Peroxisome Biogenesis Disorder-Zellweger Spectrum Disorder (PBD-ZSD)

A Patient-Caregiver Resource Guide

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Introduction

Your child has been diagnosed with Peroxisome Biogenesis Disorder-Zellweger Spectrum Disorder (PBD-ZSD). You may be feeling confused and overwhelmed by this diagnosis, but the more you know, the more empowered you will feel to support your child.

This resource is intended to help get you started on the path to learning about PBD-ZSD to help you be the best advocate you can be for your child. In the following pages, you will find useful information about PBD-ZSD, including what to watch for, what to ask your doctor during scheduled visits, and many helpful resources to keep you connected to the PBD-ZSD community.

What is Peroxisome Biogenesis Disorder-Zellweger Spectrum Disorder (PBD-ZSD)?

PBD-ZSD is a rare, genetic condition caused by the loss of peroxisome function. Previously, PBD-ZSD was thought to be four separate diseases known by various names, so you may hear other names used for this disorder (*See* **Figure 1**). It is now believed that PBD-ZSD is one disease with a range of symptoms and severity.

Figure 1. Other names for PBD-ZSD

- Zellweger syndrome
- Zellweger spectrum disorder
- Zellweger's
- Neonatal adrenoleukodystrophy (NALD)
- Infantile Refsum disease (IRD)
- Heimler syndrome

What are peroxisomes?

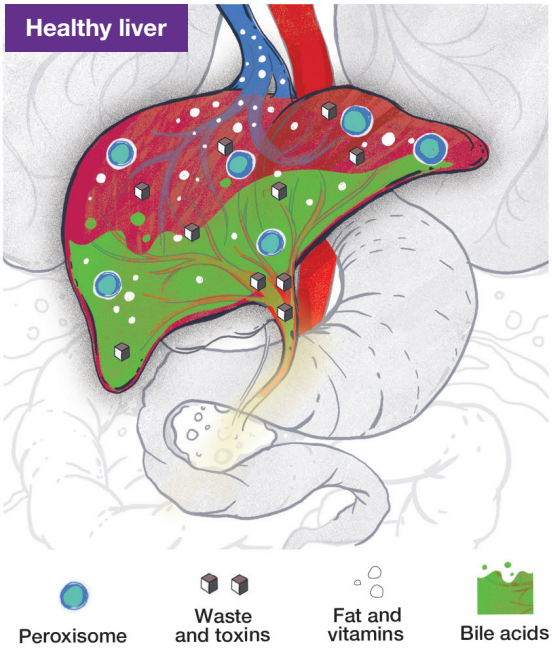
Peroxisomes (pronounced: puh-ROK-suh-SOHMs) are in nearly every cell in the body; they help to make bile acids, which digest fats and fat-soluble vitamins that are important nutrients for growth and development.

Peroxisomes are important parts of cells in the body that are responsible for many key metabolic functions, such as breaking down **fats**, including very long–chain fatty acids (also called VLCFA), and other chemicals, and getting rid of waste so that the body can function properly (*See* **Figure 2**). In people with PBD-ZSD, a permanent change in the *PEX* gene family (the set of genes that controls peroxisomes) leads to less or no peroxisome function. If peroxisomes are not working correctly, cells can't perform their normal functions, which changes the body's usual routine and leads to many problems over time.

A **fat** comes from plants or animals, is oily or greasy, and is part of the food we eat.

Because peroxisomes are normally in nearly every cell of the body, PBD-ZSD can affect many different organs, including the brain, eyes, liver, bone, and kidneys (*See* **Figure 3**). Peroxisomes play a role in different organ systems too, so when they don't function properly, it can lead to a variety of symptoms. Some people with PBD-ZSD may have multisystem complications, including neurological problems and seizures, delayed growth and development, hearing and vision loss, liver injury, poor muscle tone, and skeletal and dental abnormalities.

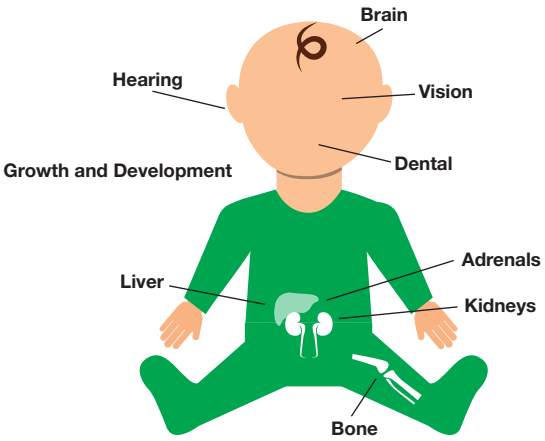
Figure 2. The role of peroxisomes in the healthy and damaged liver



Peroxisomes help produce bile acids, which are important to help the liver function correctly and eliminate waste from the body.

In PBD-ZSD, non-working peroxisomes cannot produce healthy bile acids; instead, toxic bile acids get trapped in the liver, cause damage, and the liver cannot function properly.

Figure 3. PBD-ZSD can affect many different systems and parts of the body



What are some of the common symptoms of PBD-ZSD?

PBD-ZSD is a spectrum disease, so it will affect each patient differently. How the disorder affects patients depends on their age when PBD-ZSD symptoms first appear, the number of functioning peroxisomes they have, and the rate at which the disease progresses. Some children show severe symptoms that are seen soon after birth, such as weak muscle tone (also called **hypotonia**); difficulties with feeding; hearing and vision loss; and seizures. Affected children may also have bone abnormalities (including a large space between the bones of the skull) and distinctive facial features (*See* **Image 1**). Others show milder forms of these symptoms that may not be easily recognized as PBD-ZSD. Children and adolescents with PBD-ZSD often have growth and developmental delays, liver problems, adrenal insufficiency, kidney stones, dental issues, and some degree of intellectual disability (*See* **Image 2**). Early medical evaluations are important to recognize symptoms and begin treatments that might slow the disease.

Hypotonia refers to weak muscle tone that may affect the ability to suck and swallow, hold up the head, move, and breathe.

Image 1. Child with severe form of PBD-ZSD

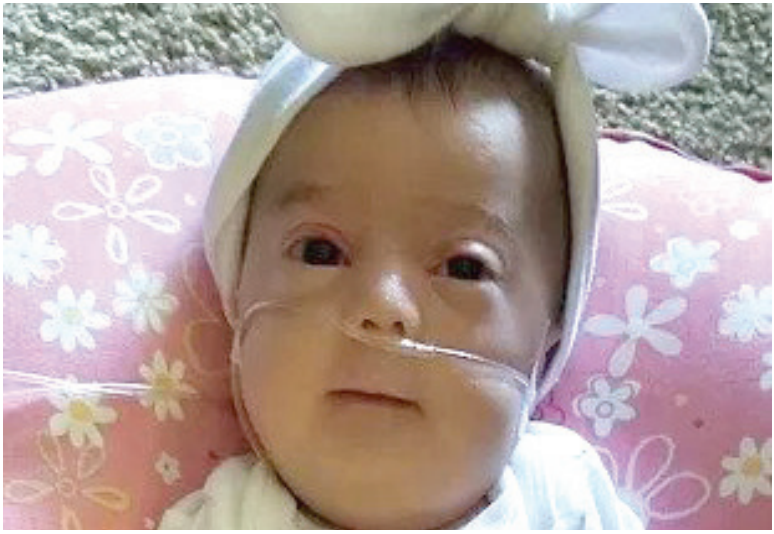


Image 2. Child with mild-to-moderate form of PBD-ZSD

Every patient is unique and may not experience all of the same symptoms; the severity of each person's symptoms may be different; and even the timing of when symptoms first appear in a person's life may not be the same for all patients. This makes it especially important to watch your child for any symptom changes or new symptoms, and to bring your child in for routine check-ups so that your doctors can provide care on a timely basis.

How did my child get PBD-ZSD?

Autosomal recessive means both genes in a pair must be abnormal to cause disease.

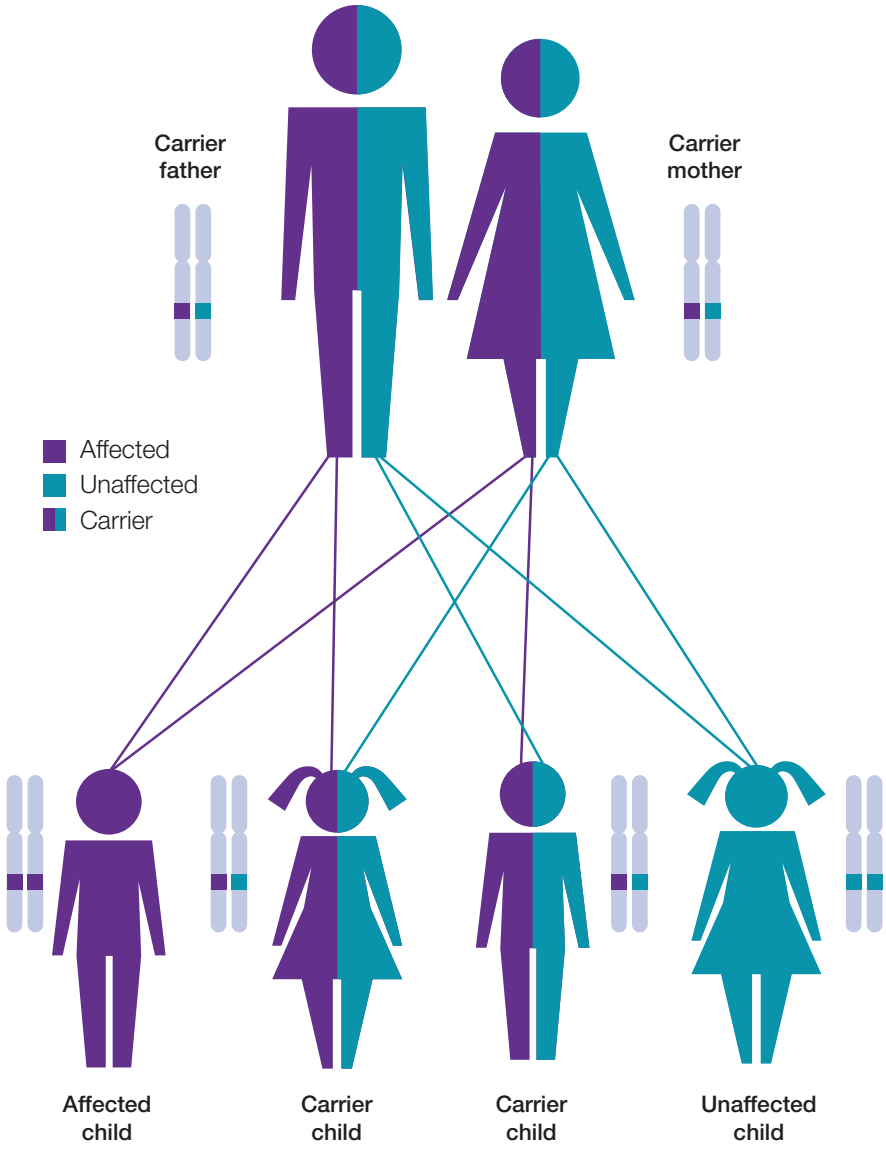
All children inherit genes from their parents (one copy of each gene from each parent). PBD-ZSD is an **autosomal recessive** disorder caused by a permanent change in a gene in the PEX family. This means that both parents must carry the non-working gene, and children with PBD-ZSD inherit two copies of the non-working gene (one from each parent). It is important to understand that no one picks the genes that he or she passes on to his or her children, so no one is to blame for passing on PBD-ZSD.

A **gene** is a part of a cell that controls the appearance of a person or other living thing. Genes come in pairs. One gene comes from the mother and the other gene comes from the father.

A **carrier** refers to a person with only one non-working gene in the pair. This person is usually not affected with the condition.

Figure 4 outlines how genes are passed from parents to children: each carrier parent has a non-working gene (shown in purple) and a working **gene** (shown in teal). With each pregnancy, this carrier couple has a 1 in 4 (25%) chance that they would both pass down their non-working copies of the gene and have a child affected with PBD-ZSD. There is also a 2 in 4 (50%) chance that one of the parents would pass down a working copy and the other a non-working copy and then have a child who is a **carrier** of PBD-ZSD but is not affected with the disorder. Finally, there is a 1 in 4 (25%) chance that both parents pass down the working copies of the gene and have an unaffected child, who doesn't have PBD-ZSD and isn't a carrier. Each pregnancy is an independent event, so some carrier couples may have more or fewer children with PBD-ZSD than anticipated by these percentages.

Figure 4. Autosomal recessive inheritance: how PBD-ZSD is passed from parents to children

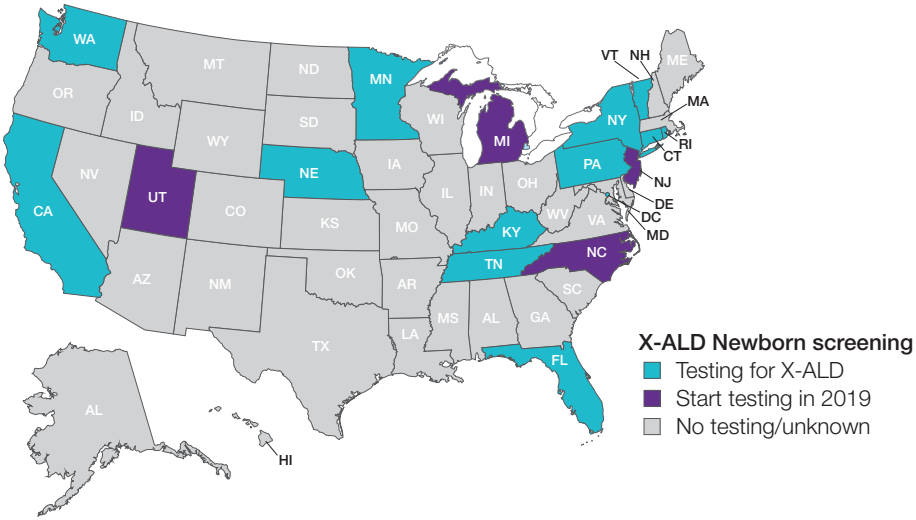


How many people have PBD-ZSD?

Although it is a rare condition, PBD-ZSD patients have been identified all over the world. In the United States, it is estimated that PBD-ZSD occurs in 1 out of every 50,000 to 70,000 individuals. This estimate may be low—PBD-ZSD may be hard to recognize and diagnose because not all children have the same symptoms.

In 2016, the United States Department of Health and Human Services recommended that testing for another peroxisomal disorder, called X-linked adrenoleukodystrophy (or X-ALD), be added to newborn screening programs. This is important because the test for X-ALD can also identify PBD-ZSD and speed up diagnosis and care for affected children. **Figure 5** shows the states where this testing is part of the recommended screening for newborns.

Figure 5. Newborn screening in the US (as of April 2019)



For more information, see

Salzman R et al. ALD Info: Newborn screening. https://adrenoleukodystrophy.info. Accessed January 11. 2019.

Aiden Jack Seeger Foundation. Newborn screening. https://www.aidanhasaposse.org/newborn-screening.html Accessed May 2, 2019.

Baby's first test. Conditions screened by state. https://www.babysfirsttest.org/newborn-screening/rusp-conditions#adrenoleukodystrophy Updated April 16, 2019. Accessed May 2, 2019.

What is the prognosis for my child?

Currently, there is no cure for patients with PBD-ZSD. However, there are ways to help support your child and manage his or her symptoms. Although current treatments can only help with symptoms and do not cure the disease, they may help improve comfort and quality of life for people with PBD-ZSD. Clinical trials and **registries** are ongoing to better understand PBD-ZSD in the hope that effective treatments will become available. Remember that symptoms of PBD-ZSD vary in type and severity. Similarly, estimates for life span will differ. Children with the most severe symptoms typically do not live beyond one year of age, while children with milder symptoms can live well into adulthood.

Registries are studies that observe patients over time to learn more about a disease and effects of treatment.

What happens after my child is diagnosed with PBD-ZSD?

No matter where someone is on the PBD-ZSD spectrum, the impact of the disease is serious and lifelong, and it needs to be followed closely. You and your child's **primary care provider** (or PCP) should discuss how to best manage your child's symptoms and overall health. Following the diagnosis, your child will need a complete evaluation to know what organ systems are affected (See **Figure 6**). It will be important that you tell your child's primary care provider what symptoms you see at home.

A **primary care provider** (or PCP) refers to a physician (pediatrician, family practitioner, physician assistant [or PA], or nurse practitioner [also called an NP]) who oversees general health and manages common medical problems.

You may also decide to get genetic counseling if you want to have more children or want to have other children tested. The organizations listed as resources at the back of this guide can be good sources for practical information, education, and the latest news on PBD-ZSD. You also may be able to connect with other families with children affected by PBD-ZSD through these organizations. It may be helpful for you to talk to other PBD-ZSD patients and their family members who are going through a similar experience.

Figure 6. Initial evaluation of your child's health

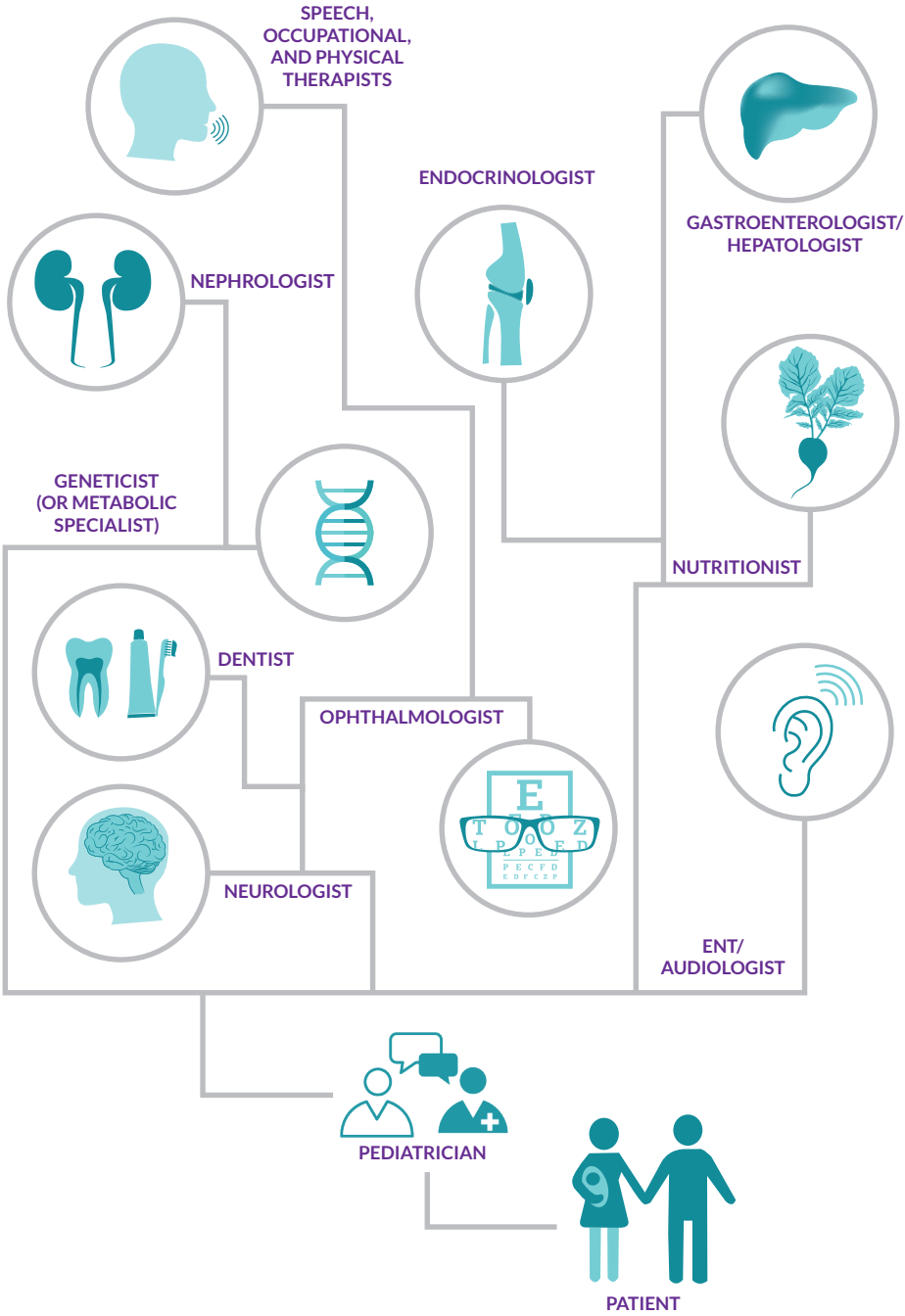
- ✓ Height/weight
- ✓ Head circumference (infants)
- ✓ Vitamins A, D, E, K (fat-soluble vitamins)
- ✓ Lipid panel (cholesterol, triglycerides)
- ✓ Liver tests: aspartate aminotransferase (or AST), alanine aminotransferase (or ALT), gamma-glutamyl transpeptidase (also called GGT), bilirubin, albumin
- ✓ Alkaline phosphatase
- ✓ Evaluation for adrenal insufficiency
- ✓ Albumin
- ✓ Prothrombin time (PT)/ international normalized ratio (INR)
- ✓ Atypical bile acid test
- ✓ Hearing and vision assessments
- ✓ Brain MRI (magnetic resonance imaging)
- ✓ Abdominal ultrasound
- ✓ Nutrition evaluation
- ✓ Vaccination history

Which specialists are involved in managing my child's care?

Not all changes to your child's health can be easily noticed, so going to routine check-ups with different specialists is crucial. Your primary care provider will determine which other types of medical specialists your child may need based on his or her exam and the symptoms you observe at home. It is important to work with a team of specialty doctors who are aware of the latest recommendations for managing PBD-ZSD (*See* **Figure 7**). These specialists will work together with you to develop the best treatment plan for your child. Routine check-ups with some or all of these specialists may be needed to monitor symptoms and adjust treatments to manage symptoms.

It is important to remember that each child with PBD-ZSD is unique and will have a unique group of symptoms and needs. As a parent caregiver, you know your child best and are the best advocate for your child's care. Your child's doctors will rely on you to tell them what you observe about your child so they can provide the best care.

Figure 7. PBD-ZSD network of care



Pediatrician: Typically, the primary care provider who manages your child's growth, feeding, and nutrition, and coordinates care with other specialists.

Geneticist (or Metabolic specialist): Assesses how your child's specific condition affects him or her, and may be involved in the daily management of your child's care. The geneticist also provides counseling about family planning.

Gastroenterologist/ Hepatologist: Monitors liver function and any nutrition or feeding difficulties. These doctors may work with a nutritionist to support growth.

Nutritionist: Assists with optimizing growth by assessing caloric intake and other nutritional needs.

Neurologist: Manages the health of your child's nervous system, largely focusing on brain function.

Ophthalmologist: Monitors changes in your child's vision and overall eye health.

Ear, nose and throat (ENT) or Otolaryngologist/Audiologist: Manages any changes in your child's hearing; also assesses the health and function of the nose and throat.

Dentist: Monitors oral health and treats issues with tooth enamel.

Endocrinologist: Manages hormonal imbalances your child may have including the potential for adrenal insufficiency; manages bone health by monitoring vitamin D and calcium intake and performing bone scans (this may alternatively be done by the nephrologist).

Nephrologist: Monitors kidney health and function.

Speech, occupational, and physical therapist: Manages any developmental challenges your child may have, such as speech, muscle control or walking.

What questions should I ask during routine check-ups?

- What signs/symptoms should I be watching for in my child?
- Which specialists might help my child?
- When and how often should my child be evaluated by a specialist?
- Is my child's growth (height and weight) improving?
- Should I modify my child's diet?
- What are my child's latest test results and what do they mean?
- Are there treatments that should be started that might prevent symptoms from occurring?
- If my child has [*insert specific symptom*], what therapy might help to manage it?
- I would like to have more children; are my future children at risk?
- Are there research studies related to my child's diagnosis?
- Where can I get more information or support?
- How might my child's symptoms change over time?
- Are there other tests that aren't considered routine that we should be doing to help monitor or uncover other symptoms that are not visible?
- Which specialists can you refer me to for monitoring other organ systems that may be affected by PBD-ZSD?

My Questions

Our Network of Care

Pediatrician:	NAME: CONTACT INFORMATION:
Geneticist (or Metabolic specialist)	NAME: CONTACT INFORMATION:
Gastroenterologist/ Hepatologist	NAME: CONTACT INFORMATION:
Nutritionist	NAME: CONTACT INFORMATION:
Neurologist	NAME: CONTACT INFORMATION:
Ophthalmologist	NAME: CONTACT INFORMATION:
ENT / Audiologist	NAME: CONTACT INFORMATION:
Dentist	NAME: CONTACT INFORMATION:
Endocrinologist	NAME: CONTACT INFORMATION:
Nephrologist	NAME: CONTACT INFORMATION:
Speech, occupational, and physical therapist	NAME: CONTACT INFORMATION:

What other resources are available to help my child?

Global Foundation for Peroxisomal Disorders (GFPD) provides support and community to families, information on research, scientific papers; sponsors family and scientific conferences.
Available at: www.thegfpd.org

Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Braverman NE, Raymond GV, Rizzo WB, et al. *Mol Genet Metab* 2016 Mar;117(3):313-321.

This article summarizes expert recommendations about PBD-ZSD management. Print this article and bring it to your doctor visits to share with health care providers. You can find it at this web site:
Available at: www.eorder.sheridan.com

Understanding ZSD.com provides useful information about what to look for and how PBD-ZSD is monitored; it includes a link to guidelines for your doctor to review.
Available at: www.understandingzsd.com

ChiLDReN (Childhood Liver Disease Research Network) is a collaborative team of doctors, nurses, research coordinators, medical facilities, and patient support organizations working to advance the understanding of rare liver diseases.
Available at: www.childrennetwork.org

Global Genes® Allies in Rare Diseases works to eliminate the challenges of rare diseases faced by 350 million people worldwide, while unifying the rare community under a symbol of hope—the Blue Denim Genes Ribbon®.
Available at: www.globalgenes.org

Gene Reviews [Internet]. Zellweger Spectrum Disorder. Steinberg SJ, Raymond GV, Braverman NE, Moser AB. Adam MP, Ardinger HH, Pagon RA, et al. eds.

NORD® National Organization for Rare Disorders offers broad coverage of rare diseases for patients, parents, and health care providers; provides information on access to treatment/financial support.
Available at: www.rarediseases.org

U.S. National Library of Medicine is the world's largest biomedical library and includes **Genetics Home Reference**, a guide to understanding the effects of genetics on health.
Available at: www.ghr.nlm.nih.gov

Registries

Registries are studies that observe patients over time to learn more about a disease and effects of treatment. Two registries open for enrollment are:

Longitudinal Natural History Study of Patients with Peroxisome Biogenesis Disorders

REPLACE Registry for Patients
For more information, go to: www.thegfpd.org

- PBD-ZSD is a rare, genetic condition with a range of symptoms and severity
- Signs and symptoms related to PBD-ZSD can include poor muscle tone, poor feeding, delayed growth and development, hearing and vision loss, seizures, liver injury, and dental and other bone problems
- It is important to work with a team of specialty doctors who are aware of the latest recommendations for managing PBD-ZSD
- Support groups and other resources are available to help you learn more about PBD-ZSD and get involved in the PBD-ZSD community

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