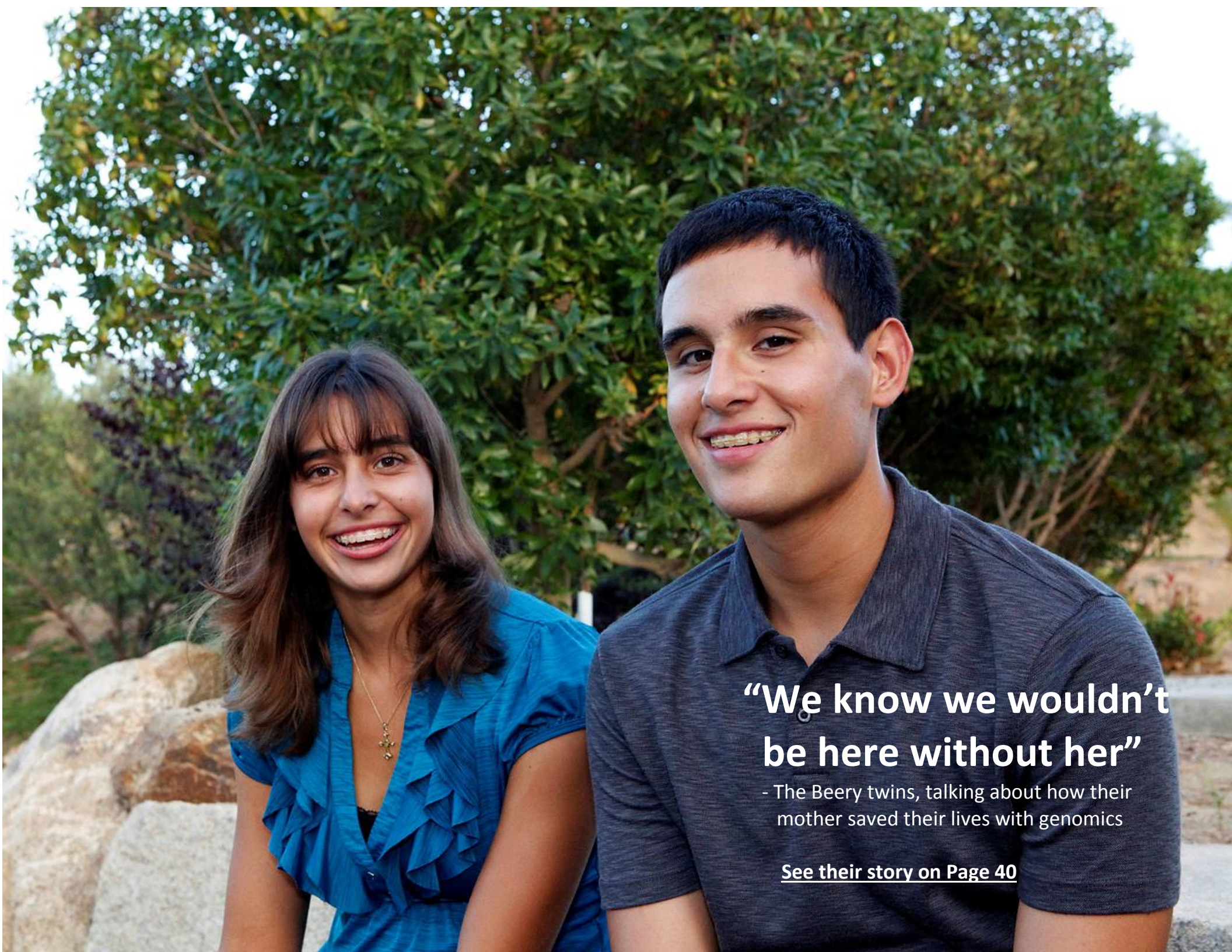
Diagnosing Rare Diseases

Giving Families Hope Through DNA Testing, Crowdfunding and Access to Experts

Ana Sanfilippo and Jimmy Lin MD, PhD, MHS


“My son Nic would not be alive today without sequencing”
- Amylynne Santiago Volker
See their story on page 35



“We know we wouldn’t be here without her”

- The Beery twins, talking about how their mother saved their lives with genomics

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John Crowley started a biotech company to save his children's lives – and he did.

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Rare Genomics Institute is a 501(c)(3) non-profit organization focused on diagnosing and treating children with rare diseases and their families. Currently, it is under fiscal sponsorship of a 501(c)(3) non-profit, Syndromes Without A Name (SWAN).

V3-002-031214

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1. Rare Genomics Institute Overview

At Rare Genomics Institute (RGI), cutting-edge technology in genome sequencing, and partnerships with over 50 world-class scientists from top medical institutions across the world, are dramatically changing the way rare diseases are diagnosed and treated. Our non-profit has pioneered discoveries and treatments for children with rare diseases that no one could previously help and the opportunities are only accelerating.

There are over 30 million people in the US that suffer from rare diseases and over 300 million globally. According to the National Institute of Health, rare and genetic diseases affect one in every ten Americans, and about 75% of rare disease patients are children. Despite the combined large number of people affected by rare diseases, only about 15% of rare diseases have organizations providing support or advocating for them. In other words, 85% of patients with rare diseases do not have organizations advocating on their behalf. "Too many patients with those diseases live their lives undiagnosed or with no potential treatments. They live without hope for a cure," says Dr. Jimmy Lin, President of Rare Genomics Institute.

Rare Genomics Institute is a non-profit biotech venture that enables genome sequencing primarily for children with rare and orphan diseases. Our mission is to help these patients find diagnoses, treatment, and cures. We connect expert scientists with families to utilize the most advanced technologies to diagnose and accelerate research for their children. We provide access to an innovative funding mechanism called crowdfunding, where many people donate small amounts, to help families with the cost of sequencing.

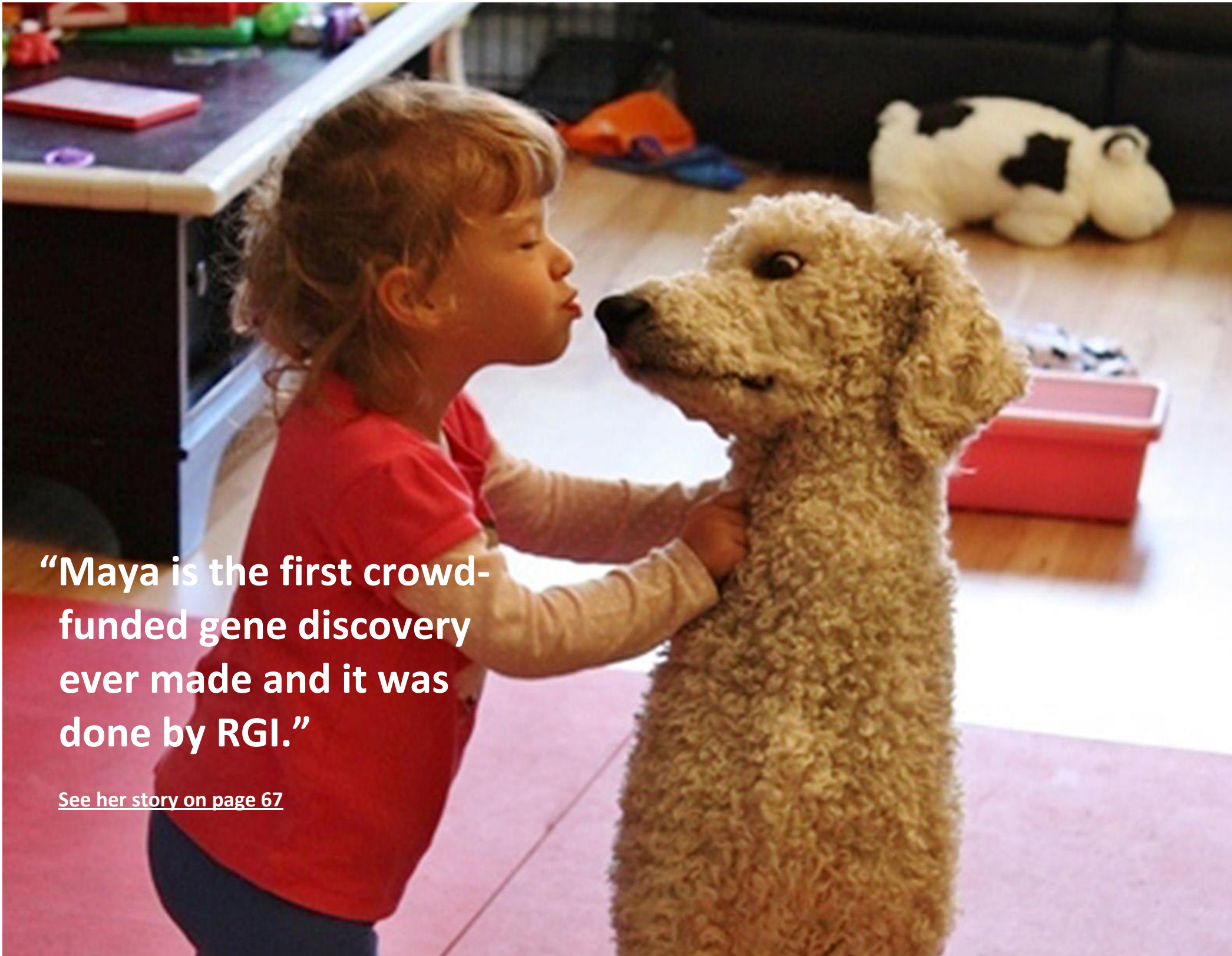
Dr. Jimmy Lin is the founder of Rare Genomics Institute and was the lead computational biologist for the cancer genome sequencing efforts at Johns Hopkins. This sequencing of the first cancer exomes has helped start a revolution in cancer genomics. After completing his MD/PhD at Johns Hopkins, Dr. Lin started Rare Genomics Institute, along with colleagues at Harvard and Yale.

"If you have a sick child, it's not a rare disease; it's the only disease that matters."

RGI is more than just an organization: we are a community dedicated to helping rare disease patients find a cure. We work alongside patients and their families to guide them by providing tools, knowledge, and connections so that they can better understand their disease and help advance research towards a cure. We believe every one of our patients deserves more out of life.

Some rare diseases affect as many as 200,000 people, but some are so rare that they affect one or two people in the world. When a disease is rare and it affects so few, it is often difficult for doctors to identify the disease and, until now, the hope of therapy and cure has been distant. Research has revealed that 80% of rare diseases have identifiable genetic origins; so genomic sequencing and analysis is at the forefront of providing the key to unlock the mystery of these devastating illnesses.

RGI's researchers and scientists conduct personalized analysis to help to provide families with answers. Our wish is to bring hope for their



“Maya is the first crowd-funded gene discovery ever made and it was done by RGI.”

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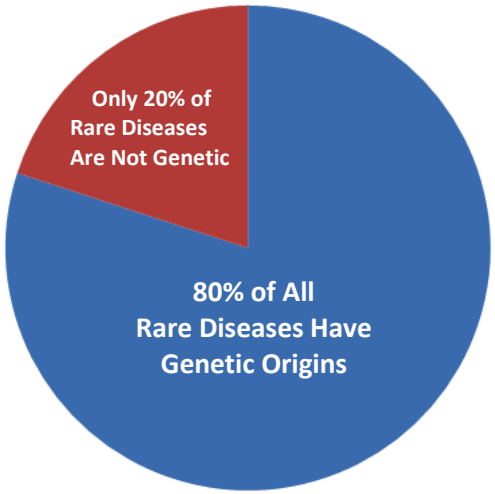
child's disease and an improvement in their quality of life. "What we learn can be used around the world and help many suffering from rare diseases," says Dr. Lin.



Rare diseases affect 300 million people worldwide, and 80% have genetic origins. There are over 30 million people in the US with a rare disease.

Many of the families we work with feel the frustration of lack of research for rare diseases and the significant cost of research. They have likely gone from specialist to specialist on a diagnostic odyssey, searching for answers.

Recent advances have substantially reduced the cost for sequencing: the price of whole genome sequencing has dropped about a million-fold from billions of dollars to thousands of dollars. This shift gives many patient families critical access to diagnostic sequencing to find the real cause of their child's illness.

The Demystifying Genomics section simply explains how DNA and DNA testing works. Exome sequencing, in particular, provides patient families with targeted information that helps them get on the right course for treatment. This information saves families from the emotional burden of desperately looking for answers using tests that are outdated. In addition, these discoveries are very likely to help more people in the future, as we learn more about the causes of these devastating illnesses.

As we continue to build our genome database, we are able to gather information and knowledge so that we can improve outcomes for many patients with rare diseases.

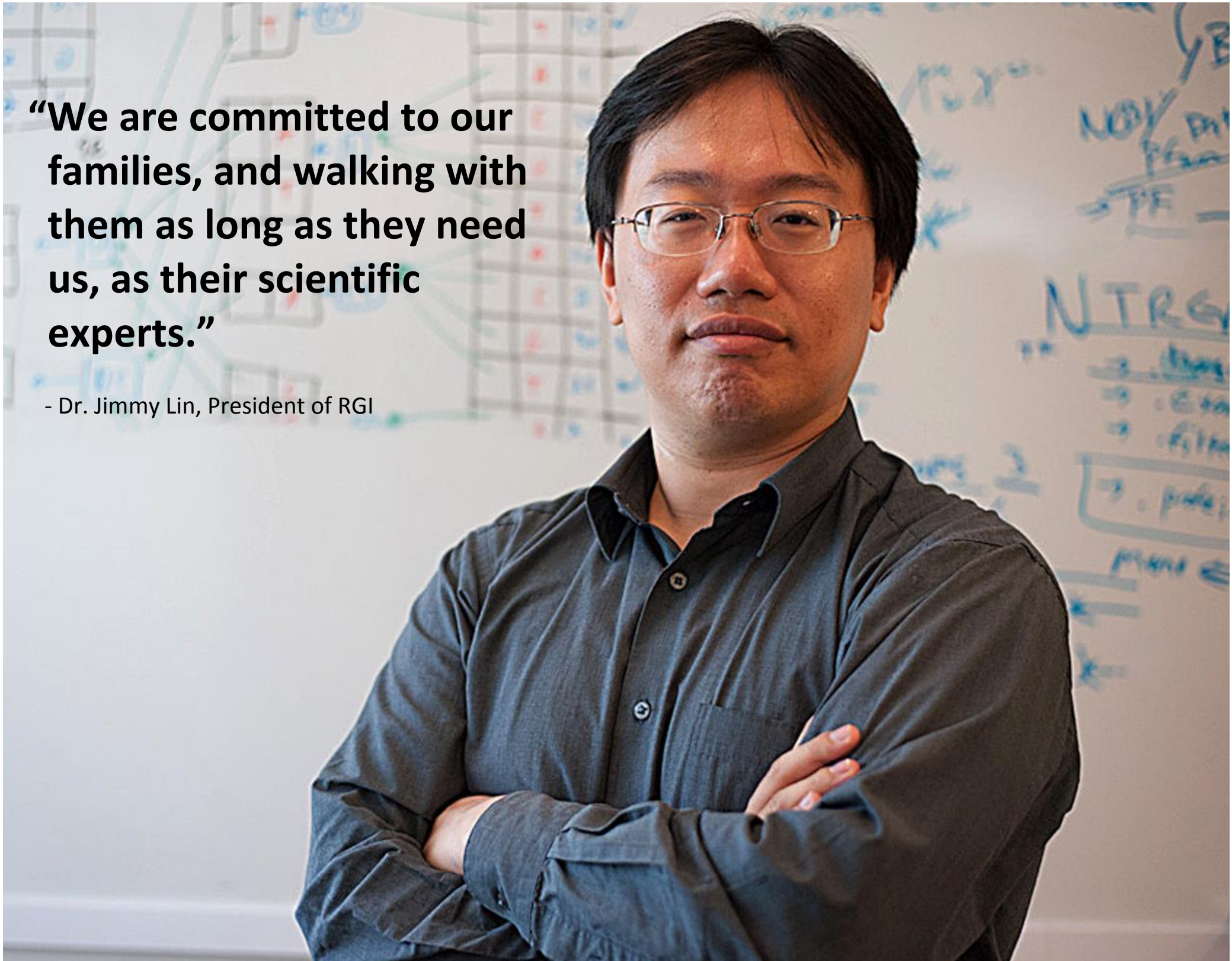
"World's first crowdfunded genome sequencing project uncovers a four year old's unknown genetic disease."

- Forbes Magazine

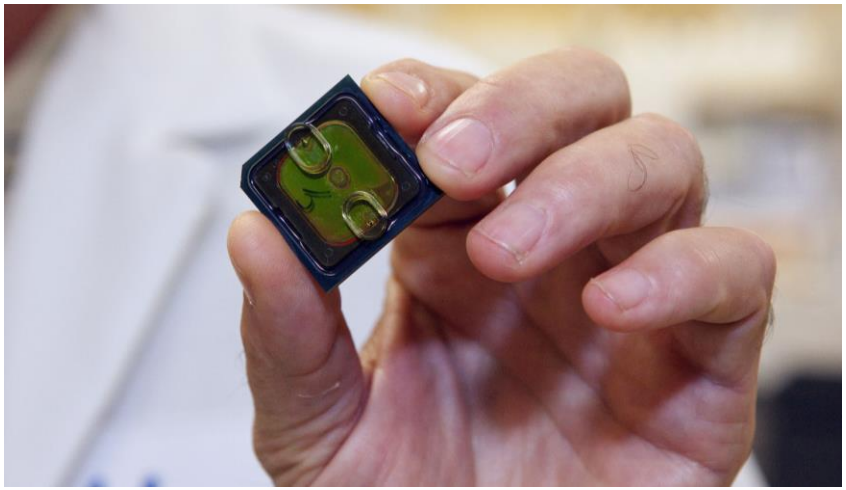
With the RGI process, the team analyzes genetic information from the patient and both parents to compare DNA differences between them. This technology has significant advantages in cost, especially given that some patients spend years on a diagnostic odyssey with no answers. For newborns with health problems, exome sequencing can help find answers quickly and is a fraction of the medical costs for a day in the neonatal intensive care unit.

Quick Facts About Rare Diseases

- There are between 7,000 and 8,000 rare diseases that are known, and less than 400 approved treatments for them
- 30 million people with rare diseases in the US and 300 million worldwide
- 75% of rare diseases affect children
- 30% of rare disease patients die before the age of 5
- 80% of rare diseases have identifiable genetic origins
- Rare diseases are often chronic, progressive, degenerative, and life-threatening
- Rare diseases are often disabling: the quality of life of patients is often compromised by loss of autonomy
- Patients and their families experience a high level of pain and suffering


“We are committed to our families, and walking with them as long as they need us, as their scientific experts.”
- Dr. Jimmy Lin, President of RGI

Crowdfunding has revolutionized fundraising – not only for the arts, but also for education, development, and social justice. We leverage this fundraising mechanism to the benefit of our patients to fund their research projects. We are committed to helping families harness the connective power of the Internet and social media in innovative ways.



Scientist shows a microchip used to perform genome sequencing. The DNA tested on these chips is used to diagnose patients with rare diseases.

First, patients and families apply on the RGI website. Patient advocates are assigned and help support our families every step of the way, connecting them to our researchers. Our crowdfunding platform can be used for raising money for genetic sequencing and has a very high success rate. The patients' DNA is then sequenced and the analysis begins. In the final step, our geneticists provide comprehensive analysis to determine the disease cause and potential treatment plans.

We are pleased that major media like The Wall Street Journal, Time, CNN, Forbes, Nature, TED and many more top organizations have featured the work RGI is doing in helping rare disease patients.

Through our research with families and experts, we have assembled a Parent's Toolkit in this book with some of the best practices and resources for our patients and families. This is a resource for families to gain insights from others that have shared a similar medical journey. This book contains the results of dozens of rare disease interviews, with many family case studies including key lessons learned, and interviews with leading experts in the field of genomics.

None of this work would be possible without the great RGI sponsors and partners like Syndromes Without a Name (SWAN), Assay Depot, Autodesk, Roche, Harnisch Foundation, among others. We thank them for helping us continue to work toward cures and understanding rare diseases for our patients. We are committed to our mission and together we will further medical knowledge, treatment and cures for rare diseases.

"80% of rare diseases have identifiable genetic origins."

When you have a sick child, it's not a rare disease to you and your family; it's the only disease that matters. RGI understands this, and we approach every patient as if he or she were a member of our own family. RGI researchers are leading the way in personal genomics. By diagnosing and understanding the underlying genetic abnormalities that lead to rare diseases, we will continue to make discoveries about how children's genetic background impacts their health. Together, we bring the hope of a cure to our patients and their families. Thank you for your support.

“After 14 years with no diagnosis, last year we pursued gene sequencing through RGI and finally found an answer.”

- Jeneva Stone

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Demystifying Genomics

2. Demystifying Genomics

DNA is the molecule that encodes the genetic information and is the blueprint for all of life. If your body is a computer, then the DNA is the software that runs all the processes and assembly instructions for the hardware. DNA is critical to all of life and can tell us an enormous amount of information regarding who we are, our health and our medical issues.

For every person there are approximately three billion bits of DNA information, called nucleotides. Most individuals receive one copy from the father and one copy from the mother. Apart from effects due to nutrition, infectious disease, or other outside influences, your genetic information is largely responsible for your health and many of your physical characteristics. Genes are sections of DNA that together provide the information of life.

Your Genome

The compilation of all the genes within an individual is known as the genome. The genome is the entirety of an organism's hereditary information and all of the genes in an individual – about 22,500 genes. The genome comprises these nucleotides -- represented by four letters A, T, C, G - which combine to form our "genomic code." A portion of the genomic code corresponds to sequences that are translated into proteins.

Gene Sequencing

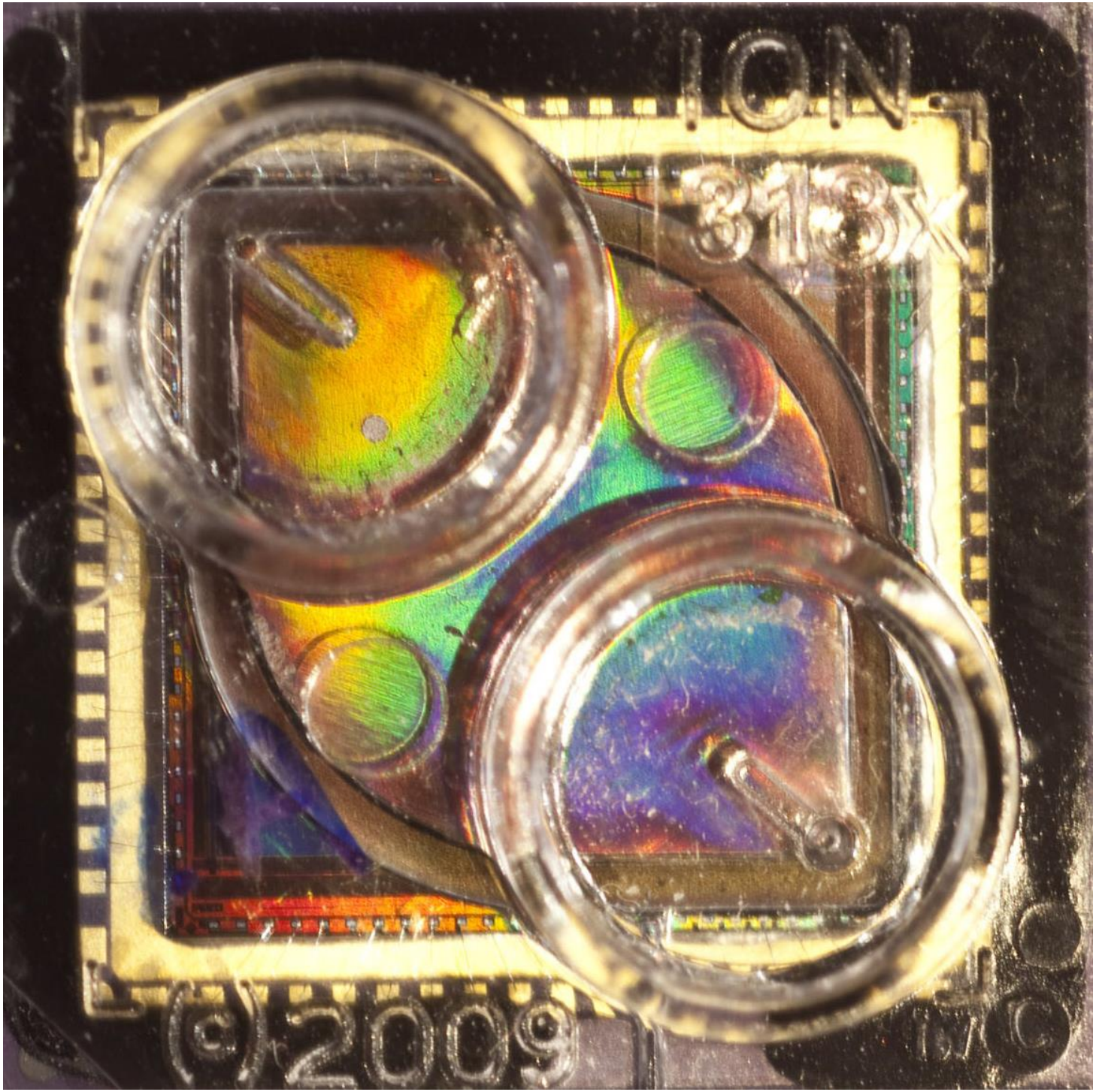
DNA plays a critical role in human biology. When doctors suspect a genetic cause to a sickness, genetic testing can be performed to determine the cause. Genetic testing helps determine the DNA sequence information of genes in an individual. With this information, depending on the sequence, doctors can determine the disease status, predisposition to diseases, and progression of known diseases. As some therapies can target specific sequence differences, doctors can identify treatments that would be effective against certain diseases. For example, individuals with cystic fibrosis often have a specific change in a transporter gene that is related to the disease. Definitive diagnoses for this disease can be provided with gene sequencing.

"Your exome makes up only 1.5% of your genome. However, almost all of the most valuable information is there."

In early 2000, the human genome project announced completion of the first versions of the human genome. For the first time in human history, scientists were able to determine the sequence of most of the three billion bases in a small group of individuals. These initial projects entailed costs on the order of a billion dollars. What has been amazing is that there has been exponential growth in the capabilities of the technology and the consequent drop in the pricing of genome sequencing. Approximately a decade after the initial project, the price has dropped a million-fold. Genome sequencing can be accomplished for individuals for under ten thousand dollars. Experts estimate sequencing a genome would cost less than a thousand dollars within the next 5-10 years.

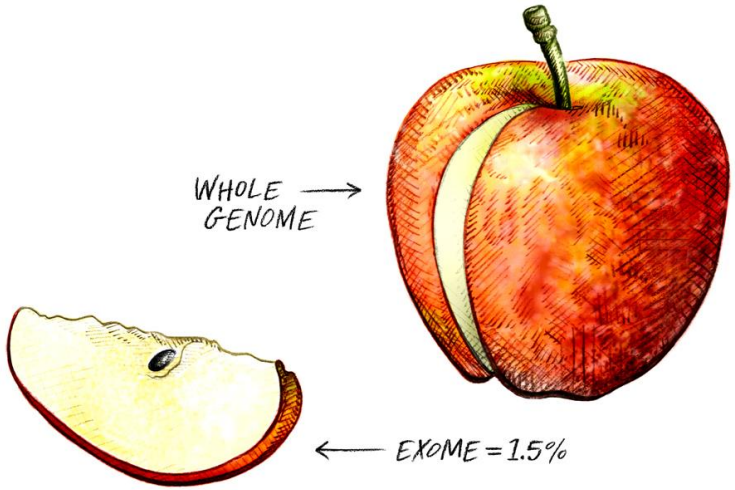
Exome Versus Whole Genome Testing

For comprehensive genetic testing, there are currently two offerings: whole exome sequencing and whole genome sequencing. Whole genome sequencing entails sequencing all 22,500 genes. This process allows researchers to generate large quantities of data, which can then be analyzed. In comparison, the exome makes up only 1.5% of your genome. However, almost all of the most valuable information is there.



This silicon chip used by a sequencing company can read an entire human genome or the smaller exome. Patient blood or other samples are segmented into DNA parts (A,C,T,G) and the liquid is flowed in one small slit and out the other to read the pH and which correlates to the genome or exome.

Since many genetic disorders are correlated with mutations in protein-coding genes, most physicians and scientists who use sequencing technologies for diagnostic purposes start with an analysis of the exome. If the whole genome is represented as an apple, one small slice of the apple is the exome. Exome sequencing and analysis typically takes less time than whole genome sequencing at less than half the cost.



The whole exome contains 1.5% of your genome but it is most of the useful information for diagnosing genetic issues. It is lower cost and faster than the full genome sequencing.

Other Genetic Testing

Although genomic sequencing is now available for the first time to the public, there have been various other methods to investigate the genome. For example, karyotyping examines all the chromosomes and is able to diagnose genetic diseases with large changes, such as Down syndrome. Another test, fluorescence in situ hybridization (also known as FISH), uses short DNA sequences to paint the chromosome to look for markers for diseases. Other methods such as DNA microarray can provide a low-resolution survey of the genome and can detect large changes, such as deletions or amplifications. In addition, single genes can be sequenced as well, one at a time. Genomic testing allows higher throughput, higher resolution, and potential lower cost methods for all these tests.

Precision Medicine

Due to the dramatic drop in the prices of genome sequencing, there is now the possibility of treating diseases based on specialized, individual molecular traits, a field often called precision medicine. Currently, medical practice is based on symptoms and more macroscopic diagnostic methods (such as pathology, radiology, chemistry, etc.). For people sharing the same diagnosis, there is not that much difference in their treatment. For a disease with many possible treatments, currently the selection of pharmacotherapy is mostly based on trial and error.

"Genomics will allow precise prescription of drugs and more effective treatment for the whole population."

Precision medicine is a movement to use our molecular level to tailor therapies based on each individual, sometimes also known as personalized or individualized medicine. For example, using genetic information on how well an individual metabolizes a drug, dosage can be adjusted to optimize treatment and outcome. Additionally, for many drugs, people with specific genetic changes do not respond to treatment. Therefore, determining this information allows more precise therapies based on individual molecular genetic differences.

There is great excitement about precision medicine. However, we are just at the beginning. There is now the start of high growth in the number of people sequenced, and as more and more information becomes available, scientists are better able to understand the function of the different genes. In addition, as different drugs are applied to different patients with genomes sequenced, researchers can start to determine which drug is better for a given genetic profile. This approach will allow precise prescription of drugs and more effective treatment for many. As an example, cancers are currently being genetically grouped in dozens or even hundreds of subtypes. Each cancer can have vastly different types of prognosis and treatment but can be precisely targeted based on the patient's genetics and the genetics of the tumor.

Some Numbers to Know About Your Genes…

22,500 Genes in Your Genome

12,500 Genes Not Understood

7,000 Genes Somewhat Understood

3,000 Well Understood Genes

1.5% Of the Genome is the Exome

23 Pairs of Chromosomes

- There is one unique set of genetic information per person.
- There are two copies of genomes in each individual, with one from the mother and one from the father.
- The well understood genes will only increase over time.

How RGI Uses Genomics to Diagnose Your Child

STEP 1 → **Get DNA Sample From Child & Parents**

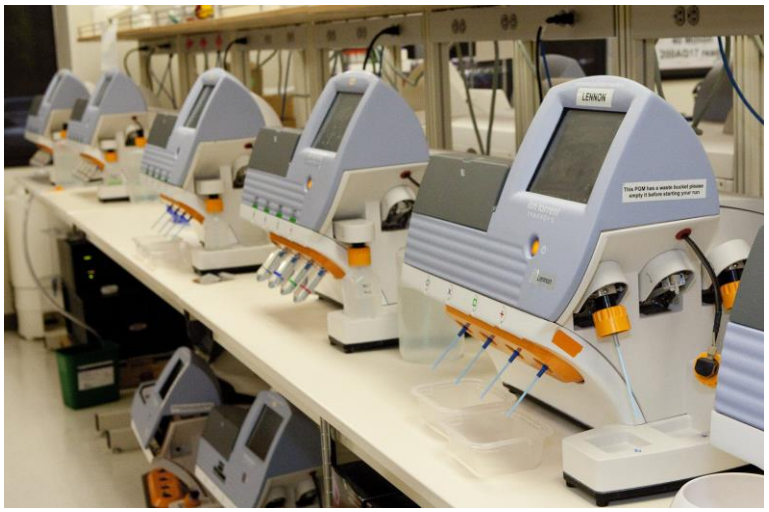
STEP 2 → **Sequence the DNA**

STEP 3 → **Analyze the Results**

STEP 4 **Identify Abnormal Genes and Provide Report**

The Right Diagnosis

Currently, for the patients and their loved ones, one of the most difficult aspects is getting to the right diagnosis. For many families, the diagnostic odyssey lasts years and even decades. Families trek all over the US and world seeking answers, looking to connect to the right specialists that can give them more clues, and directions for their diseases. Often, not knowing what is wrong is one of the hardest challenges. The right diagnosis is the first foundational step that sets into motion all subsequent plans to help the patient.



DNA sequencing machines that use the microchip technology.

Obtain DNA Samples from Child and Parents

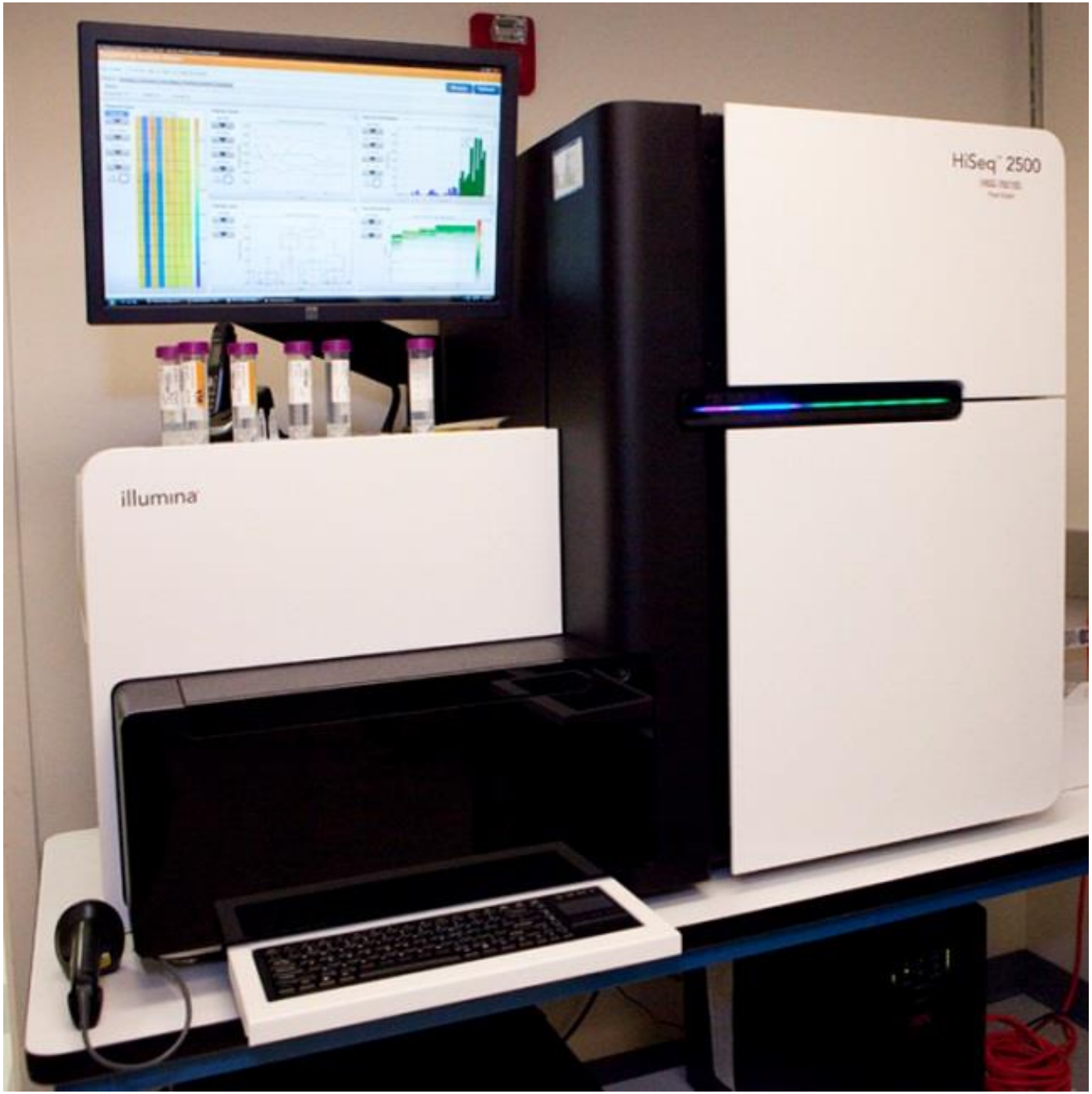
RGI helps patients have their genes sequenced to aid with the diagnosis of previously undiagnosed diseases. Scientifically, the start of the genomic process is the collection of DNA. The best way to get DNA is to take it from blood. If a blood draw is difficult, DNA can also be abstracted from saliva or a cheek swab. However, because there is a lot of non-human DNA in the mouth (e.g., from bacteria), this source is generally not preferred.

"The right diagnosis is that first foundational step that sets into motion all subsequent plans to help the patient."

After taking the blood sample, DNA is abstracted from the tissues. The process starts with breaking open the cells and removing all the non-DNA content. The samples are then filtered, centrifuged and separated to extract the DNA.

Sequence the DNA

There are generally two technologies used for sequencing exomes and genomes. The first uses a technology that takes the DNA bases (A, T, C, G) and converts the information to digital information on a single-use semiconductor chip. This technology is fast, scalable and cost effective.



This sequencing machine sequences up to 50 people's exomes at a time and takes about two days for one cycle. It uses the technology of high-resolution cameras and optics.

There are several different chips with a range of sensors from approximately 1 million to over 600 million on each disposable chip. The sensors read the information. This technology has evolved to require smaller amounts of DNA needed to exome sequence. With this technology, only 50 nanograms of DNA is needed. In the past, the time requirement to sequence has been six to eight weeks. Currently, the most advanced type of this technology enables results in several days or less.

The second technology used for sequencing involves high-speed high-resolution cameras. In this method, DNA molecules and primers are first attached on a slide. This technology amplifies the molecules and puts it on a solid surface of a device called a flow cell. A camera takes many images of fluorescently-labeled DNA. The sequencing machines photograph these flow cells and provide the information needed to read the DNA. They typically run up to 50 people's DNA with each cycle.

Analyze the Results

For rare diseases, typically the DNA is sequenced for the child and both parents. The DNA tests look for differences among the three DNA samples. Once the exome sequencing is completed, it can also be compared to public databases. Differences between the exome and public databases are focused upon, and are called variations. On average, tens of thousands of variations will be identified for a patient's exome. Genetic variations that are present in the general population that are not known to cause disease are filtered out. The result is a list of thousands of variations that may or may not be related to the disease in question.

Identify Abnormal Genes

As there are still a lot of variations to consider, additional filtering strategies are important to isolate the possible gene or genes that are causing the illness. Since parents share 50% of the genetic makeup with their children, their genomes serve as a good filter. If both parents are normal, we can remove all the variations that are also present in the parents. If either of the parents is affected, we can look at what is shared between the people affected by the disease. This step helps filter the thousands of possible differences to tens.

From the dozens of variations that result from the filtering process, there is a significant interpretative step that takes place, and takes time. First, we mine existing databases for knowledge of each of the candidate genes and see if the differences can account for the observed phenotype. Then we use different prediction algorithms to assess how much damage this variation can cause the gene in question. Next, we look for patterns and related pathways of these genes to known diseases. Approximately 25-33% of the time, there is one most likely gene that can explain the disease. The rest of the time, lists of most probable genes that may cause the problem are determined.

Provide Interpretation and Reports

Currently, the most difficult part is the last step – the interpretation. As scientists are still in the beginning stages of understanding the human genome, most of the genes are not well understood and the databases are still somewhat sparse. As more and more genomes are sequenced and each individual gene is annotated in more detail, this process will become much easier.

Each additional genome that is sequenced, adds to the progress of making each subsequent genome easier to analyze. There are public initiatives to create large repositories of such information. This information will be critical for the future of precision medicine. In the meantime, a lot of expert manual curation of the results is needed. Some of the more technical major gene databases include www.omim.org and www.orpha.net.

When the analysis and interpretation of the DNA results is complete, there is a meeting with the parents to clearly explain the findings and make recommendations on the best course of action. For many parents, this meeting marks the end of the years-long investigation of not knowing what is affecting their child, and allows them to start making life decisions. Some parents try to connect with researchers and experts studying the genes, and others look into repurposed drugs and clinical trials (Please see the Parent's Toolkit later in this document for more information.) In many cases, as the genes are not well understood today, they choose to focus on treating the symptoms. The key is to getting genes sequenced for rare diseases.

Genetic Breakthrough with PKU Saves Thousands of Lives

The Amazing History of PKU - One of the most important breakthroughs in genetics was discovered almost by accident through a concerned mother's determination. At age four, Borgny Egeland's youngest child still wore diapers, and could not walk or speak. Her six-year old child had trouble walking and had difficulty talking. She took her children to dozens of specialists over many years, but no one was able help them. Eventually, she became frustrated and even more determined.

In many genetics cases, we have seen that the love and persistence of a mother or father leads to breakthroughs. Borgny's case was no exception.

"The discovery of PKU has given hope and opportunity to many other children."

Borgny started to look for things that were different with her children. She noticed the children's urine had an odd smell and thought this might be a clue to what affected them. She began gathering it daily and took it to a well-known doctor near where she lived - Dr. Folling. After in-depth testing spurred on by Borgny's observations, Dr. Folling discovered a serious genetic problem with the children's metabolism, called phenylketonuria (PKU). PKU stops the body from digesting certain proteins and can be very debilitating, as she had seen. As it turned out, there was a dietary solution for PKU, which now allows children to live normal lives with a food supplement.

PKU is an inherited genetic disease where the body of those affected cannot break down a required amino acid, phenylalanine, which is part of daily protein intake. This mother's concern and her doctor's testing led to the genetic medical breakthrough that makes PKU treatable through diet alone, including avoidance of high protein foods. Today, newborns are routinely screened in US hospitals within 48 hours of birth for PKU. It has probably saved tens of thousands of children's lives, and all because a mother was determined to find out what was wrong with her children.

Genetic Disorders Overview

There are general categories of genetic factors that can cause rare diseases. Most rare diseases are genetic in nature and are difficult to diagnose and treat. Some common symptoms hide underlying rare diseases. Limited scientific knowledge of rare diseases or inadequate information can lead to misdiagnosis. Please consult your doctors and medical personnel for any advice. The following below are a list of different categories of rare diseases. The categories are not mutually exclusive with some diseases belonging in multiple groups and with some categories as subsets of others. Not all diseases discussed are genetic and can be determined via genetic sequencing and many diseases with a possible genetic component have yet to be understood in that way. This table is by no means meant to be comprehensive, but to give readers a general overall of these types of diseases.

Category	Description	Example Diseases	Example Incidence	Example Diagnostics	Example Therapies
Blood disorders and immune-deficiencies	Diseases that result in the absence or dysfunction of the different types of cells and factors in the blood (e.g. red blood cells, white blood cells, platelets, coagulation factors)	Sickle cell anemia, Hereditary spherocytosis, Hemophilia, Thalassemia, Von Willebrand disease, Thrombophilia, Combined immune-deficiencies, Hypogamma-globulinemia, McLeod syndrome	1 in 5000 in the U.S. (Sickle cell anemia). 1 in 600 African-American infants (Sickle Cell Anemia). 1 in 5000 in the U.S. (Hereditary Spherocytosis)	Genetic testing, blood smear, antigen assay, collagen binding assay, blood count, bleeding time, bleeding time, platelet count, pro-thrombin time	Blood transfusion, bone marrow or cord blood transplants, hydroxyurea, folic acid, analgesics, oxygen supplementation
Chromosomal	Caused by chromosomal alterations (deletions, amplifications, duplications, etc.).	Down syndrome (Trisomy 21), Wolf–Hirschhorn syndrome, Velocardiofacial syndrome, Trisomy 18, Trisomy 13, Cri-du-chat, Williams syndrome, DiGeorge syndrome	1 in 1,000 births (Down syndrome). 1 in ~3000 live births (DiGeorge syndrome). 1 in ~40,000 births (Cri-du-chat).	Chromosomal karyotype, ultrasound, blood-based bio- markers, chorionic villus sampling (CVS), amniocentesis, analysis of circulating fetal DNA.	Symptom based therapy. Supportive therapy, occupational therapy, physical therapy, speech-language therapy
Cognitive and develop-mental	Category of diseases that primarily affect learning, memory, perception, and problem solving, social ability, communication, intellectual ability, and restricted, repetitive, and stereotyped patterns of behavior.	Autism and autism spectrum disorders (may or may not include intellectual disability), Fragile X syndrome, other syndromic and non-syndromic intellectual disabilities. Older criteria included Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS).	1 in 88 births in the U.S. (Autism). 1 in 4,000 males and 1 in 8,000 females (Fragile X Syndrome). Frequency of intellectual disabilities of all degrees ranges from 1-3% of the population.	Genetic testing, Southern blot analysis test, polymerase chain reaction (PCR) analysis, physician assessment based on standard criteria.	Supportive therapy, applied behavior analysis (ABA), medications, occupational therapy, physical therapy, speech-language therapy, pharmacotherapy

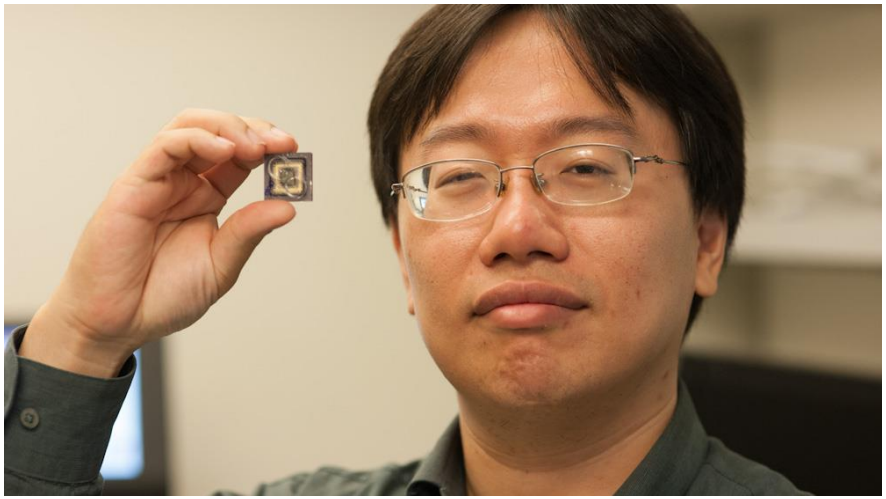
Category	Description	Example Diseases	Example Incidence	Example Diagnostics	Example Therapies
Connective Tissue	Alterations in these genes may change the structure and development of skin, bones, joints, the heart, blood vessels, lungs, eyes, and ears.	Marfan syndrome, Ehlers-Danlos syndrome, Loeys–Dietz syndrome, Epidermolysis Bullosa, Alport syndrome, Stickler syndrome, Congenital contractural arachnodactyly (Beal's syndrome)	1 in 5,000 to 10,000 (Marfan syndrome) ~50 in 1 million live births (Epidermolysis Bullosa), 1 in 5,000 people (Erhlers-Danlos syndrome)	Genetic testing, clinical presentation, collagen typing via skin biopsy, echocardiogram, and lysyl hydroxylase or oxidase activity.	Pharmacotherapy (e.g. beta-blockers, losartan, analgesics), symptom treatment, brace for scoliosis, surgery to repair aorta, eye surgery
Skeletal	A subset of connective tissue disorders that include rare heritable diseases that affect bones and/or joints.	Achondroplasia, Spina Bifida, Treacher Collins syndrome, McCune–Albright syndrome, Hypophosphatasia, Osteogenesis imperfect.	1 in 25,000 (Achondroplasia) 1 case for every 20,000 live births (Osteogenesis Imperfecta)	Genetic testing. Clinical presentation, SDS-PAGE, Cyanogen bromide (CNBr) mapping, thermal stability studies	Surgery, supportive orthopedic, somatotropin (recombinant human growth hormone), nutritional counseling
Epigenetic	Epigenetics involves genetic control by factors other than an individual's DNA sequence. One type is imprinting, where certain genes are expressed in a parent-of-origin-specific manner.	Prader Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome, Silver-Russell syndrome	Between 1 in 10,000 to 1 in 25,000 births (Prader Willi syndrome). Between 1 in 50,000 to 1 in 100,000 births (Silver-Russell syndrome)	Genetic testing (DNA-based methylation testing), clinician assessment, high resolution chromosomal analysis (HRCA), fluorescence in situ hybridization (FISH)	Physical therapy, growth hormones, supportive therapy, physical therapy, behavioral therapy, sleep treatment, pharmacotherapy
Endocrine	The endocrine system is a complex collection of hormone-producing glands that control basic body functions such as growth and sexual development.	Congenital adrenal hyperplasia (CAH) due to 11-beta-hydroxylase deficiency, McCune-Albright syndrome, Kallmann syndrome, 21-hydroxylase deficiency	Up to 1 in 100,000 – 200,000 births (CAH). 1-10 in 1 million population (McCune-Albright syndrome)	Genetic testing, kidney function testing, steroid assays, cortisol, aldosterone, serum electrolytes	Steroids or hormonal supplementation, fertility treatments, pharmacotherapy, surgery
Metabolic	Inherited conditions that result in dysfunctional metabolism, which involves the chemical reactions in the body to convert or use energy. Most are due to deficiency of an enzyme.	Phenylketonuria (PKU), Maple syrup urine disease (MSUD), Smith–Lemli–Opitz syndrome, Lesch-Nyhan syndrome, medium chain Co-A dehydrogenase deficiency, galactosemia	1 in 15,000 births in the U.S. (PKU). 1 in 180,000 births in the U.S. (MSUD). 1 in 380,000 population (Lesch-Nyhan syndrome).	Genetic sequencing, enzyme assay, analyte assay, amino acid analysis via ion exchange / gas chromatography or tandem mass spectro-metry	Dietary changes, pharmacotherapy, enzyme replacement, bone marrow or organ transplant, behavioral management, ortho-pedic intervention

Category	Description	Example Diseases	Example Incidence	Example Diagnostics	Example Therapies
Lysosomal Storage Disorders	A subset of metabolic disorders that specifically have dysfunction in the lysosome, which are organelles in the cells that break down waste products of metabolism.	Hurler syndrome, Sanfilippo syndrome, and other MPS syndromes, Niemann-Pick disease, Tay-Sachs disease, Gaucher disease, Fabry disease, Krabbe disease, Pompe disease	1 in 25,000 births in the U.S. (MPS syndromes) 1 case per 40,000 population (Pompe Disease)	Genetic sequencing, enzyme assay, quantitative and fractionation test via electrophoresis or chromatography.	Enzyme replacement, bone marrow or organ transplantation, symptomatic therapy, pharmacotherapy, physical therapy.
Neurological	Neurological disorders include seizures, sleep disorders, trauma, infections, movement disorders and spinal cord injuries	Microcephaly, Huntington disease, Aicardi syndrome, Severe myoclonic epilepsy in infancy (Dravet syndrome), Lennox Gastaut syndrome, Landau-Kleffner syndrome (LKS), Infantile Spasm (West Syndrome), Early infantile epileptic encephalopathy (Ohtahara syndrome)	1 in ~10,000 (genetic epilepsy) 1 in ~30,000 (Dravet syndrome) 1 per ~4000 live births (Lennox-Gastaut Syndrome) 900 cases reported in the U.S. (Aicardi syndrome)	Head circumference, genetic testing, triplet repeat testing, complete blood count, electrolytes, glucose, urine organic acids, hepatic enzymes, creatine kinase, serum amino acids, endocrine tests, cerebrospinal fluid evaluation	Pharmacotherapy, hormone therapy, physical therapy, nutritional therapy (e.g. ketogenic), intravenous immunoglobulin (IVIG)
Neuro-muscular	Neuromuscular disorders affect the nerves that control voluntary muscles including arms and legs. They may also affect heart muscle.	Dystonias (including Generalized, Focal, Segmental), Muscular dystrophies (including Duchenne, Becker's, Limb-girdle, congenital, facioscapulohumeral, oculopharyngeal, distal, and Emery-Dreifuss)	1 in 3500 live male births (Duchenne). 1 in 30,000 live male births (Becker's).	Genetic testing, Magnetic resonance imaging (MRI) and computed tomography (CT) scanning of the brain, blood chemistries, liver functions, ceruloplasmin levels	Physical therapy, supportive therapy, muscle relaxants, surgery, nutritional therapy, pharmaco-therapy, neurochemo-lytic interventions, deep brain stimulation
Respiratory	Diseases that affect the lung and respiration.	Cystic fibrosis, alpha-1 antitrypsin deficiency, interstitial lung disease, pulmonary arterial hypertension	1 in 3,200 births in the U.S. (Cystic fibrosis) 1 in ~4,000 in U.S. European ancestry (alpha-1 antitrypsin deficiency)	Genetic testing, lung function testing, serum alpha1-antitrypsin levels, functional assay, hepatic function	Supportive therapy, antibiotics, pharmacotherapy, gene therapy, surgery, dietary changes

The Sequencing Process

3. How Does the Sequencing Process Work?

Rare Genomics Institute provides many of the latest medical advances in genomic sequencing to patients with rare diseases. We understand the financial strain and emotional stress for the family desperate for an answer to their child's illness. RGI also provides an online crowdfunding mechanism to help rare disease families raise money for genetic sequencing projects. Genome sequencing of patient and both parents gives the most comprehensive DNA picture, comparing and looking for reasons for the condition.



This is one of sequencing chips that allows RGI to read changes in DNA.

The impact of the information obtained and knowledge of new pathways can be life-changing. RGI has created an easy process to help families find answers. With over 7,000 rare diseases affecting about 30 million people in the US alone, Rare Genomics Institute helps patients design personal research projects to solve complex problems. In many cases, doctors believe there is a genetic problem with these children, but they cannot pinpoint the cause, until now. Without a diagnosis, clinicians and doctors cannot provide the best possible care and treatment for the child. This has left parents searching for answers.

With genome and exome sequencing, a diagnosis can frequently be made and targeted treatments for the best outcome can occur. When the results are given, families have the information they need to proceed with the best care for their child. While not common, sequencing can lead to cures and therapies that completely change the lives of the child and their families. Please see the case studies later in the book for success stories on Nicholas Volker, Alexis and Noah Beery, Travis Putjenter and other families.

Many families spend years putting their children through hundreds of conventional tests that are not sophisticated enough to find these subtle genetic mutations. For each patient with RGI, there is a team member that follows the case and answers questions that families may have every step of the way.

One way to explain the difference between a common and rare disease is if you have a car, and it has a broken windshield wiper or mirror, you can still drive it. For most people, these are common diseases. However, if you have a leak in your engine, it's a much bigger problem. Many children with rare diseases have a defect in critical genes. These are critical processes in the body that are not functioning properly.

One RGI family said that before sequencing, they felt like they had been wandering aimlessly in a new city in a fog. After sequencing, now they have a map and lights. They know where they are going and how to proceed to care for their child. Targeted treatment and best therapies can now be focused on the children to meet their needs. The sequencing is the critical piece that allows patients to connect with these medications or best approach to treatment. You need a diagnosis before any possibility of finding a treatment. Once you figure out the problem, then you connect with the drug or treatment therapy.

Steps in the Overall RGI Process

STEP 1 Connect with RGI → **STEP 2** Our Advocates Contact You → **STEP 3** Provide Records → **STEP 4** Clinical Visit → **STEP 5** Crowdfunding the Costs → **STEP 6** Analysis and Results

Step 1: Connect with RGI
Through the website (www.raregenomics.org) there is an application form. The form includes providing medical information on the patient. Once submitted, it will then be evaluated by RGI.

Step 2: RGI Patient Advocate contacts the patient's family
The RGI patient advocate is the contact person who will continue with the patient throughout the process. RGI patient advocates set up an informational phone call to explain the RGI process and answer any questions.

After the informational phone call, a follow-up form will need to be filled out to match the patient with the correct clinical research site. Each RGI site has world-class researchers specializing in DNA sequencing with expert clinicians interpreting the results. The site will be determined based on patient needs, distance to the site and availability. Some sites have 1-6 month waiting lists.

Step 3: Patient family responsibilities
All medical records from all visits with a patient's past physicians will be collected and reviewed at the medical appointment with a clinical geneticist. See the Parent's Toolkit for Rare Diseases, for a great example of how Jeneva Stone, mother of Robert, organizes her son's medical records.

Step 4: Research site clinical visit
The clinical geneticist will review the patient's medical records and determine if the patient will become part of RGI's patient families. If the geneticist believes RGI's services will help the patient, all samples will be taken at the clinical visit after the parent consent form is signed.
The clinical geneticist will determine any necessary testing prior to completing the sequencing. The geneticist decides the best course of action for the patient. This would mean whole exome or genome sequencing.

Step 5: Crowdfunding

Samples will be taken at the research site clinical visit. However, all payments must be made before the analysis begins. RGI provides an online crowdfunding program to help patients raise money to pay for sequencing and analysis. RGI helps families create a patient profile, which allows parents to share their child's photograph and medical story on the RGI website. Friends, family, or anyone can donate directly to the child's site to raise funds in the fastest, most efficient way. Every RGI fundraising campaign has been a success so far but it is not expected to be 100% for all cases. We encourage families to reach out to their network of friends and family for support.

"RGI will continue to walk with families as scientific experts who really care."

- Rare Genomics Institute

Step 6: Analysis and Results

Please note that these are rare diseases and that the analysis typically takes several months. The RGI patient advocate is there to provide updates on progress and answer any questions along the way.

The scientists and clinical geneticists on the team will work to discover the possible causes of the patient's illness and hopefully a treatment or next steps for families to provide the best possible care for their child. Not every case has a diagnosis, but sequencing is far more accurate than most other methods. These geneticists are trained and work in the most prestigious medical institutions. They personally and carefully analyze the patient's samples to provide the comprehensive medical diagnosis and interpretation utilizing sequencing. The patient families will hear the results from the site as soon as they are able to provide them.

Final Points

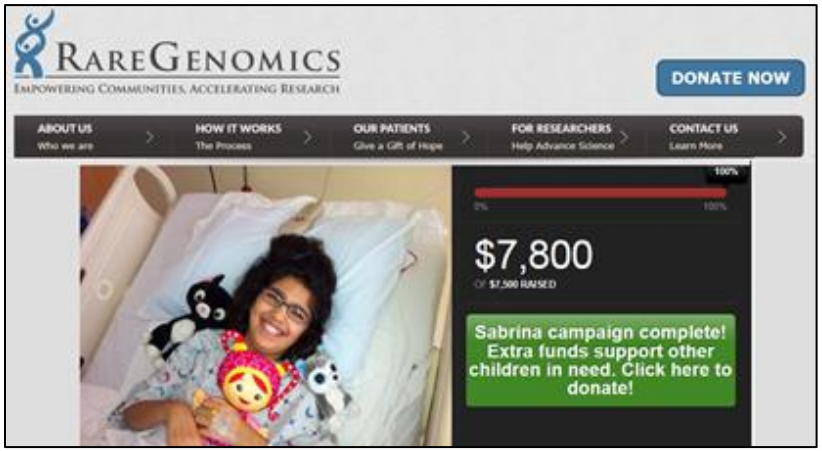
The most important point is that the undiagnosed rare disease child needs to be diagnosed, if possible. This will get them on the right path to therapies. For some children, their disease will only be discovered through genomic sequencing. To avoid years investigating major medical problems with no concrete answers, diagnosis or therapies, RGI enables parents to have resources and access to a top team of doctors to determine the diagnosis and plan of action to help their child.

RGI provides a map through genomic sequencing. When we understand the disease, we can work to help the individual child as well as all children with the disease. Dr. Jimmy Lin explained, "RGI will continue to walk with families as scientific experts who really care. We solved Robert's case and found his diagnosis after his family searched for over a decade. Robert and his family are now on the right track. They have a map. We want to not only help Robert Stone who has Dystonia 16 but all the Roberts. Studying Dystonia 16 may provide answers to all dystonias and movement disorder diseases."

Crowdfunding

4. Crowdfunding Your Genome Test

Crowdfunding dramatically changes how personal medical research is done. RGI is a community dedicated to helping rare disease patients find hope for therapies and a cure. We work alongside patients and their families, providing them with the necessary tools, knowledge, and connections so that they can better understand the cause of their disease. We believe that every patient deserves more out of life and through crowdfunding our patients gain access to what would otherwise be cost prohibitive.



Sabrina and her family raised more money than was needed to fund her sequencing.

The Current Situation. There are 7,000-8,000 known rare diseases, probably many others not known**.** The current model for biomedical research is not designed to address so many diseases, or diseases that affect so few patients like rare diseases do. As a result, less than 5% of rare diseases have any type of therapy. Many families have staggering medical bills from taking their child from doctor to doctor, hospital to hospital, in search of an answer to what is making their child so sick.

Until now, the answer to genetic questions through genome sequencing was completely out of reach for many people financially.

The Solution. We provide access to one-of-a-kind research programs utilizing top experts at major medical institutions around the world so that new breakthroughs, diagnoses and therapies are discovered. Rare Genomics Institute uses a crowdfunding model as a tool to raise money, raise awareness and fund these lifesaving, life-changing projects for patients and their families. Powerful connections through the Internet share patient stories of children suffering from rare diseases across the country and around the world. Anyone, anywhere can donate or fund these life-changing projects through RGI's website.

"I couldn't believe how many people wanted to help and how quickly we reached our goal for our son."

- Jeneva Stone, mother of Robert

RGI conducts individualized genome research projects on the children with rare diseases and their parents to uncover inherited gene mutations to find answers and to find therapies. This is done via either exome or genome sequencing – and combining sequences not only from the child, but also the mom and dad.

Mutations are changes in the genetic code of a gene that affect what it does or its function. Inherited gene mutations are those that can be passed on from a parent to a child. RGI focuses on patient-driven research by analyzing not only the rare disease patient's genes but the parents as well. This patient-driven research is focused on the child's disease and needs, right now.

The dramatic reduction in the cost of complete genomic sequencing from hundreds of thousands of dollars to about $7,500 for a three exome sequencings of parents and child has changed medical outcomes and shifted the focus. With the family's permission, results are openly shared worldwide so other sick children can benefit from the discoveries.

Realizing the emotional and financial strain on parents of children with rare diseases, RGI partners with families to ease the pressure of caring for a sick child and offers a unique funding capability. The quest for answers has forced many families to spend their life's savings to help find a cure for their child's devastating illness. To address the cost of genome sequencing, RGI has developed a platform to help patient families raise money for their genomic sequencing utilizing the innovative web-based platform of crowdfunding.

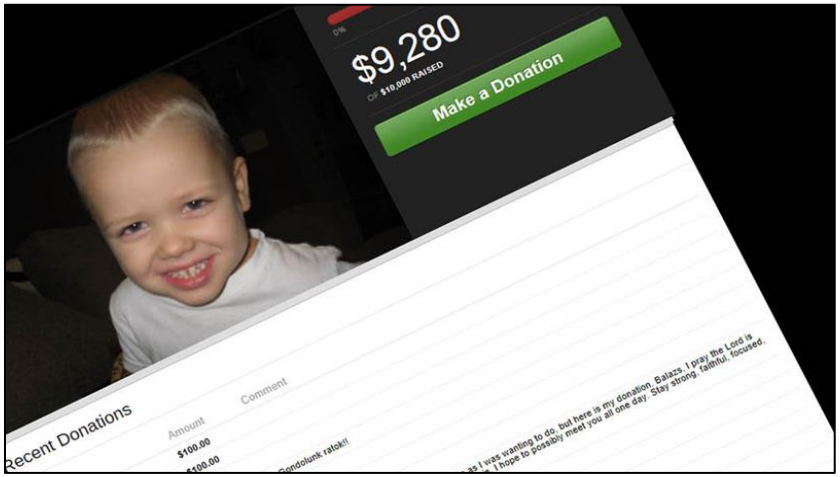
"At this point, the only path to her diagnosis lies in genome sequencing, and RGI support can help to make this a reality for our family."

- Dana, mother of 5-year-old Maya

RGI's crowdfunding generates money to fund the research projects designed to diagnose, seek a cure and improve the quality of life of our patients. A simple step-by-step process begins an online platform to help families raise money for research projects for their child. Our mission is not only to solve complex diseases and find therapies, but give hope for patients and families that want answers. The partnership, commitment of doctors, researchers and families takes another step forward to help find an answer to the cost of genome sequencing.

What is crowdfunding? Crowdfunding is based on a simple principle. As the name suggests, it is asking a crowd of people to donate money to individual research projects that we have helped design for our patient's with rare diseases. This is a new patient-driven approach to solve these complex rare diseases.

It's not complicated. Patient families customize their microsite quickly. A goal is set for the amount of money the child's research project will cost. The patient families are able to write whatever they choose about their child or their medical journey searching for help and answers to their child's rare disease. The site offers patient families the opportunity to put a picture of their child and only a first name. This gives a face and name to the illness and can reach people worldwide who may want to help and donate to the cause of finding a cure. Once the research project is on the site, patient families and friends start talking about the site, visiting the site, and donating to the site. The power of connection through the Internet and social media drives more interest and people to the site to help support and give money to a great cause.



Balazs' story and donation page with words of encouragement from friends, family and anonymous donors helped him quickly reach and exceed his goal.

How much time and money will this take? Your microsite can be set up in minutes; it is user friendly, and you do not have to be tech savvy to figure it out. It costs nothing to set up and only a small service fee is assessed once several thousand dollars is donated. The time it

takes to reach the completed funding goals for research projects averages from one day to four months. Typical donations are under $50.

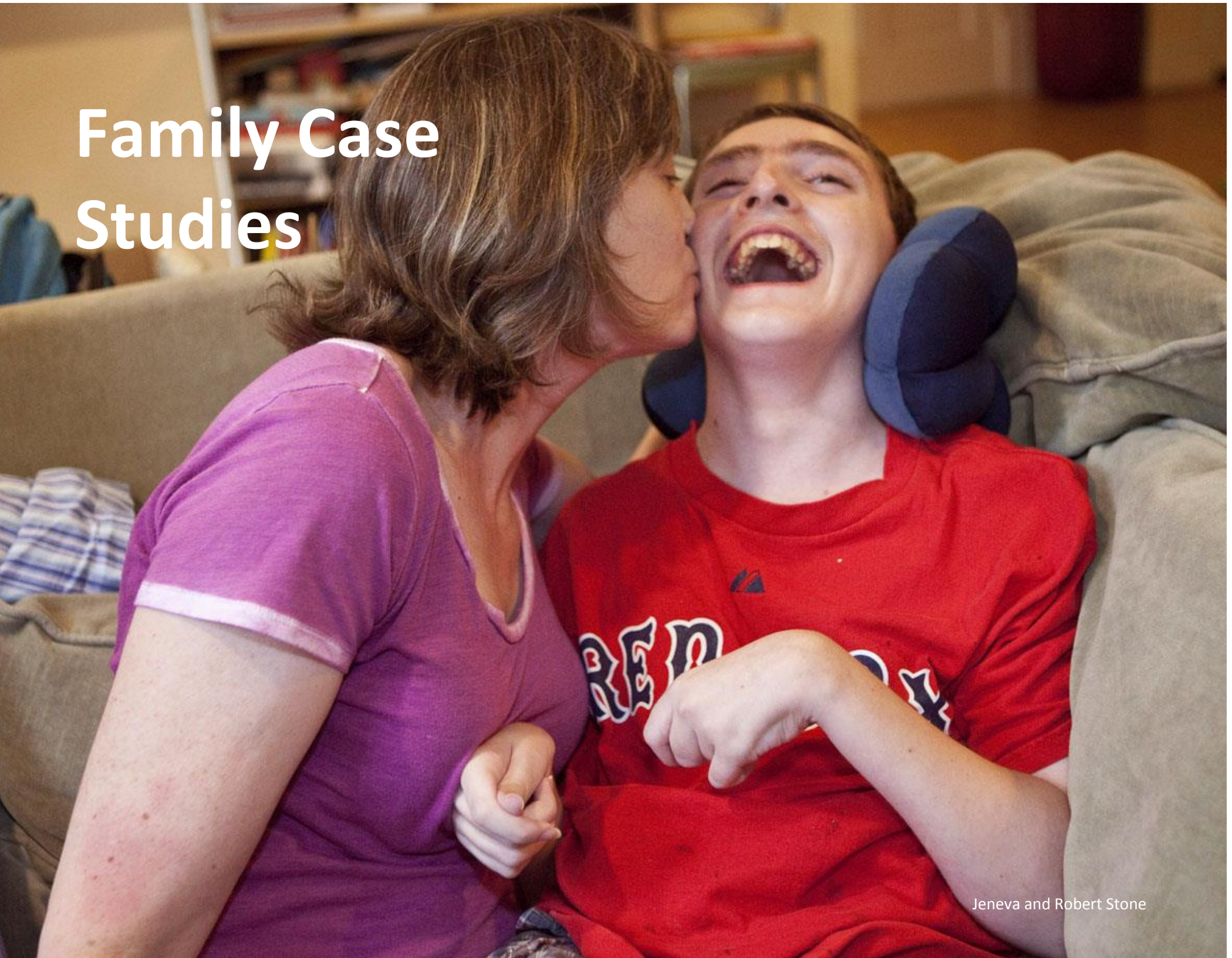
How can this help families during difficult times? Family, friends and others watch parents' efforts helping their courageous child through his or her illness and want to help, but don't know the best way. This platform connects people to the research project, outlines the project and the goal that needs to be attained. The amount donated can be large or small - there is no minimum or maximum donation. Donors can write words of hope and encouragement with their name as they donate, or some may choose to be anonymous donors. It's also a third-party non-profit which encourages donations.

How does RGI crowdfunding work? RGI will gather information on your child and tell you what the goal is for the research project. You let friends, family and others know the microsite is running on http://raregenomics.org/donors. The "For Supporters" page tells all the stories of the patients RGI treats and each individual research project designed to help these courageous children with rare diseases. Anyone can make a donation using a credit card or PayPal.

Typically, it takes a few months to raise the total amount for genetic sequencing. One RGI parent explains, "You never know what life brings to us, but we try to be strong, and with the help and love of friends and family, we can work hard together to beat this."

Have any comments or ideas for the ebook?
Email us at ebook@raregenomics.org.

Family Case Studies



Jeneva and Robert Stone

5. Rare Disease Family Case Studies

Nicholas Santiago Volker – Alive Because of Genomics

166 Surgeries Later… Genome Sequencing Saved Nine-Year-Old Nic's Life

Surviving over 160 surgeries and 800 overnights in a hospital in his young life, Nicholas Santiago Volker was cured, thanks to DNA sequencing, from a gut disease that almost killed him. Healthy until about two years old, Nicholas had a cut that wouldn't heal, becoming an abscess. This was just the beginning of a four-year medical mystery that baffled doctors.

For the next four years, Nicholas suffered from holes forming on his skin that went all the way through his intestines. He got sicker and sicker, developed sepsis and had high fevers. At four years old, Nicholas weighed only 17 pounds, and doctors had to remove his colon. For a short time, after this surgery, Nicholas got better.

Then he got sick again. Doctors tried every medication and treatment they could. And he got worse. They could not get his mystery illness under control and almost every day, Nic would go into the operating room. "He often went in wearing his batman cape," his mom said. Just in 2009 alone, he went through one hundred surgeries. His mother explains, "We had a routine. He went into the operating room so they could clean out his wounds." He couldn't eat or drink, so he had total parenteral nutrition, TPN. "I just remember seeing him with lines all over him giving him antibiotics and food, and he had a wound VAC (vacuum assisted closure) attached to him. They had to keep him clean so he wouldn't die of an infection."

"My son is the comeback kid."

- Amylynne Santiago Volker

Amylynne continued, "No matter what he was going through, he'll never tell you he's having a bad day. He's lived with one hundred percent inflammation and still, if I asked him how he was doing, he'd tell me, 'I'm fine mom, I'm fine.' He never complained. I tried not to cry in front of people," she said as she fought back tears. At the same time Nic was reassuring his mom, doctors had told her he was dying. They knew that Nic's body could not keep fighting this illness.

His doctors and parents then made a decision that saved his life. In 2009, Dr. Howard Jacob, Director of Human and Molecular Genetics at the Medical College of Wisconsin decided to try to do something they had planned to do five years later, but Nic couldn't wait until then.

Nic rests on his dad's shoulder after playing and getting tired out. He is the first patient in the U.S. diagnosed and saved by exome sequencing.

Nic has survived over 166 surgeries and was diagnosed through exome sequencing found to cure a life threatening inflammatory disease.

For the first time ever in medicine, doctors sequenced Nic's DNA and found a diagnosis, a single change in his DNA made him so sick. Nic had a genetic mutation on a gene called XIAP and needed a new immune system. In July of 2009, he got a cord blood transplant from an anonymous donor.

"We saw him get better in the first two weeks," Amylynne said. "He could play. He became really active. At four years old, all he ever wanted to do was play, and now he finally could." Forty- two days after the transplant, he was eating normal food. He could eat his pizza rolls and steak. "He's the comeback kid," his mom said.

"Without the sequencing, my son wouldn't be alive today."

-Amylynne Santiago Volker, mother of Nic

Nicholas Santiago Volker's case is leading the way in genetic medicine. Nic is the first patient diagnosed and saved by exome sequencing. His illness and the sequencing that saved his life showed the world the potential to treat unknown diseases using this technology. His sequencing uncovered the real cause, and he went from a life threatening inflammatory disease to running around like every other kid his age. "He makes you realize what's important in life. I don't sweat the small stuff," Amylynne said.

Takeaways:

1. Genomic sequencing found a cure, otherwise impossible. Nic went from over 100 surgeries in one year to cured of his gut disease. He and his doctors proved that DNA sequencing could solve the odyssey of an excruciating disease.

2. A mother's commitment, persistence, and unceasing determination to not lose hope combined with genetic sequencing saves her son. This is one of the most important factors in terms of helping a child with a rare disease.

3. Nic helped pave the way for genetic personalized medicine. His case proved that DNA analysis leads to breakthroughs, provides targeted treatment and cured his gut disease.

4. To help with the stress of caring for a sick child, Amylynne uses yoga and works out.

Please note Nic is not an RGI patient but his story is cited to help families better understand the rare disease process.

Nic kisses his mom, Amylynne Santiago Volker, who tirelessly cares for him throughout all of his illnesses, including over 160 surgeries and 800 nights spent in the hospital.

The Beery twins suffered from severe medical problems, but now play sports and live normal lives.

Alexis and Noah Beery: Gene Sequencing Saves the Lives of Twins

Dedicated Parents and the Power of Drug Repurposing

Twins Alexis and Noah Beery had a genetic illness that baffled doctors. They were born in August 1996 and soon after coming home from the hospital, their parents knew something was wrong. First diagnosed at two years old with cerebral palsy, the Beerys began questioning the diagnosis.

The twins suffered seizures, balance and coordination problems, vomiting and missed developmental milestones. Alexis kept getting worse. In the first four years of life, they had over 80 tests done. "Nobody could give us answers," Joe Beery, the twins' dad, said. Alexis continued to spiral downward, losing any motor abilities she once had. At five and a half years old, Alexis could walk and move around in the morning, but by 11:00 a.m., she could not walk, sit up, or swallow food. Her eyes would roll up and her hands would tremor. For part of the day, she could do the things she wanted to do, but later she could not function.

Retta Beery, the twins' mom, desperately searched for answers. She went to the Emily Center at Phoenix Children's Hospital and pored through hundreds of medical journal articles. She read everything she could to learn more about what could possibly be making her children so sick. She recalls, "I was constantly researching everything they were experiencing."

Then, a breakthrough happened when Retta found an article about Segawa's Dystonia, a rare disorder that resembles cerebral palsy. The difference is that a child with Segawa's Dystonia can function at a higher level early in the day then quickly gets worse throughout the day. Retta immediately thought this was just like Alexis.

This disorder had a treatment, a drug called L-dopa, which was used for Parkinson's disease. After taking Alexis to a new doctor with her theory, the doctor agreed to put Alexis on it. Once she received the medicine, even "after taking a quarter of one pill, for the first time in her life, Alexis slept through the night," Retta said. Alexis astonishingly improved. "She was able to walk to the car on her own and put her seatbelt on by herself. She was never able to do that before."

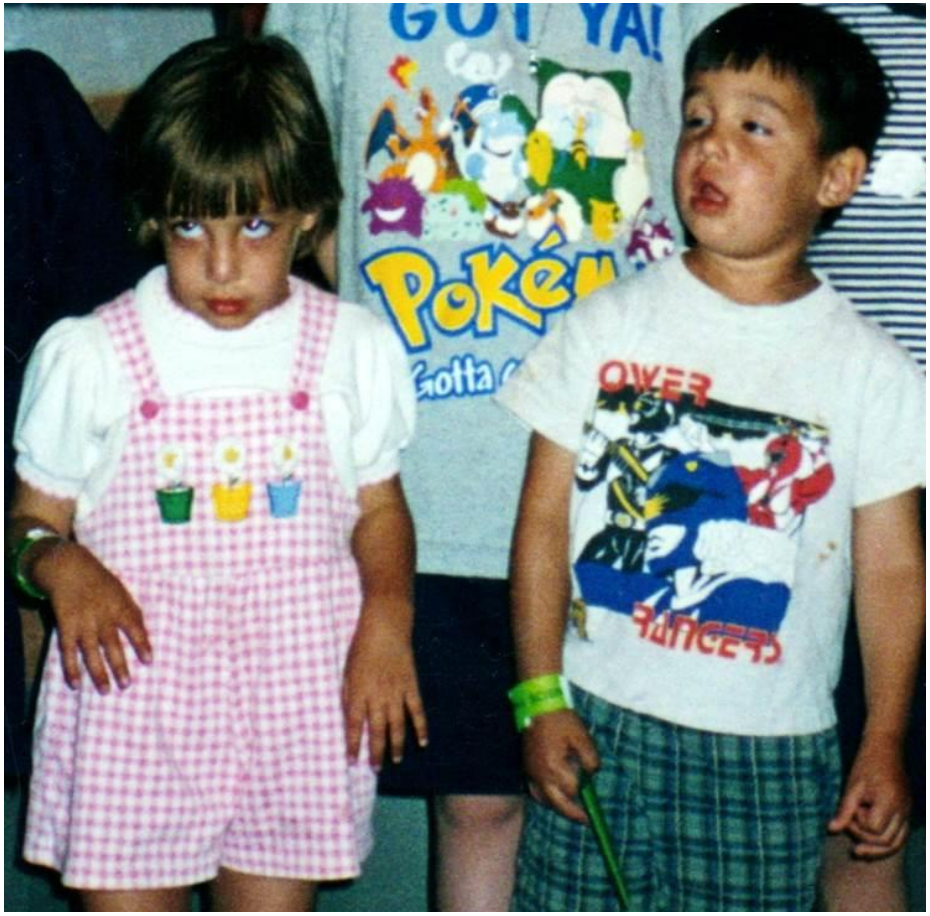
The twins turned six in August 2002, and Alexis really responded to the L-dopa. Noah still had the cerebral palsy diagnosis and still suffered from vomiting every day. At first, doctors did not want to put him on L-dopa. Retta explained, "I had a clear reason to believe that he will benefit from it."

"The gene sequencing gave us answers and a new life. To see our kids doing all the things that we only dreamed of, is truly a miracle."

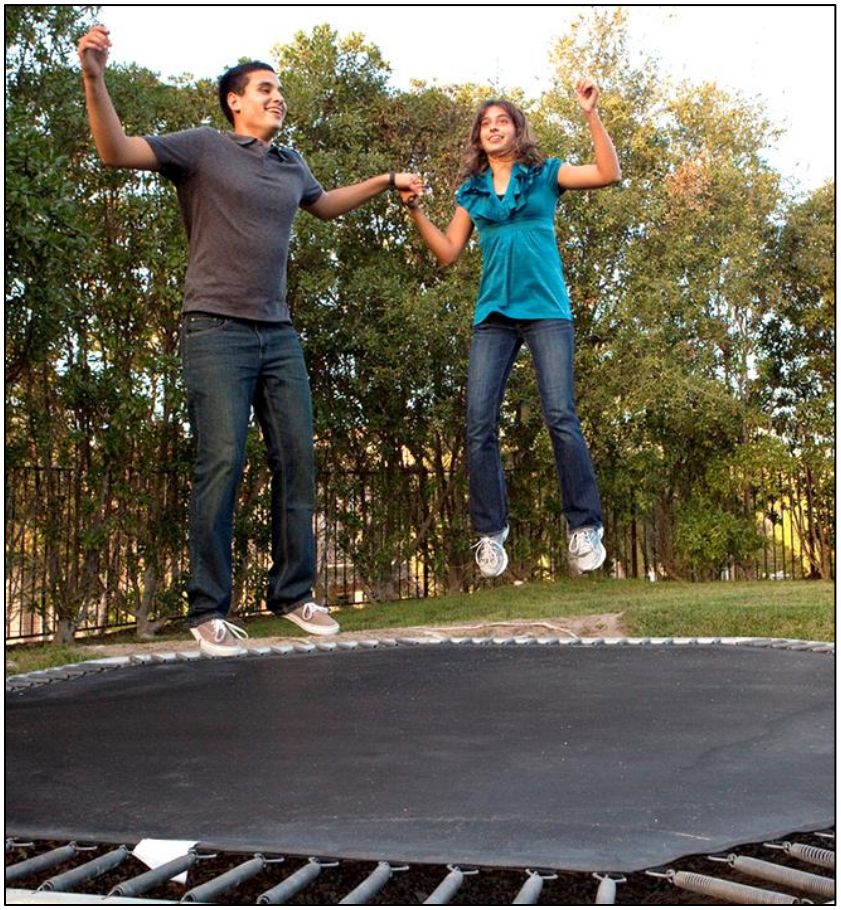
-Retta Beery, mother of the twins

When he was put on the L-dopa, the vomiting stopped. The doctors agreed Noah did not have cerebral palsy; he had dystonia like his twin sister. The twins made remarkable improvements athletically and in school. Noah's attention in school improved, and they were able to do all the things they wanted. Doctors told the Beerys to get the twins in every sport. Their bodies are like plastic, they needed to rebuild them.

Then Alexis suffered a life-threatening setback. She had a cough for years that suddenly changed. In a two-month time span, Alexis went to the emergency room seven times turning blue from lack of oxygen and with severe breathing difficulties. The current medicine to treat what doctors thought the twins had was not enough. They needed to get to the root of the problem, and they needed to save Alexis.



Before
At age 5, Noah and Alexis Beery suffered for years with a misdiagnosis of cerebral palsy, but were eventually diagnosed correctly.



After
At age 17, with the relentless determination and research of their mom, the correct diagnosis was found, and the twins are active healthy high school students.

For over a decade, the Beerys did everything to search and find answers. Joe Beery was a successful airline CIO who even changed industries to try to help his kids. He started working for Life Technologies, a California biotech company that makes gene-sequencing equipment. Retta and Joe believed sequencing the twins' genomes would find answers and hopefully lead to a cure.

The twins, their brother, both parents, and grandparents were sequenced. Within two months of genome sequencing, the exact problem genes were isolated. In November of 2010, the Beerys learned that Alexis and Noah, now 14 years old, had not one, but two inherited mutations that could end their lives. Dopamine Responsive Dystonia, DRD, and more specifically, SPR, is caused by mutations in the sepiapterin reductase gene. Not only did they find the problem, but they found a treatment.

"I knew with gene sequencing we would find something," Retta said. The Beerys already knew that there was a problem with low levels of dopamine, so the L-dopa was fixing that. Only through whole genomic

The First 6 Years for the Beery Twins

Retta Beery kept track of all of the medical procedures and visits for her children over the first six years of their lives.

Blood drawn 200+ times
Countless ER visits
Multiple pediatricians
Multiple X-rays
1 surgery (Alexis)
5 EEGs
8 MRIs
8 CT scans
9 Ultrasounds
3 Upper GI's
3 pulmonologists
3 ENT's
5 Allergists
1 Oral surgeon
1 Genetic doctor
4 Gastroenterologists
6 Neurologists
1 Pediatric urologist
5 Naturopathics
4 Pediatric ophthalmologists
4 Orthopedic surgeons
Physical therapists
Occupational therapists
Speech therapists

The Results …

1. Incorrect Diagnosis of Cerebral Palsy
2. Treatment Centered on the Incorrect Diagnosis
3. Huge Financial, Emotional and Physical Costs

sequencing, they learned that they had a second mutation involved with serotonin. With this new information, doctors prescribed a serotonin precursor that is readily available at pharmacies.

After starting the new medicine, the cure was dramatic. Within a month, Alexis was back to school, running track and playing basketball. Noah was healthy too and played club volleyball. When Alexis was asked what she remembers and how she felt being sick, she explains, "The hardest thing was that I couldn't reach people. I could do the stuff I wanted to do for part of the day, but then it would all go away. I knew something was wrong not being able to walk or talk. I felt trapped and frustrated. I felt bad not having that ability for a long period of my life."

"I knew with gene sequencing, we would find something."

- Retta Beery, mother of the twins

Alexis and Noah were helped immediately after genomic sequencing revealed their complete diagnosis. Genome sequencing changed the outcome of their lives. The twins now have no symptoms. They are leading normal, active lives.

This case demonstrates how genomics is leading the way to making a precise diagnosis in many cases and potentially enabling life-changing, lifesaving treatments. The Beery case shows the love and commitment of the parents to find the answer, the full treatment for their children. Joe Beery brought his commitment to rare diseases to his position on the board of Rare Genomics Institute. Retta is an Advisor for our Patient Advocacy Team. From personal experience, the Beerys know what it's like to search for answers when no current information or treatment is there. They want to help others find answers for their children

Once diagnosed with cerebral palsy, they now run under seven minute miles. The twins are now leading active lives. Only a few years earlier, Alexis had life threatening breathing complications.

Takeaways:

1. Gene sequencing led to the complete diagnosis and life-changing drug therapy for the twins. Joe Beery's decision to change jobs and work for Life Technologies introduced the Beerys to gene sequencing. The decision to do gene sequencing saved the twins' lives. Alexis and Noah Beery live normal lives now.

2. A parent's relentless determination can lead to therapies for even the rarest of diseases. Retta Beery's research informed doctors and dramatically improved the twin's condition.

3. Joe Beery is on the RGI Board. Retta is a speaker, founder of a nonprofit, and an advocate for her children and others with rare diseases. She is an advisor for the RGI Patient Advocacy team. They are using their experience to help other families suffering from rare diseases.

4. Parents are part of the medical team and the most important advocate for their children. You can become extremely knowledgeable about your child's illness to help their outcome.

5. Get organized. Retta said, "Take notes and have your questions written down before the doctor's appointment. You can keep them on a smart phone. This way you will not forget anything important that you wanted to discuss."

6. Research all medications and talk to your doctors about what your child is taking to find out risks and potential bad interactions.

7. You are in a partnership with your spouse for the best interests of your child. Establish roles. If one parent is better at communicating with the doctors and medical team, let them take the lead in that area, and your role is to support their efforts.

Alexis and Noah Beery are thankful to their mother's determination and relentless search for answers. "We know we wouldn't be here without her."

Debbi and Travis Putjenter - A Television Show Saves a Son's Life

The Power of Drug Repurposing

When Travis Putjenter was about a year and a half old, Debbi and Scott Putjenter, Travis' parents, started to notice something odd was happening to their son. First, it was very subtle. Then he started regressing from milestones, like falling over when he sat up. They began taking him to doctors. For about a year they went from doctor to doctor, and no one could tell them what was wrong. When Travis was two and a half, he was diagnosed with cerebral palsy, CP.

His parents were devastated but decided to deal with it the best way they could. They accepted his diagnosis, but Travis kept getting worse. He was losing mobility, and they again went to more doctors. No one could answer the question, "What was happening to him?" They were told he must just have a unique case of cerebral palsy.

Travis walked until about 6 years old. But following two foot surgeries to correct his feet from turning inward, his abilities abruptly declined. He lost his ability to walk and was confined to a wheelchair. He couldn't use his arms or hands. He was completely dependent on his parents for feeding, clothing and bathing. His voice was very soft, and he could barely talk or hold his head up.

Despite his situation, Travis always remained a happy child with a good attitude. Throughout his childhood, Travis' family loved sports, and they would always take Travis with them. He watched his brother play baseball. They always included Travis in the family activities.

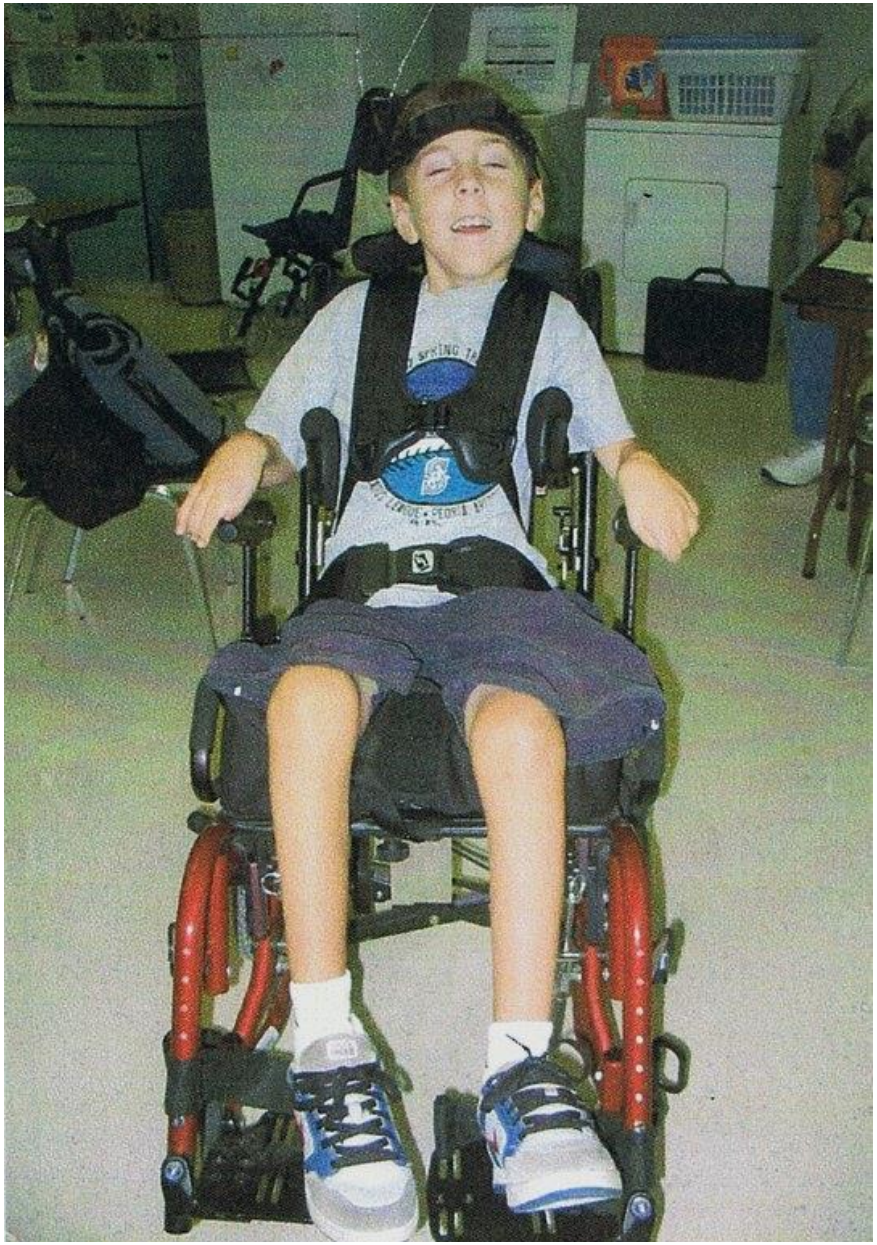
One night when Travis was almost 14 years old, everything changed. Scott had made a stand for the remote control so when Travis was placed on the floor to watch TV, he was able to change the channels by himself. Scott carried Travis out of his wheelchair and put him on the floor, and then Debbi and Scott went into another room. Travis was lying on the floor watching TV. He flipped channels and started watching the Discovery Health channel when the show *Mystery Diagnosis* came on.

"Mom, Dad, I think that's me."

- Travis Putjenter, whispering and pointing to the television

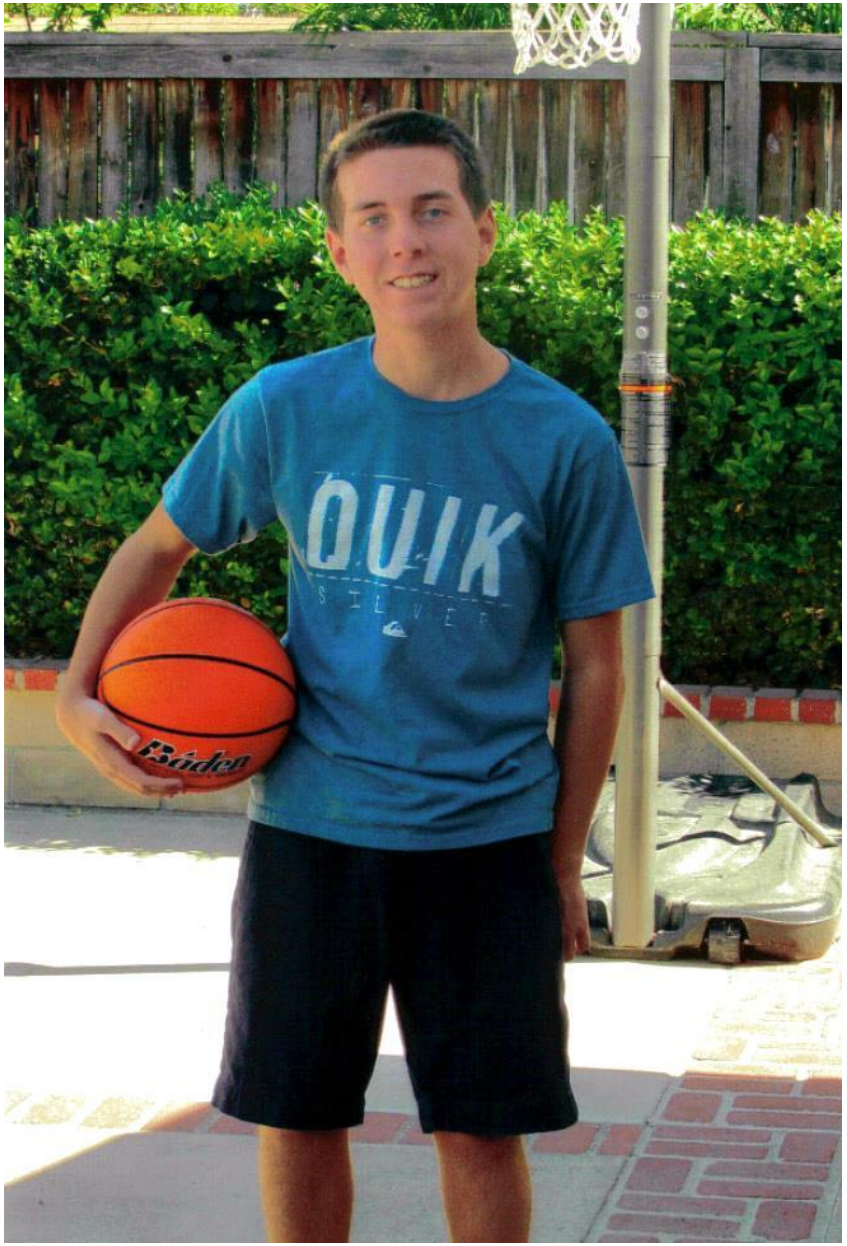
Travis saw the Beery story on Discovery Channel's Mystery Diagnosis and told his parents this was about him – and it saved his life.

Mesmerized, he watched the story unfold about Noah and Alexis Beery, the California twins that were misdiagnosed with cerebral palsy when they were young, but their mother questioned the diagnosis. The twins' mom, Retta Beery, wouldn't give up and searched for answers until she found a medical article that described dopamine responsive dystonia (DRD). DRD is a genetic disorder that affects dopamine, a brain chemical needed for muscle development and movement. The disorder mimics



Before

Travis was misdiagnosed with cerebral palsy when he was two and a half and continued to lose mobility. He spent years in a wheelchair before seeing Mystery Diagnosis.



After

Travis is an active healthy teenager after seeing the Mystery Diagnosis story about the Beery twins and getting on the correct therapy.

cerebral palsy, but one difference is that children can function at a higher level during part of the day. Retta went to her doctor with her article, and this ultimately saved her children's lives. Today, they are active, healthy teenagers.

Lying on the floor, Travis whispered in his soft voice for his parents to come in the room, "Mom, Dad, I think that's me." Scott said, "We started watching the television show. Then we backed it up, and replayed it again, and again. We went to the computer and Google searched Dopamine Responsive Dystonia, and it fit Travis." We thought, "How could this one thing be what is happening to our kid?" They contacted their physician and Travis started on L-dopa.

Scott and Debbi were concerned at first to give Travis the L-dopa. After taking the first dose, Travis started making jerky movements with his arms. "I was so scared. What are we doing to our son?" she said to Scott. He reassured her that it was much better than where he was. Within a week, Travis could hold his head up, and he found his voice. Travis was speaking in sentences, not single words.

Within two weeks, he could open his fingers and throw a ball. On his fourteenth birthday, he grabbed finger foods, and by the end of December of that year, he was able to eat on his own. From that point on, his body was like a newborn. He followed the progression of a newborn, rolling, crawling, scooting, pulling up, and then within a year, he started walking again. His physical therapist would set goals for the next appointment, and by the time Travis got there, he was already past those goals. This all happened in 8th grade. By his sophomore year of high school, Travis was playing tennis on the high school tennis team.

"Without seeing the Beery's story on Mystery Diagnosis, I don't know if our son would be alive today."

- Debbi Putjenter, mother of Travis

Debbi and Scott reflect on their journey. They said they went through a time when they were angry. Angry at the years Travis missed of his childhood confined to a wheelchair - the soccer and baseball games he could only watch others play. He missed out on 10 years of his childhood, and so did they. Then, they felt guilty. "We should have searched more for answers," Scott laments. But now, they are thankful for the life he has and his future. Scott says the biggest thing that troubles them is, "How many other kids are out there like Travis? How many parents are being told, 'Your child has a unique form of CP,' when it really isn't that at all. This is curable. Look at him."

Debbi says the best thing about her son Travis is that he was very accepting of how he was. "He was never upset. He just felt this is how it is," she said. Once he started to get better, he was so excited. "Now, this is what I can do!" Travis tells his parents. "He never felt he was missing out on something. He is a blessing," his mom said. But from the years in a wheelchair, Travis developed scoliosis and has had to endure three back surgeries. The rods broke twice in his back, but today Travis is doing well.

Debbi says, "Without seeing the Beery's story on *Mystery Diagnosis*, I don't know if our son would be alive today." Ironically, the original show on the Beery's had aired years before Travis saw it. The night Travis turned on the show, it was a random rerun from seven years before.

Travis Putjenter was confined to a wheelchair for most of his life. He was eventually diagnosed with DRD, which can be overcome with dopamine, and it allows him to live a normal life. He is now an avid fan of tennis and basketball.

Takeaways:

1. The Putjenters did everything with Travis. He was always included. Their older son played baseball from childhood through college, and they would load Travis up and take him to the games. Travis is a huge sports fan, so they took him to many professional sports games.

2. Travis was always mentally capable. “His brain works great, his body didn’t,” Debbi said. He developed his own style of learning. He was in all the regular classes, but he had an aid. He never really had to study much, his mom recalls. He had developed an incredible memory and remembered everything. He was always a straight-A student.

3. “Don’t just try to fit what you’re seeing into something. If it doesn’t fit the diagnosis, look further,” Scott said. Be aware of conditions that mimic other diseases like how DRD mimics cerebral palsy. Travis did not have the key indicators of CP. With Travis, there was no birth trauma. He had normal MRIs. He was a planned cesarean delivery, and there was no problem during the pregnancy.

4. Use your ingenuity to make your child’s life easier. Scott made a stand so Travis could have the independence to change channels on the TV.

5. Parents should not feel guilty. Rare diseases are just that, rare. With some rare diseases, only a very small number of cases are known and reported, so very few doctors have ever seen them.

6. Rare disease parents would greatly benefit from a symptoms database for rare diseases, so they can search unique behaviors they are seeing and get more information and insights.

7. Rare disease parents should publicize breakthroughs with their child’s disease and use the media to make other parents and families aware of them.

Please note Travis is not an RGI patient but his story is cited to help families better understand the rare disease process.

The Putjenter family is close and happy that Travis survived early symptoms of the disease. Like many rare disease families, his brother Tyler included Travis in most social situations and sports.

Robert Stone's Story – Genomics Used for A Diagnosis After 14 Years

Fast Crowdfunding and Community Building Leads to a Breakthrough

Robert was born in 1997 and was a typical, happy baby until just after he turned one. Then over the course of three days, he had brief episodes of slowed or interrupted movements. This culminated in a dramatic medical breakdown.

At first, "It was a few seconds on vacation in our hotel, when he fell backwards and just froze. Then he got up and looked fine. What did I just see?" Jeneva Stone, Robert's mother, asked herself. "You can't press rewind on your life." The reasonable explanation was he was tired, off schedule.

Then, "It was so sudden and so terrible and completely out of the blue," Jeneva describes the day when he had his medical crash. He lost use and control of his arms and legs, his mobility and his ability to communicate.

Jeneva took Robert to numerous doctors for testing and the months turned into years without a diagnosis. All diagnostic testing strangely came back normal. "At first you feel like you won the lottery when you get negative test results for some life threatening disease, but after over a decade, you are devastated when test results have no diagnosis," Jeneva said.

Fifteen years later, Robert, now 16, is in a wheelchair and has a feeding tube. Although difficult, he tries to communicate using his limited mobility. He lifts his right hand for "yes" and his left hand for "no," or by facial expressions. Robert's parents always believed there was some rare genetic disease causing Robert's condition.

"After 14 years with no diagnosis, last year we pursued gene sequencing through Rare Genomics Institute and finally found an answer."

- Jeneva Stone

Jeneva connected with Rare Genomics Institute through another mother who has a child with an undiagnosed medical condition. "I saw it as a last-ditch effort to figure out what was wrong," Jeneva says. The Stones brought Robert and their binder filled with over 100 diagnostic tests to RGI. After years of testing with no answers and many medical bills, the Stones decided to try raising money for Robert's genomic sequencing through RGI's crowdfunding campaign.

"We empowered an entire community," Dr. Lin of Rare Genomics Institute said, and within six weeks, Robert's campaign reached its fundraising goal of $7,500 for sequencing the parents and Robert. The average donation was less than $50. About one-third of the money came from complete strangers and the rest from a community effort using Facebook to tell family and friends about the RGI crowdfunding site for Robert.

Roger Stone moves his son Robert from his wheelchair to the family couch. Robert suffers from a very rare muscular disease called Dystonia 16 - which only 8 other people in the world have. His family spent 14 years trying to get him diagnosed and finally got a diagnosis from Rare Genomics Institute in 2012.

Robert began genomic sequencing, and within 9 months, the researchers found what was causing Robert's condition. Robert and his parents finally had a diagnosis. He has a syndrome called Dystonia 16. Robert is only the ninth person ever reported to have this syndrome. "It was a one in three billion lightning strike," explained doctors to the Stone family. This would never have been diagnosed without exome sequencing.

"We always knew the science would catch up to Robert. We didn't give up, we found out what was wrong with him."

- Jeneva Stone

The only other people with this illness are in Brazil and one in Germany. He has an extremely rare combination of two mutations, one on each copy of a gene called PRKRA. The diagnosis gave the family answers and a sense of peace. They found the answer for Robert. They didn't give up, and they were right. They now know what they always suspected, that Robert has normal intelligence. They always believed he did. He does understand them.

With diagnosis, they can use medications that can be targeted for his illness and work better. They are using a repurposed drug called Sinemet, for Parkinson's disease to initiate movement. The knowledge of what caused their son's illness has given the Stones new information to understand and improve his quality of life. "We'll do whatever we can to connect with people who are doing research in this area," Jeneva said. They are now hoping that this discovery will lead to new treatments for their son and others with dystonias and movement disorders. "We always knew the science would catch up to Robert," Jeneva said. "We didn't give up, we found out what was wrong with him."

Takeaways:

1. Crowdfunding enabled a medical breakthrough. A fourteen-year medical mystery for Robert Stone and his family was solved from many $25 or $50 donations from friends and family on RGI's crowdfunding site. Now they can focus on targeted treatments for their son.

2. Exome sequencing found a disease so rare that it would never have been solved without sequencing. He is the ninth person ever diagnosed with Dystonia 16. The only other reported cases in all medical literature are in Brazil and Germany.

3. Many times genomic testing will reveal a more important result. An exact diagnosis tells you what it is, and what it is not. Some thought that a child with severe physical disabilities automatically had severe mental disabilities. Some assumed Robert could not understand or communicate. Exome sequencing determined he had a movement disorder. He does understand and can communicate. The Stones now know with certainty what they always suspected, that Robert has normal intelligence.

4. Document your child to track patterns. "You can't rewind your life," Jeneva said. If you think something is odd or not quite right, write down and describe what you observed and write the date that it happened.

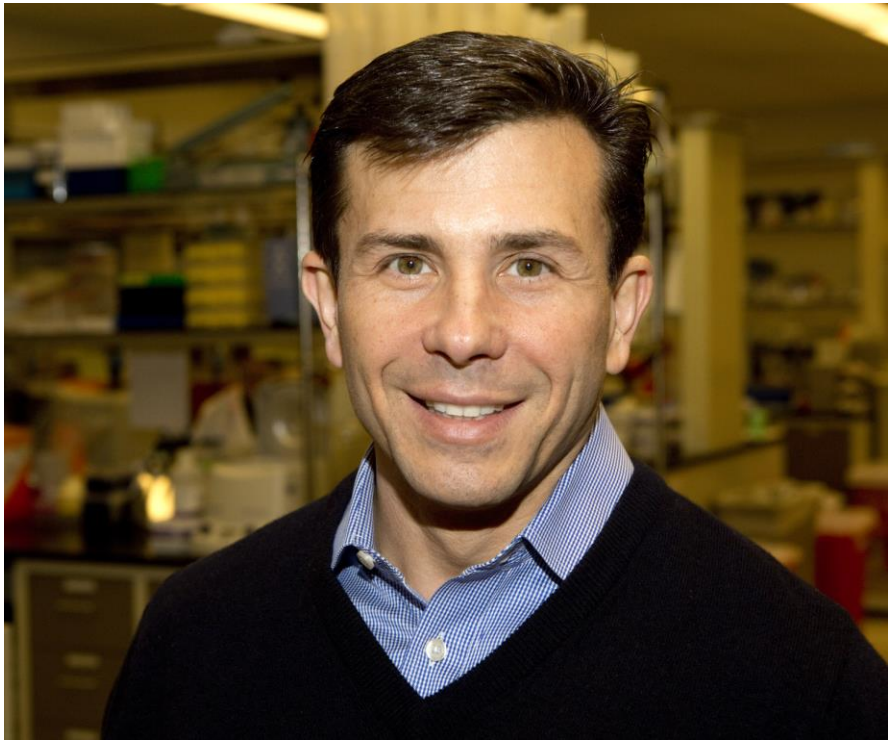
5. Construct a binder that contains all your relevant and significant medical records, including MRI disks. The binder that Jeneva Stone kept for her son Robert was so well done that it is famous among doctors. You should get a copy of every lab report on lab stationary. Not every lab runs tests the exact same way. This will give you the most accurate information and smallest chance to have to repeat the same test. Get test results and any other medical reports. See the Parent's Toolkit section for a detailed breakdown and photos of what was in her binder and how she organized it. Doctors have said having this information and organizing it can save 3-6 months of time to diagnosis.

6. Building a community around your child adds great value. Jeneva Stone, Robert's mother, is a writer. She has built of community of support around her and her son. She has written in prominent journals on disability and parenting. She has been a strong advocate for her son.

7. What happened to Robert and finding this diagnosis can be used to help others suffering from rare diseases. Research can be done on Robert's Dystonia 16, other dystonias and movement disorders.

Heroic Parent Saves Kids' Lives by Building a Biotech Company

John Crowley's Amazing Rare Disease Story Was Made into the Movie *Extraordinary Measures*



When Megan Crowley was fifteen months old, her parents, Aileen and John Crowley noticed she was missing some of her developmental milestones. She was having difficulty putting weight on her legs and pulling up, so they decided to take her in for testing.

At the time, Aileen was also pregnant with their third child, Patrick. On March 13, 1998, just days after Patrick was born, John and Aileen were told the results of Megan's muscle biopsy. Fifteen-month-old Megan was diagnosed with Pompe disease, a rare fatal disease where toxic levels of glycogen form in the muscles. The doctors actually got the results the day Patrick was born, but decided not to tell the Crowleys that day.

John remembers the day they received the news about Megan. They met with the neurologist, and he opened a medical textbook and turned to the page on Pompe disease. He read a few sentences to the Crowleys. Pompe disease was a fatal neuromuscular disease. The life expectancy for children with infantile Pompe disease was two years. He explained that he had never before seen a case of it. He then told them to go home and enjoy the remaining time they had with her.

On the car ride home from the neurologist, John and Aileen were shocked and in disbelief. Their beautiful daughter's second birthday was not far away. Later that night Aileen went to bed with Patrick, and John began searching the internet for information on Pompe. After several hours, he found an article about researchers at Duke working on an enzyme replacement therapy for Pompe disease. He was so excited he woke Aileen up to tell her about it. She asked what it meant. "I think it means that there's hope for Megan," he said.

"I think it means that there's hope for Megan."

- John Crowley

Like many parents confronting a rare disease in their children, they experienced the shock, grief and denial, but then they focused on determination. After hearing from doctors there was nothing else they could do, they became determined to save their children. They later found out that not only did Megan have Pompe disease, but Patrick did too.

Quickly John connected with Duke and started immediately gathering all of Megan's medical records. He was at Kinkos making copies when he

John Crowley holds a picture of his three children, Megan, John and Patrick. Megan and Patrick have Pompe disease. John started a biotech company to speed research and developed an enzyme replacement therapy that saved his children's lives.

came across an x-ray taken the day Megan was born. After she was born, Megan was taken to the neonatal intensive care unit for a few hours. John was there with her while Aileen recovered from delivery. In a short time, Megan seemed fine, and she was able to go home right away.

But that day while making copies, for the first time he saw the x-ray from the day she was born. The report showed Megan had profound cardiac enlargement, and there was a recommendation of immediate follow up care. No one had told them. Somehow, it had been missed.

"Realizing he was in a race against time to save his children and frustrated by the slow rate of progress, John decided to risk everything to find a cure for his children."

John was no stranger to life's challenges or hard work. Growing up in New Jersey, he had a normal childhood until he was seven years old. Then on January 12, 1975, he woke up and found out that his father, a police officer, had died on duty. John remembers this as the first defining moment in his life. His life changed forever.

Now, with a recent MBA from Harvard, a J.D. from Notre Dame, and a B.S. from Georgetown, he had a bright future and was working as an executive at a large pharmaceutical company. He had a great job and health benefits that his children would soon really need.

Like her father, from an early age, Megan showed she shares the same determination and courage. When she was two years old, in one week alone, she almost died three times. After a team of doctors and nurses revived her after she had crashed, they told the Crowleys they didn't think she would make it through the night.

When she woke up the next morning, John remembers her brown eyes locked on his and then Aileen's. She was on so much medication that she couldn't move, but they knew from that look, she was going to fight to live. This was another defining moment.

Realizing he was in a race against time to save his children and frustrated by the slow rate of progress, John decided to risk everything to find a cure for his children. He found Dr. William Canfield, a scientist, who had been working on Pompe disease for ten years. Canfield needed more funding for his work. John quit his job and started a biotech company with Canfield called Novazyme Pharmaceuticals to work on the enzyme replacement therapy. He became CEO and set out to raise money to fund the research.

John was on a mission to drive research into Pompe disease. He met with scientists, medical institutions, advocacy groups and venture capitalists to focus research, raise money and find a cure. John and Aileen never wanted to have regrets, and they wanted to do everything possible to save their children.

Although they had hope and asked about the "special medicine" their dad was making for them, Megan and Patrick's health continued to deteriorate. Pompe disease affects the skeletal muscles, making them weaker. It also affects the diaphragm, so breathing is more difficult and cardiac function is compromised. They were both put on ventilators and were in wheelchairs. When Megan was five years old, she learned that kids can die from Pompe disease. She looked at her dad who was home at the time, surprised with the realization. She said, "I can die from this? What are you doing home, go, go."

Despite their health problems, they are happy kids. Megan, always quick-witted and intelligent, offered her suggestions on the color of the special medicine. She told her dad that the medicine he was making should be the color "bubble gum pink" like the walls of her bedroom. She felt that a clear medicine was boring. Megan's energetic personality lit up the Crowley house as she raced around in her pink wheelchair.

At the headquarters of his company, Amicus Therapeutics, John Crowley points to one of the many photos of their patients that line the walls.

In only eighteen months, John raised $27 million and Novazyme grew from a team of 4 people to 120. With a promising new therapy for Pompe disease, Novazyme was bought by Genzyme for $137.5 million, and John became an executive there. Myozyme is the name of the "special medicine" and is an enzyme replacement therapy that can stop and reverse the life threatening enlargements of their hearts caused by the disease. Although he accomplished an incredible amount in a short amount of time, every day of the eighteen-month process, John thought to himself, "This is taking so long." He was racing against time. Their hearts were getting weaker.

When the clinical trials started, John faced another challenge. The clinical trials for the life-saving medicine were designed for infants and children under three years old. After all of his work, Megan and Patrick did not fit the clinical trial guidelines, so they were not going to get the medicine their dad risked so much to make to save their lives.

John tried to get another clinical trial, a sibling trial that Megan and Patrick could enter, but there was concern of a conflict of interest with John being an executive at the company. Megan and Patrick were running out of time, so John decided to resign from Genzyme to eliminate any concerns about his executive role.

On Megan's birthday, December 16th, 2002, the Crowleys were told the news that Genzyme found a small hospital willing to do the sibling clinical trial allowing Megan and Patrick to have the life-saving "special medicine" their dad helped make for them. On Christmas Eve, the Crowleys received the letter approving their clinical trial with a note telling them to put it under their Christmas tree. To this day, the Crowleys still have the letter.

On January 9, 2003, just after Megan's sixth birthday, they finally received the first dose of medicine. After taking the enzyme, they were laughing and giggling. Their bodies were finally processing the huge amounts of sugar that they were unable to process before now.

At their first echocardiogram after starting the therapy, their enlarged hearts were dramatically smaller and working better. After Megan and Patrick started the infusions, quickly they saw other improvements, especially in Megan. She went from limited mobility to sitting up. They could talk and eat by themselves. Today, the "special medicine" their dad worked tirelessly to develop for them is now the standard of care for Pompe disease.

Today, the "special medicine" their dad worked tirelessly to develop for them is now the standard of care for Pompe disease.

What role did the medicine play in his children's lives? John explained that their life expectancy was two years, and now they are 16 and 17 years old. The medicine saved their lives from the heart disease that threatened them and gave them a much higher quality of life. They are looking forward to their futures.

Despite her physical challenges, nothing stops Megan from reaching her goals. She is looking forward to her future, and talks frequently about colleges. Like many teens, she spends a lot of time talking with friends and on her phone.

From the years in a wheelchair and Pompe's effect on the skeletal muscles, Megan and Patrick have developed scoliosis. Last year, Megan made the bold decision to have surgery to straighten her spine. Understanding the risks of the surgery, including the risk that she may not survive the operations, last summer Megan said yes to surgeries where rods and screws would be placed into her vertebrae. This would straighten her spine that was turned about 100 degrees.

John and Aileen knew about the surgery, but they also knew the risks. John says he was worried, but only Megan knew if she was strong enough to handle the surgeries. She made the decision. Last summer, Megan endured three surgeries on her spine at Columbia Medical Center. There was a complication in the second surgery, and they had to remove the rods they placed in her back. Megan almost died.

Seeing Megan in such pain bought John and Aileen to tears, but Megan recovered and decided to go through a third surgery. This surgery was successful and Megan reached her goals for the summer. She wanted to get back to school on time from her surgeries and go wedding dress shopping with her cousin who was getting married.

Megan is always optimistic about her future, and her courage and resilience makes her a great role model for other kids facing the challenges of living with a rare disease.

When asked what you would tell children living with a rare disease, John said, "If you are living with a rare disease, focus on living, despite your challenges. You can have the same hopes, dreams and ambitions as anyone unaffected by an illness. You can do anything other kids can do. Don't let it frame who you are."

"If you are living with a rare disease, focus on living… You can have the same hopes, dreams and ambitions as anyone unaffected by an illness. You can do anything other kids can do."

- John Crowley

John Crowley showed the world his exceptional dedication and drive to save his children's lives. The Crowley's story has been made into a book called *The Cure: How a Father Raised $100 Million - And Bucked the Medical Establishment in a Quest to Save his Children* by Wall Street Journal writer Geeta Anand. It has also been made into a movie called *Extraordinary Measures* with Harrison Ford and Brendan Fraser. The Crowleys have put the spotlight on rare diseases and are strong supporters of research in rare diseases.

John Crowley continues to drive research and development toward therapies and cures for rare and orphan diseases as CEO of Amicus Therapeutics. Amicus Therapeutics is a biopharmaceutical company focused on next -generation therapies for lysosomal storage diseases (LSDs).

With all of his many accomplishments throughout his life, when asked what he's most proud of, he said, "Being a dad." When we asked him how he felt about saving his children's lives, he teared up and said, "I felt I had done my job."

Takeaways:

1. Parents need to be their child's greatest advocate. Be informed and deeply research your child's illness. No one is thinking of your child every day like you are.

2. The Crowley's family journey became a book and a major motion picture. Hollywood told the remarkable story of their family but John said their story represents the challenges of many rare disease families. Through their story being made public, they hope to drive much more awareness for rare diseases and for the unmet needs of those affected by them. He urges other parents to create awareness of their child's rare diseases.

3. For children living with a rare disease, "Focus on living, despite your challenges. You can have the same hopes, dreams and ambitions as anyone unaffected by an illness. You can do anything other kids can do."

4. As with many rare disease families, parents should use their professional and any other skills they have to help their children. While there are no guarantees, extraordinary efforts can lead to great results for your children and a better quality of life.

Amicus Therapeutics is developing novel, next generation therapies for genetic diseases, targeting lysosomal storage diseases (LSDs).

Balazs' Story – An Unexplained and Severe Seizure Disorder

Fast Crowdfunding Enables the Gene Sequencing Process Now

Balazs looks like a normal, happy seven-year-old boy, but he has a condition that has perplexed doctors for most of his life. For over six years, Balazs' doctors and family have been trying to figure out what is causing him to have debilitating seizures.

When Balazs was four months old in 2006, his mom, Zsuzsanna Darvai, thought he was not developing like her older son had at that age. Then at nine months old, suddenly his lips turned blue. This lasted about two to three minutes and was over. Her pediatrician tried to reassure her that he was fine. He thought she was exaggerating. The next morning when she was changing his diaper, again he turned his head to the left and his lips turned blue. She took him right to the pediatrician. While she was in the waiting room of the pediatrician's office, it happened again, his head went to the left, he couldn't move and his lips turned blue. She ran with him back to the doctor and showed him.

Balazs and Zsuzsanna were taken by helicopter to a hospital in Pensacola, Florida. The pediatric neurologist put Balazs on medication right away. Balazs continued to have petit mal seizures. More medication was given, but the seizures were not under control. The Darvai family started a six-year search for answers and medication that could prevent these devastating events.

Balazs could not sit up until after he turned one. By two and a half, he had some behaviors that looked like autism: not having eye contact and screaming uncontrollably. He can move but he wears braces to support his ankles. To help with the developmental delays, he has spent the last four years in occupational therapy, speech therapy, physical therapy, and Applied Behavior Analysis (ABA therapy) for autism. Although he can follow some directions, he needs to be watched constantly.

"If you have hope, you have everything. Don't give up and don't be discouraged, you can do a lot of things to help your child."

- Zsuzsanna Darvai, mother of Balazs

Desperate for answers, Balazs' mother has tried alternate therapy including hyperbaric oxygen treatment for his motor development. Balazs could not walk more than two to three steps at two years old. Hyperbaric oxygen therapy increases air pressure above normal pressure so the patient's lungs can fill with more oxygen than normal. This is carried through the blood to increase growth factor and stem cells for healing. Zsuzsanna said, "His motor skills jumped tremendously with this treatment. After the fifth day of treatment, he could walk up and

Balazs suffers from seizures that are unpredictable and uncontrollable even with multiple medications. Exome sequencing and a successful crowdfunding campaign through RGI will hopefully lead to answers and maybe a therapy.

down the street." When he was two years old, he had forty treatments. For one hour a day, Monday through Friday for two months, he went through hyperbaric oxygen therapy. At three years old, he had another forty treatments and at four years old, twenty treatments." It's expensive, $150 a treatment, and it's not covered by their insurance. However, he responded to it, so the Darvais continued to pay to do anything to help their son. Now, he can walk and run around.

"I don't want to accept the fact that we don't know and may never. You have to be persistent."

- Zsuzsanna Darvai, mother of Balazs

Balazs has endured countless medical tests including 5 days in a hospital bed with video EEG (electroencephalogram), measuring the electrical activity in his brain. They took him off his seizure medication for the testing. As Zsuzsanna was driving him home from the hospital, he again had a seizure. Zsuzsanna explains that if he was not on the medications, he would have both grand mal and petit mal seizures every fifteen to twenty minutes. He has had MRIs but they did not reveal anything about the cause of the seizures. So far, he has been on six different seizure medications and nothing has worked.

Over the past year, he has been on three different seizure medications at the same time and is still suffering seizures. Balazs has a weakened immune system and low muscle tone as well as the developmental delays. He has immune deficiency hypogammaglobulinemia, so once a month, a nurse comes to his home to give him an IVIg medication intravenously. Despite his developmental delays and seizures, Balazs is a very happy little boy who always smiles. He willingly puts his arm out for the three hour IV to begin his immune deficiency treatment.

Balazs' neurologist told Zsuzsanna that of the 2,000 patients he sees, many have seizures, but very few are like Balazs that stop breathing completely for so long. Why was this happening to him? Why was his body resistant to so many medications? Many times Zsuzsanna was told by doctors to "accept the fact that we don't know what's wrong with your son. Be happy, he's developing. Don't look for any more answers. It won't change anything." Zsuzsanna said, "I don't want to accept the fact that we don't know and never will. You have to be persistent. So many families have similar problems; you are really on your own."

Balazs is getting ready to go into school sitting with his protective older brother.

Then one of Balazs' doctors, a geneticist from Gainesville, heard from a patient about Dr. Jimmy Lin and his work with exome sequencing. Balazs' doctor called Dr. Lin and talked with him about Balazs. He recommended Zsuzsanna try exome sequencing because Balazs has many different issues and exome sequencing for rare diseases is what Dr. Lin does. She immediately contacted Dr. Lin.

"RGI helps patients start fundraising within hours of receiving the information."

By sequencing Balazs' exome, his parents, and his brother, they hope to uncover what is causing his uncontrollable seizures. The Darvai family put together a crowdfunding site and Zsuzsanna wrote letters to community members to raise money for her son's testing. Her efforts worked. Balazs quickly reached and exceeded his fundraising goal.

Balazs, his parents and his brother completed exome sequencing. With both parents and a sibling, they will have the most complete picture and comparison of the genetic makeup of the family to look for similarities and differences. Top researchers are now analyzing the results. "You can't give up hope. In today's world, science is constantly changing, especially with the work Dr. Lin is doing. They understand more and more about the genetic coding all the time, so they can figure out more things," Zsuzsanna said.

The Darvai family is waiting for the results of their exome sequencing which will appear in the next version of this book. Zsuzsanna believes, "If you have hope, you have everything. Don't give up and don't be discouraged, you can do a lot of things to help your child."

Takeaways:

1. Balazs' family connected with RGI and through RGI's crowdfunding site raised over $10,000 for his gene sequencing. The impact of the community and a mother's persistence writing letters to ask for help, worked. They even had a kick-a-thon to raise money. She used her skills and network to help raise money for her son.

2. RGI can help patients start fundraising within hours of receiving the information. Sometimes RGI describes itself as "a nonprofit in a box for rare diseases."

3. Balazs' family is from a smaller community. Even if the patient is from a rural community, and not close to a major academic center, they can still have access to top doctors. RGI provides this connection vital for diagnosis and treatment with top researchers that have expertise and experience seeing many children with rare diseases.

Maya's Story – Only Diagnosed Through Gene Sequencing

Fast Fundraising for Gene Sequencing Yields a Fast Diagnosis for a Unique Disease

RGI patient Maya Nieder after years of searching, was finally diagnosed.

In a record-setting few short hours after posting Maya's story and picture on the Rare Genomics Institute's crowdfunding website, her genome sequencing goal was not only reached, but exceeded. Maya received 142% of her fundraising goal with donations from family members, friends and complete strangers who wanted to help an adorable little girl with severe developmental delays.

"Like others her age, she loves to read books, paint, and play with her dog … but unlike others her age, she has a host of issues that leave her unable to speak, run, or climb stairs."

- Maya's mother, Dana

Finally, Maya's mother, Dana, could get an answer to the question she asked for 3 ½ years as she brought her daughter to specialist after specialist in a quest to find out, "What's wrong with my daughter?"

Maya's parents had no answers even after years of doctor visits, testing, and searching. They watched Maya suffer from severe developmental delays, including difficulty communicating, and hearing loss. On her own, she can only communicate a few words, and she has great difficulty with walking and climbing. After connecting with RGI, the family started getting some answers for the first time.

Maya did not walk until well after her second birthday and can only say a few words without using her talker, a communication device. Maya endured multiple operations, but still no one could tell her parents what exactly was wrong. Doctors suspected something genetic was causing Maya's condition. After countless tests including six genetic tests, each

screening for multiple genetic diseases, they were still left with no answers for Maya.

Shortly after speaking with the RGI team, Maya's family decided to try RGI's genome sequencing to try to determine what was wrong. After their insurance company did not agree for payment, Rare Genomics Institute helped the family establish an Internet fundraising platform to pay for the sequencing costs – called crowdfunding.

"She could have seen all the doctors in the world. They would not have solved this without genomic sequencing."

- Dr. Jimmy Lin

They were surprised at how quickly they reached their fundraising goal for Maya's genomic sequencing. The fundraising page was uploaded to RGI's website with Maya's picture and her parents' words. They described Maya who, "like others her age, she loves to read books, paint, and play with her dog - but unlike others her age, she has a host of issues that leave her unable to speak, run, or climb stairs." Maya's mother, Dana, also had a popular blog and posted her campaign to all her followers. Friends, family and strangers donated the funds necessary to begin the sequencing so her research project could begin right away. Maya and her parents were all sequenced using full exome sequencing to give a deep understanding of what was wrong with Maya.

In less than 6 months after her project began, Yale researchers determined 4-year-old Maya had a new gene variant never before seen that was responsible for her developmental delays. The gene responsible was a gene active in fetal development and early childhood. Maya had a brand new disease, never before seen in any research. "She could have seen all the doctors in the world. They would not have solved this without genomic sequencing. The disease was previously not described," said Dr. Jimmy Lin. "It's not in any medical books. Now they are actively studying it at a top medical institution."

Maya was the first crowdfunded gene discovery ever made.

Takeaways:

1. Through RGI sequencing, Maya was successfully diagnosed. She is the first one in the world to have this new disease. “She could have seen all the doctors in the world. They would not have solved this without genomic sequencing.”

2. Researchers got the necessary funding to immediately begin analyzing Maya’s DNA and remarkably, in less than 6 months, a new gene variant was discovered and a devastating disease was caused by this critical gene. The family had the answer to their search.

3. This disease is now being actively researched and studied at a top medical institution. This would not have been possible without genomic sequencing. Post-diagnosis, the goal is to find the answers on this disease, and it has stimulated interest and funding to learn more about the gene variant.

4. When Maya’s crowdfunding RGI site launched, the community successfully and quickly supported her fundraising efforts. In less than 6 hours, she exceeded her goal and raised 142% of her funding to do her sequencing. The excess funding was used to help other patients.

5. Maya’s mother, Dana, writes an award winning personal blog called “Uncommon Sense” about raising a child with special needs. She has built a support network and community for parents trying to help their children with rare diseases and special needs. There is great power in developing a community for support.

Gay and Lilly Grossman's Story - Never Giving Up

Hope for the Future

Lilly Grossman as a toddler

When Lilly was an infant, Gay Grossman, her mother, said she started noticing some things that were different. As her only child, she couldn't compare Lilly to a sibling, but when they went to playgroups, she saw Lilly had lower muscle strength. She was not crawling or standing like the other kids. Lilly did not sit up when other children her age were. Gay remembers, "It looked like she didn't want to sit up; it wasn't like she sat up and fell over." In 1999, at her sixteen-month visit to the pediatrician, Gay said she knew something was wrong. Lilly was not crawling or walking. Her pediatrician reassured her that until a child is eighteen months old, it is considered normal if they are not walking. He told her he expected her to just start walking any day.

"The tremors became so severe that she started screaming throughout the night … twelve to thirty times a night."

- Gay Grossman-Lilly's mother

When Lilly was 17 months old, Gay took her over to a friend's house who had a nine-month-old daughter. Her friend happened to be a physical therapist. When Gay saw her friend's daughter and what she was able to do, "It was like night and day difference," she said. She knew then that something was very wrong with Lilly.

When Lilly was eighteen months old, Gay and her husband were both sitting watching her play. At that moment, they both saw it. Lilly was reaching for a little truck, and her arm and neck and head tremored. "Something is wrong," Gay said. Lilly had her first tremor. From then on, the tremors increased. Gay took Lilly to a neurologist who did an MRI. He told the Grossmans Lilly probably had cerebral palsy, CP. They accepted the news.

Shortly after seeing the first neurologist, who did the MRI, Gay took Lilly to the Rainbow Babies and Children's Hospital in Cleveland to have her evaluated for physical and occupational therapies. She could not stack blocks, and she could not raise her arm up. When she was two and a half years old, the Grossmans took Lilly to the Cleveland Clinic. There a skin

Lilly is a prolific blogger and writer despite physical limits. She has written a 124 page book called, *The Girl They Thought They Never Knew,* which is available on Amazon. Her blog is called Lilly Grossman's Life and technology has greatly enhanced how she lives.

biopsy was recommended right away and testing began to try to find an answer. They received a more accurate diagnosis. She had some characteristics of mitochondrial disease, so she was put on a mitochondrial cocktail of vitamins and supplements. They followed Lilly's progress and helped Gay with the school and all of Lilly's needs.

When Lilly was only four years old, she woke up almost hourly with tremors. Over time the tremors became so severe that she started screaming throughout the night as her body shook, constantly waking her. This happened every night, and twelve to thirty times a night. She looked like she was having a grand mal seizure. Her tremors were now happening during the day too.

Steve broke the silence, "Did you hear her say normal life expectancy?"

-Steve Grossman- Lilly's father

Doctor after doctor, specialist after specialist, no one could figure out why she had such severe tremors and why she couldn't walk. They looked for brain tumors, metabolic disease, and they thought she had mitochondrial disease. Gay recalls, "We also tested chromosomes, syndromes and any disease that resembled her symptoms. All tests came back normal." Gay and Steve, Lilly's dad, were frustrated and lost after taking Lilly to world-renowned doctors all over the country, getting every test possible and coming up with normal results. With mitochondrial disease, 80% of children do not live until they are 20 years old. Gay and Steve always told each other, "Lilly will be one of the 20%."

Sleep deprived for years, Gay and her husband Steve never took a vacation away from Lilly that was more than five hours away. Doctors told the Grossmans that Lilly could get dehydrated very quickly. If she got sick, she would need to receive an IV, intravenous therapy, within five hours to protect her vital organs. She did not have the reserves that typical children do.

For years, they would alternate nights getting up with Lilly, comforting her through her tremors and screams. By the end of sixth grade, Lilly

Lilly has maintained a grade point average of over 3.5, despite her undiagnosed illness causing tremors to wake her 12-30 times a night for years.

started losing weight for the first time, so she was taken for a muscle biopsy; a test they had hoped not to do due to its invasiveness. Gay asked about genome sequencing, but doctors said it was not ready for the general public.

Lilly could use a walker up until sixth grade. Since middle school, she's been in a wheelchair. The physical demands of switching classes all day meant that Lilly had to stop using a walker and move to a power wheel chair. Gay and Steve constantly searched for answers. One day Gay came across an article by NPR called, "Genome Maps Solve Medical Mystery of Calif Twins." Gay and Steve had moved from Ohio to California in 2005 to have a warm climate, hoping that would help with Lilly's condition. The Beery twins and their family both lived in southern California. Gay met Retta Beery, whose research led to a treatment for her twins that allows them to have a normal life after they were misdiagnosed with cerebral palsy.

"They know the genes affected now, and they know she had a future."

Retta introduced Gay to someone who told her about a study at Scripps Translational Research Institute where they were sequencing the patient and both parents. Lilly was the first patient enrolled. She was sequenced, and they found two affected genes. "The first thing they told us after genome sequencing was that Lilly had a normal life expectancy," Gay said. There was silence on the way home from the hospital. Steve broke the silence, "Did you hear her say normal life expectancy?"

Until that moment, the Grossmans had a different future in mind. They thought about colleges close to home, and now, for the first time, they could offer Lilly more options. The genome sequencing does not have a treatment or cure for Lilly now, but she is on Diamox for her tremors, and they are better than they were. Through the night, Lilly's tremors are measured using an iPad app and a watch. She considers it a good night if she gets up four to six times, an average night means waking twelve times and a bad night means she wakes about thirty times.

Doctors described Lilly's affected genes as gears on a bike, if the gears don't work, the bike doesn't. They know the genes affected now, and they know she has a future. For Gay and Steve Grossman, they can see the future for Lilly and not fear a medical crisis. They have recently taken vacations together to Brazil and Gay has gone to Italy without Lilly, knowing that her health is not in jeopardy. This summer they plan to take Lilly to Europe for the first time, so she can see countries she's dreamed of visiting.

Through Lilly's involvement with IDIOM, the project at Scripps, her tremors and sleep patterns are being studied. Lilly wears some monitoring equipment and Gay sends the results daily. Gay believes that they did do the best they could for Lilly. They have answers and "can somewhat live like other people do, not constantly worried," said Gay.

Takeaways:

1. Never give up. Gay Grossman asked about genome sequencing, and then read about the Beery success story. Lilly found the Beerys online and Gay contacted Retta Beery. The parents had tremendous determination and caring.

2. Connect with other parents and share stories and information. Other parents may be able to connect you with a doctor that can help. Retta introduced Gay to someone who informed her about the study at Scripps. You can learn from other parents. If a parent says, "I know someone and you should call them." Gay says she always calls.

3. Genome sequencing can provide a diagnosis otherwise not possible but may not be able to solve the issue today. With information comes power and some answers can be found. This can be life changing.

4. Involvement in research or a study can possibly help find a treatment or therapies now or in the future.

Please note Lilly is not an RGI patient, but this story is cited to help families better understand the rare disease process.

Lilly Grossman has a great sense of humor and makes bunny ears behind her dad as a photo is being taken.

Victoria Jackson and Ali Guthy - Getting Huge Impact from Foundation

Building a Very Successful Rare Disease Foundation from the Ground Up for NMO

Victoria Jackson is a successful cosmetics entrepreneur and Hollywood makeup artist, and her husband Bill Guthy is co-founder of one of the world's largest marketing companies, Guthy-Renker. They would have never guessed that their lives would change so dramatically overnight after just coming back from a family vacation with their three children.

Victoria recalls, "We had just gotten home, and our daughter Ali started to complain about what she called 'an eyeball headache.'" Victoria originally thought fourteen-year-old Ali had an eye irritation or infection. Overnight, Ali began to lose her sight around the edges in that eye. Then she lost her ability to see color in one eye. What started out as an eyeball headache was now something much more serious.

Victoria and Bill immediately took her to specialists. They went to an ophthalmologist, and he then sent them to a neuro-ophthalmologist. The doctors told Victoria that Ali had optic neuritis. Victoria asked, "She is so young and healthy, why would she have that?" The doctor said he wanted to do some blood work, and he started checking boxes on the paper work to order tests. Victoria looked at the boxes he was checking and saw the disease, NMO. Victoria questioned, "What's that box?" He replied, "NMO, but I've never seen anyone with that. NMO, that's a nightmare." He then tried to assure Victoria that NMO was so rare, it's not going to be that. In fact, up until that point he had never even ordered the test.

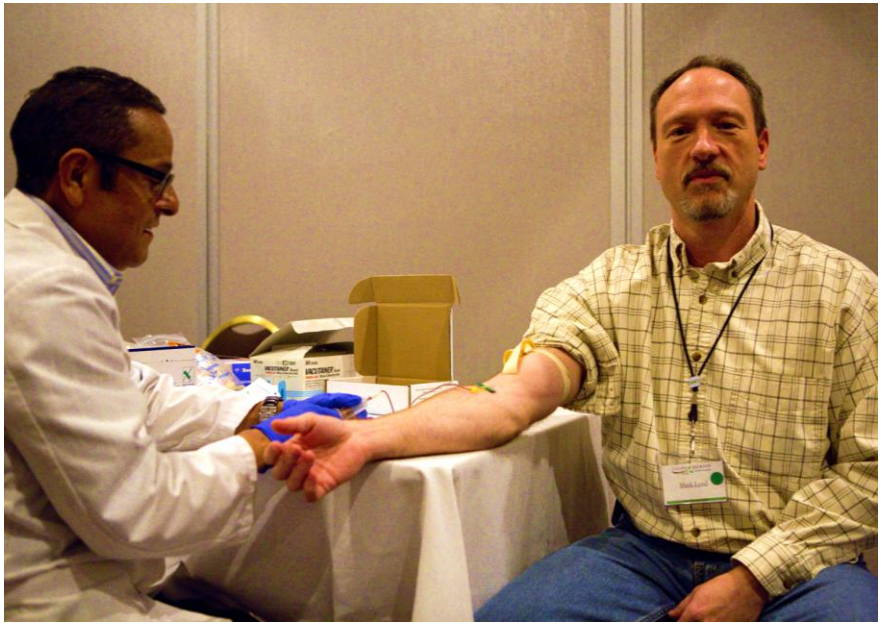
"One of the hardest parts of having a child with a rare disease is that you have to make major decisions based on limited knowledge."

- Victoria Jackson

The test came back positive as NMO, neuromyelitis optica. At first, he said sometimes there are false positives and then repeated the test, but again the results showed Ali had NMO. Victoria remembers, "The neuro-ophthalmologist called us back and said Ali had about four years to live." Shocked and in disbelief as to how their healthy, beautiful daughter could possibly start with some eye pain, and now have only four years to live. He continued to explain if she does live, in four years she could be possibly blind and paralyzed. Victoria asked the doctor what she should do. He said, "If it were my child, I'd be at the Mayo Clinic, tomorrow." That's exactly what Victoria and Bill did with Ali.

When Ali was diagnosed, Victoria googled NMO and there were about three sentences of information on it, and it was all bad news. They found that the one doctor doing research on NMO was Dr. Brian Weinshenker

Blinded from NMO as she entered culinary school, chef Christine Ha did not let her disease stop her from achieving her dreams. She competed and won the Master Chef television competition and is an inspiration for rare disease patients.



Hundreds of NMO patient blood samples have been collected to help researchers analyze, find therapies and hopefully a cure.

at the Mayo Clinic. When they met with him, he examined Ali and said she would have a transverse myelitis attack sometime in the next 3-6 months. He then started to describe what that might look like. The attack would not be the same for everyone, but expect numbness, electrical pain in your body and trouble walking.

NMO is rare and often misdiagnosed as multiple sclerosis, MS. The lesions are different in NMO in that it affects the optic nerve and spinal cord. The attacks are unexpected, and they occur much faster than the progression of MS. With NMO, you don't really know where it is going to go or when.

At the Mayo Clinic, Victoria asked Dr. Weinshenker, "Are you doing any research?" He said that he was doing some. Victoria said, "You are about to do a lot more. I'm a mom on a mission, and I have a checkbook." From that moment forward, Victoria says, "I've never gone out of that mode. After hearing the doctor's news about Ali, my journey began and I decided to put the foundation together. I closed the book on cosmetics, and opened it on medicine." Victoria and her husband started the only foundation dedicated to finding a cure for NMO, the Guthy-Jackson Charitable Foundation.

"We hold a conference once a year for 400 people including NMO patients, their families and the top scientists."

- Victoria Jackson

Within three months of the conversation with Dr. Weinshenker at Mayo, Ali did have her first transverse myelitis attack, and since then, she has had a total of sixteen transverse myelitis attacks. Victoria said, "One of the hardest parts of having a child with a rare disease is that you have to make major decisions based on limited knowledge and test cases." With rare diseases, there are not many clinical trials or studies, and the patient populations are small. She became determined to change that.

Victoria's mission began by building a team. She looked around the world for those working on NMO. Bill and Victoria personally funded the Guthy-Jackson Charitable Foundation. She insists that everyone has to work together and share data to make sure we are not overlapping. When asked how she has been so successful in research and collaboration she said, "I surround myself with really smart advisors. I use my business skills to look at the big picture. It's a recipe, and not one person is going to cure it. You have to work together. My success is due to reminding the doctors why they went into medicine, to help people."

Many local emergency room physicians may not know what NMO is. With patient-to-patient differences, many NMO patients are first misdiagnosed as MS and treated with medications that are not effective for their true illness.

"When something has no conversation around it like NMO, you have to turn up the volume. NMO is going to make a difference. We decided to redesign a blueprint on how you work together," says Victoria. The

Guthy-Jackson Foundation built its own biorepositiory to gather NMO patients' blood for researchers to study. In the beginning, Victoria hired a nurse to travel around the world to NMO patients and take blood samples. Today they have a joint venture with LabCorp. Victoria has built a consortium of research in 17 countries all working together on NMO.

Top NMO researchers, doctors and pharmaceutical companies are available at the conference to answer questions directly from NMO patients.

Once a year they host a scientific meeting with scientists, researchers, and patients. Patients have access to the world's specialists in NMO at the conference, and they donate blood to be used in research. Family members of patients with NMO also donate specimens. Hundreds of patients and family members come together to learn and aid in research by giving blood. The patients can ask questions and find out about clinical trials of drugs.

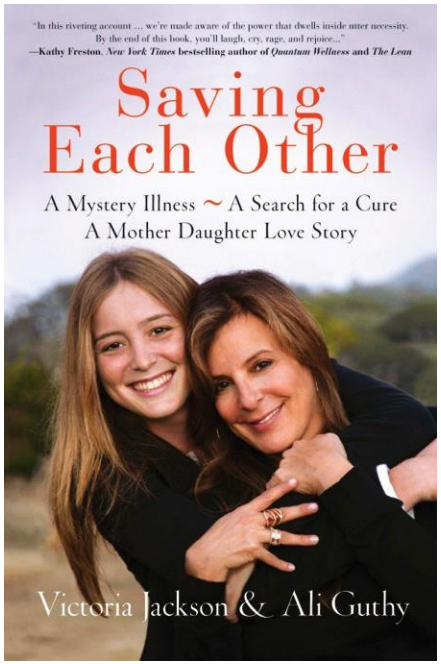
Victoria said, "When you're the only person in town doing this, it all falls on your shoulders. We were climbing Everest in NMO in the beginning, and now that we have amassed all this data, we are looking at the connection between MS, Lupus and other auto-immune diseases.

She explains her success with the medical community, "Everyone can see I'm not working with any agenda except I'm trying to find a cure for my daughter. I don't want to own any intellectual property. We are genuine of heart and love and that's how we run our foundation. The family is paying for all the doctors and the patients to come together."

"We told all of our research scientists they owned all of the intellectual property, but they had to collaborate and share everything."

- Victoria Jackson

Victoria and her daughter, Ali Guthy, have written a book together called, "Saving Each Other: A Mother-Daughter Love Story" about their journey from diagnosis to now. Ali believes her energy and positivity have turned things around for her. She is not a victim of her circumstance. At first, Ali did not want to know what was wrong with her; she just wanted to continue her life. She now explains, "My mantra changed from 'Ignorance is bliss' to 'Knowledge is power.'"



Victoria and Ali have published a book on their experiences searching for a cure for NMO. They give their book away along with several others to each conference attendee.

Takeaways:

1. This is a very well-run foundation. Researchers and scientists working together and sharing information greatly increase the ability to find cures. "We have nurtured and supported these relationships. When they work together, they can show the world, we can cure this," said Victoria Jackson.

2. Patient's Day brings 200 patients together with top NMO scientists, doctors and researchers. It allows patients to have direct access to these experts and they can ask any questions and connect with other patients.

3. Advice to families: "It's devastating, and it changes your life. You have to go through whatever process you have to do. Have your dark days, and then decide what to do with it. And do it. Do what helps you move forward in a positive way. Everyone has to go through it individually," she said, "I was a makeup artist, I made lip-gloss. You never know what you are capable of." What is important is how you take that news and turn it around into something positive.

4. This is an amazing time in the world of medicine. The foundation is studying repurposed drugs too. "The science is directing us and the key is the science. The science takes us down the road," Victoria says. "We ask, 'What are the drugs that would potentially stop this disease process?' We then asked the pharmaceutical companies, 'What do you have in this particular category?' Everyone is working together. The pharmaceutical companies are coming in because we are doing the heavy lifting with all these groups."

5. The foundation collects blood /DNA samples from hundreds of patients to make it much easier for scientists to do research on the disease. They have a partnership with LabCorp to collect blood samples from NMO patients from all over the world as well as the hundreds of patients who have traveled internationally to Patient Day.

6. Ali and Victoria wrote a book about their search for a cure that is inspiring and informative for both NMO and other rare disease patients. Books are effective in getting information out about the disease and helping the greater good. There are not many books on rare diseases written from the family's point of view and there is an opportunity to get the word out and heal.

7. Partnerships can be a powerful way to increase the effectiveness of the foundation and speed of impact.

Impressive stats and partnerships from the NMO website

8. As a person with a rare disease, Ali Guthy believes, "Knowledge is power." The foundation supports this idea and gives NMO patients information, access to experts and connection with each other.

   Please note Ali is not an RGI patient but her story is cited to help families better understand the rare disease process.

"We are genuine of heart and love and that's how we run our foundation."

- Victoria Jackson

Around 200 NMO patients are flown in by the foundation for the annual NMO conference, where they talk to top researchers, and learn from others with the disease. Patients and their families give blood for a biorepository for the scientists to work on their research for therapies. The disease disproportionately affects women.


Expert
Interviews

6. Interviews with Experts

Interview with Genomics Expert Dr. Ada Hamosh

Clinical Director of Johns Hopkins Institute of Genetic Medicine

"Never give up on your kid," says Dr. Ada Hamosh, Clinical Director of the Institute of Genetic Medicine (IGM), at Johns Hopkins and RGI expert. With over 2,000 unique genetic patients each year, Dr. Hamosh relies on her training and experience when she sees tough cases and systematically finds answers and diagnoses for children with rare diseases. In addition to her position as Clinical Director of IGM, she is Scientific Director running OMIM, the Online Mendelian Inheritance in Man website (www.omim.org) and Dr. Frank V. Sutland Professor of Pediatric Genetics at Johns Hopkins. Dr. Hamosh is an expert at genomic analysis and sequencing. "You have to know what you're doing," Dr. Hamosh says. Exome sequencing and specialized training can solve the most complex genetic cases, and many of her patients have multiple system problems.

"Your job as a parent is to optimize your child's options. Give them every opportunity, and one of the most important is to see a geneticist."

- Dr. Ada Hamosh, Johns Hopkins

"We don't have enough 'normals' today to know everything about what's normal or not. As more people are sequenced and the database of genes expands, our ability to understand and predict outcomes improves. This technology works well but with the clinical aspects, we are still learning. What we understand well are 3,000 genes. We know some about another 7,000 genes and there are 12,500 we need to learn," Dr. Hamosh says. OMIM is an online catalog of human genes and genetic disorders used worldwide. Dr. Hamosh is leading the efforts to continue to build that database.

The clinical labs will reference the exome test to the Human Gene Mutation Database (HGMD) and OMIM to try to determine if it is a new or known mutation, but the clinical analysis is key. "Clinical information

Christian is a long time genomics patient, and Dr. Hamosh examines him at her clinic at Johns Hopkins Hospital.

is developed by the doctor seeing the person whose genes are sequenced, and observing them and associating that information with the sequencing. If you have a diagnosis, and use OMIM, you can get to many other resources for many diseases. This is great for physicians," she explains.

There are several tests used in genetics. Many of our patients have come in with other genetic tests that have been inconclusive or negative previously. Sometimes families went on a diagnostic odyssey looking for answers for years because, "there wasn't a technique to make the diagnosis," says Dr. Hamosh. They couldn't make a diagnosis because the technology wasn't there. "Now we have that ability with exome sequencing. We needed a technology to say, 'Aha, this is the diagnosis.'"

What a diagnosis gives families is a stop to the odyssey. They know what is wrong, and that is powerful. "We can tell them, 'You're not responsible. We can't control what genes we pass on,'" she tells parents who sometimes blame themselves for their child's illness.

Having a diagnosis has value in many ways. You need a diagnosis to offer prenatal services, and it will also help if parents plan to have other children. For some rare diseases, there are other interventions. For a disease like ALD, a rare, genetic disorder in boys that causes a breakdown of the myelin sheath surrounding nerve cells in the brain, "You want to make that diagnosis before the brain is affected. Bone marrow or cord blood transplants have been effective, so if there is a treatment for a rare disease, the earlier the better, before the disease progresses."

We asked Dr. Hamosh about what suggestions would she give parents if they had a sick child and no one could explain what was wrong. She explains, "I know what to do. If you have a rare disease, go to a geneticist. That's what we do for a living. Some doctors can miss a known diagnosis because they do not know enough about rare diseases."

"Never give up on your kid."

- Dr. Ada Hamosh, Johns Hopkins

"Your job as a parent is to optimize your child's options. Give them every opportunity, and one of the most important is to see a geneticist. Put them in all the therapies you can," says Dr. Hamosh. "If it's something we know and understand, we can tell them all the organ systems involved and what to expect. We will look at all the body systems from a genetic basis."

"Some tests are done because we won't know the function without them. I can't see the brain without a brain MRI," says Dr. Hamosh. "Some people can have normal function with an abnormal brain. An echocardiogram for the heart, an ultrasound of the kidneys, a skeletal survey, hearing tests, and eye exams are routine exams for geneticists. They need to do a clinical exam to understand if there is a problem to manage or if multiple organs are involved. Repurposed drugs have worked well in some cases like for Marfan syndrome. Even if you know the problem gene, knowing the pathway and physiology will get you to the best medicine or therapies."

Emily and Christian are young patients of Dr. Hamosh and have a genetic condition that leads to slower physical and mental growth – accompanied by severe ADHD.

Clinical labs are successful about 25-40% of the time finding a diagnosis for rare diseases. Getting to the right provider that understands and sees this regularly gives you the best options. “Use all resources available; there are community resources, and healthcare resources to do the best for your family member. You are not alone. Join a support group,” Dr. Hamosh recommends. “You are not the only person on the planet with it.”

As more people are sequenced, we continue to learn more information about our genes and their meaning. “This gives us the ability to interpret what we understand and counsel on what we have gathered but do not know today. Exome sequencing still becomes a valuable part of the medical record to answer future questions as they come up and as we learn more. Proper integration of this information into the electronic health record is essential,” said Dr. Hamosh.

“With exome sequencing, we have the best ability to give a diagnosis, a prognosis and understand complications. We can provide targeted therapies. We can look at what’s changed from normal and then prescribe the medication that’s most effective. A definitive diagnosis allows us to do appropriate anticipatory care and testing. With genetic conditions passed on to children, it allows for prenatal testing. This provides parents options and knowledge.”

Takeaways:

1. “Never give up on your kid,” says Dr. Ada Hamosh, Clinical Director of the Institute of Genetic Medicine (IGM) at Johns Hopkins and RGI expert. With over 2,000 unique genetic patients each year, Dr. Hamosh relies on her training and experience when she sees tough cases and systematically finds answers and diagnoses for children with rare diseases.

2. Focus on the diagnosis - What a diagnosis gives families is a stop to the odyssey. They know what is wrong, and that is powerful. As more people are sequenced, we continue to learn more information about our genes and their meaning. “This gives us the ability to interpret what we understand and counsel on what we have gathered but do not know today.”

3. Get a geneticist involved with the diagnosis. Geneticists are trained to look at multiple systems and have deep insights into exome and genome data as well as the practical expression of genetic issues.

Emily hugs Dr. Hamosh before her family leaves the genetics clinic. She has taken care of Emily, her brother Christian, their mother and aunt for many years. While Dr. Hamosh is one of the top genomics experts in the US, she spends a great deal of her time in clinics seeing patients.

Interview with Genomics Pioneer Dr. Howard Jacob

Innovator who sees huge potential using genomics to improve healthcare

Dr. Howard Jacob, Director of Human and Molecular Genetics at the Medical College of Wisconsin received an email one morning from colleague Dr. Alan Mayer. Dr. Mayer was the pediatric gastro-enterologist for Nicholas Santiago Volker. Mayer began, "Dear Howard, I am writing to ask if there is some way we can get his genome sequenced?"

Dr. Mayer went on to explain Nic's medical history, the grueling story of a four-year-old little boy who had endured and battled sickness after sickness. In his young life, many, many times, he defied the odds when most thought he wouldn't. He had lived through over 100 surgeries. Daily, he went into the operating room to get cleaned out from the gut disease that was nearly killing him. No one could figure out what was making Nic so sick. By 2009 alone, Nic spent over 600 days in the hospital. For nine consecutive months, he could not eat or drink anything. In his entire life, nine-year-old Nic has spent 800 overnights in the hospital.

"If we didn't do anything, we know the outcome - he won't make it. If we do the sequencing, at least he's got a chance."

– Dr. Howard Jacob

Dr. Jacob had been working toward the goal of using genome sequencing clinically, but he projected that to happen in the clinic by 2014. In 2009, there were no published reports of any patients that had been diagnosed using sequencing. No one had done this.

"Here you have a little boy who's been in the hospital six months continuously," Dr. Jacob said, "If we didn't do anything we know the outcome—he won't make it. If we do the sequencing, at least he's got a chance."

Then, there were the financial constraints. In 2009, the economy was bad and getting funding for the exome sequencing wasn't easy. Dr. Jacob gathered his team and they figured it could be done for $75,000. This was a significant drop from the cost only a few years before this. However, Amylynne and Sean, Nic's parents, faced the reality that Nic was already almost at his lifetime medical insurance cap of two million dollars. And insurance didn't pay for this anyway.

Dr. Howard Jacob of the Medical College of Wisconsin shows his own genome. It lists his conditions and predispositions, and updated reports are automatically sent to his iPad.

Dr. Jacob had an idea. He had a company, and he went to the board and told them about Nic. He said, "I am going to tell you a story, but if I tell you this story, you will want to write a check." He asked the investors in his company to help fund exome sequencing for Nic. "We don't know what's wrong with him, and we have to do sequencing, which would serve as a pilot project for others."

Dr. Jacob secured the funding and the Medical College of Wisconsin sequenced Nic's exome. This was the first clinically sequenced genome ever, and also the first sequencing that saved someone's life. "We had some intense meetings about what to do with this. We knew this was very serious and we needed to figure it out. This fundamentally changed my life," said Jacob. The exome sequencing identified a previously unknown mutation responsible for the gut disease that was jeopardizing his life. "Without this sequencing, we would have never found out what was wrong with him," Dr. Jacob said.

Nic's treatment was a bone marrow transplant taken from umbilical cord blood. Dr. Margolis, the surgeon who would perform the transplant, needed to be sure. There is a high mortality rate in doing the transplant. He wasn't willing to take that risk with Nic's life. Unexpectedly, a paper came out that linked it to gut disease. There was enough reason to go ahead.

After the success with Nic, we looked to expand our clinical operation. Many questions came up. What is the future for genomics and medicine? How do you implement genomic information clinically? How do you give the data back to patients? What data do you give patients? Some say that the physicians should decide what information to tell the patients. Dr. Jacob believes that the patient working with their physician needs to determine what information they want to know or not know.

"Without this sequencing, we would have never found out what was wrong with Nic Volker."

- Dr. Howard Jacob

For families, especially those with sick children, genomic information gives them the answer. There may be a cure, a treatment. If there is no cure, or not one today with what we understand about genomics, parents still know what they are dealing with and can stop searching for answers. They know they did everything they could to figure out what's wrong with their child, so they don't feel a sense of guilt that they didn't find the right doctor or search hard enough for answers.

With genomics, there is a lot of discussion about the cost. Dr. Jacob is quick to respond that a more important question is, "What is the value?" He explains, "First, it's your family history. Many people don't know much about their family history, yet every time you go to the doctor, the first thing you are asked to do is fill out a medical history. The history has conditions or diseases family members have had. You are relying on oral tradition and your families' accuracy disclosing all medical illnesses and conditions that may be in your genes. Many families don't keep track of

this information." He points out, "Your genome is part of your family history."

Dr. Jacob opens his iPad and shows an application called "My Genome." Jacob had his genome sequenced, and the information populated on his iPad. "My mom had breast cancer and so did my grandmother. I have two teenage daughters," Jacob said. He had the discussion with his daughters, "Do you want to know if I'm carrying these genes?" They said yes, and then had a deep, family discussion on genes. "That's personalized medicine," said Dr. Jacob. While they do not carry any known variation in BRCA1 or BRCA2 breast cancer genes, Dr. Jacob does have variants in these genes. The question is what they mean.

Some may call it a gift to future generations, the knowledge of what you have today or may be at risk for in the future. Updates are automatically made directly to his iPad, so if a gene is unknown today, when discoveries are made, you receive information right on your iPad.

You can carry it with you to your doctor's appointment. It's a very different way to look at family history of illnesses. Through this app, physicians have updated genetic reports about you at their fingertips. "As more people become sequenced, we may determine why some have severe reactions to certain medications and some do not, based on genes," he explains. "If I had a toothache and I'm prescribed a medication, I can check my genome to see if I will have a bad reaction to that medication. If I do, I'll go on a different one."

"Genomic information is important, to the patient, the family and society," he said. The scale and focus should be on clinical care. A patient's individual genetic information can be used to make important healthcare decisions. This is not only important to the patient. If through testing, the patient learns they carry a gene for cancer, this is important for children and family members to know. However, the family and patient need to decide if they want this information.

The more people sequenced, the more we will learn. Parents of sick children could be told of the risk of the condition or disease affecting other children they might have. We as a society can learn about variations in genes that affect common diseases. One case study Dr. Jacob discussed is about a little girl named Avery. Avery has irreversible neurological damage. Yet, if she was sequenced earlier, they would have found out what was wrong with her. It was treatable - if caught earlier. Dr. Jacob's hope for use of sequencing for the future is, "No more Averys."

"Genomic information is important, to the patient, the family and society."

- Dr. Howard Jacob

"One day I hope we may sequence all newborns. Sequencing a baby's genome at birth would give doctors the ability to screen and learn much more about genetic conditions. Genetic disorders would hopefully be found right away and treatments started at the earliest stages before conditions got worse. It would also enable parents to know what they are dealing with, so they are not searching for answers and instead focus on taking the best care of their child," said Dr. Jacob.

Takeaways:

1. Medical conditions present differently from patient to patient. Genomic sequencing is a diagnostic tool that gives physicians a level of information they have not had access to before now.

2. Genomic sequencing saves a great deal of time, money and stress related to the disease at hand. It gives parents answers so they can stop searching. This can mean, in cases like Nic Volker, saving a life. Parents and patients need to know that finding out information not related to the disease at hand could cause stress. As a result, they need to make sure they work with a genetic counselor or clinician well versed in the nuances of these choices.

3. We are learning more every day in genomics. When more people are sequenced, we have more data and can understand the action of more genes on both a family and societal basis.

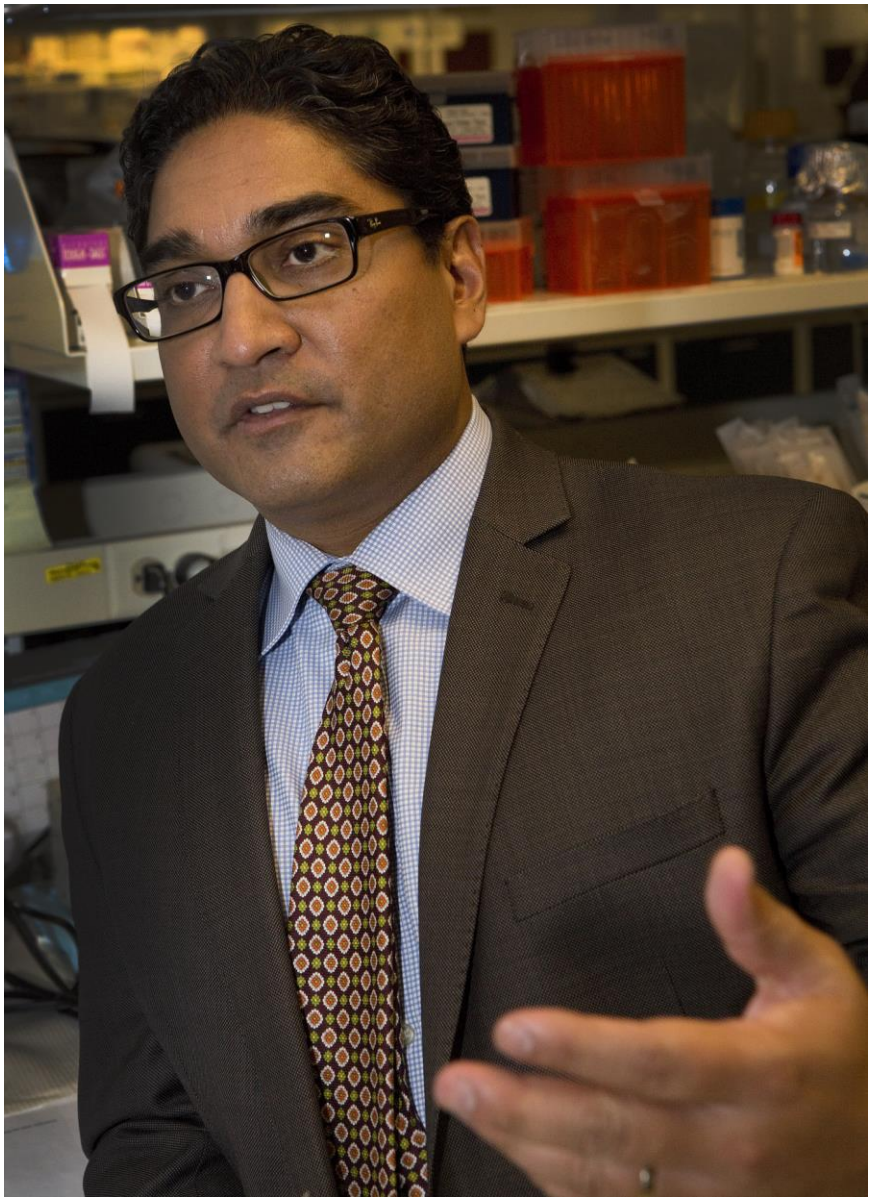
4. Genomics may give doctors the ability to prescribe the most effective medication for the individual at the beginning of treatment. The benefits are reduced side effects and safety concerns with medications and targeted drugs for the illness based on the individual. For patients with cancer, as an example, the right medication targeted to the specific tumor or disease can lead to better outcomes.

5. In the future, your genome will most likely give a more accurate family history and tell you your risk factors. It is a tool today and for the future. If you are healthy today, it gives you a basis moving forward and new discoveries about genes update automatically.

Genomes are data intensive and each one requires about 2 Terabytes of storage. Dr. Howard Jacob stands next to two large drive bays holding 500 Terabytes or about 250 fully sequenced human genomes.

Interview with CEO Panna Sharma on Genomics in the Future

CEO of Cancer Genetics, which uses the DNA of specific cancers for personalized treatments



"Genomics is changing the whole paradigm of healthcare as we know it," says Panna Sharma, CEO of Cancer Genetics (CGIX). Cancer Genetics is focused on the diagnosis and disease management in cancers, specifically hematological and urogenital cancers. "Cancers dictate what they will and will not respond to, and with this technology, we can go after them disease by disease," says Mr. Sharma.

"Genomics is changing the whole paradigm of healthcare as we know it."

- Panna Sharma, CEO of Cancer Genetics

The successful use of genomic information can be illustrated by breast cancer care and how research, development and genetics have increased survival. The protocols are complex. As we learn more about diseases like cancer, we understand that treatments are becoming more personalized.

Genomics gives doctors a comprehensive diagnosis. The benefits of genomics in cancer care are many, including avoiding the need for repeat tests with outdated techniques. We know we can find the right treatment for the particular cancer type right away. Genomics information allows us to target therapies, which leads to improved outcomes.

Some cancer treatments like chemotherapy suppress the immune system. If the drug is not a good fit for the patient's cancer type, it doesn't do enough to stop the disease. Now you have a patient with a weakened immune system, and a potentially aggressive cancer. Cancers are heterogeneous and cancers of the blood, like leukemia, have 89 different subtypes and these subtypes can predict long-term survival outcome. One patient may live 30 years and another may live 2-3 years.

Genomics also saves a tremendous amount of time. Patients get correct treatment faster, avoiding the trial and error approach, so they are not on a treatment that is ineffective. Time can be critical with certain cancers. In one case study, a patient spent $93,000 in insurance and three and a half months merely trying to figure out what he had. First, doctors thought it was Lyme disease, then an auto-immune disorder, but finally it was determined he had an aggressive type of leukemia. Genomics leads to targeted testing as well as drug selection based on personalized medicine. Patients get to the right treatment that their body is likely to respond to best and fastest.

“Not every cancer has a treatment protocol but genomics helps give us important information as we are evolving and learning how to reach the most effective therapies,” says Mr. Sharma.

Takeaways:

1. Genomics has tremendous capabilities in diagnostics, prognostics, and therapies. Earlier and more personalized diagnosis leads to better outcomes. We are at the very beginning of a revolution where patients can receive a more accurate diagnosis and treatment plan specifically designed for their body and their personal genetic makeup.

2. Genomics can get patients into the right treatment programs early. Diagnostically, cancers and other diseases are heterogeneous. The clinical course of cancers of the blood, as an example, is difficult to predict through diagnosis. “We know it’s a genetic disease, so putting people in risk classes is important to get patients in the right treatment protocol as soon as possible.”

3. The power of genomics medicine is changing care. Genomics gives us greater insight to treat these diseases. As an example, there are 89 subtypes of leukemias and lymphomas that can be identified via genomics. One may not hurt you for 30 years and another needs the most aggressive treatment. Genomics can tell you what cancer subtype it is and the best therapeutic approach – and it can save your life.

4. There is no one medication that is perfect for every cancer patient, because everyone is different. Furthermore, incorrect medication may aggravate cancers. Some drugs can weaken a patient’s immune system but not affect the cancer, giving it a blank slate to grow or change over the months. Genomics and personalized medicine are changing care for cancers and other diseases.

Dr. Matt Harms – RGI Genomics Expert from Washington University

A Correct Diagnosis After 10 Years Gives Parents Answers

For over a decade, a young woman suffered from unexplained muscle weakness that progressively became worse and took away her ability to play sports and even made walking difficult. With the help of her parents, she navigated through a maze of neurologists, therapists, and neuromuscular specialists looking for answers. After years of testing, doctors concluded that a nerve disease called congenital spinal muscular atrophy was causing all her problems. She was happy to have an answer but disheartened to learn that this disease was currently untreatable and that potential therapies were decades away.

When Dr. Matt Harms, a RGI expert, discovered one of the genes causing congenital spinal muscular atrophy, the young woman's doctors asked him to evaluate her. He did a clinical exam on her and immediately knew that she did not have this disorder – the disease he had been studying affected the thigh muscles first while the patient's thigh muscles were the only ones in her legs that were still strong. Dr. Harms recommended exome sequencing to find the cause, a recommendation that changed everything.

Through exome sequencing and his analysis, Dr. Harms discovered the real cause of her illness - mutations in the GNE gene called Hereditary Inclusion Body Myopathy (HIBM). Dr. Harms performed subsequent testing on her muscle to prove this was the cause. HIBM is a rare genetic disease that has lower levels of an enzyme that makes sialic acid, which is important for muscle functioning. For over ten years, she had the wrong diagnosis. Even worse, her treatment plan had been aimed at a nerve disease when the entire time, she was suffering from a muscle disease. Fortunately, medications for HIBM are already in clinical trials, offering hope that soon her disease may be treatable or possibly cured. Experienced clinicians who are used to evaluating complicated diseases and are trained to analyze and interpret exome sequencing can put the pieces of the puzzle together. This leads to more accurate diagnosis, which in turn leads to a more accurate prognosis, and the best possible care for a patient.

"A correct diagnosis gives parents answers and allows them to understand their child's illness for the first time. Now, they can focus on preventing the illness from defining the child."

- Dr. Matt Harms

"If they would have gotten in touch with RGI sooner, we would have recommended exome sequencing and identified the right answer earlier," Dr. Harms says. "She would have received the corrective diagnosis which would have put her on the right course much earlier. She and her parents could have focused their energy toward understanding the illness she actually has." Armed with the correct diagnosis through RGI, she is now considering joining the clinical trials involving a medicine designed to improve muscle strength.

"A correct diagnosis gives parents answers and allows them to understand their child's illness for the first time. Now, they can focus on preventing the illness from defining the child," says Dr. Harms. This patient and her parents now have answers to the many questions they

have worried about for years. Will she be able to go to college? What careers could she pursue? What is life like for others with her illness? Is this a concern for future children? This knowledge allows them to finally plan for the future.

Takeaways:

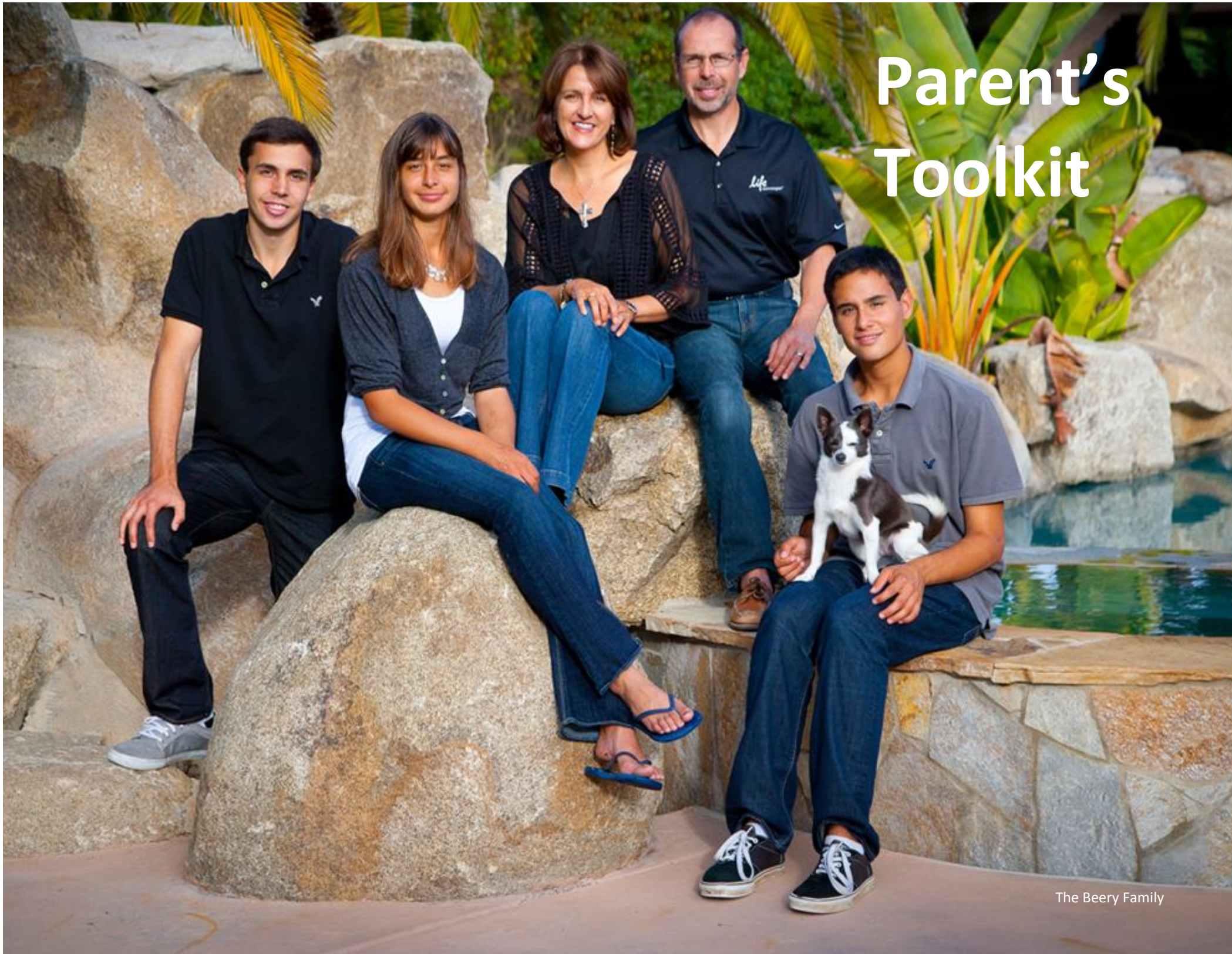
1. Through exome sequencing, an accurate diagnosis was made after many years of misdiagnosis. The disorder was identified, giving her an opportunity to participate in clinical trials that could markedly improve her condition.

2. HIBM parents are carriers of the disease. Carriers are not affected by it, but if two carriers have a child, there is a 25% chance with each pregnancy of having a child with HIBM. There is a 50% chance the child will be a carrier and a 25% chance they will not carry any mutation of HIBM. Her family was now armed with this information.

3. Exome sequencing finally gave this patient's parents accurate answers, helping them know what to expect for the future. They can now focus on understanding the illness she has and make their plans accordingly.

Have any suggestions or comments for the ebook?
Email us at ebook@raregenomics.org

Parent's Toolkit



The Beery Family

7. The Parent's Toolkit

Hundreds of millions of people worldwide suffer from rare diseases. However, because each individual disease affects a smaller number of people, funding for research and treatment into these conditions is usually very limited or not available at all. We have seen that too often, these patients are left without hope of a therapy, and families are left with little understanding of the disease.

Most parents do not have any medical training. Lack of medical knowledge, lack of connections and lack of resources can make many parents feel there is little hope of finding a therapy or a cure.

But it shouldn't be like this.

"Every time a person's genome is sequenced and studied, it adds depth of medical knowledge, improving the chances that a course of treatment—or even a cure—might eventually be found. For the families, genomics allows them to access the most advanced scientific knowledge about their children's conditions," says Dr. Jimmy Lin, President of Rare Genomics Institute. "We are here to interpret this scientific information and use our expertise to guide our patients and their families on the correct course to provide the best quality of life. We're here to change things around."

We understand that families struggle for years with a child with a rare disease, and this is why RGI was started. RGI is committed to helping patients with rare disease and their families. We recruited a team of researchers and clinicians from top research institutions around the world. Through us, patients can gain access to genomic sequencing, expert analysis and interpretation services.

Because most rare diseases are genetic in nature, we believe that genome sequencing is a powerful tool to help patients in a way that conventional diagnostics cannot. As expert biomedical researchers, we have the capabilities and the resources to help patients sequence their genomes in the hopes of finding a cure. Several years ago, this technology was not affordable. Even with the dramatic decline in price due to technological advances, we realize our families with sick children are often under financial strain, making access to these technologies difficult.

We came up with a solution. RGI helps families raise funds for sequencing and connect them to scientists that are experts in their field. RGI uses a crowdfunding platform to help our patient families pay for the cost of genomic sequencing. We are doing everything we can to make our medical expertise and capabilities accessible to our patients including utilizing the Internet to bring the hope of a cure to our patients.

At RGI, we continue to ask ourselves with every patient, with every family, with every medical decision, "If this were my child, what would I do?"

Our site helps families tell their medical journey and gives others the ability to donate directly to fund the research effort of sequencing your child's genes to find a cure. The Internet, supported by social media, has the capability to quickly spread a single message out to thousands of people who want to help others. Though we do not expect it to occur forever, to date all of our family crowdfunding requests have been 100% funded.

RGI understands the frustration and desperation parents feel when they have a sick child with an undiagnosed disease. We understand that all parents want their children to get well and have the best possible care. This is why we continue to ask ourselves with every patient, with every

family, with every medical decision, “If this were my child, what would I do?”

At Rare Genomics Institute, we bring together scientists and clinicians who share our passion for helping rare disease patients. We are committed to our patients and to helping give you answers that were not technologically possible before now. We want to spread the word because the results can be life changing.

As a 501(c) (3) not-for-profit organization funded primarily through the generosity of donors who believe in our cause, donated funds go directly to supporting patient-specific research. We also raise funds through grants from academic institutions, foundations, private donations, and other financial sponsors. We are dedicated to making a difference in the lives of our patients and finding cures to rare diseases.

The RGI team has interviewed dozens of family members and children with rare diseases, doctors, geneticists and other medical experts. Many themes began to emerge on what parents have learned and how they got through this difficult process. There are over forty specific items in the toolkit. Many are shared here and fall into several major categories.

- Parent’s determination and commitment
- Tracking your child
- Doctors and medical
- Researching your child’s condition
- Getting your genome or exome sequenced
- Building your rare disease community
- Insurance, costs and schools
- You, your family and relationships
- Focusing on the greater good

Please check out the RGI website for video interviews with rare disease families in this ebook and on our web site at:
http://www.raregenomics.org

7A - Most Important Tool in the Kit

1. PARENT’S DETERMINATION AND COMMITMENT

A parent’s love and determination has a huge impact, likely the greatest impact. Parents need to be their child’s advocate. There are so many cases in which the parent’s dedication led to breakthroughs, diagnoses, therapies, and at times, cures.

“Use all your resources and connections,” says Dr. Ada Hamosh, Clinical Director of the Institute of Genetic Medicine, Johns Hopkins.

Retta Beery (above) researched and learned as much as she could about her children and their condition. She read hundreds of medical articles and found one that showed a rare condition called Segawa’s Dystonia that mimics cerebral palsy. Her twins had until that point, been misdiagnosed with cerebral palsy. Her determination and insight led to the life-changing therapy for both her children – and they are living normal lives as a result.

Jeneva Stone, mother of Robert, searched for answers for her son for over a decade. Through RGI’s exome sequencing, they found the cause of his illness, Dystonia 16. He is the ninth known case throughout the world. Now he is involved with top researchers studying his condition.

7B - Tracking Your Child

2. TRACKING YOUR CHILD

Parents need to make a list of actual problems or observations with dates to track patterns or changes in their child's condition. Jeneva Stone remembers her son Robert's movement changes were so short at first that she thought to herself, "Did that just happen, but you can't press rewind in your life. So you have to write down what you see and when. You will likely forget if you do not."

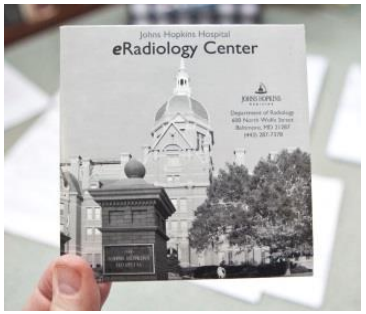
Retta Beery noticed that her daughter Alexis was much better in the morning and progressively got worse during the day. This was not consistent with her diagnosis of cerebral palsy. Cerebral palsy does not change during the day. When Retta read about Segawa's dystonia, she immediately thought that the symptoms were exactly what she observed in Alexis. This observation led to the first step in the road to a successful diagnosis. After genomic sequencing, both twins were completely diagnosed, a treatment was found and ultimately they are leading normal lives now.

3. PUT ALL YOUR RECORDS TOGETHER IN ONE PLACE

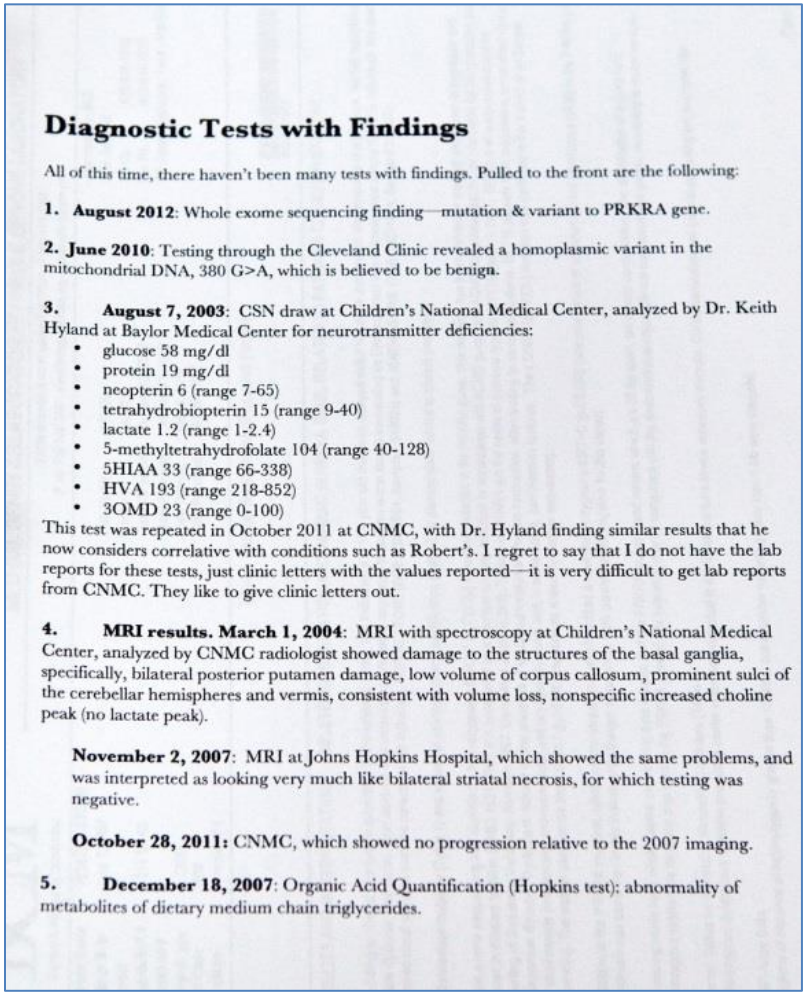
Bring all of your records. Have a copy of your child's medical records and test results in your own home file or on a disk. Families do not realize that it can routinely take three months to get records if families do not bring them to the clinical site visit. This greatly slows down the process. Jeneva Stone, mother of Robert, has a great example of an organized binder holding all of her son's relevant medical information. Doctors have commented that this has made their job much easier.

She titled the binder: Relevant Medical History with his name and date of birth. Her first section is Diagnostic Tests with Findings, (see photo) she bolded the month and year, for example, August 2012, and then listed the testing done, the name of the doctor performing the test or analysis of the test, where it was done and then the results. This is critically important so that tests are not repeated. Some labs perform tests differently, so they will know how it was done if you have the records. This is one of the best ways to be your child's advocate.

Jeneva Stone's medical binder on her son Robert.



Jeneva Stones medical binder contains CDs of lab reports and MRIs



Diagnostic Tests with Findings

All of this time, there haven't been many tests with findings. Pulled to the front are the following:

1. **August 2012**: Whole exome sequencing finding—mutation & variant to PRKRA gene.

2. **June 2010**: Testing through the Cleveland Clinic revealed a homoplasmic variant in the mitochondrial DNA, 380 G>A, which is believed to be benign.

3. **August 7, 2003**: CSN draw at Children's National Medical Center, analyzed by Dr. Keith Hyland at Baylor Medical Center for neurotransmitter deficiencies:
   - glucose 58 mg/dl
   - protein 19 mg/dl
   - neopterin 6 (range 7-65)
   - tetrahydrobiopterin 15 (range 9-40)
   - lactate 1.2 (range 1-2.4)
   - 5-methyltetrahydrofolate 104 (range 40-128)
   - 5HIAA 33 (range 66-338)
   - HVA 193 (range 218-852)
   - 3OMD 23 (range 0-100)

   This test was repeated in October 2011 at CNMC, with Dr. Hyland finding similar results that he now considers correlative with conditions such as Robert's. I regret to say that I do not have the lab reports for these tests, just clinic letters with the values reported—it is very difficult to get lab reports from CNMC. They like to give clinic letters out.

4. **MRI results. March 1, 2004**: MRI with spectroscopy at Children's National Medical Center, analyzed by CNMC radiologist showed damage to the structures of the basal ganglia, specifically, bilateral posterior putamen damage, low volume of corpus callosum, prominent sulci of the cerebellar hemispheres and vermis, consistent with volume loss, nonspecific increased choline peak (no lactate peak).

   November 2, 2007: MRI at Johns Hopkins Hospital, which showed the same problems, and was interpreted as looking very much like bilateral striatal necrosis, for which testing was negative.

   October 28, 2011: CNMC, which showed no progression relative to the 2007 imaging.

5. **December 18, 2007**: Organic Acid Quantification (Hopkins test): abnormality of metabolites of dietary medium chain triglycerides.

Every section is summarized so doctors can easily understand what has been tested previously and what the results were.

She also has a section for MRI reports and the institution where it was done, with the month and year. She has disks with this information readily available in her binder. She keeps and organizes all Explanation of Benefits (EOBs) from insurance companies. Jeneva Stone keeps them in a separate file so she always knows where they are if there is an insurance question.

4. KEEP TRACK OF AS MUCH OF YOUR MEDICAL RECORD AS POSSIBLE

RGI is building a database for electronic health records that families themselves can control. This will give patients the ability to keep their tests, laboratory results, medical history, diagnoses, medications, treatment plans, radiology imaging studies in a digital version of a patient's chart. The advantage is that this can be in real-time, and it is securely and quickly available for those authorized to use it. It is very important to have information readily available so that there is not a long delay in getting medical records. It's also important because you will be asked many questions. Some of the questions most geneticists will ask are:

- When did the symptoms start?
- What is your family history?
- What studies or tests were completed?

Having knowledge and immediate access to these important facts can greatly speed up the process to diagnosis.

Amy Clugston, parent of a daughter with an undiagnosed condition, noticed a change in her child's breathing. She took her to an ear, nose throat specialist, ENT. Nothing was found. Later her daughter had an MRI. Amy requested a copy of the medical records for the MRI. She found her daughter had a large nasal polyp on the MRI. It couldn't be seen during the regular ENT exam. The neurologist told Amy the MRI was normal. Amy reviewed the notes on the report, brought this to the doctor's attention and subsequently the polyp was removed from her daughter.

5. TAKE REGULAR PHOTOS AND VIDEO OF YOUR CHILD

Document your child with pictures over time, at least four times a year until they are four years old, and then at least every year. With any major change in symptoms or physical characteristics, take pictures, date them and put them in your binder. During a clinical exam, it is vital to have records of all important tests in a binder or online database. Your child may have physical features that change over time and without pictures, it is hard to describe to treating physicians.

A geneticist can observe differences in physical characteristics over a period of time, for example three years. One child may have wider set eyes at age two, and this may change over time, but this picture may help a doctor understand the history when your child is six. As Jeneva Stone described above, "You can't press rewind in your life." Keep these in your binder or stored online, making sure it is available at your clinical visits.

Additionally, if any other family member shares some of the same physical characteristics as your child, take a picture. Bring this to the doctor's appointment as well. This will provide additional information for the physicians as they look at family history.

6. BE EXTREMELY ORGANIZED

Retta Beery recommends taking notes, so when you go to the appointment, you are prepared. She has used her smart phone to keep medication names readily available as well as questions she has for the appointment. Zsuzsanna Darvai, mother of Balazs, starts writing her questions down weeks before the doctor's appointment. She uses the time to think about all the questions she wants answered. Many parents have said if they are not prepared, they leave the appointment and realize they forgot to ask some important questions.

7C - Doctors and Medical

This is not medical advice and you should consult your doctor and other medical professionals before making any decisions.

7. CONTACT RGI

The clinical exam at RGI or one of their many partners is very important. The geneticists have specialized training and experience from some of the world's best medical institutions. They have seen many rare disease cases. Many doctors and pediatricians have only heard about rare diseases when they were in medical school or seen very few. Email contact@raregenomics.org to get started.

8. WORKING WITH DOCTORS

As a parent, you are a very important part of the team. You are with your child the most. If you observe changes in their condition or their behavior, communicate this to the medical team. If you have questions, ask them. With the complexity of rare diseases, many are not well understood. You are providing valuable information. It is very important for all team members to listen carefully so that the best progress can be made for your child. There should be one physician that is coordinating the team and care for your child.

Follow the doctor's advice and keep all team members informed. With rare diseases, your child may be seeing multiple specialists, including a geneticist. The field of genetics is changing so fast, and many doctors know traditional medicine much better than advances in genomics and rare genetic diseases.

Good communication is essential. If a procedure is recommended for your child, Gay Grossman recommends researching the procedure and then asking another doctor for a second opinion. It's a team – your team, and another opinion may provide better understanding and comfort.

9. A DIAGNOSIS IS VERY IMPORTANT WITH RARE DISEASES

Many families have been searching for years for a diagnosis of their child. Without a diagnosis, it is difficult to get services approved through insurance. Many children with rare diseases have developmental delays requiring occupational therapy (OT), speech therapy, and/or physical therapy (PT). When insurance companies do not approve these based on lack of a diagnosis, substantial financial burden is placed on the families.

Sequencing is one of the most important diagnostic tools available. Finding a diagnosis enables families to provide this information to receive therapies as well as individual education plans (IEPs) at school, so the child gets all the services he needs. Finding a diagnosis also helps lower stress and guilt from parents. They now have an answer and do not have to continue on an odyssey of searching. With a diagnosis, parents were able to finally take vacations, get sleep, know if they should have other children, plan for their child's college, and in several cases find out that their child would not suddenly die.

10. WORKING WITH RESEARCHERS AND SCIENTISTS

When you meet with the doctor from RGI or partner organizations, make sure you bring all the important medical information about your child. This will give them the most knowledge as they try to uncover what is causing your child's illness.

11. MEDICAL TRANSPORTATION ASSISTANCE

Travel should not be the limiting factor as to whether a child receives the proper medical attention. These organizations help with medical travel expenses - Air Charity Network, National Patient Travel Center, Aubrey Rose Hollenkemp Children's Trust Foundation. See the Research URLs section for details on how to contact them.

12. DIET

Be aware of your child's diet. Is there anything in it that could be exacerbating a symptom? Ask your doctor and do research in connection with your child's illness to see if they should eat or stay away from certain foods. Consulting with a nutritionist and finding a cookbook with healthy recipes may benefit your child.
http://health.nih.gov/search_results.aspx?terms=Nutrition

13. THERAPIES ARE POSSIBLE

Today, most rare diseases do not have therapies or cures, but some rare diseases have diet therapies like PKU and others use repurposed drugs like losartan and L-dopa. Alexis and Noah Beery live normal lives after using L-dopa and a serotonin supplement.

Raising awareness on rare diseases and the many people that are affected by them collectively has helped improve efforts toward cures for rare diseases. The Orphan Drug Act provides incentives to pharmaceutical companies for investment in research and development. Rare diseases have traditionally not been very profitable, so in the past, companies focused efforts on diseases affecting large patient populations.

Genomic sequencing provides information about genes that helps researchers use the most advanced technology and gain insights into related pathways of disease. Existing therapies can be studied to determine if they can be used for a rare disease. Researchers and scientists are using genomic information to work toward new therapies and cures.

Patients with rare diseases often have developmental delays, some of which can be managed by other therapies including speech therapy, occupational therapy, and physical therapy. The role of speech therapy is to improve and manage communication and swallowing disorders. The goal of occupational therapy is to give people the abilities they need to be independent in everyday life. Occupational therapy involves personal care, domestic tasks, improving function and independence. This will limit the need for help from others or the use of devices. The goal of physical therapy is to improve mobility, function and movement with relief from pain.

14. CLINICAL TRIALS

Some rare disease patients have taken part in clinical trials of new drugs and therapies. There are obvious risks associated with them. They are only applicable to very few diseases and you need to involve medical professionals to research this. See the Research URLs section for more detailed information about these organizations:

- Rare Diseases Clinical Research Network at http://rarediseasesnetwork.epi.usf.edu
- ClinicalTrials.gov - http://www.clinicaltrials.gov
- The National Institutes of Health has a NIH Patient Recruitment Office - http://nih.gov/health/clinicaltrials/findingatrial.htm
- There is a large private clinical trials office run by Centerwatch - http://www.centerwatch.com

Lilly Grossman is at an Easter egg hunt but has difficulty walking, and suffered from severe tremors most of her life. She has been sequenced to determine the cause and is involved in a study at Scripps Translational Research Center.

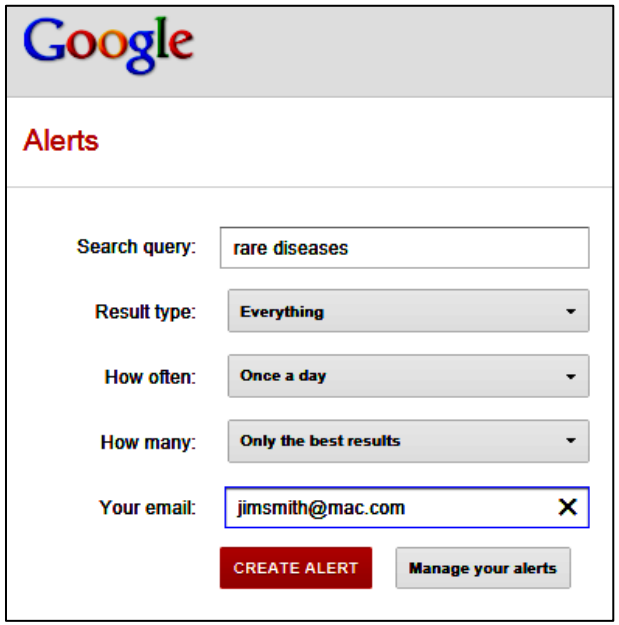
7D - Researching Your Child's Condition

15. BECOMING A RESEARCH EXPERT

Many rare disease parents do massive research, and get to know and stay in touch with the disease researchers. There are so many cases where the parents found research that led to breakthroughs in testing or therapies. We have compiled websites that provide valuable information:

- Rare Disease information – Patient Friendly
- Rare Disease information – More Technical
- Parent Knowledge Sharing
- Transportation Assistance
- Clinical Trials and Research
- Advocacy Groups and Patient Information
- Genomics and Public Policy
- Books and Magazines

For more information on each of these topics, see the RGI website or Research URLs section of this book.



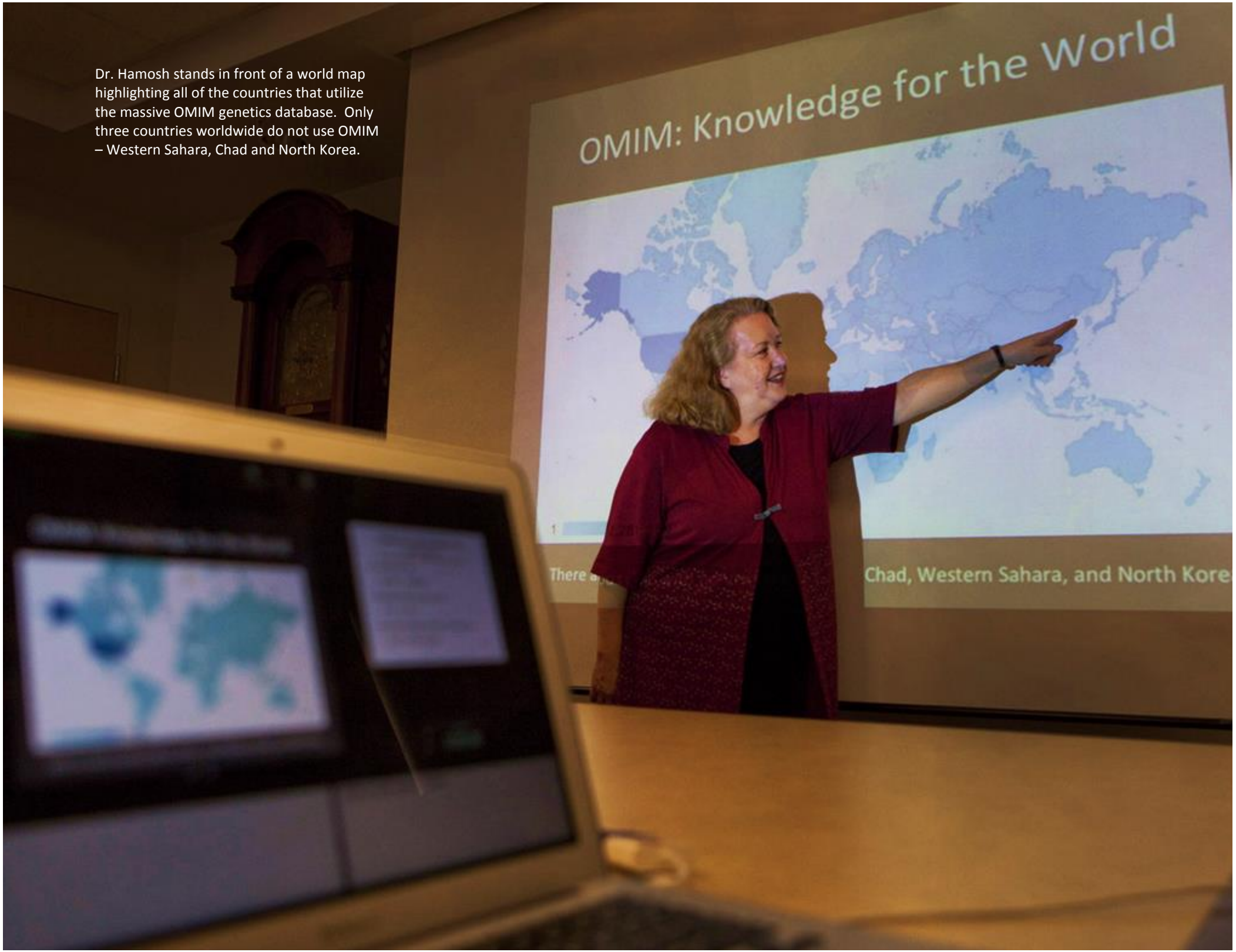
You can set up Google Alerts on a disease or symptom

16. UNDERSTAND THE PROCESS THOROUGHLY

Understand the genomic and medical process. These are rare diseases, which are difficult problems, and solutions are not easily available. Be an asset and helpful member with the team of doctors trying to provide an answer. If you have a child with a problem and your doctor does not know what is wrong, find a physician at an academic center. Larger hospitals see more patients and can better direct you to resources that your child will need.

17. SET UP GOOGLE ALERTS ON YOUR CHILD'S DISEASE

Sign up for Google alerts for terms associated with your child's disease or symptoms and you will get a daily email from Google with 1-10 links per day. http://www.google.com/alerts



Dr. Hamosh stands in front of a world map highlighting all of the countries that utilize the massive OMIM genetics database. Only three countries worldwide do not use OMIM – Western Sahara, Chad and North Korea.

7E - Getting Your Genome or Exome Sequenced

18. DOING GENOME TESTING

Getting the child's and parents' genomes sequenced is very important. This may be key to diagnosis, treatment and potential therapies. Once you have done the genome sequencing, it remains useful and provides important information throughout your life and future generations. Targeted medications and therapies can be used for illnesses based on the sequencing results.

19. CROWDFUNDING YOUR GENOME TEST

RGI's crowdfunding helps parents raise money for genome sequencing. We understand the costs of caring for a sick child. Crowdfunding is a tool and resource designed to raise money so the work and analysis of your child's sequencing can begin as soon as possible. This allows many people to help. It establishes a target financial goal and an important reason to give.

20. USE PROVEN CROWDFUNDING LETTERS TO HELP RAISE FUNDING

RGI has a collection of fundraising letters that were successfully used to raise the targeted amounts quickly through crowdfunding. Some best practices from patient parents are explaining that the tests are to help their child, the donation goes through a third-party - RGI and that it's a non-profit. Jeneva Stone, RGI patient Robert's mom, explains, "It renewed my faith in people when we reached the goal." Facebook is very effective for raising money, finding similar groups and telling people it's tax deductible. RGI provides crowdfunding experts to help you with this process.

21. MORE FAMILY DNA TESTS CAN HELP

Comparison of genetic sequencing among multiple family members like siblings, parents and grandparents, improves the analysis process. The trio of child and parents' genome sequencing provides great information. Any other siblings, whether affected or not by the illness when sequenced, can provide valuable insights to compare and diagnose.

7F - Building Your Rare Disease Community

22. BUILD SUPPORT AND FIND OTHERS WITH THE SAME DISEASE

Blog, write, communicate and get the word out. Start a Facebook group on your disease or connect with one. Build an online community or become part of one. Build a community related to your child's disease with a website, or through social media. Please see the Research URLs section for useful websites.

At the yearly symposium on the rare disease NMO, patients were invited to fill out a form writing their names, addresses and contact information so that support groups could be formed at a local geographical level. The idea is to connect the rare disease patients to support each other, not only online, but face to face if possible without traveling great distances during the year.

Here are a few examples of successful websites and online communities providing information, connection and support.

- Retta Beery's website is about their family's experience and solving a medical mystery for their twins that ultimately led to their ability to lead normal, healthy lives. Retta is a patient advocate and speaker helping other families with rare diseases. The site has important resources and articles.
  http://thebeerys.com

- Jeneva Stone and Dana Nieder developed communities to share insights and build a network to learn from each other. Jeneva Stone's blog is Busily Seeking…Continual Change. Dana Nieder's blog is Uncommon Sense.

- The Myelin Project's primary purpose is to accelerate research on myelin repair. Myelin is damaged by multiple sclerosis, leukodystrophy and the many other demyelinating disorders. Newborn screening has made important advances to create early diagnoses for ALD.
  www.myelin.org

- Hunter's Hope is a foundation established to find information and research on Krabbe Disease and related leukodystrophies.
  www.huntershope.org

23. CONTACT LARGE ADVOCACY AND RESEARCH GROUPS

Find specialized sites to help you find information, studies, and connections to other families facing similar situations. Here are some examples of larger advocacy groups.

- Cystic fibrosis - http://www.cff.org/aboutcf
- Batten Disease Support and Research Association (BDSRA) http://www.bdsra.org
- ALS Amyotrophic lateral sclerosis (ALS), often referred to as "Lou Gehrig's Disease - http://www.alsa.org/
- Huntington's Disease - http://en.hdbuzz.net/
- Multiple Sclerosis - http://www.nationalmssociety.org
- Guthy-Jackson Charitable Foundation- http://guthyjacksonfoundation.org/

There are about 7,000 rare diseases. See a thorough list (alphabetized by name) with links on the National Institute of Health website and the Global Genes website:

http://rarediseases.info.nih.gov/GARD/browse-by-first-letter/A
http://globalgenes.org/rarelist/#A

24. USE YOUR PROFESSIONAL SKILLS TO HELP YOUR CHILD

We constantly see parents using their skills and experience to help provide clues or solve their child's illness. They do research and connect with other people or advocacy groups with rare diseases. Knowledge sharing can be impactful. Use your personal and professional skills however you can to help your child – writing a book, making a film or getting involved in advocacy groups.

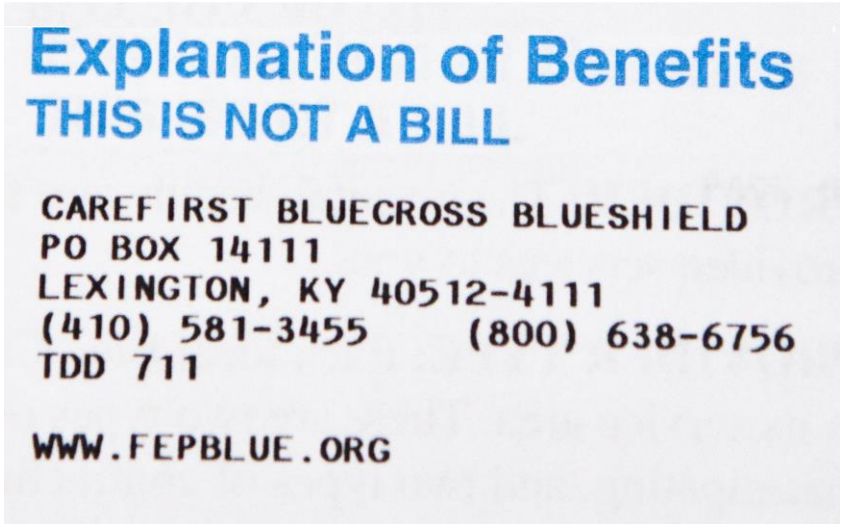
25. HELPING OTHER RARE DISEASE FAMILIES

Help others with rare diseases outside of your child's disease. While the diseases may be different, the process and road to a diagnosis may be similar. In addition, the more children are sequenced, the more genes are discovered to help everyone with understanding their own genomes.

Have any sites we should add or comments for the ebook?
Email us at ebook@raregenomics.org.

7G - Insurance, Costs and Schools

26. DEALING WITH INSURANCE COMPANIES


Explanation of Benefits
THIS IS NOT A BILL

CAREFIRST BLUECROSS BLUESHIELD
PO BOX 14111
LEXINGTON, KY 40512-4111
(410) 581-3455 (800) 638-6756
TDD 711

WWW.FEPBLUE.ORG

Parents need to become experts on their insurance. If you have questions on what's covered, talk to your human resources department at work and regularly contact the insurance company. Exome sequencing is now being covered by some insurance companies. Find out and know your coverage.

Jeneva Stone, parent of RGI patient, Robert, recommends having a separate insurance file so you always know where to find the information and can compare what is charged and paid. Keep and organize all explanation of benefits (EOBs). Every letter from an insurance company should be dissected, evaluated and contested where needed.

Insurance is important for sick children. Some medical equipment, such as wheelchairs, can cost $15,000 or more. Many parents with sick children have made decisions to stay with jobs based on the best insurance to help care for their child.

When children have rare diseases, it is important to know your insurance, ask questions, keep great records and pursue strongly.

27. INSURANCE AND THE AFFORABLE CARE ACT

With the Affordable Care Act, insurance providers cannot discriminate against individuals that have genetic diseases or pre-existing conditions. Importantly for rare diseases, there are no longer lifetime insurance caps. For more description and explanation of current laws, see the National Human Genome Research Institute site at http://www.genome.gov/10002077

For more detailed and state specific information on genomics, there is a legislative database with searchable topics such as consumer genetic testing and privacy health insurance coverage. There is an explanation of each of the topics. You can highlight one or more topics and then search it by the state where you live at: http://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm

There is a separate database for regulations that can be searched on a state-by-state basis. Some states have regulations for genetic non-discrimination in employment and insurance, health insurance coverage, genetic privacy and research. The Cornell Legal Information Institute at http://www.law.cornell.edu/states/listing will allow users to click on the name of the state to obtain information on regulations.

28. WORKING WITH YOUR CHILD'S SCHOOLS

Your child deserves the resources or services that he or she is entitled to receive. Do your own research and become aware of what is available and what is legally required. For example, if your child has trouble communicating, find out what device will help the most. Be a part of the educational team and do not be afraid to ask questions and advocate for your child to receive services.

Some parents bring in doctor's clinical notes and connect outside professionals with the school team so everyone can share information, and your child can thrive at school. Jeneva Stone told her son's school, "He is a developing child - leave the door open. He should be treated with an open mind." The school responded favorably after having many discussions.

If your child needs an Individualized Education Plan (IEP), it is important to understand what it is and how it can benefit your child's education the most. In addition to having clinical notes, if you are having difficulty, consult with a specialist who handles IEPs.

Wrightslaw (www.wrightslaw.com) is an important resource for parents, educators and advocates to understand special education law and accommodations, evaluations and other topics for children with disabilities. A section on frequently asked questions covers a wide variety of useful topics.

There are a few other web resources about special education, inclusion and augmentative technology, as these issues affect many children with rare and undiagnosed diseases. These three sites may be helpful:

Law, Health Policy & Disability Center: http://disability.law.uiowa.edu.
The Burton Blatt Institute: http://bbi.syr.edu/
The University of New Hampshire Institute on Disability at http://iod.unh.edu/Home

29. CROWDFUNDING FOR YOUR PERSONAL MEDICAL SUPPORT

There is a new form of online fundraising called crowdfunding. You can set up a campaign on a crowdfunding site and then send emails to friends and family asking for donations. The site takes a small percentage between 3-12%. There is a good explanation of medical crowdfunding in the Washington Post.

http://articles.washingtonpost.com/2013-07-01/national/40301720_1_sites-travel-expenses-chip

A general crowdfunding site that allows medical money raising is: www.Indiegogo.com.

There are at least are four other sites that are more focused on medical fundraising:

www.GoFundMe.com
www.YouCaring.com
www.FundRazr.com
www.GiveForward.com

Setting up a crowdfunding campaign makes it much easier to ask for medical donations. Getting the media to cover your story can help significantly in raising money.

One of the largest crowdfunders with a huge following is Kickstarter, but you need to produce a physical end-product like a book for the campaign. You cannot use it to just raise money directly for medical bills.

7H - You, Your Family and Relationships

30. BE HOPEFUL, BUT SET YOUR EXPECTATIONS

Cures are not available with most rare diseases. More is being learned every day about genes and their functions. There are new drugs and drugs that may be repurposed for different uses. Many parents enter into these situations with great hope, but know that the purpose of the project is to find answers. As new genes are discovered, there will be more cures and therapies in the future.

31. PARENTS NEED TO TAKE CARE OF THEMSELVES PHYSICALLY AND EMOTIONALLY

Parents need to manage and care for their emotions. The diagnostic odyssey often is filled with many highs and lows. Sometimes, parents are very excited about a potential diagnosis, physician, or treatment, only to find out later that their expectations are set too high. The result can be a great let down. A lot of parents have a support network or community to cope with all the highs and lows.

Amy Clugston said it helps to reach out to other parents and organizations. She said for her, volunteer roles help her heal. Amy is a parent of a child with an undiagnosed disease, an advisor on the patient advocacy board at RGI, and the President of SWAN, Syndromes Without a Name - USA.

For her, gaining as much knowledge at summit meetings and overnight stays helps her feel better by being able to lower stress. She is learning and taking a short break from her normal routine. As Gay Grossman relates, many parents of children with rare diseases are sleep-deprived. Her daughter woke screaming from uncontrollable tremors twelve to thirty times a night. Sleep is very important for your brain to relax and recharge so that you can stay healthy. Amylynne Santiago Volker works out at the gym to relax and relieve stress. She and others find yoga to be very helpful. Your health is vital and your child needs you to stay as healthy as you can.

Emily came from school to her doctor's appointment with her favorite horse bag. Parents and schools need to work together and communicate to provide the best resources for the child.

32. YOU ARE A TEAM

Joe Beery recommends being a team with your spouse and the medical community. Early on, Joe and Retta Beery established roles. Retta was the one who interacted with the doctors and medical staff and Joe supported all of her efforts. "It's a partnership," said Joe. You, as parents, are the most important part of the medical team for your child. You are with your child more than anyone else is, so your input is invaluable.

33. YOU DON'T HAVE TO SOLVE ALL PROBLEMS TODAY – AND YOU PROBABLY CAN'T

Rare disease parent Jeneva Stone told us that it was so overwhelming to try to plan every aspect of her life long term with so many unknowns, and her son's disease took ten years to get diagnosed. She was on a perpetual treadmill. Her suggestion is to only plan 2-3 months in advance and just react to things as they happen.

Nic Volker plays with a neighbor's dog. Pet therapy has been used to help people cope with health problems as well as providing comfort and a companion.

34. BUILD OR USE DEVICES TO MAKE THINGS EASIER

Many rare disease children can't lift books or knapsacks. Research and know what devices may make your child's life easier. What can help them be most successful at school or in their free time relaxing? As an example Scott Putjenter made a stand for Travis to use to change channels on the TV. Before Travis found a successful, life- changing treatment, he was in a wheelchair with limited mobility. Scott carried and placed him on the floor where he liked to watch TV. The stand gave Travis the independence to change the channels by himself.

35. A POINT OF VIEW FROM THE PATIENT

Put your energy toward positivity. "Do not be a victim of your circumstances," recommends Ali Guthy, who has neuromyelitis optica, (NMO), a rare autoimmune disease. Ali believes your attitude can help you through the most difficult situations and times of crisis. Ali talks of the importance of not only being a survivor, but a thriver. She does not let the cards she has been dealt in life determine who she is.

36. TALKING TO YOUR CHILD ABOUT A RARE DISEASE

Many parents would willingly switch places if they could with their sick child. Talking with your child on an age appropriate basis about their illness is important. Be honest, but discuss it in a way that will reassure them and that they can understand. Talk to your child's doctor about what to say. Amy Clugston said she would tell her daughter what to expect before each appointment. She started doing this as she realized at the same point in the parking garage of the doctor's office, her daughter would begin to cry. She then told her what they were going to do. She reassured her daughter, and this can alleviate some of the stress of the unknown. Children can "read" their parents. Try to stay calm and focused. Your child will react to you.

Parents should talk to children in an age appropriate way about their illness, so they understand what is happening and know what to expect at the doctor's appointment. Some children with rare diseases have had their blood drawn over 200 times.

7I - Focusing on the Greater Good

37. FINDING MEANING IN YOUR EXPERIENCE

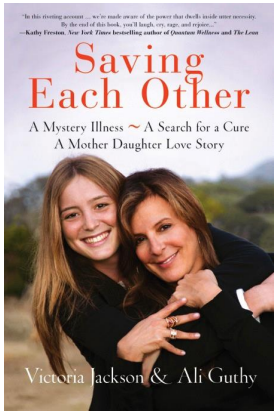
Having a child with a rare disease and seeing your child in pain, enduring surgeries and years of no diagnosis or the wrong diagnosis, can be the most stressful experience a parent can have. One of the ways many parents have dealt with this is to look to help others in a larger way. The meaning many parents take away is that "I am here to help others with my experiences."

38. RAISING MONEY FOR RESEARCH ON YOUR CHILD'S DISEASE

If your child has a diagnosis and if an advocacy or support group exists for that disease, it may be good to join forces. Patti Chapman, Chairman of the Board and U.S. Myelin Project President, recommends researching and talking with large advocacy groups for parents who want to raise money for a disease their child has. She says raising $10,000 on your own and trying to fund research yourself with this, may not benefit your child as much as giving the money to a larger, vetted organization in the disease state that has established relationships with medical institutions and research projects already in motion.

39. WRITING A BOOK

Your story can be inspirational and help others. What you have learned can help others navigate through the medical system of rare diseases. Share best practices with other families to save them time and emotional heartache. Victoria Jackson and her daughter, Ali Guthy, wrote the book, "Saving Each Other: A Mother -Daughter Love Story". It's about the dramatic change in the course of their lives in 2008 when Ali, then 14 years old, was diagnosed with neuromyelitis optica, (NMO), a rare autoimmune disease. At the time, doctors told Jackson that Ali had 4 years to live. This is a story of a mother's determination to not accept a dire prognosis and their journey to create a new blueprint for medicine, NMO and rare diseases.



40. USING TV, FILM AND MAJOR MEDIA TO GET THE WORD OUT

Rare Disease parent Retta Beery decided to tell her children's story after being misdiagnosed with cerebral palsy on the show, *Mystery Diagnosis*, in the hopes of reaching other families. The story of Lorenzo Odone was told in the movie *Lorenzo's Oil.* Television, film and media are effective tools to raise awareness to a broad audience. Travis Putjenter saw the Beery's story and it led to his successful therapy with the same disease.

41. SPEAK AT AND ATTEND CONFERENCES

Learn everything you can about your child's rare disease. One way to gain more knowledge is to attend conferences on your child's disease. The speakers at conferences are usually the experts in the field. Conferences can give updates on important advances in research or clinical trials. Some parents have become patient advocates and speakers at conferences to share their insights and help others.

Retta Beery speaks to James Watson who won a Nobel Prize for discovering DNA. Retta was the keynote speaker at Cold Spring Harbor Lab's genomic conference in New York where Dr. Watson has an office.

42. BUILDING A LARGE IMPACT

While it is not possible for everyone, the Guthy-Jackson Foundation has had one of the most impressive impacts. The foundation is focused on finding a cure for Neuromyelitis Optica, NMO. NMO is an autoimmune disease where the body's immune system attacks healthy cells in the optic nerves and spinal cord. Often misdiagnosed as multiple sclerosis, MS, NMO attacks can cause temporary or permanent blindness and paralysis.

Victoria Jackson and her husband, Bill Guthy, began the foundation when their daughter was diagnosed with NMO. Victoria Jackson is well known for her successful cosmetic line. Bill Guthy is co-founder and manager of one of the world's largest television direct marketing companies, Guthy-Renker. The Guthy-Jackson Foundation is based on four principles: Spend all of the funds on research with the top scientists in the field. Make sure the scientists collaborate. Build a huge blood bank of genetic material for the scientists to study. Throw an annual conference that shares the most advanced research and flies in hundreds of people with the disease.

Establishing a Patient Day for a specific rare disease can be very effective. The NMO Patient Day is a day in the yearly NMO symposium where 200 patients with NMO come together and learn from question and answer sessions from experts from around the world that attend the event. Patients ask questions directly to a panel of world experts in NMO. Patients share stories, connect with each other, gain knowledge and have the opportunity along with a family member to donate blood to further research the disease. LabCorp takes blood samples that patients and family members donate during the event. Scientists collaborate and learn about patient concerns and build a biorepository for research to find a cure.

Hundreds of NMO Conference blood samples from patients have been collected to help researchers analyze, find therapies and hopefully a cure someday.

A Parent's Determination and Lorenzo's Oil

Lorenzo Odone was born in 1978. He spoke Italian, French and English and appeared to be intelligent and healthy, but at age 6, he was diagnosed with ALD, adrenoleukodystrophy. ALD is an inherited disease in boys where the myelin, the protective covering on nerve cells, is progressively destroyed resulting in brain failure and death.

When Lorenzo was diagnosed, he was only given a few years to live, but Lorenzo's parents refused to accept this fate. They started on an exhaustive quest to find a cure for his disease. At first, doctors tried to dismiss them, but Augusto Odone, Lorenzo's father, refused to give up. He went to the National Institute of Health library and read everything he could on his son's illness in these pre-internet days.

Augusto read that the brain damage was believed to be caused from a buildup of fatty acids in the blood. He researched and developed oil from grapeseed and olive oil that he hoped would reduce the fatty acids. Soon after he gave it to Lorenzo, remarkably Lorenzo's levels of fatty acids decreased.

The oil


Lorenzo's Oil Film (courtesy Myelin Project)

The love, devotion and will of Lorenzo's parents got attention from Hollywood, and the movie *Lorenzo's Oil*, was made. Dr. Hugo Moser, the world's expert in ALD later confirmed that the oil protects boys if given before the symptoms start. Augusto describes Dr. Moser, "through this journey, I found not only a brilliant partner in ALD research, but a dear friend whose support has been invaluable to our family all these years." Lorenzo was not expected to survive his tenth birthday, but he lived past his thirtieth.

Augusto and Michaela Odone, Lorenzo's parents, founded the Myelin Project, a 501 (c)(3) nonprofit, to fund research into myelin diseases and leukodystrophies and openly share information among scientists.

"You never know until you try"

- Augusto Odone, Lorenzo's father

The Myelin Project started in 1989 and its primary purpose was to come up with new therapies that would stimulate remyelination to improve the quality of life and potentially find a cure. "There are many different presentations of the disease, and it varies greatly among patients making it hard to detect and diagnose," says Patti Chapman, Chairman of the Board and U.S. Myelin Project President. In the most severe form, X-ALD, time is critical before the brain is irreparably damaged. ALD causes profound demyelination of the brain. This results in a failure of conduction of impulses both to and from the brain leading to severe neurologic dysfunction. Therapies are dependent on diagnosis and progression of the disease making early detection life-saving.

Patti Chapman met Augusto and Michaela in 1987 and was impressed by their dedication and resolve to find a cure for their son, Lorenzo. Like Augusto and Michaela, Patti's family has also been affected by ALD. Her younger brother, Bobby, passed away from ALD at the age of five, her surviving brother, Richard, lived only ten years after he was diagnosed with x-linked ALD, and one of her sons currently suffers from adult onset X-ALD, or AMN, adrenomyeloneuropathy.

Research and development play critical roles in finding cures. Many frustrated and desperate parents want to raise money for research. Patti understands this all too well and recommends researching and talking with large advocacy groups. She says raising $30,000 on your own and trying to fund research yourself with this may not benefit your child as much as giving the money to a larger organization in the disease state that has established relationships with medical institutions and research projects already in motion.


Researching
OMIM – Online Mendelian Inheritance in Man
www.omim.org
OMIM®
Online Mendelian Inheritance in Man®
An Online Catalog of Human Genes and Genetic Disorders
Updated 26 October 2013
Search
Sample Searches
OMIM Tutorial
Advanced Search: OMIM, Clinical Synopses, OMIM Gene Map , Search History
Mirror sites: us-east.omim.org, europe.omim.org

Click for Table of Content

8. Researching Rare Diseases

Despite how isolated you may feel as a parent or how unique your family's particular situation is, there are growing numbers of organizations and information centers to support you. Most parents we have interviewed have told us they want to do deep research and would like to see what other parents are using. There are many cases where the parents found the research that led to breakthroughs in testing or therapies for their children.

Please note that while many of these sites are not highly visual, they contain very useful information in your efforts to learn more about rare diseases, options and about other parent's experiences.

The information in this eBook, Diagnosing Rare Diseases, and any other Rare Genomics Institute (RGI) eBook, is for educational purposes only. It should not be used for personal diagnostic or treatment purposes. If you have questions regarding a medical condition, always seek the advice of your physician or other qualified health professional.

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RGI is, within this eBook, providing certain information about rare diseases, genomics, case studies, and other information. The comments are generally based on professional suggestions, published experience, experiences of families of children with rare diseases, interviews and other materials, but do not represent therapeutic recommendations or prescriptions of any type. For any specific information and advice, consult your personal physician or other medical professionals.

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Please visit www.RareGenomics.org for much more comprehensive information. Check out the video on RGI that features interviews with families in this book and Dr. Jimmy Lin.

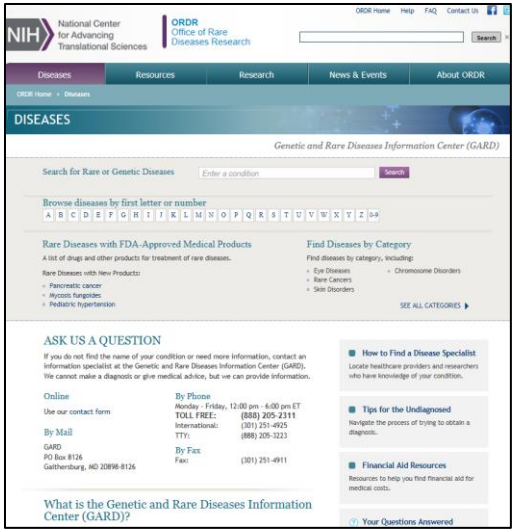
Have any research sites or ideas for the ebook?
Email us at ebook@raregenomics.org.

8A - Rare Diseases - Patient Friendly Sites

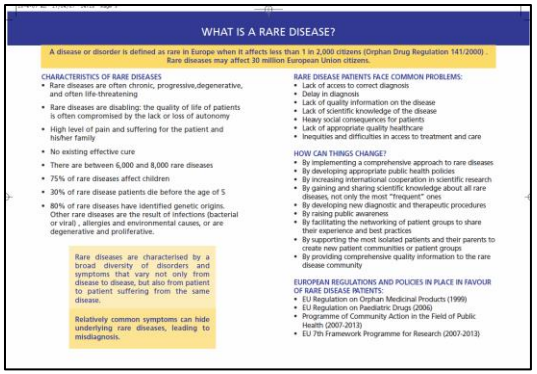
Personal Genomics Education Project
This site covers some social, ethical and legal concerns that accompany genetic testing.
http://www.pged.org

My 46 Research Sequencing Project
This site gives an introduction to genetics. There are basic facts about genome and exome sequencing.
http://www.my46.org/intro/what-is-genetics

Science and Technology Resources on Rare Disease
This site defines rare diseases and introduces policies that have been established concerning them in the recent past.
http://www.istl.org/07-fall/internet1.html#introduction



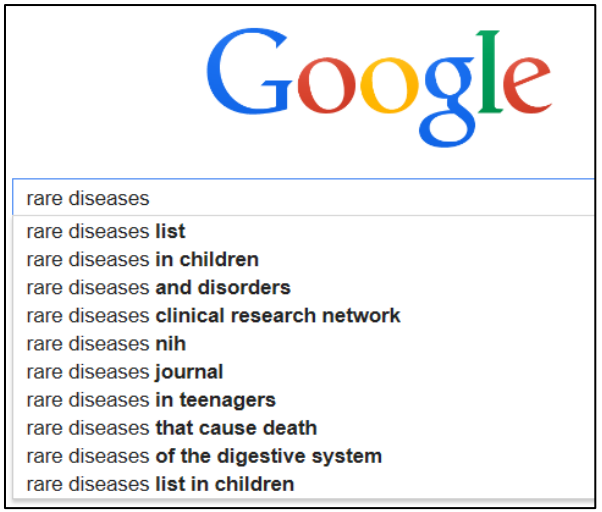
Genetic and Rare Disease Information Center (GARD)
GARD combines the efforts of two agencies within NIH to help people find information about genetic conditions and rare diseases.
http://rarediseases.info.nih.gov/GARD/Default.aspx



Eurodis Rare Diseases Fact Sheet
This is a short guide to the defining qualities of rare diseases.
www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf

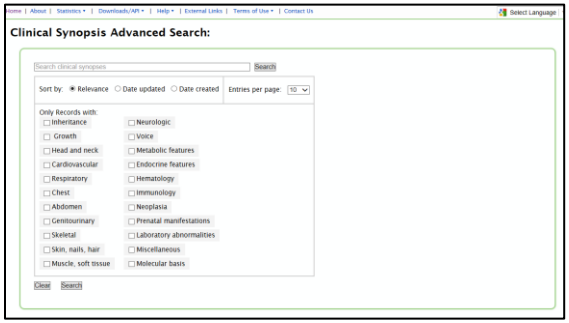
National Human Genome Institute Education Portal
This is the National Institute of Health (NIH) education site on genetics. This site has fact sheets, glossary of terms and online kits.
www.genome.gov/Education

National Geographic Genographic Project
They offer a $199 test that looks at about 150,000 markers that are mostly related to who your ancestors were and where they came from over the last 70,000 years. About 1.6M people have done the test. This is not a substitute for exome or genome sequencing.
http://genographic.nationalgeographic.com



Google
Many parents tell us that their first searches start with looking into symptoms on Google.com and then into families of diseases and eventually into individual genes if they get a diagnosis.
www.google.com

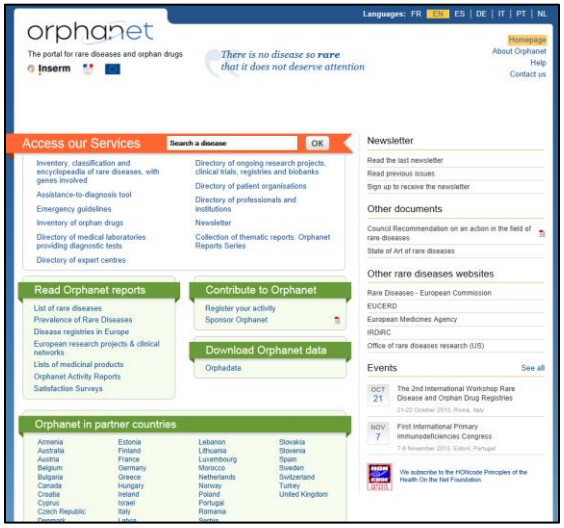
8B - Rare Diseases - More Technical Sites



Online Mendelian Inheritance in Man (OMIM)

OMIM provides a deep medical database of human genes and genetic phenotypes. It is one of the best technical sites in the industry.

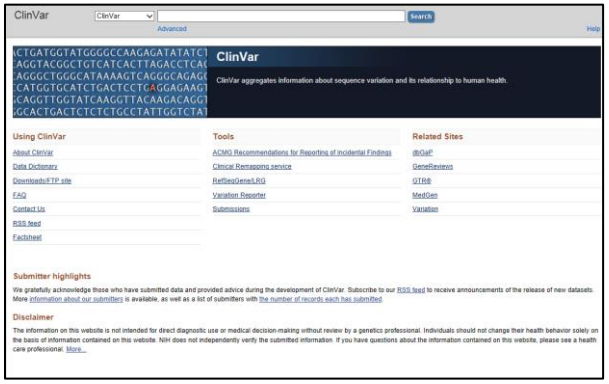
www.omim.org



Orphanet

This is a reference site for rare diseases and orphan drugs. Orphanet has an inventory and encyclopedia of rare and orphan diseases. It also has an inventory of drugs.

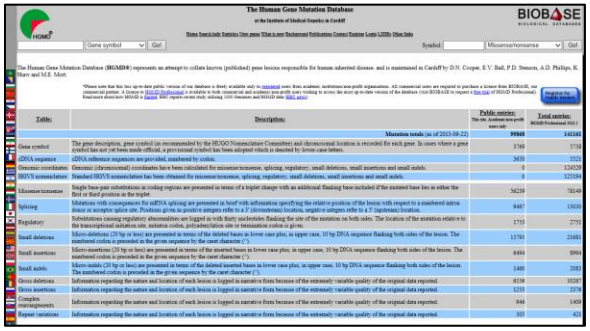
http://www.orpha.net



ClinVar

ClinVar collects information on gene sequencing variation.

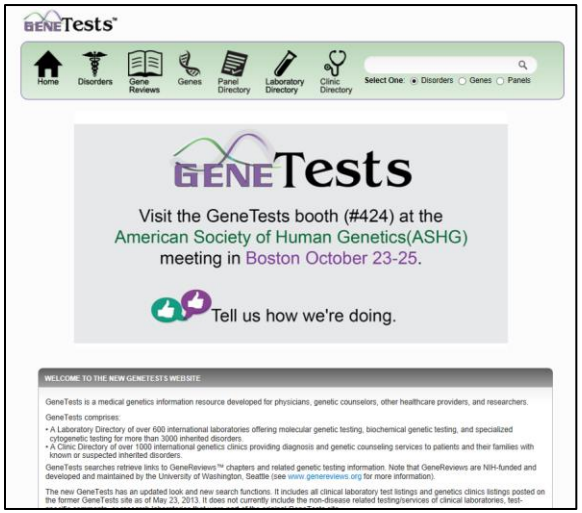
http://www.ncbi.nlm.nih.gov/clinvar



The Human Gene Mutation Database (HGMD)

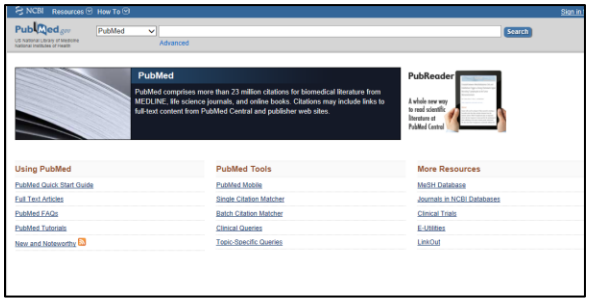
This site compiles a list of published mutations associated with disease.

http://www.hgmd.org



GeneTests

This is a medical genetics information resource developed for physicians, genetic counselors, other healthcare providers, and researchers.
http://www.genetests.org



Pubmed

This site compiles information from biomedical literature.
www.Pubmed.org - http://www.ncbi.nlm.nih.gov/pubmed

The FDA Office of Orphan Products Development (OOPD)

The mission is to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.
http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

NIH Undiagnosed Diseases Program

The Undiagnosed Diseases Program (UDP) pursues two goals: 1) to provide answers to patients with mysterious conditions that have long eluded diagnosis, 2) to advance medical knowledge about rare and common diseases.
http://rarediseases.info.nih.gov/research/pages/27/undiagnosed-diseases-program

International Rare Disease Research Consortium (IRDiRC)

Irdirc has two goals. These are to deliver 200 new therapies by 2020 for rare diseases and establish ways to diagnose rare diseases.
http://www.irdirc.org/

8C - Parent Knowledge Sharing Sites

Other rare disease families and loved ones can be invaluable resources for information and support. Below are some examples of communities of patients/families in dialogue about their experiences, primarily via blogs. This is a small sampling of what is out there.

Ben's Friends
BensFriends.org is a network of safe and supportive patient communities for anyone affected by a rare disease.
http://www.bensfriends.org

Retta Beery's website
Retta Beery's research solved a medical mystery for her twins that was life changing. They are leading normal lives. She is a patient advocate and speaker helping other families with rare diseases. The website has important information and links about dystonia and genome sequencing.
http://www.thebeerys.com

Busily Seeking…Continual Change
RGI parent of Robert Stone and award winning writer describes her medical journey with her son and parenting in her blog.
http://jgirl3.blogspot.com

Hope Knows No Boundaries
The mission is to educate, inspire, and enable patients and future patients to use their voice in their medical care and provide resources to help them navigate the medical system. The goal is to help patients receive personalized medicine by connecting them to the right specialists, facilities, and diagnostic tools for answers and treatment.
www.hopeknowsnoboundaries.org.

In Need of Diagnosis (INOD)
In Need of Diagnosis (INOD) provides help and support to individuals with undiagnosed conditions.
http://www.INOD.org

Inspire
Inspire provides a network of various special interest medical communities (i.e. for a given disease) and allows its users to join groups about medical issues that are important to them, as well as befriend those with similar interests.
http://www.inspire.com

Little Miss Hannah
This is a network of bloggers directly affected by rare diseases. Blog topics range from encouragement, personal stories, medical record management workshops, media awareness and using social media for support.
www.littlemisshannah.com/about-gauchers-2/rarediseasesupport/more-special-kids

*Emily, who is a genomics patient of **Dr. Ada Hamosh**, puts a stethoscope on her mom's head at her appointment.*

Marble Road

Marble Road connects patients and their families to resources and information centers, such as Check Orphan, The Children's Rare Disease Network, the Global Genes Project or the Coalition of Patient Advocacy Groups. It also gives voice to patient in need of charitable service, as well as posting press releases.
www.marbleroad.wordpress.com

Moments, In the Undiagnosed World (SWAN)
This blog provides information and resources to try to prevent children with rare disorders from, "Falling through the cracks." Topics include patient stories, policy, general information, empowerment, selecting the proper care, psychosocial support, advocacy for awareness and increased contact with the medical community, continuity of care, expediting the diagnostic process, etc.
www.undiagnosed-moments.blogspot.com

Parenting Special Needs
This site hosts forums for special needs and undiagnosed illnesses.
http://special-needs.families.com/blog/agnoizing-journey-the-undiagnosed-child#

Parents Helping Parents (PHP)
PHP helps families who have children of any age with special needs. PHP's family resource and service staff field calls from families having children from infancy through their child's adulthood into their 50's and 60's. They say it is never too late to call PHP. Adult siblings who have responsibility for the care of their sibling with a disability call PHP too.
http://www.php.com

Patients Like Me
This site offers connection with those suffering from similar ailments. It provides treatment reports and research reviews, as well as patient testimonials.
www.patientslikeme.com

Rare Disease Blogs
This blog features a largely European network. In addition to patient families, it also targets advocates and foundations, which serve patients. Blog topics often center on access to treatment, national/international policy, patient representation and rare disease conferences and campaigns.
www.rarediseaseblogs.net

RareConnect
RareConnect was envisioned by EURODIS (European Rare Disease Organization) and NORD (National Organization for Rare Disorders) to be a place where patients and family members affected by rare diseases can connect.
https://www.rareconnect.org/en

RareShare
This site connects members of the rare disease community. Rareshare is for patients, families and healthcare professionals. The site offers the ability to share information, update your rare disease community and find new resources.
http://rareshare.org

Treatment Diaries
Treatment Diaries primarily features testimonials of the families of patients. Its goal is to connect families with diseases.
www.treatmentdiaries.com

8D - Transportation Sites and Other Assistance

Your child's treatment or diagnosis may require that you travel. We know this may be difficult but there are services that may be able to help your family's travel needs. We recommend that you consult more than one service, and do so as soon as you know you are traveling to give your family more time and more options. Don't be discouraged if the first service you try does not work out, just call them with any questions.

Air Charity Network
4620 Haygood Road - Suite 1 Virginia Beach, VA 23455
Phone: 877-621-7177
E-mail: http://aircharitynetwork.org/contact-us
Website: http://aircharitynetwork.org
They setup flights on a geographic basis. Go to the website for more information based on your location.

National Patient Travel Center
4620 Haygood Rd, Ste. 1 Virginia Beach, VA 23455
Phone: 800-296-1217 or 757-512-5287
Email: info@nationalpatienttravelcenter.org
Website: http://www.patienttravel.org

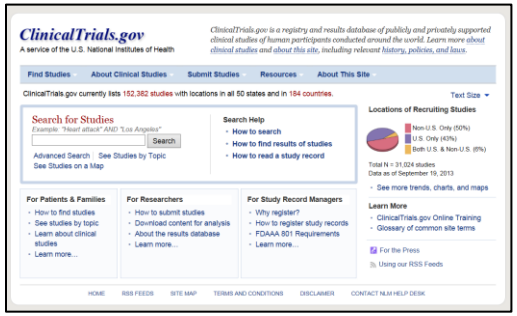
Aubrey Rose Hollenkemp Children's Trust Foundation
This service provides financial assistance for medical expenses for children diagnosed with serious illnesses. Families must demonstrate a financial need.
Aubrey Rose - 3862 Race Road Cincinnati, OH 45211
Phone: 1-513-265-5801
Website: http://www.aubreyrose.org
email: nancy@aubreyrose.org

Needy Meds (For Drug Assistance)
Needy Meds provides information about programs for people who are unable to afford medications and other costs.
P.O. Box 219 Gloucester, MA 01931
Phone: 800-503-6897
Website: http://www.needymeds.org

Medication Assistance
The Partnership for Prescription Assistance helps patients who qualify get prescription drug coverage. They connect with 475 public and private programs including about 200 offered by biopharmaceutical companies.
1-888-477-2669
https://www.pparx.org/en

8E - Clinical Trials and Research Sites

These sites provide information about clinical trials. Please consult your doctors or medical advisors for information.

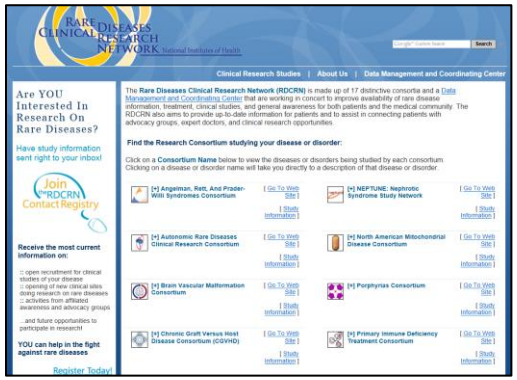


Clinical Trials.gov

This site gives information on specific diseases and clinical trials involving those diseases. All US studies receiving government funding and most private industry studies are on this government site.
http://www.clinicaltrials.gov

The National Institutes of Health (NIH)

This site provides background information about clinical trials and links to other sites. They are located in Bethesda, MD, at the NIH Patient Recruitment Office.
http://nih.gov/health/clinicaltrials/findingatrial.htm
Toll free: (800) 411-1222
Email: prpl@cc.nih.gov



Rare Diseases Clinical Research Network

This site provides information for patients about specific rare diseases and connects patients with advocacy groups, expert doctors, and clinical research opportunities.
http://rarediseasesnetwork.epi.usf.edu

Centerwatch

This site provides information about clinical trials for patients and clinical researchers. For information about clinical trials sponsored by private sources, contact:
http://www.centerwatch.com

8F - Advocacy Groups and Patient Information Sites

Global Genes Project
Global Genes Project is a rare and genetic disease patient advocacy organization. The non-profit organization is led by TEAM Rare and promotes the needs of the rare and genetic disease community under a unifying symbol of hope – the Blue Denim Genes Ribbon.
http://globalgenes.org

Genetic Alliance
This organization provides information and resources concerning genetic disorders, as well as connections to a network of others dealing with the same issues.
http://www.geneticalliance.org

NORD - National Organization for Rare Diseases Patient Information Center
The Patient Information Center at NORD is comprised of specialists who serve to answer your questions about resources, networks, clinical trials, etc. It includes a board of nurses, genetic counselors, physicians, and a rare disease database.
www.rarediseases.org/patients-and-families/patient-info

Every Life Foundation
http://www.everylifefoundation.org
The Every Life Foundation for Rare Diseases is dedicated to accelerating biotech innovation for rare disease treatments through science-driven public policy.

INOD - In Need of Diagnosis
This organization, "Advocates for increased accuracy and timeliness of diagnoses and is a resource center for those who suffer with illnesses that have eluded diagnoses."
http://www.inod.org/home0.aspx

The Myelin Project
A non-profit established by Augusto and Michaela Odone to accelerate research on myelin repair. Their son, Lorenzo, was afflicted with adrenoleukodystrophy, ALD.
http://www.myelin.org

SWAN-USA (Syndromes Without A Name)
SWAN is a nonprofit established to advocate for children and young adults who have syndromes without a name. SWAN provides advice, support and information to inform and educate the medical community, schools, social services and the public on the needs of these children.
http://www.undiagnosed-usa.org/about-us.htm

8G - Genomics and Public Policy Sites

National Human Genome Research Institute- Issues in Genomics
The National Institutes of Health provides policy, legal and ethical issues in genetic research, such as coverage and reimbursement of genetic tests or informed consent.
http://www.genome.gov/Issues

Genetic Alliance
Genetic Alliance details their participation in health reform, particularly regarding relevant genetic issues.
http://www.geneticalliance.org/policy.issues

Genetics and Public Policy Center
This site is devoted specifically to delivering up-to-date information on public policy in genetics. One can find daily updates on research and policy reform, along with publications.
http://www.dnapolicy.org

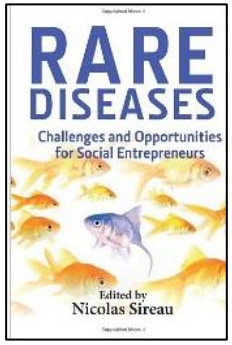
Have any ideas or comments for the ebook?
Email us at ebook@raregenomics.org.

8H - Books and Magazines

There are very few up-to-date rare disease books and almost none for families. However, many books on genomics are generally available.

Patient-Friendly Books

Rare Diseases: Challenges and Opportunities for Social Entrepreneurs by Nicolas Sireau (2013)



Exploring Personal Genomics by Joel T. Dudley and Konrad J. Karczewski (2013)

Rewriting Our Understanding of Genetics, Disease, and Inheritance by Nessa Carey (2012)

Genetics: From Genes to Genomes by Leland Hartwell, Leroy Hood, Michael Goldberg and Ann Reynolds (2010)

The Immortal Life of Henrietta Lacks by Rebecca Skloot (2011)

Genetics for Dummies by Tara Rodden Robinson (2010)

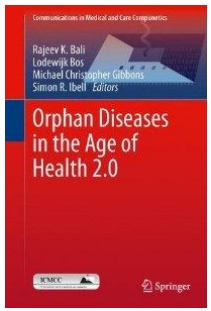
The Forever Fix: Gene Therapy and the Boy Who Saved It by Ricki Lewis (2013)

The Cure: How a Father Raised $100 Million- And Bucked the Medical Establishment – In a Quest to Save his Children, by Geeta Anand (2009)

Neuromyelitis Optica NMO –What You Need to Know, A guide for patients, their families and caregivers by the Guthy-Jackson Charitable Foundation (2013)

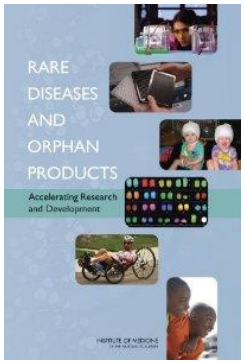
More Technical Books

Rare Diseases in the Age of Health 2.0
(Communications in Medical and Care Compunetics) by Rajeev K. Bali, Lodewijk Bos, Michael Christopher Gibbons and Simon Ibell (2013)



A Guide to Human Gene Therapy by Roland W. Herzog and Sergei Zolotukhin (2010)

Rare Diseases and Orphan Products: Accelerating Research and Development by Committee on Accelerating Rare Diseases Research and Orphan Product Development, Board on Health Sciences Policy, Institute of Medicine and Marilyn J. Field (2011)



Next Generation Sequencing: Translation to Clinical Diagnostics by Lee-Jun C. Wong (2013)
A Guide to Human Gene Therapy by Roland W. Herzog and Sergei Zolotukhin (2010)

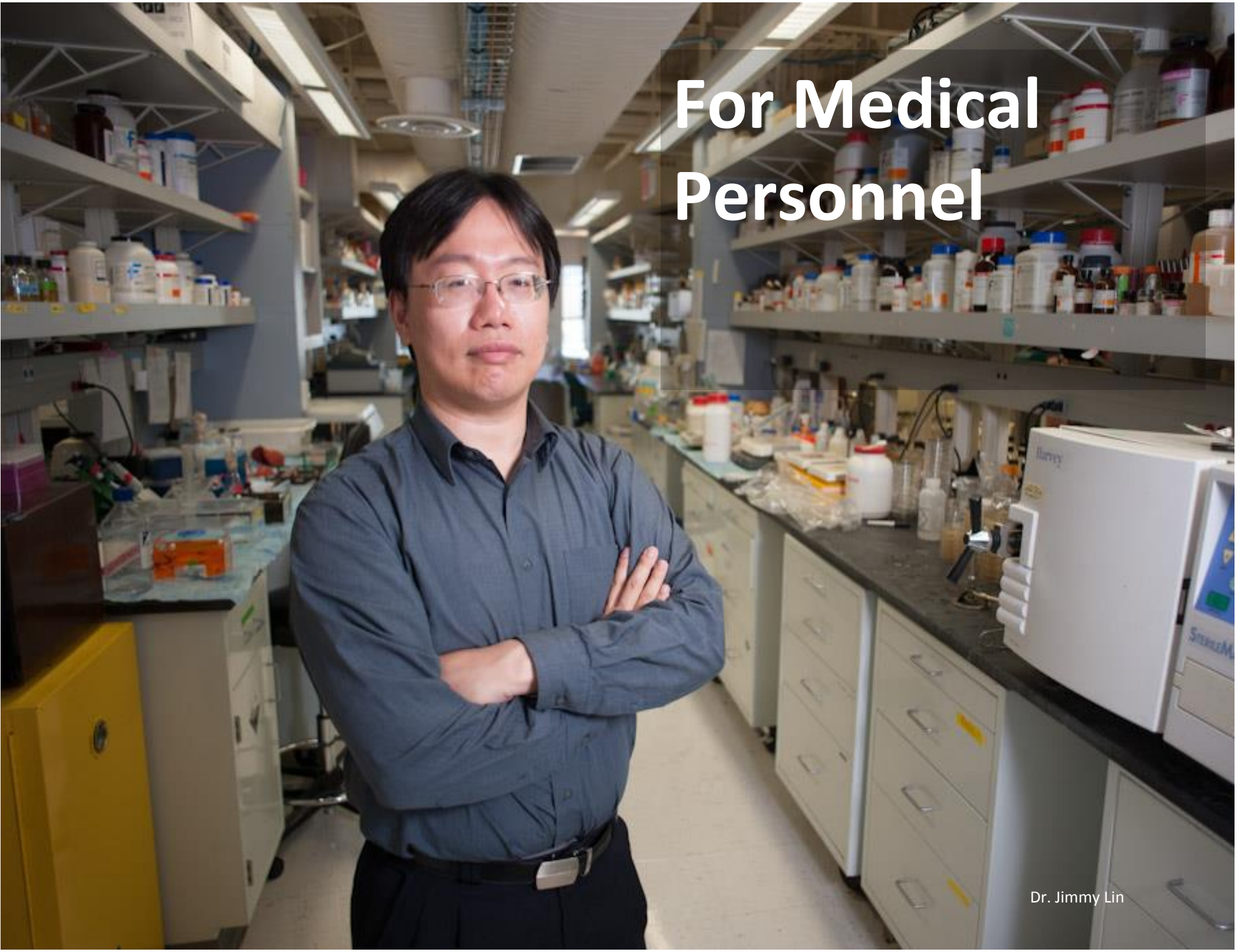
Orphanet Journal of Rare Diseases
(Online journal) http://www.ojrd.com/

New Scientist Magazine
http://www.newscientist.com/search?doSearch=true&query=rare+diseases

The Scientist Magazine
http://www.the-scientist.com/?articles.list/tagNo/116/tags/rare-diseases

Genome Web
http://www.genomeweb.com/

Have any sites we should add or ideas for the ebook?
Email us at ebook@raregenomics.org.


For Medical Personnel
Dr. Jimmy Lin

9. Information For Medical Personnel

We would like to thank our many current and future medical partners for trusting us with the care of your patients and their families. We greatly value our relationship and partnership with our referring physicians, and realize the important role you have in helping RGI continue to work toward diagnoses and advancement of treatment for rare diseases in children. We are committed to utilizing our expert team of over 50 top researchers and clinicians, advanced technology in exome and genome sequencing and interpretation to provide acceleration in discovery of cures and critical access to patients suffering from rare diseases.

RGI's breakthroughs in medicine have led to partnerships with eighteen major genomics sites in the most prestigious academic institutions in the country. Some of these sites include Harvard, Yale, Columbia, Stanford, Washington University, Emory, and Duke. RGI is leading the way by establishing an extensive international collaboration of researchers worldwide. RGI has many international sites in a growing list that includes RGI-Singapore, RGI-Malaysia, RGI-Israel, RGI-India (partnered with ORDI), RGI-Canada, RGI-Australia, and RGI-Spain. Additionally, RGI has patients and research projects in fourteen different countries around the world.

"This model, enabled by advances in technology, hits all the right buttons for changing healthcare – patient-centric, innovative, collaborative and economical."

- Forbes Magazine

"Still, every time a person's genome is sequenced and studied, it adds depth of medical knowledge, improving the chances that a course of treatment -- or even a cure -- might eventually be found. For the families, genomics allows them to access the most advanced scientific knowledge about their children's conditions," says Dr. Jimmy Lin, President of Rare Genomics Institute.

RGI has gained worldwide recognition for its advances and innovation in genomic sequencing and crowdfunding for research projects. Forbes magazine describes RGI's approach to rare diseases, "this model, enabled by advances in technology, hits all the right buttons for changing healthcare – patient-centric, innovative, collaborative and economical." With the dramatic decrease in price of one million fold for exome sequencing, this diagnostic tool provides comprehensive information to

solve the medical mystery of diagnosis, not otherwise possible in many rare disease cases.

RGI is a non-profit organization that brings together scientists who share our passion for helping rare disease patients. Similar to Kickstarter, but for our rare disease patients, we leverage the crowdfunding capabilities of the web to bring the hope of progress towards a cure to our patients, offering a platform to raise money for families to pay for sequencing. When a diagnosis is made, patients will be on a better course for treatment.

For parents of children with rare diseases that have been on a diagnostic odyssey for years, this finally gives them the answer that they have been looking for. With this answer, parents can then "optimize their child's therapeutic options so they have the best outcome," says Dr. Ada Hamosh, Clinical Director, Institute of Genetic Medicine, at Johns Hopkins, and Scientific Director of OMIM. Parents then know what they are dealing with and can pursue the best therapies available for their child. Diagnosis helps them realize that it's not their fault, "they are not responsible" for their child's illness says Dr. Hamosh.

RGI's team of clinical geneticists can provide an accurate expert diagnosis in a very cost effective manner. In addition to the exome sequencing expertise, geneticists have clinical experience with specialized cases and unique presentation of symptoms that many physicians do not have or have never seen. A geneticist can see what organ systems are involved. In the clinical exam, they look at every area with a genetic lens, the brain, the heart, the kidneys, skeletal system, the eyes, and hearing.

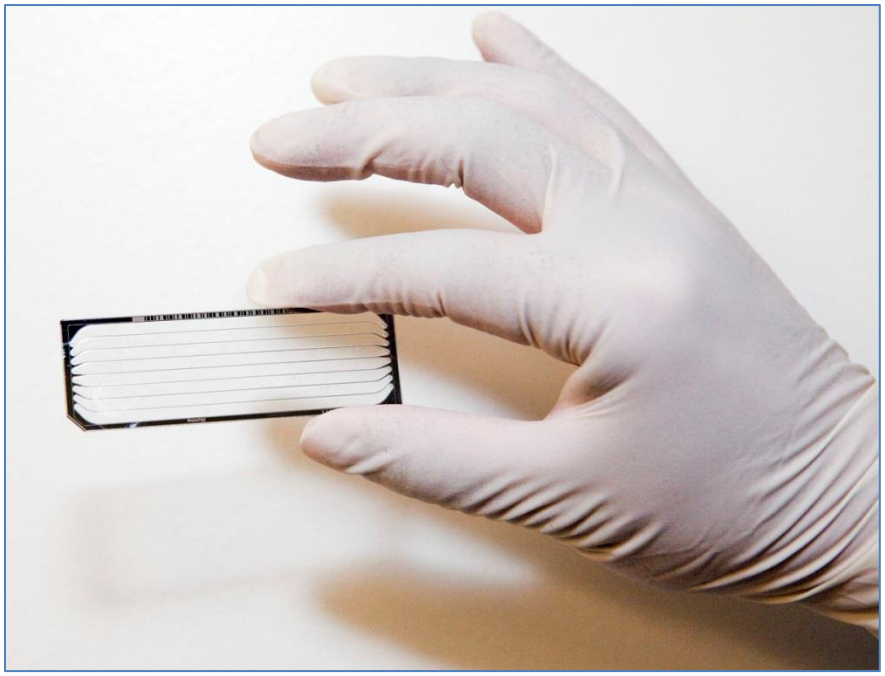
Through the exam, clinical geneticists can utilize their experience and extensive training to detect problems and determine the best course of action in testing and treatment. With the field of genetics constantly changing and the history of medical school education on genetics being limited, pediatricians suspecting a genetic underlying disorder in children can connect families to RGI to receive the best available diagnostic treatment and expert analysis.

This means financial cost savings and emotional cost savings. Families with undiagnosed rare disease children have many financial burdens. Many families take jobs and stay in jobs for years for the sole basis of better insurance for their sick child. However, the financial cost savings for many struggling undiagnosed rare disease families is secondary to the emotional savings in time and stress. Often it is years of suffering with the burden of trying to do what is best for their child when specialist after specialist sees something wrong but does not have a diagnosis. This leaves the family members with frustration and devastation when another test result comes up negative or inconclusive, as they are attempting to do everything possible to help their child.

"The first few years, you feel like you won the lottery when you get negative test results saying it's not some life threatening disease. But after over a decade of tests, you become devastated when another test comes up negative or unknown."

- Rare disease parent Jeneva Stone

The Stone family lived over a decade with their son, Robert, being undiagnosed. Through RGI and exome testing, he was finally diagnosed with the genetic disease Dystonia 16. Robert is one of only nine known medical cases throughout the world. With the only other cases in Brazil and one in Germany, this would never have been diagnosed without exome sequencing. As Jeneva Stone, Robert's mother describes, "the first few years, you feel like you won the lottery when you get negative test results saying it's not some life threatening disease. But after over a decade of tests, you become devastated when another test comes up negative or unknown."



DNA flow cells are used for high quantity genome sequencing.

"An early diagnosis stops the diagnostic odyssey. It's powerful."

- Dr. Ada Hamosh, Clinical Director, Institute of Genetic Medicine, Johns Hopkins

Now a streamlined solution is possible to end the years of unknown in many cases. Parents can look to others with the illness and see what to expect. They can plan and move forward with their lives with a sense of peace that they did not give up on their child. They did everything possible to find out what was wrong. RGI's use of whole exome and genome sequencing, along with the medical team to analyze and interpret the results coupled with crowdfunding capabilities to help with the sequencing costs provides medical expertise to the patients and families that need it.

The technology has made enormous improvements for geneticists to diagnose rare diseases. With about 1,500 geneticists across the United States, RGI has partnered with scientists from top medical institutions.

We have had major media coverage including 130 top newspapers, journals and television programs such as Forbes, CNN, and Nature, for RGI's innovative approach and impact on rare diseases. We are committed to our patients and families to use our skills, knowledge and training to give them the answers they need so they can take the best possible care of their child. We look forward to helping you and partnering with you.

For medical personnel only please contact us at doctors@raregenomics.org.

Dr. Andy White - RGI Expert Diagnostician

The Importance of Finding Out What's in Your Child's DNA

RGI expert Dr. Andy White of Washington University has a long waiting list of patients. As a pediatrician who works in an innovative diagnostic center, one of only a handful of its kind in the entire United States, Dr. White sees patients that no one else has been able to diagnose. By the time they find out about Dr. White, many families have spent years looking for answers.

He is a real life version of the hit TV show character Dr. House, the doctor that sees the most puzzling medical cases, in *House.* Dr. White explains, "RGI and genomics give us a skill we just don't have. RGI's sequencing technology substantially increases our ability to make a diagnosis."

When seeing the toughest pediatric cases, he says, "Sometimes families come in with file boxes from 98 other doctors over the course of years. It takes weeks to go through the boxes." He explains, "Most pediatricians see healthy children or children with common illnesses like colds, and strep throat. Out of a typical doctor's office of 2,000-3,000 patients, they may see one unique case. I see these cases every day. Experts who study this have vastly more rare disease experience. This gives us deeper insights in clinical exams. We notice subtle behavior or actions. These are right on our radar," he said.

Dr. White explains exome sequencing as basically looking at a map of the US at night. The big cities are easy; they light up well at night. These are like common diseases. We know these areas. The rural areas are the dark areas; they don't light up well at night. These are the rare diseases, and exome sequencing is needed to detect these diseases.

"RGI sequencing gives us a better diagnostic tool to understand the entire problem, not just through clinical exam, or looking at previous abnormal lab studies and test results. Exome sequencing brings a whole new facet to our ability to make a diagnosis. It's important to find out what the child's DNA is. We can find out if it's what we expected or not. Patterns can evolve where we can tie physical complaints with genes," he said.

"RGI and genomics give us a skill we just don't have."

- Dr. Andy White

When asked how he describes exome sequencing to his patients and families, Dr. White says, "I draw on the white paper on the exam table. I go back to their high school biology lesson and write ATCG on the paper in big letters. Then I tell them that exome sequencing tells us if in their child this T should be a G. If that's the case then this is where the mistake is that's causing all the problems. This makes sense to most people."

Takeaways:

1. Rare disease clinicians routinely see the toughest cases that many physicians only read about in medical textbooks during medical school. They have more expertise in diagnosing rare diseases. There are several dozen of these diagnostician centers across the country that look at the rarest diseases.

2. Gene sequencing from RGI gives him the best diagnostic tool available to understand the entire problem, not just through a clinical exam, or looking at previous abnormal lab studies and test results.

3. It's important to find out what the child's DNA is. This will always be valuable information, and parents can find out if it's what is expected or not. Patterns can evolve where you can tie physical complaints with genes. We may not fully understand everything today, but we are learning more about genes every day. New technologies and other approcahes are constantly being developed.

RGI Team

10. The World-Class RGI Research Team

Dr. Jimmy Cheng-Ho Lin, MD, PhD, MHS

Founder and President of Rare Genomics Institute

Dr. Jimmy Cheng-Ho Lin is the Founder and President of the Rare Genomics Institute, an organization that developed an innovative approach to accelerate research and find cures for rare genetic diseases. Dr. Lin was the lead computational biologist for the groundbreaking cancer genome sequencing efforts at Johns Hopkins. Their sequencing of the first 100+ cancer exomes in five different tissue types has helped lay the foundation for a revolution in cancer genomics. After completing his MD/PhD at Johns Hopkins, along with colleagues at Harvard and Yale, Dr. Lin started Rare Genomics Institute, a non-profit biotech venture that crowdfunds genome sequencing for children with rare and orphan diseases.

Dr. Lin has over 14 years of experience working with integrating complex data structures, analysis and infrastructure creation. At Yale, he developed one of the first ever online comparative genomics resources. In addition, he made significant contributions to create a structural genomics database. At Johns Hopkins, Dr. Lin led the computation biology and infrastructure for the first ever genome-wide sequencing of any disease. He utilized this experience to create a patient-centered platform for patient communities to design, conduct, and raise funding for genomics studies.

Dr. Lin received his Bachelor of Science from Yale in Cognitive Science, and Molecular Biochemistry and Biophysics. He received his Master of Health Science in Bioinformatics from Johns Hopkins School of Public Health. His PhD was in Cellular and Molecular Medicine from Johns Hopkins. Dr. Lin also earned his MD from Johns Hopkins School of Medicine.

Partnering with industry leaders and academia, RGI continues to build a patient empowered research network for rare diseases, encompassing all 7,000 different known rare diseases. His team of over 50 top scientists from all over the world is actively working to help patients with rare diseases find diagnoses, therapies and cures.

Dr. Lin was most recently a faculty member in the Pathology Department of Washington University in St. Louis, where he worked to develop a clinical genomics workflow for cancer and rare diseases as part of the Department of Genomics and Pathology. He has been published in over 56 peer-reviewed articles. Some of his work has appeared in journals such as Science, Nature, Nature Biotechnology, Nature Genetics, Cell, and the Proceedings of the National Academy of Sciences of the United States of America (PNAS).

Our World-Class Research Partners

RGI Researchers and Scientists Are Among the Best in the World

Rare Genomics Institute partners with the some of the world's top medical and research institutions. Harvard University, Washington University in St. Louis, Johns Hopkins, Columbia University Medical Center, Stanford School of Medicine, and the National Cancer Institute are a few of the prestigious partners. RGI has worked and connected with many of the best and brightest scientists to join our mission. Such access gives us a great opportunity to help our rare disease families and their children.

Harvard Medical School has agreements with 17 research and clinical affiliates and over 10,000 physicians and scientists with an extensive network and synergistic approach to solving complex problems. Internationally known, Harvard's accomplishments are many, including 15 researchers contributing to nine Nobel prizes. Harvard's Personal Genome Project began with the goal of sequencing complete genomes of 100,000 participants and publicizing the results. Their mission is to understand and study genetic and environmental factors in health.

As one of three National Institute of Health (NIH) funded sequencing centers in the United States for the human genome project, Washington University is a leader in genomics. The School of Medicine has made strong contributions in both discovery and human health throughout the world. They are one of the leading medical research, teaching and patient care institutions in the nation, and currently ranked sixth in the nation by US News & World Report.

Johns Hopkins Medicine is home to the McKusick-Nathans Institute of Genetic Medicine that specializes in heredity and genetic medicine to treat diseases. Johns Hopkins has been ranked as a top medical school in the US News & World Report's annual rankings for 21 years in a row. Of the 4,800 US hospitals, Johns Hopkins placed first in 5 medical specialties and has top rankings in 11 more.

Columbia University Medical Center has The Center for Human Genetics with experts in research in diagnosis and genomics. Columbia is a world leader in research, health, medical education and patient care.

Stanford Medicine has been a top-ranked medical institution in the U.S. and around the world for adult and pediatric patient care. Stanford Hospital and Lucile Packard Children's Hospital's discoveries and focused real life applications have dramatically improved diagnostic, treatment and prevention. Both hospitals consistently rank among the best.

The National Cancer Institute is dedicated to cancer research. As part of the National Institute of Health, the National Cancer Institute strategically focuses on cancer prevention, detection, diagnosis, treatment, control, palliative care, and survivorship. Rare Genomics Institute and Oncogenomics in the Pediatric Oncology Branch work together to provide genomic analysis for pediatric oncology patients.

Our Many Other Researcher Partners

We have over a dozen other research partners.

Yale University has world–renowned biomedical research expertise. Yale researchers have identified more than 40 human disease genes involved in heart attacks, hypertension, osteoporosis, stroke and rare diseases. The Yale Center for Mendelian Genomics is one of the world's leading centers for human genetics.

Emory University's Department of Human Genetics (DOHG) has 41 full-time faculty members with funding of over $15 million per year. The Division of Medical Genetics has three large clinical laboratories that give patients cytogenic, biochemical and molecular diagnostics. The division of medical genetics has clinics and inpatient consultations in several Atlantic hospitals. DOGH combines research and comprehensive clinical genetics capabilities.

The University of California at Berkeley has over 350 academic programs and a faculty of 22 Nobel laureates, and is one of the preeminent universities in the world.

The University of Maryland is home to the Institute for Genome Sciences (IGS). IGS has become a center of excellence for the application of genomics to medicine. IGS's research and collaborations have helped develop a new understanding of infectious diseases, bioinformatics, environmental science and microorganisms relating to health and disease.

The University of Washington School of Medicine (UWSM) has been ranked as the number one primary care medical school in the country since 1994. UWSM researchers are international leaders in genome sciences – contributing to next generation DNA sequencing technology and spearheading the identification of candidate genes in rare diseases, like Miller and Kabuki Syndromes.

The University of California Los Angeles (UCLA) Health System is known for outstanding, comprehensive medical care throughout the world. UCLA Health System includes Ronald Reagan UCLA Medical Center, UCLA Medical Center, Santa Monica, Resnick Neuropsychiatric Hospital at UCLA, Mattel Children's Hospital, and the UCLA Medical Health Group.

The Institute for Genomic Medicine (IGM) is a 501c3 non-profit affiliated with the Utah Foundation for Biomedical Research. The organization's missions are to implement an infrastructure for clinical genomic sequencing and interpretation, to build public trust in genomic medicine, and to urge insurance companies to reimburse genome sequencing in clinical settings.

The University of California in San Francisco (UCSF) is consistently ranked as one of the nation's top hospitals by the U.S. News and World Report rankings. UCSF Medical Center is known throughout the world for innovative patient care, advanced technology and pioneering research.

RGI also partners with the Barrow Neurological Institute and Dr. Vinodh Narayanan of Arizona Pediatric Neurology and Neurogenetics Associates to collaborate on novel approaches to providing comprehensive evaluation and care to children suffering from neurological disorders. The Barrow Neurological Institute is an internationally recognized neurological center. Complete Genomics provides outsourced analysis and data management software to enable large-scale disease projects.

Advisory Boards

Science Advisors

Rare Genomics Institute has 26 world-renowned scientists and leaders on our science advisory board. Our advisors work at Harvard, Columbia, Johns Hopkins, Cornell, Yale, Stanford, the National Institute of Health and other top medical institutions in the United States and around the world. They are experts in their respective fields, and are dedicated to improving the lives of our patients, using the latest technological advances in science to accelerate advances, discoveries and cures for rare diseases. We are proud to have them on our team.

Dan MacArthur, PhD

Research Leader in Genetics

Dr. MacArthur is a group leader at the Analytic and Translational Genetics Unit at Massachusetts General Hospital, an assistant professor at Harvard Medical School, and a research affiliate at the Broad Institute of Harvard and MIT. His research focuses on understanding the functional impact of genetic variation using genome sequencing data. He completed his PhD at the Institute for Neuromuscular Research Institute in Sydney, Australia.

Wendy Chung, MD, PhD

Clinical and Molecular Geneticist

Dr. Chung is a clinical and molecular geneticist who directs the clinical genetic program at Columbia University. She was a recipient of the American Academy of Pediatrics Young Investigator Award and is the Herbert Irving assistant professor of pediatrics and medicine. Dr. Chung received her MD from Cornell University Medical College and her PhD from The Rockefeller University in genetics.

Gholson Lyon, MD, PhD

Assistant Professor in Human Genetics and Research Scientist

Dr. Lyon is an assistant professor in human genetics at Cold Spring Harbor Laboratory and a research scientist at the Utah Foundation for Biomedical Research. He is also board-certified in child, adolescent and adult psychiatry. He earned an MPhil in Genetics at the University of Cambridge, England, and then received a PhD and MD in the combined Cornell/Sloan-Kettering/Rockefeller University training program. His research focuses on the genetics of neuropsychiatric illnesses and on rare Mendelian diseases and the development of clinical-grade exome and whole genome sequencing.

Jay Shendure, MD, PhD

Assistant Professor in Genome Sciences

Dr. Shendure is an Assistant Professor in the Department of Genome Sciences at the University of Washington. With collaborators at UW, his group was the first to demonstrate that the massively parallel sequencing of the 1% of the human genome that is protein coding, known as the "exome," could be used to cost-effectively identify genetic mutations causing human disease. He received a bachelor's degree from Princeton University and received his PhD and MD from Harvard Medical School.

Business Advisors

Our business advisors are successful entrepreneurs and investors, top industry consultants and major business leaders. Some of our advisors have children with rare diseases and know firsthand the struggles families face.

Rob Wolcott

Executive Director, Kellogg Innovation Network

Dr. Rob Wolcott is Executive Director of the Kellogg Innovation Network (KIN) and on the faculty of the Kellogg School of Management, Northwestern University. Dr. Wolcott teaches corporate innovation and entrepreneurship for Kellogg. His book *Grow From Within: Mastering Corporate Entrepreneurship and Innovation* and other work has appeared in *The Wall Street Journal, Business Week, The Financial Times* and *The New York Times.* Wolcott received an MS and PhD in Industrial Engineering and Management Science from Northwestern University.

Jim Golden

Partner and Chief Management Scientist, Accenture

Dr. Jim Golden is a Partner and Chief Management Scientist at Accenture. He leads The Global Pharmaceutical Analytics Practice and supports the Global Healthcare Data Analytics Group. Dr. Golden is a Major in the US Air Force Reserve. He has a BS in mathematics and computer science from Rhodes College; a MS in computer science from the University of Tennessee Space Institute; and a PhD in mechanical engineering from Vanderbilt University.

Joe Beery

CIO, Thermo Fisher Scientific

Joe Beery serves as the Chief Information Officer and Senior Vice President of Thermo Fisher Scientific. He previously served as the CIO and Senior Vice President of America West Holdings Corporation (US Airways Group, Inc. merged with AWHC), and CIO and Senior Vice President of US Airways. Mr. Beery holds a BS in Business Administration from the University of New Mexico. He is a parent of twins leading normal lives after genome sequencing revealed their rare disease.

Ken Harrington

Director of Entrepreneurship Center, Washington University Business School

Ken Harrington has spent over 25 years as a senior executive for seven start-up companies. Since 2001, he has led the $15 million campus-wide entrepreneurship expansion of Washington University's Skandalaris Center for Entrepreneurial Studies. He consults on entrepreneurship concepts, regional development thinking, university-industry partnerships, and innovation in large organizations. He earned an MBA from the University of Pennsylvania's Wharton School and a BS from the University of Vermont.

Mike Hettwer

Serial Entrepreneur

Mike Hettwer is a serial entrepreneur who has built six companies focused on marketing and the web. His last two agencies created 300 web sites and drove over $1.2B in revenue online for clients. He is an expert at driving large amounts of web traffic, search engine optimization, web conversion and online marketing. Mike is executive director of the non-profit TEDxMidwest which brings 40 world-class speakers to Chicago annually. He has photographed science stories on dinosaur and archeology expeditions for National Geographic and holds a B.S. in Electrical Engineering.

Patient Advocacy

RGI's patient advocates are dedicated to helping our patients throughout the process. After the application is filled out on the website, they will contact patients and answer questions. Our cohesive team guides our patients and families every step of the way.

Romina Ortiz

Vice President of Patient Advocacy

Ms. Ortiz builds resources and leads the efforts and care for our patients and their families throughout the process. She works in the Department of Clinical Immunology at Johns Hopkins and holds a MS in Molecular Microbiology and Immunology from Johns Hopkins. She received her BS in Neuroscience from Johns Hopkins.

Retta Beery

Advocacy Advisor

Speaker and patient advocate, Retta Beery is involved with various medical institutions and organizations to provide support and direction in the management and care of patients with rare diseases. After years of research, she discovered her twins had been misdiagnosed by some of the top specialists in the world. Her twins were genome sequenced, and a discovery was found leading to a treatment that saved their lives.

Austin Spurlock

Assistant Director of Patient Affairs / Patient Research

Mr. Spurlock focuses his research on improvement in communication and support for RGI families. He holds a BSBA in Human Resources and Organizational Behavior from Washington University in St. Louis.

Lindsey Cholewa

Education Coordinator

Ms. Cholewa's experiences with US EPA and major organizations span almost ten years and her skills range from analytical laboratory operations to managing revenue and sales functions as a business analyst. She creates and contributes to educational pieces for RGI focused on raising public awareness of medical research and rare diseases. She received an MBA from Webster University and a BS in Biology from the University of Alabama.

Amy Clugston

Advocacy Advisor

Parent of a child with physical and developmental challenges that evaded a diagnosis, Ms. Clugston founded Syndromes Without A Name (SWAN) in the US. She is a speaker and is dedicated to helping families, advocating and being a voice for those who are undiagnosed. She understands the families' medical journey firsthand and is dedicated to helping them throughout the RGI process.

RGI Management

Dr. Imran Babar

Vice President of Scientific Affairs

Dr. Babar is a Senior Associate on the Private Equity team at OrbiMed Advisors, the world's largest life science focused investment firm. Prior to joining OrbiMed, Imran was a biotechnology associate at Cowen & Company. Imran completed his PhD in Molecular Biology at Yale University in Dr. Frank Slack's laboratory, where he researched microRNAs as both causes and treatments for cancers. Prior to Yale, Imran completed his BA in Biology at Carleton College and conducted research at MIT and NIH.

Dr. Meisha Bynoe

Director of Operations

Dr. Bynoe received her PhD in Microbiology at Yale University, during which time she was a fellow of the Howard Hughes Medical Institute. Her thesis work involved the examination of how herpes viruses avoid the human immune response. She has also conducted research in various other fields at UCSF, MIT and Singapore's Institute of Bioengineering and Nanotechnology. Meisha holds undergraduate degrees in Biology and Music from MIT.

Dr. Johnathan Franca-Koh

Vice President of Business Affairs

Dr. Franca-Koh received his BSc and PhD in Cell and Molecular Biology from the University of London. He subsequently joined the laboratory of Peter Devreotes at Johns Hopkins University as a post-doctoral fellow to research cell migration and chemotaxis. He is currently a Staff Scientist at the J. Craig Venter Institute.

Dr. Marisa Dolled-Filhart

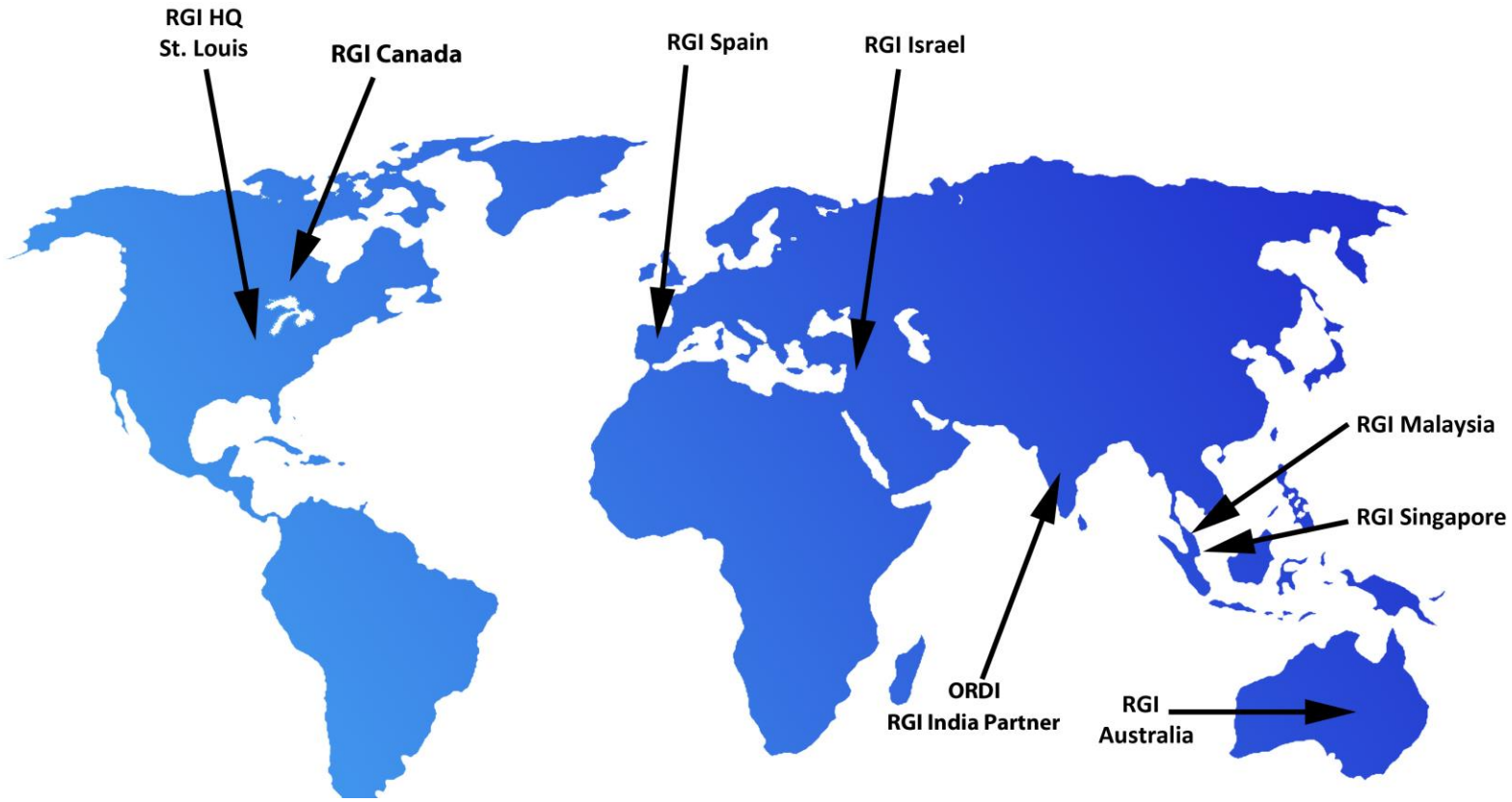
Vice President of Strategic Alliances

Dr. Dolled-Filhard received a BA in Biology from Cornell University, where she was a Coca Cola National Scholar. She completed her MPhil and PhD in Genetics at Yale University, where she was awarded a US Department of Defense Breast Cancer Research Fellowship. She has several years of operational and strategy experience from scientific and business development positions at HistoRx (a Yale biotech startup) and Quintiles.

RGI International Branches

RGI is a leader in the field of genomic sequencing, analysis and interpretation. "We are expanding our role throughout the world. We are bringing this technology to countries that do not have it," says Dr. Jimmy Lin, President of Rare Genomics Institute. "We know the potential and the need, and our mission is to improve the quality of life for our patients in every country. This is our biggest priority."

Our global expansion includes seven international sites. We have RGI-Israel, RGI-Singapore, RGI-Australia, RGI- Malaysia, RGI-Spain and RGI-Canada and RGI-India (partnered with ORDI). Our patients, researchers and projects span fourteen countries. Our partnerships with the best clinicians and researchers around the world will continue to make a bigger footprint on rare diseases. Our operations are growing, and our international expansion has further advanced our abilities to find cures. We are dedicated to building RGI International, and to sharing discoveries and best practices around the world. Our innovations in diagnosis and treatment can bring new answers and new options to rare diseases affecting the lives of millions of people.



RGI – Israel

RGI-Israel is the foremost genomic sequencing provider in Israel for genetic diseases. It supports local Israeli patients with rare genetic diseases of unknown origin. RGI-Israel works in close collaboration and under the guidance of RGI-USA. The combined teams leverage this collection of genomes together to improve current knowledge and tools to find the cause of genetic diseases.

RGI – Australia

RGI–Australia is building its team, recruiting top scientists and partnering with premier medical institutions in Australia. We are working with many of the best researchers in the field of genomics in Australia to enable them to conduct genomic sequencing to solve difficult rare disease cases.

RGI – Malaysia

RGI-Malaysia is the first genomic sequencing institute in the country. We are bringing our platform and recruiting top researchers to provide this valuable diagnostic tool to a country that does not have it. RGI-Malaysia will collaborate with all RGI international sites and RGI-USA to share best practices and advances in genomics.

RGI – Spain

RGI-Spain is in the process of developing its infrastructure. We are creating a leadership team to support the large population and need for genomic sequencing of rare diseases. They have established relationships with experts in their field of genomics to work in collaboration with RGI-USA and other international sites. RGI-Spain will provide high levels of genomic sequencing and interpretation analysis.

RGI – Singapore

RGI –Singapore is the first genomics site in Asia and works with the Genome Institute of Singapore in the National University Hospital. It has brought top doctors on board and established sequencing capacity and sequencing machines to provide researchers with the ability to analyze and interpret the results. This team has worked to successfully solve complex cases, not otherwise possible without genomic sequencing.

RGI-India (Partnered with ORDI)

RGI –India is part of the Organization of Rare Diseases in India. Working with some of the leading academic and commercial institutions in India, RGI-India is helping to bring not only technology but also a voice for the population of rare disease patients in India. The team is building the research infrastructure and expects to enroll the first patients in early 2014.


Results

11. RGI Results

Rare Genomics Institute was founded three years ago and in this short time has gained recognition around the world for its innovative approach to research, diagnosis and treatment of rare diseases. RGI's strategy and breakthroughs in medicine have led to partnerships with eighteen major genomics sites in the most prestigious academic institutions in the country.

Some of these top medical partners include Harvard, Yale, Columbia, Stanford, Washington University, Emory, Johns Hopkins, Duke, and UCLA. RGI is leading the way by establishing an extensive international collaboration of researchers worldwide. Our international sites include RGI-Singapore, RGI-India, RGI-Malaysia, RGI-Israel, RGI-Australia, and RGI-Spain. Additionally, we have patients and research projects in fourteen different countries including the UK, Chile, China, India, New Zealand, Ireland, Canada, Russia, Singapore, Israel, Australia and Spain.

Through its precision analysis and genomics expertise, RGI has already discovered eight gene mutations. RGI has provided answers, diagnoses, and treatment plans to families who have searched for years before finding RGI. Most rare diseases are genetic in nature. This breakthrough technology of genome sequencing has the power to help these patients in a way that conventional diagnostics cannot.

RGI's innovation extends to crowdfunding. We partner with families affected with rare diseases. We know many are under financial strain, making access to such technologies difficult. To address this need, we harness the power of the Internet to help families raise funds and pay for sequencing. Through RGI's crowdfunding platform, parents describe their medical journey online and family members, friends and strangers use the social connectivity of the internet to donate directly to fund these life changing research projects. Patients and families connect and have access to scientists who can help them.

"This (RGI) model, enabled by advances in technology, hits all the right buttons for changing healthcare – patient-centric, innovative, collaborative and economical."

- Forbes Magazine

"We hope we're able to democratize science and create a method to address these rare diseases from the bottom up," says Dr. Lin. "Our goal is to provide a platform where any patient community can fund any research of any disease." RGI 's initiative has led to national partnerships with the National Cancer Institute, the National Institute of Health, the Personal Genome Project, and the Utah Foundation for Biomedical Research.

RGI's innovative approach to medicine has led to major media coverage and it has been featured in the press over 130 times in journals,

newspapers and magazines such as Bloomberg, Forbes, the Wall Street Journal, and Huffington Post. “This model, enabled by advances in technology, hits all the right buttons for changing healthcare – patient-centric, innovative, collaborative and economical,” Forbes magazine.

RGI scientists and clinicians are committed to helping patients and to life changing advancements in medicine. RGI impacts four core areas. First, RGI scientists and clinicians custom design personalized research projects for each patient and rare disease. RGI supports researchers who have projects in genomics sequencing by providing knowledge, best practices, exomes, research activities and supplies. RGI provides access to grants and a crowdfunding platform to raise funds online. Finally, RGI is committed to teaching and educating the public about rare diseases. This helps patients and families understand the illness. “Combining all these elements, we create research projects that would not otherwise exist, tailored for each individual and each rare disease.”

“Ultimately, we want the voices of rare disease to be heard, while helping to accelerate the science behind a cure.”

- Kevin Lustig, CEO of Assay Depot, an RGI partner

RGI is dedicated to bridging the gap in funding rare diseases. RGI teamed up with 19 life science companies to launch a Rare Disease Research Competition. The event was a huge success and they donated over $500,000 worth of research services and prize money to help others advance the cause of looking for cures in rare diseases. "This competition brings the life science community together to study rare diseases in an unprecedented opportunity to empower afflicted families and under-funded researchers,” said Kevin Lustig, CEO of Assay Depot. "Ultimately, we want the voices of rare disease to be heard, while helping to accelerate the science behind a cure.”

RGI‘s genomic technologies allow clinicians and biomedical researchers to remarkably improve their diagnostic capabilities. Genomics provides critical insight into diseases both rare and common that affect millions of people in the US and around the world. The data obtained by genomic sequencing will allow clinicians to better understand diseases and target

therapies that are most effective to patients with those diseases. “We are learning more every day and understanding the genetic bases of drug response and disease,” Dr. Lin said.

RGI is committed to using its team of top scientists and clinicians to provide the most powerful insights into rare diseases and connections to change the future of diagnostic medicine. This ability enables patients to have access to the best therapeutic treatments for their illness. Patients and families no longer have to spend years on a diagnostic odyssey looking for answers and causes of illness. They can get diagnosed and then have top clinicians recommend the best course of treatment or cure for them.

RGI believes that research into rare diseases will unlock and discover treatments for rare diseases as well as common or chronic diseases.

Chemicals used to help diagnose your child’s DNA.

The future involves finding cures to mysterious illnesses affecting mostly children using biotechnology and expertise. To solve the problem of difficult access to data, we are creating databases and storage capabilities for specimens. RGI’s strategic platform organizes patient medical data in one place that is easily accessible to them. Our patients will have a unique identifier so they can be anonymous and private with their

information sharing it with only specific researchers, or they can make it public. Patients can be matched with others with the same condition to share research and treatments, enabling communities to form.

The network will enable patients to share information, providing hope and access to the latest developments in their rare diseases. This database allows researchers and scientists around the world to do any research for any disease, so together we can use the genomic information to analyze and help solve more rare diseases helping the over 300 million suffering from them.

Have any ideas or comments for the ebook?
Email us at ebook@raregenomics.org.

12. How to Help

Rare Genomics Institute is leading the way with innovative solutions for rare diseases. We connect rare disease patients with world-class scientists and offer a crowdfunding platform to help them raise money for genome sequencing. We are changing the way rare diseases are diagnosed. This change leads to faster results, correct diagnoses and effective treatment plans and cures. We need your help.

WE NEED YOUR HELP TO GIVE HOPE AND DIAGNOSIS

Providing resources to fund high performing researchers and cutting-edge technological advances in sequencing, leads to results for desperate patients and families along with pivotal outcomes. RGI's transformative role in rare disease discoveries translates into medical solutions for sick children. We have a diagnostic discovery tool that is fundamentally changing medicine. Donations to fund RGI's work will help us accelerate research to benefit all of our patients and discoveries that will potentially impact thousands of rare disease patients. What we learn from rare diseases can give insights into medical pathways affecting common diseases like cancer. We are making changes that can have global impacts on medicine and help suffering patients everywhere.

SPREAD THE WORD

RGI has a culture of action-oriented people. RGI has created a paradigm shift in medical treatment for rare diseases. We are striving to make changes and give hope, answers and cures dramatically changing the lives of millions of people. Volunteer your time and talents. We are proud of the work we do and hope you join us in this important cause. We are bridging the gap, giving rare disease patients access to world class experts doing cutting edge genomic sequencing, and crowdfunding to help families pay for it. Join us.

Our website offers opportunities to donate funds for children and RGI at http://www.raregenomics.org/donors.php.

There are other ways you can help us, and we can help you.

- To get the next free version of this rare diseases e-book, and future rare disease e-books, tools and videos, send your email address to: ebookupdates@raregenomics.org
- Send the ebook to other rare disease parents.

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13. Media Coverage

"World's first crowdfunded genome sequencing project uncovers a four year old's unknown genetic disease."

Life changing stories like this have catapulted RGI into the spotlight for driving change in medicine in the fight for cures with rare diseases. The Wall Street Journal, Time, CNN, Forbes, Nature, and many other top journals, newspapers, as well as television programs have featured RGI's medical innovations. Genomic sequencing technologies and a collaborative team of over 50 top scientists and clinicians, paired with an entrepreneurial crowdfunding model for sequencing costs, have helped fuel a medical movement in genomics. Rare disease is an area of medicine where few are experts - RGI is one of those few.

When one hears the words rare disease, many think only a small subset of the population is included in this group. Surprisingly, hundreds of millions of people around the world suffer from the 6,000-8,000 different rare diseases. We would like to see that change. Rare diseases have lacked research and funding, which has led to patients suffering without hope of a cure and on a seemingly endless quest from doctor to doctor to find an answer. RGI's initiative has led to partnerships around the world and to six international RGI sites including Australia, Singapore, Malaysia and Spain. We have patients and researchers in 14 different countries.

Here's what the major media is saying:

THE WALL STREET JOURNAL.
WSJ

Crowdfunded genetics leads to first crowdfunded gene discovery

"What's amazing is the small amount of money raised and the fact that this actually led to this discovery. It led to the first sequencing of this genetic disease."

Businessweek

Crowdfunded Searches for Medical Miracles

'"There are millions of kids wandering from place to place that no one is really helping," says Lin. And given the destructive power of these rare diseases, he believes some will yield major discoveries about the broader human genome. "It's the right moment in terms of where genomics is and where social media and online giving is," he says. "It's the first time in history that this is possible."'

http://www.businessweek.com/articles/2012-08-02/crowdfunded-searches-for-medical-miracles

Forbes

Holy Genetically-Engineered Organisms Batman - Synthetic Biology Has a Banner Month

'"Through RGI's network of academic institutions and crowdfunding, we hope to remove the barriers to technology access and funding to empower families like Maya's to advance research for their loved one's rare disease" founder Dr. Jimmy Lin said. But when these technologies are combined, as Singularity University synthetic biologist Andrew Hessel explains, things get downright revolutionary. "Right now, this work is being done by scientific leaders, but with these sorts of democratizing breakthroughs, it won't take much to create whole industries. An eco-system is developing. The pipeline of potential applications is going to be enormous."'

TED Names 2012 TED Fellows and TED Senior Fellows in Most Competitive Selection Process to Date

Dr. Jimmy Lin, President of RGI, was selected as a TED fellow. TED fellows are "Amazing cross-disciplinary innovators from around the world," said Tom Rielly, the director of the TED Fellows program. "TED chose Jimmy for his unorthodox approach to pushing past the walls of conventional healthcare funding and treatment to help desperate families."

A growing number of patients turn to crowd-funding sites to defray medical costs.

"The non-profit Rare Genomics Institute, for example, 'was created two years ago to help families raise money to sequence genes of patients with rare genetic diseases, a process that generally costs about $10,000 and is rarely covered by insurance."'

New DNA Techniques End Mystery of What Ails Baby Patrick

'"The human genome is a code for making all the body's cells and proteins. Sequencing all the relevant portion of a child's DNA costs about $2,500", said Lin. "That's a fraction of the bill for a day in the neonatal intensive care unit -- about $8,000. Everyone who has a child with an unexplained condition should have access to this," said Lin, who established the Rare Genomics Institute to help families pay for their children's sequencing when insurers won't.'

Decoding DNA for Rare Diseases

"Rare Genomics Institute matches sufferers with scientists in search for cures. RGI is inverting the top down nature of medical research by allowing patients to crowdfund their own research on the RGI website, and prime the pipeline for rare disease research."

The Promise in Unraveling The Mysteries Of Rare Diseases

http://www.npr.org/2013/06/10/190398619/the-promise-in-unraveling-the-mysteries-of-rare-diseases

Gene-Mapping For Newborns? 2-Day Test Can Spot Diseases In Babies

'"More than 20 percent of infant deaths are due to a birth defect or genetic diseases, the kind caused by a problem with a single gene. While there are thousands of such diseases – from Tay-Sachs to the lesser known Pompe disease, standard newborn screening tests detect only a few of them. And once a baby shows symptoms, fast diagnosis becomes crucial." Specialists not involved with the study said it signals the long-promised usefulness of gene-mapping to real-world medicine finally is close." Genomic sequencing like this is very practical and very real now," said Dr. Arthur Beaudet of the Baylor College of Medicine, "which also is working to expand genomic testing in children."'

Salon - Kickstarting a Cure

"One doctor is crowdfunding the hope of twenty-five million Americans who struggle from rare, debilitating diseases."

nature

Turning point: Jimmy Lin

“I want to give viewers a taste of the desperation that these people feel with nowhere else to turn. Then I want to make it clear that science can potentially help. I need to bring that connection to life. But connecting the public to science through a grass-roots funding mechanism is the big idea we want to propel” Dr. Jimmy Lin said.

Los Angeles Times

Counting on the generosity of the crowd

‘"The traditional funding model from the top down or from foundations is very hard to reach these patients," said Lin, 32, a native of Taiwan who has been studying in Baltimore the past 10 years. "There's a funding problem, and because of the funding problem, there's a lack of researchers studying these diseases. We not only help with the funding," added Lin, "we provide links to researchers and physicians."’

Bloomberg

Curing Cancer Relies on Genome Mapping With DNA Evidence Guiding Treatment

‘“This is going to be transformative to medicine,” said John Niederhuber, former director of the U.S. National Cancer Institute from 2005-2010, and now executive vice president of the Inova Health System hospital chain in northern Virginia. “It’s difficult to be undiagnosed. I worry that when she turns five and goes to school, I’m going to have to fight for services and therapies if I have nothing to write in the chart,” Nieder said.’ (speaking about RGI patient Maya)

THE HUFFINGTON POST

Finding a Home for Orphan Diseases

‘"How is sequencing the DNA of orphan diseases going to help those who are ill?" This was one of the first questions I asked Jimmy Lin when I spoke with him. He told me that there are researchers who want to work with the genomes of people who suffer from orphan diseases, but do not have the information necessary to do so. Both academic and clinical laboratories have shown interest in attempting to crack the codes of these ailments, but without the sequenced genomes being readily available, the research was always doomed before it began. Now, though, genome sequencing has reached a point where it is within reach of almost anyone who wishes to have it done.’

Forbes

Your Genome's on an iPhone (Trying to Call Home...)

“The Rare Genomics Institute acts as the project management office and organizers of this unique and virtual process. This model, enabled by advances in technology, hits all the right buttons for changing healthcare – patient-centric, innovative, collaborative and economical.”

SCIENTIFIC AMERICAN™

Rare Disease Science Challenge-–Your Call to Action!

‘“The Rare Genomics Institute provides hope to children suffering with a rare disease. Most rare diseases are genetic in nature, caused by a mutation somewhere in the 3.2 billion bases of human DNA. The Rare Genomics Institute uses crowdfunding to pay for sequencing of the sick child’s genome and then assembles a network of academic specialists who work together to identify the child’s genetic mutation.”’

Click for Table of Content

14. Appendix

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Please note that we have looked at many documents and websites as part of our research for this ebook. We hope we have correctly attributed all information. Please let us know about anything we should add.

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Acknowledgements

Thank you to the following people and organizations for their contributions to this book:

- Retta and Joe Beery, with Noah and Alexis Beery, for sharing their family's story and information for parents and families of children with rare diseases. A special thanks to Retta Beery for sharing her extensive network and deep knowledge as a patient advocate and speaker in genomics.
- Jeneva and Roger Stone, Amylynne and Sean Volker, Debbi and Scott Putjenter, Gay and Steve Grossman, Amy Clugston, Hugh Rienhoff, Zsuzsanna Darvai and their families for sharing their personal experiences and information for other parents.
- Victoria Jackson and Bill Guthy and the Guthy-Jackson Charitable Foundation for sharing their story and knowledge.
- Dr. Ada Hamosh of Johns Hopkins and Dr. Howard Jacob of the Medical College of Wisconsin for sharing their insights and expertise in genomics for patients, families and physicians.
- Dr. Matt Harms and Dr. Andy White for their contributions and information for parents.
- Panna Sharma of Cancer Genetics (CGIX) for his knowledge on cancer, genomics and the future.
- Peter Vander Horn and James Helmer of Life Technologies.
- Patti Chapman and Dr. Ian Duncan of the Myelin Project for their work and knowledge on myelin research, Lorenzo's Oil and adrenoleukodystrophy (ALD).
- John, Megan, Aileen and Patrick Crowley for sharing their amazing and courageous story – and for helping so many rare disease families.
- The RGI staff for their review and volunteers for contributions to this book.
- This e-book was written by Dr. Jimmy Lin and Ana Sanfilippo. Rare Genomics Institute (RGI) is responsible for all of the content. Book layout and design by Mike Hettwer and Mike Gorgo.

Photo Credits

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Founder and President of Rare Genomics Institute

Dr. Jimmy Cheng-Ho Lin is the Founder and President of the Rare Genomics Institute, an organization that developed an innovative approach to accelerate research and find cures for rare genetic diseases. Dr. Lin was the lead computational biologist for the groundbreaking cancer genome sequencing efforts at Johns Hopkins. Their sequencing of the first 100+ cancer exomes in five different tissue types has helped lay the foundation for a revolution in cancer genomics. After completing his MD/PhD at Johns Hopkins, along with colleagues at Harvard and Yale, Dr. Lin started Rare Genomics Institute, a non-profit biotech venture that crowdfunds genome sequencing for children with rare and orphan diseases.

Ana Sanfilippo

President of Linde Consultants

Ana Sanfilippo is founder of Linde Consultants, a healthcare consulting firm. Diagnosing Rare Diseases was written to help patients and families through the rare disease process by contributing to their understanding of genomics, sequencing and crowdfunding. The book was created from many interviews with patients, families, and leading experts. Their unique insights and important takeaways were developed into case studies, expert interviews and a Parent's Toolkit.

Ana has extensive experience in the pharmaceutical industry in sales, marketing and training. She advises organizations on strategy, customer engagement, commercialization, and product development with a deep understanding and focus on patient needs. Ana has a BS in Business Administration from The University of Illinois at Urbana-Champaign and an MBA with Distinction from Kellstadt Graduate School of Business at DePaul University with specialization in Health Sector Management and Change Management / Leadership.

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V3-002-031214