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A JOURNAL SENTINEL SPECIAL REPORT

Newborn screening saves babies, but lives can be shattered when state labs ignore science and common sense.

The price of being wrong

MIKE DE SISTI / MILWAUKEE JOURNAL SENTINEL

Mel Russell, 6, sits between his parents, Melbourne III and Nicole, at the Milwaukee County Courthouse in September. As a newborn, Mel was not diagnosed with the metabolic condition that later caused him to have a stroke and suffer brain damage.

ELLEN GABLER MILWAUKEE JOURNAL SENTINEL

Everyone in the courtroom could agree on this: If the acid in Mel Russell's blood had been a minuscule amount higher, the little boy's condition would have been caught before he suffered brain damage.

Computer software at the Wisconsin State Lab had rounded up one marker on his test results, hitting a number that meant Mel should be immediately referred to a specialist. The newborn probably had a rare, yet treatable metabolic disorder.

But a manager at the state lab reviewed the results. And 0.1998380 wasn't quite 0.20.

The baby received no treatment.

Now 6½, Mel sat in a big, wooden chair inside the Milwaukee County Courthouse in September. He moved to his mom's lap as lawyers introduced themselves to a room of 45 potential jurors. Over the next two weeks, 12 of them would have to decide:

Who was responsible for the fact that Mel has a hard time dressing himself?

That he needs a full-time aide in his first-grade classroom?

That he receives speech and occupational therapy several times a week?

That he likely will never be able to manage his own diet or live independently?

When Mel was 18 months old, he woke up one October morning at home in Menomonee Falls, moaning and running a slight fever. His mom propped him up against a pillow, as she did most mornings, and handed him a sippy cup of milk. But this time, Mel couldn't hold it.

One arm was limp. So was one leg. His gaze went off to the side. His dad took him to urgent care. Thirty minutes later, an ambulance rushed him to Children's Hospital of Wisconsin.

He's brain dead, thought his dad, as doctors and nurses swarmed the toddler.

Little Mel had suffered a stroke. Doctors later discovered it was brought on by a metabolic crisis — toxic substances had built up in his blood, eventually overwhelming his body and brain. Further tests showed he had propionic acidemia, a disorder where the body can't process certain fats or proteins. If identified at birth, as it is supposed to be, the disorder can be treated with a regulated diet and a child can develop normally.

Instead, acid had been building in Mel's blood for the first year and a half of his life.

It's a condition every state in the nation sets out to catch through a test called newborn screening.

A baby's heel is pricked within a few days of birth, blood is collected and sent to a public health lab where it is screened for dozens of serious, yet treatable genetic disorders. The test is required by law in all 50 states. About 1 in 800 babies is born with a condition that can lead to death or brain damage if left untreated. Like Mel, the babies usually appear healthy at birth.

On April 8, 2010, six days after Mel was born, the Wisconsin State Lab mailed his pediatrician a blue piece of paper with his newborn screening results: *POSSIBLE ABNORMAL.*

The report instructed Dr. Laurie Grunske to collect another blood sample from Mel and send it to Madison for a retest. She did and a week later more results came, this time on white paper: *NORMAL.*

The actual values were listed below, with a note that a ratio used to screen for metabolic disorders remained elevated. There were no recommendations or instructions for follow-up.

Dr. Grunske took the stand on the seventh day of the trial. In her 25 years as a pediatrician, she had reviewed nearly 2,000 newborn screening results from the state lab.

She told the jury she reviewed Mel's first results and followed the lab's request to send in another blood sample. When she saw the second results, *Normal* had meant just that to her.

She was in court defending herself because of less than two ten-thousandths of a point — the difference between Mel's 0.1998380 and the state lab's alert value of 0.20.

If Mel's result had stayed rounded up, all six of his markers would have been abnormal. He would have been immediately sent to a metabolic specialist, per the protocol of the state lab. But it hadn't stayed rounded up, per the protocol of the state lab.

Now Dr. Grunske — and only Dr. Grunske — was being blamed for the damage that had been done to Mel Russell.

Each state has own approach

Newborn screening is heralded as a lifesaver for about 12,000 babies in the United States each year. And it is, but no one wants to talk about the kids whose conditions are missed.

Parents might never find out an overlooked genetic disorder is the reason their toddler can't speak, stops growing or won't follow the rules. *It's autism,* some doctors conclude.

Parents can opt out of newborn screening for religious reasons, but nearly 98% of the 4 million babies born each year in the U.S. are tested shortly after birth. State public health laboratories screen for as many as 58 genetic disorders.

Each state aims to detect affected babies while not flagging too many "false positives." Every baby flagged must be tracked down for diagnostic testing to determine if he or she really has a disorder. That costs time and money, so the parameters for a positive screening can't be too broad.

Lab officials say they don't want to worry new parents unnecessarily, or create a "cry wolf" scenario where doctors ignore alerts because too many babies are found not to have a disorder.

It's a balance of time, money and science. But a Milwaukee Journal Sentinel investigation has found that the science is often ignored.

Testing varies significantly between states, some of which don't follow scientific standards or common sense. The consequences can be devastating, yet changes in a lab are often made only after a child dies or suffers irreversible harm. When a child becomes brain damaged and faces a lifetime of expensive care, the lab usually can't be sued to cover any costs. That falls to parents and taxpayers through Medicaid and other programs for children and adults with disabilities.

Mistakes in newborn screening can crop up anywhere in the process — blood could be collected incorrectly; a test might be botched or misread; samples may be sent late to state labs, as a 2013 Journal Sentinel investigation found.

But even when everything goes according to plan — and all procedures are followed — children still suffer because underlying policies are flawed.

In a hearing two months before the trial, Milwaukee County Circuit Judge John DiMotto met with attorneys from both sides on the fourth floor of the Milwaukee County Courthouse. Mel's attorney had made a motion to keep out testimony from an expert aiding in the defense of Dr. Grunske. The expert planned to talk about the Wisconsin State Lab.

Both sides agreed results from the state lab were "confusing" and "not clear." The expert for the defense had described the state lab's policies and procedures as "distinctly unusual" in a deposition. A pediatrician and world-renowned metabolic expert for Mel's side said he "would love to see them changed."

"I see the state lab as being a red herring here," the judge said. "This is not a case about the state lab. This is a case about how Dr. Grunske responded to the reports that she received."

DiMotto ruled the defense's expert could not testify. He reasoned that Debra Freedenberg, medical director of the Texas newborn screening program, had not given testimony in her deposition that the Wisconsin State Lab had breached a defined standard of care shared by public health labs throughout the country.

"She basically said, each lab, as long as they develop policies and procedures, they can do their own thing," DiMotto said in his ruling that day. "So, perhaps, in the United States there are 50 different ways that states do this."

In fact, there are. And that is a problem.

■ A child's life-threatening condition might be caught in one state but missed in another because there's little uniformity in the policies, procedures and cutoffs used to screen disorders. States often fail to consider factors known to affect the accuracy of results, such as age and birth weight.

■ Babies with borderline results are most at risk. Yet state labs typically only report whether results are normal or abnormal, so a pediatrician wouldn't know if a baby was on the verge of being flagged for a serious disorder. That fact could matter years later when a child isn't developing properly and doctors are searching for an explanation.

■ In each state, people with competing interests have a say in how newborn screening is done. Lawmakers, doctors, laboratory professionals and representatives from health departments, hospital associations and advisory groups all weigh in. Much of the disagreement focuses on costs; hospital associations generally fight increases even though screening is usually covered by insurance. Each baby's

screening ranges from $30 to $160, depending on the state.

■ States say they can't improve screening because they are constrained by costs, and lawmakers won't approve more money to fund the state lab. In 2004, a lab manager in North Carolina warned that computers needed to be reprogrammed to correct a known flaw in methodology. Money wasn't found for the programming; North Carolina kept doing its $45 test the same way. At least one baby suffered catastrophic brain damage as a result.

■ For years, a federal advisory committee has discussed trying to bring more uniformity to newborn screening. But little action has been taken to standardize the way screening is done despite known advances in science.

■ State governments are generally shielded from lawsuits under "sovereign immunity," a principle from English common law meaning "the king can do no wrong." The idea is that lawsuits could bankrupt the state and prevent it from providing services to the rest of the community. As a result, parents of injured children can't recover money from the state to help care for their child's lifelong disability, so they sue someone else — like a pediatrician, or others who may not be primarily at fault.

There's no way to tell how many babies have been overlooked for a serious genetic disorder. A new national clearinghouse that collects data from state labs to monitor their performance doesn't have any 2015 data tracking "missed cases" — one of eight quality indicators. Participation in the clearinghouse is voluntary, and states self-report data.

A few months after Mel Russell got sick, the newborn screening advisory committee in Wisconsin gathered for a regularly scheduled meeting.

It was January 2012. The group talked about Mel's case and agreed they needed to review cutoffs for his disorder and similar conditions.

They delved into specifics at another meeting nine months later. When compared with other laboratories, Wisconsin had one of the highest cutoffs used to screen for Mel's disorder. Two markers are used: one was "significantly higher" than other labs; the second was comparable to most other states. In other words, Mel's condition could have been caught if he lived somewhere else.

Lab directors say setting cutoffs requires a balance of time and money. A high rate of false positives could overwhelm the lab — both in staff time and costs for follow-up. However, most states aren't using advancements in technology that would reduce false positives, better detect disorders and possibly cut costs.

At the time of Mel's birth, about six babies in Wisconsin each year received "definite abnormal" reports for his type of disorder. About two of those children actually had a metabolic disorder; the rest were false positives.

About 80 babies received "possible abnormal" reports like Mel did. In some years, none of those 80 would have a disorder; in other years, follow-up tests would determine one child was affected.

So the trade-off in Wisconsin each year was getting a second sample from about 90 babies, to avert death or brain damage for two or three of them.

After considering how Mel was missed, the committee agreed to lower the primary cutoff by 28%. Scientific developments also led to a change in methodology a few months later. Now when a baby is flagged for this type of disorder, the lab does a second, more specific test on the blood sample already at the lab. The approach accommodates the lower cutoff and reduces false positives reported to parents and doctors.

Upgrades to the lab's procedures did cost money — about $110,000 a year, lab officials say, with an additional one-time expense of $25,000 for new equipment. Most of the cost was adding a staff member to do more specific tests for several disorders. Plus, there was a higher volume of babies to re-screen — about one or two each day, compared with one re-screen every four or five days with the old cutoff.

"The committee decided it was worth the workload and expense," said Patrice Held, co-director of the lab's newborn screening program. "There is definitely a cost and a reality behind it."

Lost potential

"What is the price of being wrong?" That's the question one of Mel's lawyers posed to the jury on the last day of the trial.

$3 million. Mel's lost earning capacity.

$7 million. The cost for him to live in a group home from 18 until he dies in old age.

$6 million. His care if he lives at home with his parents, and then with one of his two little sisters after their parents die.

Mel's lawyer, Chuck Hehmeyer of Philadelphia, had spent much of the last two weeks making the case that the little boy would never lead a normal life.

At 6, Mel struggles to write with a pencil and put on his own shirt. He's known to hit, spit, run out of the room and tear things up at school.

Hehmeyer stood behind a lectern as he addressed the jury.

"One of the issues we have not talked about much: pain and suffering and disability. He has no friends. How hard is it for a special needs child to grow up? How hard is that going to be for him? Do you think he's going to fall in love and be married? Have kids? Will he have friends? Will he have a job like you do?"

Mel is much different from his younger sister Elise, who also has propionic acidemia. Elise was diagnosed at two weeks old and her parents have carefully managed her diet ever since. She is now a typically developing 5-year-old.

The perfect control. That's what Hehmeyer called Elise. He argued that Mel would be just like her if his pediatrician had done things differently.

The newborn screening results weren't Dr. Grunske's only clue the baby was sick, Hehmeyer said. Soon after Mel stopped breastfeeding at 9 months, he started vomiting. Not normal baby spit-up, but projectile vomiting. Mel was constipated and listless. He wasn't making eye contact as much — *Did he have autism,* his parents wondered?

He had been in the 90th percentile for weight soon after he was born. By six months, he'd dropped to the 50th. At one year, he was in the lowest tenth. Something was wrong.

Hehmeyer hadn't sued the Wisconsin State Lab because he knew there was no point.

There are exceptions to sovereign immunity, but mistakes or an oversight at the state lab are not among them. A family in California had already made that argument and lost.

In 1998, the California Supreme Court ruled unanimously that the state could not be sued over flaws in its newborn screening program. Opening up the state to such liability would lead to no program at all, the court reasoned, and many more children would be hurt as a result.

The decision stemmed from an incident eight years earlier, when a lab contracted by the state failed to detect that Sierra Creason was missing her thyroid. The condition, congenital hypothyroidism, is easy to treat and one of the most common conditions for which babies are screened.

By the time doctors diagnosed Sierra at six months, the baby's growth was stunted and she had suffered severe brain damage. She was blind, never walked and only learned to speak about 100 words. When she died in 2014 at age 23, she was the size of an 8-year-old.

"It was a brutal life," her mother, Claudia Creason, said in an interview with the Journal Sentinel.

Sierra's newborn screening test had showed a low level of thyroid hormone, which can be one indicator of the disorder, but not the one used in California at the time. The state's testing protocol didn't require low levels be reported to the doctor.

In addition to deciding that the state was immune from liability, the court ruled that it couldn't be sued for choosing a particular testing policy.

A normal report

It is the policy of the Wisconsin State Lab to *not* round up test results. The lab director explained this to Mel's mom in an email a year after her toddler suffered permanent brain damage.

Nicole Russell had been trying to figure out how Mel's condition had been missed: Maybe a software glitch at the state lab?

"I do not believe that there was any malfunction of our software, nor was there any deviation from our reporting protocols," Charles Brokopp, the lab director, wrote in the fall of 2012.

He explained that even though the computer had rounded up one of Mel's six markers, a lab manager who reviewed the raw data realized it was technically below the 0.20 cutoff.

That one marker was why Dr. Grunske had received the "possible abnormal" report for Mel's first test, instead of a "definite abnormal" report and referral to a specialist.

But the jury didn't hear any of those details. The case was not about the state lab, Judge DiMotto had decided, so he would not allow a discussion in court about how the state lab did its work.

It was Dr. Grunske's interpretation of Mel's follow-up test that the jury heard about.

Mel was two weeks old when Dr. Grunske received the results at her office in New Berlin.

This is a repeat specimen collection of an initial positive finding. Test result (s): NORMAL.

Below that was something else: *THE FOLLOWING RATIO REMAINS ELEVATED.*

It listed something called a C3/C2 ratio, and noted Mel's was higher than normal. In court, everyone agreed that a pediatrician would not be expected to know the significance of a C3/C2 ratio — which helps detect certain metabolic disorders — or even that it exists. That's a specialist's area.

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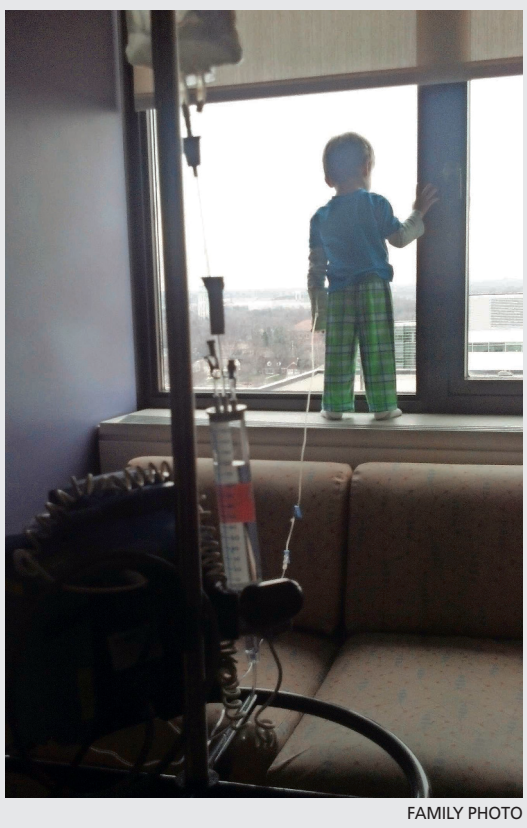

FAMILY PHOTO

Mel Russell sits on his bed at home in Brookfield with "Ungung," his favorite stuffed animal.

Left: Mel looks out a hospital window at 18 months old, shortly after his metabolic crisis.

Below: Melbourne Russell III (from left); Silvia, 2; Mel, 6; Elise, 5; and Nicole Russell gather in their Brookfield home. Mel has a metabolic disorder that was not diagnosed until after he suffered a stroke and brain damage. Elise suffers from the same disorder but was diagnosed shortly after birth. She is a typically developing child.

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"He has no friends. How hard is it for a special needs child to grow up? How hard is that going to be for him? Do you think he's going to fall in love and be married? Have kids? Will he have friends? Will he have a job like you do?"

CHUCK HEHMEYER,
MEL RUSSELL'S ATTORNEY

But Hehmeyer argued that Dr. Grunske should have called an expert to find out what it meant.

Her defense team disagreed.

"When the state lab sends you a normal report, you don't second-guess the state lab," her attorney, Michael Johnson, said to the jury during his opening statement. "It's a normal report."

Johnson went on to explain how the state lab used different colored pieces of paper to alert a pediatrician when they needed to take action: Yellow for definite abnormal, blue for possible abnormal, white for normal.

Mel's second result came on white paper.

"There is no dispute in this case: The state lab missed Mel Russell," Johnson said. "Why is Dr. Grunske the only one sitting here?"

'Something's wrong with Jonathan'

Loree Oliver carries her son on her hip as she answers the door to her North Carolina home.

"Say hello, Jonathan." The boy curls his head against her neck, peeks up and mumbles something. They live about 15 miles from Charlotte in a cream-colored house at a "T" in the road.

Inside, she puts Jonathan down on the living room carpet. He scoots past the coffee table on his stomach, using a halting Army crawl to move forward. He grunts and says a few things only his mom can understand.

Jonathan turned 6 in September. His mom pulls up some videos on her phone: Jonathan, almost 2, running toward a giant gumball machine at the amusement park. Jonathan dancing in the backyard at a family reunion. Jonathan, soon after his second birthday, riding a tricycle up the sidewalk.

"That was my little dude," she said. "Just ripping and running and doing everything."

Now, he can't walk by himself.

Jonathan's fate can be traced to a day more than six years before he was born.

It was July 9, 2004, and members of North Carolina's newborn screening advisory committee were gathered for a regularly scheduled meeting. Susan Weavil told them the state lab had a serious problem.

Weavil worked at the lab as supervisor of tandem mass spectrometry. That's technology that vaporizes compounds after they are extracted from a spot of blood, separates them, and estimates their concentration. Too much or too little of a compound can indicate a metabolic disorder.

Weavil laid out the problem: The state lab needed to factor in a baby's age when setting cutoffs. Compounds in blood can fluctuate considerably in the first few weeks of life.

A baby's blood sample is taken within a few days of birth. Babies who need a retest might be two weeks old or older when the second sample is collected. Using the same cutoff for a newborn and two-week-old baby could cause the lab to overlook the older baby's disorder.

The committee had known about the problem and had put in a request to fix it. At the July meeting, members were told it hadn't been fixed because the lab doesn't control the computer programmers who work for the state.

That day, Joseph Muenzer, a geneticist and member of the committee, reiterated the need for change: The different cutoffs were especially important when screening older babies for a particular category of disorders where the body has a hard time breaking down amino acids and fats. The compounds measured for those disorders are known to drop soon after birth. The plan was to have Muenzer and others from the committee sit down with the state lab staff and hammer out a plan. But the change was never made.

When Jonathan Page was born in 2010, blood was collected from his heel and sent to the North Carolina State Lab for testing. *Abnormal*. Following standard protocol, it was tested a second time the next day. Again, *abnormal*.

The results suggested something could be wrong with certain enzymes in Jonathan's body. If an enzyme doesn't function properly, it can't break down amino acids or fats, so they build up, turn into acid and poison the body.

Jonathan needed a retest from a new blood sample. By now, he was two weeks old. The baby seemed healthy, but his mom brought him to the doctor to have more blood collected. A week later his pediatrician received the follow-up report: *Normal*.

As he grew, Jonathan loved going to basketball games where his older sister, Cayla, was on the cheerleading squad. His mom was sure he'd play sports — even as a toddler he'd run around the living room with his football, counting off and hiking the ball.

About a week before Christmas, Jonathan wasn't feeling well. Just over 2 now, he'd had the flu but seemed to be getting better. A cousin who was visiting got up early one morning to change his diaper.

"Something's wrong with Jonathan!" she screamed.

Jonathan was lying on the bed, eyes staring straight ahead. He was breathing hard and wouldn't move. They called 911.

Jonathan was taken to a nearby hospital, then transferred to Levine Children's Hospital where he was put in intensive care. For five days he was in a coma. By day four, doctors told his mom what was wrong: Jonathan had a disorder called methylmalonic acidemia, also known as MMA. His body couldn't break down certain proteins and fats.

If the disorder is caught early and treated with a special diet, a child can develop normally. But it was too late for Jonathan.

So much acid had built up in his body that he suffered a stroke, causing damage to both sides of his brain. He woke up from the coma on Christmas Eve.

"He was just like a newborn baby," his mom said. "He couldn't really move. He couldn't sit up … couldn't hold his head up."

Jonathan was in the hospital for 55 days. He needed a feeding tube and started therapy: physical, occupational, speech.

He's in kindergarten now but needs a full-time aide. He spends most of his time in a wheelchair. His movements are uncontrolled and lurching; he can't write his name. Loud noises scare him. A recent haircut took nearly an hour because he needed to take a break every few minutes. He'll never be able to live on his own. His lifelong care will cost millions. That's just one reason his mom decided to sue.

"Nobody deserves to experience what my son experienced," Oliver said. "My dreams for my son were shattered."

Susan Weavil is named in the lawsuit; her last name is Bowman now. She's the woman who supervised tandem mass spectrometry in North Carolina and told the advisory committee in 2004 the lab needed to adjust cutoffs to account for a baby's age. Shu Chaing is named, too. She managed the newborn screening lab and had been there since they started using tandem mass spectrometry in the late 1990s. The women are being sued personally for failing to change cutoffs for older babies.

The lawsuit alleges both women knew or should have known Jonathan's retest at two weeks old would produce incorrect results. Giving results that said *Normal* to his pediatrician was negligent, the lawsuit asserts, since they knew standards for a newborn didn't make sense for a two-week-old baby.

Mel Russell's lawyer, Chuck Hehmeyer, is representing Jonathan, too. Hehmeyer won't talk about the case; neither will Jonathan's mom, nor officials from the state lab or health department, which oversees the lab.

Attorneys for Bowman and Chaing are arguing that the women should be immune from liability. Their request for a dismissal of the case was denied, but it is now being considered by the state's appellate court.

North Carolina still has not adjusted the cutoffs for age. The lab's director, Scott Zimmerman, told the Journal Sentinel the ranges are appropriate for babies between zero and six months of age. Published research says otherwise; other states adjust their cutoffs by age.

David Millington has been on North Carolina's advisory committee since 1990. He's retired now but ran the biochemical genetics lab at Duke University School of Medicine for 30 years.

Millington said that while the committee recommended the change in 2004, the state budget didn't fund the programming work.

"You are dealing with limited resources and budget constraints that can boggle the mind with the stupidity of it," he said. "But you have to deal with it."

Newborn screening is not an exact science, Millington added. Many factors can influence results: When a baby last ate, how the blood is collected, if a sample is left in hot or humid conditions.

"It's an evolving process," he said. "We are going to have to live with a few failures."

Policies and procedures

The damage to Mel Russell's brain was obvious. Soon after he was rushed to Children's Hospital of Wisconsin, a neurologist pulled up his brain scan to show his dad, Melbourne Russell III.

"That's an empty spot," the doctor said, pointing to a dark area where little Mel's brain should have been developing.

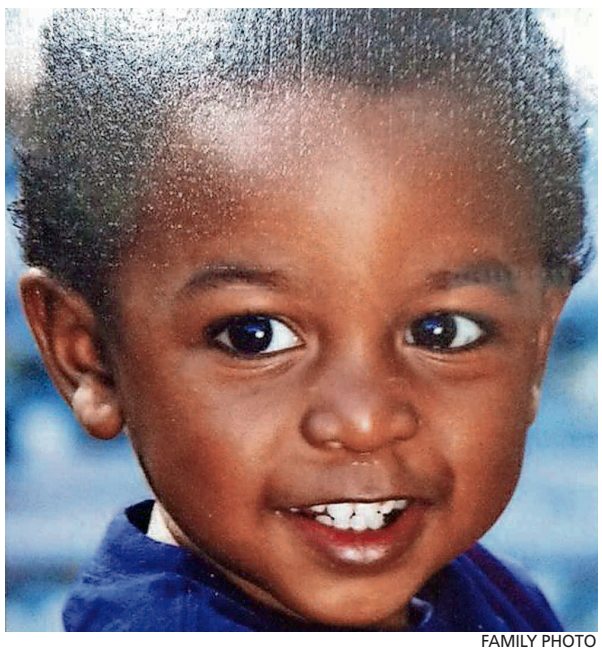
But the boy was young. Maybe he could make up for it: Kids are resilient and brains are amazing, the doctors said.

Plus, Mel's parents would do anything to help him get better.

On the way home from the hospital a few days later, the Russells stopped at a grocery store to stock up on low-protein food Mel could safely eat. Thanksgiving was coming. They'd have spaghetti, not turkey, Nicole thought.

But as the months went by, it was clear Mel wasn't making up for it. At 2, he couldn't crawl up a stair. He wasn't able to catch a ball.

"He was in a fog," his dad said.



FAMILY PHOTO

Jonathan Page, at age 2, before he suffered a stroke and subsequent brain damage from an undiagnosed metabolic disorder. Jonathan's newborn screening test in North Carolina did not detect his condition at birth, as it should have.

NANINE HARTZENBUSCH

Jonathan Page, 6, leaves a haircut appointment in October with mom Loree Oliver (left) and sister Carli Carpenter. Jonathan can't walk on his own and has significant disabilities.

"It's an evolving process. We are going to have to live with a few failures."

DAVID MILLINGTON,
MEMBER OF NORTH CAROLINA NEWBORN SCREENING ADVISORY BOARD

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Dr. Laurie Grunske sits in court in September. She was sued for malpractice on the grounds that she should have provided more comprehensive care for Mel Russell soon after he was born.

Mel's little sister Elise, who had the same condition, had been detected by newborn screening and was doing well.

Nicole was thankful for that, but devastated Mel had been missed. That's why she requested his medical file, which had his newborn screening results.

At first, she said, the state lab director, Brokopp, was dismissive, ignoring phone calls and emails. But eventually, Brokopp invited Nicole and her husband to Madison. They were given a tour, met some lab technicians and learned how newborn screening works.

Then Brokopp and two lab employees listened as Mel's parents explained what had happened to their son. Nicole showed them a picture of little Mel.

"All three of them were crying by the end of it," Mel's dad said. "It definitely hit them pretty hard."

Brokopp said he'd investigate. In that email two weeks later, he reiterated that the cutoffs were the cutoffs and everything in Mel's case had been followed according to the protocols of the state lab.

In fact, the state lab did not have a strict policy for evaluating blood samples, the Journal Sentinel has found.

The lab's practice was to have the director of newborn screening review potentially abnormal results, and then make a decision as to what to report to the pediatrician.

So when one marker on Mel's first blood sample missed the cutoff by a minuscule amount, the newborn screening director could have determined he should see a specialist.

Then there was Mel's second sample, which was tested three times, per protocol at the state lab.

For the primary marker used by the state — a compound called C3 — two of Mel's results were below the cutoff. One was above it — by more than one-and-a-half times. That was the cutoff later described to the advisory committee as "significantly higher" than those used by most other labs.

For the C3/C2 ratio, *all* of Mel's results were above the state's cutoff. Two were

“So, perhaps, in the United States there are 50 different ways that states do this.”

JOHN DIMOTTO,
JUDGE HEARING THE RUSSELL FAMILY’S CASE

nearly double the normal ratio, one almost quadruple.

Yet the lab sent a *Normal* report on white paper, with the note that the baby’s C3/C2 ratio was elevated.

In court, Dr. Grunske told the jury it had been her understanding the state lab would call a doctor directly if there seemed to be a problem, or give specific instructions if a baby needed additional care.

‘Artificial line in the sand’

Dietrich Matern thinks newborn screening should be as uniform as the food at McDonald’s.

“The burgers taste the same wherever you go,” he said. “Newborn screening should be the same way. It should be the same everywhere, with slight differences we don’t notice.”

Matern is co-director of the biochemical genetics laboratory at Mayo Clinic in Rochester, Minn. The lab specializes in treating and diagnosing patients with metabolic conditions. He’s been involved with newborn screening for most of his 25-year career, and believes there is already a better way to address variability in newborn screening.

He sits on a committee that advises the U.S. Secretary of Health and Human Services on the topic. Those who have been on the committee acknowledge it’s a peculiar group: well-meaning, but with little power and ability to enact change in state public health labs.

Labs have different budgets and equipment. They screen for a different number of disorders: 31 in Georgia; 44 in Wisconsin; 58 in Missouri.

Most states require a single screen, but about a dozen require two for every baby — one blood sample taken shortly after birth, the second a week or two later — because they believe babies will be missed if they require just one.

Cutoffs to detect disorders vary considerably. While lab directors talk about the problems with false positives, a study published five years ago found that 43% of newborn screening cutoffs were set at a level where false *negatives* were likely to occur. A false negative is much worse than a false positive: That’s when a baby with a condition is missed entirely.

At a meeting in February, Matern reminded his fellow committee members that their group was created 13 years ago in part to “ensure uniformity for all babies across the country.”

That uniformity doesn’t exist.

The committee itself often has a hard time agreeing on a best approach. Even when members do, each state can make its own decisions.

Matern is clear that newborn screening isn’t black and white. Biology expresses itself differently in each person, and many factors influence the metabolites analyzed to detect disorders. Labs may use different equipment and methods, and each sets its own reference ranges based on the population it tests.

What frustrates Matern is that labs aren’t taking advantage of a worldwide collaboration meant to control for many of those factors and create more uniformity in testing for all babies.

The software is free and available to any medical professional who wants to use it. It was developed under a federal grant and is meant to help labs more accurately determine which babies have a disorder, while also reducing false positives. It can even save states money.

Since 2004, researchers and labs around the world have been building a database of true-positive cases to better predict which babies have a genetic disorder. It started out as quality improvement project for labs in seven states — Wisconsin, Minnesota, Illinois, Indiana, Michigan, Ohio and Kentucky — although it’s not fully utilized by most, including Wisconsin.

The software draws on screening results from 30 million babies throughout the world, 19,000 of whom were diagnosed with metabolic disorders.

Instead of relying on cutoff values that may be arbitrary or outdated, labs can compare each newborn’s results with babies who have actually been diagnosed.

An algorithm analyzes results from each child tested by a state lab and flags those whose results are similar to babies known to have a disease. The software also can reveal how a lab’s cutoffs might miss babies.

When Mel Russell’s results are plotted using the software, it’s obvious he falls among the 324 babies diagnosed with propionic acidemia whose results are in the database.

You also can see clearly how Wisconsin’s cutoffs can miss children.

Since 2004, at least 38 babies with Mel’s disorder worldwide had test results below the cutoff used by the state lab. Their results fall in a range that would have prompted the lab to issue a *Normal* report. Even the new cutoffs set after Mel’s stroke would miss 10 babies known to have propionic acidemia.

In early November, Piero Rinaldo gave a presentation about the screening software to part of the federal advisory committee. Rinaldo is a clinical biochemical geneticist — a colleague of Matern’s at Mayo Clinic — and the lead doctor developing the software.

Rinaldo explained how in 2013, the software reduced the number of false positives in Minnesota to just 17, resulting in a false positive rate of 0.024% for metabolic disorders tested by tandem mass spectrometry. That’s compared with an average false positive rate of 0.51% for more than two dozen state labs.

Although the numbers might seem like a modest improvement, when applied to 4 million newborns screened in the U.S. each year, it means just 960 babies would receive false positive results using the software, compared with 20,400 babies when it’s not used. Studies have shown similar results in Sweden, Italy and California.

Not only is the software more likely to catch borderline cases and to save parents unnecessary worry, fewer re-screenings of false alarms means lower costs for testing materials and staff time.

At the November meeting, Rinaldo also explained a newer element of the software that weighs factors known to affect test results — for example, birth weight and a baby’s age in hours when blood is collected.

At six labs, the software was able to reduce false positives by 55% in screening for congenital hypothyroidism, one of the most common disorders, which affects about 1 in 2,000 children.

The approach helps rid newborn screening of such heavy reliance on cutoffs, which Rinaldo called an “artificial line in the sand” at the meeting. He declined to comment for this article.

After Rinaldo’s presentation, committee members and other leaders in newborn screening weighed in.

Bob Currier, who works for the California state lab, lauded Rinaldo’s work, saying it’s a big improvement over how screening for congenital hypothyroidism is currently done.

Because of its poor performance, the existing test would be “laughed off the stage” if it were proposed now, Currier said. Yet it continues to be used in most states, including Wisconsin and California.

Matern said he doesn’t know why more state labs aren’t using the software, but he hopes they will.

“You want to make sure everyone is treated the same and you want them to get the best treatment, not just OK treatment,” he said. “That’s what I want to achieve: It doesn’t matter where you are born, you will be picked up. And if you aren’t affected, you will be left alone.”

Different sides of the cutoff

Each morning, Eli Wade takes a small, whitish pill from his mom or dad and pops it into his mouth. He’s 4½ and has been on the medicine since he was six weeks old.

That’s when a doctor in Michigan determined Eli’s thyroid wasn’t working properly. He was diagnosed with congenital hypothyroidism — the most common, preventable cause of intellectual disability — and was started on hormones the next day. The doctor didn’t want to take any chances because thyroid hormone is crucial to a baby’s brain development and growth.

Eli’s older brother, Micah, takes a small, whitish pill every morning, too.

Micah is almost 8, but his dad has to crush his pill. He wets his finger, scoops powder from the pill crusher and wipes it on the inside of the little boy’s cheek. If Micah is grouchy, he might bite. It’s one of the few ways he can communicate.

Eli is a chatty and active 4-year-old. Micah can’t speak.

Micah doesn’t have a fully functioning thyroid either. But that wasn’t discovered until he was 2½ years old.

Thyroid hormone is crucial in the first three years of life, affecting almost every cell in the body. A healthy thyroid gland at the base of the neck pumps hormones throughout the body, helping a young child’s brain, bones, nerves and organs develop.

Before Micah was diagnosed, doctors told his parents not to worry about his delays. As the boy became more obviously impaired — unable to speak words he once knew — the doctors thought he might have autism.

His little brother was on the lucky side of the numbers used by Michigan’s state lab.

On Eli’s first test, he was flagged for congenital hypothyroidism. The test evaluates something called thyroid stimulating hormone. TSH is produced by the pituitary gland and tells the thyroid gland to make and release thyroid hormones into the blood.

AL LASSEN / FOR THE MILWAUKEE JOURNAL SENTINEL
Micah Wade, 7, covers his ears to avoid hearing the TV in his room.

FAMILY PHOTO
Micah Wade uses a book with laminated pictures to communicate at his home in Kalamazoo, Mich. Almost 8, Micah doesn’t speak. When he was born, Micah was slightly below the cutoff used in Michigan to detect congenital hypothyroidism, a disorder where the body produces an inadequate amount of thyroid hormone.

Eli’s TSH level was 35. His pediatrician was alerted that the baby’s hormone levels were slightly above the cutoff of 33 used in Michigan in 2012.

Three years earlier, Micah’s test results from the Michigan state lab simply read: *Normal*. In fact, his TSH level of 30 was close to his little brother’s, but slightly below the cutoff of 33.

If Micah had been born 50 miles away in Indiana — cutoff 25 — or across state lines in Ohio — cutoff 22 — his results would have been flagged as abnormal.

Micah communicates mostly by patting pictures in a laminated book he carries or by grabbing someone’s hand to show them what he wants: crackers, milk, a toy.

“He’s pretty much lost what his life could be,” said his mom, Jessica Wade.

There are different ways to screen for congenital hypothyroidism. The Journal Sentinel compared states that use the same methodology as Michigan.

Kansas and Colorado have a cutoff of 20 when measuring TSH. Wisconsin and Connecticut are at 30. Some states adjust their cutoff for babies after a certain age, since TSH levels drop considerably after the first 24 to 48 hours of life. Other states don’t adjust cutoffs.

“I have to admit, it bothers me,” said Thomas Foley, a pediatric endocrinologist from Pittsburgh who helped develop the first screening test for congenital hypothyroidism using TSH in the mid-1970s.

“I really don’t know why there isn’t uniformity,” he said.

Missed opportunities

Mel’s dad hates driving by the condo where they lived when Mel got sick. It’s just a few miles up the road from their new house in Brookfield, so he sees it a lot.

“It was such a nice condo,” he said.

He doesn’t like to look at pictures taken in the condo either.

That’s where they lived soon after Mel was born — a very happy time. It had taken years for Nicole to get pregnant. The couple had been together since they were teenagers. They met at the Wisconsin State Fair when Nicole was 15 and Melbourne was 16. They waited 10 years to get married.

“We’re planners,” Nicole said. “We always knew we wanted to have four kids.”

“TWO kids,” her husband joked.

Melbourne Russell IV was the first grandchild on both sides. His sister Elise was born a year and a half later.

Elise was five days old when the Russells learned her first newborn screening results were abnormal.

Dr. Grunske immediately referred them to a geneticist at Children’s Hospital of Wisconsin. Elise’s second blood sample was taken and sent to the state lab in Madison.

Elise was nine days old when the state lab called Dr. Grunske and told her Elise’s second test was abnormal. It was a Friday. According to her notes, Dr. Grunske talked with a geneticist at Children’s Hospital: The baby had another appointment on Tuesday. She could wait to be seen.

No one called the Russells.

That Sunday, Mel couldn’t hold his sippy cup.

His parents still wonder: *If they’d been told about Elise on Friday, could someone have caught Mel before it was too late? Since propionic acidemia is inherited, would doctors have asked about Mel?*

“Everybody failed us.” Nicole said.

That included Dr. Grunske.

The Russells felt she should have told them about Mel’s elevated C3/C2 ratio when he was born. *Maybe we could have done something*, they thought.

“We needed to know, and let us make that decision,” Nicole said. “To think that I wouldn’t want to know that about my child is absurd.”

Then there was Mel's vomiting. The constipation. The weight loss.

During the trial, Mel's lawyer made the case that his pediatrician should have done more.

In fact, she did, her lawyer argued.

Dr. Grunske referred Mel to a pediatric gastroenterology clinic run by Children's Hospital in New Berlin. There, he was seen multiple times by a nurse practitioner and once by a doctor.

But no one figured out what was wrong with Mel until it was too late.

The Russells say they weren't looking to blame someone. What happened to Mel just didn't make sense.

After finding out how narrowly he was missed by the lab's cutoffs, Nicole contacted the state advisory committee to make sure the same thing didn't happen to another baby. She was included in one of the meetings by conference call while the committee talked about fixing the problem.

Mel's dad said they were glad when they heard the cutoff would be lowered.

"What happened with Mel already happened, and there's nothing we could do to change it," he said.

"I also think there is anger, too," Nicole added quickly. "There were so many kids before Mel. Everyone knew this was possible and they didn't change the system before this happened with Melbourne.

"I still think they are going to miss kids," she said. "Not just in Wisconsin."

The Russells found a lawyer through a parents' group for kids with metabolic disorders. Hehmeyer declined to take Mel's case three times since you can't really sue a state lab.

But Nicole pushed. As he vetted the case, Hehmeyer talked to other pediatricians. Some said they would have handled Mel's results differently. They would have asked about the elevated ratio.

That left Dr. Grunske.

"It felt like something we needed to do for our boy," Nicole said. "When Melbourne is older, we want him to know we did everything we could."

The verdict

It took the jury about four hours to decide whether Dr. Grunske was to blame.

Mel's parents had been waiting in the hallway as the jury deliberated. Lawyers for both sides stuck close to the courtroom in case the judge needed their input on questions sent down from the jury room.

Then came this question: If Dr. Grunske wasn't at fault, did they need to sort out monetary damages?

No.

Hehmeyer wasn't going to make Mel's parents wait any longer.

He came into the hallway through the double wooden doors of the courtroom.

"We lost," he said. "I'm sorry."

Mel's parents stood in silence. They walked across the black and white marble floor and sat on a long wooden bench. Mel's dad put his arm around his wife's lower back.

"I wanted to go home," Nicole said. She didn't want to see the jury.

A few minutes later, everyone in the hall was motioned into the courtroom. The jury came in and the judge read the verdict.

Dr. Grunske's face turned red. She dabbed her eyes with a tissue. Mel's parents sat expressionless. When it was over, Dr. Grunske walked over and shook their hands.

"We don't hate her," Nicole said later.

The Russells went home to Brookfield and tried to take a nap. Neither could sleep.

They picked up the kids early from school.

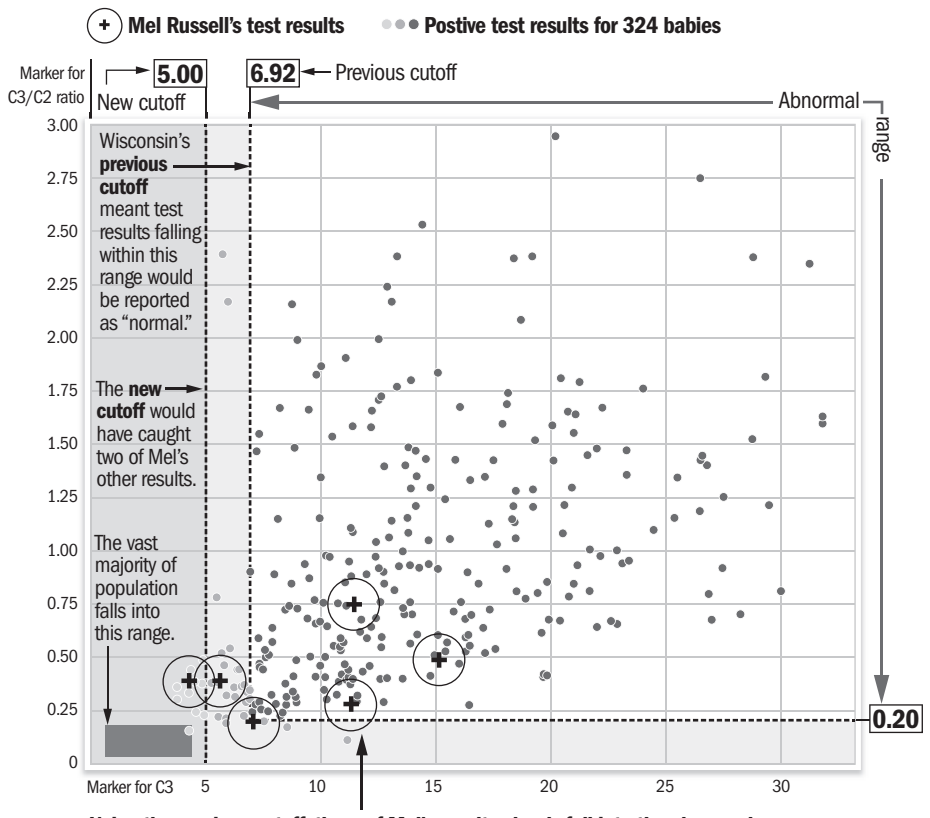
"It was really hard seeing Melbourne," Nicole said. "I remember just squeezing him and trying not to cry. I didn't want him to see it."

Nicole cried. Mel didn't notice.

A better way

A database of true-positive cases can help labs better predict which babies have a genetic disorder, without relying so much on cutoffs. The database, which started in 2004, contains test results for babies from participating states and countries worldwide. When Mel Russell's results are plotted using the database's software, it's obvious he falls among 324 babies diagnosed with propionic acidemia.

Mel Russell's Wisconsin State Lab results for propionic acidemia compared with 324 babies diagnosed with the disorder



Using the previous cutoff, three of Mel's results clearly fall into the abnormal range, one is borderline and two are normal. Using the new cutoff, five of Mel's results qualify as abnormal, with one normal.

Sources: Region 4 Stork (R4S), Journal Sentinel reporting

Journal Sentinel