The Newborn Screening Story

How One Simple Test Changed Lives, Science, and Health in America

APHL

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Association of Public Health Laboratories

Acknowledgments

In 2012, APHL convened a panel of laboratory, public health, healthcare, advocacy, and newborn screening experts to share their lessons learned and stories of the past 50 years. Participants included:

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Dedication

Like birth itself, newborn screening is an everyday occurrence that can never be taken for granted. When we encounter the birth experience directly, most often at hospitals, we feel a moment of admiring wonder at the people in health-care who handle these momentous events day in and day out. We're not as likely to see the heroism of the researcher, the laboratory scientist, the person who handles the paperwork, the courier, the metabolic specialist, the policymaker—or of the parent caring for a child with a rare condition. But their commitment and skills are vital to babies' lives and health. The pioneers of newborn screening understood this, and the ones who today work continually to improve the system carry that understanding forward. This book is dedicated to all of these heroes.

"Newborn screening creates a passion that drives people to put in much more than 40 hours a week. You can see the impact of your work immediately."

Harry Hannon, PhD, chief emeritus,
Newborn Screening and Molecular Biology Branch, CDC

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"The incredible dedication of the people in public health shines in the newborn screening lab."

Scott Becker, Executive Director, APHL

Photo courtesy of Mila Becker

Foreword

By Scott J. Becker, MS
Executive Director,
Association of Public Health Laboratories

Although 2013 marks a celebration of 50 years of newborn screening, the program itself has often been a quiet enterprise, happening behind the scenes. It saves or improves the lives of more than 12,000 babies each year, but mention it to most, even to many of those in healthcare, and you're still likely to be met with confusion or lots of questions.

The enormous good that newborn screening has brought America's families makes this relative obscurity surprising, but through my personal experience, I can understand why such a powerful program has gone unsung.

In fact, once when I tried to explain the importance of newborn screening, the audience fell asleep. Another time, the audience started to cry. It was the spring of 2001, and my audience was my firstborn, a baby girl.

To the surprise of the hospital staff, I followed her screening process avidly, from the heel prick to the results—fortunately, clear. That's how I learned that when it comes to newborn screening, understanding what actually happens behind the scenes is the key to appreciating its value.

This book and APHL's 50th Anniversary of Newborn Screening campaign bring the realities of newborn screening to center stage. You'll encounter the people who make a difference in babies' lives, from the nurses who take such care over every sample to the parents who are pushing, not only for the benefit of their own children, but for children into the future.

Of course, closest to me are the contributions of public health laboratories, which analyze 97 percent of our country's newborn screening tests. The incredible dedication of the people in public health shines in the newborn screening lab. Because the effects of some of the conditions screened for can begin to do damage within such a short time frame, lab scientists feel compelled to maintain a swift, unbroken chain of testing and relaying results back to follow-up personnel, hospitals, specialists, or parents. But we also see that people at all points in the system are continually innovating and exploring to find ways to improve this system—and help more people.

We in public health laboratories don't usually proclaim these accomplishments. But we're changing our ways this year—and it's for an important reason. We want parents to make sure their babies get screened and to take follow-up action if tests are positive.

So we have been making our point loud and clear: with stories on our blog and newborn screening website, through social media, through exhibits and open houses at public health labs around the country, at professional conferences and at events in Washington, DC. We even put the message up on a jumbotron in New York City's Times Square: *50 years of saving babies' lives!* This time, no one is falling asleep.

The smiles of my daughters are to this day the light of my life. It is my privilege to help put the spotlight on those who play a role in ensuring other parents have the same happiness.

Maren is just one of the more than 12,000 babies each year in the United States whose lives are saved or improved through newborn screening.

Photos courtesy of Honey Stecken

Introduction

From the moment Maren Stecken was born, she was in danger of irreversible brain damage or death—and no one knew it.

Born in February 2012 in South Fork, Colorado, Maren was full term and an easy delivery. She ate, slept, and made all the right noises. The doctors and nurses agreed: she was beautiful, strong, and healthy.

Like nearly every one of the 4 million babies baby born in the United States every year in hospitals, birthing centers, and homes, Maren had her heel pricked about 24 to 48 hours after being born. Five drops of her blood were pressed onto a piece of filter paper about the size of an index card. Her card was one of hundreds sent from the hospital to the Colorado public health laboratory that day for newborn screening.

All the time, inside the infant's body, acids and toxins were slowly building up to dangerous levels, putting her at risk of brain damage or death. Maren had been born without an essential enzyme that could break down proteins. Every kind of food, including breast milk, can become like a poison to babies with such metabolic disorders.

Maren's mother, Honey, brought her new baby home and settled her in with her father, her 6-year-old brother, and her grandmother. Friends and relatives agreed: Maren was beautiful, strong, and healthy.

Hours of expert testing

Meanwhile, about 250 miles away at the state lab, the piece of paper with Maren's blood sample was cut into small discs and put through a complex system of chemical combinations and exacting equipment, to test for 35 different conditions, as Colorado law has determined. Over the next several days, the tiny blood samples were broken down to the molecular level, with reactions observed, measured, compared. Experts trained in the precise protocol for testing took a look, and more experts checked their conclusions.

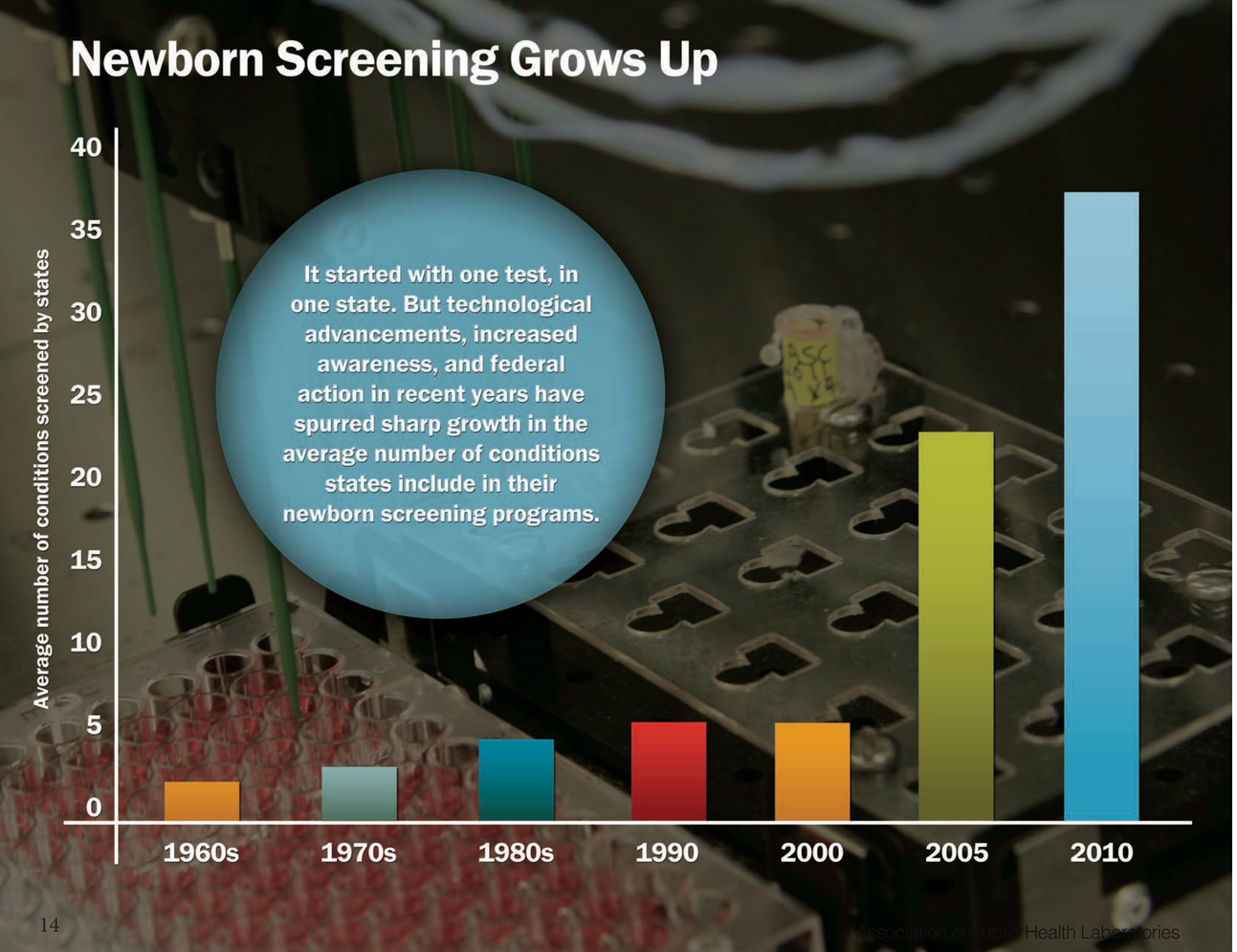
Back in South Fork, on Sunday not quite two weeks after the birth, Honey took Maren and her son to a friend's birthday party. As 6-year-olds played and celebrated all around them, Honey got a call. It was a local doctor, but one she didn't know. He'd been asked to contact her by a geneticist in Denver. Some numbers on Maren's newborn screening were higher than normal. Could she bring Maren to the children's hospital in Denver?

The newborn screening had picked up evidence of a rare condition, propionic acidemia. The screen helped catch it in time. With treatment and a special diet, Maren could live—even thrive.

Expanding success story

Maren is just one of the more than 12,000 babies each year in the United States whose lives are saved or improved through newborn screening. She is part of what the Centers for Disease Control and Prevention have called one of the greatest public health achievements of the 20th century—and a public health success story that is expanding in the 21st century.

In the early 1960s, researchers, pediatricians, nurses, and parents greeted with excitement and hope the news that a new test had just been developed to detect an "invisible" condition. It could screen for phenylketonuria, or PKU, which had caused countless deaths and cases of severe intellectual disability. And the test had promise in finding even more conditions.



That promise is being fulfilled. Today, most states screen for at least 27 of the 31 conditions recommended by the federal government, and many screen for about 50 conditions in all. On the recommended list are metabolic disorders such as PKU and propionic acidemia. There's also congenital hypothyroidism, found in about 1 in 3,000 babies; catch and treat it within three months of birth and prevent a lifetime of intellectual disability. And sickle cell disorder: early use of antibiotics can prevent frightening health consequences. One of the latest to be added to the list is SCID, which many know as "bubble-boy disease." An early stem cell transplant can actually cure this. Also on the list is a simple, noninvasive hearing test—because managing hearing loss early can make it easier for a child to learn to talk. Cost, while relatively low, is not a barrier: Every baby receives screening. Depending on the state, a combination of insurance, hospital support, and state and federal funding keeps the programs going.

Who invented that first test? Who discovered these conditions, and their treatments? How can the lab be sure the results are correct? Who decides what tests are given? These are the kinds of questions parents and caretakers have—and these questions will be answered in this book.

But the scientists, healthcare professionals, and administrators who work in newborn screening know the most important question is always: How is the baby doing?

The first steps

Maren took her first steps two days before Christmas 2012. It didn't surprise her mother that she started walking early: "Even when I didn't know anything was wrong, I knew she was a fighter. She's very persistent, very inquisitive, and happy."

Most parents don't think twice about newborn screening. Many aren't even aware it's being done. The parents who do know well, they might sometimes feel they know a little too much about it.

This is why Honey Stecken and the others in this book shared their stories. As Honey wrote to APHL:

"The wonderful thing about my daughter's story is that there is no story. Because of newborn screening, we have not been a family in crisis, but instead, we have been a family empowered with knowledge.

Now, whenever I see a pregnant woman, I stop and take a quick moment to say, 'Make sure you ask about your baby's newborn screening. It saves lives. It saved my daughter.'"

Maren Stecken

Dr. Robert Guthrie: *The Father of Newborn Screening*

Photo courtesy of the Museum of disABILITY History

Chapter 1
Origins

"It began with our second child, John," wrote Robert Guthrie, in a medical journal article about the breakthrough he developed that has saved hundreds of thousands of lives.

"He is mentally retarded. John stimulated me to go into research aimed at preventing mental retardation and developmental disabilities."

More often than not, the big discoveries, the world-changing ideas, come back to the actions of individuals with a certain driving combination of outsider perspective and deeply personal mission. Guthrie, considered the "father of newborn screening," has a secure place among those rare individuals.

Bob—as he preferred to be called—a PhD, MD and father of six, had the kind of wide-ranging scientific mind that today might have had him developing software, giving TED talks, and being called an "outlier." He called himself a hillbilly.

Born in the Ozarks in 1916, the son of a traveling salesman, and raised in Minneapolis, he never lost a sort of raw practicality and determination bred in his culture and honed through the Depression, relates his biographer, Jean Holt Koch. But along with his down-to-earth nature, he had some big dreams—ones even he wasn't certain how to realize.

High school graduation found him in the bottom third of his class—so he went to night school to fill in the blanks in trigonometry and science. To attend college in Minneapolis, he was willing to sleep on an army cot on the landing of a rooming house, which was the best he could get for 75 cents a week. But he flunked anatomy because he cut classes to attend lectures on quantum mechanics. Was he going to be a doctor, an astronomer, or maybe a writer? He wasn't so sure.

What finally caught and focused his roving intellect was the universe of bacteria, or as he called it, "bugs." In a burst of energy and strategic shuffling of classes in his peripatetic academic career, he ended up earning six degrees in six years, including a medical degree and a PhD in bacteriology. He married and had children, but his career continued checkered: bouncing from the NIH to university work to the Sloan Kettering Institute (where he advocated using two therapies simultaneously

A Note on Terms

In some quoted historical material in this book, "mental retardation" and similar terminology are used. We understand that these terms are no longer appropriate, and we do not intend any stigmatization or endorsement through their use here. Such terms are used only when necessary for accurate citations.

Screening Begins in the States

As the effectiveness of the PKU test became known and advocates made the case, states around the nation began to institute mandatory newborn screening programs.

1963
Massachusetts
Oregon
Delaware*
Vermont*

1964
Louisiana
New Jersey
New York

1965
Alabama
Alaska
California
Colorado
Connecticut
Florida
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Maine
Maryland
Michigan
Minnesota
Missouri
Montana
New Hampshire
Ohio
Oklahoma
Pennsylvania
Rhode Island
South Carolina
Utah
West Virigina
Wisconsin

1966
Georgia
Kentucky
New Mexico
Texas
Virginia

1967
Arkansas
Nebraska
Nevada
North Dakota
Washington

1968
Tennessee

1973
South Dakota

1979
Arizona

1980
District of Columbia

1983
North Carolina
Wyoming

1985
Mississippi

* Sources vary on dates screening was established.
Therrell, B., & Adams, J. (2007). Newborn screening in North America.

in leukemia treatment; radical then, it's now standard). He was known for working around the clock and sleeping wherever was convenient at a hospital or lab.

By 1954, he and his family had settled near Buffalo, New York, where he researched childhood leukemia. The Guthries were finally settling down. Yet their son John's development was a constant source of concern.

Lab full of kitchen tools

With John, the Guthrie family entered into a "diagnostic odyssey," the sort that parents of children with rare conditions know too well. Access to specialists and his father's own specialized knowledge made no difference—the cause of John's intellectual disability was never determined.

But one of these specialists, Robert Warner, MD, of the Children's Rehabilitation Center, would pose the challenge that led to Guthrie's greatest achievement. In seeking help for his son, Guthrie had become a parent-advocate. One of his many activities was acting as local chapter head of the National Association for Retarded Children (NARC, later called The Arc). He invited Warner to speak to the group, and the two hit it off, talking research over coffee and keeping in touch on new developments.

During one of these discussions, Warner told Guthrie about a metabolic disorder, PKU, which caused thousands of cases of intellectual disability each year. The damage resulted from an inability to process phenylalanine, an amino acid, and could begin just hours after birth.

Researchers had recently discovered that a special diet could help abate the damage, but patients' blood levels of phenylalanine needed to be constantly monitored. Warner was having a hard time with that—the only blood test available was expensive and complicated. Could Guthrie come up with something safer, simpler, and better?

PKU wasn't the cause of Johnny's disability, but Guthrie was immediately taken by the puzzle. He told Warner he would "use bugs to cure mental retardation."

With the help of Ada Susi, a nurse who had become his chief technician, Guthrie began working on the problem. For a while in his cancer research, Guthrie had been using filter-paper discs on agar, a gel used in labs to culture bacteria. If bacteria grew, it meant the sample on the paper held a compound the bacteria "liked." Guthrie had been doing research with a certain substance that stopped bacterial growth. But phenylalanine was like kryptonite to this substance; it disabled it and let the bacteria flourish. If phenylalanine was in the sample being tested, he reasoned, it would knock out the substance and the bacteria would grow. Phenylalanine presence would be obvious, quickly.

In his lab, to the surprise of many visitors, he used a simple office hole punch to make the discs, and kitchen glassware for agar trays. Using filter-paper discs soaked in serum from PKU patients, he developed a simple, accurate test within three days.

Around this time, bad news hit his family again—his 15-month-old niece, Margaret, had become suddenly, severely developmentally delayed. The cause was PKU—discovered too late.

Couldn't every child be tested sooner, routinely, to avoid what happened to Margaret? Guthrie wanted to develop a test that would give every baby a fighting chance. "I knew that routine infant screening for PKU would be impossible if serum was required, but I thought that the test might work with whole blood," he wrote.

"I found that this was so. I then realized that a simple way to collect discs of whole blood from an infant was to stick the heel and blot the emerging drops of blood with filter paper." The paper then was punched into discs that went into lab dishes. Within hours, a technician could see results.

Righting Wrongs

Changing Attitudes About Disability

Newborn screening for PKU was an innovation at the right place and time to gain widespread acceptance.

In the 1950s and 1960s, American families brought intellectual disability into the open.

A small group of parents in 1953 started the National Association for Retarded Children, now called The Arc, which quickly grew and established local chapters. The group's narrative of its history vividly portrays the attitudes of that time:

"[L]ittle was known about the condition of intellectual disabilities (at the time referred to as 'mental retardation') or its causes. There were virtually no programs and activities in communities … Emboldened by their collective desire to raise their children in the home and their stubborn refusal to accept that institutionalization was the only option, The Arc's founders fought even harder. Like every parent of any child, they wanted more for their children."

But it took a particularly visible family of advocates to change the popular perspective on both the prevention of intellectual disability and on the need for full participation of people with disabilities in American life.

The cover of the September 22, 1962 *Saturday Evening Post* headlined an article by Eunice Kennedy Shriver, "Hope for Retarded Children." The president's sister wrote: "Like diabetes, deafness, polio, or any other misfortune, mental retardation can happen in any family. … And yet, as I have learned, we are just coming out of the dark ages in our handling of this serious national problem. … In this era of atom-splitting and wonder drugs and technological advance, it is still widely assumed that the future for the mentally retarded is hopeless."

She reminded readers nationwide that Nobel- and Pulitzer-prize winning novelist Pearl S. Buck had written movingly about her own daughter, who was disabled by PKU. And she told of her work with Johns Hopkins' Dr. Robert Cooke, who himself had two children with intellectual disability and who led research that would benefit newborn screening and families for years to come.

Eunice Kennedy Shriver, of course, became famed for founding the Special Olympics program. But she was also a founder of the National Institute of Child Health and Human Development at NIH, a critical group in newborn screening.

One factor that won President Kennedy's support for this new institute was the PKU story presented to the nation in *Life* magazine in 1962. Two sisters, Sheila and Kammy McGrath, both had PKU—but Sheila, the oldest, was intellectually disabled because the condition had not been caught in time. Kammy, on a special diet from infancy, was developing typically.

Like the stories of many parent advocates who worked for more research, more services, and more justice, the McGraths' story was as sad as it was inspiring—and it produced extraordinary changes not only in healthcare but in society.

"Like every parent of any child, they wanted more for their children."

The Arc

"It was a very simple idea, like inventing a safety pin, but it made possible the testing of every newborn baby before leaving the maternity hospital," Guthrie said in 1990.

In 2013, more than 50 years after his discovery, lab scientists still use blood drops on filter paper for newborn screening tests. Carefully protected and tracked information about each baby is on a card attached to the filter paper. In every step of the process, everyone involved has the same goal Guthrie did: get results fast, safely, for every infant.

A race begins

The simplicity and safety of the "Guthrie cards" was groundbreaking, and those in the health system and public health were quick to realize that. Could the blood-spot cards be used to test for other conditions? Even as Guthrie and other researchers pursued that path, they knew they still had babies to save from the effects of PKU. They also had to put the new test on trial in a real-world mass screening to determine if it could deliver on its tremendous promise. And they had to get the word out—both to get participants in the mass testing trial and to speed the adoption of testing.

Public health programs, arguably, always share a sense of urgency. After all, if a preventive measure, treatment, or solution can bring health and survival benefits to all, one can't do anything less than bring it to the greatest number of people as quickly as possible. At the same time, there must be certainty that it will bring benefits. For as much confidence as Guthrie and his colleagues had, the tests still had to complete scientific trials. Guthrie determined that if 400,000 tests revealed 40 PKU cases, it would show the test was working. It would match up to what was understood to be the PKU prevalence at that time.

The federal government, in the person of Arthur Lesser, MD, head of the Maternal and Child Health Division, came up with funding; the March of Dimes was another early backer. Guthrie set up a "factory" in a cottage near Buffalo Children's Hospital. The tests and materials were packaged and printed at a sheltered workshop for adults with mental disabilities. Each kit came with a label from NARC reading: "Retarded children can be helped."

"Our goal was to package the test so that everything would be 'instant,' like instant coffee," Guthrie wrote. "In that way the laboratories testing for PKU would not have to employ trained bacteriologists but could easily mix the ingredients and perform the test with existing personnel." He and his colleagues also ran four-day training programs, hosting some in Buffalo and traveling to teach others.

An early and enthusiastic advocate was Robert MacCready, MD, Massachusetts state laboratory director. Offered 10,000 tests as part of the trial, he upped the ante: Every newborn in his state would be tested, he declared. He went to Buffalo to learn personally from Guthrie how to perform the test. Every time MacCready's testers found a PKU case and were able to avert damage, he would promote the good news to the press. Before long, every hospital in his state wanted in on the testing program.

"The object was to identify each and every baby with PKU—as soon as you could, so you could start them on the diet within the first few days of life," Harvey Levy, MD, of Boston Children's Hospital, who created a medical history of newborn screening, told a writer for the hospital.

By 1963, Massachusetts became the first state to pass a law requiring newborn screening—marking the program's official birthday.

'Seat of our pants'

Like his father, Guthrie said, he became a "traveling salesman," touting his test far and wide. As a result, Oregon became the second state to legislate screening, largely because Guthrie happened to sit on a plane next to Oregon's state child health manager.

"The state lab director at the time, Gat Brandon, took a look at the test kit and said: 'This is the most Rube Goldberg-looking contraption I've ever seen. It ain't got a chance in hell of working.

All Hands on Deck

In the pioneer days of newborn screening, Bob Guthrie used every community contact he had to help get his test out there. Guthrie's biography, *The PKU Story,* tells of how his program coordinator, Sally Bloom, had been a volunteer with the National Society for Jewish Women—donating her time to the cause until Guthrie noted her enthusiasm and strategic thinking. She remembered: "Bob can stand in front of an auditorium full of people, wearing a hand-me-down suit and one red sock and one blue one, and in two minutes have everyone in the palm of his hand."

Bloom's volunteer brigade as well as students doing community service prepared test kits, logged results, and even punched out blood specimens from test cards. New York's newspapers reported on the efforts, bringing more attention. It wasn't laboratory work as practiced today, but it fostered wider understanding of the newborn screening process and established the importance of education and transparency.

But we'll give it a try,' " remembers Neil Buist, MD, consultant to the Oregon health department, metabolic specialist, and university professor. "He discovered that it did indeed work well."

Buist, who among other recognition has an annual award in his name given by the Society for Metabolic Diseases, recounts how Guthrie's test development touched off a period of fast and furious research. "We were really flying by the seat of our pants. Bill Murphey came to Oregon then, and he had been working in the lab with Guthrie in Buffalo as a senior assistant for years and was very hot on newborn screening. He said, 'I've got several other ideas for testing. Let's just do 'em.'"

Basing its work on Guthrie's model, the Oregon team started trying out other screening tests Guthrie's lab had developed for other conditions, such as galactosemia and tyrosinemia—both of which can be fatal if untreated. They offered to do screening for other states and even internationally. Oregon's Northwest Regional Newborn Screening Program is still the largest in terms of geographic range in the nation, testing more than 170,000 newborns each year for six states, including Alaska and Hawaii, and the Navajo nation on the border of Arizona and New Mexico.

"We were like the British Empire for a while," Buist jokes, "because the sun never set on our newborn screening."

Dramatic saves, national notice

The workmanlike approach that followed from Guthrie's lead served newborn screening well for the early years. Scientists and physicians in states around the country took the reins. In Maryland, microbiologist and laboratory director Joe Joseph helped establish the public health lab in that state as an early nexus for newborn screening. If a lab capacity, test, or technique didn't exist, scientists, doctors, nurses, and hospital workers would create one. And often, if medical journals or the medical community wouldn't listen, Guthrie would go to the local newspapers.

The stories of dramatic benefits from blocking PKU damage grabbed the attention of the public—and of politicians. R. Rodney Howell, MD, now professor of Pediatrics and Chairman Emeritus at the Miller School of Medicine of the University of Miami in Florida, witnessed this new energy: "It was what most people consider the most remarkable time, in the early 1960s, after Kennedy had been elected. He was keenly interested in the subject because of his sister Rosemary."

Howell was working in metabolism (today called biochemical genetics) at Duke and NIH. He was tapped to come to Johns Hopkins as the Joseph Kennedy Scholar under a program instituted by that family's foundation and led by Robert Cooke, MD, himself the father of two children with intellectual disability (and who had devised one of the first tests for cystic fibrosis).

"At that time young people would come to our clinic, and we had nothing we could do for them," Howell remembers. "There was tremendous excitement—we'd known about this condition since 1934, and now it seemed we'd got something that would really benefit people."

The clinic was helping alleviate PKU through diet, but screening held the promise of prevention. To Howell, as to those in Oregon, the test appeared so "crude" that he wondered if it would work. But he also believed that simplicity would allow mass screening. By the late 1960s, he was helping the state of Maryland establish a program.

As screening advanced, questions remained, however. Guthrie had not published a peer-reviewed study of his work by 1963; this and other uncertainties meant the American Academy of Pediatrics and the American Medical Association did not yet support universal newborn screening for PKU. Was mandating screening tantamount to legislating medical practice? That was the concern for some states. Another was the difficulty of getting good follow-up treatment, including making sure parents knew what to do. However, groups such as The Arc and the March of Dimes pushed for mandatory screening.

By the early 1970s, individual states had added screening for more conditions. In Guthrie's lab, Michael Garrick, PhD, was creating a test for sickle cell anemia using the dried-blood spots. Other tests were developed for conditions ranging from maple syrup urine disease to congenital adrenal hyperplasia. But the next major leap in newborn screening came with a test for the devastating condition of congenital hypothyroidism.

The next target

An endocrine disorder that can lead to severe intellectual and physical disabilities after the first three months of life, congenital hypothyroidism is caused by the lack of the thyroid hormone. But treatment is simple and relatively inexpensive: a few drops of medication once a day. As with PKU, the key to preventing damage is early detection.

In Canada in the early 1970s, Jean Dussault, MD, went to work on the disorder and had a fortuitous circumstance. He wrote:

What is PKU?

Phenylketonuria is a metabolic disorder that affects body chemistry—people born with it can't process a part of protein called phenylalanine, which is in most foods.

About 1 baby in 19,000 is born with PKU in the United States each year. These babies appear normal for the first few months of life, but as the unprocessed protein builds up in their bloodstream, brain damage results.

With newborn screening for PKU, babies can be put on a special diet or formula, and this damage can be avoided. A person with PKU may have to stay on the special diet for life.

Since the institution of newborn screening for PKU in 1963, many adults with the condition have experienced healthy lives and have children of their own.

"The laboratory space allotted to us was situated near the provincial laboratory of the Quebec Network for Genetic Medicine, which was screening for phenylketonuria and tyrosinemia using filter paper blood samples. Why not T4!"

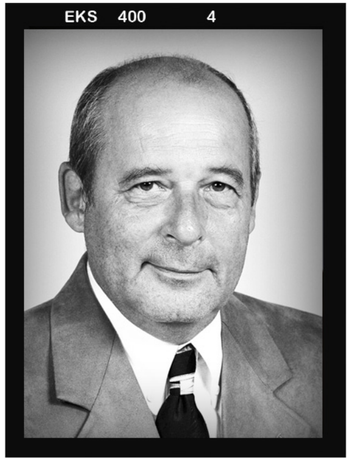
Checking the levels of the T4 hormone via filter-paper samples, Dussault discovered in 1973, could reveal congenital hypothyroidism. In 1975, William Murphey, PhD, in Oregon, began working on a mass screening program built on his work.

The March of Dimes and The Kroc Foundation funded further study in the United States with Delbert A. Fisher, MD, a pediatrician and endocrinologist who led a committee on screening as well as researching ways to implement the testing on a wide scale. By 1976, states were beginning to institute congenital hypothyroidism screening.

Although details on how and when congenital hypothyroidism screening is best done continue to be researched and improved, all states had added the test by 2000. About 1 in 3,000 babies annually in the United States are found to have congenital hypothyroidism.

Dussault, who died in 2003, was given among many other honors the Robert Guthrie Award from the International Society for Neonatal Screening. Despite the demands caused by his research, he remained a working physician, continuing to see and stay in touch with patients over the years. His colleague, Jack Puymirat, MD, remembered him at a memorial: "Jean remained a modest man. He always declined to apply for a patent for the neonatal blood test for congenital hypothyroidism that he developed because he considered his discovery as being a part of the public domain. In remembering Jean Dussault, we should focus on his personal example as a physician-scientist who could be intellectually rigorous and highly productive, while at the same time most compassionate and gentle in his manner towards all."

Congenital hypothyroidism screening is regarded as a clear success story, just as much as PKU screening is. Yet congenital hypothyroidism screening wrought change in the overall newborn screening system as well. Congenital hypothyroidism tests were radioimmunoassays (RIAs)—tests that use radioactive materials to measure a property in the blood, such as hormone levels in this case. RIAs are robust, inexpensive, and highly sensitive, but because they require using radioactive materials, they need to be done in regulated laboratories.



Dr. Jean Dussault

Combined with the increase in the number of tests being sought by states and parents, this use of radioactive materials meant that Guthrie's simple test had evolved into a system that could never again rely on just kitchen tools or volunteers. Newborn screening would require a sophisticated environment of support: professional-level skills, training, equipment, and leadership. The health system would rise to the challenge.

Speedy Solutions

Increasing Automation in Screening Processes

Because time is of the essence in newborn screening, innovators have made efficiency a priority. At a conference in 1975, a pair of these innovators met, with results that would benefit newborn screening for years to come.

An inventor, Robert Phillips, had invited several in the field to see a demonstration of his new automated device, the Punch Index Machine, which could punch four holes in the filter paper used in the screening test, holes that were the right size and number needed for consistent, quality testing. At the demonstration was Bob Guthrie, and also Bradford Therrell, an environmental chemist who had begun working in newborn screening. Phillips and Therrell realized they had the same birth date—and also had in common the drive to improve screening.

The Phillips Power Punch makes the correct size holes for specimen testing and helps keep lab work consistent.

"This machine really opened up newborn screening to become much more automated and cost effective," Therrell writes, allowing screening programs to add more conditions and speeding up a labor-intensive task. "As luck would have it, about the same time that the Phillips' Punch Indexers were becoming popular and programs were expanding … microcomputers were being developed." Therrell applied the benefits of automation and computerization and later, advances in robotics, to the Texas newborn screening lab to cope with the massive volume of screening duties there, making it one of the first labs to automate systems.

Therrell also went on to launch the National Newborn Screening and Genetics Resource Center and its database, in 1999. Phillips, just before his death, in 2010, was developing the Phillips Power Punch, suited for DNA testing. His family has donated to public health labs these last working models.

"There was tremendous excitement—we'd known about this condition since 1934, and now it seemed we'd got something that would really benefit people."

R. Rodney Howell, MD, professor of pediatrics and chairman emeritus, Miller School of Medicine of the University of Miami

Milestones

1934

Ivar Asbjørn Følling

discovers method for detecting PKU

1949

Linus Pauling, PhD

is first to study sickle cell anemia at molecular level

1953

Horst Bickle, MD

determines dietary changes can prevent PKU damage

James D. Watson and Francis Crick

model double-helix DNA structure

1961

Robert Guthrie, PhD, MD

creates first simple, inexpensive newborn screen, for PKU

1963

Mary Efron, MD

helps develop mass screening methods for amino acid disorders with lab at Massachusetts General Hospital

1972

Sickle Cell Anemia Control Act

funds sickle cell disease research centers and clinics

1973

Jean Dussault, MD

develops screening method for congenital hypothyroidism

Michael D. Garrick, PhD

develops screening for sickle cell and hemoglobin disorders

1976

Genetic Diseases Act and Medical Device Amendments

promise funding and reliable devices for newborn screening

1977

Songya Pang, MD and Maria New, MD

develop screening for CAH

1978

CDC and Harry Hannon, PhD

launch Newborn Screening Quality Assurance Program

Genetics Services Branch

created by U.S. Maternal and Child Health Bureau; helps lead coordination and outreach

1981

Thalassemia Initiative

developed by MCH to help find babies at risk

1982

Colorado

is first to screen for cystic fibrosis

1983

Council of Regional Networks for Genetic Services

established by MCHB to unite programs and resources

1984

Barry Wolf, MD, PhD

and lab at Henry Ford Hospital develop screen for biotinidase deficiency

1988

International Society for Neonatal Screening

forms to bring together experts worldwide

1989

Francis S. Collins, MD, PhD

isolates cystic fibrosis gene

National Human Genome Research Institute

established to map human genome

1990

David Millington, PhD

develops idea to use tandem mass spectrometry (MS/MS) in newborn screening

1993

Donald Chace, PhD

further develops MS/MS for newborn screening, along with Edwin Naylor, PhD

National Institutes of Health

recommends newborn screening for hearing disorders

1998

Michele Lloyd-Puryear, MD, PhD

serves on American Academy of Pediatrics Newborn Screening Task Force setting 10-year plan for improvement

1999

Bradford Therrell, PhD

helps establish National Newborn Screening and Genetics Resource Center

2000

Children's Health Care Act

funds advances in newborn screening system

2003

R. Rodney Howell, MD

helps steer Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC), bringing together experts and parents to improve newborn screening

2005

American College of Medical Genetics

determines Recommended Uniform Screening Panel, a list of conditions for which all states should screen

2005

SACHDNC endorses the Recommended Uniform Screening Panel of 29 conditions

2008

Newborn Screening Saves Lives Act

establishes grants for follow-up care and public education

Genetic Information Nondiscrimination Act

protects against discrimination because of differences in DNA

2010

SACHDNC

recommends adding SCID to universal screening panel

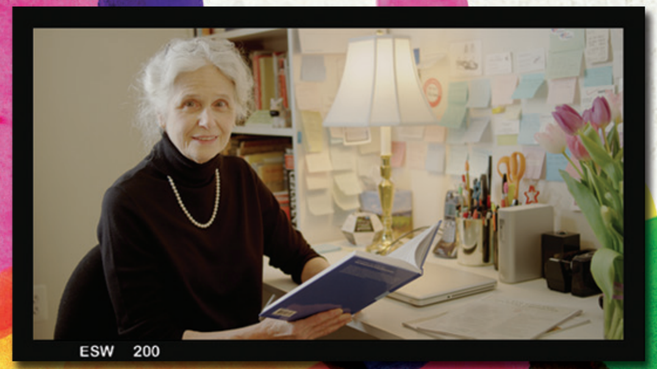
2012

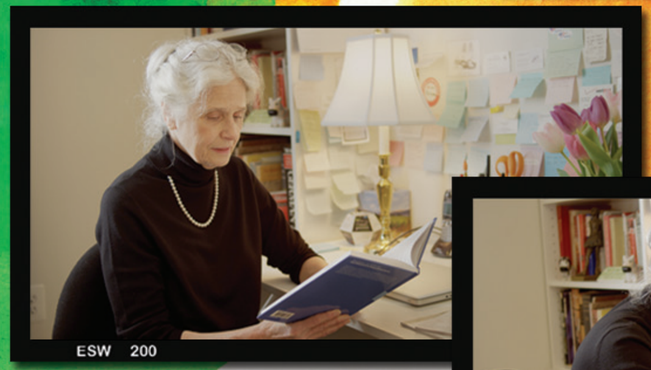
CCHD

or chronic congenital heart disease added to RUSP

"Whenever one part of the healthcare system changes, we need to look at what else will be affected. I just don't want my babies in danger."

Susan Panny, MD, American Academy of Pediatrics chapter champion for newborn hearing screening





Photos courtesy of Daryl Pittman

Chapter 2

Health

The pediatrician had been in the same situation herself, exhausted and working an all-night shift, so she knew what to say. "I want you to stand up. You have to get up and walk around," she told the neonatologist. "If you're not on your feet you won't hear what I'm telling you."

It was 1 a.m. and Susan Panny, MD, pediatrician and then-medical director of the Maryland newborn screening program, was calling a hospital about a baby in trouble. One of her specimens had tested extremely high, far above range, for isovaleric acidemia, a type of metabolic disorder that can be deadly for newborns.

The hospital needed to rush the baby to Johns Hopkins hospital, about 100 miles away, where a metabolic specialist could see the baby immediately. It was urgent, she stressed. Then she made calls to specialists and others needed to get the baby proper care. Then she called the hospital again.

The hospital hadn't yet moved the baby to Hopkins. They had attempted to begin treatment themselves in the neonatal intensive care unit. The hospital didn't realize it, but Panny knew the baby needed a definitive diagnostic workup from specialists to get the correct treatment. The baby had to go to Hopkins immediately, she said.

She continued to call the hospital until she knew the baby was headed to Hopkins. And then she checked in with Hopkins regularly.

Simple test, complex system

Today, healthcare practitioners know that if just one piece of the newborn screening system isn't functioning optimally, the results can be disastrous. But in the early days, few perceived newborn screening as a system at all. Ownership, roles, and responsibilities were not clearly defined.

With the Sickle Cell Anemia Control Act in 1972, doctors and labs began to frame newborn screening as a system. In the 1980s, more participants—including public health agencies, hospitals, pediatricians, and specialists—began to coordinate efforts.

"Newborn screening is simple to do, but it's definitely not a simple issue," says Judi Tuerck, RN, MS, and currently a consultant, who led newborn screening follow-up for 25 years for the multi-state program based in Oregon.

"When I became involved in newborn screening, in the late 1970s, there was no follow-up…no way to know if the baby had actually gotten on treatment." She created, with Neil Buist, the first practitioner manual—the template for most manuals today—with

algorithms for follow-up, which tracked specimens and infants from the hospitals to labs to treatment.

"Today, virtually every state has a robust follow-up program," Tuerck says, as well as an ongoing education program for doctors and nurses in the community and for parent education.

Buist among others credits Tuerck with developing these education programs: "She got the idea that newborn screening is not just a lab activity, and what we need is a full circle."

A major move forward came in 1985 with the creation of the Council of Regional Networks for Genetic Services (CORN) to establish systems for newborn screening and get them to work well. One of CORN's first actions was to define newborn screening as a multi-part system—comprised of screening, follow-up, diagnosis, treatment or management, and evaluation—and publish guidelines. Later, education was added to this framework.

Fifteen years later, the American Academy of Pediatrics' landmark "Blueprint for the Future" report delivered the same message: "The newborn screening program's efficiency and effectiveness depends on the smooth integration of sample collection, laboratory testing, follow-up, diagnosis, timely treatment, and tracking of outcomes."

And here's how one parent describes the importance of every single part of a well-functioning newborn screening system:

"Alena was exactly one week old, and her diagnosis of galactosemia was caught just in time. I shudder at the thought of what could have happened had I not read the brochure, had the lab not been working that Thanksgiving weekend, had the physician from the Oregon Metabolic Clinic not tried everything to reach us, had our pediatrician not had the guts to tell us about her feeling that something was wrong…"

Every step mattered in 2003 in Oregon when Beate Weiss-Krull was leaving the hospital with her new daughter, Alena. She happened to see a brochure about newborn screening, and asked a nurse about it. The nurse checked her chart and saw that Alena's screening had somehow not been done. Alena had her heel pricked on the way out of the hospital. Her screening revealed that she had galactosemia, which can cause disability or death within a few weeks if not treated.

Today, Weiss-Krull writes a blog about her family, including sharing recipes for children on special diets, ones her healthy daughters, Alena and Mia Rose, who also has galactosemia, enjoy. But stories of near-misses like this give all involved in the system the impetus to keep improving it.

Power of persistence

Generally, the system works like this: the public health lab sees unusual results on a screen and contacts the state follow-up program, where specially trained nurses contact the hospital where the baby was born or the pediatrician, using phone, fax, or mail, depending on urgency. Many pediatricians or even hospital doctors may never have dealt with some of these extremely rare conditions, so the follow-up nurses begin to line up specialists, support, and treatment as well. Screening results aren't the final word; diagnostic tests still have to be done to determine whether a baby truly has the condition. For the follow-up healthcare workers, it takes careful training to convey the right amount of urgency without causing undue anxiety or an unnecessary treatment.

Something as simple as the rise in the use of cell phones can put babies in jeopardy, says Kathleen Moline, a nurse who runs the follow-up program for the Virginia state health department. "Numbers change a lot, and people screen unknown phone numbers. We're figuring out how to make sure the

Alena and Mia Rose Weiss-Krull

Sam and Grace Williams

Callie Zenda

Their stories are all different, but each child's health today rested on reliable newborn screening and coordinated follow-up.

Photos courtesy of families

mother recognizes that the call is important and knows to answer," Moline says.

Follow-up teams have helped get care to migrant farmworker families, homeless families, families who speak languages other than English, and families with multiple last names. They've connected with families who have given incorrect phone numbers and addresses, as well as families who won't answer the phone.

It takes persistence to get through to families experiencing the sleep deprivation and chaos that comes with a newborn—and whose babies may look perfectly healthy. Even a pediatrician can't see these conditions—only a lab test can detect them. Betsie Zenda, of Ohio, remembers the day she and her daughter Callie returned from a well-baby pediatrician visit where she'd been told everything was fine.

But when she walked into her home, she had five voice mails from an unfamiliar number. It was a hospital doctor saying, with increasing urgency, that her newborn's screening results indicated a problem. It was PKU.

In the hospital after Callie's birth, "the nurses and doctors didn't really explain much about the screening, and even told me I probably wouldn't have to worry about it after we left the hospital," Zenda says. Immediately after receiving the news, she called her pediatrician, who "didn't have a lot more answers than the hospital doctor, but she had a plan. A portion of her residency happened to be with a geneticist."

Within a half-hour, Zenda and her baby had an appointment with a specialist.

Reactions like "Why isn't my own doctor calling?" and "How could a hospital not know?" are common. There's always room to improve the system, and significant efforts are being made to do so. Many hospitals use checklists to ensure every step is followed correctly. Some systems also informally provide checklists to parents, so they'll know what's happening.

Clearing up misperceptions

Despite these efforts, the full story of newborn screening hasn't reached everyone. Newborn screening leaders still report hospitals and pediatricians calling the screen "the PKU test," when it is so much more, or obstetricians who don't talk about newborn screening at all.

Natasha Bonhomme, vice president of strategic development at Genetic Alliance, a consumer education organization, points to just one of the misconceptions it clears up on a regular basis: "People get prenatal genetic testing and newborn screening confused all the time," she says. "To most, newborn screening is just a piece in the continuum of care. Our challenge is getting this information out so that people have time to absorb it."

So education about newborn screening has become a priority in the past decade. In 1999, the Health Resource and Services Administration funded the National Newborn Screening and Genetics Resource Center to launch its website with information for healthcare professionals and families.

More outreach opportunities came with passage of the Newborn Screening Saves Lives Act. In 2009, with funding from the Maternal and Child Health Bureau, Genetic Alliance launched its Baby's First Test website, which has grown into an interactive online program that reaches out to parents and professionals alike and is relied on as a strong information source.

For professionals, APHL is launching an interactive website and data repository in conjunction with its Newborn Screening Technical assistance and Evaluation Program (NewSTEPs), to help harmonize programs across the system.

Even when questions are critical of the system, they need to be heard, Bonhomme says. "We try to bring all voices to the table."

State health departments, public health labs, and even test equipment manufacturers provide newborn screening information and education to hospitals, pediatricians, and nurses.

With 40 years of nursing experience, Virginia's

Drive-by Delivery?

Susan Panny, MD, started noticing a strange trend in 1991—more unacceptable newborn screening specimens arriving at the Maryland lab. The numbers rose until, by 1994, nearly a third of specimens weren't usable. Research and data revealed the problem: "They were sending mothers home from the hospital within 24 hours after a birth," she says, explaining that it may take at least 24 hours before an infant's blood shows evidence of some conditions.

In the 1990s, healthcare and insurance systems believed they could save money through shorter hospital stays. Media and advocates dubbed it "drive-by delivery."

Panny took her data to the state legislature. She was criticized by legislators and in the media in the long battle, but she won, with legislation that ensured a proper interval before screening.

"Whenever one part of the healthcare system changes, we need to look at what else will be affected," Panny says. "I'm happy to save money. I just don't want my babies in danger."

Moline knows well that getting the sample isn't as simple as it sounds. The baby's heel has to be warmed for a few minutes before the procedure. Filter paper has to be placed in a special area of the nursery to dry—never in a plastic bag. In the early days, Buist and Tuerck had to stop practitioners in small towns from putting specimens on radiators to dry out—heat can destroy a sample.

Since 2004, the rate of births occurring at home has risen nearly 30 percent in the United States. As home births become more common, and birthing centers with midwives more widely used, there has been more outreach and education to midwives. But special populations, such as people in rural areas and on tribal lands, have been wrapped into the system from the beginning. Amish communities, for instance, tend to have both home births and a higher incidence of some inherited conditions, so outreach to these families—and working with the lack of phones or cars—has been particularly important in several states.

Information and protection

Every filter-paper card used in newborn screening is accompanied by a form with the parents' contact information, a coding number to protect the baby's identity, and places to check off all information that could affect lab results, such as baby gestational age, weight, and height, which are essential to determining normal levels of some blood substances. Other questions include: "Is the baby on antibiotics?" "Has the baby had a transfusion?" These can change screening results.

In some states, labs share results with specialists and pediatricians simultaneously. It's part of the "enabling" role public health labs play, providing the bridge between the screening and the specialist. Furthermore, even in states where commercial labs do the actual screening, state health departments usually handle the follow-up that comes immediately afterwards.

> *"The system was totally broken, and no one seemed to understand the frustration from the pediatrician's point of view."*
>
> **Michele Lloyd-Puryear, MD, PhD**

Moline and her team regularly communicate with hospitals to shape system improvements. Virginia, like many states, is creating programs and processes that keep the newborn screening system healthy in the face of changes in healthcare, hospital administration, regulations, and insurance requirements.

One of these changes, according to Moline, is that some hospitals are hiring out pediatric care to specialist companies. This means that the doctor handling screening in the hospital won't be the same physician that the family would use in the community—and passing news of a positive result from one doctor to the next could use up time where there is little to spare, as well as increase the chances for follow-up to fall through the cracks.

Photo courtesy of Genetic Alliance

"Continuity of care is vital, and all physicians are concerned with this," Moline says.

And the system isn't complete until the family is connected to the right rare-condition specialist. In the early days of screening, Neil Buist used to fly to towns from Alaska to Idaho to get treatment started and counsel pediatricians. Even today, rural areas lack metabolic or hemoglobin disorder specialists, and families may need to travel great distances for treatment. Depending on the state, there are programs to help families find specialists and financial assistance.

Educating parents

One of the most dangerous and persistent problems in follow-up is the "no news is good news" assumption. Closing that gap, and getting pediatricians and parents to check on screening results, has been a recent focus in education.

Even being a nurse is no guarantee that a parent will have any kind of education in these rare conditions. Becca Williams is a labor and delivery nurse—and her husband is a nurse as well—yet they still had to look up the condition when they were told their tiny twins had tested

Are You Sure?

A false positive happens when a follow-up test to a positive screening confirms that a child does not have the condition. False positives can occur for many reasons: the test was performed too early, the baby did not eat enough, or the specimen was too small. False positives raise concern because they are thought to lead to parental anxiety and overuse of medical services.

Beth Tarini, MD, of the University of Michigan studies ways to improve communication between parents and providers within public health screening programs such as newborn screening. A recent study by her research team showed most children insured by Medicaid with false-positive newborn screening results did not log more healthcare visits than those with results showing no conditions.

But this is just the beginning of examining this issue. "To not screen because screening must result in false positives would put an end to any medical screening," wrote George Cunningham, MD, MPH, formerly California's chief of the genetics diseases branch, in *The Lancet* in 2005. Nevertheless, avoiding false positives is a big reason labs have so many quality controls.

Screening vs. Diagnosis

Newborn screening is just the first step in determining whether a baby has a condition. If a screening result is outside the typical range, diagnostic testing must be done to confirm the condition.

Some labs put newborn samples through two stages of screening for the same conditions, using different testing techniques, to narrow down or confirm results. But even this second-tier testing is still screening—not diagnosis.

Typically, the newborn screening program communicates newborn screening results that fall outside the typical range to a designated care provider—usually the pediatrician—who then talks with parents about what's next and orders further definitive testing as needed.

positive for PKU after their blood was taken in the intensive care unit.

"We thought having preemie twins was hard enough," Williams says. "I was so confused. No one in our family has PKU. No one has any kind of genetic disorder. How could our children have this? *It must be a mistake,* is what I kept thinking.

"The NICU ran the screen again, as is the protocol in a positive test," she says. "Once again, positive. We were immediately set up with the doctor and nurse practitioner from the PKU clinic."

In this case, the system worked—Sam and Grace are happy and healthy. Among their favorite foods: a special kind of pizza that works with their PKU treatment diet.

Behind the improvements

But the system hadn't always worked so well. When Michele Lloyd-Puryear, MD, PhD, found herself in tears on the phone with the District of Columbia health department, the pediatrician knew she had to do something to improve the newborn screening system.

It was 1997, and she was working with a largely poor, immigrant population. Newborn screening was critical for these babies, who, she knew from experience, might not have another doctor visit for a long time. As her offices were conducting a second round of screening, which is standard in a number of states, the District had suddenly cut off funding. Not only that, but she couldn't get information on the results from her first screening, because those had been done in the hospital by a different pediatrician.

"The system was completely broken, and no one seemed to understand the frustration from the pediatrician's point of view," Lloyd-Puryear says.

Lloyd-Puryear couldn't understand it. She'd recently been working with a mobile unit in New York City providing care for people who were homeless—and even under those circumstances, medical records and patient histories were downloaded nightly and available to doctors. Why not with newborn screening?

When she was brought on as chief of the Genetic Services Bureau at the federal Maternal and Child Health Bureau, she saw her chance: "I said hot damn, we're going to do something about this!" She insisted her co-worker, Marie Mann, MD, MPH, who also knew well the newborn screening system and challenges, become deputy. She wrote up a five-year plan, with newborn screening at the top of the list. Communication and uniformity were top priorities.

Today, Lloyd-Puryear is the first to say that she was naïve about how quickly things could change. But newborn screening pioneer Rodney Howell calls her "incredibly courageous."

What's next?

In late 1998, MCHB formed the Newborn Screening Task Force, with Lloyd-Puryear at the helm. Its "Blueprint for the Future" report is generally seen as shaping newborn screening into its next few decades—if not the next 50 years.

Convened by the American Academy of Pediatrics, with funding and direction from Health Resources and Services Administration (HRSA), MCHB, and the U.S. Department of Health and Human Services, the task force pulled together multiple major health agencies and organizations: NIH, the CDC, the Agency for Healthcare Research and Quality, Genetic Alliance, the Association of State and Territorial Health Officials, the Association of Maternal and Child Health Programs, and APHL.

Everyone in the system had a place at the table to develop common goals. "The public health community was ready," Lloyd-Puryear says. "They embraced what we were doing. Laboratorians were so protective of the newborns. They fought hard to get the systems approach.

"Connecting the labs to the chaos of the healthcare delivery system was the challenge," she says. She laughs about how in early meetings many had thought electronic health records—still a major challenge for healthcare—would make the process "a cinch." But, she says, "at least now there's the recognition of how important this is."

Even with the dramatic success and support of newborn screening programs, there would always be the question: What's next?

The Newborn Screening Saves Lives Act in 2008 fueled outreach, education, and coordinated follow-up. Several collaborations by Regional Genetics Groups are working to improve long-term quality of life for people with these conditions by connecting them to accessible care via their "medical home," or usual source of health services.

Today parents—and increasingly those whose conditions were caught by newborn screening who are now grown up and caring for themselves—are turning their focus to the long term. Newborn screening is just the beginning of their story.

Disorders and Conditions

Most conditions screened for in newborns are caused by a genetic mutation—any change that alters the instructions specified by the DNA. The disorders may be passed down through families or arise with no family history.

Endocrine disorders affect the body's glands that produce and release hormones. Hormones are chemicals that regulate normal growth and body functions. Babies with congenital hypothyroidism are missing their thyroid glands entirely or do not produce enough of a particular thyroid hormone.

Metabolic disorders affect the body's ability to use nutrients. For example, infants with PKU have difficulty breaking down the amino acid phenylalanine, which is in eggs, milk, meat, and other sources of protein.

Hematologic disorders—also called hemoglobin disorders or hemoglobinopathies—affect the body's ability to make hemoglobin, the part of red blood cells that carries oxygen.

Out of the Lab

Hospital Tests Catch Conditions

Sydney Mayer

Photo courtesy of the Mayer family

There's more to newborn screening than blood tests. Hearing and heart condition screens are now done in the hospitals by more and more states. Both take just a few minutes. The hearing test takes place within 24 hours of birth, while the heart screen takes place after a baby is 24 hours old.

The heart screen, or pulse ox test, measures how much oxygen is in the blood, thereby detecting a host of heart problems, including critical congenital heart disease (CCHD)—a frightening condition that can result in sudden death in a baby who a minute earlier looked perfectly fine.

Sydney was born in July 2012, in a hospital that had started doing the pulse ox test six months before. The test wasn't mandated by the state—the hospital had chosen to do it. Sydney's test indicated low oxygen levels in her body.

"Without this test, our baby appeared healthy, but little did we know that there was a silent killer on the inside," says Deanna Mayer, Sydney's mother. Subsequent tests showed the baby's heart was healthy, but doctors still needed to get her oxygen levels up to normal. Sydney was kept in special care for a week as she was slowly weaned off oxygen and began holding her own levels.

"The doctor informed us that if the test would not have been performed, we would have been sent home and everything could have been okay," says Sydney's mother. "However, there is that 1 percent chance we could have woken up to a blue baby. That's a chance I don't think most parents would be willing to take."

CCHD is the most common of all birth defects, occurring in about eight in every 1,000 live births. Its symptoms can include abnormal chambers, holes in the heart, or abnormal connections. CCHD's complications can be deadly—but if detected early, it's treatable. CCHD was added to the list of recommended tests for states in September 2011, and as of 2013, some states have added it to their panels.

The other in-hospital test, a hearing screen, isn't as urgent, but it makes sense to catch any hearing loss early. It can be a life-changer for a baby who may not have regular pediatrician visits. Early detection makes talking, learning, and adjusting to hearing devices easier.

The test uses either a tiny earphone or sensing electrodes. Sounds are played, and brain response is measured. The baby often sleeps through the test.

"That's a chance I don't think most parents would be willing to take."

Deanna Mayer, mother

Fears and Follow-up

“We Were the ‘Other Conditions’ ”

Damian Larks

After getting the call about her newborn son, Damian, Laura Larks couldn’t sleep—so she went online.

Her pediatrician had called that evening. It wasn’t definite, but Damian’s screen had come back positive for a rare condition known as 3MCC. The doctor asked several questions about how the baby was doing and trusted Larks’ judgment as the mother of six children. Damian could be kept at home that night, but he would need to come in the morning. Even though time always matters with these conditions, this kind of instruction to take it easy can sometimes be made, depending on lab results and the baby’s general health.

Photos courtesy of Larks family

At her computer, Larks recalled the newborn screening brochure Delaware gave to expectant parents. It listed “cystic fibrosis, sickle cell, and ‘other conditions.’ We were the ‘other conditions.’ ”

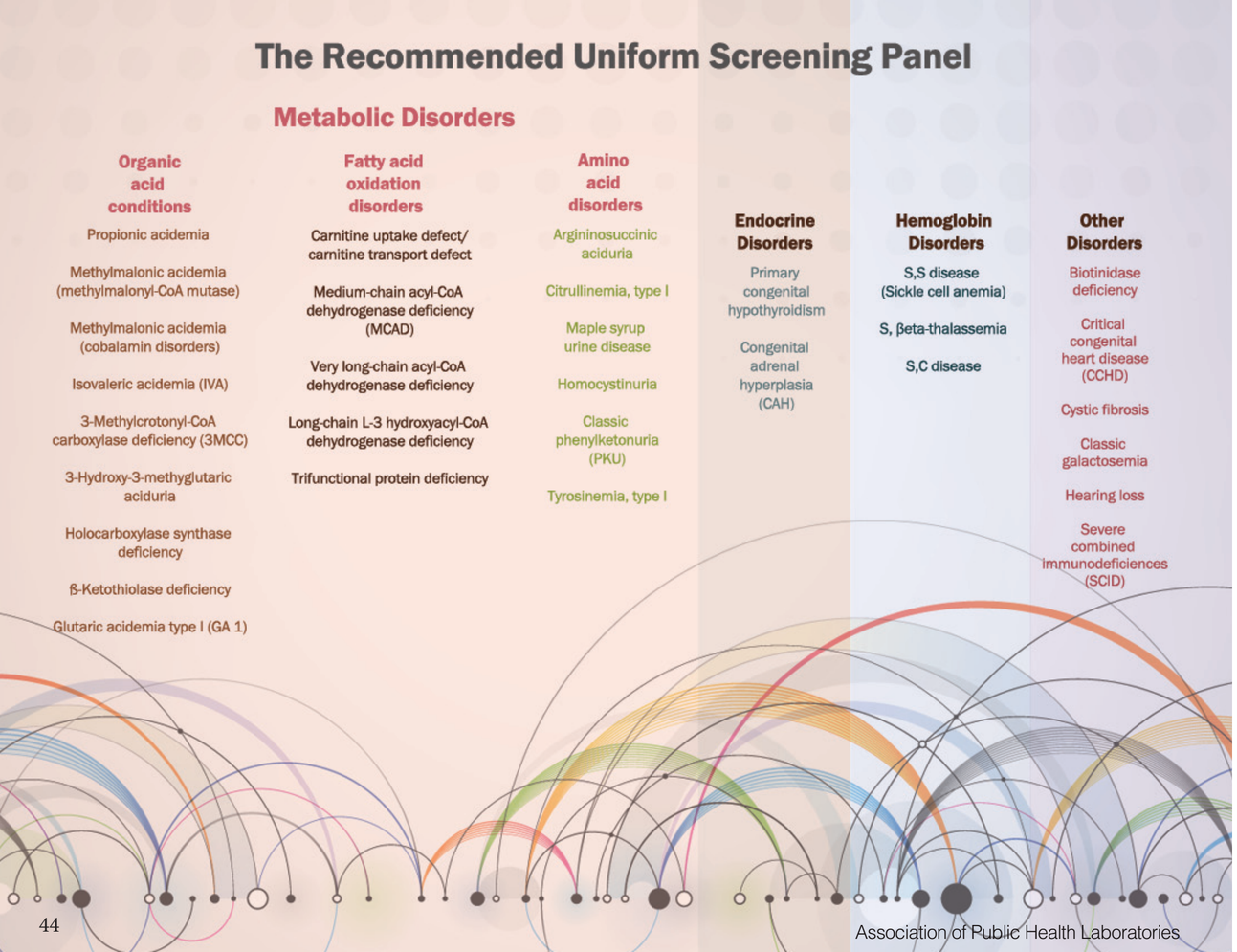
Investigating 3MCC, she says she found “horrible stories—children who had died or were blind. I was terrified.”

But the next morning, the pediatrician told her a different story. In many states, screening for 3MCC had only begun in 2006. The children she was reading about online had most likely experienced a health crisis. Because Damian’s condition had been caught early and because he could start treatment nearly immediately, he was unlikely to experience such severe effects.

Reassurance and helpful follow-up continued at all levels. Larks got to know the people at the state health laboratory, as well as chair of pediatrics for Christiana Care Health System, Louis Bartoshesky, MD, who would call or email her personally when she had questions about medical news or studies. “He went above and beyond,” she says.

As medical director of Delaware’s newborn screening program and the head of collaboration with Nemours A.I. DuPont Hospital for Children, where Damian was cared for, Bartoshesky brings together stakeholders from agencies and organizations as well as individuals working for improved newborn and children’s care.

These advocates now include Larks. She spoke at Delaware meetings on newborn screening, and today the brochure given to new parents includes 3MCC among its “other” conditions—and a photo of a healthy Damian.



Who Decides About Screening?

Group Gives Evolving, Essential Guidance

By the turn of this century, newborn screening lab technology had advanced to the point where more than 40 conditions could be detected from a single specimen.

Not every state or every healthcare system had moved that quickly. The reasons were many—differences in needs, resources, funding, capacities. But this uneven pace created a crisis in newborn screening. Among parents and advocates, the situation was clear: Where a baby was born could make a life-or-death difference. What were the essentials for which every state should screen?

While the federal government couldn't dictate testing policies to states, it could support a way to get guidance. The American College of Medical Genetics (ACMG) was charged by HRSA's Maternal and Child Health Bureau to come up with answers. The group pulled in experts from multiple disciplines and organizations, from March of Dimes President Jennifer Howse, MD, to longtime newborn screening scientists and physicians such as Harry Hannon and Bradford Therrell.

The ACMG's intensive review resulted in the Recommended Uniform Screening Panel, a list of conditions every state should include. The group also created a secondary panel, made up of conditions occasionally revealed as a result of screening that may or may not become a problem but about which the group felt parents should be informed.

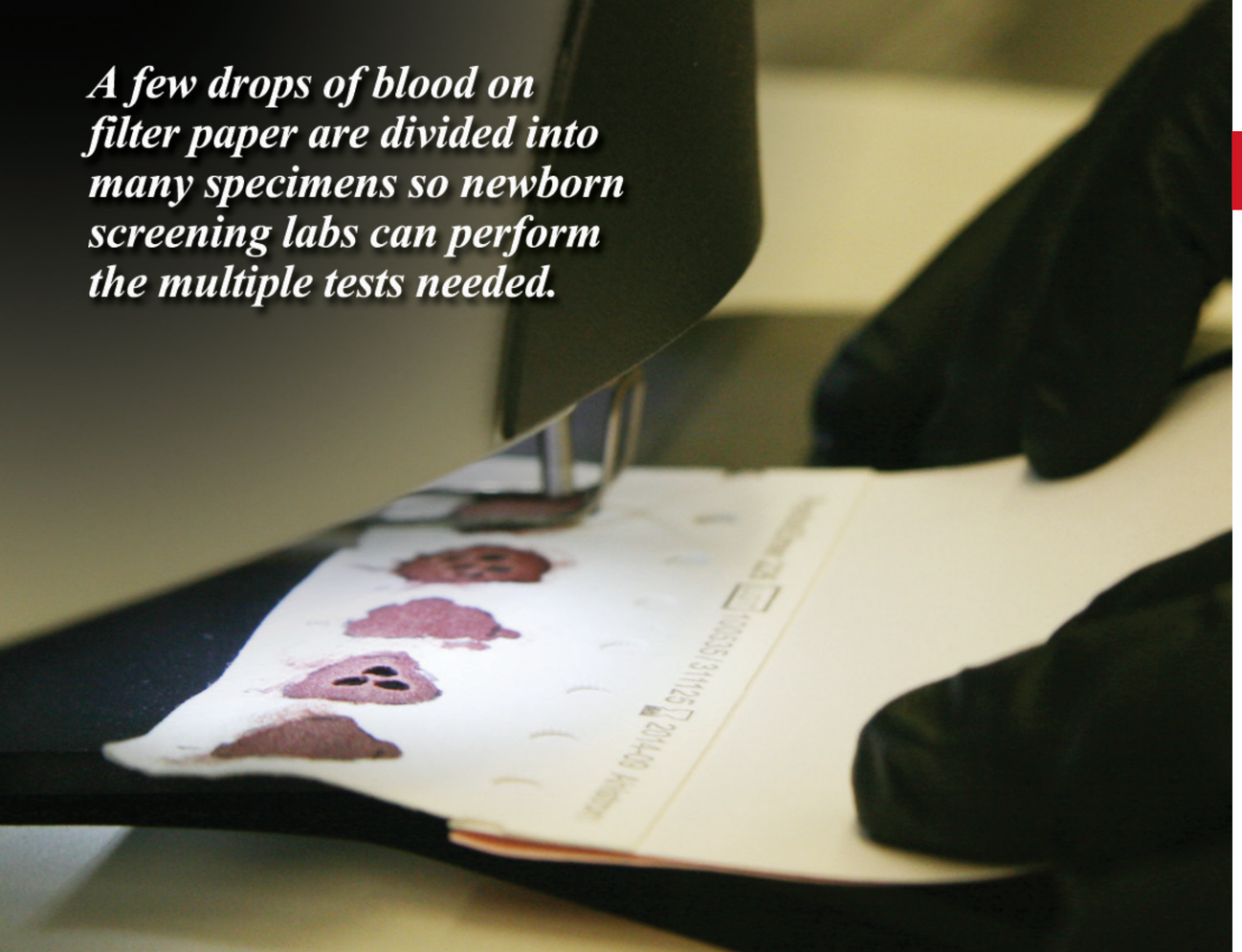
Next, HRSA formed the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC), which includes parent-advocate members as well as other experts from fields including medicine, bioethics, and law. The committee studied the list of conditions carefully and gave approval. It also developed a transparent, open way that people can propose conditions for the list and oversees that process today.

With the stakes so high, determining inclusion on the list is no simple matter. Both groups used as guidelines the Wilson-Jungner criteria, established by the World Health Organization in 1968 and considered the "gold standard" for screening. While a complete discussion of these standards can (and does) fill volumes, their essence informs newborn screening choices.

- It should be a well-defined condition—it's clear whether a baby has it or not.
- A good screening test must be available to all.
- Diagnostic confirmation of the screen result is possible—further testing will show whether the baby has the condition.
- Treatment in the early or pre-symptom period will lead to better outcomes.
- Screening will result in benefits to the baby.

The final point is usually the highest priority.

The committee also considers a few more factors when looking at recommendations. Are they evidence-based? Can state public health systems handle them? And an important point: Concerns about insurance, liability, or legislation should never be part of the decision.



A few drops of blood on filter paper are divided into many specimens so newborn screening labs can perform the multiple tests needed.

Chapter 3
Science

Scott Shone, PhD, fought to keep his car on the road in the strong winds as he headed home from the newborn screening lab, where he is program manager. It was about three hours before Hurricane Sandy would make landfall, and a New Jersey highway was not the best place to be. The governor had closed down all state offices, but a storm has never stopped a baby from being born.

So Shone and 18 other newborn screening lab staff had come to work anyway. They had already worked extra time on Saturday to get ahead in anticipation of what was shaping up to be a historically destructive storm.

UPS, which usually delivers specimens from hospitals, was also shut down that Monday—at least to the general public. For newborn screening, it made an exception. The lab workers quickly processed every specimen delivered and got tests started. At 2 p.m., Shone sent most of the workers home, and he and the few remaining followed a few hours later. From home, he put the emergency plans into place, arranging for the state Medical Coordination Centers and New Jersey State Police officers to transport samples from the hospitals to the lab.

On Tuesday morning, Shone and a few staff members who lived close to the department of health went into the lab and got back to work. By Wednesday, all but two staff members reported (one, 86 years old, was out of town with family; another was stranded without public transportation). But the mail notifications of test results had to go out, so staff took them to the post office and paid out of pocket to get more than 500 pieces of critical mail to pediatricians around the state.

"The laboratory took a minor hit when solar panels blew off our roof and smashed into the skylights in our atrium," Shone wrote to his lab colleagues nationwide after the storm. "Otherwise…the newborn screening laboratory remained 100 percent functional throughout the storm."

This is just one instance in years of newborn screening where labs powered through a crisis. After Hurricane Katrina, the flooded Louisiana public health lab near New Orleans rigged a converted mental health clinic with equipment from a local hardware store—and got help in newborn screening from neighboring states. Not only natural disasters but competing crises, such as salmonella epidemics and influenza pandemics, strain lab resources and make preparedness plans essential. Perhaps most dangerous of all are the human-created crises: Sudden cutbacks and furloughs from state budget problems also activate emergency measures. Newborn screening is an essential function with essential workers; timing and quality can never be compromised.

Where the job gets done

"These people go home every night, and they've got spots in front of their eyes," says Charles Brokopp, MPH, DrPH, director of the Wisconsin State Laboratory of Hygiene.

This kind of dedication under all conditions is the standard in public health laboratories around the country. The bulk of newborn screening work is done in labs that depend on sophisticated, minutely calibrated scientific equipment—and on people who can stuff envelopes quickly. They're places where reminders to wear protective gear are posted next to cute baby photos, where technicians with years of training can spend days doing the same tasks over and over, then suddenly swing into action to help prevent death or brain damage to an infant perhaps hundreds of miles away, whose name they may never know. And each day, the science behind what they do is being improved by researchers and laboratory equipment manufacturers worldwide.

Today, many routine medical tests are done in hospitals and doctors' offices, but the public health lab is the only place that can handle newborn screening. Only public health labs offer personnel with high-level training and experience, complex equipment, and the ability to process high-volume operations with attention to quality and privacy. Most important, the public health lab is charged to help protect all members of the public—and the point of newborn screening is to protect every baby.

State public health programs vary widely in structure and scope. Some labs work under a state health department; others are allied with university systems or hospitals. New York's state public health laboratory is the Wadsworth Center, a strongly research-focused laboratory, performing more than 11 million screens a year and doing cutting-edge work on new tests. The New England Newborn Screening Program is based at the University of Massachusetts and screens about 500 babies a day, getting specimens from Massachusetts, Maine, New Hampshire, Rhode Island, and Vermont.

Let's look at a typical day of newborn screening at Virginia's public health lab. Guiding the way is Wanda "Willie" Andrews, director of laboratory operations, who ran the newborn screening program there for 13 years.

First, she explains, the newborn screening "day" is actually 24 hours long, including sample collection. And in Virginia, it happens six days a week. Andrews changed the newborn screening lab to a Monday-through-Saturday schedule shortly after she started, which meant the state health department's follow-up nurse team as well as specialists and treatment centers had to go to six days, too. Through this and creating other lab efficiencies, she got reporting time on normal samples down to 24 hours.

"It was a big deal, but we were doing it for the right reasons," Andrews says. "A baby with maple syrup urine disease can crash in seven to 10 days."

Only about a month after instituting the six-day work week, the benefits were clear. When a congenital hypothyroidism screen done on a Saturday showed out-of-range numbers, the doctor and specialists were able to start treatment right away. The mother later sent a picture of her healthy child and a thank-you letter to the lab.

"When I got that letter, I said: 'This is why we do what we do,'" Andrews says.

A day in the life of a lab

Virginia's Division of Consolidated Laboratory Services, in Richmond, buzzes with activity. To streamline processes and cut costs, the commonwealth brought all of its public health-related laboratory functions together in 1972—the first lab in the nation to do so. Today the consolidated lab handles everything from routine cow's milk testing to West Nile Virus

to chemical hazards, performing more than 6 million tests a year.

These different types of testing don't happen in the same place or on the same equipment, however. The building houses several lab areas, with passage among them restricted by a card-key system and security guards.

Newborn screening has its own department—a general lab area, a mass spectrometry area, and an area for data processing. Photos of babies and cards and letters from parents adorn the walls and bulletin boards.

The newborn screening process begins while most people are still asleep. Couriers pick up samples at hospitals throughout Virginia, routing them through a spoke-and-hub system so that as many as possible arrive at the lab by 6:30 a.m. On a Tuesday, the lab's busiest day, more than 1,000 specimens will be tested.

Courier cars and trucks unload samples in Tyvek envelopes at the lab's secure loading dock. A conveyer belt delivers them to the data area, where 10 computer support personnel open the envelopes and collect the filter-paper cards with the dried-blood spot specimens and infant information forms. Samples from home births have been collected from a network of nurses and midwives. States develop different systems to ensure tests come in from Native American reservations and military bases.

Staff give each sample an identification number, entering data into the the laboratory information management system (LIMS). Premature babies' information and samples are separated for special treatment.

In the lab, specialized automated equipment punches out uniform-size discs from the filter papers. The paper discs are treated in different ways depending on the tests being done—as of this publication, Virginia runs dried-blood tests for 28 conditions. Many discs are placed into microtiter plates, which look like miniature muffin tins, filled with different types of reagents—chemicals that react with the sample and detect abnormalities.

Behind one set of secured doors, data workers are entering all essential information about each baby into the computer system. At the Virginia lab, two workers enter the same data to avoid errors.

Behind another set of secured doors, at different stations in the newborn screening lab, workers are running endocrine or hemoglobin tests, reviewing results, entering data, or re-running tests with abnormal patterns. Some tests are conducted using tandem mass spectrometry, which allows many tests to be run at the same time. Some samples are sent to the molecular lab for DNA-level testing.

If any testing instrument shows a critically abnormal result, the lab workers immediately call the state health department, where specially designated follow-up nurses contact pediatricians and specialists—and keep on calling until it's certain the baby will be taken care of. In Virginia, the nurse team tracks these babies until they are diagnosed, the test comes up negative, or the baby is 6 months old.

Results deemed abnormal but not critical are handled according to their urgency. Lab workers send results through to the data room as soon as tests are complete. There, printers crank out hundreds of form letters informing pediatricians of normal results and a few letters recommending further testing or treatment for less urgent conditions. As a backup to calls and faxes, letters confirming abnormal results are also sent to pediatricians.

A few staff members gather in a small room. Their fingers fly as they fold letters and stuff envelopes, all coded to get to the right pediatricians. Most of these results go out with the evening couriers.

Keeping up with change

Along with managing the everyday urgency of screening, Andrews is constantly dealing with the business of a lab. "Is this instrument getting old? Does it need replacement? Should we pull in a new instrument that can do a wider range of testing or is less hands-on?"

"When you're dealing with life-threatening conditions and rapid turnaround time in a high-volume lab, it's essential to have strong personnel who can multi-task efficiently," she says, adding that the lab also builds partnerships with other state and commercial labs for emergency backup.

Like many other labs, the Virginia lab is working toward more electronic information sharing. Despite progress—Andrews is ahead of the curve, having pushed IT processes from her earliest days—newborn screening labs must consider several factors before computerizing operations. Above all, they must protect confidentiality, both within the lab and among hospitals.

Then there are issues of how different computer systems communicate, what hospital systems can accommodate, and how pediatricians work. Meanwhile, obsolete technologies always need to be upgraded—at the time of writing, Andrews is working with a vendor to replace her lab's aging LIMS system.

Virginia is large and diverse: It includes remote rural areas and impoverished urban neighborhoods, horse-country estates and some of the wealthiest suburban counties in the nation. At every socioeconomic level, there's great diversity of language—Korean, Vietnamese, Spanish, Farsi, and more. Any electronic records system for newborn screening would need to work for all hospitals, in all areas.

Meanwhile, new conditions and tests are being considered for the newborn screening panel. As chair of Virginia's newborn screening subcommittee, Andrews works with pediatric specialists, parents, genetic counselors, and follow-up nurses to make recommendations on such changes.

Andrews must determine how many new employees to hire, whether the lab will need more space and equipment, and how it can all be done cost-efficiently. Qualified laboratorians need a high level of specialized training and experience, which is no easy task considering the field faces a looming labor shortage. As soon as SCID testing is approved in Virginia, the lab will have to start immediately so as not to risk missing a single case.

Despite what still remains to be done, Andrews points out the massive leaps in progress labs like hers have already made. For example, automation and IT have made testing much less labor-intensive. She can remember a time when testing media needed to be mixed by hand. Today, her lab has instruments with robotic arms and what are called "walk-away instruments—machines that can do in a minute what it takes humans hours to do," she says.

The quality factor

Just as many people don't realize how critical it is to keep newborn screening programs operating

"When you're dealing with rapid turnaround time in a high-volume lab, it's essential to have strong personnel who can multi-task efficiently."

Wanda "Willie" Andrews, director of laboratory operations, Virginia Division of Consolidated Laboratory Services

Data into Action

Newborn Screening Helps Researcher Improve Understanding of Sickle Cell Disease

A "side effect" of newborn screening is its ability to provide public health research information.

Melissa Creary, MPH, PhD(c), a health scientist with the Division of Blood Disorders at the CDC, is exploring collection of newborn screening data to improve knowledge and awareness of hemoglobinopathies—a group of blood disorders including sickle cell disease and thalassemia.

Creary was born with sickle cell, so she knows the challenges. "My life's passion is to raise awareness of the disease and to help increase quality of life for those who have it," Creary says. "I'm glad the CDC is now working to close the many public health gaps found with this disease."

In 2010, she helped launch the Registry and Surveillance System for Hemoglobinopathies (RuSH) in collaboration with the NIH National Heart, Lung and Blood Institute and seven pilot states. The pilot project collected state-specific, population-based data on sickle cell disease and thalassemia: how many people are living with these conditions, where they receive their medical care, the health problems they experience, and more. It may become the basis for a national system states can use to pinpoint where more education, awareness, treatment, and funding are needed.

"We wouldn't be able to collect that sort of data without newborn screening," Creary says.

"We want to get the word out about the seriousness of sickle cell and then provide the adequate understanding and follow-up. Part of the pull of this job for me was that I could give a voice to the voiceless."

Melissa Creary

under adverse conditions, many don't realize how exacting the standards for quality are. It's not simply about keeping the programs going, but keeping them impeccable. "What it comes down to is that every baby is important to us," says Michele Caggana, ScD, newborn screening director at New York's Wadsworth Center. The rules and guidelines reflect labs' awareness that human lives are in the balance.

But getting from Guthrie's ad hoc labs of the early 1960s to today's stage of multiple quality checks and careful controls took some doing, some vision, and some help from the U.S. Centers for Disease Control and Prevention.

"Newborn screening creates a passion that drives people to put in much more than 40 hours a week," says Harry Hannon, PhD, chief emeritus of the Newborn Screening and Molecular Biology Branch of the CDC, after a 42-year career with the agency. "You can see the impact of your work immediately."

Hannon went to work at the CDC in 1961, straight out of high school. He'd grown up just a few miles from the CDC's new Communicable Disease Center, had watched it being built, and was determined to work there. Newborn screening was barely established, much less developed as a career field. He started out prepping sewage samples for polio testing and worked his way through Georgia State as a lab technician. He left Georgia for grad school in Tennessee and was winding up postgraduate work at Oak Ridge National Laboratory when he decided to check back at the CDC for any job openings.

Within a few years, he had not just a job but a mission. In 1977, Bill Murphey, once at Guthrie's lab and now in Oregon, had asked the CDC for assistance. A newborn screening test for congenital hypothyroidism had been developed, and it required radioactive materials. Such mass screening would serve a pretty big public health need, his supervisor said. Could he help?

At the time, newborn screening was being done piecemeal, often in hospitals. Even the CDC was making its own screening materials. With more tests, and tests involving potentially hazardous materials, such ad hoc approaches could get dangerous.

Hannon, Murphey, and other leaders of that time huddled at the CDC and ended up setting the course for the next several decades of newborn screening: To help the most babies, there needed to be standards, guidance, and centralization.

Thus began the CDC and APHL quality assurance program for newborn screening, in 1978. Hannon started out with a lab staff of two

Help for Researchers

Researchers seeking to improve newborn screening or develop cures for conditions need data, specimens, and links to the latest discoveries. Because of the nature of newborn screening research, they also need ethical and regulatory guidance. The robust source for these resources is the Newborn Screening Translational Research Network and its Coordinating Center.

The Newborn Screening Saves Lives Act established the Hunter Kelly Newborn Screening Program, and the network's coordinating center is a key component. With funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development at NIH, the American College of Medical Genetics and Genomics developed the center. With Michael Watson, PhD, a longtime newborn screening expert who helped lead the development of the uniform screening panel, as principal investigator, the center provides resources ranging from webinars to opportunities for collaboration.

and two types of hormones to test. By 2013, the Newborn Screening Quality Assurance Program provided services to more than 85 U.S. newborn screening labs, 31 manufacturers, and more than 500 labs in 67 other countries.

It's a volunteer program but one that labs take seriously. It makes it possible to check every critical action of a newborn screening lab, its staff, and materials and equipment used. For instance, as part of one proficiency testing program, a specially coded dried-blood specimen might show up at a lab, which would then process it as usual. But this specimen is a test—and the CDC program knows the right answers. If the lab doesn't get it right, quality assurance gets involved immediately to help the lab.

One of the biggest innovations driven by Hannon was, as with Guthrie's invention, simple on its face—and it also involved a piece of paper. In the early 1980s, Hannon heard complaints from labs about the filter paper; uneven quality was leading to errors and the need to repeat tests. So he established a program manufacturers could voluntarily follow to get consistent quality. Today, filter paper is analyzed by the quality assurance program before distribution to labs.

Another advance was his leadership in establishing standards for sample collection—again, simple on its surface; prick the heel, blot the blood. But unless everyone is doing it the same way, with the same time restrictions and the same level of attention, the lab can't get accurate results. Getting consistent standards required cooperation from all parts of the medical system as well as the labs. The document Hannon wrote became a set of standards that resides in the Clinical and Laboratory Standards Institute. These standards have consequences; if a condition is missed and the standards weren't followed, the question of why may come up in court.

In 1979, the Conference on a National Model for Standardization of Neonatal Hypothyroid Screening Programs was held, in Atlanta. It was the seed for the later gatherings; realizing the expanding scope of newborn screening, Bradford Therrell in 1981 launched the National Symposium on Laboratory Aspects of Newborn Screening, which became the National Newborn Screening Symposia series. These meetings have in recent years brought together more than 400 leaders to share best practices and research. These conferences led not only to scientific advances, but to many of the changes in policy and legislation in the past several decades, changes that have saved more babies from death and disability. Hannon would play a role as one of the leaders addressing the discrepancies in newborn screening conditions tested for among the states.

MS/MS revolution

By 2000, developments in the lab would end up changing the entire newborn screening system. As early as 1990, at Duke University, David Millington, PhD, came up with the concept of using two mass spectrometry instruments to run multiple tests for multiple conditions at the same time. Researchers Don Chace and Ed Naylor ran with it, and the tandem mass spectrometry—MS/MS for scientists—paradigm shift had begun.

Still using the same dried-blood spot, a lab with the right equipment (albeit expensive equipment run by specially trained laboratorians) could screen for upwards of 30 conditions at a time. Advances in computing made it possible to make the data received meaningful (but this meant laboratorians needed IT skills and understanding). It even allowed testing for conditions that had before been impossible or extremely difficult to detect.

With every benefit came a challenge. What to screen for, how to keep up quality and accuracy, and how to pay for what promised to be not only a lifesaving technology, but eventually a money-saving one? Centralization and collaboration had come to the newborn screening environment just in time—labs needed to share progress more than ever before.

At the 50-year mark of newborn screening, a new challenge arises. Carla Cuthbert, PhD, FCCMG, FACMG, is chief of the Newborn Screening and Molecular Biology Branch at the CDC's Division of Laboratory Sciences. She emphasizes that her first role is to sustain and strengthen what's working—the strides made in quality so far. But preparation and planning for any new conditions added to the screening panel is an ongoing but always changing task. For instance, her group had been preparing for and supporting for some time the expansions in screening, including molecular testing capacities, demanded by the addition of SCID testing in many states.

Molecular testing, which uses DNA, can make people a little uneasy, Cuthbert says. However, she says, "it's really just like other testing, but evaluating another set of markers in the body."

Molecular testing also made state labs a little nervous, but for other reasons. Although many state labs have molecular testing capacity, most only use them for a small percentage of what is already a small percentage of out-of-range screens—for instance, to further test a screen that is out of range for cystic fibrosis, in order to discover how serious the variety of the condition might be. To suddenly vault into screening every sample through molecular techniques is daunting. But the CDC, in collaboration with APHL, is ready with training, resources, and assistance to ensure quality.

What gives scientists pause, after all, Cuthbert points out, is their concern for quality. "These are very committed scientists," she says. "When you look at a screen, you are immediately aware of how this could change that family's life."

"When you look at a screen, you are immediately aware of how this could change that family's life."

Carla Cuthbert, PhD,
CDC Newborn Screening Branch chief

The climate of quality, care, and collegiality among the public health laboratories provided a place to transform newborn screening from a simple test to a system of care for babies that would welcome more input from more people concerned with all aspects of maternal and infant health. The next phase would involve not only scientists, doctors, and laboratorians, but parents, legislators, economists, government agencies, educators, and communicators—a true public health enterprise.

Translating Labspeak

A Look at Newborn Screening Labs for Non-Scientists

With more than 29 lab-tested conditions on the roster, newborn screening can't be done in a single test. Instead, different types of tests are used, depending on the best technique to get the job done. Not all labs have capacity to do DNA-level screening, for example.

Much newborn screening equipment and materials are supplied by PerkinElmer Genetics, which also performs newborn screening analysis for several states that choose to use commercial lab services.

PerkinElmer's lab has analyzed more than 4.5 million newborn samples since 1994 and provides help and answers to researchers and parents alike. Here is a look at some of the types of testing done in the newborn screening lab:

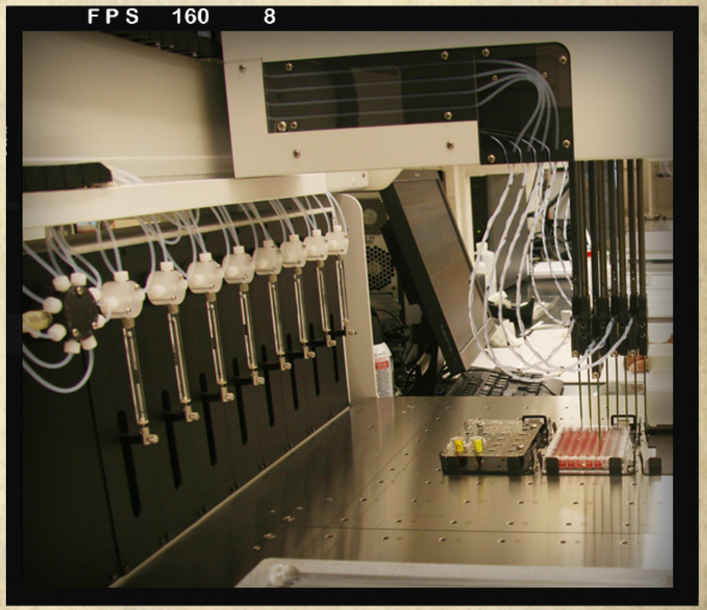
Biochemical analysis looks at levels of substances and enzymes in the body. It includes the kinds of procedures most non-scientists visualize when they think "laboratory"—test tubes, filter papers, and cultures, for instance. Today, it also involves much more, with many automated processes; it is considered "high-complexity" testing, with strict training and quality requirements. It is often used to detect biotinidase deficiency, CAH, and galactosemia. Accurate results depend on a good-quality sample.

Molecular technologies detect genetic mutations in DNA. In newborn screening, it's most often used as a second round when a biochemical test comes up with an abnormal result, or to pinpoint the type or severity of a condition. Labs use a process called polymerase chain reaction (PCR), often compared to a photocopying machine for DNA: Suspicious chunks of DNA are pulled out and artificially replicated thousands of times until there's enough material for lab equipment to analyze. With PCR, tests that once could take days can be done in minutes. Because it involves genetic material, training and safety precautions are vital.

Tandem mass spectrometry (MS/MS or "mass spec") is considered the revolutionizing test method in newborn screening, enabling a level of accuracy and speed that has made it possible to test for multiple conditions at once—and to test for some conditions, such as MCAD, that can't be detected any other way. In some ways, it's biochemical testing on steroids. Alcohol is added to the dried-blood specimen to "pull out" several hundred molecules for study. The mass spectrometer then weighs the molecules—determines their mass—and sorts them.

MS/MS is often compared to a change-sorting machine—after you've sorted the quarters from the dimes, it's easier to count up the stacks. If a certain molecule stacks up too high, it's an indication of a condition. The molecules then get sorted by a second MS, working in tandem with the first, separating them even more specifically—as you'd sort your Pennsylvania state quarters from your Massachusetts ones, for instance.

Obviously, this type of testing is highly specialized. It's now possible to determine when a high level of a chemical is most likely due to a condition or simply because a baby was premature, for instance. Or, say, a laboratory technician finds a sample with an elevated level of a chemical called C8. That can be a sign of either MCAD or MADD. But only MADD also causes an unusual level of a chemical called decanoylcarnitine. Tandem mass spectrometry tests for both, and more, pinpointing the condition.



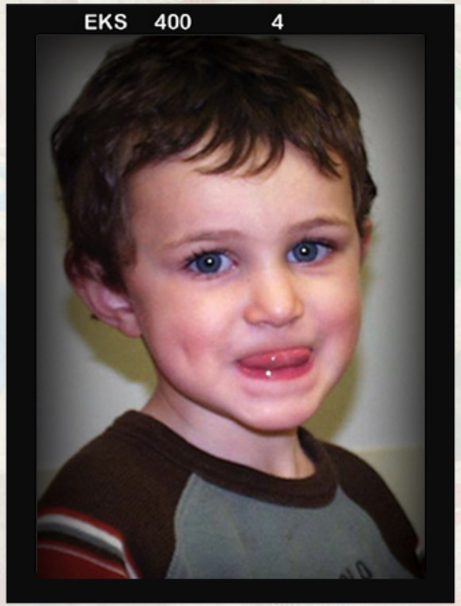
At the Virginia lab, equipment with robotics helps ensure efficiency and consistency.

Working for Survival

For Lab Staff, It's Personal

It didn't look like they could make the deadline. It was 2002, and the Iowa State Hygienic Laboratory was preparing to add biotinidase deficiency to its list of conditions for newborn screening. But adding a condition means more than pushing a button. If an instrument isn't calibrated perfectly, a technician not thoroughly trained, a follow-up specialist not ready to take new patients, the cost can be high—false positives causing undue anxiety; or worse, missing a case.

So the lab program manager told the staff it would have to delay adding the condition, just for a few weeks. Biotinidase deficiency can be deadly—but it is also very rare. The condition occurs in about 1 in 60,000 births. And in Iowa, where 40,000 babies are born each year, the likelihood of missing one positive in the few-week delay was very low.



Gage Blunt

Photo courtesy of Blunt family

But a longtime lab worker disagreed. She felt strongly the test should be added as planned, and she was prepared to do whatever it took, whatever other challenges arose, to keep it on schedule. She persuaded the manager, and together, they rallied the rest of the staff. The team put in extra hours and energy.

Gage Blunt was that one baby in 60,000. A single week after the new test was added, the lab detected biotinidase deficiency in his newborn screen. If the lab hadn't pushed to make the deadline, he would have been missed.

Biotinidase deficiency can cause seizures, breathing problems, hearing and vision loss, and extreme developmental delays. Vitamin B supplements, given early, can prevent damage.

"We were shocked when we received that call," says Gage's father, Shane Blunt. "I had no idea what the disease was or anything."

The family goes to the Iowa City lab periodically for tests to make sure Gage is developing normally. "He's an intelligent, vibrant young man," says his father. "He's good at sports, but different from his two older brothers. He's more into skateboarding, and he loves animals.

"He was a local celebrity at the lab for a long time," adds Shane Blunt. "The lab staff was absolutely amazing—they felt like they were growing up with Gage."

"We were shocked when we received that call."

Shane Blunt, father

it a practice to bring parents in to talk to her lab staff, so they can feel the same connection.

"Something just clicked," for Carla Cuthbert, PhD, now chief of the Newborn Screening and Molecular Biology Branch at the CDC's Division of Laboratory Sciences. As a biochemical genetics fellow, she attended a newborn screening conference, and the logic appealed: "This makes sense for patients," she remembers thinking, "to get them as early as possible, and give them the best possible chance for a healthy life."

For Jane Getchell, DrPH, MT(ASCP), now senior director of public health programs at APHL, her transformative experience came not in the lab, but during a picnic for children with PKU. "I saw parents measuring out grapes to feed their kids," she recalls. "That's when it hit me: We really do make a difference in their lives."

These scientists—a special blend of problem solver and public servant whose goals are too big to fit inside a cubicle—are the strength of newborn screening programs nationwide. However, their numbers are dwindling.

The newborn screening field faces a potentially troubling shortage of young laboratory scientists. In the near future, there may not be enough talented, passionate public health professionals to carry out this vital work.

The National Center for Public Health Laboratory Leadership and its partners are working to avert this shortage. The goal: to attract more students to public health and newborn screening careers.

Through online college courses, support for STEM festivals across the United States, and even board games, the partners are correcting misperceptions about life in the lab and introducing students to this career path.

"It's Stephen's legacy. His life really has an impact. He got a bill passed."

Jana Monaco, mother, advocate

The Monaco family, from left: Stephen, Jana, Nicholas, Tom, Caroline, and Alex

Chapter 4
Policy

It wasn't until after Christmas that Jana Monaco got around to picking up the photos from Memorial Day weekend. This wasn't that long ago—it was 2001—but things change so fast. Instant digital photos weren't so common then. You snapped photos on film and brought them to a store for developing. And once in a while, when life became overwhelming, you didn't pick up those photos for a long time.

The last photo on the roll showed 3-year-old Stephen, her third child, smiling and stirring cake batter. It had been a good holiday; he'd helped make a cake for his grandmother's birthday. But really, his mother didn't have to see the photo to remember. It's a day she has replayed in her mind, over and over.

The morning after the photo was taken, when she went to wake up her son, he didn't respond.

He was in a coma for weeks. They said the prayers and made the pledges so many parents do: If he survives, we'll do something to make sure this never happens to anyone again.

Stephen opened his eyes again on Father's Day. He had severe brain damage caused by isovaleric acidemia (IVA), an inborn condition that had been with him, invisible but working its harm, all his short life. A special diet from birth would have prevented the damage.

In 1997 in Virginia, when Stephen was born, the state screened newborns for eight conditions. IVA was not one of them.

Some of the thoughts that seared through Monaco's shock at the time are ones that still resonate today, when she testifies to legislators, when she gives presentations on newborn screening: North Carolina, right over the state line, screened for IVA in 1997. Her first baby had been born in North Carolina. If Stephen had been born in North Carolina …

"That photo turned out to be so valuable in advocacy," Monaco says. "It drives home the impact of these disorders and how a child can decline so rapidly."

In the years since, she has done a great deal to make sure this never happens to anyone again.

In the world of newborn screening, you'll meet parents who have undergone unspeakable pain, and yet talk about being given gifts: doctors and nurses who keep in touch on a child's progress; researchers and laboratorians who stay to run just one more test; specialists and lab equipment manufacturers who develop bonds with families affected by genetic conditions. Add to this legislators and representatives from nonprofit organizations, who keep fighting for solutions in the face of funding cutbacks and legal issues.

It wasn't until the turn of this century that

these diverse types began pulling together in a concentrated way. It's a difficult journey, and each step needs to be taken carefully so as not to stumble over what's scientifically possible, what's feasible, what's respectful of rights, what best protects babies, what brings true benefit, and what simply raises false hope.

But it's a journey many states are taking. Today, Virginia screens for 30 conditions, including IVA, and is considering adding more.

So many stories

Newborn screening programs vary from state to state—and in some ways, this is perfectly reasonable. States don't have the same geography, resources, or education systems, either. But there is common ground. States don't have the same number of roads or the same transportation needs, yet there's a federal highway system that provides the logic and structure that allow industries to plan logistics and individual drivers to know where they are.

As more conditions became easier to pinpoint, the stories of inequities across state lines, like that of Stephen Monaco, became more frequent. Jana Monaco says her reaction is typical: "At first, I thought everybody should be screening for everything."

Jill Levy-Fisch has heard many such stories—and she has her own, of a son whose condition, SCAD, took a three-year "diagnostic odyssey" to pin down. (New York, where her son was born, now screens for more than 40 conditions, including SCAD.) Today he and his older brother, who also was discovered to have SCAD, are doing fairly well, but knowing what could have been led Levy-Fisch to join the Save Babies Through Screening Foundation in 2002.

Founded in 1998 by Tera and Dallas Mize, Save Babies is the only national nonprofit devoted solely to newborn screening advocacy, and its website, savebabies.org, is a source for education. Like several similar advocacy groups, it grew from a "kitchen table" endeavor to one that has a place at the table in statehouses and in Washington. Levy-Fisch, now president of Save Babies, says that while positive stories are increasingly joining the heartbreaking ones, there is still more work to be done to ensure all babies have equal access to available screening tests no matter where they are born.

But this advocacy is still wrenching work. One story on savebabies.org is of the struggles of Ellie Kate McLaughlin, who died at the end of 2012, shortly after turning 7. Born with nonketotic hyperglycinemia (NKH), for which her home of Oklahoma does not screen, Ellie Kate was "a fighter," wrote her mother, Ryan. Her second daughter, Lucy, also has NKH. Because of Ellie Kate, they knew to get an outside screening specifically for the condition. As a winner of the Mrs. Oklahoma pageant, Ryan McLaughlin made newborn screening her platform and used the title for every opportunity to get the word out on newborn screening.

A small army of parents like her manage, after days and nights of caring for children with special needs, to keep making the effort to let people know.

"States are doing a phenomenal job with the testing they're doing, but given budgetary constraints, some aren't doing all the tests that are available," Levy-Fisch says. "It goes back to education—educating the legislatures. I want to see more movement—but everyone's come a long way."

Caring champions

It would be easy for parents whose children have suffered to give up on the system entirely, become adversarial, and call for dismantling and overhaul. What typically happens instead is that once they educate themselves on newborn screening, they see that it's an evolving system and that those working in it are allies. Talk to a parent, and before long they'll be thanking specialists such as Piero Rinaldo, MD, of Mayo Clinic, and the late Paul Fernhoff, MD, of Emory University and the CDC, for their unstinting efforts and caring attitudes. Levy-Fisch praises the state health departments for follow-up efforts, and calls the lab workers the "unsung heroes."

What was needed was a transparent, accessible way for parents to make these ideas for improvement known. In the late 1990s, the March of Dimes, a newborn screening champion since it helped fund Guthrie's early studies, took the issue to Capitol Hill. Working with Sen. Edward Kennedy, then chairman of the Committee on Health, Education, Labor, and Pensions, the organization was able to bring focus and attention to shape newborn screening's rapid growth. Physicians and researchers throughout the field call this effort from the March of Dimes "indispensable" to what followed.

In 2000 came passage of the Children's Health Act, which freed funding for HRSA to give to MCHB to make a difference.

To continue without coherent federal guidelines put states in the position of having to make decisions in isolation—rather than learning from best practices and sharing resources in areas ranging from medicine to law. But pressure for coherence, uniformity, and improvement in the screening system was coming from all sides.

If a journal article can be said to comment dryly, the 2000 AAP newborn screening task force report at least gave that impression, saying "it is interesting to note" that some states testing for the comparatively rare condition galactosemia still didn't think it necessary to test for sickle cell, which occurs at a much higher rate.

The general climate at that time encouraged detecting health disparities and correcting unequal access to care, with efforts led as much by physicians in individual practice as by the then-Surgeon General, David Satcher, MD, PhD.

Conversation about discrepancies was entering the media and popular culture. The television drama ER aired an episode in 2000 with a plotline about a baby who crashed from a metabolic disorder the state didn't screen for at the time, with the show wrapping up with a fictional doctor on the show passing around a petition for expanded screening.

The March of Dimes became one of the first health agencies in the United States to publicly advocate for a national standard in newborn screening, when it began urging in 2000 that every baby, regardless of which state he or she was born in, be tested for a core group of at least eight specific metabolic conditions.

The March of Dimes list of recommended screenings grew to 10 (including hearing deficiency), and then to 21, as the organization encouraged all states to take action to expand their testing programs through legislative or regulatory action. It was time to correct what March of Dimes President Jennifer Howse, MD,

Secondary Panel

In a typical newborn screen, the laboratorian might see evidence indicating many more conditions than the ones she's set her instrument for. Cause for alarm? The American College of Medical Genetics group says no, but put 26 of these in a secondary panel of conditions that should be reported, so that parents and pediatricians can make decisions on follow-up.

Howell uses a common analogy to explain the nature of the secondary panel: Say you're in a car accident, and in the emergency room they give you an X-ray. There's no damage from the accident, but the X-ray reveals a spot on your lung. Does the doctor tell you about it?

Of course, most agree. The newborn screen results might not indicate anything dangerous—the condition might never manifest. "I guess it's just an Americanism, this transparency," Howell says, pointing out that in some other countries, pediatricians and parents are told only about conditions for which they've requested screens.

called "a basic lack of equity: it's a patchwork quilt of coverage—a devastating patchwork."

Science was changing fast as well. Completion of the Human Genome Project was on the horizon, and curiosity about how the discoveries around it would impact testing for genetic disorders was high. Tandem mass spectrometry had pushed laboratory science to a turning point. The message was: set guidelines and policy, or technology could run in directions that could cancel out the benefits gained for babies and families so far.

As capacity to "screen for everything" became possible, the questions abounded. How to determine where to draw the line? What was the harm in "screening for everything"? Where was the infrastructure in screening and follow-up to make more comprehensive screening worthwhile?

What's best for the baby

The upshot, in 2002, was that the American College of Medical Genetics (ACMG) would lead in developing a Recommended Uniform Screening Panel, guidelines all states would be encouraged to meet. It determined that the ultimate guide of policy would be what's best for the health of that individual baby—not for the healthcare system or public health or even the family. Other guiding principles included recognizing that newborn screening is a system, not simply a test; and that quality control of the testing process was essential.

Meanwhile, as the panel went through all the research and evidence on dozens of rare conditions, the U.S. Secretary of Health and Human Services established the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, or SACHDNC. It is, as those on the committee admit, a tough acronym, but that has not affected its influence or importance. This was the first time parents and advocates had an official voice in making recommendations on newborn screening.

The first parent to be on the committee? Jana Monaco.

"It was a great group," says Howell, its founding chairman, not least because it wasn't just "Washington bureaucrats." The committee had access to the ACMG work as it was being done; when ACMG turned in its recommendations for 29 conditions to be screened, the committee spent a year examining the list. All decisions were required to be evidence-based. By 2005, the committee had determined that the list could, indeed, serve as a recommendation for every state in the nation.

Howell remembers a co-worker asking him why he was spending so much time and effort on something no state would be compelled to follow: "Everyone knows the states have their own committees and guidelines. The federal government doesn't tell the states what to do." But Howell—and Monaco—quickly saw how influential the guidance would be. And Drs. Lloyd-Puryear and Mann of MCHB were instrumental in helping to get informational materials out to all the states.

In the few years after the Recommended Uniform Screening Panel was published, the average number of conditions screened in states took an enormous leap. Today, every state screens for at least 27 of the 31 recommended conditions on the panel, and many screen for more.

Continued calls for expansion

By 2003, the March of Dimes had begun a nationwide campaign with the release of its first National Newborn Screening Report Card, which showed serious inequities among the 50 states. The ability of the March of Dimes to get the discrepancies into the public dialogue led to more citizens pushing for change and drove all states to adopt expanded newborn screening.

In 2004, a story from California got nationwide attention: A pilot program screening for glutaric acidemia type 1 (GA1) had caught this destructive condition in one baby boy—and another baby born just 60 miles away suffered irreversible damage because his GA1 hadn't been caught. Both California babies were named Zachary, and the "tale of two Zacharys" became a rallying point. Hannon was quoted in the *Wall Street Journal,* calling the discrepancies in screening "a national tragedy." One of several sad ironies is that the divergence resulted from an attempt to add new conditions; California program leader George Cunningham, MD, MPH has long encouraged expanded screening.

But with this occurrence, all states were on notice to re-examine their screening policies. In 2005, thanks in part to Monaco's advocacy, Virginia mandated screening for all the conditions on the panel. Monaco says: "It's Stephen's legacy. His life really has an impact. He got a bill passed."

That same year the SACHDNC made its recommendation to the Secretary: Use the Recommended Uniform Screening Panel. Later, severe combined immunodeficiency (SCID) and critical congenital heart disease (CCHD) were added.

The SACHDNC continues to be influential. It's the place to go for parents, advocates, and scientists seeking to have conditions added to the panel. Full instructions are posted on the HRSA website on how to start the process, as well as reports detailing why conditions have been accepted or rejected. Genetic Alliance, through Baby's First Test, offers technical assistance to those seeking to get a condition considered. In the most recent SACHDNC meeting, Pompe disease, a condition advocates have sought for some time to add to the panel, was moved to the evidence review stage.

'Bigger than we imagined'

"You want to be angry at someone," Monaco says about her family's experience. "But we were learning quickly that this was bigger than what we imagined." In searching for help for Stephen, she linked up with the Organic Acidemia Association, one of the larger groups that provides resources and support for families with children with metabolic disorders.

Visitors are greeted with a slide show of healthy children and adults with organic acid conditions as well as information on specialists, diets, and getting help. Parents and those with conditions are finding the story doesn't end with diagnosis, or even with treatment. Many have taken on long-term follow-up as their next battle.

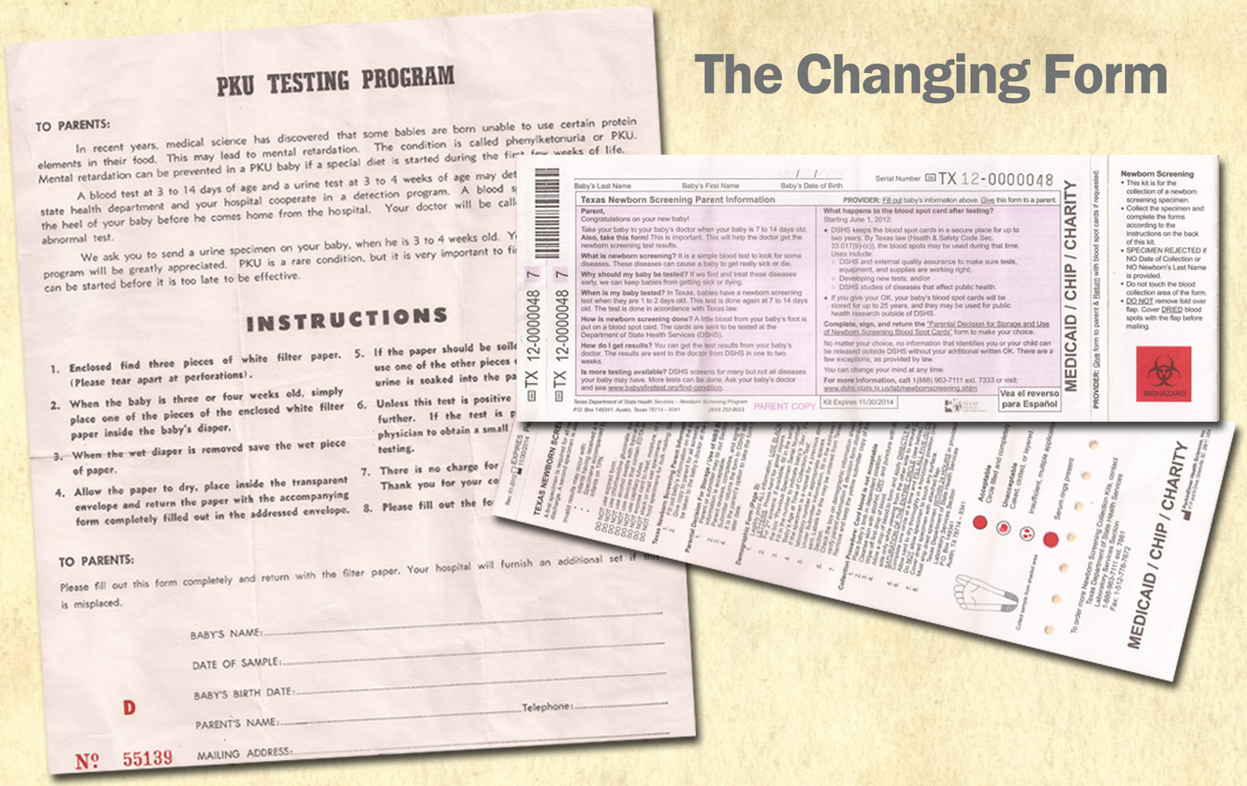
Over 50 years, many with these rare conditions have grown up and become part of American life—working, raising families, and becoming advocates or entering healthcare. For instance, Rahul Kapoor, a student in Georgia, was screened as a newborn, but his condition,

Social Media Changes Game

Raising awareness and funds, rallying advocates, connecting families to information and others dealing with the same challenges—social media has made the world of newborn screening a smaller, more powerful place.

It started with forums for parents with many questions and few answers. Today these parents befriend one another through helpful posts and sharing notes on Facebook and other social media platforms. APHL's blog and website have many stories of families affected by newborn screening and information sources for families and scientists alike. APHL, Saving Babies through Screening Foundation, and several more share videos on YouTube and Vimeo and snapshots on Pinterest to educate, inform, and inspire.

Dissemination of the latest research and one-click advocacy have brought together families that might have been separated by thousands of miles. Add to this the "mommy blogger" trend of the past few years—estimated at about 3.9 million women's blogs, often focused on family issues. It's not hard to see why some in the community attribute the rapid progress and transparency around newborn screening to the rise of social media.



The Changing Form

The form that goes with the newborn screening specimen has changed over the years in response to needs for more information and to protect privacy. What began as name and address has become a source of further information, both for the lab and the parent.

beta thalassemia, was missed. At age 4, he became sick—but he was able to recover with blood transfusions. He still takes medication and gets transfusions today, as he works on his microbiology degree. His hope: to attend medical school and specialize in hematology.

Others have started websites or online campaigns. A big issue for many with metabolic, endocrine, and hemoglobin disorders is the expense of special diets, formulas, and medications on which their lives depend and the lack of programs, insurance and otherwise, to help make these affordable.

Following the money

Cost, for an individual or for a family, has never figured overtly into the newborn screening equation. It is one of the first questions those just hearing about newborn screening ask—but one that is rarely brought up by those in the field. A baby is not prevented from having screening on the basis of cost; ensuring every baby is screened is the point of the public health program. Individual states cover the costs in different ways, through a combination of programs, insurance coverage, hospital arrangements, and government funding.

But with healthcare costs a critical issue today, researchers are studying the cost benefits and cost-effectiveness of newborn screening. For conditions that can lead to severe physical and intellectual disability, the costs in medical bills and lost potential are high.

Families of children with inherited disorders know this well. For instance, SCID, a deadly immune deficiency, was added to the panel in 2010.

"Families can run up hospital bills in the millions of dollars," Howell says of SCID. "These babies, when untreated, can end up in the intensive care unit with terrible, overwhelming infections. The tragedy is that after these infections, they end up dying. But now we have a great test, and the treatment is relatively inexpensive.

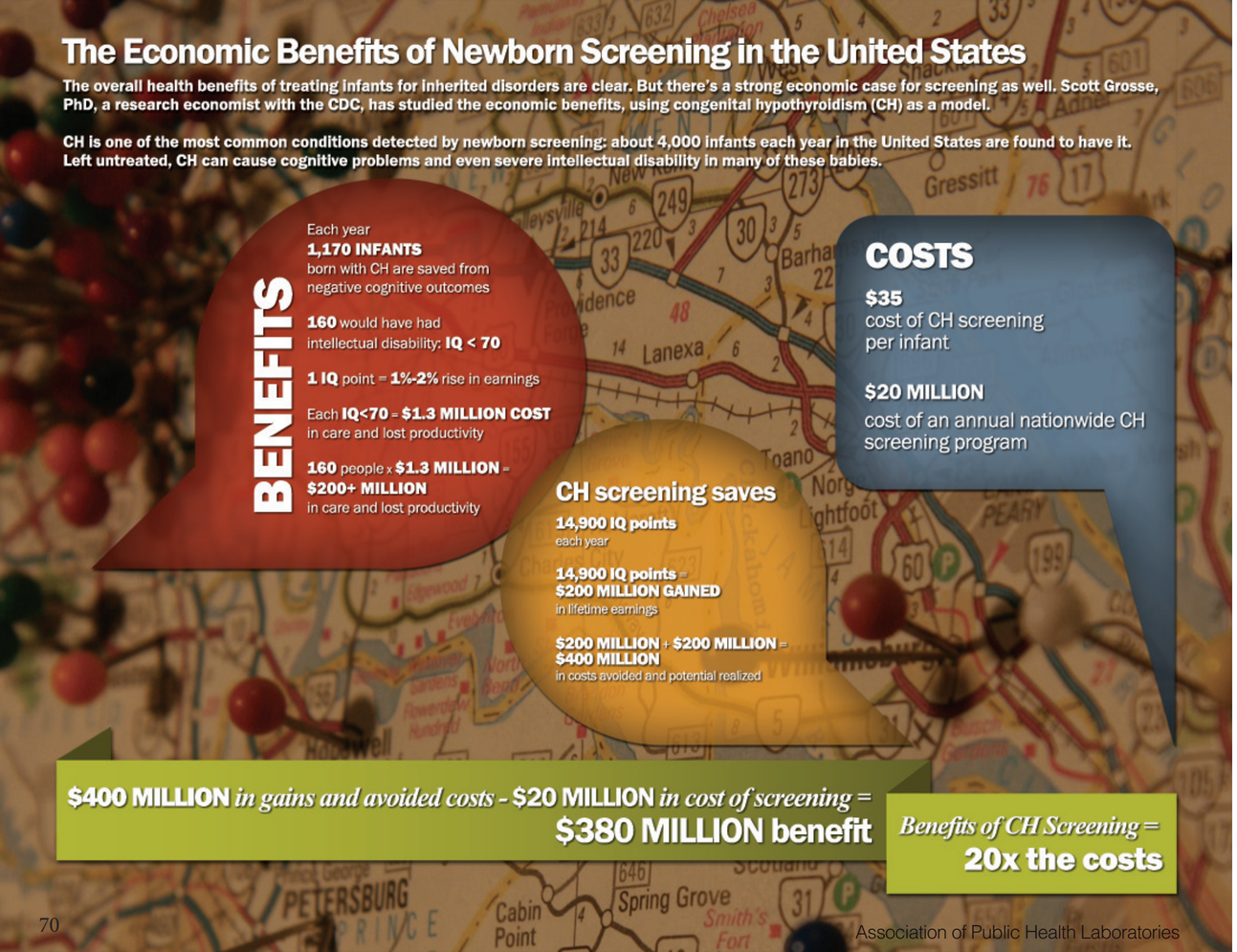
"So when you talk about adding disorders to the panel, you may not be talking about adding costs," he says. "It may be money-saving as well as lifesaving."

Also, the fact that newborn screening uses largely existing infrastructure and personnel helps keep costs down. A public health laboratory is the most obvious example; to set up a new, separate facility only for newborn screening could be prohibitive. Nurses and midwives require just a short training to add newborn screening specimen collection to their skills.

The March of Dimes' support statements are emphatic that cost must never be allowed to drive policy or decisions about what conditions are screened. Other organizations, from medical associations to corporations, agree.

But cost does come up indirectly. An essential factor for the ACMG group was determining whether a test that could be performed on a mass basis exists—and developing such tests involves investment. The imperative that the condition be able to be treated necessitates a strong follow-up system with sufficient staffing and specialist expertise. For instance, in rural areas in particular, metabolic specialists are hard to find; things haven't changed much since the days when Neil Buist of Oregon would fly to a town in Idaho or Alaska to treat children and consult with general pediatricians.

And funding is always difficult, says Jelili Ojodu, MPH, who in his position as director of the newborn screening and genetics program at APHL is often working on policy statements and helping states get resources. Some states generate revenue from insurance



and hospital fees paid for newborn screening but don't invest it back into the program, leaving newborn screening labs scrambling to keep up. State-ordered budget cuts, layoffs, and furloughs can affect quality and also delay instituting screening for new conditions because states can't afford the technology and training required.

"The states are using public dollars and weighing the benefits," Ojodu says. "A screen may be picking up one baby every 10 years, and they have to weigh this against the cost of providing clean water for the state."

A legislative mandate for screening an additional condition doesn't automatically come with an additional multiplex screening setup, a new clean room in a lab, and a couple of highly-qualified technicians to perform the testing—or even with funding to do so. By 2004, as ACMG and the Advisory Committee were working on their recommendations, APHL had trained about 25 states in mass spectrometry use, but the labs could see tough times ahead. As APHL pointed out in a policy statement that year:

"Today, there are not enough mass spectrometers in the country to immediately implement an expanded panel of screening. In order to implement [expansion] on a national basis, there must be an understanding of the funding mechanism to support it. … APHL … strongly believes federal financial support will be necessary to assure that children in all states benefit."

An act to save lives

Encouraging states to cover more conditions would mean finding funding to help them do it. As early as 2002, some in Congress had seen this, and Sen. Chris Dodd and Rep. Lucille Roybal-Allard had introduced twin bills for the Newborn Screening Saves Lives Act.

It was pushed in session after session until it succeeded, in 2007, as a bipartisan effort sponsored by Sens. Dodd, Orrin Hatch, and Hillary Clinton. The Act keeps the SACHDNC going and expands its responsibilities. It adds muscle to lab quality control and provides for contingency planning if there are emergencies that could affect newborn screening programs. It reshaped the NICHD research program as the Hunter Kelly Newborn Screening Research Program. And it established a clearinghouse: Baby's First Test.

But one of the major ways the Newborn Screening Saves Lives Act works is to give the people who see what needs to be done the resources to do it, through grants for programs that those working directly with families can create themselves. From making a video promoting prenatal education on newborn screening to developing a toolkit for midwives and doulas, what is produced through this funding goes toward making newborn screening more effective and building bridges throughout the system—so no family experiences a preventable tragedy.

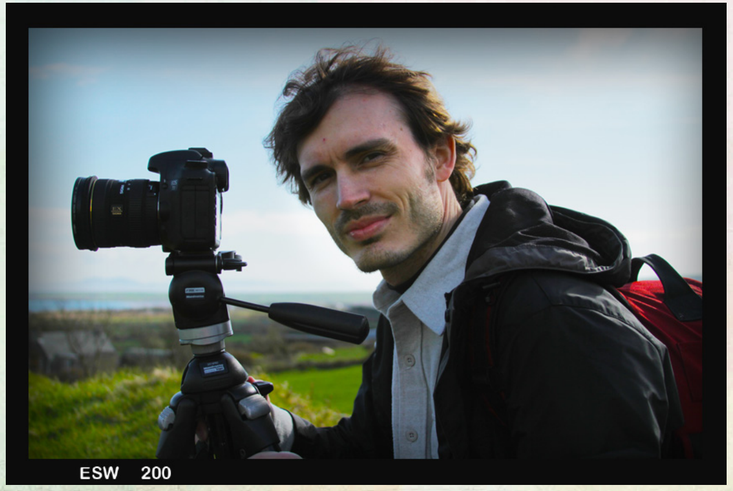
But as 50 years have shown, there is nothing static about newborn screening. Without continued and consistent funding, programs that have proven to help parents and states can vanish. At the time of publication, the Newborn Screening Saves Lives Reauthorization Act was being introduced in the House, by Roybal-Allard and Rep. Mike Simpson, once again with advocacy support from the March of Dimes. What would happen without reauthorization? The SACHDNC, Baby's First Test website for parent information, the CDC's lab quality assurance programs, the Hunter Kelly program—many of the strides forward made by and for both parents and science—could be wiped out.

As Roybal-Allard said in a House address: "Unfortunately, critical gaps and challenges remain. … No child should die or suffer from preventable disabilities that could have been detected at birth."

The Next Generation

Helped by Newborn Screening, Videographer Becomes an Advocate for Others

To truly understand newborn screening, Kevin Alexander had to see its impact. While researching footage for a documentary, he viewed clips of people with PKU who hadn't been diagnosed early enough: those living in institutions, struggling to hold a fork, dress themselves, or walk without help. All of them had started out looking and acting like healthy newborns—but the condition, which renders the body unable to process certain substances, had waged its silent harm over the first year of life.



Kevin Alexander

"The only difference between them and me is that they weren't screened," he says.

After Alexander tested positive for PKU as a newborn, in 1980, his parents immediately put him on a special formula and diet to stop PKU from causing damage. As an adult, he earned a master's degree, traveled the world, and covered news, such as when Hurricane Katrina hit his home state of Louisiana. Then he decided to turn the lens on himself, making a video about his life with PKU.

In his video, he talks about the challenges he faced—feeling like he didn't fit in, struggling to maintain a social life, trying to hide his condition and his diet. The video also shows how he lives a full life today with PKU.

Generating 13,500 views in under a year, Alexander's video is now one of the first things people see when they search YouTube for "PKU." And making it sparked a new phase in his life.

As an advocate for the more than 20,000 people currently diagnosed with PKU, Alexander has talked about the condition at newborn screening conferences in Finland and Brazil, lobbied Congress to make the special formula he drinks more widely available, and used his film company to produce educational videos. His website and Facebook page provide young people and parents with trusted information and a place to discuss and debate issues ranging from newborn screening to living with disability.

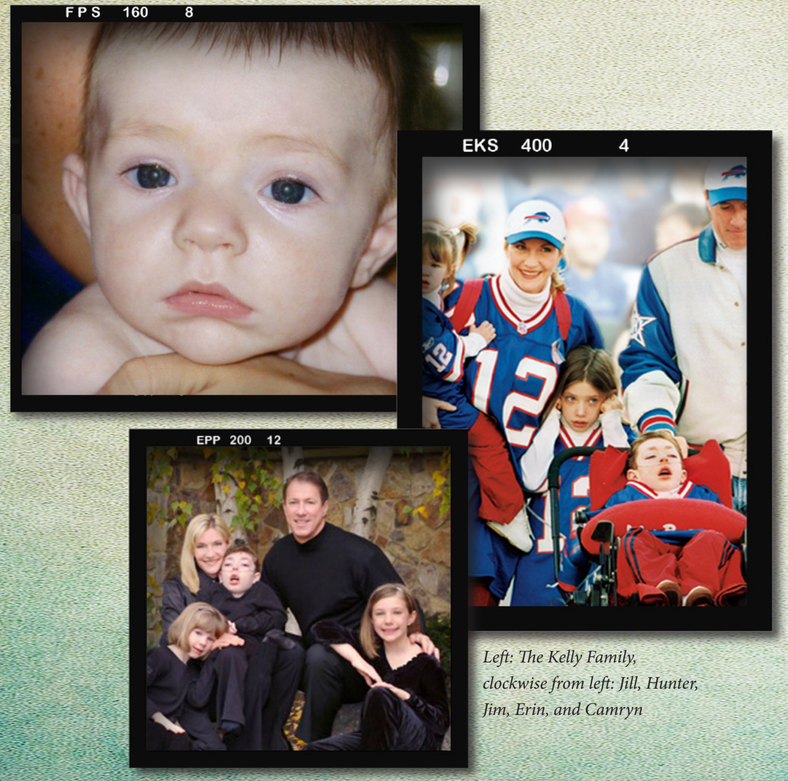
The success of his video had a personal impact as well. It encouraged Alexander to finally do what he had always wanted: found a film company.

"Much of what I do in film is centered around health topics," he says, "because so much of my life revolves around PKU and the help I got from newborn screening."

> ***"The only difference between them and me is that they weren't screened."***
>
> **Kevin Alexander, adult with PKU**

Adding a Test

Newborn Screening Rises to the Challenge



Left: The Kelly Family, clockwise from left: Jill, Hunter, Jim, Erin, and Camryn

Photos courtesy of Hunter's Hope Foundation

The governor announced it at his 2005 state of the state address—and the lab had to live up to it.

New York would have "the most comprehensive no-cost newborn screening program in the nation," George Pataki said, and it would add testing for Krabbe disease to its screening panel.

"No one had ever done this before," says Michele Caggana, ScD, director of the state's newborn screening program at the Wadsworth Center. "Could the Krabbe test be scaled up and folded into a screening program that was already chugging along, every day?"

New York has often been ahead of the curve in newborn screening because its state public health laboratory, the Wadsworth Center, is also a center for research. It had been exploring testing on a large scale for Krabbe and other lysosomal storage disorders (LSDs), caused when the body lacks the ability to create a certain enzyme. Krabbe is rare but devastating; most children with the infantile form don't live past 24 months. There is no cure, but cord blood transplants performed as early as possible can be a treatment that helps stabilize the disease.

A father's determination

Newborn screening for Krabbe was the goal of a determined father who lost his son, Hunter, to the condition. NFL Hall of Fame Quarterback Jim Kelly and his wife, Jill, became tireless advocates for screening, research, and treatments for Krabbe and other LSDs, establishing the Hunter's Hope Foundation. The Foundation has made extraordinary strides nationwide in raising awareness and supporting research. Its work has been such that in 2010, NIH renamed its newborn screening research program after Hunter Kelly. And Kelly's home state would become the first to offer newborn screening for Krabbe—the "hope" he speaks of would be extended to all babies in the state.

The lab had a tough, intensive job ahead. A program handling more than 1,000 samples daily would have to ensure the new test was validated, regulated properly, and accurate over thousands of uses. The screen is complex; mass spectrometry finds out-of-range results, and DNA technology then further pinpoints the condition. The state would also need to connect families to critical diagnosis, follow-up, and support services, which, because of the rarity of the condition, are few and far between.

It took 20 months to get the program established. Even as some states begin to explore adding Krabbe testing, families, researchers, labs, and legislatures are watching New York to see its progress—and learning from the Kelly family's advocacy.

One of these is the Morris family, in Texas. Their second child, Seth, was saved by newborn screening: His PKU was caught and treated. The family became newborn screening hawks with their third and fourth children—they followed up, they got results, but both sons had clean screens, no conditions found.

But at 8 months, Greyson, their youngest, started "going backwards, losing skills," his father, Bill Morris, says. Diagnosis: Krabbe.

"My wife and I are the 1 in 4 million," he wrote. "We share not one but two different recessive traits in our genetic makeup." And two recessive traits can add up to a child with a genetic disorder.

Six days before his first birthday, Greyson died in his father's arms. Out of his grief, Bill Morris eventually became a political activist, "outraged" that his state didn't test for more conditions. He lobbied for expanded newborn screening in Texas. The result was Greyson's Law, which established a state newborn screening advisory committee with parent participation and added conditions to the state's screening panel. While Krabbe was not on the Texas list as of publication, the expanded services and added voices are what the Morris family knows will make the difference to other families' futures.

Photo courtesy of Coleman family

Chapter 5
Future

Over the years, Rodney Howell, MD, shared his university office with a handsome tiger-stripe cat named Chester.

The cat played an important role in the learning process: “Sometimes, people would come in with a problem that had a very simple solution,” Howell explains. “And I would tell them that it sounded like a problem Chester could solve.

“Even Chester would have been perfectly aware that newborn screening for PKU was successful,” Howell says.

But, he adds, there are other issues around newborn screening that are not so obvious.

In recent decades, with the world-changing discoveries and developments associated with the human genome, research in the areas of bioethics, psychology, and sociology have run in tandem and in equal regard with that of the scientific investigation of new tests and treatments.

From individual state legislative decisions to those of the Secretary’s Advisory Committee, the whole picture is being taken into account—and that picture is complex. Pioneers and those making the latest advances alike are looking ahead to shape practice and policy that will extend newborn screening’s 50-year history of saving babies into the next decades.

Scientific horizons

First, let’s look at what’s on the horizon in science. What spurred the most expansion and the most changes in newborn screening is the tandem mass spectrometry screening method—and it’s not even a DNA test. What made it revolutionary was the speed and sensitivity with which it could screen for multiple conditions at once—setting up “too much information” dilemmas even before the genome issues are introduced.

However, labs are increasingly doing genetic testing as part of newborn screening. The most common use is to pinpoint the type and severity of a disorder. A positive initial screen for cystic fibrosis or sickle cell anemia, for instance, is usually subject to a round of DNA testing. This further testing for a condition can determine whether the baby has a type that can benefit from early treatment, a milder form, a type that might not manifest until later in life, or whether the baby simply has the “trait,” or carrier gene.

Hannon, having seen newborn screening technology progress since the 1970s, says one future development could flip that algorithm—a test could begin with DNA screening and from there enhance the diagnosis through more traditional methods.

Whole genome testing is still prohibitive—both in terms of cost and in volume of data—for mass screening programs. Howell says that while advances in cloud computing may make whole genome cheaper and simpler even within

International Perspectives

A Global Glimpse of Newborn Screening

Nearly all developed countries today do some form of newborn screening. PKU, the first condition to be screened for in the United States, is also the condition most screened for worldwide. This is followed by congenital hypothyroidism, which has a relatively high rate of prevalence.

Ireland and New Zealand were the first countries after the United States to institute newborn screening programs, in 1966. Both have robust programs, with Ireland in 2011 adding cystic fibrosis screening because of the high occurrence of the condition there. Other countries are just beginning their screening programs, many with the help of the CDC's newborn screening quality assurance program, which provides support to more than 500 labs in 67 countries worldwide.

Tandem mass spectrometry changed screening as suddenly in other countries as it did in the United States. Costa Rica, for instance, with the help of donated mass spec equipment, in 2004 managed to up the number of disorders tested to 24. But mass spec testing also brought with it questions about how many conditions should be tested and about sharing information—European countries, for instance, are generally reluctant to work with any information that could imply genetic discrimination. And healthcare financing systems are the biggest divider between the United States and other nations. Nevertheless, the Recommended Uniform Screening Panel developed in the United States has served as a model or example for other countries.

Sharing best practices works both ways. The International Society for Neonatal Screening works with APHL and in 2013 holds its annual meeting in conjunction with APHL's annual Newborn Screening and Genetic Testing Symposium.

Photo courtesy of Jelili Ojodu

Newborns and parents visit the Sickle Cell Disease Clinic at Komfo Anokye Teaching Hospital, Kumasi, Ghana.

five years, the problem has always been getting meaningful information out of the huge mass of data.

However, he notes that whole exome methods on the dried-blood spot, a simpler and cheaper method, could be employed in labs. Exome sequencing, in effect, looks at a relevant chapter of a genome instead of reading the whole book. Getting good results here would depend on having a vast and quality "library" of books and chapters with which one can compare the exomes and genomes. Once again, the problem with rare diseases is that they're rare, as many doctors point out—and even advanced genetic research can't work around that fact.

APHL's Ojodu also sounds the note of caution. "Yes, we're inching closer to being able to do whole genome on a population basis, but we haven't yet considered all the implications. What about finding predispositions that may or may not show up later—when we can't tell if it's a major health concern, mild health concern, or not a health concern at all? And even with 29 or 30 conditions screened for in the labs, that's hundreds of thousands of data points—and that won't fit in the medical chart. Until we get our electronic health records in line with what we need right now, we're not able to meet the challenges of whole genome testing.

"We talk about the difference between screening and diagnosis, and with whole genome you're blurring that line," he continues. "Diagnosis isn't what we do in public health laboratories."

In fact, the next generation may not involve laboratories at all. Tricorder may be a word familiar from science fiction, but it's actually becoming a reality in medicine. "I don't know if that's in our lifetime," Ojodu says of the small, hand-held devices beginning to be tested on the market, which can pick up medical vitals through a quick external scan, "but in the next 50 years, newborn screening may have to merge into diagnosis."

But there isn't a researcher in these areas who doesn't also point out the other dimension here: How to ethically and practically deal with this information.

"What are you going to do with technology that spits out more information than you want?" asks Neil Buist. "There is a moral responsibility that once you do the tests, you should be able to handle the fallout from all of them. But there's a danger that the loudest voice will win an unwarranted seat at the table," he says, and rare conditions will be put in the position of battling for scarce resources.

Keeping Information Safe

After initial testing, a small amount of dried blood remains on the filter-paper card. What happens to it?

Residual dried-blood spots are generally stored at state public health laboratories, university and laboratories, or private laboratories contracted by the state.

Although storage time and exact procedures vary by state, several layers of protection are standard. Residual samples are assigned a code separate from any identifying information and placed in a secure facility accessible only by employees with data privacy training.

Any request to use samples for research purposes must be approved by an institutional review board, a body that makes decisions about using human specimens in research.

Stored samples can have many uses. For parents, these include rapid retesting. On the public health level, these unbiased, complete samples can be used to help states better understand health trends.

50 years, same questions

When newborn screening began, there was nothing like today's bioethics field, says Jeffrey Botkin, MD, MPH, professor of pediatrics and medical ethics at the University of Utah. Genetic science spurred that development. Yet "the debate in the 1960s was like today's: Do we have the right kind of evidence to introduce this test at the population level, and how do we understand the benefits associated with testing for it?"

"There's still the tension between those who say, 'full speed ahead,' and those who have caution."

Expanded screening capacity has brought with it an expansion of goals and potential. The most prominent example of this is in the expanded concept of benefit. Start with the idea that the top consideration in adding a condition is that catching that condition early directly benefits that individual baby. A screen that reveals a condition is followed by treatment that averts damage—in congenital hypothyroidism, for instance, a daily dose of a hormone means intelligence develops normally. Clearly, the baby benefits.

But are there other ways a baby can benefit, even if a condition can't be treated? What if screening spares the baby and her family numerous tests and treatments as part of a long "diagnostic odyssey" to discover what's wrong? Does it benefit a baby if the family knows what's ahead—if, even if they know the condition can't be treated, they can find the best care, therapies, management programs; can rearrange the family lifestyle, priorities, finances?

Several are answering yes. As chairman of the Muscular Dystrophy Association, Howell says some families of children with Duchenne muscular dystrophy say they would have welcomed knowing the diagnosis soon after their child was born. Even though there is no effective treatment, they say, they would have liked the chance to begin special programs to make their child's life and health better generally.

The SACHDNC provides a mechanism to elect conditions to the screening panel and for these elections to be reviewed scientifically and from a public health perspective. Conditions are continually being proposed for review, and out of that very process comes new knowledge and experience in making future decisions.

Education and understanding

Newborn screening also has the capability to let a person know if they carry a gene for a particular condition. This type of knowledge of "carrier status" is in no way a factor unique to newborn screening. It's been the biggest issue for most people since genetic investigation came to prominence. Do you want to know or don't you? How much do you want to know? While adults by the thousands have been enthusiastically using mail-order "trace my DNA" services, the question is far more complicated when a baby is involved.

With the genetics field—complex to begin with—constantly changing and responding to new information and discoveries, it's not unusual for families to be confused and uncertain. Baby's First Test and individual associations for newborn conditions offer access to research, family experiences, and answers to questions about genetics and family history.

It's also important to remember that not every condition a baby is born with is inherited—a condition can simply be the result of a random genetic mutation. No matter how much you know about your genes, and no matter how this knowledge guides your actions, mutation can occur. Finding out why these mutations occur is yet another important area of research.

More practical and pressing—yet less debated—is how the healthcare system can handle new conditions. As Maryland newborn screening specialist and pediatrician Susan Panny points out, with a dearth of specialists and pediatricians who might have to see four to six children in an hour, "the picture is not bleak—but we have to monitor very carefully the changes in the healthcare system."

As years go by, more children with newborn conditions will grow up. How are they doing? What are their challenges? Understanding this fully is not only important for their health, Botkin points out, but for making decisions on newborn screening in the future: It shows what the true benefits are and what families need. But currently, there is little in place to collect this kind of health data.

Researchers and bioethicists have for more than a decade been studying whether there are consequences of "too much information," saying false positives and uncertainty about future health can set up anxiety that a family might never quite get over. While there is still much back-and-forth and not sufficient study as of this publication, one thing has been pinned down: When a family is educated and counseled about newborn screening, outcomes are better all around.

This reinforces those in the field who say that no matter what the next 50 years hold, one area can and should expand without reservation: communication and education.

"Being handed a brochure is not enough for people anymore," says Jill Levy-Fisch of Save Babies Through Screening. "It has to extend to a real conversation. Families can't assume that no news is good news: Ask for the results and have that conversation."

The CDC's Carla Cuthbert, like many of the leaders in newborn screening today, started out in the field as tandem mass spectrometry was changing many of the basics. She knows the importance of communication and guarding quality through times of rapid change. "We understand how disruptive some of these technology platforms can be," Cuthbert says. "Activities in the lab have far-reaching effects. It opens a huge door."

But these changes are an inevitable result of the motivation to keep making newborn screening better. "We're always looking, and monitoring, to find innovative ways to improve screening," Cuthbert says. "It's a privilege to work alongside these scientists who are developing more tools to identify and help children with these conditions."

The next 50 years

Newborn screening means asking questions that strike at the heart of medical care and public health: What is benefit? What is evidence? What do I need to know in order to act? What's more, these questions aren't the stuff of late-night philosophy discussions but of real families facing real decisions, every day. These discussions inform the practical and routine, yet critical and urgent, nature of every activity in the newborn screening system, from a lab technician reading screen results that hover on the edge of the safe range, to a nurse calling a mother with information, to a legislator deciding on funding for a new program.

As confounding as these questions may be, continuing to face them with transparency, inclusiveness, and care is the mission of the next 50 years. When Bob Guthrie died, in 1995, tandem mass spectrometry was just beginning to change newborn screening. Yet he saw his invention inspire other revolutionary changes, in how our society defined disability and in what we believed was possible through science. Tomorrow, the way we define disorders and what is possible in treatment and prevention will change further, through the advances being made today.

"How in the world would we ever have guessed it would go this far?" Hannon asks, looking back on 50 years.

What would he tell someone in a lab in 1963? "I'd tell them to hang in there: This is going to be a big deal. You're going to save thousands from severe adverse outcomes. I'd tell them what a great impact they would have."

Helping States Advance

Stepping Forward with New Education, Data, and Resources

As he worked his way through his undergraduate years in a small ob/gyn clinic, Jelili Ojodu doesn't remember hearing much about newborn screening. Even later, during his graduate work in maternal and child health at The George Washington University, or while at Georgetown University working on an NIH project to reduce infant mortality in Washington DC—still nothing much. Now, as director of the newborn screening and genetics program at APHL, he's part of the effort to change that trend.

"That's why we're highlighting the achievements of 50 years—we want to create awareness among regular folks, so they can understand what newborn screening is about," he says.

"We talk the talk, and we understand it, because it's part of our everyday life, but what's important is empowering the mother and the families. Everything is a blur at the point they're in the hospital, and that's why it's not the right place to start talking about it. You want some understanding prior to having the baby."

Working with the CDC, APHL has made strides in education and outreach to communities and parents. At the same time, the organization also assists newborn screening from the other side—helping the state labs themselves.

"We can talk about how good the labs are—and the lab is an essential component," says Ojodu. But to help the states requires something more. "It's dealing with the system issues, with training, follow-up, and technical assistance, where our members wanted help. We saw the niche, and saw that with staff and leadership and funding, we could do this."

In 2013, APHL is launching NewSTEPs, the Newborn Screening Technical assistance and Evaluation Program, in collaboration with the Colorado School of Public Health and funded by HRSA's Genetic Services Branch. States can use the NewSTEPs' interactive website, data, and resources to improve their programs—and improve results for newborns.

It's a continuation of the work Ojodu and APHL have been doing for about five years, as new technology both revolutionized newborn screening and made it vastly more complex. "We began developing policy statements on everything from the role of private labs to quality assurance and quality control," Ojodu says. As states began to ask for more help, it became more obvious that the labs needed to be able to talk as a collective—and that a number of federal agencies needed to hear the labs' point of view. So in 2008, newborn screening and genetics got its own program area within APHL.

"Now, we have almost perfect harmonization," between federal recommendations and state action, he says, pointing to the fact that every state screens for at least 27 of the 31 recommended conditions. "But at the end of the day, no matter what the feds say, newborn screening is a state program. For every condition added to the recommended screening panel, we want to make sure the public health program can handle it."

Among future challenges are bringing the public health laboratories' knowledge of quality best practices to tests being done beyond the lab, such as heart and hearing screenings done on newborns in hospitals.

"I used to hear stories about families screened for four conditions who knew that across the border, there was screening for 40 conditions. Thank God that the harmonization has increased to the point that almost all have the full screening recommended."

"What's important is empowering the mother and the families."

Jelili Ojodu, director, APHL Newborn Screening and Genetics Program

Jelili Ojodu

Genes and Information

How Much Do You Want to Know?

Newborn screening can raise the question: What do you want to know? The answer can lead to life-changing decisions.

First, you want to know your children are healthy and getting the best treatment. Fred Hill knows that, and he also knows that ultimately, that's enough.

But he also knows he has sickle cell trait—not the disease itself, but a genetic mutation that could be passed on to his children. If he marries someone who also has the trait, their child could have sickle cell disorder, a disorder that causes red blood cells to deform. It can lead to a pneumonia-like illness or even stroke or early death.

Aryiana Hill

Photo courtesy of Hill family

He was told he had the trait when he was 16, and he says he took the knowledge seriously. When he got older, he asked women he was serious about whether they, too, had sickle cell trait. He had two healthy children in a previous relationship and two with his wife, Yvette. Then the couple welcomed Aryiana, in 2002. And she has sickle cell disorder.

At first, he told the newborn screening follow-up nurse that the results were "medically impossible." He knew his status, and his wife's. But follow-up diagnostic testing was all positive. What had happened?

Ary has sickle beta thalassemia, a variant of sickle cell anemia. Yvette Hill had been told she carried the trait for beta thalassemia, which she had been told was "a Mediterranean blood disorder. No one mentioned sickle cell." She had found out about 10 years after their marriage, when a relative had become ill.

"I thought about what my baby was going to go through," Fred Hill says. "This wasn't what I ever would have wanted for my children." He met with an attorney about whether Yvette should have been told more. The attorney said the first question would be whether Fred would have married Yvette if he'd known.

The couple spoke up honestly: No. Neither would have married, knowing what would be ahead.

They both make it clear that they have no regrets about their marriage or children. Fred Hill didn't pursue a lawsuit. They have a happy family, and while Ary has had a few ups and downs, she's "a normal kid," Fred Hill says, currently enjoying cheerleading. But his views on screening and testing are the same ones he had when told of Ary's screening results: "I'd rather get to the bottom of it—get tested, get my wife tested. That way we have some insight on what's going on with our child."

"I thought about what my baby was going to go through."

Fred Hill, father

Vicki and Fred Modell with Dawson Bornheimer

Clockwise from top left: Mike Bornheimer, Fred Modell, Melissa Bornheimer, Dawson Bornheimer, and Vicki Modell

Conclusion

Vicki and Fred Modell don't typically travel from their New York home on September 25. The date is their son Jeffrey's birthday.

In 1986, when Jeffrey was 15 years old, they lost him to complications from primary immunodeficiency (PI). Two years later, the Modells established the Jeffrey Modell Foundation (JMF), which for decades has worked on diagnosis, treatment, and cures for PI. Their work focuses on promoting early detection for all primary immunodeficiencies. Severe combined immunodeficiency, or SCID, is one of these—one on which they'd been able to make some progress.

So on September 25, in 2008, they decided to make an exception.

A research team the Modells had worked with in Wisconsin asked them to come to a follow-up meeting about newborn screening for SCID. It would be hard, but travel for that purpose would be OK, they thought; maybe even a good idea.

"When we got there, in walks a handsome couple wearing blue t-shirts that read 'Dawson has big dreams,'" Vicki recalls. "We had no idea who Dawson was or what this meant." The couple introduced themselves as Melissa and Mike Bornheimer. They were, they told the Modells, the parents of the first baby with SCID identified through newborn screening. The Modells' support had helped make it happen.

That same day, Dawson was getting the bone marrow transplant that would cure his SCID and allow him to have a healthy childhood.

"They presented us with this unbelievable birthday gift," Vicki Modell says.

It was a gift that came out of decades of work and much pain. It was the result of labs, advocates, scientists, healthcare workers, physicians, legislators, state health departments, and more coming together for the same mission. It was a mission that all believed could be accomplished; SCID could actually be screened for and cured, with enough innovation and resources. They saw the thread of what is possible and followed it, and it turned into a lifeline.

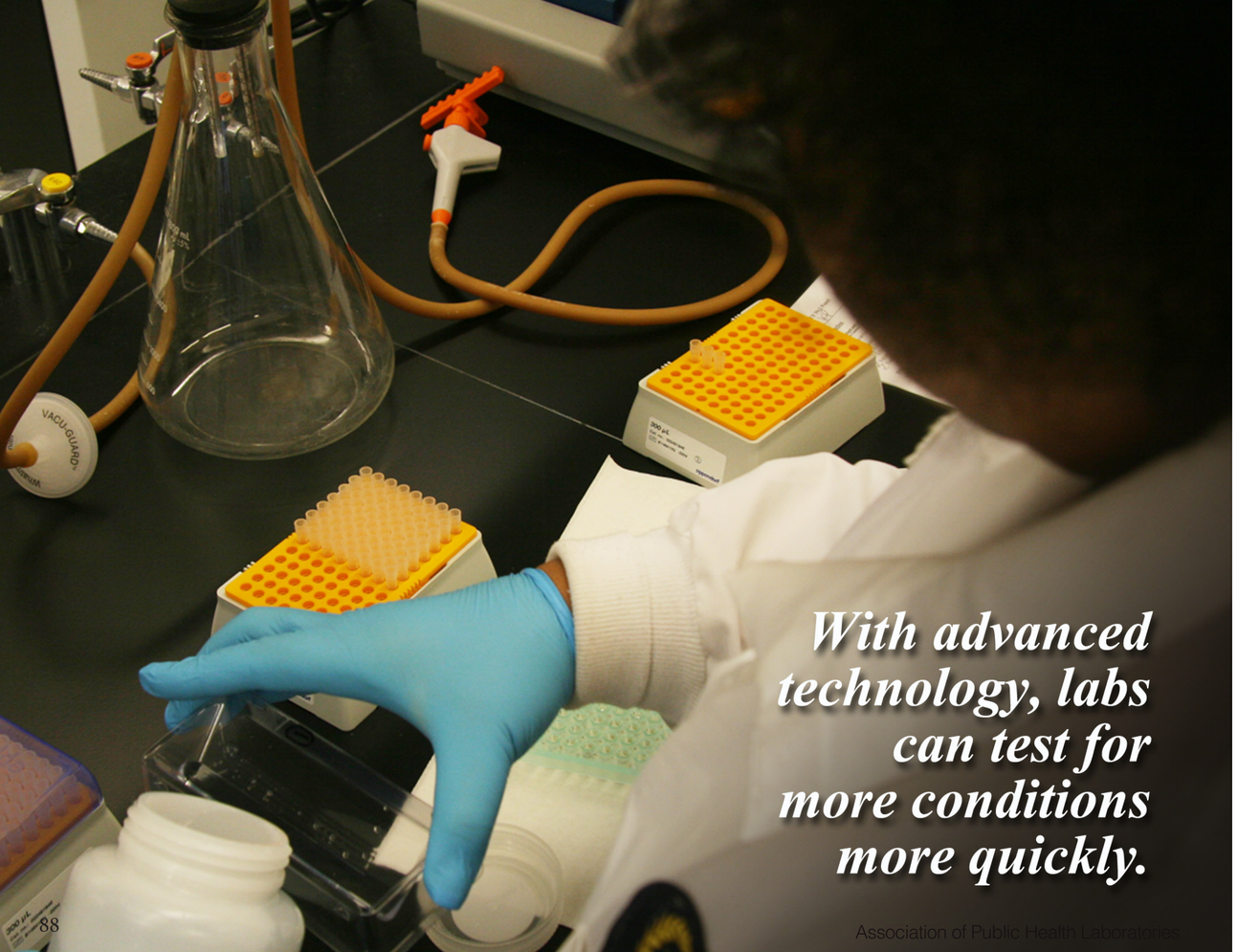
The story contains the elements that will shape newborn screening into its next 50 years—new technologies, thoughtful advocacy, and inventive collaboration.

Tragedy into action

In 1970, Vicki and Fred welcomed baby Jeffrey into the world, happy and healthy. At 9 months, hospitalized with a high fever, he was diagnosed with an immune deficiency.

Jeffrey grew up like other kids his age, but he became sick often. His body had a hard time fighting infections. At age 15, he succumbed to pneumocystis pneumonia, losing his battle for life against the complications of primary immunodeficiency.

"All his life, he would say to us: 'Come on, you guys are smart, you went to college, please do something to help me,'" Vicki Modell recalls. "This hurt us, because we were doing everything



With advanced technology, labs can test for more conditions more quickly.

we possibly could—but science hadn't yet caught up with Jeffrey."

After their loss, in 1987 they established the Foundation, whose day-to-day work focuses on research, physician education, patient support, public awareness, advocacy, and newborn screening. By 2012, the Foundation had created a global network throughout 70 countries, with more than 200 Jeffrey Modell Centers.

Support for science

Jeffrey Modell did not have SCID, the most severe form of immune deficiency disorder and one that is usually fatal within the first year of life. But the Modells realized that with SCID, they could make a lifesaving difference.

"I couldn't stand to hear from another family whose baby had died from SCID," Vicki Modell says. "Especially when there are treatments and cures—so we decided to put much of our efforts toward newborn screening for SCID."

In 2001, Vicki Modell testified in Congress for support of SCID newborn screening. But she was told the screening test wasn't ready yet—it had to be very accurate and ready to use on the mass scale required by newborn screening programs.

The Modells had their target. They helped support a joint research collaboration with the National Institutes of Health and Affymetrix in 2005 for SCID newborn screening using microarray technology. When they went to a meeting at the CDC with public health officials studying testing methods that could screen for SCID, they met public health researchers and scientists from the Wisconsin State Laboratory of Hygiene.

That state's public health lab is part of the University of Wisconsin-Madison, so it has always had a dynamic research component as part of its mission. Through the 1970s and '80s, the lab, under newborn screening pioneer Ron Laessig, PhD, and the scientist he had hired, Gary Hoffman, had automated and centralized its work to be able to test for more conditions more quickly. Laessig had also worked with the state legislature to make adding conditions to the state screening panel less political and more streamlined and science-based. These factors combined to make the state public health lab the ideal place to advance the SCID test.

Another essential piece: In 2008, the Modells allied with the Children's Hospital of Wisconsin to put its resources toward the pilot program. And lastly, the CDC's quality assurance program helped with lab studies and test improvements.

"The lab brought the equipment, knowledge, and capacities to do clinical genetics work—capacities not available in every lab," says Charles Brokopp, DrPH, president of APHL and director at the Wisconsin State Laboratory of Hygiene. The team, led by Mei Baker, MD, rolled out the first newborn screen for SCID in just one year. In the pilot screening run of 10,000 babies, there was one positive—Dawson.

A true cure

Babies with SCID lack the antibodies that give them immunity. For the first month or two of life, the infant is living on "borrowed" immunity from the mother. This also creates a vital window for a bone-marrow transplant—the baby in effect has a clean slate in immunity, so new bone marrow won't be rejected. Early detection and early transplant takes advantage of this window. Miss the window, and the alternatives are transplant rejection—which can be lethal—or the infections that SCID can cause—also deadly.

"We're not just treating. We're curing this condition," Brokopp says. "If we can give babies normal white blood cells, the cells will start reproducing." About 90 percent of babies treated early will develop a normal immune system and live a normal life.

That's what Dawson is living now, his mother says. In 2010, with a working screening test and their first baby saved, the Modells and

Bornheimers went to Washington, DC. Melissa Bornheimer testified to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. The vote from the 26 members of the committee was unanimous: Add SCID to the uniform screening panel.

That meant every state would be encouraged to test for SCID. But the federal agency can't dictate state laws. The Modells took a deep breath and added another enormous goal to their list: Get every state to mandate SCID screening.

"We started with the big states, to gain some traction," Fred Modell says. They met with leaders, state legislatures, and even the U.S. Secretary of Health and Human Services. It was obvious, they say, that for states, money was the obstacle. (Costs depend on a state lab and health system's starting point, but a Washington state analysis, to give an example, puts costs of adding SCID testing at about $7 per baby.

But as University of California, San Francisco pediatrician and researcher Jennifer Puck, MD, put it when making the case to her state: "With SCID screening, we'll get healthy citizens rather than huge medical bills.")

In February 2012, the Jeffrey Modell Foundation announced it would fund every state with one dollar per every baby screened for SCID. It worked. States began adding the test, and success stories abounded. In Connecticut, just one week after adding the test, a baby was saved through SCID detection. By 2013, 20 states screen for SCID, and 23 states are preparing to start screening for it.

"It's actually a curable condition," says APHL's Jelili Ojodu. "Yet due to all kinds of factors—important ones, such as finance—not all states are screening for it. We would like to find ways to enable states to make it happen."

"We are 100 percent committed to getting every state screening for SCID," Fred Modell says. "Babies are dying every single day in states without the SCID test. If we have the assay that can work, and we can intervene with a bone marrow transplant, and we can do so with all the state economics working, we should be testing everywhere. SCID cannot wait."

Today, it's SCID. Tomorrow, any one of a dozen damaging conditions could be the one that can be cured. Legislation will change, the healthcare system will change, and science will change. Even the filter-paper test strips like those used by Dr. Guthrie may be replaced by some other method. What will stay the same for the next 50 years is the will to protect our most vulnerable and our source of hope: the newborn.

In October 2012, the first baby with SCID in Florida was detected. Baby Aaliyah's test returned positive just 19 days after Florida began SCID screening for all newborns. Aaliyah's test was confirmed positive, and the family came in to meet with the bone marrow transplantation team—all within six days.

Photo courtesy of Weiss-Krull family

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Many parents and healthcare professionals whose stories appear in this book have also shared their stories on the APHL LabLog. Read expanded stories or learn more at blog.aphl.org, tag: newborn screening.

Parents and consumers can get information on newborn screening and links to resources on follow-up and rare disorders through APHL and the CDC as well as through Baby's First Test (www.babysfirsttest.org), Save Babies Through Screening Foundation (www.savebabies.org), and March of Dimes (www.marchofdimes.com).

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35 years of innovation and collaboration continues

PerkinElmer is the world leader and largest manufacturer of newborn screening instruments, reagents, sample collection devices, and software. PerkinElmer products have demonstrated proven performance and have been used to screen 413 million babies in 90 countries.

Help in Crisis

Instruments and reagents contributions from PerkinElmer helped ensure uninterrupted newborn screening in Louisiana after Hurricane Katrina.

Action in Partnership

Because of its acknowledged partnership with the Utah state laboratory, PerkinElmer was able to work with Utah in 2006 when the lab urgently needed to implement chronic hypothyroidism, cystic fibrosis, CAH, and galactosemia screening. No delay in reporting results were experienced.

Advancing Screening for the Future

In 2010 PerkinElmer Genetics partnered with the state of California to provide a newborn screening service for SCID as part of the Genetic Disease Screening Program. To date, approximately 1 million newborns have been screened, 50 babies have been identified with SCID, and 15 have received a bone-marrow transplant.

Reaching milestones together

- **1977** Gamma counters used for congenital hypothyroidism screening in Switzerland
- **1985** First newborn reagent kit launched in Europe
- **1993** First AutoDELFIA® instrument delivered to Italy
- **1995** State of Florida initiates newborn screening with AutoDELFIA test system
- **2000** Specimen Gate™ Software initial deployment for neonatal screening in Ohio
- **2001** NeoGram MS/MS reagent kit launched
- **2009** GSP® Instrument and GSP Neonatal hTSH reagent kit receive FDA clearance
- **2011** LSD screening offered at PerkinElmer Genetics
- **2012** Panthera-Puncher™ 9, next-generation puncher launched

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