractors worked together to design a new space for the Mass Spectrometry Laboratory. The new lab:

Has approximately

100

mass spectrometers

Was built to maximize employee's

- Comfort
- Safety
- Efficiency

The lab was designed to reduce heat and sound produced by mass spectrometers.

- It has venting systems that connect bench cores to an exhaust fan to redistribute heat.
- It has walls with sound boards and special ceiling tiles that absorb noise.

The lab includes a new preanalytic area to prepare specimens for mass spectrometry testing.

- The lab is near the Clinical Toxicology Laboratory to reduce time between specimen preparation and testing.

ARUP Takes a Forward-Thinking Approach to Newborn Drug Screening

The telltale signs of drug withdrawal are present: sweating, watery eyes, and agitation. Newborns who have been exposed to drugs in utero experience physiological symptoms that are similar to those seen in adults with substance use disorders who are undergoing withdrawal.

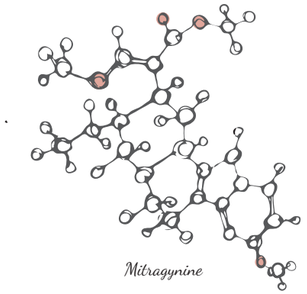
But how can healthcare providers be certain that withdrawal is the reason for the symptoms, and what is the best way to find out?

ARUP Laboratories offers newborn drug screening that provides quick, qualitative results that support time-sensitive clinical and social management decision-making, said Gwen McMillin, PhD, DABCC (CC, TC), FAACC, scientific director for the mass spectrometry platform and medical director of Clinical Toxicology at ARUP.

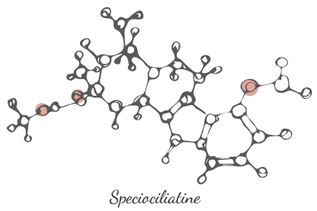
"We're not here to judge or question why people use drugs. That's not our job," she said. "Because we come from the clinical laboratory perspective, our overall goal is to help the patient and the provider."

Self-reported drug use is generally unreliable, so biological testing may be needed to detect prenatal drug exposure. ARUP uses what it believes is the best approach to deliver quality information quickly.

For example, more than a decade ago, ARUP started offering drug screening for prenatal drug exposure on umbilical cord tissue as an alternative to meconium, an infant's first stool. Umbilical cord tissue has proven to be valuable as a specimen type for evaluation of in utero drug exposure because, unlike meconium, it can be collected at birth. Drugs deposit consistently along the length of the cord, and for that reason, it also doesn't matter which portion of the cord is collected for testing.



Mitragynine



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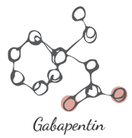

Gabapentin

Actionable results are also delivered more quickly because ARUP was an early proponent of the philosophy that clinicians do not need to follow the traditional screen-with-reflex approach for drug testing. Rather than screening with an immunoassay, then confirming results with a mass spectrometry test, ARUP starts with the more accurate, more sensitive mass spectrometry test to save time.

ARUP test results note the drugs that the test detected but do not provide the concentrations of those drugs. McMillin said quantitative results typically aren't necessary for clinical and social management decision-making, and it can be difficult to endorse their accuracy. Reporting qualitative results minimizes the risk of results being miscommunicated or misinterpreted.

Reflecting the Real World

A commitment to aligning newborn drug screening with clinical needs also informs ARUP's test development efforts.

ARUP collaborates with hospital delivery units as well as representatives from children and family services agencies across the nation to understand when new drugs should be added to screening panels. "Without talking to clients, without getting into the trenches, we really don't know who we're serving," McMillin said. "Collaborating with clinicians and other caregivers is a really valuable way to learn more about what we should be seeing or how we could improve things."

For example, conversations with providers led ARUP to be the first clinical lab to add gabapentin to its screening panels. The drug is often prescribed as an alternative to opioids or in combination with opioids for pain management. It is currently not on the federal schedule of controlled substances and has historically been believed to be safer and have less abuse potential than opioids. However, hospitals started seeing newborns who were displaying withdrawal symptoms, even though their drug screens were negative. Further investigation revealed that their mothers had been prescribed gabapentin during pregnancy, and the drug is now recognized to precipitate and potentially worsen the severity of drug withdrawal symptoms.

Kratom, an herbal extract that is often used recreationally for its opioidlike effects, is another example. Regular kratom use is associated with drug dependency, and cessation of use can lead to withdrawal symptoms. ARUP recently added kratom to its fetal drug exposure detection panel for meconium specimens, in addition to its standalone test for umbilical cord specimens, to detect fetal exposure to the extract. "There is perception that kratom is harmless because it is considered legal in most places," McMillin said. "It's important to know that [kratom] is a potential cause of withdrawal symptoms in neonates to help inform medical management decisions, such as the risks of continuing to use kratom while breastfeeding."

> *"We're not here to judge or question why people use drugs. That's not our job."*
>
> **Gwen McMillin, PhD, DABCC (CC, TC), FAACC, ARUP Scientific Director for the Mass Spectrometry Platform and Medical Director of Clinical Toxicology**

Gwen McMillin, PhD, DABCC (CC, TC), FAACC, scientific director for the mass spectrometry platform and medical director of Clinical Toxicology at ARUP Laboratories, reviews numerous cases every day to deliver results to providers.

Far-Reaching Consequences

ARUP's expertise in newborn drug testing is also having a positive impact on public health.

"The reason that we work with ARUP is because we trust the quality and accuracy of the testing," said Torri Metz, MD, MS, associate professor of Obstetrics and Gynecology and vice chair for research of Obstetrics and Gynecology at the University of Utah.

In 2021, Metz collaborated with ARUP on anonymous umbilical cord sampling across Utah to get a sense of how common drug use is during pregnancy. As a result of this collaboration, she was able to identify "hot spots" for perinatal drug use. From a public health standpoint, this allowed more targeted interventions, such as educating clinicians to talk with patients about substance use and pregnancy in affected regions, and finding ways to link patients to multidisciplinary care and addiction services. Data collected in the study were also used in a successful grant application for resources to reduce morbidity and mortality from substance use disorders during pregnancy in Utah.

"Our relationship with ARUP is really critical to education intervention," Metz said.

Alice To, alice.to@aruplab.com

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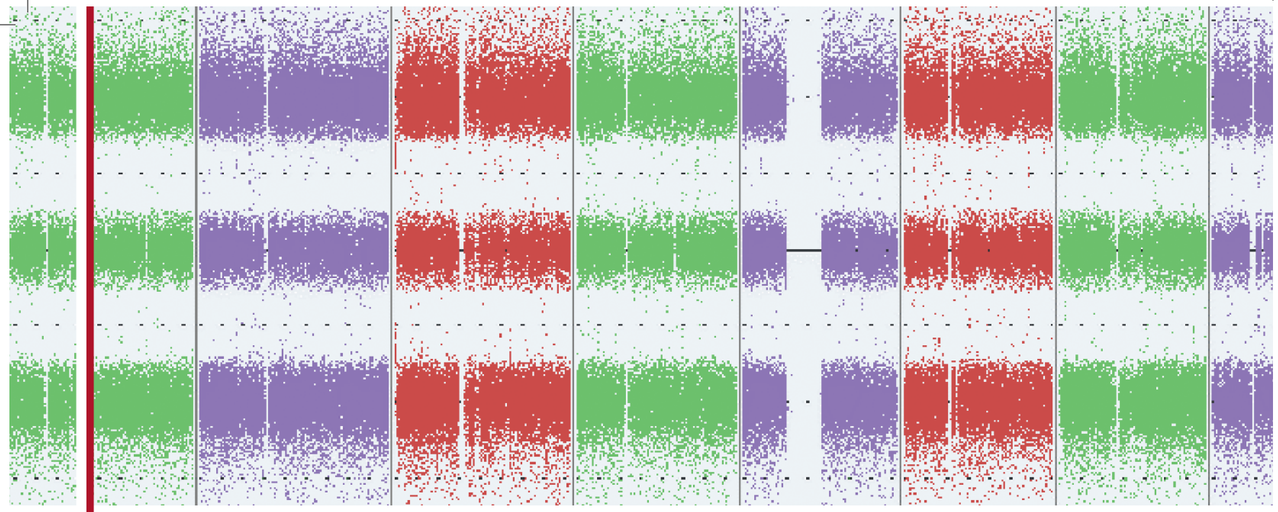


Answers Patients Can Trust

ARUP Expands Capacity for Cytogenetics Testing, Offering a Full Test Menu, Access to Related Tests, and Broad Testing Expertise

The image that appeared on the fetal ultrasound was not what the parents had expected to see. A small, bell-shaped ribcage, setback jaw, and digits that were not fully separated all indicated that the fetus had skeletal abnormalities. What were they seeing? What was happening with their baby?

The couple looked to ARUP Laboratories for answers.

Their physician collected amniotic fluid and ordered a chromosomal microarray (CMA) test to investigate whether a missing or extra piece of chromosome material might explain what the ultrasound revealed. A skeletal dysplasia sequencing panel also was ordered to determine whether a genetic variant could be the cause of abnormalities that might only worsen.

Before either test was performed, though, a genetic counselor at ARUP got to work. Drawing on years of experience, she reviewed the case, carefully studying the indications for testing and all other available information, before moving forward with the CMA test.

The microarray showed an abnormality at chromosome 14 that led her and other ARUP experts to suspect uniparental disomy (UPD), a condition in which a fetus gets both chromosomes from the same parent rather than one chromosome from each parent. The genetic counselor recommended that the physician test for UPD14 before testing for skeletal dysplasia. That test confirmed that the fetus did indeed have UPD14, or the genetic imprinting disorder known as Kagami-Ogata syndrome, the symptoms of which matched what they saw by ultrasound.

The parents got their answer.

In the Cytogenetics and Genomic Microarray Laboratories at ARUP, careful review of all prenatal test orders and communication with ordering providers ensure that the correct tests are ordered and are performed in the right sequence to minimize the risk of a misdiagnosis that could lead to irrevocable clinical decisions, said Danielle LaGrave, MS, LCGC, who has worked as a genetic counselor at ARUP since the Cytogenetics Lab moved from the University of Utah to ARUP 15 years ago.

"We recognize that each sample represents a patient, and we make sure that everything is handled the way we'd want our own samples to be handled," she said. "We take great care to ensure that people seeking potentially life-changing information get the correct information."

Meticulous review of test orders is just one way in which the Cytogenetics and Genomics Microarray Labs at ARUP distinguish themselves, said Section Chief Erica Andersen, PhD, FACMG. Using chromosomal analysis/karyotyping, fluorescence in situ hybridization (FISH) testing, and genomic microarray analysis, her labs perform constitutional cytogenetics testing to diagnose genetic abnormalities such as that found in the rare Kagami-Ogata syndrome case, or in more common chromosomal conditions such as Down syndrome. The labs also perform cancer cytogenetics testing to detect genetic abnormalities for the diagnosis, prognosis, treatment, and monitoring of cancer, particularly hematologic cancers.

> ***"We recognize that each sample represents a patient, and we make sure that everything is handled the way we'd want our own samples to be handled."***
>
> **Danielle LaGrave, MS, LCGC, ARUP Genetic Counselor**

In recent years, as more boutique labs closed or began discontinuing cytogenetics testing, ARUP committed to supporting this complex and highly specialized testing area for the long term, investing in instruments and space and continuing to build the expertise necessary to increase testing capacity and boost volumes by 20% a year through 2026.

"This isn't something you can do overnight. It takes long-term planning," Andersen said. "We're very proud of what we've built so far and of the high-quality testing we do here."

Full Menu, Broad Expertise

In Cytogenetics, ARUP surpasses competitors when it comes to the range of tests offered and the specimen types accepted for testing. As one of the nation's four largest reference labs, and with a single-site operation, ARUP enables clinicians to have all related testing performed in one place and to have the results reviewed and reported in the context of all other testing. Andersen and the medical directors in her labs work closely with colleagues in hematopathology, molecular genetics, and other specialized testing areas to review and consult on concurrent testing across disciplines.

"We're able to provide great depth of knowledge and expertise at every level," Andersen said.

As part of their expansion, the Cytogenetics and Genomic Microarray Labs have incorporated automation and will continue to automate additional tasks, understanding that ever faster turnaround times are paramount when patients and their loved ones are waiting for critical results. The labs also are increasingly using artificial intelligence to help hasten methods such as karyotyping, a process in which the number and structure of a person's chromosomes are analyzed to detect abnormalities.

Regardless, highly trained experts will always be needed to perform the analysis and get it right, Andersen said.

"A chromosome analysis test, for example, typically involves two cytogenetics technologists, a senior reviewer, and a medical director," she said. "That's four pairs of trained eyes on every single result."

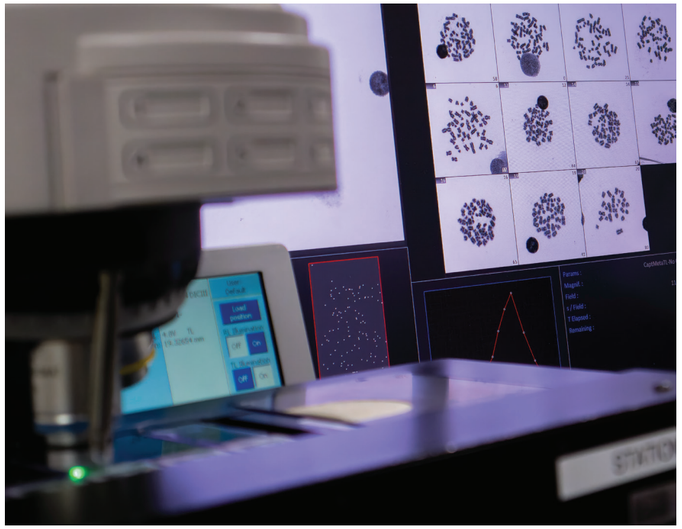
The availability of expertise can be a limiting factor in many cytogenetics laboratories, and such expertise is hard to come by, so ARUP develops its own. The company invested in an internal training program that is overseen by Jill Johnston, a cytogenetics tech specialist. Since joining ARUP, she has trained nearly 35 cytogenetics technologists and helped them earn American Society for Clinical Pathology (ASCP) certification. Johnston also is vice chairwoman of the ASCP Cytogenetics Exam Committee, which makes sure the exam is up to date and covers current practices.

Her special brand of expertise is replicated throughout the labs.

On the cancer side, ARUP is certified by the Children's Oncology Group (COG) and has a specialized group to manage and review pediatric cancer cases. To earn the certification, a lab must maintain an abnormality detection rate greater than 55%. Andersen said that under an ongoing project led by Medical Director Bo Hong, MD, FACMG, ARUP's COG quality metrics are strong and improving all the time.

"We're making continuing improvements and in the right ways, and people in the field recognize that," Andersen said. "The level of quality and service we deliver is something we really like to highlight."

In addition to the COG certification, ARUP attained "star status" as an active submitter of genetic variant data to ClinVar, a resource supported by the National Institutes of Health (NIH) and the Clinical Genome Resource (ClinGen) that is dedicated to broadening knowledge about human genetic variants and their impact on health. Through collaborative work between ClinGen and ARUP, Andersen, along with genetic counselor Zoe Lewis, MS, LCGC, has spearheaded several projects involving genomic copy number variants (CNVs) encountered during CMA testing. One such project involves an internal process to reevaluate CNVs, including those with uncertain clinical significance. This reevaluation is performed as evidence emerges in the literature or when a clinician requests reanalysis to provide more up-to-date information about these uncertain results to patients and their families.



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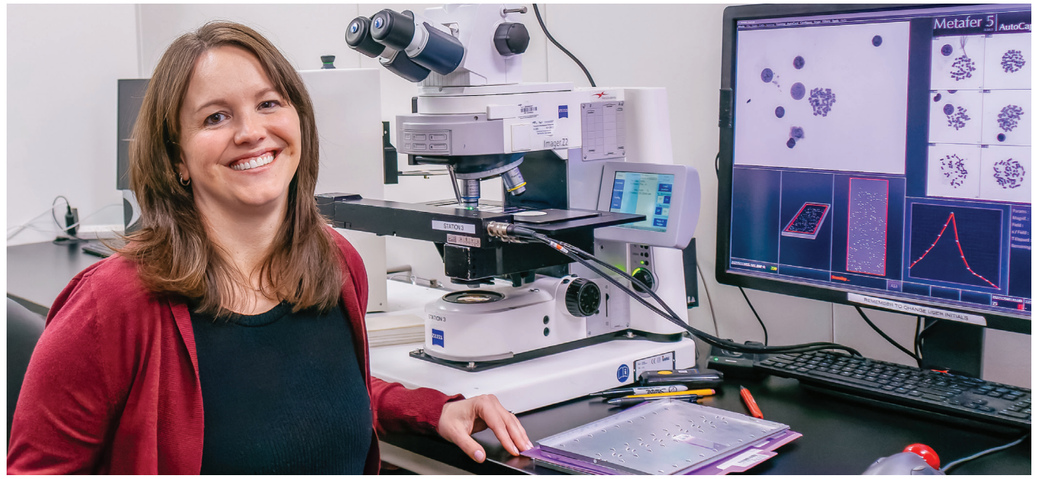

Erica Andersen, PhD, FACMG, ARUP's section chief of Cytogenetics and Genomic Microarray since 2018, is a leader in research that aims to deepen understanding of recurrent copy number variants and what they mean clinically.

Critical Thinker, Born Leader, Expert Researcher

These and other differentiators for ARUP's Cytogenetics and Genomic Microarray Labs all can be traced back to Andersen, who has been section chief since 2018.

A lifelong Midwesterner, Andersen visited Utah for the first time when she came for the interview that landed her a fellowship at ARUP from 2011 to 2013. "I couldn't believe how amazing the laboratory, the people, and the training program were," she said.

Her work as a fellow with Sarah South, PhD, FACMG, who directed Cytogenetics at the time, completed the educational circle that began when Andersen's father, a chemist and a geologist, sparked her interest in science as a child.

She was 8 years old when her dad was diagnosed with oligodendroglioma, a rare brain tumor that eventually took his life when Andersen was 14. Around that same time, a cousin to whom Andersen was close was diagnosed with acute lymphoblastic leukemia (ALL). Her experiences with illness in her family ultimately led her to study genetics and pursue laboratory medicine as a career.

Andersen found her passion as a biology undergrad at Macalester College in Minnesota and through graduate school in genetics at the University of Wisconsin. Her cousin survived ALL, and both Andersen and her cousin earned their PhDs in science. In Andersen's case, through interactions with clinically focused labs and colleagues, "I found cytogenetics, my passion, which brought me to ARUP."

Her ascent since joining ARUP has been swift. Within five years of completing her fellowship, she became section chief, leading a team that includes nine medical directors, seven genetic counselors, and a sizable staff.

Andersen was promoted to section chief because her ability to lead was apparent from the start, said ARUP Executive Vice President Julio Delgado, MD, MS, who selected Andersen for the position in 2018 when he was chief medical officer (CMO).

"She is a critical thinker who asked the right questions. Immediately, she demonstrated that she understood where we were going," he said. "She has a natural disposition for thinking of ways to gain operational efficiency."

Delgado knew appointing someone so early in her career was a bit of a risk. Yet, "I saw her potential, and she has done an amazing job," he said.

"The team she leads is incredible," added ARUP Chief Medical Officer Jonathan Genzen, MD, PhD. "They excel not only in their technical expertise and their ability to accurately interpret cases, but in their skill at optimizing systems."

Andersen's reputation as an expert in her field only continues to grow.

On the constitutional cytogenetics side, she is deeply invested in improving understanding of clinically encountered CNVs, and particularly, recurrent CNVs. She works to provide expert guidance on interpretation of these CNVs and to lend understanding to what they mean clinically. She is a member of ClinGen's Copy Number Variant Interpretation Guidelines Working Group and cochairwoman of its Dosage Sensitivity Working Group, which collects evidence supporting or refuting the haploinsufficiency and triplosensitivity of genes and genomic regions.

On the cancer cytogenetics side, Andersen is focused on improving diagnostic workflows for multiple myeloma and myeloid disease. She leads a project at ARUP on digital FISH development and is a member of the Cancer Genomics Consortium's Working Group on Multiple Myeloma.

"Her work with these professional groups is very important for her own advancement, but also for ARUP," Delgado said. "She has a lot to contribute and is at the forefront of medicine. Our clients and their patients definitely benefit from that."

Work That Matters

For their part, Andersen, LaGrave, and other members of their teams say they are frequently reminded of why they chose cytogenetics as a specialty.

Diagnoses such as that in the rare Kagami-Ogata syndrome case are shared and communicated accurately with families every day, providing the answers they so anxiously await so they can obtain the best clinical care.

"I wanted to do meaningful work that truly helps people," Andersen said. "We're very fortunate that we're able to do that here."

Lisa Carricaburu, lisa.carricaburu@aruplab.com

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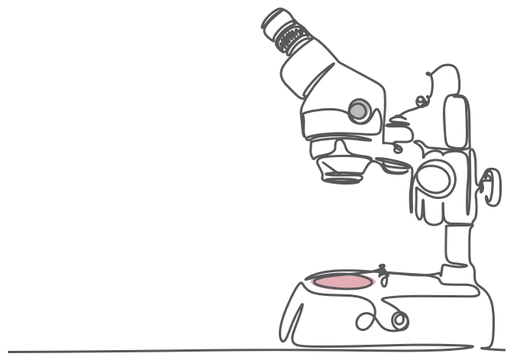

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ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.