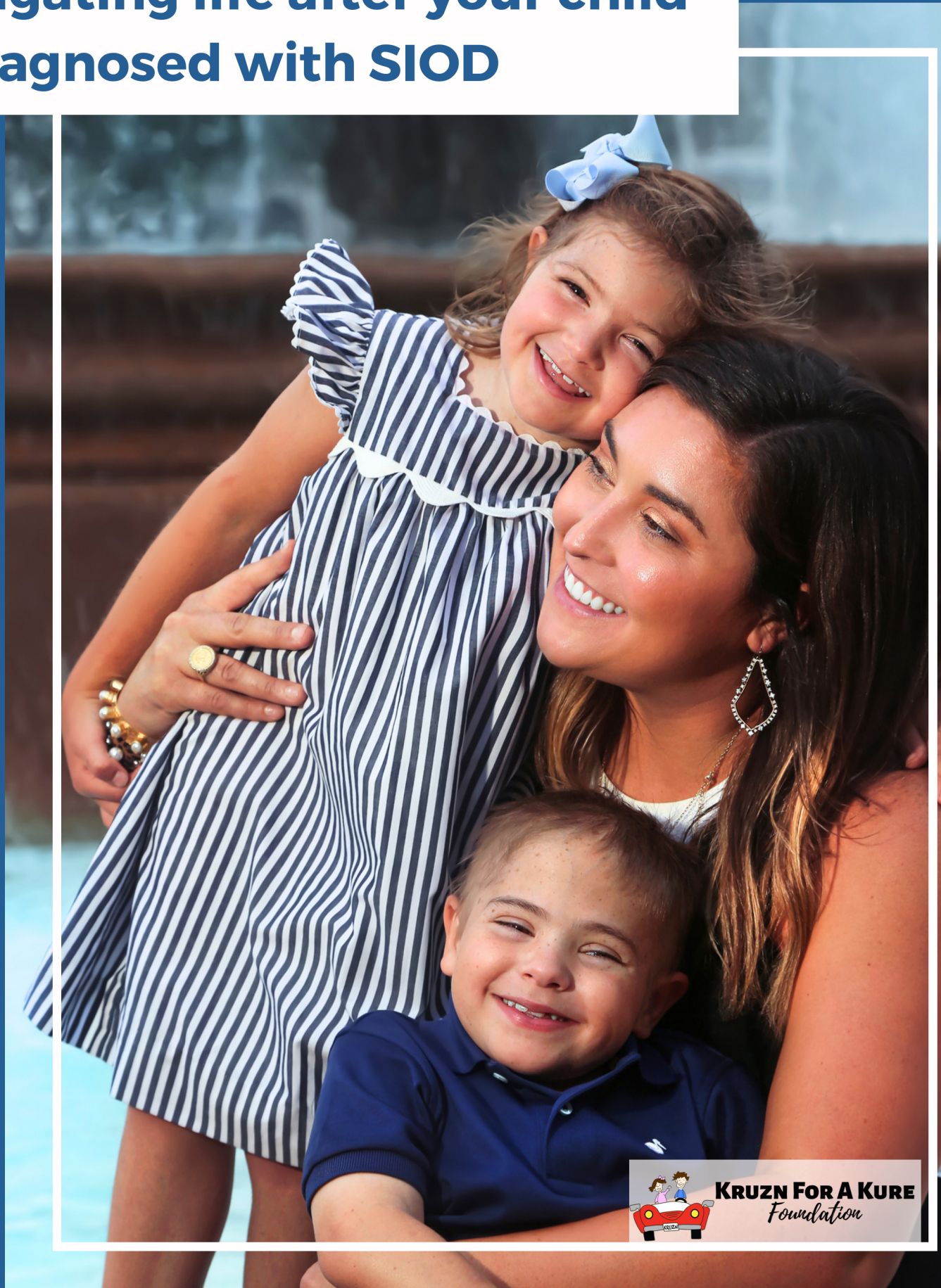
NEXT STEPS

Navigating life after your child is diagnosed with SIOD



KRUZN FOR A KURE
Foundation

We've walked in your shoes.

Kruzn For A Kure was founded by Jessica Davenport in 2016 after she received the diagnosis that both of her children had SIOD.

From the time he was nine months old, we spent two years and went through at least ten specialists to help us put together the puzzle. Later, we genetically tested our daughter out of precaution since it's a recessive mutation, even though she presented no clinical symptom at that time. On August 24th, 2016, we received a call explaining she also had SIOD. Our world turned upside down. Our children were the first siblings in the United States, making this a 1 in 80 million chance.

To know you could potentially lose both of your children by nine years old, it's an unbearable pain as a parent. You're mourning something that hasn't happened yet. Then on the flip side of that, you have this fire that just lit inside of you and are ready to take on the world to fight with everything you have to save them. And that's what we did.

In 2016, we started Kruzn For A Kure Foundation to raise funding for research. We started from scratch, finding a doctor to take this on since there wasn't anyone actively working at the time of our diagnosis in 2016. We wanted to honestly give hope again to SIOD families across the world and honor the ones who lost their child to this horrific disease.

Thankfully, a doctor at Stanford, Dr. Dave Lewis took on our research. (Dr. Lewis was referred to us by Dr. Boerkoel, who found the SMARCAL1 mutation in SIOD years prior.)

Kyle & I had to learn and live in a philanthropic and scientific world quickly. Our community rallied with us, alongside us, and lifted us on the hard days. Our story spread further and further in our local community and social media. We're blessed to live in such a giving small town in Muscle Shoals, AL. Since starting our nonprofit, we've raised over 3 million dollars, mainly by a lot of people doing a little bit. For the last seven years, we've sustained sending $30,000 monthly to keep salaries and supplies funded in Dr. Lewis' SIOD lab. All donations are primarily funded by individual donors within our community or social media.

We are in this TOGETHER!

As part of the SIOD family, we hope to provide you with resources and support through your journey.

Everyone deals with this diagnosis and its impact on their family differently. Whatever your process is, please know that you are not alone.

This guide is intended to help walk you through the initial questions most families have about SIOD, including what to do next.

We hope this information will help you find support and be proactive in caring for your child.

WHAT DOES A DIAGNOSIS OF SIOD MEAN FOR YOUR CHILD?

SIOD is a life-limiting, rare disease that affects multiple systems in the body, including the kidneys, growth plates and cartilage, heart and arteries, lungs, and immune system.

The average lifespan of children with this diagnosis is 9-11 years old.

Despite all of this, we are here to help you learn about treatments and strategies to help your child live as normal and healthy of a life as possible.

HOW IS SIOD DIAGNOSED?

The diagnosis of SIOD is made on clinical findings.

The most definitive diagnostic findings are skeletal dysplasia (spondyloepiphyseal dysplasia), renal dysfunction (urinary protein loss), T lymphocyte deficiency (particularly for naïve CD4 and CD8 T cells), dysmorphic facial features, and hyperpigmented macules.

Anthropometry can help to distinguish SIOD from other forms of chronic kidney disease: a sitting height: leg length ratio of < 0.83 is consistent with a diagnosis of SIOD whereas a ratio of > 1.01 is indicative of non-SIOD chronic kidney disease.

DNA testing for mutations in the SMARCAL1 gene is available to confirm the diagnosis.

HOW DOES SIOD AFFECT MY CHILD'S BODY?

Children with SIOD typically do not respond to treatment with steroids for kidney disease, which can result in kidney failure. Nearly half of children with SIOD will have vascular disease that can result in a stroke or recurrent migraine headaches. Older children and young adults with SIOD may also experience congestive heart failure and lung disease. There is also an increased risk of developing cancers, such as those of the blood system.

CARDIOVASCULAR SYSTEM

Half of SIOD individuals develop clinical signs of atherosclerosis. The onset is often in early childhood and relentlessly progressive. The disease is not abrogated by renal or bone marrow transplantation nor by cholesterol lowering agents, although the cholesterol lowering agents and renal transplantation can slow the progression by mitigating factors such as high blood pressure and high blood lipid and cholesterol levels. Consistent with the atherosclerosis resulting from an intrinsic defect of SIOD tissue, the vascular disease does not recur in the transplanted kidneys. Besides atherosclerosis, splitting and fraying of the arterial internal elastic layer and thickening of the muscular layer of the arterial walls have been found on autopsy. The latter finding may be a complication of high blood pressure or an intrinsic defect in the blood vessels. A few patients have also developed subaortic stenosis, one patient showed severe bicuspid aortic stenosis and one patient had extensive fatty infiltration resembling that of arrhythmogenic right ventricular cardiomyopathy.

ENDOCRINE SYSTEM

Approximately 42% of individuals with SIOD have reduced thyroid function. However, to date, the poor thyroid function has not caused clinical symptoms (subclinical hypothyroidism). Among those who have received thyroid hormone supplementation, the correction of thyroid hormone levels does not mitigate other symptoms of SIOD.

RENAL SYSTEM

All reported affected individuals have eventually developed renal dysfunction. The kidney disease is characterized by progressively worsening loss of protein in the urine and ultimately concludes with renal failure. The progressive renal disease is not responsive to immunosuppressant therapy. The diagnosis of renal dysfunction is usually made concurrent with or within the five years following the diagnosis of the growth failure. Renal failure requiring dialysis or kidney transplantation usually develops within the subsequent 11 years, although the rate of progression varies greatly. Because renal disease causes high blood pressure and high levels of blood cholesterol and lipids, the theory is that it accentuates the vascular disease of SIOD; however, renal transplantation does not prevent progression of the atherosclerosis. The incidence of a single kidney may be higher than in the unaffected population and this is associated with a more rapid onset of renal failure.

PULMONARY SYSTEM

Several patients have died from pulmonary complications including pulmonary emboli, pulmonary hypertension, and lung disease. Lung abnormalities identified by autopsy include diffuse thickening (hyperplasia) of the airway (bronchial) smooth muscles, enlargement (emphysematous changes) of the gas exchange regions (alveoli), and diffuse hyperplasia of the pulmonary artery smooth muscles. The last finding could account for the pulmonary hypertension observed in some patients.

PHYSICAL TRAITS

Most affected individuals have distinctive physical features. These include fine hair (60%), a thin upper lip, a broad, low nasal bridge (68%), a bulbous nasal tip (83%), and disproportionately short stature (98%). Additional features include excessive inward curvature of the lumbar spine (lumbar lordosis, 84%), a protruding abdomen, and hyperpigmented macules (85%) on the trunk and occasionally on the neck, face, arms and legs. Less common physical features include absent or small teeth and corneal opacities (19%).

GROWTH AND SKELETAL SYSTEM

Growth failure, which is often the first obvious sign of SIOD, occurs despite normal growth hormone production and is not corrected with growth hormone supplementation. In most affected individuals, the growth failure begins prior to and continues after birth; however, some affected children do have normal birth lengths and weights and their growth failure is not noted until after birth (range: 0 to 13 years, mean: 2 years). The heights of those who survived to adulthood were 136-157 cm for men and 98.5-143 cm for women.

The short stature arises generally because of spondyloepiphyseal dysplasia (86%), a disorder of skeletal growth; it does not arise as a complication of their renal failure.

REPRODUCTIVE SYSTEM

Few SIOD patients have reached sexual maturity and of the ones who have, no children were subsequently born. However, the patients who have survived to adulthood did develop with secondary sexual characteristics and the women have menstrual cycles. The autopsy of two affected males revealed that sperm production was affected in a varying degree. In one patient, the testes showed interstitial fibrosis and absence of sperm (azoospermia), whereas the other had less interstitial fibrosis individual and produced some sperm.

HEMATOPOIETIC AND IMMUNE SYSTEMS

Nearly all affected individuals have some blood cell deficiency. Deficiency of T lymphocytes, a subgroup of white blood cells that plays an important role in immunity, is most common (97%) and is usually present at birth. Reductions in both CD4 T cells, which regulate multiple aspects of the immune system and CD8 T lymphocytes, which are important in the control of viruses are typical.

However, in addition to a deficit of T lymphocytes, the hematopoietic disturbance can include any or all other blood cell lineages. These hematopoietic cell deficiencies reflect reduced production of these cells by the bone marrow, and affected individuals are more prone than unaffected ones to developing decreased hematopoietic cell levels in the blood as a side effect of drug therapy. Affected individuals are also less responsive to the effects of G-CSF therapy to increase bone marrow production of neutrophils and erythropoietin therapy to increase the bone marrow production or red blood cell precursors.

Because of their immunodeficiency, affected individuals have an increased risk for opportunistic fungal, viral and bacterial infections. They also have an increased risk of more severe infections. The immunodeficiency is also associated with immune dysregulation disorders, such as autoimmune blood diseases.

CENTRAL NERVOUS SYSTEM

The central nervous system shows both multiple developmental and ischemic changes. The developmental defects include brain malformations suggestive of aberrant neuronal migration including heterotopia, irregular cortical thickness, incomplete gyral formation, poor definition of cortical layers, and hamartia. Additionally, adolescent and adult patients have very few neural progenitors (stem cells). Despite these malformations, most SIOD patients have normal social, language, motor, and cognitive development until the onset of symptoms from reduced brain blood supply (cerebral ischemia).

The cerebral ischemia can either temporarily or permanently disturb the blood supply of a given area of the brain and thereby cause temporary (47%, transient ischemic attacks) or permanent (44%, strokes) dysfunction. The cerebral ischemic attacks and strokes are often precipitated by acute changes in blood pressure, such as following the administration of high doses of steroids. Ischemic changes include loss of neurons and myelin, gliosis (scarring), brain atrophy, and degeneration of infarcted regions including atrophy of the cerebellum. Likely as a complication of the cerebral ischemia and atherosclerosis, a few of the patients have also manifest Moyamoya disease.

Another common neurological feature in SIOD patients is severe migraine-like headaches (60%). The cause of the headaches is still unknown but they tend to be more severe and refractory to anti-migraine medications that migraine-like headaches in the general population. In one patient a reversible cerebral vasoconstriction syndrome was suspected.

HOW HAS SIOD BEEN TREATED TRADITIONALLY?

Traditional treatment for SIOD involves simply managing symptoms. Treatments are selected to address individual symptoms as they develop.

When kidney failure progresses, children must receive dialysis and eventually a kidney transplant to stay alive. Stem cell transplants can also be used to treat immunodeficiency and blood abnormalities.

Blood-thinning medications such as pentoxifylline, acetylsalicylic acid, dipyridamole, warfarin, and heparin can transiently improve blood flow through the atherosclerotic arteries but do not provide enduring relief from cerebral ischemia. Treatment with acyclovir and some antibacterial agents has been beneficial for preventing or reducing the frequency of opportunistic infections. Hip replacement effectively treats degenerative hip disease.

ARE THERE NEW TREATMENTS?

Because of the research that has taken place, Stanford has developed a revolutionary new treatment.

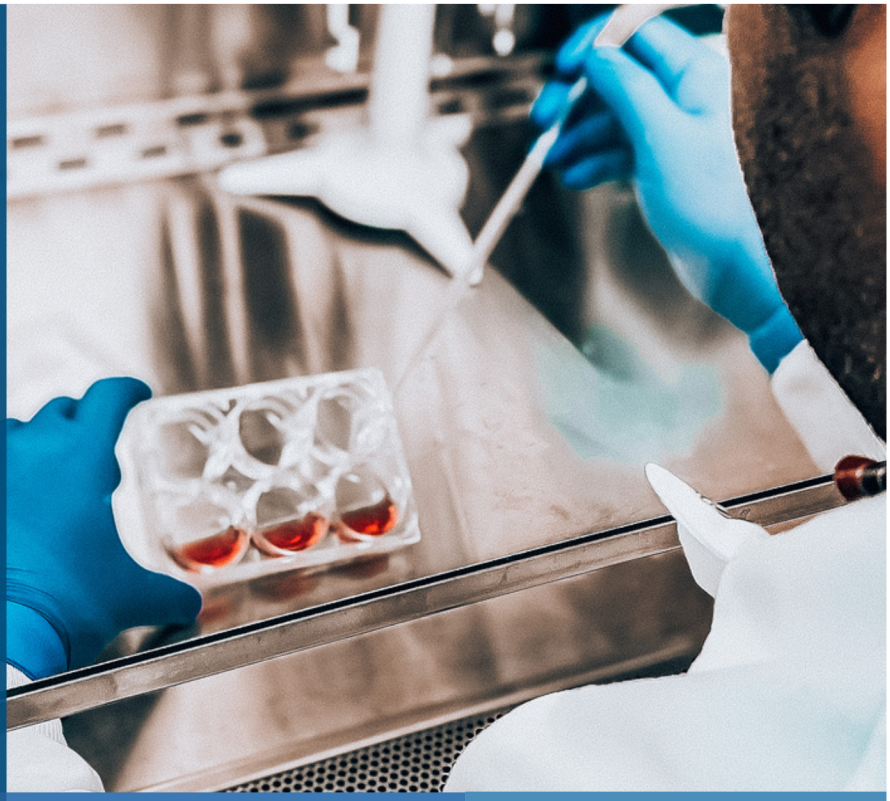
They offer a novel approach to treating SIOD that's a potential cure for the kidney disease and immune problems caused by SIOD. This treatment is called a dual immune/solid organ transplant (DISOT). It is a two-transplant approach—a haploidentical stem cell transplant, which provides your child with a new immune system, followed by a kidney transplant from the same donor, usually a parent. Since your child's new immune system recognizes its new kidney, it is less likely to reject it. DISOT recently earned FDA approval and was featured in the New England Journal of Medicine.

This research that provided this new means of treatment was funded by Kruzn For A Kure Foundation

DRUG THERAPY

Our Research Lab at Stanford University is currently working on ground-breaking treatment possibilities. They have spent the last seven years trying to understand the disease and how it works, and now they are at a point to specifically target the mutation of the Smarcal1 protein.

This project takes place in 3 phases.



PHASE 1

Modeling of Neurovascular Disease in SIOD Objective: Use the brain-on-a-chip system maintained underphysiologic conditions to study effects of the lack of SMARCAL1 protein on blood vessel cell function in a brain organoid. To gain insight as to how SMARCAL1 protein causes disease, such as migraine headaches with neurologic dysfunction, this will be constructed using blood vessel cells that can be treated with a drug to induce SMARCAL 1 deficiency.

PHASE 2

Small and Large Scale Drug Screens for Neurovascular Disease.
Objective: Perform Screens of repurposed small molecule drugs and a large scale small molecule screen to identify drugs that can correct the biologic abnormalities in the neurovascular model of SIOD. Validate any positive hits in each screen using the Brain on a Chip System.

PHASE 3

Commence Drug Testing and FDA Approval

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Caring For Your Child

Be the advocate.

If your child is diagnosed with a rare disease or condition it can be difficult to find information or a community of other families who share your experience. In this guide, you'll find resources that are created to help you as you begin to navigate life as the caregiver for a child with a rare medical condition like SIOD.

YOU are the most important advocate when it comes to seeking care for your child's medical conditions or special needs. While you will meet specialists who have expertise related to your child's needs, you are the expert when it comes to your own individual child. Being their voice can be intimidating at times, but this resource can help you prepare for those moments when you may feel overwhelmed by medical needs and decisions.

Traveling For Medical Care

It may be necessary to travel to another city or state for medical care if the expertise needed to treat your child's rare condition are not available close to home. These resources can help you locate medical experts, find clinical trials and treatment options, and find lodging, transportation and other travel related support for your family.

- Ronald McDonald House Charities® operates houses and other support services around the world for families of children undergoing medical treatment. Use the RMHC Chapter Locator to see if there is a Ronald McDonald House near your destination that may be able to house your family near your child's medical services.
- Financing your travel or finding funding for treatment needs or devices not covered by insurance can hinder your child's care. This Red Treehouse guide has resources for finding funding for your family if you have a child with medical or other special needs.
- If you are traveling for medical care check out Mercy Medical Angels to see if you may qualify for financial support for your trip. If you're traveling by air with a child who has complicated medical needs be sure to check with the Transportation Safety Administration for accommodations that may be available for your family.

BUILDING YOUR CHILD'S MEDICAL CARE TEAM

Most primary care providers are not familiar with SIOD, so having someone who is willing to learn about the condition with you is critical. We've put links below that you can share with your healthcare provider to help give them more information about this disease. The more you and your child's medical team know, the easier it will be to coordinate the best care for them.

A key priority of building your child’s care team is confirming that your primary care provider is comfortable coordinating care for children with complex medical needs. This means they will be collaborating with multiple specialists and integrating you, the parents, as critical members of the healthcare team.

Early in your child’s life, you may only need a few specialists to help monitor their health. As your child gets older and the disease progresses, their care team network will expand. Sometimes this information can be difficult to maintain and organize.

Additionally, you have the option to allow your child’s deidentified medical records to participate in research that will increase knowledge about SIOD as scientists continue working to develop treatments.

Doctors, nurses, and medical professionals have trained for years to learn how to diagnose, treat and care for patients, but not every doctor knows everything about every condition. You may find that when you attend appointments with non-specialists or make a visit to an urgent care center, for example, that you know more about your child’s diagnosis than anyone else in the room. Should you find yourself in a situation where your child needs emergency care, or treatment for an injury or illness unrelated to their rare diagnosis, it will be important to be prepared to speak up about their needs in case it may impact treatment decisions.

WE CARE ABOUT YOU AND YOUR FAMILY

SIOD FACEBOOK SUPPORT GROUP

This group is for families of those affected by SIOD. This is a safe place to ask questions and voice your concerns! We are all in this together to save our children's lives!

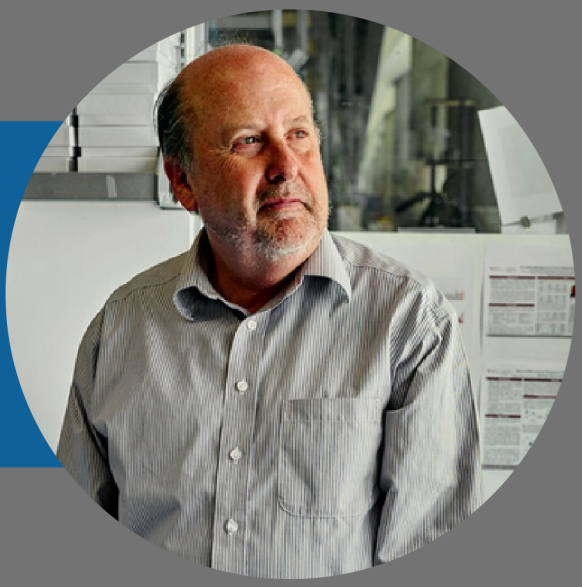
KRUZN FOR A KURE WEBSITE

We have tried to make our website filled with as much information as possible. One of the biggest pieces of this are the stories of other children diagnosed with the disease. We'd love for you to add your story when you are ready.

JOIN THE FACEBOOK GROUP

KRUZN FOR A KURE WEBSITE

OUR MEDICAL ADVISORY BOARD



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