Precision Medicine Becomes a Reality

In some settings, precision medicine remains more aspiration than reality, but at UCSF Benioff Children's Hospital San Francisco, a new Center for Maternal-Fetal Precision Medicine, a groundbreaking Neuro-Intensive Care Nursery (NICN) and a Personalized Genomics Clinic are offering patients and families an ever-widening array of diagnosis and treatment options. UCSF has been at the center of precision medicine since convening many of the world's thought leaders in this field for a summit in May 2013.

Center for Maternal-Fetal Precision Medicine

The new UCSF Center for Maternal-Fetal Precision Medicine’s team-based approach draws on expertise from geneticists, pediatric surgeons, obstetrician-gynecologists and pediatricians. A robust research program supports clinical care, which also includes patient outreach and education, with the goal of ensuring that a woman and her fetus get the best treatment at the best time depending on individual circumstance, says perinatologist and clinical geneticist Mary Norton, MD.

Norton co-directs the center with pediatric and fetal surgeon Tippi Mackenzie, MD, who says, “We consider genetic and genomic profiles, biomarkers, comorbid conditions, environmental factors, imaging, personal preferences and psychosocial circumstances to tailor our approach to the whole person.”

Two examples demonstrate the advantages.

• The center is poised to test a treatment for alpha thalassemia major, a rare blood disorder that can lead to nonimmune hydrops fetalis, which is fatal without a blood transfusion before birth. UCSF is one of the few settings that do the transfusions. Now the Food and Drug Administration (FDA) is considering a UCSF phase 1 clinical trial in which physicians will couple the transfusion with in utero stem cell transplantation from the mother. An international meeting recently came to a consensus that this is the best possible strategy, because it offers the possibility of a cure with minimal procedural risk.

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Perspective

In the two and a half years since UCSF convened a summit of world leaders in precision medicine, remarkable discoveries are informing real-world applications. Precision medicine may have become something of a buzz term, but the broad concept – getting precise and personalized treatments to every patient at just the right time – is the key to modern medicine.

At UCSF Benioff Children’s Hospitals, precision medicine continues to expand in important ways. Advances in our understanding of genomics and genetics inform the work of our Center for Maternal-Fetal Precision Medicine, our Neuro-Intensive Care Nursery’s efforts in neonatal-onset epilepsies and epileptic encephalopathies and our Personalized Genomics Clinic. All of these programs provide answers and treatments for families that never had answers or treatments before.

Of course, precision medicine goes beyond genomics and genetics. Pediatric emergency patients in the area now have expanded access to child-friendly care environments, as well as clinicians specifically trained in pediatric emergency care, in our San Francisco and Oakland hospitals. Young people suffering with inflammatory bowel disease take advantage of the latest noninvasive diagnoses, the most advanced treatments – and a host of clinical trials. Children with ear, nose and throat disorders that complicate their development can see our team of fully integrated, fellowship-trained pediatric otolaryngologists in San Francisco, Oakland and four Bay Area satellite clinics.

We are excited by these advances – and know well that our continued coordination with all of you is what makes the advances work over time for our shared patients. For that, we thank you.

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Integrated, Accessible Care for Childhood Ear, Nose and Throat Conditions

Expert otolaryngology is essential for mitigating disorders that can compromise healthy development. To expand access to this type of expert care, UCSF Benioff Children’s Hospitals in San Francisco and Oakland have fully integrated their divisions of Pediatric Otolaryngology – Head and Neck Surgery. Five fellowship-trained pediatric specialists are now available to see children at both sites – as well as at four Bay Area satellite clinics.

“Much-needed expertise and family-centered care is now more accessible for a comprehensive range of childhood ear, nose and throat disorders,” says pediatric otolaryngologist Garani Nadaraja, MD.

The Value of Up-to-Date Clinical Expertise

Physicians who have essential clinical and surgical experience, awareness of the latest research and practice guidelines and access to advanced technology treat the full range of otolaryngological disorders, from sleep apnea to neck masses, sinusitis and airway problems.

The team’s surgeons are well versed in minimally invasive surgical techniques, including balloon sinuplasty, salivary gland endoscopy and endoscopic airway surgery. Because they are part of an international academic community, UCSF teams are well prepared to help families make decisions that are the best for their children.
“A team approach to the care of children with more complex otolaryngologic conditions leads to improved family understanding, increased patient safety and better clinical care,” says pediatric otolaryngologist Dylan Chan, MD, PhD.

Three unique programs exemplify the team approach for a variety of conditions:

- **Hearing loss:** Pediatric otolaryngology, audiology, speech-language pathology, social work and genetics jointly evaluate children with long-term hearing impairment to help families understand the nature and cause of their child’s hearing impairment and support the child’s communication development through assistive devices and educational services.

- **Voice and swallowing:** A pediatric otolaryngologist and specially trained speech-language pathologist jointly see children with voice, resonance or swallowing disorders. Evaluations can include in-office endoscopy.

- **Complex aerodigestive disorders:** Children with complex feeding and airway conditions have coordinated clinic visits and procedures with pediatric otolaryngology, pulmonology, gastroenterology and speech-language pathology.

### Personalized, Family-Centered Care Matters

While broad access to the multidisciplinary, team-based expertise of UCSF pediatric otolaryngological specialists is important, so is a commitment to the individualized needs of the child and family, says Kristina Rosbe, MD, chief of Pediatric Otolaryngology – Head and Neck Surgery.

“Our mission,” she says, “is to provide the best care to children and their families, from a simple visit for recurrent ear infections to a lifelong relationship for a complex airway disorder.”

For more information, call 415-353-2757 or 510-428-3233.

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### When to Refer

Refer patients to UCSF Benioff Children’s Hospitals for any of the following conditions:

- Acute and chronic ear disease
- Airway management and surgery
- Cochlear implantation and bone conduction devices
- Congenital and acquired head and neck anomalies
- Head and neck neoplasm, including thyroid disease
- Hearing loss
- Microtia, aural atresia and otoplasty
- Obstructive sleep apnea
- Salivary gland disease
- Sinonasal disorders
- Skull base anomalies and neoplasms
- Stridor
- Tongue-tie
- Vascular malformations
- Velopharyngeal insufficiency and cleft palate
- Voice disorders
• The center can also perform whole-exome sequencing in fetuses and neonates with hydrops fetalis and other congenital abnormalities to understand the genetic basis and guide more precise therapies.

“We’re taking advantage of many new developments in genetics and genomics, and our patients get the benefit,” says Norton. For more information, contact Dr. Norton or Dr. Mackenzie at 415-476-0445.

Personalized Genomics Clinic

“Increasingly, physicians turn to whole-exome sequencing to find causative genes for undiagnosed patients,” says geneticist Anne Slavotinek, MBBS, PhD, director of the UCSF Personalized Genomics Clinic, which she established in 2013 with co-director Joseph Shieh, MD, PhD. “Sometimes we uncover conditions for which there are targeted treatments,” she says. “Sometimes it’s more of an informational process, so we can help families and community physicians anticipate future health needs.”

The clinic meets on the second and fourth Monday of each month. Clinicians consult on the value of whole-exome sequencing for each individual and family, facilitate consent processes and testing, and discuss test results and therapeutic options. To improve turnaround time for the tests, the clinic is now setting up in-house testing with the UCSF Institute for Human Genetics.

Patients may undergo sequencing for many concerns, which include:
• Autism
• Birth defects
• Family’s genetic questions
• Multiple congenital anomalies
• Seizures with no clear cause
• Undiagnosed intellectual delays

“In more and more of our patients, we’ve been able to pinpoint a diagnosis for people who have gone undiagnosed and without a treatment plan for years,” says Shieh. Genetic counselor Marta Sabbadini, PhD, is the clinic’s third practitioner.

Because there are more than 20,000 variants per exome and because knowledge about the variants grows and changes rapidly, interpreting the tests is a complex challenge. At a research-intensive medical center like UCSF, when a new variant is discovered or treatment options expand, the clinic can quickly make these available.

And when findings reveal a patient is at risk for an unanticipated condition, an academic medical center can move quickly to call in appropriate specialists, co-manage patients with community physicians and help families prepare for and even prevent the identified conditions. For example, secondary findings at the clinic have revealed patients at risk for cancer, renal disease and heart disease.

“The key,” says Slavotinek, “is having the expertise and experience to interpret variants and provide the counseling.”

For more information, contact the Personalized Genomics Clinic at 415-514-1783 or 415-476-9997.
Advances for Neonatal-Onset Epilepsies and Epileptic Encephalopathies

“Seizures in newborns are often due to acute insults, such as hypoxic-ischemic encephalopathy [HIE] or stroke, but a percentage of seizures have a genetic origin,” says pediatric and neonatal epileptologist Maria Roberta Cilio, MD, PhD, a world-renowned expert in assessing and treating rare pediatric epilepsies. “These genetic epilepsies are underdiagnosed and may require different, targeted treatments, such as sodium channel blockers for neonatal epileptic encephalopathy due to KCNQ2 mutations.”

UCSF neonatal neurologist Hannah Glass, MD, MAS, director of Neonatal Neurocritical Care Services, says that when newborns with seizures don’t respond to standard treatment, specialty centers like the UCSF NICN can sometimes identify causes using advanced monitoring techniques. For example, video electroencephalography (EEG) can show specific features suggesting a genetic-based epilepsy.

“These types of results are why we continuously monitor any child at risk for seizures – which are not always readily apparent in newborns – and have built close collaborations between neonatologists and neurologists,” says neonatologist Fernando Gonzalez, MD.

Interpreting the tests is key. In addition to Cilio, the NICN works closely with neuroradiologists who specialize in newborn brain conditions. In multiple cases, an abnormal magnetic resonance imaging (MRI) result has led to the diagnosis of a rare congenital disorder, and advanced neuro-imaging techniques such as MRI spectroscopy can help diagnose metabolic causes for neonatal-onset epilepsies.

At the UCSF NICN, continuous video EEG recording and interpretation is available 24/7 and is deployed immediately for any neonate with suspected brain injury or seizures.

“Any newborn who is seizing or at risk for seizures should be referred to a center that can readily perform continuous EEG monitoring and interpretation, since not all seizures can be diagnosed clinically.”

Testing New HIE Treatments

The UCSF NICN has been a leader in making hypothermia a standard of care for hypoxic-ischemic encephalopathy (HIE). Led by principal investigator Yvonne Wu, MD, a clinical trial – Neonatal Erythropoietin And Therapeutic Hypothermia Outcomes in Newborn Brain Injury (NEATO) – seeks to determine if erythropoietin, given with hypothermia, is safe and effective to use as a treatment to further reduce the risk of neurologic deficits after HIE.

For more information, contact the NICN at 415-353-1565.
Whether treating a growth plate fracture, administering sedation that is sensitive to cognitive development or easing the concerns of an anxious child, physicians and nurses specifically trained in pediatric emergency care can dramatically improve the patient experience, says David Jaffe, MD, chief of Pediatric Emergency Medicine at UCSF Benioff Children’s Hospital San Francisco.

“At a full-service, dedicated children’s hospital like ours, families experience a child-friendly environment from the moment of arrival,” he says.

New Developments Expand Access

Such care is now more accessible to more families throughout Northern California, due to:

• The February 2015 opening of San Francisco’s only free-standing children’s hospital, in Mission Bay, which is on track to increase UCSF’s pediatric emergency volumes by more than 60 percent in its first year of operation.

• Affiliation with the renowned and high-volume emergency department at UCSF Benioff Children’s Hospital Oakland.

• The expansion of helicopter and rapid response transport services, including a heliport at the new hospital.

“We have a highly collaborative clinical environment staffed entirely by board-certified pediatric emergency physicians and pediatric nursing staff,” says Barbara Feldhauser, manager of the UCSF Children’s Emergency Department in San Francisco.

“And with our expanded transport options, we can mobilize even more quickly to take a child to tertiary care or conduct on-site rescues; in short, to provide more consultation and support for community physicians,” says Steven Bin, MD, medical director of the UCSF Children’s Emergency Department in San Francisco.

Multiple Enhancements to Patient Care

The Oakland-San Francisco affiliation has already led to considerable knowledge exchange, which means patients receive the benefit of shared expertise that extends beyond experience with the latest treatment modalities. It also means a patient experience fully sensitive to the unique concerns of children and their families, with characteristics that include:

• Ease of access: The emergency departments at UCSF Benioff Children’s Hospitals both have a number that any referring provider can call 24/7 to get expert consultation and begin the process of referral.
  - For San Francisco, call 877-822-4453 (877-UC-CHILD).
  - For Oakland, call 855-246-5437 (855-CHO-KIDS).

• Dedication to pain management: For example, clinicians use a needle-free injection system, which uses pressurized gas to propel medication through the skin and into the subcutaneous layer, to numb the skin for painless IV starts.

• Coordinated follow-up care: The Family Information & Navigation Desk (FIND) Program aims to minimize social and environmental factors that have a negative effect on the health of patients and families. Trained staff and volunteers routinely screen for basic social needs and then connect families to community resources.

“We also are talking about a collaboration with Oakland on a fellowship, which will enhance research and training in pediatric emergency medicine and ultimately lead to discovery of cutting-edge practices in patient care,” says Jaffe. “Most places aim to give the best of today’s care; we aim to provide the best of tomorrow’s.”

For more information, call the Children’s Emergency Department at 415-353-1818.
Kevin Hahn received a diagnosis of ulcerative colitis at age 12. With the help of his UCSF physicians, he managed the condition with medication until just after his 18th birthday, when the disease spiked. He spent the next months fighting through discomfort and medical procedures, but continued to play basketball and baseball, eventually being named 2014 Boys’ Athlete of the Year by the San Mateo Daily Journal.

Ultimately, Hahn, his family and the clinical team decided it was time for a colectomy. Two months after the successful procedure, Hahn began college. A complication and the need for two additional bowel surgeries forced him to drop out for the semester, but he was back at school again in January 2015.

An Underdiagnosed Condition

Hahn exemplifies the potential for young people with inflammatory bowel disease (IBD) to lead normal lives, says Melvin Heyman, MD, chief of Pediatric Gastroenterology, Hepatology and Nutrition at UCSF Benioff Children’s Hospital San Francisco and director of the UCSF Inflammatory Bowel Disease Program.

Hahn also demonstrates the challenge of managing IBD, which affects approximately 1.6 million Americans; as many as 25 percent of cases present during childhood. Partly because he was diagnosed early, Hahn has thrived, but IBD is commonly misdiagnosed as something else, such as lactose intolerance, stomach virus or school avoidance behavior. Even when IBD is diagnosed properly, it can be difficult to tell whether the IBD is ulcerative colitis, which affects only the large intestine, or Crohn’s disease, which affects the entire digestive tract.

That’s why, says Heyman, physicians should refer any child with suspected IBD to an academic medical center like UCSF. At such places, pediatric gastroenterologists, surgeons, radiologists and anesthesiologists deliver expert, team-based care with pathologists, immunologists, nutritionists, psychologists, ostomy nurses and social workers.

“Pediatric expertise in relevant disciplines brings an understanding of young people’s unique challenges, from diagnosis through long-term follow-up, [and that’s why Heyman] and his team bring me and others in early,” says pediatric surgeon Lan Vu, MD.

At UCSF:

- Pediatric gastroenterologists and pediatric surgeons work with dedicated researchers to explore the underlying causes of IBD and to create new therapeutic options.
- Pediatric radiologists – whose expertise includes noninvasive magnetic resonance enterography (MRE) – improve diagnoses while minimizing radiation exposure.
- Pediatric anesthesiologists use protocols that help guard against negative cognitive outcomes during surgery, particularly in children under age 2.
- Specially trained pediatric nurse practitioners speed healing postsurgery and understand the value of sensitively delivered follow-up care.

“We also have a number of clinical trials and a large database of pediatric patients, so we can ultimately plan to best match new medications to individual patient profiles,” says Heyman.

Partnering with Patients, Community Physicians

The team approach includes a commitment to making patients part of the care team. “Patient input is essential, because therapy is always directed at improving our patients’ quality of life,” says pediatric nurse practitioner Maura O’Day.

“Because a colectomy is more than a physical adjustment, we help families know what to anticipate and follow patients as part of a team that includes community physicians,” says Vu.

For more information, contact the Inflammatory Bowel Disease Program at 415-514-4423.
# CME Courses

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<tr>
<th>Course Title</th>
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<td>49th Annual Advances and Controversies in Clinical Pediatrics</td>
<td>May 19-21, 2016</td>
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The complete rankings for UCSF Benioff Children’s Hospitals are:

- #8 Diabetes & Endocrinology (Best in Bay Area)
- #10 Nephrology
- #12 Cancer (Best in Bay Area)
- #13 Neurology & Neurosurgery (Best in Bay Area)
- #16 Neonatology
- #18 Gastroenterology & GI Surgery (Best in Bay Area)
- #19 Pulmonology
- #22 Urology (Best in Bay Area)
- #25 Cardiology & Heart Surgery