



A MULTI-DISCIPLINARY APPROACH TO DIAGNOSIS CENTER FOR MARFAN SYNDROME DRAWS ON MANY EXPERTS TO IDENTIFY PATIENTS

Gwen Rohrer knew almost immediately that there was something unique about her newborn son, Dylan. "The doctors were measuring his head, and looking at his fingers," she says. Rohrer spent 17 months watching and worrying before an eye examination and an echocardiograph cemented the diagnosis: Dylan had Marfan syndrome, a connective tissue disorder caused by mutations in the fibrillin 1 gene.

Dylan, now 12 years old, came to Lucile Packard Children's Hospital in 1991 to consult with pediatric specialists at the Stanford University Center for Marfan Syndrome and Related Connective Tissue Disorders. Founded in 1988 by cardiovascular surgeon D. Craig Miller, MD, the center is one of only about five comprehensive

centers in the nation specializing in Marfan syndrome. It brings together many physicians and disciplines to treat every aspect of pediatric and adult Marfan cases.

A DIFFICULT DIAGNOSIS

Although Marfan syndrome affects about one in 5,000 people, many don't know they have the disorder. The severity and number of physical symptoms of Marfan syndrome can vary wildly, making accurate diagnosis difficult, particularly in children. People with Marfan syndrome are frequently tall, with loose joints and disproportionately long arms, legs and fingers. They may have long narrow faces with deeply set eyes and sunken or protruding chests. Many also experience lens dislocations, which can cause blindness, and painfully flat feet.

Although some people with Marfan syndrome are clearly affected, the relatively mild signs exhibited by many can be passed off as intriguing, but not alarming, quirks of nature. A rapidly growing adolescent might appear thin and gangly but not have Marfan syndrome. Dismissing warning signs is a high-stakes game, however; if left undiagnosed, the weakened connective tissue of the aorta can rupture, causing a life-threatening aortic dissection.

"There is no single diagnostic test for Marfan," says Dan Murphy, MD, pediatric cardiologist at Packard Children's Hospital. Because Marfan syndrome can be caused by more than 100 different mutations in the very



DANIEL MURPHY, MD,
Pediatric Cardiologist at
LPCH and
DAVID LIANG, MD, PHD,
Cardiologist at Stanford
Hospital & Clinics

large fibrillin 1 gene, genetic testing is often not a practical means of diagnosing the condition.

"We rely on careful clinical evaluation by a group of physicians with extensive experience," Murphy says. "Kids are

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A MULTI-DISCIPLINARY APPROACH TO DIAGNOSIS

CENTER FOR MARFAN SYNDROME DRAWS ON MANY EXPERTS TO IDENTIFY PATIENTS

Continued from cover

sometimes referred after a visit to an ophthalmologist or orthopedist, but some of the signs can be very subtle. The center allows us to provide the children with a uniform medical evaluation, with all of the experts in one place, communicating with one another.”

“We can't always tell with 100 percent certainty after looking at a patient,” agrees Stanford Hospital & Clinics cardiologist David Liang, MD, PhD. “Diagnosis still is a little bit of an art.” Because an affected parent has a 50-percent chance of passing Marfan syndrome to a child, Liang and Murphy also consider a patient's family history. But a spotless background doesn't guarantee a clean bill of health: the mutations that cause the syndrome can also arise spontaneously within the egg or the sperm of an unaffected parent.

EARLY DETECTION IS CRITICAL

A generation ago, the life expectancy for a person with Marfan syndrome hovered in the 30s. However, early diagnosis, coupled with the use of beta blockers to reduce blood pressure and surgery to replace an expanding aortic root with tougher man-made materials, allow many Marfan patients to live into their 70s and beyond. After diagnosis, a child returns regularly to the center for ongoing monitoring of the size of the aorta and other medical problems that are caused by Marfan syndrome.

“One thing about Marfan syndrome is that everybody is different,” says Murphy. “We want the kid to see the ophthalmologist to get their eyes taken care of. We may want them to see the orthopedist, because scoliosis and foot deformities can cause serious disability. It's also very important to teach the family about the syndrome and the importance of the medication.”

The center brings together pediatric and adult experts from cardiovascular medicine, cardiothoracic surgery, genetics, ophthalmology and orthopedics,

MARFAN QUICK FACTS:

- Affects one in 5000 people
- Can be difficult to diagnose
- Often fatal in early adulthood if not treated
- Caused by more than 100 different mutations in a single gene
- Patients can live a normal lifespan with proper monitoring
- Children of affected parents have a 50 percent chance of inheriting Marfan syndrome

MARFAN TIP-OFFS:

- Disproportionately long arms, legs and fingers
- Loose joints
- Scoliosis
- Sunken or protruding chest
- Long, narrow face with deeply set eyes and shallow cheekbones
- Flat feet and long toes
- Lens dislocations or nearsightedness

Not all symptoms are necessary for a diagnosis.

as well as physicians specializing in obstetrics, gynecology, urology, neurology, endocrinology, rheumatology and thoracic surgery, to help both the children and their families.

As children with Marfan syndrome grow older, they may rebel against the disease that prevents them from playing contact sports and leaves them looking different from their peers. Some might even stop taking their heart medication in an effort to just be normal.

“In the last 12 years I've seen two teenagers who came in with much larger aortas than the year before,” says Murphy. “In both cases the kids had stopped taking their medicine. We can do things to keep the patient's lifestyle as normal as possible and improve the survival, but it relies on teamwork with the patient. Most would not consider themselves to be particularly limited.”

Over the years, Packard physicians worked together to correct Dylan's scoliosis and sunken chest, monitor his heart function and repair his failing mitral valve. They now expect Dylan to live a normal life span, thanks to ongoing management that requires the expertise and coordination of many different disciplines. “It used to be you just had to wait for the person to die,” says Rohrer. “Nowadays, doctors fix them. They do miracles.”

The Center for Marfan Syndrome and Related Connective Tissue Disorders brings together many disciplines to provide a uniform evaluation and address all aspects of clinical care:

- Cardiovascular medicine
- Cardiothoracic surgery
- Genetics
- Ophthalmology
- Orthopedics
- Obstetrics
- Gynecology
- Urology
- Neurology
- Endocrinology
- Rheumatology

For more information about Marfan syndrome contact the National Marfan Foundation at www.marfan.org. To contact the Stanford Center for Marfan Syndrome and Related Connective Tissue Disorders, call patient coordinator Sunny Pellone at 650-725-8246 or visit the center's website at Marfan.stanford.edu.



LPCH WELCOMES NEW DIRECTOR OF CARDIOVASCULAR INTENSIVE CARE UNIT

Stephen J. Roth, MD, MPH, a nationally recognized cardiac intensivist and researcher at Children’s Hospital Boston, has been named director of the cardiovascular intensive care unit at Lucile Packard Children’s Hospital at Stanford, effective October 1.

“Dr. Roth is a wonderful addition to our team,” says Frank L. Hanley, MD, director of the Children’s Heart Center at Packard. “His exceptional experience and leadership skills will further enhance our ability to treat children needing this very special care.”

A FOCUS ON CARDIAC PATIENTS

Besides overseeing patient care in the CVICU, Roth will be developing new hospital programs focusing on clinical care, research and training in the subspecialty of pediatric cardiac intensive care. Roth will also be appointed an associate professor of pediatrics at the Stanford University School of Medicine.

Daniel Bernstein, MD, Packard’s chief of pediatric cardiology and co-director of the Children’s Heart Center, lauded Roth’s “national reputation as a splendid teacher, researcher, clinician and team builder. Best of all, he’s a first-rate physician who’s a proven and compassionate leader in the post-surgical care of children with congenital heart defects.”

At Children’s Hospital Boston, Roth was the associate director of the cardiac intensive care unit and the director of



STEPHEN ROTH, MD, MPH

Director of LPCH
Cardiovascular Intensive
Care Unit

clinical research. He was also associate chief of the division of intensive care cardiology and an assistant professor of pediatrics at Harvard Medical School.

“This is a great opportunity for me,” says Roth. “The Children’s Heart Center at Packard is bringing together an outstanding group of cardiologists, surgeons, anesthesiologists and nurses who are dedicated to the care of children with heart disease. As director of the CVICU, I look forward to collaborating with this multi-disciplinary group to manage these children.”

RESEARCH INTERESTS

Roth’s research, teaching and patient care contributions are extensive. His research leadership has been primarily focused on the reduction of postoperative morbidity and mortality of children who require major cardiac surgery. Roth has been a co-principal investigator in several clinical trials of both groundbreaking surgical techniques and investigational drugs.

His current research focus is on the design and execution of prospective clinical trials in pediatric cardiac patients and includes participation as a co-principal investigator and steering committee member in the NIH-sponsored Pediatric Heart Network. As a member of Harvard’s faculty, Roth played a leading role in educating

cardiologists and cardiology trainees in the critical care of children with both congenital and acquired heart disease. He plans to continue this role in building a major training program in this specialty at Packard.

Roth received his MD at the Yale University School of Medicine and his MPH at the Harvard School of Public Health. His undergraduate degree in biochemical sciences is also from Harvard. He has been published extensively in peer-reviewed medical journals, has lectured internationally about pediatric cardiovascular health and disease and has been listed by the group Best Doctors in America as one of the nation’s leading physicians.

To Packard’s chief of pediatric intensive care, Lorry Frankel, MD, “Dr. Roth’s background, experience and reputation for innovation will play an important role in helping us achieve our vision.”

Roth called his move to Packard Children’s Hospital “exciting,” adding that, “among children’s hospitals in the country, Packard has developed a high degree of momentum, and this is especially the case within the Children’s Heart Center. It’s very appealing to be a part of a team that is focused on developing innovative therapies for children with congenital heart defects.”

“Packard has developed a high degree of momentum, and this is especially the case within the Children’s Heart Center,” Roth says.

COMPARING OUTCOMES TO IMPROVE QUALITY IN PERINATAL CARE



**JEFFREY GOULD,
MD, MPH**
LPCH Neonatologist

Peer pressure can be a good thing. That is, if it's used to ensure that everyone benefits equally from proven medical techniques. Lucile Packard Children's Hospital neonatologist Jeffrey Gould, MD, MPH, has a lot invested in the idea that hospitals around the state can improve the quality of their care simply by comparing themselves to their peers.

"Our goal is to improve the health of pregnant women and newborns by making sure that approaches to illness that have been demonstrated to be effective are actually being carried out," says Gould, a professor of pediatrics and director of the perinatal epidemiology and health outcomes research unit at Packard Children's Hospital and the Stanford University School of Medicine. He is the principal investigator of the California Perinatal Quality Care Collaborative, or CPQCC, conceived to provide a better way to evaluate neonatal care provided by specific hospitals.

DEVELOPING NEW METRICS

Neonatal health has been steadily improving over the past several years, thanks to medical advances that allow physicians to keep smaller and smaller babies alive. From a statistical standpoint, however, such good news is a mixed blessing.

"We have always used mortality as an index for quality of care," says Gould, "but it is becoming difficult to judge a hospital on that basis, because mortality is becoming such an uncommon event. Fortunately, very few infants die."

CPQCC provides interactive web-based databases that allow individual member hospitals to assess their performance in scores of neonatal outcomes, such as their relative rates of nosocomial infection and chronic lung

disease in babies of various weights. Significant deviations from benchmark goals set by the group's Perinatal Quality Improvement Panel can highlight practices that may need to be changed. More than 60 hospitals in the state are members of the group, accounting for nearly all of the major neonatal intensive care units.

Another unique aspect of the effort is the number of different organizations involved. The California Department of Health Services, the Office of Statewide Health Planning and Development, the Regional Perinatal Programs of California, the Pacific Business Group on Health and the David and Lucile Packard Foundation are just a few that are working to meet the challenge of providing better care for newborns.

"When states do initiate widespread quality improvement programs," says Gould, "it's usually from top down. In this case, the California Association of Neonatologists has been instrumental in establishing CPQCC. We have a tremendous base of neonatal and obstetric experts to prepare toolkits for member hospitals, and we prepare databases to allow them to know how they're doing."

The toolkits, which can be freely downloaded from the group's website, include evidence for particular clinical approaches and information about how to implement best practices. Four toolkits now available address common issues and decisions facing many obstetricians and neonatologists: antenatal steroid treatment, postnatal steroid administration, nosocomial infection prevention and improving initial lung function. A toolkit focusing on feeding practices in premature infants is planned for future distribution.

"Another thing on the drawing board is an effort to address the unique needs of California's very rural hospitals," says Gould. "While most of the databases available today are centered around the major cities, a huge part of the state is quite isolated. No one has ever tried to

determine how to modify teaching programs and care improvement efforts to be more useful to rural hospitals."

A PERINATAL DATA CENTER

In addition to providing member hospitals throughout the state with up-to-date assessment of their performances, the CPQCC data center, managed by Gould, is a gold mine of statistics about neonatal health in California. Gould and his colleagues at Packard Children's Hospital will use the information to catalogue neonatal illnesses and outcomes in order to identify previously unseen associations between social, biological and healthcare factors.

"We want to understand why some infants in difficult health situations get through fine, while others, subjected to the same stresses, end up with chronic respiratory problems and brain damage," says Gould. "Is it something that we are missing clinically, or is there a biological basis that we have just not learned about yet? We are in a very good position to finally understand some of these issues."

The combination of many different disciplines and experts at Packard Children's Hospital and Stanford University School of Medicine make the hospital an excellent place to tackle such questions.

"There are world leaders in perinatal medicine, genetics, infant development, social sciences and health services research at Stanford and Packard Children's Hospital," says Gould. "Having a vision that combines these things is extremely important. Given an appropriate research platform, these experts will be able to advance our understanding of perinatal illness and to design special interventions to prevent and cure these conditions."

For more information about the California Perinatal Quality Care Collaborative, or to download specific toolkits, visit www.cpqcc.org or call 650-723-5763. Dr. Gould can be reached at 650-723-5711.



THE WEEKEND MYTH

CPQCC FINDS WEEKEND BIRTHS DO NOT HAVE HIGHER MORTALITY RATES

The California Perinatal Quality Care Collaborative strives to correlate neonatal outcomes with quality of care in more than 60 neonatal intensive care units throughout the state (see accompanying story). Recently CPQCC researchers at Lucile Packard Children's Hospital, the University of California, Berkeley and the State Department of Health Services used data from the effort to debunk long-standing concerns about higher mortality rates associated with weekend vs. weekday births.



"We've found that weekends are not an inherently more dangerous time to be born," said senior author and neonatologist Jeffrey Gould, MD, MPH. "Instead, the fact that there is a proportionally higher percentage of very tiny babies—who are more likely to die—born on weekends than during the week inflates the observed mortality."

Weekend deliveries have been saddled with a seemingly deadly reputation after studies published in the 1970s and '80s suggested that infants born on weekends are more likely to die than those born during the week. "One thing these studies didn't do, however," says Gould, who is also a professor of pediatrics at the Stanford University School of Medicine, "was control for the fact that there might have been more emergency births on the weekend."

Gould and his colleagues at CPQCC pooled data from more than 1.5 million births throughout California from 1995 to 1997 to confirm that overall neonatal mortality increased on Saturdays and Sundays. However, they also found that weekends accounted for 17.5 percent fewer births than would be expected had the births been distributed randomly. When they homed in on the birth weights of this subset of newborns, they discovered why.

Many physicians prefer to induce labor in women whose fetuses are at risk but

healthy enough for delivery during the week, when ample support staff is available. The same is true of cesarean sections, which were used to deliver about 20 percent of the infants in the study.

But while jump-starting labor or performing a cesarean is a reliable way to get a baby out, it is much harder to thwart premature labor to keep a small, underdeveloped baby in the uterus. The battle to prevent delivery of these sickest fetuses can as easily be lost on the weekend as during the week. The researchers found that 0.95 percent of infants born during the week could be classified as "very low birth weight." In contrast, infants of very low birth weight made up 1.1 percent of all weekend births.

When the researchers correlated mortality rates with birth weight, the difference between weekday and weekend birth vanished, confirming their theory: Fewer deliveries of more acutely ill newborns create the perception that all weekend births are more dangerous. The finding, which was published in the June 11 issue of the *Journal of the American Medical Association*, should relieve concerns that the higher death rates are due to inadequacies in hospital staffing or experience and allay the fears of women with uncomplicated, full-term pregnancies who begin labor on the weekend.

VACCINE TRIAL:

A CALL FOR PEDIATRIC VOLUNTEERS

A flu shot in the fall can prevent a nasty bout of illness in the winter. Lucile Packard Children's Hospital researchers are seeking healthy children between the ages of three and nine who received the flu vaccine last season to participate in a study of children's immune response to influenza.

Just in case potential volunteers aren't won over by altruism, the researchers are offering \$30 per visit to kids willing to donate blood samples three times: twice before receiving the vaccine and once one month later. A numbing cream will be used to minimize this discomfort to the child, and the flu shot is free.

"We're finding that people in the medical field are volunteering their own kids," says study coordinator Nancy Bouvier, PNP. "Parents are using the hook 'Well, you're going to get the flu vaccine anyway, so here's a chance to make some money'."

For more information or to enroll in the study, call Bouvier at 650-498-7284.

RESEARCH MAY IMPROVE ANTI-REJECTION TREATMENT

MICROARRAYS CAN PINPOINT CERTAIN TRANSPLANT RISKS



MINNIE SARWAL, MD
LPCH Nephrologist and
Molecular Immunologist

A simple test may pinpoint children at high risk of rejecting newly transplanted kidneys, say researchers at Lucile Packard Children's Hospital and the Stanford University School of Medicine. The research, which also identifies more than one type of acute rejection, may increase the long-term survival of transplant patients and reduce the severe side effects caused by common anti-rejection drugs.

Acute rejection affects 15 percent to 40 percent of kidney transplant recipients nationwide and is a leading cause of retransplantation or death in these patients. Although the tissue inflammation and cell damage that spell trouble for a transplanted organ are easily diagnosed with a light microscope, this technique can't identify the molecular rabble-rousers at the root of the problem. As a result, physicians have wondered whether patients experience more than one type of acute rejection.

A CELLULAR VIEW OF REJECTION

In a new study published in the July 10 issue of the *New England Journal of Medicine*, Packard Children's Hospital pediatric nephrologist and molecular immunologist Minnie Sarwal, MD, PhD, used microarray technology to peek behind the scenes in more than 60 pediatric kidney transplant patients. The technique, which simultaneously examines more than 12,000

unique human genes, allowed lead author Sarwal and her colleagues to divide episodes of acute rejection into at least three distinct subgroups based on their global gene-expression profiles.

Surprisingly, one of the three subgroups associated with particularly poor outcomes expressed many genes specific to B cells, which had previously been cleared of significant wrongdoing in transplant rejection. Further research pinpointed clumps of B cells within slices of the transplant tissue. The presence of the cells suggested a way for physicians to better employ anti-rejection drugs.

"Although physicians realize that clinical responses to treatment for acute rejection range from complete response to no response, we currently have very few clues to target the high-risk patient group or to individualize treatment," says Sarwal, who is also an assistant professor of pediatrics at the Stanford School of Medicine. "If we can now figure out which of the more serious rejections are due to these B cells, we can treat them completely differently, perhaps by using antibodies to specifically wipe out B cells in these patients."

T cells traditionally have been pegged as primary troublemakers for transplant recipients. While anti-rejection drugs such as steroids do a good job mollifying agitated T cells marshalling for an attack, B cells have mostly been ignored because they make up a relatively small proportion of host cells in the transplanted tissue. The researchers found, however, that when kidneys became peppered with B cells after transplantation, steroid treatment was less successful in treating the rejection.

"What's happened is we've failed to realize that the immune system is very clever and redundant," says Sarwal. "It may have developed a mechanism to assist the T cells to attack the transplanted kidney by recruiting the B cells, which rev up the T cells and increase their efficiency."

Although a simple laboratory test can identify congregations of B cells, most episodes of acute rejection are currently treated in a hit-or-miss fashion.

"We may waste two to three days giving high doses of steroids only to find the rejection episode is steroid-resistant," says Sarwal. "Even when we then try antibody therapy, many of these patients will fail to get all their kidney function back, and are more likely to lose their kidney over time." Indiscriminate use of anti-rejection drugs can also cause other problems, including growth inhibition and an increased risk of infection and cancer.

The researchers are now experimenting with ways to allow noninvasive monitoring of transplant function from blood or urine samples, eliminating the need for a biopsy. Eventually, they hope physicians will be able to identify possible rejection episodes early by monitoring the expression of a few key genes.

"We need to begin using drugs in a more educated manner," says Sarwal. "Ideally, we will be able to avoid over-immunosuppressing our patients with drugs that are clearly not working and that increase their risk of cancer and infection and inhibit growth in children."

Sarwal's colleagues include co-author Oscar Salvatierra, MD, professor of pediatrics and of surgery and director of the pediatric kidney transplantation program, and Patrick Brown, MD, PhD, professor of biochemistry and a Howard Hughes Medical Institute investigator.



OSCAR SALVATIERRA, MD
Director of Kidney
Transplantation Program



FACULTY AND PUBLICATIONS UPDATES

MOSHFEGHI NAMED HEAD OF OPHTHALMIC ONCOLOGY



DARIUS M. MOSHFEGHI, MD

Darius M. Moshfeghi, MD, has been appointed assistant professor at the Stanford University School of Medicine department of ophthalmology, where he leads the pediatric vitreoretinal surgery service and is head of ophthalmic oncology.

He is the author of more than 40 peer-reviewed articles and 10 book chapters and has been invited to speak at national meetings on topics of pediatric vitreoretinal surgery, ophthalmic oncology, photodynamic therapy, and quantitative angiography. He has an interest in adult and pediatric eye tumors, and, in particular, their imaging characteristics.

Moshfeghi has received awards from the Heed Ophthalmic Foundation, the Ronald G. Michels Fellowship Foundation and the National Eye Institute and has been named a Paul Kayser International Scholar. Practice locations include Palo Alto, Menlo Park, Santa Clara and Salinas.

KIM JOINS DIVISION OF GENERAL SURGERY



STEPHEN KIM, MD

Stephen Kim, MD, has joined the division of pediatric general surgery at Lucile Packard Children's Hospital. Kim, who was born in Seoul, is an accomplished and versatile minimal access surgeon focused on the multidisciplinary care of children with intestinal disorders and short gut syndrome.

During his tenure as a medical student at the University of Virginia's School of Medicine, Kim completed a clinical rotation at Yonsei University Severance Hospital in Seoul, where he developed lasting professional ties with many Korean physicians.

After completing a surgical residency at the University of Chicago Hospital, he studied cellular transplantation and tissue engineering of the small intestine and liver as a research fellow at the Children's Hospital of Boston, Harvard Medical School. Most recently, Kim completed a fellowship in pediatric surgery at the Children's Hospital and Regional Medical Center in Seattle, Washington.

KAY ELECTED TO LEADERSHIP ROLE AT AMERICAN SOCIETY OF GENE THERAPY



MARK KAY, MD, PhD

Mark Kay, MD, PhD, professor of pediatrics, has been elected to a three-year term to serve successively as vice president, president-elect and president of the American Society of Gene Therapy. The ASGT is the preeminent international association for gene therapists and has more than 3,000 members. Dr. Kay's election to this position signifies his international reputation for excellence in the study of human gene therapy.

Kay received his PhD in developmental genetics in 1986 and his MD in 1987, both from Case Western Reserve University. He completed a pediatrics residency and a three-year fellowship in medical genetics at Baylor College of Medicine before joining the University of Washington faculty in 1993 as an assistant professor of medicine with adjunct appointments in pediatrics, biochemistry and pathology. He joined Lucile Packard Children's Hospital as an associate professor of pediatrics at Stanford's School of Medicine in 1998.

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