The ability to scan one sample for some two dozen inherited disorders is about to cause an explosion in neonatal screening; few health systems are prepared for the consequences

Fast Technology Drives New World of Newborn Screening

A new grassroots movement is raising a ruckus about genetic disease screening—but not for the reasons you might guess. Its leaders want more testing, not less. Specifically, they want every newborn screened for a variety of inherited diseases for which early intervention might prevent disabilities. These activists—many of them parents of affected children—claim that ethicists and public health officials have resisted a new technology that can check thousands of blood samples a day. And health agencies are responding to their campaign.

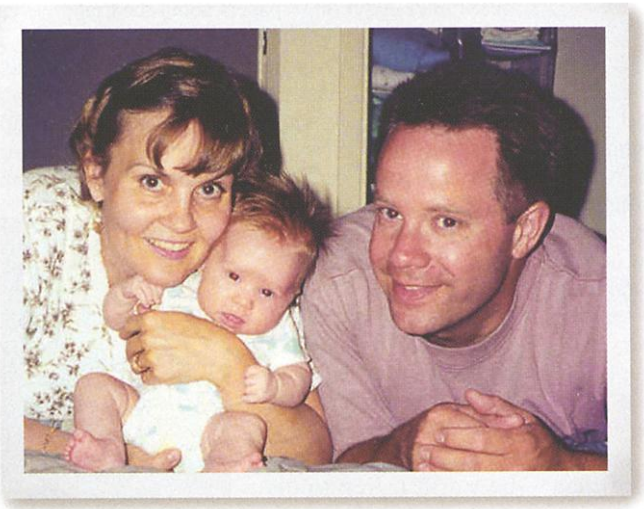
"We are going to see an explosion of newborn screening," predicts Edward McCabe, a pediatrician and geneticist at the University of California, Los Angeles. This explosion is triggered by a technology developed to identify one particular metabolic disorder. In an unplanned bonus, it enables screeners to find at least two dozen others in one fell swoop. As a result, U.S. states, which began mandatory screening programs in the 1960s and now monitor 4 million births a year, might soon quadruple the amount of genetic disease data they collect and interpret. And many are unprepared. Countries in Europe and Asia are grappling with the same issues.

Public health experts have argued for moving slowly. They say that the new technology will generate false alarms, trigger costly backup tests, focus on rare diseases for which there are no treatments, strain counseling services, and burden families with medical costs. But advocates of expanded screening regard these arguments as a smoke screen put up by states that lack funding for the new equipment or don't want to turn the job over to others. They ask: How can it be wrong to want more information about what ails a child, especially if it could save a life?

The making of an activist

Sirpa Waananen, a new recruit to the movement, expresses these views with a passion born of personal experience. She's outraged that her own state, California, has delayed offering parents the new screening technology, called tandem mass spectrometry. She became an activist after her 4-month-old daughter, Nora, died last summer of a metabolic disorder called long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency.

Waananen's education about LCHAD deficiency began on 9 August, she says. Before driving home from her first day of training as a flight attendant, she phoned her sister in Northern California to see how Nora was doing. The baby seemed very sleepy, her sister said. They consulted a pediatrician, who advised a trip to the emergency room. The emergency room doctors couldn't identify a problem at first. But by the time Waananen got to the hospital, she says, her normal, happy baby had slipped into a coma, and "I came home to a dead child."



Radicalized. Sirpa and Jay Waananen with Nora, who died at 4 months from an undetected metabolic disorder.

CREDIT: S. AND J. WAANANEN

Postmortem tests Waananen arranged at the Mayo Clinic in Rochester, Minnesota, produced unequivocal results: Nora had genes from both parents that had made her liver unable to process long-chain fatty acids, placing her at risk for sudden metabolic collapse. A recent Mayo Clinic study by Piero Rinaldo estimates that 5% of deaths in the United States attributed to sudden infant death syndrome are caused by such metabolic disorders.

Waananen claims, with medical backing, that Nora could be alive today if her LCHAD deficiency had been diagnosed. The disease can be fatal but might also be controlled by diet and monitoring. Waananen is angry that for 2 years California has owned tandem mass spec machines that could screen for metabolic disorders but hasn't used them. The state didn't have the logistical support, according to an official. Nor has it informed parents about private testing, Waananen claims, because she believes "a damned ethicist" argued that it would place an extra burden on poor families.

The controversy has erupted in other states—including Mississippi and Illinois, where legislatures have passed or are considering laws requiring that parents be informed about private tandem mass spec testing for diseases such as LCHAD deficiency and similar metabolic disorders. Several states already offer it, and more, including California, are launching pilot studies (see map, p. 2274).

McCabe, who chairs the top U.S. government advisory committee on genetic testing, says tandem mass spec is coming, whether we're ready or not. In the past, he argued against too rapid deployment, on the grounds that health agencies would be hard pressed to track and retest children, much less treat all those tagged with positive results. But now, he acknowledges, the revolution is at hand: "Let's identify whatever [disorders] we can and try to develop resources to treat the children."

The machines

Tandem mass spec was developed a decade ago by researchers at Duke University in Durham, North Carolina, in collaboration with the North Carolina health department. The "big deal at that time," recalls toxicologist Donald Chace, was Reye syndrome, a pattern of infant deaths tied to aspirin. The

Duke team—which included Chace, now at a private company; David Millington, still at Duke; and Charles Roe, now at Baylor College of Medicine in Houston—wanted to identify inherited metabolic disorders that are distinct from Reye syndrome but might be confused with it. By combining two mass spectrometers, they developed a way to scan blood proteins and yield a clear profile of a fatty acid oxidation disorder called medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. It occurs in 1 of roughly 15,000 babies of European ancestry, a prevalence comparable to that of phenylketonuria (PKU), a disorder for which many countries already require screening. Both MCAD deficiency and PKU can lead to serious brain damage, but if the disorders are detected early enough, damage can be avoided through strict dietary controls.

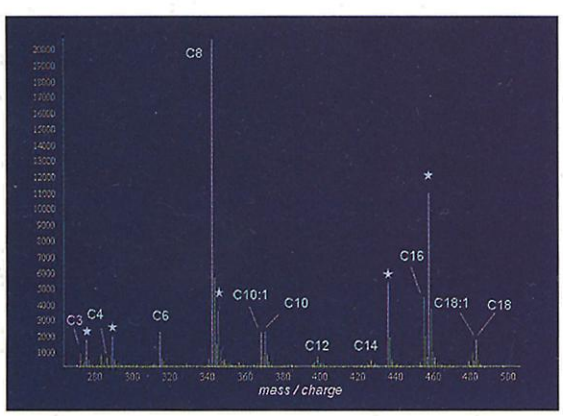
Tandem mass spec works like a coin-sorting machine, Chace explains. A sample is injected into the first instrument, which weighs the mass of the molecules, creating a precise inventory of types, like nickels, dimes, and quarters. Then the molecules are fragmented and passed through a tube to the second machine, whose task is streamlined for speed: It looks for unique fragments of just 65 metabolites, tallying the quantities of each. "It is very accurate and fast," he says, yielding a metabolic profile in about 2 minutes. A skilled interpreter can spot abnormal patterns and get confirmatory testing.

The team created software and began doing metabolic profiles of newborns in the early 1990s, with backing from a company called Neo Gen Screening in Pittsburgh, Pennsylvania. Neo Gen has deep roots in this community. Its founder and president, Edwin Naylor, was a postdoc under Robert Guthrie, a microbiologist at the State University of New York, Buffalo, who pioneered U.S. newborn screening. Guthrie, who had a PKU-affected child, created a cheap system to check for this disorder, detectable by excess phenylalanine in the blood. The system Guthrie invented, now used globally, involves taking a few drops of blood from every newborn and depositing them on filter paper. The papers are sent to a central lab, where technicians punch out samples and place extracts on bacteria that grow when exposed to phenylalanine. With child advocacy groups, Guthrie lobbied to get state health labs to adopt the system in the 1960s. Aiming to reduce the public cost of caring for PKU-affected children, all 50 states have mandated PKU screening.

Low-tech. State and private labs use a system designed in the 1960s to collect blood spots from 4 million U.S. newborns each year. They can be used to screen for many diseases.

The blood drops collected from every newborn in the United States for PKU testing are key to the impending massive expansion of diagnostic screening. As Chace explains, the cheap and easily stored Guthrie papers work perfectly well for tandem mass spec or more sophisticated DNA testing.

Naylor started using tandem mass spec for newborn screening in 1992 at the Magee-Womens Hospital in Pittsburgh; 2 years later, he spun off the lab as his own company, Neo Gen. Chace joined the company as chief scientist in 1997. For the cost of processing a single sample for PKU, Neo Gen added a screen for MCAD deficiency; now it promises to check for a total of 43 disorders at $25 a child. The company has also added many specialized tests to its menu, including ones for cystic fibrosis and sickle cell disease. It is investigating direct DNA-based screening for hearing loss and other diseases. Naylor boasts: "We became the first program anywhere in the world using tandem mass spectrometry for routine newborn screening." Several other nongovernment labs, including those at Baylor and the Mayo Clinic, also offer a variety of tests.



CREDITS: D. CHACE/NEO GEN SCREENING

High-tech. Tandem mass spectrometry quickly reveals anomalies, like this C8 spike indicative of MCAD deficiency.

Mounting pressure

When advocacy groups* heard of the new technology, they teamed up with its long-time local champions, such as geneticist Harvey Levy of Children's Hospital in Boston, to have it adopted for MCAD deficiency screening.

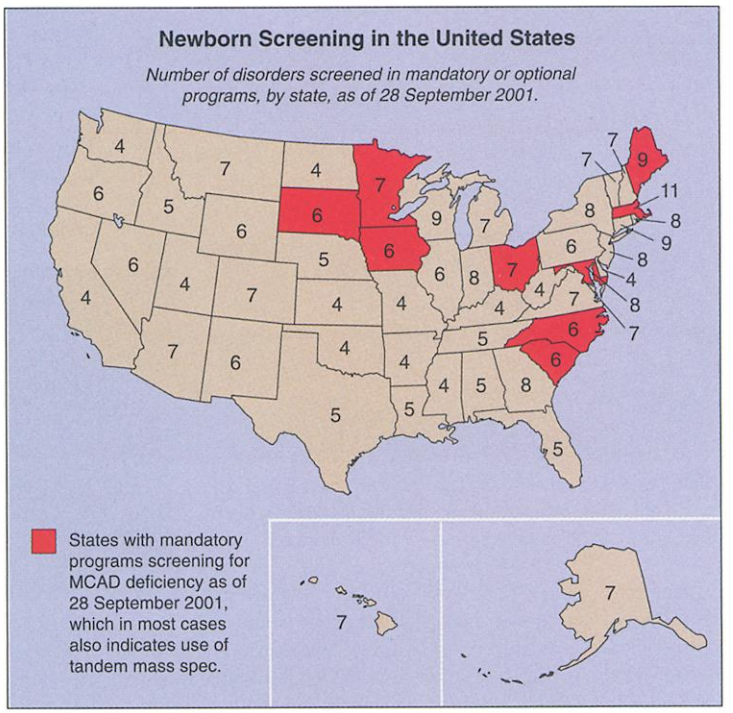
In March 1999, according to Trish Mullaley of the National Coalition for PKU and Allied Disorders, "all the support groups got together in the Boston area and said, 'We need to form a coalition.' " They realized that tandem mass spec could quickly and cheaply pick up a wide variety of devastating problems, "all of them different but all similar" in that early intervention improves survival, says Mullaley. "We were tired of hearing that a baby does OK in Massachusetts because we have screening, but a child with the same disorder in Maine has brain damage."

The drive led to a "supplemental" program in five New England states, all of which send samples to Massachusetts for testing. The pilot project—like many public screening programs in the United States and Europe—gathers more data than it reports, informing parents only of disorders that are considered treatable. Before they are enrolled, parents are asked if they want to opt out, but they aren't asked for consent. (Maryland is an exception; it obtains written consent.) Only about 3% opt out. "The pilot program is a good approach," Mullaley believes: "It allows [Massachusetts] to collect data for a mandated program down the road."

* Prominent advocacy groups include the Fatty Oxidation Disorders Family Support Group in Greensboro, North Carolina; the March of Dimes Birth Defects Foundation in White Plains, New York; the National Coalition for PKU and Allied Disorders in Mansfield, Massachusetts; the National Urea Cycle Disorders Foundation in La Canada, California; and the Tyler for Life Foundation in Winston, Georgia. Some have teamed up with Neo Gen, referencing it on their Web sites.

This fall, the March of Dimes added its clout to the campaign. It decided to include MCAD deficiency as one of the "minimum core tests" recommended for all newborns, says associate medical director Nancy Green. "This has tremendous implications for us and for the field," she acknowledges, because tandem mass spec is required to do MCAD deficiency testing efficiently, according to Green. The new policy means that the March of Dimes "will be lobbying in every state to try to get legislators to appropriate resources" to use this technology.

In addition to popular support, tandem mass spec is getting a boost from the courts: Lawsuits by families of sick children who were not screened are forcing hospitals to pay attention. One lawyer who's made a name taking these cases to court is Charles Hehmeyer of Philadelphia, Pennsylvania. He rejects arguments that only the most treatable metabolic disorders, such as MCAD deficiency, should be screened for, and he grumbles that experts defend their caution with a familiar Catch-22: "We can't do the screening [for new disorders] because we don't have validated results" on the rate of false positives. They don't have the results, he argues, because they won't do expanded screening. But that's changing.



The programs

Government labs are moving into the field as quickly as they can afford to do it themselves, although quality and test criteria are far from uniform. A handful of U.S. states are using tandem mass spec. Elsewhere, Australia took an early interest, and the public screening program in New South Wales has been using tandem mass spec since 1997. In Europe, Germany appears to be leading the way, according to Adelbert Roscher, Bavaria's director of newborn screening. Bavaria ran a large trial that screened 350,000 newborns with tandem mass spec. The "overwhelmingly positive results," Roscher says, along with good data from a study in Heidelberg, persuaded the government to commit to screening all newborns in Germany using this technology by the end of 2002. But Roscher adds that the program will focus at first on very few disorders.

The Netherlands has begun a study of tandem mass spec for MCAD deficiency testing, according to Rodney Pollitt of Children's Hospital in Sheffield, U.K., a leader in newborn screening. France has not embraced the technology, nor has Japan. But Britain is moving toward it, Pollitt says, albeit unevenly. Six large U.K. labs have already switched to tandem mass spec for PKU testing, according to Pollitt, but proposals to add MCAD deficiency and other disorders have "become stuck in disagreements between various academic factions"—and they "lack funding."

In Britain, a major assessment in 1997 found justification for adding MCAD deficiency and possibly three other disorders to the newborn screening regimen. But it rejected most candidates because the disorders were rare and because the children were likely to be profoundly disabled in any case. And the report refused to give tandem mass spec a general endorsement, noting that "there is insufficient evidence to assess the economic value of screening for other inborn errors of metabolism"—that is, other than PKU.

The issue of children's long-term outlook—and whether early identification makes a difference—is a hot topic among many U.S. advisory committees too, according to geneticist Brad Therrell of the University of Texas Health Science Center in San Antonio. "We are having lots of debates over how important is it that you have a cure or treatment" for disorders to be included in a routine screen, he says. "Not all these disorders are treatable or have the right kind of outcome," he notes. But like McCabe, he feels that more studies are showing that children with inherited disorders do benefit from early treatment—even if their long-term chances are not good—and that the prevailing view now is: "Let's learn more about the disorders and hope that we can develop cures and treatments."

The debate is no longer hypothetical in California, which is preparing now to take the plunge into expanded newborn screening. The largest U.S. jurisdiction to embrace mass spec—with over 520,000 newborns to screen annually—California is moving carefully toward a January launch of its new pilot program. George Cunningham, director of the state program, says Waananen is correct: The state has owned two machines for a couple of years. But, he explains, "we couldn't offer the service statewide until we had a funding mechanism" to pay for the expanded testing, follow-up, and quality control. "To set up a coordinated system is very complicated," and "we didn't get any new positions to staff the program, so we were not in a position to absorb another big workload."

But the legislature has doled out a funding increase of $3.9 million and ordered the program to move along. A mandated report on results from the pilot is already late. But Cunningham, an advocate of expanded screening, says he is determined to avoid mistakes others have made, such as generating "a lot of false positives." He doesn't want people to have to come in for expensive confirmatory testing that causes anxiety and possibly wouldn't be covered by insurance.

Positive MCAD deficiency results will definitely be reported to parents, but Cunningham says the biochemical "cutoff values" could be different in California because its screening population is not mainly European but 50% Hispanic. "We will be collecting normal values by more than 16 ethnic groups," Cunningham says. But the state will be cautious about adding new disorders to the reporting list from the 20 to 30 that might be identified. For those with a poor outcome, "it may not be useful" to promise results because it won't be possible to offer informed counseling or therapy.

Although the penetration of tandem mass spec into public screening programs might be patchy and uneven, it is advancing rapidly. The age of "genetics in action," as Green of the March of Dimes calls it, has arrived. It's no longer a question of "can we do this?" says McCabe. The question is: "How are we going to finance it?" And the states that are rushing ahead to expand the scope of newborn screening might not be ready for the consequences. –ELIOT MARSHALL