UC Irvine Health

# Eradicating Rare Diseases


Advances in medical knowledge make this the perfect time to push for solutions to rare diseases, and UC Irvine Health's contributions to that progress make us the ideal place to lead the charge in research that translates into treatments and cures. We have gathered a cadre of expert physician-scientists and are expanding the technology to explore the genetic causes and mechanisms of rare diseases.

Nothing is more thrilling than to successfully slow or treat a disease so patients can lead normal, healthy lives. The field of clinical genetics represents a promising pathway to new and better treatments for many rare diseases.

With your support, we can greatly accelerate our journey along that path.

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# New Hope
# for Patients With Rare Diseases

A disease is called rare when it affects fewer than 200,000 people. Finding a doctor experienced enough to diagnose a rare disease is difficult. Learning no treatment exists can be devastating.

Collectively, rare diseases pose one of the most complex and urgent challenges of our time. Nearly 7,000 such conditions exist, affecting more than 25 million Americans — many of whom are children. Globally, an estimated 350 million people are living with — and in many cases dying from — these debilitating diseases.

Historically, even the most gifted and diligent physician-scientists have faced daunting challenges in diagnosing and treating such diseases. The rarity of many disorders fuels their elusiveness. Because sample sizes of patients are hard to assemble, too much remains unknown about the causes and courses of many rare diseases. Even with the most advanced technology, accurate diagnoses currently can be made in fewer than 40 percent of cases — and proven treatments exist for only 5 percent of rare diseases.

UC Irvine Health aims to accelerate rare disease research to seek answers, treatments and cures.

We invite you to join us in giving hope to people with rare diseases — and turning that hope into a new reality.

## The Challenge of Rare Diseases

In 1983, Congress passed the Orphan Drug Act, providing economic incentives for pharmaceutical companies to invest in rare disease research. Since then, the Food and Drug Administration has approved nearly 500 medicines for rare diseases, almost half of which have been developed in just the past decade. The mapping of the human genome, completed in 2003, paved the way to discovering root causes of thousands of rare diseases. Despite these advances, however, approved treatments remain unavailable for 95 percent of rare diseases. Even for the diseases that do have therapies, more effective approaches, and even cures, are yet to be discovered.

Meanwhile, federal support for bioscience research has plummeted in recent years, from one in three grant submissions funded to as few as one in 20 today. The outlook is even bleaker for research into rare diseases, which by definition affect a dramatically smaller population than heart disease, cancer, diabetes or other common conditions. Yet, funding research into rare diseases holds great potential for progress.

Much remains to be learned. In spite of some significant breakthroughs, less than 40 percent of rare diseases can be accurately diagnosed today. And without understanding the mechanisms causing the disease, treatments cannot be targeted.

Philanthropic funding for rare disease research is essential for helping the 25 million Americans who suffer from such a condition. The investment also can enable investigations that become spring-boards to understanding and treating more common ailments.

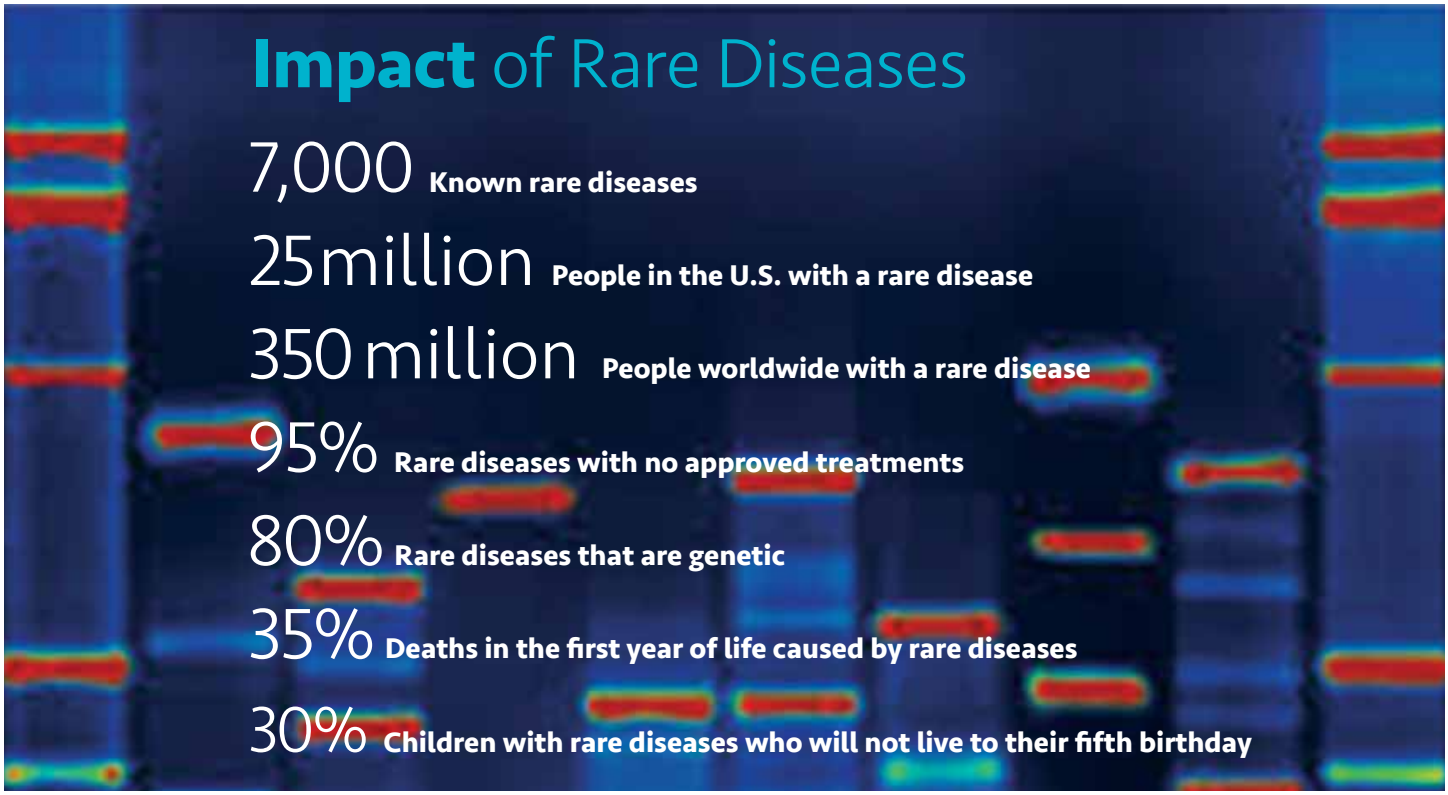
UC Irvine Health is dedicated to opening up new pathways toward the ultimate destination of ensuring effective cures and therapies for every rare disease — and shedding new light on all human disease.

## Genetic Keys

Nearly 80 percent of rare diseases are caused by genetic abnormalities; the remainder stem from infection, allergies and environmental causes. Since most rare diseases have genetic roots, genes also provide the most fertile ground for cultivating potential therapies.

Today, high-throughput screening instruments process vast amounts of data that, combined with classical research techniques, can answer vital questions about cellular behavior and interactions faster and more accurately than ever before. Where it once took a year to search for the root cause of a genetic problem, researchers can now find the answer in approximately six weeks.

Now that they are often able to isolate the gene causing a disease, UC Irvine Health researchers can take the crucial next steps to identify the molecular cause. One day, they hope to alter the mechanism driving each disease, closing off its pathways through the body before symptoms even appear.



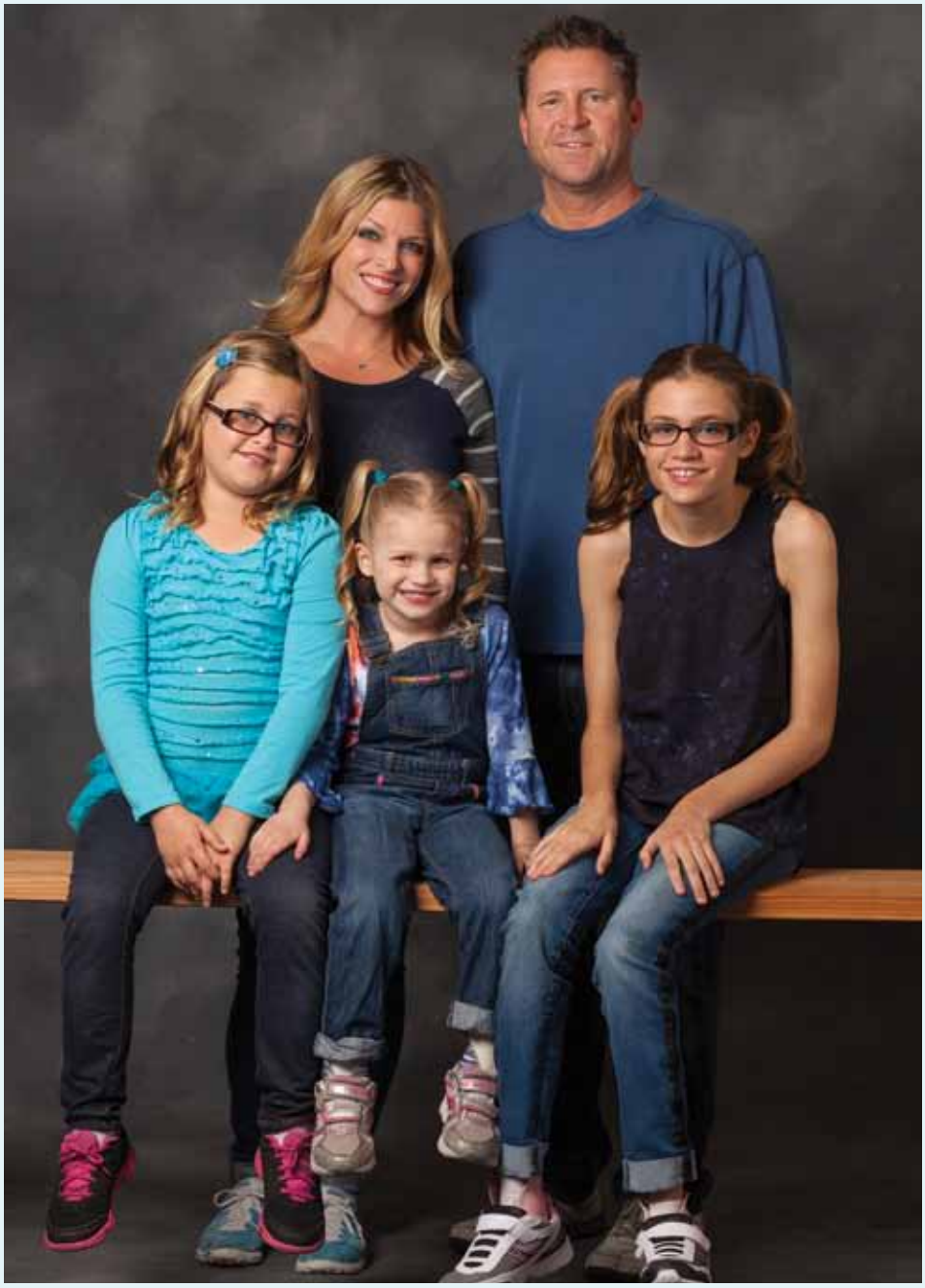

## Building upon Breakthroughs

Dr. Kimonis and her colleagues have established UC Irvine Health as a leader in the field of rare disease research, diagnosis and treatment.

Dr. Kimonis was the first scientist to map and identify mutations in the valosin-containing protein (VCP). She also developed the first genetically modified mouse exhibiting key clinical features of human diseases that are largely triggered by mutations in VCP. This new model enables researchers to examine how these degenerative disorders progress, providing a platform for studies that could translate into potentially lifesaving treatments.

UC Irvine Health is a Rare Diseases Clinical Research Network (RDCRN) site for Prader-Willi syndrome, a complex genetic condition characterized by weak muscle tone, excessive appetite and delayed development. This research has resulted in several clinical trials being conducted at UC Irvine Health for a treatment for the extreme hunger and obesity seen in patients with the disorder.

A lysosomal diseases center focuses on Pompe and Fabry disease research and education. This includes an informative outreach program for patients and healthcare providers, involving experts who advance knowledge in the lysosomal disorders.



## The Spooner Family's Struggle

Every year in the U.S., up to 4,000 children will develop a condition that prevents mitochondria from absorbing nutrients so the cells they inhabit can power the body. Even though the numbers make this condition uncommon, a disease never seems rare if it strikes you or a loved one — especially when it happens twice in one family.

Ask Cristy and Rick Spooner. Two of their three daughters, Cali and Ryann, are afflicted with mitochondrial complex I deficiency. Their bodies cannot generate enough energy from food to function properly. Eldest daughter Cali first showed symptoms as an infant. She suffered violent seizures, and neurologists could not figure out the cause. She has grown up enduring significant motor, cognitive and emotional impairment, and cannot walk unaided.

When Ryann, their third daughter, demonstrated the same symptoms, a doctor told Cristy and Rick that winning the lottery twice was more likely. Their lottery brought only misery, which the family braved as stoically as possible while still seeking answers.

Dr. Virginia Kimonis met the Spooner family early on in their search for a diagnosis and treatment. At that time, no answers were available. Then, 14 years later, Dr. Kimonis contacted the Spooners about a new test called exome sequencing. It can thoroughly search the genes — up to 30,000 in the human body — for disease-causing mutations in a matter of weeks.

Cali, Ryann and their parents submitted blood samples, which were sent to Ambry Genetics, a testing company that partners with UC Irvine Health.

The sequencing revealed that Cali and Ryann had inherited mutations in the nucleotide-binding protein-like gene from both parents. This led to their condition. Cristy and Rick were carriers of the disease, even though they were unaffected by it.

While a cure for mitochondrial complex I deficiency remains elusive, Dr. Kimonis has devised a therapy of vitamins and enzymes to ameliorate the disease's affects. But that only helps treat the symptoms. She and her colleagues are determined to find a cure.

# Rare Insights into Common Conditions

Importantly, discoveries illuminating the understanding of rare diseases also open up the path of progress for more common conditions. In this way, many more people can benefit from this research. Examples of research at UC Irvine Health with this potential include:

- VCP disorders, with ramifications for neurological diseases including amyotrophic lateral sclerosis and frontotemporal dementia
- Nucleotide-binding protein-like gene mutations, providing hope against Parkinson's and other neurodegenerative diseases
- Prader-Willi syndrome — advances against this genetic cause of autism and obesity could extend to aid those with autism spectrum disorders
- Lysosomal storage diseases, 50 conditions that prevent the body from recycling toxic materials, with progress against any one informing treatments for patients with the others
- Mitochondrial diseases, a group of more than 40 disorders causing debilitating physical, developmental and cognitive disabilities because of how they prevent mitochondria from powering the body's cells

# Why UC Irvine Health?

As a pioneering academic medical center, UC Irvine Health plays a unique role in the wellbeing and quality of life of people in in the local community and around the world. UC Irvine Health delivers the research breakthroughs, new generations of physicians and advanced treatments the region and the nation depend upon.

UC Irvine Health is the only academic medical center in the sixth most populated county in the U.S., serving more than 3 million people in Orange County, as well as residents of southeast Los Angeles County, the Inland Empire and beyond. Clinical trials are an integral part the commitment to discover and deliver advanced treatment. In fact, early phase studies give people access to leading-edge therapies and technologies well before they are available elsewhere.

## Cross-Continent Collaborations

Dr. Kimonis and her team collaborate with patients, pharmaceutical companies, hospitals, advocacy organizations, philanthropists and scientific partners around the world to translate laboratory discoveries into novel therapies and diagnostic tools to address a host of rare diseases. Those collegial relationships will continue to grow with additional external funding.

Research collaborations with peers at UC Irvine and across the University of California system are common. Other external partnerships include:

- CHOC Children's
- Long Beach Memorial Medical Center
- Miller Children's Hospital Long Beach
- Murdock Children's Research Institute
- The Children's Hospital of Philadelphia
- Washington University
- National Institutes of Health

## Preparing Future Pioneers

With so many rare diseases and so few therapies yet in existence, no one generation will be able to claim victory against all of them. Just as training the next generation of physician-scientists to provide exemplary care and vital cures has always been essential to the UC Irvine School of Medicine, the Rare and Undiagnosed Diseases team will encourage graduate students to push these boundaries even further into new frontiers of inquiry and innovation.

## Leading the Search for Answers

As a geneticist-physician, Dr. Virginia Kimonis explores the underlying mechanics of rare diseases to discover treatments and cures. She and her colleagues diligently pursue answers for neurodegenerative genetic muscle, bone and brain disorders; Prader-Willi and Angelman syndromes; a few of the nearly 50 lysosomal storage diseases; and a few of the 40-plus mitochondrial diseases that prevent the body from generating enough energy for normal cell function.

**Dr. Kimonis is a clinical geneticist and principal investigator in the UC Irvine Health Pediatrics Department Division of Genetics and Genomics. Through her research, she established UC Irvine Health as a Rare Diseases Clinical Research Network (RDCRN) site for the natural history study of Prader-Willi and Morbid Obesity syndrome.**

Originally from the United Kingdom, Dr. Kimonis received her medical degree from University of Southampton Faculty of Medicine. She completed residencies in pediatrics and general practice in England and a pediatric residency at Massachusetts General Hospital in Boston, as well as fellowships in clinical and biochemical genetics at the National Institutes of Health, Johns Hopkins and Washington D.C. Children's Hospital. She is board certified in pediatrics, and in clinical biochemical genetics and clinical genetics.

Dr. Kimonis is dedicated to translating basic science investigation into clinical advances for patients with rare diseases. Your philanthropic support will help keep her and her team at the leading edge of rare disease research and care, with the capacity necessary to open new horizons for the benefit of patients everywhere.

## Unraveling the Mysteries

The UC Irvine Rare and Undiagnosed Diseases team is dedicated to finding new treatments and cures for rare and serious genetic disorders; improving diagnostic techniques to uncover the mechanisms causing disease; and training the next generation of clinicians and researchers.

Philanthropic support is crucial to our progress. It also will ensure that our team of physician-scientists has access to the latest technology, so they can identify the causes and clinical courses of each rare disease — and seek its antidote.

External funding will help fuel:

- novel investigations
- new clinical trials
- outreach to families
- purchase of diagnostic tools
- data collection
- training programs for clinicians, researchers and students
- dissemination of research breakthroughs

"**What we do is always a challenge,** but it's also very exciting. Once you figure out the mutation in a gene as the cause of the disease, you can go in and try to modify the effects of that gene and a few of the and animal models to help the patient."

**—Dr. Virginia Kimonis**

## The Future of Rare Disease Research is at UC Irvine Health

However rare each condition is, taken together, these diseases affect countless lives — not just of patients, but also their loved ones. In the aggregate, rare diseases — and their more common disease relatives — present a vast need for new therapies and cures. Thanks to scientific and technological advances, the promise of life-changing research outcomes has never been greater.

The members of UC Irvine Health's Rare and Undiagnosed Diseases team are vital to fulfilling that promise — from investigations that translate into innovations benefiting patients to leading-edge education. UC Irvine Health also is dedicated to serving as a vital research hub for collaboration among leading researchers and clinicians on campus and far beyond, who are dedicated to wiping out rare diseases. Scientists across disciplines and from around the world will draw upon these resources to amplify these discoveries.

The UC Irvine Health team, in turn, will build upon theirs to achieve even greater results.

We all want to free the children of current and future generations from the threat of rare diseases. Together, we can — and will — make this happen. With your support, UC Irvine Health will revolutionize how rare diseases are researched, diagnosed, treated — and prevented.

There are many ways to support the groundbreaking rare disease research taking place at UC Irvine Health. If you would like to learn more about how you can contribute to the search for new treatments and cures for genetic disorders, please contact:

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