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.)

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.
These early relationships mixed with that entrepreneurial drive steered the company to experiment, to learn, to grow, and to thrive. Those ingredients are and will be the key to our future success.
Spirited entrepreneurialism is in ARUP’s roots; a beginning that was initially viewed as an unlikely venture and a bold move by its founders at the University of Utah’s Pathology Department. That spirit, guided by ARUP’s leaders over the last three decades, has resulted into what ARUP is today—a first-rate, national reference laboratory.

As healthcare changes at an ever-accelerating rate and the technology within it even faster, ARUP needs to rely on these pioneering roots to continue seizing new opportunities and improving value in healthcare delivery.

The history of ARUP has taught me the importance of focusing on your base and then scaling up from there. Thanks to ARUP’s early Utah clients and strong relationships—St. Marks, Intermountain Healthcare, and of course, the University of Utah—ARUP developed a strong base.

Our connection with an academic-medical institute opens the door to collaborations in sharing expertise, and provides a larger context from which to understand the healthcare environment. This link provides us insight into how to best serve our clients, which include more than 50 percent of the nation’s university medical centers and teaching hospitals.

These early relationships mixed with that entrepreneurial drive steered the company to experiment, to learn, to grow and to thrive. Those ingredients are and will be the key to our future success.

At our core we are about doing the right thing—advancing medicine and creating excellence and value for patients and our clients.

It is this ingenuity and vigor original to ARUP’s early entrepreneurial spirit that will continue to prepare us for the future.

Dean Li, MD, PhD
President and CEO, ARUP Laboratories
Hints of the disorder were there all along, some subtle, some not: the frequent bloody noses as a child; the constellation of bright red dots near her mouth; the untimely deaths and mysterious ailments of relatives.

It wasn’t until Jamie McDonald, MS, as a new mother, started noticing her 4-month-old daughter’s decreased left-side mobility that she began suspecting something much more serious than what her family had always dismissed as the “family bloody-nose thing.”

Even our family doctors didn’t take it seriously, as they too lacked knowledge about this disorder,” recalls McDonald, a genetic counselor for ARUP and the University of Utah (U of U) and an assistant professor of pathology (clinical). As a result, her family was never counseled on the associated risks of the disorder, nor advised on what could be done to prevent complications.

Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder of the blood vessels affecting about 1 in 5,000 people in the United States. If you have a parent or sibling with HHT, there is a 50 percent chance of having the disorder—McDonald’s grandfather and father both inherited it, as did she.

The most deadly, and insidious, aspect of the disorder is the arteriovenous malformations (AVM), which can form in the brain, lungs, and liver. AVMs are blood vessels that are missing capillaries, resulting in direct artery-to-vein connections that can cause shunting, hemorrhage, and death. Imagine a garden hose gushing water into a balloon and the risk of it rupturing from the rush of water.

In the lungs where AVMs are common, the absence of capillaries in blood vessels of the lungs increases the risk that clots and clumps of bacteria won’t be filtered from the bloodstream.

Also concerning are AVMs in the liver, which can significantly increase the volume of blood the heart needs to pump. "For some of my patients, it is as if they are running a marathon yet they are just sitting," says McDonald. Eventually, all this exhaustive pumping can lead to heart failure.

She Inherited our Blue Eyes and My HHT
Her daughter, Kelsey, would hardly move the left side of her body when engaging with a toy mobile or wiggling around. “My pediatrician made me feel like I was just worrying too much,” recalls McDonald who was living in Los Angeles at the time.

Kelsey's immobility became more pronounced and at nine-months old, and with insistence from her parents, she underwent a brain scan locating a large AVM in her brain. A neurointerventional radiologist treated the AVM with a transcatheter occlusion procedure.

Though McDonald was convinced that her blue-eyed daughter had HHT, the involved neurologists and neurosurgeons were not as persuaded, nor were they intent on pursuing what this could mean for Kelsey and her family members. It is not uncommon for physicians to misdiagnose complications that stem from HHT; these complications can be misleading, appearing as something else unlinked to the disorder.

This was certainly the case in 1987 for the McDonalds when there was no way to test children at a young age to determine whether they had inherited the disorder. Nose bleeds and telangiectases usually don’t show up until after 10 years old of age, though brain and lung AVMs can be present at birth.
It wasn’t until Jamie McDonald, MS, as a new mother, started noticing her 4-month-old daughter’s decreased left-side mobility that she began suspecting something much more serious than what her family had always dismissed as the “family bloody-nose thing.”
Diagnostic testing would remain elusive until 2004, when genetic testing for HHT became possible—ARUP Laboratories becoming one of the first two labs in the nation to conduct HHT genetic testing.

In the depth of a winter night, the McDonalds’ world shattered when 18-month-old Kelsey died from a massive brain hemorrhage. At the time, Jamie was five-months pregnant with her second child, who unbeknownst to her would also have HHT. So would her third.

**Fueled by Frustration**

With two toddlers, McDonald began pushing to have their brains and lungs screened for AVMs despite skeptical doctors. “I wasn’t going to risk losing another child; my attitude was let’s go looking for these before we have a problem.” Both received MRIs, under sedation, in case they had inherited HHT.

Helping children avoid this invasive medical screening further propelled McDonald down the unpaved path ahead. “This is one of the reasons why Pinar and I worked so hard in the couple years prior to 2004 to develop diagnostic genetic testing for HHT,” recalls McDonald, referring to Pinar Bayrak-Toydemir, MD, PhD, a University of Utah associate professor of pathology and a molecular genetics and genomics medical director at ARUP Laboratories.

At the time a general genetic counselor at the U of U Hospital, McDonald was increasingly frustrated by the lack of medical expertise available for HHT patients. In 1993, McDonald herself was diagnosed with lung AVMs, but no one in the West had significant experience treating lung AVMs or was focusing on HHT. So she headed to the Yale School of Medicine, the only place in the country treating and doing preventive screening for HHT at the time. There, Dr. Robert White, the “grandfather” of HHT, encouraged her to return to Salt Lake City and set up an HHT center. He connected her drive and passion with the expertise of Franklin Miller, MD, a U of U intervention radiologist, to help catalyze such a center.

Today, McDonald is the co-director of the HHT Center of Excellence—the center she helped establish in 1995 to provide expert, multidisciplinary care follows over 1,200 patients, most from out-of-state. It was the second center in North America to be recognized by the flagship organization, Cure HHT International.

“Despite being a relatively common genetic disorder, most people with this disorder don’t get diagnosed,” says McDonald. “I want to help change that.”

“This disorder has life-threatening complications but if we know the genetics for the patients and their families, then we can be proactive in monitoring and treating them. Identifying it early can save lives.”

Jamie McDonald, MS, ARUP Genetics Counselor, Co-Founder HHT Center for Excellence
Discovering Answers at Birth to Prevent Death—Testing for HHT

The first evaluation for HHT, if it runs in your family, is to test at birth for the family’s HHT genetic mutation to determine if the HHT was inherited. This test involves taking a blood sample from the umbilical cord and sending it to a diagnostic laboratory that specifically provides testing for the multiple genes that can cause HHT.

For newborns who do inherit the family HHT mutation, the risk for a brain AVM at birth is about 15 percent; approximately half of these rupture in early childhood. “That is why it is so important to have access to what Pinar is doing at ARUP,” says McDonald. “In the clinic, I can only look for what is visible—and externally visible signs of HHT often aren’t present in early childhood”.

According to McDonald, most physicians are not advising parents to pursue an early diagnosis for their children, even when one of the parents is known to have HHT. “It is remarkably undiagnosed; only the rare pediatrician will say, let’s figure this out.” The first step when a child is born to a parent with HHT is genetic testing. Most pediatricians are not comfortable ordering or interpreting genetic tests, and typically need to refer a family to a genetics or HHT clinic.

In taking a family history for adults, physicians will typically ask about cancer, strokes, heart attacks, diabetes but not HHT, or its symptoms. Ninety percent of the U of U’s HHT center’s patients come from out of state because of the lack of expertise available in diagnosing and treating the disorder.

Only one in ten individuals who have HHT have actually been diagnosed, and of those that have been diagnosed, the majority are not receiving routine screening for internal organ AVMs as is recommended by HHT experts.

Fatalities from HHT are preventable if you can identify the AVMs early. After a baby has been determined to carry the HHT gene, then an MRI before six months is recommended (regardless of whether any symptom is present). Externally obvious symptoms might not show up for 20 years, but hidden internal AVMs can be deadly early in life.

At ten-years old, the center screens for AVMS in the lungs; some 30 to 40 percent of children will have them—which can lead to strokes or brain abscesses because blood clots and clumps of bacteria are less likely to be filtered in lungs that have AVM(s). People with HHT should be evaluated and screened every five years by an HHT center.

“A lot of doctors and genetic counselors take a let’s just wait and watch approach when a baby is born into a family with the disorder,” says McDonald, adding that by the time symptoms appear, it may be too late. “If you can prove by genetic testing that a child inherited the HHT, your medical management changes at that very moment.”
Arteries have tough walls that carry fast moving blood away from the heart. Veins that usually carry slower-moving, lower-pressure blood back to the heart are not nearly as thick and tough.

In a person with HHT, the artery-vein connection is missing the web of capillaries that slow down the flow of this fast-moving blood before it enters into a vein to make its way back to the heart. As a result, these connections are fragile areas that can balloon out and burst.

AVMs are the most deadly symptom of HHT, occurring most commonly in the liver, brain, and lungs. Doctors may diagnose heart failure, stroke, or brain abscess without realizing that the underlying causes are AVMs in these various organs.

An AVM in the liver can mean the heart works much harder pumping the faster flow of blood streaming back, exhausting the heart, and potentially leading to congestive heart failure.

Normal blood vessels in the lungs are your body’s method for sifting out particles found in blood. When AVMs (blood vessels missing their filtering capillaries) occur in the lungs, blood clots or bacteria sometimes escape this filter and travel to the brain. This results in a stroke or brain abscess.
Genetic Counselor Jamie McDonald, MS, shows patient Sandy Seiler (and her husband, David) her family’s HHT pedigree harking back to the mid-1800s, to a common ancestor who immigrated to Utah with his four wives. The pedigree extends to almost 11-feet long. “Since he has descendants with HHT via multiple wives, we know it is he rather than one of his wives that had the HHT,” explains McDonald.

More than 120 members of this family have been evaluated at the University of Utah HHT Center of Excellence and received molecular genetic diagnoses for HHT through ARUP’s testing. The most recent member? Seiler’s recently born granddaughter—who was found to carry the family’s HHT mutation through ARUP’s genetic testing.
If we can find new genetic modifiers or new genes, then we can potentially find novel therapeutics to treat these patients.

Whitney Wooderchak-Donahue, PhD

We have all these pieces of a puzzle, and I feel responsible for putting them together. The fact that I am the only one with such a large collection of data makes me feel that responsibility.

Pinar Bayrak-Toydemir, MD, PhD

ARUP HHT researcher; recipient of the internationally-competitive 2015 Young Scholar Research Grant awarded by Cure HHT; discovered an HHT gene.

Jamie McDonald, MS

ARUP Licensed Genetic Counselor; University of Utah Assistant Professor (Clinical) of Pathology; Co-Director, HHT Center for Excellence; affected with HHT and mother of two children with HHT.

Pinar Bayrak-Toydemir, MD, PhD
The **Dynamic Trio**

The confluence of HHT expertise flowing from each of these three internationally respected women has established a Mecca for those looking for answers and treatment for HHT.

The University of Utah’s HHT Center for Excellence, co-founded by McDonald, is only one of two such centers in the country associated with a genetics lab, ARUP. It is the only lab pursuing HHT research beyond traditional clinical testing, which resulted in the discovery of the fourth gene associated with HHT in 2013.

“With every discovery, we’re able to increase the sensitivity of the test,” explains Bayrak-Toydemir, who has developed a significant pool of data from identifying mutations in large HHT families over the last ten years. She and her protégé Wooderchak-Donahue have collaborated with researchers in Spain and the United Kingdom to build a data pool of those with HHT but who show no known genetic markers for the disorder.

“By 2004, we could identify mutations for most families but not all of them. Then we realized there could be a whole gene missing or a partial gene,” adds Bayrak-Toydemir, noting that they have discovered different types of HHT along the way.

In 80 percent of families, HHT can be linked to a genetic mutation; in 20 percent who have HHT, there is no genetic mutation identified. “To figure this out, we are focusing on finding new genes and genetic modifiers that may cause HHT,” explains Wooderchak-Donahue. “We are also looking for novel mutations in regulatory and noncoding regions in the known HHT genes that may have been previously missed in these patients using traditional HHT molecular testing.”

She and Bayrak-Toydemir created a next-generation sequencing (NGS) panel to look for all four genes and mutations at once for each patient. (NGS technology allows researchers to interrogate multiple genes at once, often providing a quicker diagnosis than a gene-by-gene approach.)

“We complement each other,” says McDonald, referring to this combination of medical and molecular expertise. She sends her patient samples to ARUP to be analyzed; some are clear cut HHT, others a subset of HHT, and yet others can’t be genetically identified. If something new is identified, McDonald reaches out to the individual’s extended family to collect more samples for research.

“We have all these pieces of a puzzle, and I feel responsible for putting them together,” says Bayrak-Toydemir, admitting she does love a good puzzle. Requests from around the world arrive weekly from physicians who want to enroll patients in ARUP’s HHT data set. She adds, “The fact that we are the only ones with such a large collection of data makes me feel the responsibility that comes with the data. It absolutely needs to be used to help others.”

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**Genetic Tests for HHT**

HHT is a dominant disorder, meaning it only takes one abnormal copy of the gene, from only one parent, to cause the disorder. Each child of a parent with an HHT gene has a 50 percent chance of inheriting this abnormal gene. The three different kinds of genetic tests for HHT include:

- Sequencing of the genes involves looking at the precise sequence of building blocks in the sample of DNA to see if there is any abnormality.
- Deletion and duplication testing looks to see if there is a piece of the gene that is missing or duplicated.
- Single-mutation analysis (often referred to as targeted sequencing) looks to see if one particular mutation that was previously identified in another family member is present or absent.

Source: Cure HHT
“We both agreed something had to change. We felt awful, looked awful, and knew we were facing a train head on if we didn’t do something about our health,” says Carolyn Werrett, recalling when she and her husband, Andy, received the results of their annual personal health profile (PHP)—an analysis of personalized health risks. ARUP employees who want to pay lower medical insurance premiums must complete the PHP every year.

Carolyn had high cholesterol and a history of stroke, and Andy was on the verge of diabetes. Being overweight exacerbated their health problems.

By the next PHP appointment 18 months later, Carolyn had lost 55 lbs. and Andy 110 lbs. No longer were diabetes, stroke, and heart attacks a concern. Certain medications became unnecessary, as did visits to specialists. Soon, Andy will no longer need to rent his CPAP machine for sleep apnea. Aside from living healthier, happier lives, the Werretts, as well as ARUP, have saved thousands of dollars in healthcare expenses.

The Werretts improved health ripples throughout their lives. They took their first hiking trip to Zion National Park last spring and walk with their dogs almost daily. “It’s amazing how much more we move because it doesn’t hurt. We feel good,” says Carolyn. She adds that with her new well-being has come renewed confidence, which is why she recently pursued a new position within ARUP. “I would never have done that a year ago.”

**Identifying the High-Risk Populations**

Utilizing data from PHPs, ARUP Family Health Clinic Director Peter Weir, MD, and his staff have been able to identify high-risk patients and track their health trends. Some 95 percent of ARUP employees participate in the PHP program, partly because completing the PHP can save them up to 50 percent off their health premiums.
In 2011, when ARUP launched the PHP, 250 people were identified as having diabetes (type I and type II); more than 20 of those were not aware that they had the disease.

Diabetes is one of the six chronic diseases dubbed “most common, costly, and preventable of all health problems” by the Center for Disease Control and Prevention (CDC). These chronic diseases account for two-thirds of the healthcare costs in the country.

According to the CDC, as of 2012, about half of all adults—117 million people—have one or more chronic health conditions. One in four adults has two or more chronic health conditions.

Well aware of the steep costs, Weir and his staff approached the patients identified as having diabetes with the promise that if they allowed the onsite ARUP Family Health Clinic to manage their condition, they would receive their medication, including insulin and diabetic supplies, at no cost and receive the best possible care.

After hiring a clinical pharmacist, RN care manager, and certified diabetic educator, Weir was certain he could keep his promise.

Currently, nearly all ARUP employees and family members who have been diagnosed with diabetes use the health clinic to manage their condition—results that have yet to be matched at any other organization, according to Weir.

“Our PHP is about triaging the entire company to define people’s risks of chronic diseases with a particular focus on cardiovascular health,” explains Weir, who uses PHP data to create chronic disease registries for, among others, diabetes, heart disease, and asthma.

“We use a healthcare team to proactively find high-risk individuals, draw them into the clinic, and plug them into our wellness program,” adds Weir. These individuals receive routine primary care visits with ARUP’s medical providers and have access to a clinical pharmacist and one-on-one health coaching with the wellness staff.

Weir notes that many of these patients want help with improving their health because they fear not being around for their children or grandchildren.

By their next PHP appointment 18 months later, the Werretts had lost a total of 165 lbs. between them; diabetes, stroke, and heart attacks were no longer a concern. Their dogs—Daisy, Harley, and Meeko—also benefited from the healthy lifestyle improvements. “They’ve lost weight too,” says Carolyn Werrett.

What Happens in the Clinic Stays in the Clinic

To ensure the health privacy of employees, ARUP has created a strict wall of confidentiality between Human Resources and the health clinic. “Essentially, when you walk into the clinic, you are at a different company,” says David Jackson, senior vice president, strategic services.

Some of the privacy measures include:

- All healthcare records are stored and accessed from Epic, the University of Utah electronic medical record system. This information can be accessed only by the clinic’s staff and is not accessible by any other IT systems at ARUP, including human resources.
- ARUP performs routine HIPAA privacy audits.
- The insurance company that administers ARUP’s self-insurance program has no access to clinic data.
More than 20 years ago, ARUP Laboratories took a proactive approach to rising healthcare costs by adopting a self-insured approach, minus any third-party providers. “After a certain size, we decided to be the risk takers,” says David Jackson, senior vice president, Strategic Services.

The onsite ARUP clinic was originally established in 1992. At the time, the clinic was staffed with one physician assistant and intended only for urgent care and workers’ compensation claims for some 500 employees. ARUP significantly expanded the clinic in 2009 to care for nearly 3,000 employees and their families—approximately 6,500 people.

“We decided to take a run at being a population-based health clinic because intuitively we knew it made sense. Financially it made sense because our employees could get back to work much quicker when they had medical appointments,” recalls Jackson, noting the clinic had not initially price-coded patient visits, making it difficult to compare costs against other providers. “We figured if we could do it right, we could do it for less.”

Within four years the company saw healthcare costs remain flat in a national setting where on average companies saw a 7 percent increase in healthcare costs per year. Pleasantly surprised, ARUP executives gave Weir the go-ahead to further expand the clinic’s staff and services.

Today, the health clinic is staffed with seven medical providers (two physicians and five mid-level providers), along with a mental health therapist, clinical pharmacist, nutritionist, and nurse case manager. The clinic averages more than 25,000 patient visits per year. ARUP healthcare costs are still below the rising national rates.

Weir, a big believer in full-spectrum primary care, has linked the medical care of patients with the onsite wellness program that includes one-on-one health coaching and fitness training. In collaboration with the medical providers, the three certified wellness coaches set individualized goals for each patient. For example, in the Werretts’ case, the clinic staff wanted to see them on a monthly basis to monitor their health and encourage their progress. Carolyn worked with one of ARUP’s wellness coaches to become more physically fit.

“We figure out what is best for our employees and adapt it to their needs and schedules. We’re able to develop a relationship with each person and create accountability. That drives improvement in health,” says Wellness Coach Seth Bigelow, who notes that those who use all three areas of the health benefits offered—physical, mental, and medical—get the best results.

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Seth Bigelow, ARUP Wellness Coach
**Quantifying the Savings**

While there is an abundance of anecdotal feedback on lives changed (and saved) by this program, Weir cites a 2014 study done on PepsiCo’s wellness program that concludes disease-management programs have a good return on investment, with $3.78 saved for every dollar invested in the case of PepsiCo. In this study, what drove the biggest reduction in healthcare costs was a 29 percent reduction in hospital admissions, as even one hospital visit can stretch into tens of thousands of dollars.

“The PHP has allowed us to create a chronic disease care model that reduces the costs for everyone, including the patient,” says Weir.

“Work-site clinics” are a growing movement nationally; ARUP was ahead of the game launching its clinic more than 20 years ago. Near future plans include collaborating more closely with the University of Utah medical center (see sidebar) and providing support/education groups for patients with common diagnosis, like diabetes.

“As far as we know, ARUP operates one of the largest onsite clinics in the state. There is nothing secret or special about what we are doing. What makes the model successful is that it is a win-win for the company and its population,” says Weir, who accommodates visits from others around the country interested in modeling ARUP’s healthcare program. “Our focus is squarely on improving the health of ARUP employees and their families. That helps patients and, as it turns out, reduces the company’s healthcare costs too.”

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**The Business of Caring: Collaborations That Save Money**

You’re experiencing heart pangs and let your primary care provider (PCP) know. She knows you already have a stent in your coronary artery and wonders if you may need a stress test to help determine if there is evidence of an abnormal rhythm or ischemia (not enough blood flow to the heart muscle).

Your PCP can either refer you to a cardiologist (approximately a $250 visit) or send your physical exam and EKG results to the cardiologist who, over the phone, can discuss and determine with your PCP whether you need a stress test or not. If you need one, the cardiologist agrees to see you; if you don’t need one, you can leave free of concern.

This approach using e-consultation is steadily being built into ARUP’s health clinic’s model. It is happening already with the University of Utah’s Department of Psychiatry and being explored as an option with several other departments.

Such collaboration allows for quicker and less fragmented care for patients and supports referrals to specialists for more complex conditions. It also saves money for patients and the health-insurance provider, which is ARUP in this case.

**Decreasing Pediatric ER Visits for Asthma Attacks**

Another collaboration aims to decrease expensive pediatric emergency room (ER) visits for asthma attacks. The ARUP Family Health Clinic and Primary Children’s Medical Center (PCMC) partnered this past summer on the E-Asthma Project. Parents at ARUP who have children with asthma complete a weekly, online questionnaire via a PCMC portal website.

This information then flows to a care manager at the family clinic who looks for any red flags (e.g., wheezing more than usual, lethargy) and then checks in with parents to solve the issue, which may be as simple as needing a new prescription for an inhaler or a different dosage. In a PCMC study, this approach significantly decreased ER visits.
Born to an Addict
Every baby that enters this world arrives with an umbilical cord in tow. For those babies born drug-exposed, that umbilical cord is now a key connection—a hard-to-hide clue—for identifying what addictive drugs are coursing through a newborn’s veins. The drug(s) detected will help physicians determine the best treatment and what withdrawal symptoms to expect.

“We may already know the mom has an opioid dependency at delivery because most women disclose this to avoid risking withdrawal, but we also need to know what else she is taking that might affect the baby’s central nervous system,” says Karen Buchi, MD, president, Primary Children’s Hospital medical staff and chief of the Division of General Pediatrics at the University of Utah. Buchi points out these babies suffer from “drug exposure” as opposed to “addiction”—which is the behavior around drug dependency exhibited by the mother.

As the baby is delivered—when a mother is suspected of being high risk for drug use—a member of the delivery team snips off six inches of the umbilical cord and sends it to ARUP Laboratories. Because umbilical cord tissue can be sent for testing immediately after birth, this specimen type offers logistical advantages over meconium, the traditional specimen for detecting drug-exposed newborns.

As the second medical laboratory in the country to start offering cord testing (since August 2012), ARUP experts immediately begin analysis looking for more than 40 specific drugs and drug metabolites. The most common drug ARUP identifies is marijuana; the second most common drug class

Turning around results fast is crucial, because neonatal specialists need to identify and treat the symptoms to mitigate suffering and even possible death from withdrawals before the typical 48-hour window closes, when healthy mothers and their infants typically leave the hospital.
is opioids (e.g., heroin, prescription pain killers). Often there is a mix of illicit drugs and prescription drugs.

According to a Utah Health Status Update released in July 2013, between 2009 and 2012, 1,476 Utah mothers were reported to have used illicit drugs. As a result, 29.5 percent of babies born to these mothers tested positive for illicit drugs at birth—approximately 109 babies per year.

“Utah is right up there with the rest of the nation in the rate of drug exposure among newborns,” adds Buchi, citing that the U of U Hospital averages about one opioid-exposed newborn a month.

Each month, thousands of cord, and meconium, specimens arrive at ARUP from around the country. In Utah, the majority of cord specimens come from the Intermountain Medical Center, while the University of Utah Hospital still primarily sends ARUP meconium specimens. Though it varies based on the hospital, generally no consent from the mother is necessary for testing the infant if there is a medical reason to believe the child has been drug exposed in utero.

Turning around results quickly is crucial, because neonatal specialists need to identify and treat the symptoms to mitigate suffering and even possible death from withdrawals before the typical 48-hour window closes, when healthy mothers and their infants typically leave the hospital.

While cord tissue testing can take up to 72 hours, for babies who exhibit signs of withdrawals or have mothers considered high risk for drug use, the baby is frequently monitored longer. In this time period, the clinician can attain more information about the kinds of drugs in the baby’s system and determine the best treatment.

“Sometimes babies are already in the throes of withdrawal symptoms but physicians can’t determine what drugs they are dealing with until test results are available,” says Gwen McMillin, PhD, DABCC, a medical director of the Clinical Toxicology laboratories at ARUP.

The Rough Road of Withdrawals for Newborns
Known as neonatal abstinence syndrome, once the baby is born, and is no longer receiving drugs through the placenta from the mother, withdrawal symptoms begin. They can appear from one to ten days after birth, ranging from diarrhea, excessive or high-pitched crying, fever, seizures, hypersensitivity to light, touch, and sound, rapid breathing, trembling,
hyperactive reflexes, to name a few. Some infants will carry the effects of their mothers’ neonatal drug abuse for life, suffering long-term complications including brain damage and learning disabilities.

Like any addict that immediately stops drug intake, a baby experiences the same physiological impact on the body and brain. In the case of a baby being exposed to opiates, if the opiate is not replaced, the baby can die.

Affected newborns will spend their first months in a newborn intensive care unit; it can take more than a year for the effects of some drugs to wear off. Evidence reveals that these babies are more susceptible to drug addiction issues later.

“Ten years ago we were seeing significant prenatal methamphetamine use, now it’s opioids; the difference is the babies exposed to opioids have longer lengths of stay in the hospital because they go through physiological withdrawal,” explains Buchi, who has helped set up a care process for the management of opioid-exposed newborns.

“The symptoms of neonatal abstinence syndrome depend on the type of drug the mother used, how long it takes for the body to metabolize and eliminate the drug, how much of the drug she was taking and for how long,” explains McMillin, adding that whether the baby was born full-term or premature can also be a variable. Whether a baby is addicted to stimulants or “downers” will result in different withdrawal symptoms and require different treatment.

“The work we’re doing here is about the human condition; it is about the safety of children—as the risk of child abuse and neglect increases in cases of maternal drug abuse,” emphasizes McMillin, who has visited some of the babies in NICU, as well as testified in court when called to present evidence. “This is also about getting mothers the care and support they need through rehab and social services so they can take care of their children.”

**Why Is the Cord the Best Evidence of Drug Use?**

Traditionally meconium (an infant’s first stool) has been tested for detecting the presence of drugs, forming in the second trimester, and absorbing over time. However, waiting for this first stool to pass may waste valuable time, or the mother may try to dispose of it secretly, or it may pass during a difficult delivery, as happens in 10 percent of cases. The samples may be too small or sent too late for viable testing. Hair was considered as a possible specimen, but many babies don’t have enough hair to provide a sizable enough sample.

“About six years ago, we started looking for alternative specimens,” recalls McMillin, considering the placenta, the vernix caseosa (a white, creamy, film covering the baby’s skin during the last trimester), and the umbilical cord. The cord became the specimen of choice because of its practical size, easy transportability, and accessibility. “Every child comes into this world with one and it can be sent the minute the baby is born,” points out McMillin. What makes the turnaround time quicker for the cord is there is no waiting to collect the specimen.

“Sometimes babies are already in the throes of withdrawal symptoms, but physicians can’t determine what drugs they are dealing with until test results are available.”

Gwen McMillin, PhD, DABCC, ARUP, Medical Director, Clinical Toxicology Laboratories
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.

**The Wow Factor**

A record **56,000 samples** were received for processing in one 24-hour period. That’s a lot of patients counting on ARUP!

Since 2006, every child born in Utah has had a potentially life-saving connection to ARUP Laboratories. Hours after birth, a drop of blood travels from the heel of each newborn, through the Utah Department of Health, and eventually to ARUP, where experts look for a number of potentially life-threatening disorders like SCID (bubble-boy syndrome), and phenylketonuria and MCAD (both metabolic disorders).

 Besides having one of the world’s largest laboratory transport and sorting systems, ARUP Laboratories also has **one of the world’s largest specimen freezers**. At two-stories high and encompassing 7,000 square-feet, it can hold more than 2.2 million specimens.
ARUP Blood Services provides 25 percent of all blood transfused in Utah, and is the sole blood provider for the University of Utah Hospital, Huntsman Cancer Hospital, Primary Children’s Hospital, and Shriners Hospital for Children.

ARUP operates 24 hours per day, 7 days a week, 365 days a year, processing an average 45,000–50,000 specimens of blood, body fluid, and tissue biopsies per day, and performing 99 percent of all testing onsite in one central location.

Erin Baldwin and Danielle LaGrave are two of ARUP’s 12 genetic counselors who help clients and physicians understand genetic test results.
During his residency at the Henry Ford Health System in Michigan, Mohamed Salama, MD, was the young man who always had a digital camera in his shirt pocket. While training to be a pathologist, he recalls constantly aligning the lens of his Coolpix 990 camera to the microscope eyepiece to snap a shot of a slide.

Picture This:
Beauty and Disease in Digital Pathology
“It’s the way my brain works. I’m always looking for more innovative ways of doing things,” confesses Salama, ARUP’s chief of Hematopathology.

Today, his collaborative work is propelling digital pathology forward using whole slide imaging (WSI), a tool destined to change the evolution of pathology, much like functional magnetic resonance imaging (fMRI) changed neurology.

“There have always been cameras and photos taken in pathology. It is now just being taken to a different level, allowing for teleconferencing, remote consultations, and image analysis,” points out Salama. He adds that it is an invaluable tool for teaching, research, and—an area he is especially interested in driving—clinical application.

He explains that digital imaging is more practical, streamlines the workflow for quicker turnaround times, and avoids some of the pitfalls of glass slides (i.e., fading, breaking, missing). Whole-slide imaging and image analysis allows for a reliable standard, avoiding subjectivity or human error, while allowing us to see more.

“There are limitations to what our eyes and a microscope can do; with digital imaging, we can construct algorithms that can help us identify and collect data from specimens,” says Salama, who is also professor of pathology and director of the Hematopathology Fellowship Program at the University of Utah School of Medicine. For example, an algorithm can count the number of cells in a specimen or identify the repetition of a certain kind of biomarker.

**Extreme Data Drives Collaborations**

Like anything that can now be electronically delivered (i.e., bank statements, birthday cards), digital imaging decreases time and transport efforts. Salama points out that digital pathology is revolutionizing the traditional workflow involved in analyzing slides. “Once we get the tissue, the slide never has to leave the lab,” says Salama. A pathologist can circle the area of the (digital) slide tissue they want further analyzed remotely. Previously, a circle of tissue would be cut out for molecular testing and there would be no record of what exactly that area contained. Annotations and observations can also be added and shared.

High-power magnification from a whole slide image scan under oil showing cellular details of hematopoietic progenitor cells from a bone marrow aspirate smear.
As digital pathology, as well as the data collected from these images, grows, it requires an accessible and comprehensive data system. Foreseeing this need, Salama is collaborating with the University of Utah’s Scientific Computing Institute (SCI), which specializes in scientific imaging and “extreme” data management.

Through this collaboration, the institute is able to bring the software infrastructure needed for accessing and processing high-resolution images. Together with SCI’s Valerio Pascucci, PhD, and his team, Salama is developing the technology to scale pathology WSI down to an iPhone and all the way up to a super-computer. Currently, this process is being tested on one of the world’s largest computers in Saudi Arabia.

“Access to large data has become a major bottleneck for many applications, so we are specifically focusing on the challenge of accessing data and making it usable,” explains Pascucci, who is the director for the Center for Extreme Data Management, Analysis, and Visualization. “We’re able to increase speed and allow for practicability, especially when you have a lot of data and people in the loop.” Some components of this technology being developed with ARUP will be open source, while other components will be proprietary.

Such a system will benefit educational, research, and clinical environments, easing communication between experts or a professor and student.

Salama admits at the time, it took some convincing of his wife, that his old Coolpix 990 was indeed a good $1,000 investment when he purchased it as medical resident 15 years ago. It was the range of motion and how well the lens fit with the microscopes eyepiece that sold him on it. Two decades later at ARUP, hundreds of specimens a day are scanned and, with the use of algorithms, many are being mined for more diagnostic information.
Still Hoops to Jump Through
Currently, ARUP has an e-slide manager system where hundreds of thousands of slides from the past five years have been analyzed and stored. "We are working on an interface so our laboratory information systems can interact and access these images," says Brian Thompson, IT analyst, who oversees the slide manager website.

If a client or a pathologist works on a report and needs to refer to the slide, they can access it through this system. Interfacing with Epic, an electronic medical record system, is also in the works.

Despite this digital transfer of information, a glass slide is required for making clinical decisions, so the original slide is still sent. One of the hurdles ahead for the full transition to WSI in pathology is working with the Food and Drug Administration (FDA) to establish regulations. "This is such a new field that the FDA wants to make sure the new tools being used allow for quality compliance," explains Salama, who serves on the College of American Pathologists committee for digital imaging.

In the meantime, ARUP is already cresting this wave with the ability to offer imaging capabilities, pathology expertise, and programming together. "We have the power to make the most of WSI; we have everything in one place and know how to use it in practice," says Salama.

He adds that digital imaging is like any other tool, but when images are placed in context of their need, they become even more powerful. "These images help in diagnosing patients’ conditions and in time could lead to major discoveries," points out Salama. "This is content-rich material and we have to take advantage of it."

"Digital pathology is increasingly transforming pathology from a qualitative science into a quantitative one."

Mohamed Salama, MD, ARUP Chief, Hematopathology

New stain-free technology that uses 2 photon excitation and second harmonic generation along with image analysis to accurately detect and quantify fibrosis in tissue.
The Expanding Role of AMH as a Predictor of Fertility

While slowing down a woman’s biological clock remains as futile as turning back time, reproductive medicine is finding a way to peer inside the clock to gauge just how fast it is ticking.

One such clue is a test measuring anti-Müllerian hormone (AMH) concentrations, reflecting the activity of the ovaries during a woman’s lifetime and estimating her remaining egg supply. Where a woman falls on this fertility scale may help her learn the likelihood of becoming pregnant now and how that might change in the foreseeable future.

This is knowledge in demand, considering one-third of the approximately 20 percent of women who have children after 35 will experience fertility issues, according to the Centers for Disease Control and Prevention. For example, when levels of AMH fall below a certain level, the infertility treatment in vitro fertilization (IVF) becomes less successful.

“AMH testing can be helpful for women who are 35 and older and determining their fertility options,” says Erica Johnstone, MD, MHS, a University of Utah fertility and reproductive endocrinologist. “Is the window rapidly closing or is there more time?”

“AMH gives us information about a woman’s ovarian reserve or how many eggs she has left at that particular
There isn’t a specific level of AMH that will let you know whether you will or won’t get pregnant, but it can show you whether your ovaries are aging more quickly or more slowly than average.

Erin Johnstone, MD, MHS, University of Utah, Fertility and Reproductive Endocrinologist
About 20% of women in the United States now have their first child after age 35, and this leads to age becoming a growing cause of fertility problems. About one-third of couples in which the woman is older than 35 years have fertility problems.

Source: CDC

AMH testing can be a significant tool in helping clinicians improve treatment for fertility issues and provide earlier diagnosis of ovarian conditions (e.g., polycystic ovarian syndrome [PCOS], primary ovarian insufficiency [POI]). For a patient, the test results can help in planning for pregnancies and menopause, as well as monitor ovarian damage from therapies (e.g., chemotherapy) and surgeries.

Insight into AMH levels may help women going through in vitro fertilization (IVF) to get pregnant; this is a procedure in which the eggs are removed, fertilized, and implanted in the uterus. It is helpful in treating patients with hypogonadotropic hypogonadism (HH), a condition in which the testes or ovaries produce little or no sex hormones due to pituitary gland or hypothalamus problems.

Insight into an Infant’s Gender
While the bulk of AMH testing is linked to women and fertility, AMH testing may also be used to help determine the gender of an infant born with ambiguous genitalia, since girls have lower levels of AMH at birth than boys.

Genital anomalies are estimated to occur in one in 4,500 births. Some infants may have testicles that have not yet descended, others may be born with both male and female genitalia. The ability to diagnose these conditions has greatly improved in recent years due to advances in laboratory medicine such as AMH testing.

“The study of AMH is a relatively new area, with progress being made for multiple conditions,” says Straseski, an enthusiastic researcher in the area of AMH. “In the area of infertility, we’ve never had that many tools. Now we may have found something that could provide key information.” She adds that more studies are needed to realize the true potential of AMH testing.

“I love that laboratory medicine provides such an important service. After all, you can’t just X-ray a hormone to see if it is working. You need clinical laboratory tests to tell the whole story.”

Joely Straseski, PhD, Medical Director of Endocrinology, ARUP
Breakthrough Technology Spurs New Test for Non-Small Cell Lung Cancer Patients

For a patient battling lung cancer, the discomforts and risks of undergoing repeated biopsies, surgeries, and radiologic scans can now be replaced by a far less invasive method. Cell-free tumor DNA (ctDNA) technology is revolutionizing the diagnosis and treatment of cancer, and has spurred the development of a new test identifying target drug therapies for patients diagnosed with non-small cell lung cancer (NSCLC), particularly those who carry a specific gene mutation (EGFR T790M) in their tumor.

In the United States, lung cancer is the deadliest cancer for both men and women and claims more lives than colon, breast, and prostate cancer combined, according to the American Cancer Society. About 85 percent of lung cancers are NSCLC.

Scientists have discovered that tumor cells which shed DNA pieces into the bloodstream are ideal biomarkers for “reading” and monitoring the cancer. Often called the “liquid biopsy,” ctDNA technology involves simply taking a blood sample from the patient, as opposed to performing an invasive tumor tissue biopsy or surgical resection. ctDNA can reveal whether a drug therapy is still effective or if the patient has built up a resistance to the drug.

The T790M mutation of the EGFR gene is one such biomarker, and ARUP is the only large, national reference laboratory to offer a new clinical test known as EGFR T790M.

About 10 to 35 percent of patients with NSCLC have a primary mutation in the EGFR gene that can be targeted by specific tyrosine kinase inhibitor drugs. Two-thirds of patients who later acquire resistance to these chemotherapy drugs will have a detectable second-site mutation at T790M in the EGFR gene.

“I think it would be fair to liken the ramifications of ctDNA in cancer care to the monumental importance that radiology has played in cancer diagnosis and monitoring. I wouldn’t stop there, but would also liken ctDNA to the great significance that antibiotics have played in the fight against infection,” expresses Mary P. Bronner, MD, the division chief of Anatomic Pathology and Oncology at ARUP, who is also a professor of pathology at the University of Utah.

“Like radiology, ctDNA allows us to diagnose cancer and cancer recurrence, but even earlier due to the increased sensitivity of the test and the far shorter testing intervals made possible by simple blood draws at decreased cost. Like antibiotics, personalized tumor-susceptibility testing by ctDNA can also target new, specific chemotherapy drugs to individual patients’ tumors, akin to the power of targeted antibiotics for bacterial infections.”

cDNA’s sensitivity not only allows for earlier detection but more accurately represents the whole tumor burden in the patient, in contrast to the tiny tumor fraction tested from a biopsy or resection. The problem with such limited samples is that tumors are highly heterogeneous, or varied, in their cellular and genetic makeup, so limited samples may easily miss important, treatable tumor changes. Since all cells, including tumor cells, are exposed to blood flow, ctDNA sheds into the blood stream from the entire tumor or from its simultaneous spread to other organs; this offers markedly improved tumor analysis through blood sampling.

Instead of multiple radiologic imaging scans, which provide limited information, drawing blood at shorter and regular intervals provides more continuous insight into the cancer’s progression and whether a drug therapy is still working. Building up a resistance to drug therapy is common among lung and all other cancers, so knowing if and when to try a new therapy is crucial information. For those lung cancer patients with the EGFR T790M mutation, new chemotherapy drugs have been introduced that specifically target this mutation.

“Using highly sensitive technologies, such as digital droplet PCR, this test can detect lung cancer recurrence as well as tumor resistance to targeted chemotherapy drugs, and permit personalized therapy for the T790M mutation,” adds Wade Samowitz, MD, who oversees Solid Tumor Molecular Diagnostics and Histology at ARUP Laboratories and is also a professor of pathology at the University of Utah.
For a patient battling lung cancer, the discomforts and risks of undergoing repeated biopsies, surgeries, and radiologic scans can now be replaced by a far less invasive method ... Scientists have discovered that tumor cells which shed DNA pieces into the bloodstream are ideal biomarkers for “reading” and monitoring the cancer.
ctDNA technology is being developed for all cancers and holds tremendous potential for improving patient care. The possibility of using simple blood testing to screen for early curable cancer, honing in on what might be the optimal blood sampling intervals to detect recurrence and drug resistance, among many other opportunities, is the subject of intense research by the cancer-care community. We are only now seeing the very beginning of how ctDNA promises to revolutionize cancer care.

**EGFR T790M Mutation Detection in Circulating Tumor DNA**

tCTDNA testing provides a quick, less invasive alternative to traditional biopsies for the evaluation of an NSCLC patient’s **EGFR T790M** mutation status.

This test is ideally suited for monitoring blood plasma or cerebrospinal fluid for:

- Development of acquired **EGFR T790M** drug-resistant mutation in non-small cell lung cancer (NSCLC) patients receiving early generation tyrosine kinase inhibitor (TKI) therapy for non-T790M **EGFR**-genomic alterations detected at initial diagnosis.

- Response to therapy and disease progression by quantifying the levels of T790M circulating mutations in patients receiving **EGFR T790M**-specific TKIs.

I think it would be fair to liken the ramifications of ctDNA in cancer care to the monumental importance that radiology has played in cancer diagnosis and monitoring. I wouldn’t stop there, but would also liken ctDNA to the great significance that antibiotics have played in the fight against infection.

Mary Bronner, MD, ARUP Division Chief of Anatomic Pathology and Oncology
Catching Unnecessary Tests with New Duplicate Testing Measures

The red flag was waved last spring, when Cindy Meadows, an ARUP Laboratory group manager in genetics, was reviewing client reports and realized that one doctor had ordered the same genetic test on the same patient ten times, an expense that falls heavily on the patient, with genetic test costs ranging anywhere from $200 to $9,000 (e.g., exome sequencing on a patient and his/her parents).

Since then, ARUP has implemented measures to identify duplication of tests, specifically for "lifetime" tests—genetic tests that don’t need to be repeated since one’s DNA remains unchanged. "It was the right thing to do," says Meadows. "We needed to find a solution to start catching all of the unnecessary duplications, not just the blatant cases."

The results are in. Over a six-month period, ARUP identified more than $200,000 of duplicate genetic testing for all clients combined. Over time this could add up to a significant amount of unnecessary healthcare spending.

Three internal ARUP labs—the Molecular Genetics, Genetics Sequencing, and Fragment Analysis labs—identified 356 unique "lifetime" tests. In tracking these, ARUP found that clients had ordered, as duplicates, approximately 67 of these tests.

"Through our utilization management efforts, we partner closely with our clients to save them hard costs associated with sendout tests," says Brian Jackson, MD, MS, ARUP’s vice president and chief medical informatics officer. "We’re able to help our clients improve patient care by mitigating unnecessary testing and spending."

ARUP’s Genetics Division has set up flags within its system based on a patient’s name, birthday, and test-order history, so if a repeat test is requested, the staff creates an "except," canceling the test and notifying the client of the previous result. For example, if an expectant mother received a test to screen for cystic fibrosis with her first pregnancy, then if this test is re-ordered with an additional pregnancy, the system will alert ARUP staff.

"When we find a true duplicate, we’ll call the client to give them feedback on the results initially found and give them the option to cancel the test," explains Tim Mason, Integrated Oncology and Genetics Services supervisor, who oversees the pre-analytic processes for ARUP’s genetic tests.

While catching duplicates in many other non-genetic tests can be more complex due to multiple variables, such as a patient’s fluctuating physiology, one’s genetic makeup remains constant. "Generally, we’ll find the same mutations in a newborn as we will in that person at age 80," points out Elaine Lyon, PhD, ARUP’s Molecular Genetics medical director.

With the need for effective test utilization, the cost of these molecular tests, and then doing what is best for the patient, it just made it clear that this was the right thing to do.”

Cindy Meadows, Assistant Vice President, Genetics Group Manager

33
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