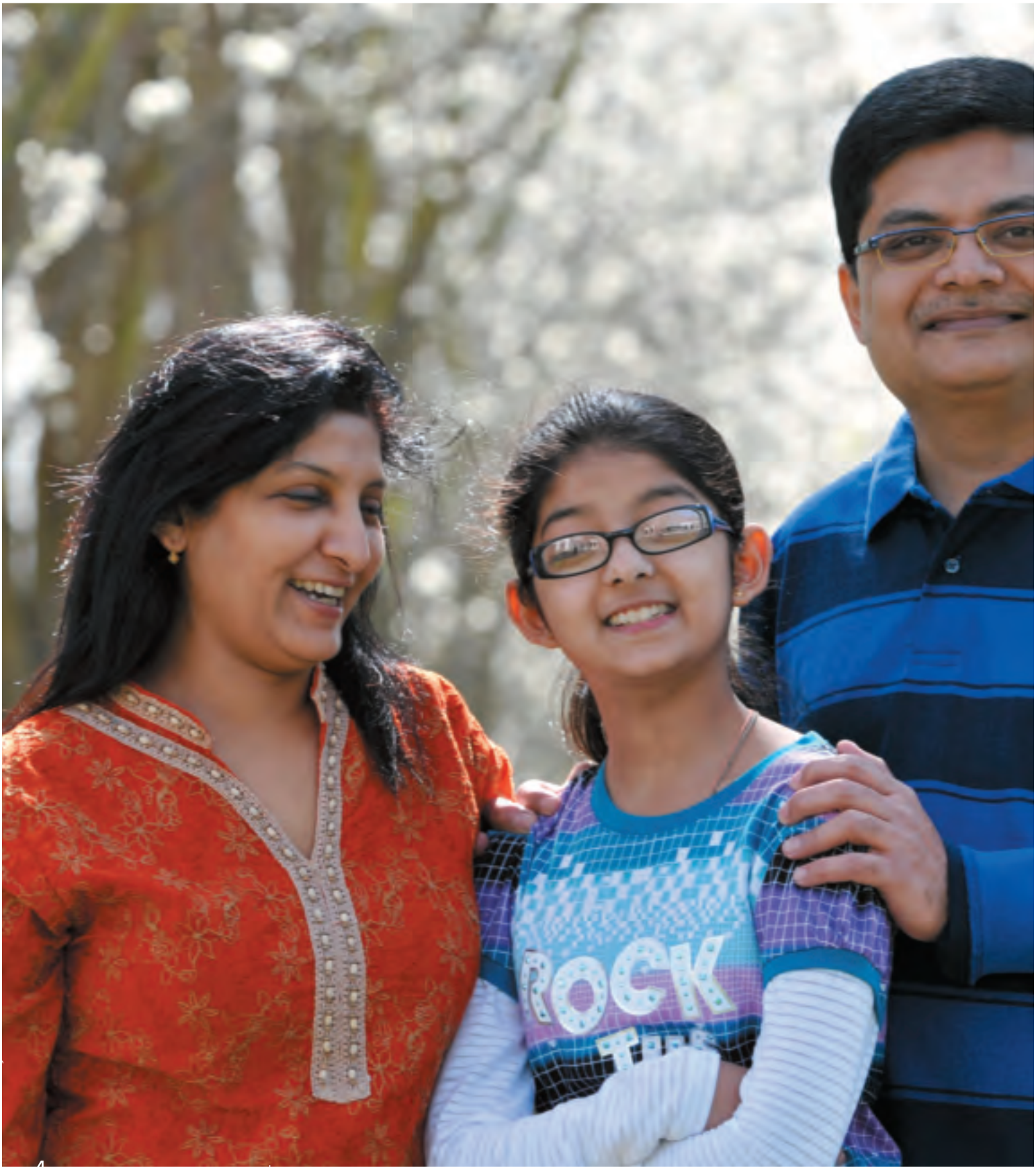
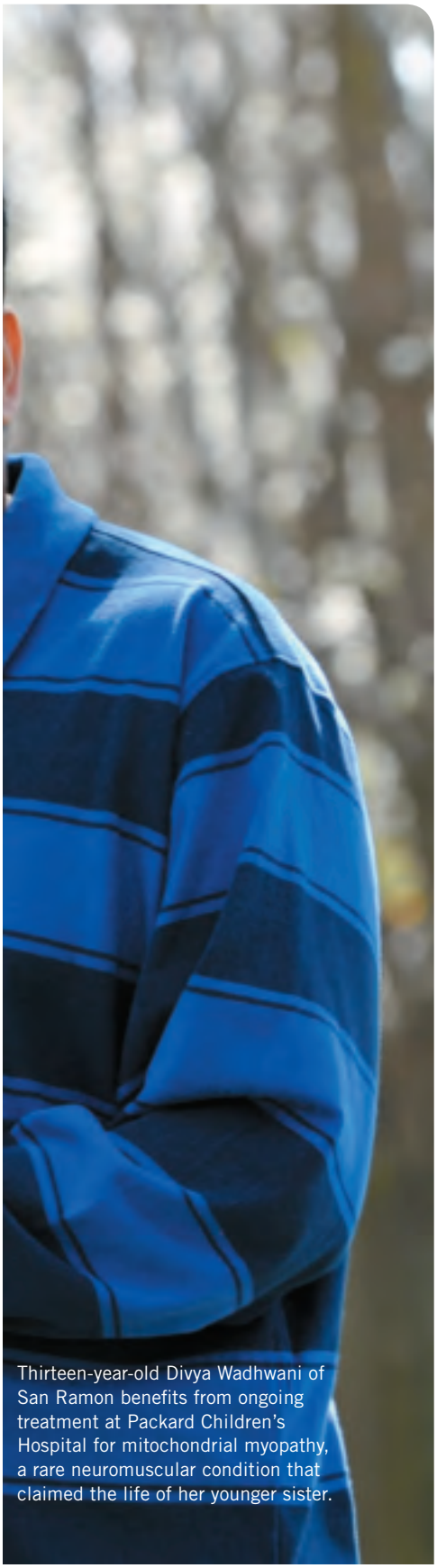
By Mark Shwartz

Living on



Hope

Researchers Pursue Improved Treatments for Rare, Complex Metabolic Disorders



Thirteen-year-old Divya Wadhwani of San Ramon benefits from ongoing treatment at Packard Children's Hospital for mitochondrial myopathy, a rare neuromuscular condition that claimed the life of her younger sister.

For Divya Wadhwani, age 13, the search for the cause of her mysterious and debilitating muscle disorder turned into an eight-year, 8,000-mile odyssey that began when she was a small child in Mumbai, India.

"Divya was perfectly fine until age 4, when her nursery school told us that she was having episodes of slumping," recalls Mahesh Wadhwani, Divya's father. "They said that her knees were buckling, and that she was falling down."

At first, Divya's doctors suspected an iron deficiency or a rare neurodegenerative disease, but those causes were eventually ruled out, and her condition worsened.

Then, tragedy struck. Divya's 2-year-old sister, Mallika, developed uncontrollable seizures and died a few months later. Doctors began to suspect that Divya and Mallika shared a mitochondrial disease, an inherited disorder that wreaks havoc on the energy-producing part of the cell called the mitochondrion.

Unfortunately for Divya, there were no laboratories in Mumbai equipped to test for these rare conditions, which affect one in 4,000 children. Then, in 2004, her father got a job reassignment to the United States, and the family moved halfway around the world to San Ramon, Calif.

Within a few months, Divya was at Lucile Packard Children's Hospital under the care of Greg Enns, MD, one of the country's leading experts on mitochondrial disease. "I strongly believe that life is an interplay of destiny and fate," says Mahesh. "You try to put things together, and everything falls into place."

> "There are probably thousands like us who are carriers of this defect, and don't realize it until the symptoms show up in our children."
>
> ■ Mahesh Wadhwani, Divya's father

Enns, director of the Biochemical Genetics Program at Stanford University, ordered a muscle and nerve biopsy, which confirmed that Divya had indeed inherited some type of mitochondrial disorder—but which one?

"Dr. Enns said that it's like going to a mechanic," says Mahesh. "We know there's a problem with the engine, but we don't know exactly what is causing it, or how you go about fixing it. That's when the genetic pursuit started, and it took four more years of extensive workup, of trying to eliminate one thing or another, to find an answer."

Finally, last year, highly specialized tests of Divya's DNA revealed a defect in a gene called POLG1, which had only recently been identified as a cause of mitochondrial myopathy, a neuromuscular condition with a range of symptoms identical to those of Divya and her late sister, Mallika. The disease is recessive; a blood workup of Divya's parents confirmed the diagnosis.

"Dr. Enns is a gem of a person," says Mahesh. "Thanks to him, we're no longer groping in the dark. But there are probably thousands like us who are carriers of this defect, and don't realize it until the symptoms show up in our children."

Catching it Early

Mitochondrial diseases belong to a larger group of illnesses known as inherited metabolic disorders. Scientists have identified hundreds of these disorders, each caused by specific genetic mutations that damage key enzymes responsible for converting food into energy or for removing metabolic waste from our cells.

Their complexity makes many of these rare diseases extremely difficult to diagnose and treat. Because their conditions often masquerade as other illnesses, many children with symptoms of a metabolic disorder are brought to the experts at Packard Children's for a definitive diagnosis.

> "Some metabolic disorders scream their diagnosis clearly. Others, like Divya's, are more subtle and more difficult to diagnose conclusively."
>
> ■ Greg Enns, MD, Arline and Pete Harman Endowed Faculty Scholar

"Metabolic disorders are challenging to diagnose because they can be caused by so many different mutations affecting so many different genes," says Enns, the Arline and Pete Harman Endowed Faculty Scholar and an associate professor of pediatrics. There are many different kinds, he adds, each caused by a unique genetic defect. "Some metabolic disorders scream their diagnosis clearly. Others, like Divya's, are more subtle and more difficult to diagnose conclusively."

Metabolic disorders may be more common than scientists once assumed, says Tina Cowan, PhD, associate professor of pathology and director of the Stanford Clinical Biochemical Genetics Laboratory. In 2009 alone, the Stanford lab conducted nearly 6,500 tests for a wide range of metabolic disorders using blood samples collected from people of all ages—newborns to adults.

"We're set up to deliver rapid diagnosis and to guide the clinicians in the follow-up care," Cowan says (see sidebar, p. 9). "For us, the magic is really the collaboration between the lab and the clinic. Greg Enns and the other doctors tell us what they need, we tell them what we need, and we all work together to make things better for the patient."

Early diagnosis is the key to treating most metabolic disorders, notes Enns. "We're excited to be able to diagnose these kids before they have symptoms, because by the time they get sick, their organs can be irreversibly damaged," he says.

At Packard, expectant mothers can be tested even before their child is born. Louanne Hudgins, MD, the Mosbacher Family Distinguished Packard Fellow and chief of the Division of Medical Genetics at Stanford, and

Greg Enns, MD, and genetics counselor Rachel Cox, MS, (right) belong to a team of caregivers who coordinate treatments for children suffering from rare, inherited metabolic disorders.

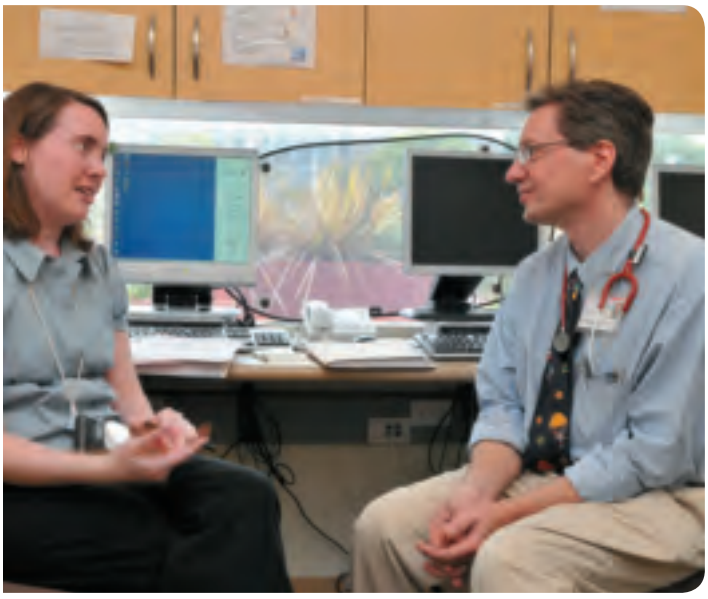
Enns, working jointly, recently diagnosed and treated a boy in the womb for ornithine transcarbamylase (OTC) deficiency, the most severe form of urea cycle defect, a disorder that occurs when the liver is missing a crucial enzyme that helps eliminate nitrogen waste. Without that enzyme, ammonia can build up in the bloodstream and cause severe brain damage if not treated quickly.

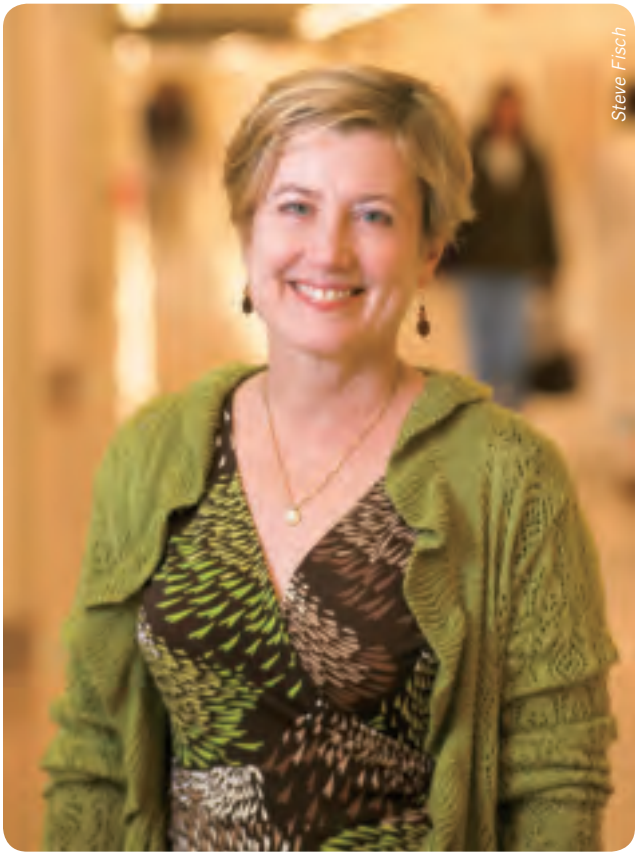
"We gave the mother a bolus of medication that lowered the ammonia while she was in labor, and when the boy was delivered, his ammonia levels were under control," says Enns. "When I was training, OTC deficiency was a death sentence or meant permanent neurological damage, at best. End of story. To see this boy stable and awaiting a liver transplant is definitely a step in the right direction. It's a wonderful era for biochemical genetics."

Newborn Screening

Early diagnosis took a giant leap forward in 2005 when the State of California expanded its newborn genetic screening program to include some 40 metabolic disorders. The screening process is simple: A few drops of blood are taken from the newborn's heel and shipped to a lab for analysis.

Newborn screening already has changed the prognoses for several metabolic disorders, including a disease called medium chain acyl-CoA dehydrogenase (MCAD) deficiency, in which a particular enzyme doesn't break down medium chain fats normally. "MCAD deficiency is the poster child for the expanded newborn screening program," says Enns. "MCAD children typically look fine, but if their body becomes stressed, say by a viral infection or flu, these kids can suffer fatal complications."





Louanne Hudgins, MD, is the Mosbacher Family Distinguished Packard Fellow and chief of the Division of Medical Genetics.

In the past, roughly two-thirds of children with MCAD deficiency died or ended up neurologically impaired. "But since newborn screening began, we've had tremendous success identifying and treating these children before they fall ill," says Enns. "Now it's unusual for a child with MCAD deficiency even to suffer neurological problems."

Enns was instrumental in convincing the California legislature to expand newborn screening to include metabolic disorders. Today, Packard is a designated Area Service Center, screening 100,000 newborns annually. When an infant tests positive, members of Enns' team, including genetics counselor Rachel Cox, MS, get the