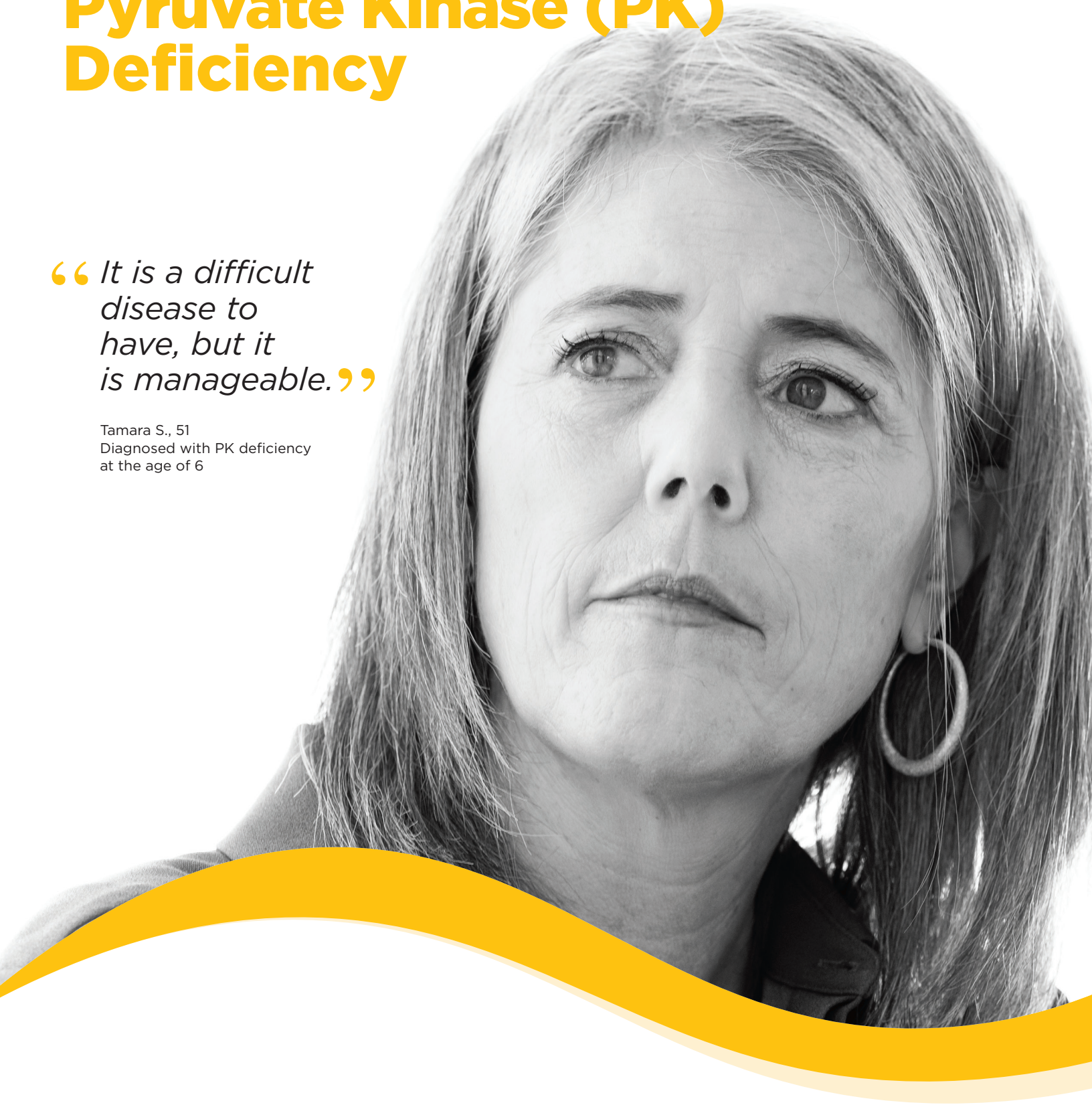
Understanding Pyruvate Kinase (PK) Deficiency



“It is a difficult disease to have, but it is manageable.”

Tamara S., 51
Diagnosed with PK deficiency
at the age of 6

Managing PK deficiency and moving forward

agios

Setting goals for managing PK deficiency

With a PK deficiency diagnosis comes some uncertainty about what to do next.

Whether you've recently been diagnosed, or you've been living with the condition for years, learning as much as you can is important. This brochure will help you get started and give you the tools to work closely with your doctor for a more empowered life with PK deficiency.

Creating a treatment journal may also be helpful. Tracking questions and symptoms can make it easier to share changes with your healthcare team and proactively manage your PK deficiency over time.

The **Resources** section at the end of this brochure provides:

- Links to more information
- Ways to find support

agios

At Agios, people living with rare genetic diseases are at the center of everything we do and every decision we make. Agios is a company committed to knowing more about PK deficiency and how it feels for those living with the disease.

Contents

4 **About PK deficiency**
The role of red blood cells and what it means to have PK deficiency

6 **Cause**
The cause of PK deficiency and how the condition is inherited

8 **Symptoms**
The most common physical symptoms of PK deficiency

10 **Complications**
Potential short- and long-term complications of PK deficiency

12 **Management**
Building a PK deficiency management plan with your care team

14 **Impact**
Understanding the greater impact of PK deficiency

16 **Moving forward**
Advocating for yourself with PK deficiency

26 **Resources**
Helpful tools, resources, and support to learn more

Look out for journal prompts as you're reading. Every note and question is an opportunity to prepare for more productive, meaningful conversations with your hematologist.

What is PK deficiency?

PK deficiency is a rare, inherited enzyme deficiency that affects red blood cells (RBCs).

PK deficiency causes hemolytic anemia. Hemolytic anemia happens when RBCs are broken down faster than they are made.

Key Terms

Red blood cells (RBCs or erythrocytes): Cells that carry oxygen throughout the body

Anemia: A condition in which the blood has lower-than-normal levels of RBCs or hemoglobin

Hemoglobin: A protein that helps RBCs carry the oxygen your body needs

Hemolytic anemia: A type of anemia that is caused by the early breakdown of RBCs in the bloodstream or by the spleen

Hemolysis: The breakdown of RBCs, which leads to the release of hemoglobin into the blood and production of bilirubin

Chronic: Lasting a long time

Catalyze: To increase the rate of a chemical reaction

Enzyme: A protein that catalyzes chemical reactions that occur inside the body

Gene mutation: A permanent change in the DNA sequence of a gene, altering the gene's ability to make a protein and causing the protein to stop working properly

Deficiency: A shortage of something

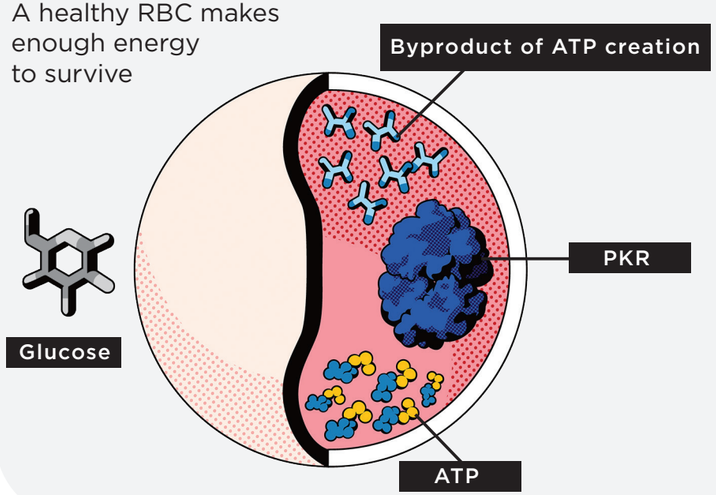
PKR (pyruvate kinase in RBC): The pyruvate kinase enzyme

Glycolysis: The process of RBCs converting glucose (sugar) into pyruvate and ATP

ATP: The primary source of energy for cells

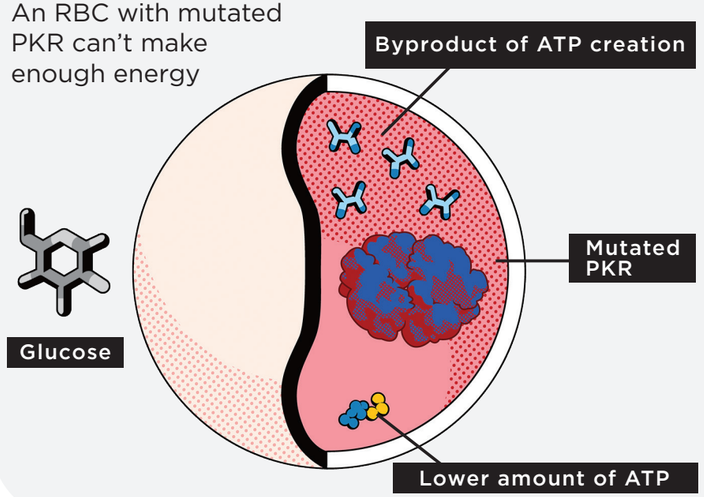
Healthy RBC

A healthy RBC makes enough energy to survive



RBC with mutated PKR

An RBC with mutated PKR can't make enough energy



The PKR enzyme performs the last step of glycolysis. RBCs convert glucose (a sugar) into pyruvate to make ATP. Deficient PKR leads to less ATP produced, so RBCs have less energy.

Healthy RBCs

After healthy RBCs are produced, they travel through the lungs, and oxygen binds to a molecule in the cells called hemoglobin. The RBCs then transport oxygen to the rest of the body. Healthy RBCs have enough ATP, or energy, made by the pyruvate kinase R (PKR) enzyme to survive this trip throughout the body.

Each RBC lives for about 120 days before being broken down and removed from circulation.

PK-deficient RBCs

RBCs that do not have enough PK, or that do not have properly working PK, have less ATP, so they die more quickly. The low levels of ATP can cause chronic hemolytic anemia (low RBC counts or low levels of hemoglobin).

DID YOU KNOW?

While healthy RBCs typically last 120 days, a PK-deficient RBC doesn't have as much energy, so it may only last a few days to weeks.

What causes PK deficiency?

PK deficiency is a genetic disease caused by a mutation in the *PKLR* gene. More specifically, it's an autosomal recessive mutation passed down from parents to their children. Genes are stretches of DNA that carry genetic information. They are found in long strips of DNA called chromosomes.

The *PKLR* gene tells the body how to make an enzyme called pyruvate kinase R, or PKR. In PK deficiency, the mutated gene creates PKR that doesn't work properly. As a result, RBCs can't make enough energy and die too soon.

Key Terms

Gene: Stretches of DNA. Different genes have different jobs, but many genes tell the proteins in our bodies how to work

Chromosome: A very long strand of DNA that's stored in the cell's nucleus and contains its genetic information. Each chromosome may contain hundreds to thousands of genes

DNA: The genetic material that tells a cell how to grow and what its job is

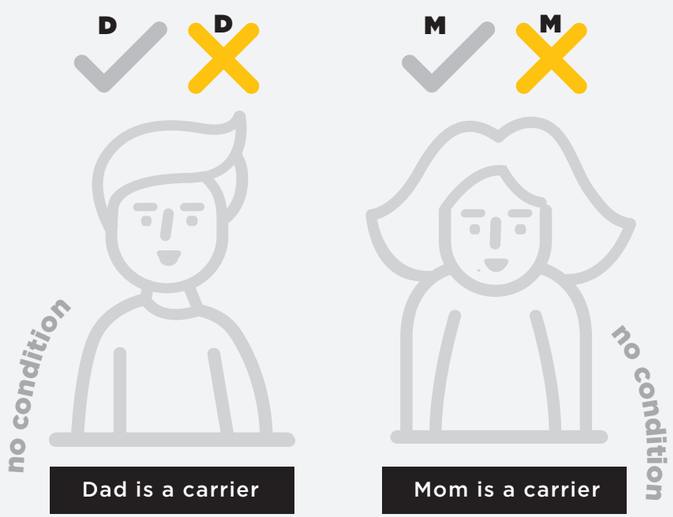
Autosomal recessive gene inheritance: A genetic disease that is inherited from receiving 2 nonworking copies of a gene

***PKLR*:** The gene for pyruvate kinase

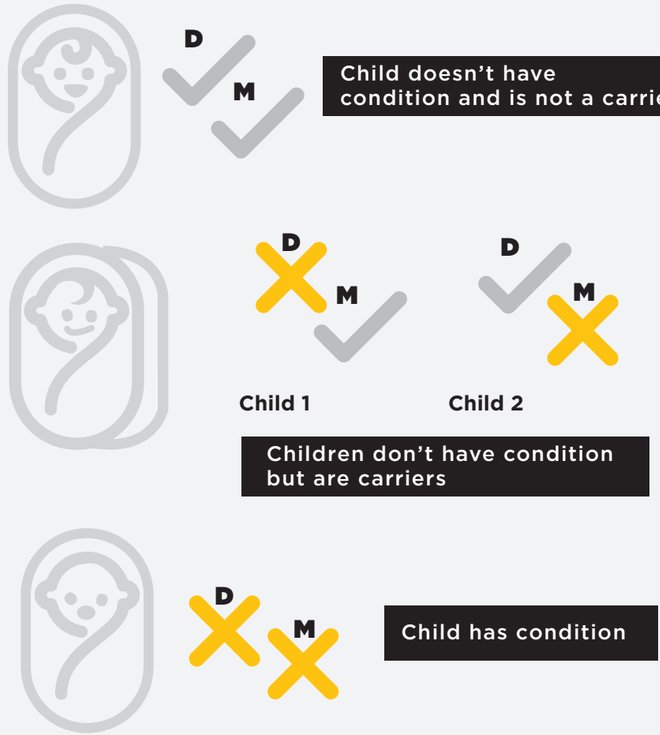
Enzyme assay: A measurement, determined by a blood test, of how active an enzyme is

Autosomal recessive inheritance

Carrying mutated *PKLR*



Inheriting PK deficiency



In an autosomal recessive gene inheritance, carriers, or parents, each have one copy of the mutated gene that they pass down to their child. Parents themselves do not usually have PK deficiency. To inherit the condition, a child receives a mutated *PKLR* gene from both parents.

Doctors test for PK deficiency in 2 ways. They can test enzyme levels with an enzyme assay, or they can perform genetic tests to identify PKLR *gene mutations. Often, doctors will use both of these methods to determine if someone is affected.*

If you have PK deficiency, or are a parent of a child with PK deficiency, your siblings or your children could be affected. Ask your doctor about testing family members.

DID YOU KNOW?

Over 300 different mutations of the *PKLR* gene have been identified. Approximately 25% of people diagnosed with PK deficiency have versions of the gene mutation that are newly discovered.

How does PK deficiency affect everyday life?

Signs and symptoms of PK deficiency are different for everyone and can change over time. Even siblings with PK deficiency can have different experiences.

Key Terms

Bilirubin: A substance created from hemoglobin when RBCs break down, which can cause jaundice and scleral icterus

Jaundice: Yellowing of the skin caused by high levels of bilirubin in the body

Scleral icterus: Yellowing of the whites of the eyes caused by high levels of bilirubin in the body

Common symptoms

- Debilitating fatigue
- Exercise intolerance
- Jaundice
- Scleral icterus

Some symptoms are mental

- Difficulty concentrating
- Brain fog

- Memory loss

“Some days are great and some are horrible and I can’t control it.”

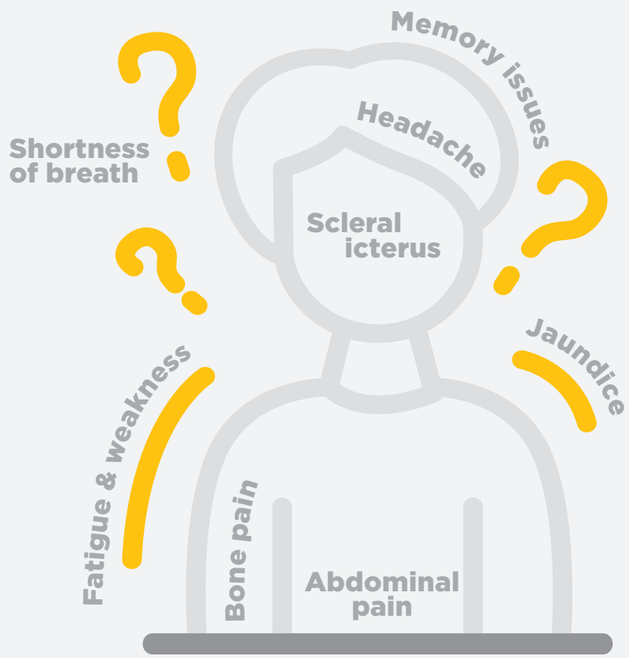
Tamara

Sometimes it’s easy to see the effects of PK deficiency. In other cases, it may be unclear, so it’s important to keep track of symptoms over time.

Additional signs and symptoms

Which of these symptoms do you have and which bother you the most? Are there any you’re just starting to notice, or that you didn’t think could be related to your PK deficiency?

Circle your symptoms and share with your doctor. If you are experiencing additional symptoms not listed, write them in below.



Being proactive is key to understanding the different signs and symptoms. It’s important to be aware and know what to look for, so you can keep your hematologist informed.

Noticing new symptoms or feeling existing symptoms getting worse may signify your condition isn’t under control.

This could mean you and your doctor need to reevaluate your management plan.

What are the complications of PK deficiency?

Different symptoms and complications can arise due to the effect PK deficiency has on RBCs. Complication severity can vary from person to person.

Key Terms

Spleen: An organ that filters blood, helps support the immune system, and removes old or damaged blood cells from the body

Splenomegaly: An enlarged spleen

Cognitive difficulties: Problems associated with memory, language, thinking, and judgment

Aplastic crisis: When the production of new RBCs temporarily stops

Gallbladder: An organ that stores and concentrates bile between meals

Gallstones: Small stones that form in the gallbladder

Iron overload: An excess of iron in the body

Ferritin: A blood protein that contains iron.

Osteoporosis: A disease where the density and strength of bones are reduced

Complications of chronic hemolysis

A lack of healthy RBCs
Low amounts of RBCs reduce the amount of oxygen in the body, causing stress on the heart and lungs.

This can lead to:
- Tiredness and fatigue
- Headaches
- Shortness of breath
- An inability to exercise
- Cognitive difficulties
- Aplastic crisis

The breakdown of RBCs
RBCs break down and release bilirubin into the bloodstream, causing:
- Jaundice and scleral icterus
- Bilirubin to build up in the gallbladder, creating gallstones

The removal of RBCs
As the spleen removes old or damaged RBCs, they may collect in the organ causing splenomegaly. Working RBCs may also be removed, leading to an increase in anemia levels.

DID YOU KNOW?

Some complications of PK deficiency appear later on in life, and may not have any signs. It's important to regularly monitor to prevent future risk.

PK deficiency can cause iron overload in the blood. Iron can collect in the tissues of the body and damage the liver and heart. It may also contribute to other symptoms, such as fatigue and abdominal pain.

Complications of iron overload

Everyone with PK deficiency is at risk for iron overload. While iron overload can be caused by frequent blood transfusions, many people with PK deficiency who don't get regular transfusions can also develop it—it can occur at any age, with any hemoglobin level.

- **Liver cirrhosis:** Scarring of the liver

- **Pulmonary hypertension:** High blood pressure that affects the arteries in the lungs and right side of the heart

- **Osteopenia:** A decrease in bone mass or bone mineral density. In severe cases it can progress to osteoporosis

- **Endocrine/hormone problems**

It's important to have a regular monitoring schedule for iron overload. Most hematologists recommend testing ferritin levels once or twice a year.

By testing the blood for ferritin (Fe), doctors can see how much iron is building up in the body. If ferritin levels exceed a certain amount (for example, ferritin greater than 500 nanograms per milliliter), be prepared to take action and ask about a potential follow-up liver and heart MRI.

Building a management plan

Studies show that patients who communicate well with their healthcare team are happier with their treatment and receive better care. Many different healthcare professionals will play an important role in managing PK deficiency.

Key Terms

Extramedullary hematopoiesis: Blood cell production occurring outside of the bone marrow, in organs such as the liver or spleen, due to the excessive production of RBCs daily

DXA (or DEXA) scan: An X-ray performed to assess bone strength

MRI: A scan performed to look for iron overload in the liver and heart

Transfusion: The process of putting blood into the bloodstream by intravenous (IV, meaning through the veins) infusion into the arm

Abdominal ultrasound: A test performed to look for gallstones or other complications involving the gallbladder

Echocardiogram (echo): A test assessing heart function and signs of pulmonary hypertension

Your healthcare team

Hematologist
A doctor who specializes in blood disorders

Family doctor or general practitioner
The doctor you see for checkups and yearly flu shots or other wellness visits

Registered nurse
In addition to nurses at your doctor's office, there are nurses who specialize in giving transfusions

Counselor or psychologist
Living with PK deficiency can cause stress and anxiety. It may help to find a support group or a mental health professional to talk to

DID YOU KNOW?

The need and timing of tests varies for everyone. Talk with your doctor about each test to determine a monitoring plan.

Regular evaluations can help make sure you're getting the right care. Many assessments to monitor for PK deficiency are done on a yearly basis, but some may need to be done more often based on transfusion frequency, the need for chelation therapy, and discoveries from previous tests.

Know the tests for monitoring your complications

Gallstones
Monitored by ultrasound if there is new or worsening abdominal pain.

Iron damage to the heart or liver
Monitored by a yearly T2* MRI scan. Patients who receive regular transfusions, or who need chelation therapy, may need to be assessed more frequently.

Osteopenia and osteoporosis
A DXA should be done in early adulthood. Results of the scan determine how often the test should be repeated.

Pulmonary hypertension
An echocardiogram should be done after age 30. Doctors determine if the test needs to be repeated based on what the picture shows.

Extramedullary hematopoiesis
A visual exam is performed regularly, with further testing if there is unexplained swelling or symptoms that indicate signs of nerve damage, such as numbness, tingling, burning, or shooting pain.

Annual blood tests for:
- Degree of anemia (hemoglobin levels)
- Iron overload (ferritin levels)
- Vitamin D levels (to help assess bone health)
- Hormone changes (to check for diabetes, thyroid problems, or sex hormone levels)
- Viruses, such as HIV, and hepatitis A, B, and C (for people who receive transfusions)

PK deficiency affects more than just the body

When navigating a chronic condition, it's normal to feel overwhelmed sometimes. Symptoms and treatments of PK deficiency may have effects on mental health, but there are ways to find support.

If you are a parent or caregiver of a child or adolescent with PK deficiency, it may fall on you to communicate your child's emotions.

When talking about physical symptoms, encourage open discussions about feelings, too. Often, physical symptoms can affect emotional and social health.

Common mental health challenges

People with PK deficiency and their caregivers participated in a poll and reported feeling:

Anxiety	Depression
84%	55%
Low self-esteem	**Social isolation**
61%	58%

If you no longer take enjoyment in activities, or everyday tasks seem too much, or if you feel sad, empty, or guilty about your condition, it could be a sign of depression. It's important to talk to your healthcare provider about these feelings.

DID YOU KNOW?

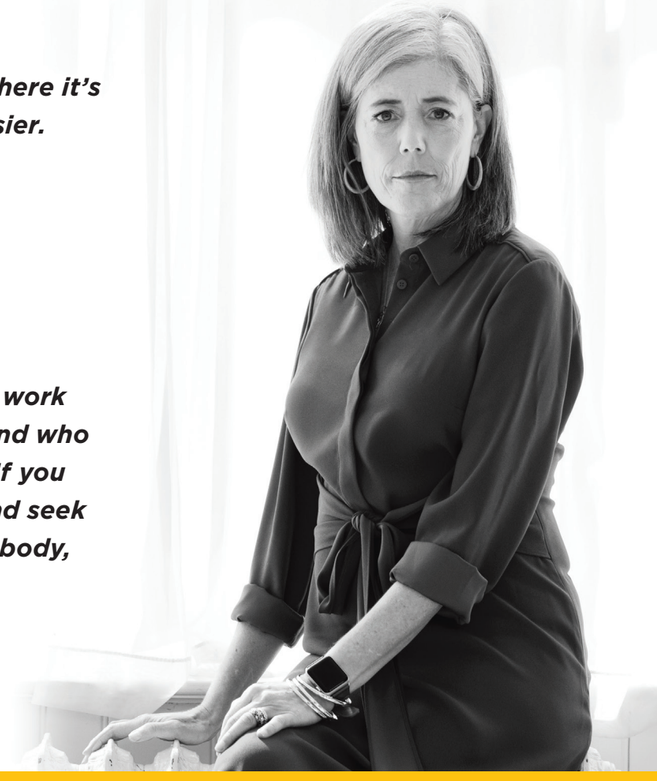
When asked about PK deficiency management methods, only 11% of participants responded that their current methods work very well. Continue gathering information and advocating for yourself to find the right plan and team that works for you.

Because the impact of PK deficiency goes beyond physical symptoms, it's also important to keep track of your feelings, and your ability to cope with everyday activities. This will help you paint a full picture when talking to your healthcare team.

> ***My parents got me into horses when I was 10. I couldn't do the swimming and the tennis and all the stuff that my sister did. The horses I could do, so I excelled at them. It gave me an outlet to not think about the bullying, the disease, and I was able to compete in an athletic event like other kids and do as well as them.***
>
> Robin

Think about the obstacles you are facing or potentially may face. Keep those in mind as you keep track of symptoms.

> ***There are different points in your life where it's harder versus other times where it's easier. That's important to know.***
>
> Tamara



> ***I ultimately found a physician willing to work with me; one who saw me as a person and who read the resources I shared with them. If you don't get that, it's okay to walk away and seek a second opinion. Ultimately, it was my body, my choices, and my life.***
>
> Molly

Taking the next steps

Being prepared can be a source of strength as you manage PK deficiency. Keeping track of goals, obstacles, and questions can help make sure you and your healthcare team come up with the right plan.

These steps and examples of discussion questions can help you prepare for your next appointment. Symptoms can affect people's lives differently, so speaking from your own experiences will be best to help your doctor understand how PK deficiency affects you.

STEP 1: Get organized

If you haven't been keeping track of your condition in a journal, a good place to start is to gather any information you may have, such as:

- Surgeries
- Transfusion history
- Blood or other lab tests
- Any other medical conditions
- Medicines or supplements you take on a regular basis

Consider keeping track of your symptoms on a weekly basis. These data can help your healthcare team understand which symptoms you have and how they affect you. If you undergo regular transfusions, for example, it may help to show what kind of effect they have, and how long those effects last.

STEP 2: Talk about daily life

Talking in detail about your life with PK deficiency can help your healthcare team get a better idea of how you feel.

To help you be specific at your next appointment, try completing these prompts.

- I enjoy the following activities/hobbies, but I can't do as much as I want to
- The symptoms that most interfere with my daily life are
- I notice my symptoms are worse during this part of my day
- The symptom that bothers me the most and why is

STEP 2 continued

It may be helpful to describe how the symptoms affect your life directly; for example:

- I always get a headache in the late afternoon so, instead of spending time in my garden, I have to lie down
- I want to be able to attend my child's school events, but can't find the energy to leave the house after 5 PM
- Sometimes I can't finish my homework because my brain gets foggy and reading my textbook becomes a struggle

STEP 3: Make connections

The chart on page 13 lists assessments and their recommended frequency. Using what you've learned, talk to your hematologist about your monitoring frequency. Think about these conversation starters and write any other topics you want to discuss:

- I've read that tests to monitor for PK deficiency complications can vary in frequency depending on transfusions, the need for other therapies, and discoveries from previous assessments. Based on my history, can we discuss how often we should be testing?
- Some assessments become more relevant at a certain age, such as a DXA scan to monitor osteoporosis and an echo to monitor pulmonary hypertension. When should we start thinking about these tests for me?

Iron overload can occur in people with PK deficiency regardless of age, transfusion history, or degree of anemia. It may be a topic worth discussing on its own. Some prompts to start a conversation include:

- I came across research that suggests people with PK deficiency should be monitored regularly for iron overload and its complications. Recent research shows that iron overload can be a concern when ferritin levels are high (greater than 500 nanograms per milliliter). How are my ferritin levels?
- I also learned that people who undergo regular transfusions, or who are on chelation therapy, may need to have their ferritin levels tested more often. What do you think about testing my ferritin levels more frequently, like every 3 or 6 months instead of every year?

STEP 4: Advocate for yourself

When discussing support options, it can be helpful to mention the methods you've learned about in your own research. You may even find resources that are new to your physician. Consider sharing a resource and any questions you have about its content.

Talking about your specific situation along with the hematologist's recommendations can help you both create an effective plan.

See some examples of discussion points below and add in your own.

- I want to be proactive about my PK deficiency. Can we talk about managing my condition and build a plan together?
- Based on the symptoms I've checked off in this brochure, what else can we do to manage my anemia?
- Some of my symptoms are affecting my daily life. What changes in my management plan can we consider based on what I'm still feeling?
- I've read that transfusions or a splenectomy could help my anemia and fatigue. It would be helpful to talk through the added risks and benefits of these options together, as well as what they might mean for me.
- I find my condition to be overwhelming sometimes, and think I may benefit from more support. Are there any groups recommended for people living with a rare condition?
- My yellow skin has started to take a toll on my self-esteem. What else can we do to reduce my bilirubin levels?

STEP 5: Set goals

Be open about the plans you have for the future. Think about what you want to do next, and ask your healthcare team if they can help you get there. Plan ahead by considering these prompts:

- My school and career plans include

- I have events with family/friends that I want to attend

- I want to be able to participate in the following activities or hobbies

The Resources section on KnowPKDeficiency.com includes additional information, including *Pyruvate Kinase Deficiency Through the Decade*. This resource includes summaries of journal articles that may help support conversations with your doctor. Consider sharing the title and author of the article, or the journal article itself.

Discussion topics might include:

- I found an article focusing on the burden of PK deficiency, and it mentioned some common symptoms that I've been noticing in myself, like memory loss and difficulty concentrating. I don't want this to further affect my career/schoolwork/hobbies/family life. What else can we consider to help?
- I read a study that talked about bone fragility, and a key finding was that long-term complications should be monitored regularly, since there are few early predictors. What can we do to proactively support my bone health?

Additional Notes

Focus on your future with PK deficiency

Moving forward, with the right information

Strong communication and a partnership with your hematologist can ensure you're getting the most out of every appointment and management method.

- Organize information to share with your doctor based on what you've learned in your own research
- Keep track of your symptoms over time, so you can give your doctor a clear picture of your health
- Make a list of any questions ahead of time, so you don't forget to ask
- Take notes during discussions with your doctor

You have tools for a productive and effective conversation about moving forward with PK deficiency. Managing PK deficiency is a process that will evolve over time. Building a strong relationship with the right hematologist can make sure you're on track, every step of the way.

Helpful resources

With the support of these resources, start advocating for yourself

Resources from Agios

KnowPKDeficiency.com

Download the *Fast Facts* brochure for additional in-depth information about PK deficiency

Read *Pyruvate Kinase Deficiency Through the Decade* to understand more about PK deficiency and the latest breakthroughs in knowledge about the condition

KnowPKDeficiency.com

Know PK Deficiency YouTube channel

Watch videos that provide information, resources, and awareness to support the people living with PK deficiency and their families

youtube.com/channel/UCF2jmKszBPS3yGVcyciizPg/videos

Know PK Deficiency Facebook page

Join the community and connect with people who have PK deficiency and their caregivers

www.facebook.com/PKdeficiency

European Organization for Rare Diseases (EURORDIS)

Hear from a community of 30 million people affected by rare diseases throughout Europe

eurordis.org

The National Organization for Rare Disorders (NORD)®

Hear perspectives on living with PK deficiency both from those who have the disorder and those who care for them

rarediseases.org/pkdpfdd-watch

As new information becomes available, we'll update the Resources page on **KnowPKDeficiency.com**. Check in there to stay up to date.

“My life, my future, depends on this.”

Molly, 32
Diagnosed with PK deficiency
at 9 months old

Goal-setting for life with PK deficiency

PK deficiency is a rare form of hemolytic anemia in which RBCs don’t have enough energy to work properly, so they die more quickly. Symptoms of PK deficiency are different for everyone and can change over time, so it’s important to keep track of how you feel.

Setting up a management plan with your hematologist can help you stay ahead of your PK deficiency symptoms and ensure you’re informed about new treatment options.

You have the power. Take action toward achieving the goals you’ve set for yourself.

Interested in what’s next for PK deficiency?

Agios is dedicated to the science and studies behind medicines to treat rare genetic disorders, like PK deficiency.

To stay informed about the latest news, resources, and research related to PK deficiency, register for updates at **KnowPKDeficiency.com**.

agios

©2020 Agios Pharmaceuticals, Inc.
All rights reserved. PKD-EU-0004