VOICE OF THE PATIENT REPORT

Pyruvate Kinase Deficiency

Externally-Led Patient-Focused Drug Development Meeting

Meeting Date: September 20, 2019
Report Date: January 21, 2020

HOSTED BY

National Organization for Rare Disorders (NORD) and Foundation for Rare Blood Diseases (SZB)

NORD® National Organization for Rare Disorders

SZB

Submitted as patient experience data for consideration pursuant to section 569C of the Federal Food, Drug and Cosmetic Act to:

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
US Food and Drug Administration (FDA)

VOICE OF THE PATIENT REPORT: PYRUVATE KINASE DEFICIENCY

This report represents the summary composed by the National Organization for Rare Disorders® (NORD) and the Foundation for Rare Blood Diseases (SZB) as a result of an externally-led Patient-Focused Drug Development meeting held on September 20, 2019, in Hyattsville, MD. This report reflects the host organizations' account of the perspectives of patients and caregivers who participated in the public meeting.

Submission: This report is submitted as patient experience data for consideration pursuant to section 569C of the Federal Food, Drug and Cosmetic Act to:

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A MESSAGE OF THANKS

Pyruvate kinase deficiency is a rare genetic disorder characterized by the premature destruction of red blood cells. On September 20, 2019, pyruvate kinase deficiency patients, caregivers and advocates came together with health care providers, industry representatives and government officials for an externally-led Patient-Focused Drug Development (EL-PFDD) meeting to have their voices heard. We heard from the community through stirring testimonies, community polling and open discussions about the critical issues patients and their families are dealing with throughout their lifetimes.

On behalf of the National Organization for Rare Disorders® (NORD) and the Foundation for Rare Blood Diseases (SZB), we'd like to express our deep gratitude to everyone who joined us for this important meeting. Pyruvate kinase deficiency is a disease with high unmet need, and one that imposes a severe burden on patients, especially in the pediatric population. Through this EL-PFDD meeting, we strove to provide researchers, drug developers, and the US Food and Drug Administration (FDA) with a robust understanding of patients' and caregivers' experiences with pyruvate kinase deficiency.

We are grateful for the community's participation and valuable input on this rare, genetic hemolytic anemia disorder, and are happy to be able to share the insights gathered through this "Voice of the Patient" report that will help inform the development of therapeutics that we hope can improve the lives of patients living with pyruvate kinase deficiency. We thank not only those who were able to attend in person but also our webcast audience, whose remote participation and input were equally valuable. In particular, we would like to extend deep gratitude to D. Holmes Morton, MD, Founder, Pediatrician and Interim Medical Director at the Central Pennsylvania Clinic, who assisted NORD with bringing together 24 Amish patients to capture their feedback for this report. We especially want to acknowledge the patient and caregiver panelists who bravely shared their stories and insights on stage.

We would like to thank the FDA for honoring our request to conduct this meeting, and for taking the time to participate. We give special thanks to all FDA officials who attended, especially to Wilson Bryan, MD, Director of the Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research (CBER), and Lucas Kempf, MD, Medical Officer, Rare Diseases Program, Center for Drug Evaluation and Research (CDER), for their contributions to this meeting. We were also privileged to hear an expert clinical overview from Rachael Grace, MD, Assistant Professor of Pediatrics at Harvard Medical School and Hematologist/Oncologist at Dana-Farber/Boston Children's Cancer and Blood Disorders Center.

We appreciate our industry sponsors and planning committee, who made our meeting possible. We also acknowledge Larry Bauer, Hyman, Phelps & McNamara, PC, for his critical input into the meeting design and excellent job facilitating the discussions.

This meeting was extraordinary and impactful not only because firsthand patient and caregiver testimony was heard by the FDA, but because it was the largest gathering of pyruvate kinase deficiency patients in the world at any time in history (there were 17 in the room). We are confident the voices of patients will significantly impact the future for all affected by pyruvate kinase deficiency, providing real hope for the future.

Sincerely,

Peter L. Saltonstall
President and CEO, NORD

Dore Peereboom
Foundation for Rare Blood Disorders

WHAT'S INSIDE

EXECUTIVE SUMMARY

Pyruvate kinase deficiency is a rare and complex genetic disorder characterized by hemolytic anemia (the premature destruction of red bloods), and results in a chronic, lifelong condition. In some instances, the disorder can be life-threatening at birth. Hemolytic anemia is associated with complications that need monitoring, including the development of gallstones, iron overload, pulmonary hypertension, extramedullary hematopoiesis, and low bone density. Pyruvate kinase deficiency is caused by mutations in the PKLR gene, which lead to a deficiency of the enzyme pyruvate kinase. Pyruvate kinase helps cells turn sugar into energy via glycolysis. The severity of pyruvate kinase deficiency can vary greatly and symptoms can be highly variable. Common supportive treatments for pyruvate kinase deficiency include blood transfusions, removal of the spleen and medications to remove excess iron from the blood (chelation therapy). There are currently no targeted drug therapeutics approved for the treatment of pyruvate kinase deficiency.

The externally-led Patient-Focused Drug Development (EL-PFDD) initiative is in response to FDA's interest in more systematically obtaining patients' perspectives on the burden of disease and impact of current treatments. An EL-PFDD meeting was held for pyruvate kinase deficiency in Hyattsville, Maryland, on September 20, 2019. Through this meeting, NORD and SZB provided a forum where pyruvate kinase deficiency patients, families and caregivers were able to share their unique insights on the impact of this disease on their day-to-day lives. Perspectives on currently available treatment options and strategies for disease management, as well as expectations regarding future treatments, were also shared.

The objective of the meeting was to increase our understanding of how patients, families and caregivers experience and manage pyruvate kinase deficiency, and the factors that are considered when treatments are chosen. This will, in turn, help researchers and the FDA understand patient preferences when developing new therapies and evaluating the benefit-risk for new treatment options for pyruvate kinase deficiency.

The voices of pyruvate kinase deficiency patients and caregivers were heard through courageous patient and caregiver testimonies, live polling of the broader audience, open discussions with meeting attendees, and post-meeting commentary. The meeting was attended in person by 61 people, and via live webcast by an additional 75 participants.

Throughout the course of these activities, the following key messages emerged:

- **Pyruvate kinase deficiency is a genetic condition with highly variable symptoms and manifestations with high unmet needs in individuals of all ages**
    - Although some individuals are not diagnosed until adulthood, pyruvate kinase deficiency can be life-threatening at birth
    - Pyruvate kinase deficiency appears with widely diverse and unpredictable symptoms and manifestations that have a huge impact on quality of life
    - Symptoms can be mild to severe and vary over the lifetime of the patient
    - Many of the common manifestations of the disease and treatments (e.g., blood clots, gallstones, liver disease) are not commonly seen in healthy children and thus can be easily misdiagnosed

    - Women often cannot take birth control pills because they have a higher risk of blood clots as a result of splenectomy
        - When they are unable to use multiple methods of birth control, women are often excluded from clinical trials, which may be partly responsible for the high (24%) clinical trial ineligibility rate experienced by pyruvate kinase deficiency patients
    - Additional complications that occur during pregnancy, including higher numbers of hemolytic episodes, cause some women to choose not to get pregnant
    - Post-traumatic stress disorder (PTSD) was often mentioned when describing the trauma of repeated transfusions, especially for young children
    - There is a concentrated population of pyruvate kinase deficiency patients in the Amish community in Belleville, Pennsylvania
        - A separate survey of patients and caregivers in this community revealed similar experiences to the more general pyruvate kinase deficiency population, with some notable differences
        - These differences included a lower rate of difficulties associated with the disease, including emotional/social challenges, and more emphasis on the concern about side effects when considering new treatments or involvement in clinical trials
    - In addition to new treatments to manage the symptoms of pyruvate kinase deficiency without significant side effects, patients are also very interested in predictors of splenectomy response, better ways to manage the complications caused by current interventions (specifically, better-tolerated iron chelators), and new devices to more easily and accurately measure hemoglobin levels
- **Patients with pyruvate kinase deficiency continuously deal with very difficult issues in their daily lives, the most important of which include:**
    - Tiredness/exhaustion/fatigue
    - Difficulty concentrating
    - Anemia
- **Patients with pyruvate kinase deficiency experience a high level of emotional and social stress/ stresses including:**
    - Anxiety
    - Low self-esteem
    - Social isolation
    - Depression
    - Bullying
- **Patients living with pyruvate kinase deficiency find that the disease limits them in various ways:**
    - They feel disconnected from others and stigmatized
    - They are unable to participate in sports/physical activities
    - They miss work or school too much
    - They have general daily function limitations

- **Patients living with pyruvate kinase deficiency are most concerned about the following issues:**
    - Iron overload caused by frequent blood transfusions
    - Worsening symptoms
    - The need for lifetime transfusions
    - Long-term risks of infection as a result of splenectomy
    - Not being able to parent or take care of a family
    - Looking different because of yellow skin/eyes
- **The most common medications or supportive treatments for pyruvate kinase deficiency include the following:**
    - Blood transfusions
    - Vitamins/folic acid
    - Full splenectomy
    - Cholecystectomy (gallbladder removal)
    - Iron chelation or phlebotomy therapy
    - Phototherapy
    - Exchange transfusion or pheresis (procedure in which the blood is filtered and separated and a portion is retained)
    - Antidepressant or antianxiety drugs
- **Current treatments for pyruvate kinase deficiency do not sufficiently manage the most significant symptoms:**
    - Only 11% of poll participants responded that their current treatments work very well, and 58% responded with moderately well
    - 14% responded that their treatments work poorly and 8% responded that they do not work at all
- **Disease manifestations and benefit-risk profiles of interventions change over time and thus are difficult to manage:**
    - Many patients feel their physicians do not know how to diagnose or manage pyruvate kinase deficiency
    - There are no standard care guidelines, perhaps as a result of the small size of the population, changes in disease manifestation over time, variable treatment courses prescribed and variability of patient responses to various interventions
    - Physician-determined targets for hemoglobin/hematocrit levels are not always in line with what targets patients feel are best for them
    - Patients feel their physicians don't understand symptoms related to anemia (fatigue, difficulty concentrating, memory issues) and will often not transfuse them despite these symptoms being associated with a very low hemoglobin level
    - Hemoglobin/hematocrit levels are not always predictive of how patients are feeling and can vary depending on environmental factors
    - Temperature (too hot, too cold), hydration, and illness can have a significant impact on hemoglobin levels and on how patients are feeling
    - There is constant consideration needed on the benefits and risks of transfusions and other interventions (such as splenectomy), and the right balance for each patient can vary over time based on their individual disease manifestations and intervention-induced side effect profile
    - Many patients feel they don't have easy enough access to transfusions
- **Many of the complications of pyruvate kinase deficiency are more a result of the current interventions than of the disease itself:**
    - Iron overload caused by frequent blood transfusions can lead to liver, heart, endocrine and other organ damage
    - There are long-term risks of infection and blood clot formation because of splenectomy
    - Side effects from iron chelation therapies can be significant and result in frequent trial and error to find the best option
- **Pyruvate kinase deficiency patients ranked the following as the most important when selecting a new treatment:**
    - Evidence the therapy improves the most bothersome symptoms
    - Severity of side effects
    - Improvements in anemia/reduction in transfusion needs
- **Without considering side effects, pyruvate kinase deficiency patients ranked the following as the most important for a future therapy:**
    - Evidence the therapy will improve or prevent future reduction in quality of life
    - Evidence the therapy will significantly decrease complications of pyruvate kinase deficiency (iron overload, gallstones, pulmonary hypertension, etc.)
    - Evidence the therapy will delay the need for transfusions
- **Pyruvate kinase deficiency patients ranked the following as the most important in their decisions to participate in a clinical trial:**
    - Potential side effects
    - Expectation to treat the underlying cause of disease
    - Need to stop current disease management regimen
    - Route of administration
    - Possibility of receiving a placebo

This EL-PFDD meeting was a critical step forward for the pyruvate kinase deficiency community. The insights collected and reported on in detail in this "Voice of the Patient" report reflect important perspectives of people living with pyruvate kinase deficiency and will help direct the FDA in partnership with pharmaceutical companies to develop the critical therapies that are desperately needed by this community. These insights will now be used to help develop a benefit-risk framework that the FDA can utilize in its regulatory decision-making. Some preliminary recommendations for this benefit-risk framework can be found in this report.

"So, in summary, products to treat rare diseases can get FDA approval based on studies in a small number of patients. I know sometimes folks think, 'Oh, we don't have enough people to get the data.' Yes, you do. Yes, you do. Developing new endpoints takes time. Again, what you say today will help us to think about the appropriate endpoints to use during drug development, but developing those endpoints needs to get started. And actually, you're already getting started…That sort of data can really help us to move drug development along faster."

Wilson Bryan, MD, Director, Office of Tissues and Advanced Therapies, Center for Biologics Research and Evaluation, US Food and Drug Administration

PYRUVATE KINASE DEFICIENCY EXTERNALLY-LED PFDD MEETING DESIGN

The patient perspective is critical in helping the US Food and Drug Administration (FDA) understand the context in which regulatory decisions are made for new drugs. Externally-led Patient-Focused Drug Development (EL-PFDD) meetings provide an opportunity for patients, their families and caregivers to share critical information about the impact of the disease on their daily lives and their experiences with currently available treatments. Patients' experiences provide valuable insight for the FDA and other key stakeholders, including researchers, medical product developers and health care providers.

EL-PFDD meetings are organized, led and paid for by patient organizations, and FDA personnel attend on a case-by-case basis. As new drug applications are filed by drug developers, the comprehensive "Voice of the Patient" report generated after the meeting is a critical additional resource for the FDA beyond the mandatory safety and efficacy data. The National Organization for Rare Disorders (NORD) and the Foundation for Rare Blood Diseases (SZB) applied to the FDA and were granted approval to host an EL-PFDD meeting focused on pyruvate kinase deficiency. This EL-PFDD meeting enabled the pyruvate kinase deficiency community to share with key FDA officials and other stakeholders the burdens of the disease and perspectives on future idealized treatments. This, in turn, will inform the FDA regarding the benefit-risk balance of treatment options, the severity of the disease and the urgency of unmet medical needs.

Pyruvate kinase deficiency is a rare condition with no targeted treatment currently available. Existing medical interventions (mainly routine transfusions and splenectomy) introduce significant risks and burdens to patients. NORD and SZB believe this rare, genetic hemolytic anemia disorder is one with an unmet need and a severe disease burden, especially in the pediatric population.

The goals of this meeting were as follows:

- Collect data and discern key insights for clinical trial design from individuals affected by pyruvate kinase deficiency and their caregivers, so that the outcomes of potential therapeutics can be measured in ways that are both clinically sound and therapeutically impactful
- Provide researchers, drug developers and the FDA with a robust understanding of patients' and caregivers' experiences with pyruvate kinase deficiency, including how individuals with pyruvate kinase deficiency view their quality of life, which aspects of the disease are most problematic for them and what actions they currently perform to treat and cope with this disease.

The EL-PFDD meeting included panelists that represent a spectrum of perspectives, including adult and pediatric pyruvate kinase deficiency patients and pyruvate kinase deficiency patient caregivers.

The voice of the pyruvate kinase deficiency patient was heard through courageous patient/caregiver testimonies, open discussions with the meeting attendees, live polling of the broader audience and post-meeting commentary.

A recording of the entire EL-PFDD meeting for pyruvate kinase deficiency can be viewed at the NORD website.

https://rarediseases.org/pkdpfdd-watch/

BACKGROUND ON PYRUVATE KINASE DEFICIENCY

What Is Pyruvate Kinase Deficiency?

Pyruvate kinase deficiency is a rare genetic disorder characterized by hemolytic anemia (the premature destruction of red bloods). Hemolytic anemia is associated with complications that need monitoring, including the development of gallstones, iron overload, low bone density and pulmonary hypertension. Pulmonary hypertension is a rare, life-threatening condition that, if left untreated, can cause death. The severity of pyruvate kinase deficiency can vary greatly. Common supportive treatments for pyruvate kinase deficiency include blood transfusions, removal of the spleen and medications to remove excess iron from the blood (chelation therapy).

What Causes Pyruvate Kinase Deficiency?

Pyruvate kinase deficiency is caused by mutations in the PKLR gene, which lead to a deficiency of the enzyme pyruvate kinase. Pyruvate kinase is an enzyme that helps cells turn sugar (glucose) into energy (adenosine triphosphate, ATP) via glycolysis. Because this enzyme is deficient, there is a lack of ATP. This leads to dehydration of red blood cells and abnormal red cell shapes. The altered red blood cell has a shortened life span (a few days to weeks, rather than the normal 120 days), leading to hemolytic anemia. As the altered red cells are destroyed, new red cells (reticulocytes) are created, creating a balance of increased red cell destruction and increased red cell production.

The PKLR gene mutations are inherited in an autosomal recessive manner. The risk is the same for males and females. Most individuals with pyruvate kinase deficiency have different variants affecting each copy of the disease genes (compound heterozygotes).

How Is Pyruvate Kinase Deficiency Diagnosed?

A diagnosis of pyruvate kinase deficiency is based on identification of characteristic symptoms (e.g., active hemolysis), a detailed patient and family history, a thorough clinical evaluation and a variety of specialized tests.

Initial lab tests may be performed to determine that anemia is present and whether it is due to hemolysis. Signs of hemolysis include a low hemoglobin level, an elevated unconjugated bilirubin level, an elevated reticulocyte count and low levels of haptoglobin in the blood.

The standard diagnostic test for pyruvate kinase deficiency is to measure the activity of the pyruvate kinase enzyme in red blood cells. Low activity of this enzyme is indicative of the disorder. Molecular genetic testing helps to confirm a diagnosis of pyruvate kinase deficiency.

The prevalence of diagnosed pyruvate kinase deficiency in Western populations is 3.2-8.5 per million (with a combined undiagnosed/diagnosed prevalence of 51 per million). With a current estimated US population of 330,000,000, the US prevalence of patients with pyruvate kinase deficiency disorder would be in a range from 1,056 to 2,805. The possible undiagnosed cases could be as many as 167,830.

What Are the Symptoms of Pyruvate Kinase Deficiency?

Symptoms of pyruvate kinase deficiency can be highly variable. In some instances, the disorder can be life-threatening at birth. Other individuals may have mild or no symptoms of the disorder and go undiagnosed into adulthood. Others may develop symptoms during childhood or as adults. The main finding, hemolytic anemia, is a chronic, lifelong condition.

Newborns

Before birth, some developing fetuses with anemia can develop a condition called fetal hydrops. This is a serious condition in which large amounts of fluid build up in the tissues and organs of the fetus. It develops because the heart has to pump a greater volume of blood to deliver oxygen than normal because of anemia. Anemia in the developing fetus can also lead to premature birth.

At birth, some infants may have significant anemia and severe jaundice (yellowing of the skin and the whites of the eyes). Jaundice is caused by high levels of bilirubin in the body. Normally, when old or damaged red blood cells are broken down in the spleen, bilirubin is released into the bloodstream. This type of bilirubin is called unconjugated (or indirect) bilirubin. The unconjugated bilirubin is taken up by liver cells, converted to conjugated bilirubin and excreted into the intestines and then into the stools. With hemolysis, an excess of bilirubin is released into the bloodstream and the liver cannot keep up with the conjugation process. Unlike in children and adults with elevated bilirubin levels, high bilirubin levels in infants can lead to kernicterus, a neurologic condition characterized by the accumulation of toxic levels of bilirubin.

Children and Adults

The most common finding in children and adults is anemia. Anemia can cause tiredness, fatigue, increased need for sleep, weakness, lightheadedness, dizziness, irritability, headaches, pale skin color, difficulty breathing (dyspnea), shortness of breath, and cardiac symptoms.

The degree of jaundice or scleral icterus is linked to the amount of total unconjugated bilirubin. This is determined both by the degree of hemolysis and by an individual's ability to metabolize bilirubin, which is genetically determined. Children and adults with pyruvate kinase deficiency can develop gallstones. The risk of gallstones is lifelong due to because of ongoing hemolysis. Affected individuals can also develop an enlarged spleen (splenomegaly). One function of the spleen is to filter red blood cells. The spleen becomes enlarged because it filters out the abnormal red blood cells.

Hemolytic episodes develop in the presence of stressors or triggers of hemolysis, which most often are infections and, therefore, more frequent in childhood. Pregnancy can also be a common hemolytic trigger.

Iron overload is one of the most common findings in patients with pyruvate kinase deficiency. Iron overload can occur both in individuals who receive blood transfusions and in those who have never been transfused. Iron overload is the abnormal accumulation of iron in various organs of the body, most commonly in the liver, but iron loading can also occur in the heart and hormone-producing organs (endocrine organs). Iron

loading is not associated with symptoms until a significant amount of iron is deposited, so it is important to monitor iron studies regularly in individuals with pyruvate kinase deficiency.

Other complications can occur in pyruvate kinase deficiency. Adolescents and adults can have weakened bones with an increased risk of bone fractures. Adults can develop skin sores (ulcers), typically around the ankles. Other less common complications include high blood pressure in the arteries in the lungs and the right side of the heart (pulmonary hypertension) and blood cell production outside of the bone marrow (extramedullary hematopoiesis).

How Is Pyruvate Kinase Deficiency Currently Treated and Managed?

There are currently no targeted drug therapeutics approved for the treatment of pyruvate kinase deficiency. Treatment may require the coordinated efforts of a team of specialists. Pediatricians or general internists, physicians who specialize in diagnosing and treating blood disorders (hematologists), obstetricians and other health care professionals may need to systematically and comprehensively plan treatment. Symptoms vary among patients, so an individualized treatment plan should be developed. Genetic counseling is recommended for affected individuals and their families.

Newborns

A blood transfusion may be necessary for the developing fetus (intrauterine transfusion) if fetal hydrops develops or if there are signs of poor growth related to anemia during pregnancy. Most newborns with pyruvate kinase deficiency will develop jaundice because of the breakdown of red cells and the inability of their immature livers to conjugate bilirubin. Some affected infants may require phototherapy for bilirubinemia. In some newborns with severe jaundice, an exchange transfusion may be necessary. High bilirubin levels in newborns require aggressive treatment to attempt to avoid the risk of kernicterus.

Infants, Children and Adults

In infants, children and adults with pyruvate kinase deficiency, blood transfusions may be used. The decision to transfuse is based not on the level of hemoglobin, but, rather, on how an individual is tolerating the hemolytic anemia. The goal is to avoid transfusions if possible, but they may be necessary, particularly in the first years of life, to support growth and development and avoid symptoms, such as fatigue or poor feeding. In older children and adults, there are no standard criteria or schedule for transfusions, especially since the symptoms differ so widely among individuals. For individuals with daily symptoms from anemia, regular blood transfusions may be recommended. Others may be transfused only for acute infections or in pregnancy. Other individuals may never have a blood transfusion.

Iron overload occurs commonly in individuals with pyruvate kinase deficiency, even in the absence of red cell transfusions, through increased absorption from the diet. Chelation agents bind with iron to form substances that can be excreted from the body easily. Phlebotomy can be used to unload iron from the body but is often not well tolerated in individuals with anemia.

Sometimes, the surgical removal of the spleen (splenectomy) may be recommended. Removal of the spleen may be considered if individuals require frequent blood transfusions or have frequent symptoms from anemia. Splenectomy, both open surgical and laparoscopic, has led to a partial improvement of the anemia in most individuals. However, this surgical procedure carries potential risks such as life-threatening bloodstream infections and blood clot formation (thrombosis), which are weighed against the potential benefits of splenectomy in each individual. Given the risk of infection after splenectomy, most individuals wait until at least the age of five years before proceeding with splenectomy.

Supportive care can include gallbladder monitoring because of the risk of gallstones. Gallbladder removal (cholecystectomy) is pursued in individuals with symptomatic gallstones and in individuals at the time of splenectomy. Folic acid supplementation, which supports increased red cell production, is often prescribed. Vitamin D, calcium and exercise may be important for bone health.

Allogeneic hematopoietic stem cell transplantation (HSCT) can cure pyruvate kinase deficiency. This has been pursued in a limited number of individuals, particularly individuals who require chronic blood transfusions. This is a major medical procedure that carries significant risk, including dying from complications related to transplant. Only a small number of individuals with pyruvate kinase deficiency have undergone HSCT in Europe and Asia. Most doctors think the risk-benefit ratio is in favor of splenectomy over HSCT. More research is necessary to determine the long-term safety and effectiveness of this therapy for certain individuals with pyruvate kinase deficiency.

What Research Is Currently Being Conducted to Develop New Therapies for Pyruvate Kinase Deficiency?

Researchers are studying pyruvate kinase activators, such as mitapivat, which act to increase the activity of the pyruvate kinase enzyme in red blood cells. Initial clinical studies of mitapivat have shown that this twice-daily, oral compound may be both effective and well tolerated. More research is necessary to determine the long-term safety and effectiveness of mitapivat for individuals with pyruvate kinase deficiency. Lentiviral vector-based gene therapy is also being pursued as an approach to therapy for individuals with pyruvate kinase deficiency.

MEETING PARTICIPANT DEMOGRAPHICS

The EL-PFDD meeting was attended in person by 61 people, and via a livestream webcast by 75 registrants for a total of 136 participants. Sixty-one of the overall meeting participants were patients or caregivers (45%), and 43 of these were present in person at the meeting venue. Others in attendance came primarily from industry, advocacy organizations and government.

The polling was made available to all patients and caregivers, and approximately 59% of them participated in the polling exercises.

Of the polling participants, 59% were pyruvate kinase deficiency patient caregivers and 41% were individuals living with pyruvate kinase deficiency. The polling revealed that 95% of the participants were US-based, with 68% identifying as female and 32% identifying as male.

Demographic Polling Questions

Where do you live?

This poll showed that most of the participants were from the East Coast (67%) and Midwest (19%) with the remaining respondents from varied locations within the US.

What is your age or the age of the person you are caring for?

There was a very broad range of ages in the patients represented: 22% were 12–17 years old, 19% were 50-59 years old, 16% were 5–11 years old, 14% were less than 5 years old, 14% were 30–39 years old, 11% were 18–29 years old and 5% were 40–49 years old. There were no patients represented who were 60 years or older.

At what age did you receive a diagnosis of anemia?

All patients represented had been diagnosed with anemia in their pediatric years: 83% were diagnosed at 0–1 years of age, 8% at 12–18 years of age, 6% at 6–11 years of age, and 3% at 2–5 years of age.

At what age did you receive a diagnosis of pyruvate kinase deficiency?

The specific diagnosis of pyruvate kinase deficiency tended to come earlier in life. Of the patients represented, 59% were diagnosed with pyruvate kinase deficiency at 0–1 years of age, 15% at 2–5 years of age, 10% at 6–11 years of age, 10% at 12–18 years of age, and 5% at 18–29 years of age.

VOICE OF THE PATIENT, SESSION 1: LIVING WITH PYRUVATE KINASE DEFICIENCY—BURDENS AND SYMPTOMS

In Session 1, the emphasis was on perspectives from patients and caregivers related to the burden of living with pyruvate kinase deficiency and the symptoms presented by this disease. The session began with stirring personal testimonies from patients and caregivers living with pyruvate kinase deficiency. This was augmented by in-depth discussion with the audience members, and by a poll of the broader audience on specific questions. Following the meeting, all attendees were able to submit additional comments via email for a period of 30 days. The results of the patient voice activities from Session 1 are summarized below.

Session 1: Patient Testimonies*

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Becky (caregiver for a three-year-old child):

"Rem is super strong. Somedays she just wants to cuddle and have us rub her legs. The whites of her eyes turn yellow. This is usually the first symptom. Following is her yellow skin. She does get crabby, dizzy and has leg pains. We are doing transfusions every three and a half weeks. Because of all the transfusions, Remy has PTSD. She gets really bad anxiety. It's hard to deal at times. She hates the pokes.

We do not go out a lot when it's cold and flu season. Remy gets sick, her counts drop. We are isolated ourselves. We give Remy extra time. We just make sure she doesn't overdo it. Remy just gets sick easier. The heat makes her feel worse."

Cathy (patient):

"When I was born with pyruvate kinase deficiency, not much was known about this disorder. Within 12 hours after birth, my bilirubin was dangerously high. It was decided an exchange transfusion must be done, and quickly. Intensive phototherapy and other supportive therapies took care of the initial crisis followed by a regimen of lifesaving transfusions and frequent blood draws.

There were times when all the grit and determination in the world wasn't enough to keep me from crashing into bed, not being sure whether I'd ever be able to get up again. These crashes were the result of pushing myself hard to accomplish what healthy people could do easily. At its worst the bone deep fatigue would affect my memory and I remember not being able to recall my phone number to give to my sick child's pediatrician."

Ai Bee (caregiver for a 15-year-old child):

"When LynnAnn was born, she was admitted immediately to the NICU of Piedmont Hospital. Her hemoglobin was only 4.2 at that time and she was 'coded blue' twice. After the rough beginning at birth, LynnAnn went through multiple blood transfusions, a heart surgery, and a liver biopsy…When LynnAnn was 12, she was formally diagnosed with pyruvate kinase deficiency…Currently, the symptoms that affect her the most are gallstone attacks, extreme fatigue, requiring blood transfusions every 2 months, and frequent hospital visits due to poor immune system.

**Patient testimonies are related verbatim throughout the report.*

We do not expect LynnAnn to be married or have children. It would not be fair to expect another person to pick up this financial burden to care for our child. We do not expect LynnAnn to be able to live independently in the future. Her extreme fatigue may not allow her to secure a permanent job. We are constantly worrying about her future and how she could afford to support herself with all these expensive medical treatment and medicine."

Tamara (patient):

"In public, random people would approach me about my jaundice with unsolicited advice—druggies wanted to know what drug I was using, law enforcement wanted to know the same thing, nurses begged me to 'get help,' and there was always the church lady offering her prayers. I hated the unwanted attention. Instead, I developed an eating disorder because I figured if I had to be yellow, I'd at least be thin. I had anorexia nervosa first, then bulimia.

At 26 my spleen was removed. There were complications and I developed a portal vein clot, esophageal varices, and bowel problems that plague me to this day. At age 35 I started having atrial fibrillation from possible iron overload, and last December I had a pacemaker installed.

Pyruvate kinase deficiency fatigue feels like a 3-year old meltdown. It's both an emotional and physical breakdown. When I'm tired it means I'm dizzy and I need to hold on to steady surfaces, my brain is foggy and I can't focus, I can't remember words, I have a headache and my body is sore. It feels like I'm drunk. I shouldn't drive or make decisions."

Alejandra (caregiver for a15-year-old child):

"Over time, we found many different symptoms that might've been difficult to identify, like his problems with his lungs, oxygen desaturations, hyper/hypoglycemia, congenital heart conditions, chronic illnesses, etc. Most patients with pyruvate kinase deficiency have complex issues, multiple symptoms, and/or variable presentation of the symptoms…Due to Jonathan's splenectomy, he's been experiencing other health problems like acute pancreatitis and inflammation of his lymph nodes. A year after his splenectomy he had a surgery in his neck to remove non-malignant tumors, then a year after that, he had his tonsils removed.

Living with pyruvate kinase deficiency can isolate you from the world, because the conventional treatment for pyruvate kinase deficiency prevents kids, teenagers, young adults, and adults to live a normal life, especially if you suffer from severe pyruvate kinase deficiency like Jonathan. Where his symptoms, amount of blood transfusions, and admissions to the hospital prevent him from having a normal social life."

Session 1: Moderated Audience Discussion

The following is a sampling of insightful comments that were made by the broader attendees during the moderated audience discussion during Session 1. Some comments were also taken from the post-meeting 30-day open comment period.

Discussion Question 1: Of all the symptoms that you experience because of your condition, which 1–3 symptoms have the most significant impact on your life?

"…probably the biggest symptom is the pulmonary hypertension, because obviously there's fatigue but that just compounds it with just your normal day-to-day activities and having to pace myself even further on the things I used to be able to do before, that just adds to it. That's probably the thing today that's my biggest impact on my life."

"…it's not just the fatigue like he was saying. To go up the stairs, it sometimes takes a huge step for him. It is really difficult just to finish the steps for him to go up to his room."

"I think that one of the biggest fears as a parent is that your son is going to have a blood clot. He cannot breathe correctly…is he having a blood clot? Or he has stomach aches and all these things. It's everything related to one another. It's like a chain reaction a lot of times and you have no explanation what is happening. Why a 10-year-old kid is having a blood clot? Doctors say, 'No, it's not possible.' Sorry. Yes, it is."

"Okay. Another one is depression and PTSD, like it is so hard…We drug her before her transfusions. We give her lorazepam before her transfusions because as soon as we pull into the hospital, she starts screaming that she doesn't want to be there, and she wants to be home. It's so hard. No matter how much her doctors want to make her feel better, and she's also three, so it's hard to explain to her that this will make you feel better. All she knows is I'm going to get poked and she just doesn't want to get poked. Pokes means hurts."

"I'm a caregiver of two pyruvate kinase deficiency patients and one of them has severe liver damage with this, and also has secondary issues with that liver damage. Couple being the extreme itching that comes with it and also causes trauma with the perforating collagenosis from all the itching. Liver damage really is a big symptom besides just iron overload."

"The irritability is significant these days too. When you're so tired, you're just angry. You're irritable, because you never feel good ever. I never feel good…And headaches, I forgot to tell you about that. Yeah, the headaches are immense. You have them a lot."

Discussion Question 2: Which symptoms affect you now and which symptoms were most significant in other times of your life?

"I am so fatigued I have a hard time working for a living at this point in my life. I've been working for about 33 years now. Also, recently I have discovered that I can't think straight, I can't concentrate, I have terrible memory loss. My anxiety about being able to speak and not forgetting what I'm saying affects me greatly right now, so standing up and doing this right now, I'm very brave to be doing this."

"The symptom that affected me when I was a young child was stomach aches. I just remember the constant stomach aches I had. I had my splenectomy at five years old and I had my gallbladder taken out at 13, I believe, and tonsils and adenoids removed when I was 14. I lived a very healthy life after all those surgeries. I lived a very healthy life for many, many, many years. Recently as I've gotten older, I seem to be, things are starting to affect me again."

"I had my splenectomy when I was five and at that point I was no longer transfusion-dependent. I only had to have transfusions before surgeries, and like I said, I just had one last week, which was my first one since then…I had obviously severe pain for years of my life with the gallbladder issue. They started at 10 years old and I didn't have my gallbladder removed till I was 14."

"Just more tired. I could tell it was a difference than just being a normal tired, to the tiredness and the fatigue that I was experiencing. And again, just the memory loss, losing my words in the middle of what I'm saying, not being able to remember even what I'm talking about. I joke to everybody that by the time I'm 55 I'm not going to know my name or my address or my phone number anymore."

"When I was younger I had less fatigue actually. Then over time I've gotten more fatigued and I got my gallbladder taken out a couple of years ago, like six years ago, because I had the attacks and that was just like the worst thing ever."

"…and I really struggled when becoming sexually active, when I had the clot, just what sort of birth control to use. Because I had a portal vein clot, so basically everything that had estrogen in it was taboo. It was really a challenge for my husband and I to figure out what to use. Yeah, now I'm done with menopause, so it's not an issue anymore. But I think that's a pretty valid concern for a woman."

"I had a very short menstrual cycle. It didn't really even last that long, like I got it late and it ended early."

"I had just a superficial blood clot when I was in college, and was having ovarian cyst rupture, was not sexually active, but I was on a very high dose birth control, and they found a superficial blood clot. Fast forward to when I got married to my husband and we had to figure that out. There are just not many options out there. Then fast forward again to after having numerous DVT clots and pulmonary embolisms, and then going on the clinical trial, you have to agree to have two [very strong, preventative] forms of contraception…After I'm having more blood clots and having to have two forms. It was so challenging and stressful, and anxiety driven, because that's something you don't want to have to think about, but you do. Having blood clots and that estrogen just does not mix, so that's not an option. It can be very scary."

Discussion Question 3: How do your symptoms and their impacts affect your daily life? Can you give a real-world example of how PKD affects your daily life?

"I was able to return to a part-time teaching position, allowing me the flexibility to care for my family and to get the extra rest I needed to stay healthy. Later, I returned to full time teaching and eventually, after five years, became so fatigued that it impacted my household, family, and work responsibilities. I would get so drowsy while driving home that I needed to routinely pull over and take a nap in the car. Overall, if I wasn't moving, I was falling asleep. It impacted all aspects of my life. I took the following year off from work but, due to embarrassment, did not disclose to my employer that it was for medical reasons. Unfortunately, this decision has had long term financial implications for my family."

"When it's summer and it's really warm, his hemoglobin drops a lot faster than normal. He usually gets the blood transfusions every three weeks. But during the summer he can take it every two weeks or even every week, because his hemoglobin drops to numbers he usually is never. During winter months, he can be around 10, 9, but summer it can be dropped down to 8, 7.9, so even the outside environment can affect the patients differently."

"I think a very high temperature heat has a very strong impact on your hemoglobin. I had the misfortune of being on a tour bus with no air conditioning once, and it was very, very warm, and I could tell within hours that this is not going to be a good trip."

"In the summertime, it's the heat. I'm not active when it's warm, it's not the activity. I don't have the stamina to be active when it's warm out, but just when it's warm, it just drops your hemoglobin."

"I would say that temperature extremes really wreak havoc on red blood cells. At least that's my experience. Then I think the other thing is that, I think one of the side effects of having pyruvate kinase deficiency is just having thyroid problems so that every single patient should have their thyroid checked almost every single visit. I mean, I really think they go hand in hand. The moral of that story is I'm on thyroid medication also, which has helped with my temperature control for my body."

"I think one of the things that she doesn't talk about too much is how getting sick will really just knock her out, like even just little things. I remember she was hospitalized about four years ago because she had mono, and parvo, which is something that you don't really see in adults except for adults with anemia."

"It's the financial responsibility of trying to make sure that everything's paid off and paid for and becoming on a first name basis with the collection agency because they're constantly calling you because you're behind on a hospital bill or whatever."

"It also affects school days. They miss a lot between being sick and it's really hard to stay active in a regular school. Sometimes during bad periods, online school is sometimes easier for them to get through and not have their education suffer any through this."

"Well, between just doctor visits alone and being sick, hospitalizations, all that, you fall back in school. It's always feeling like playing catch up. What was most important is her health of course, but education is a big importance. When they're this young, they don't understand. It's not fair to miss out on certain activities and the socialization of being in a public school, so it's a hard balance."

Session 1: Polling Results

The following is a summary of the polling results for Session 1. For a full description of the polling questions, see Appendix 3.

Have you experienced any of the following difficulties because of your pyruvate kinase deficiency (select all that apply)?

This poll revealed that there is a wide range of very serious difficulties experienced by many patients.

- 100% have jaundice/yellow in eyes, 97% have anemia, 97% experience tiredness/exhaustion/fatigue, 94% have iron overload, 91% have exercise intolerance
- 80% have shortness of breath, 77% have enlarged spleen, 74% have abdominal pain, 66% have gallstones, 66% have heart racing (tachycardia)
- 54% have bone pain, 31% have low bone density, 20% have pancreatitis, 9% have leg ulcers

Which three of the following symptoms of your pyruvate kinase deficiency most negatively impact your daily life?

This poll showed that 88% of patients feel that the tiredness/exhaustion/fatigue associated with pyruvate kinase deficiency most negatively impacts their daily life. 53% chose difficulty concentrating, and 48% chose anemia in response to this question.

Which have you experienced [relating to emotional health and social life] while coping with your pyruvate kinase deficiency (select all that apply)?

The most common responses to this question included anxiety (84%), low self-esteem (61%), social isolation (58%), and depression (55%).

Which of the following statements is true for you as related to living with pyruvate kinase deficiency (select all that apply)?

The most common responses to this question included feeling that others don't know what it's like to live with pyruvate kinase deficiency (81%), inability to participate in sports or other enjoyable physical activities (72%), missing work or school too much (67%), and general daily function limitations (67%).

What is your biggest concern about living with pyruvate kinase deficiency?

The most common concerns expressed were iron overload (87%), worsening symptoms (82%), needing transfusions forever (68%), long-term risks of infection due to splenectomy (53%), not being able to be a parent or take care of family (50%), and looking different due to yellow skin/eyes (45%).

VOICE OF THE PATIENT, SESSION 2: CURRENT AND FUTURE TREATMENTS

To understand the perspectives of pyruvate kinase deficiency patients and caregivers regarding current and desired future treatments, a panel of patients/caregivers shared their thoughts and experiences. This was augmented by in-depth discussion with the audience members and by a poll of the broader audience on specific questions. Following the meeting, all attendees were able to submit additional comments via email for a period of 30 days. The objective of the session was to gain a better understanding of the pros and cons of current treatments, and then to develop patient-focused insights on what the community values most in the development of new therapies. The results of the patient voice activities from Session 2 are summarized below.

Session 2: Patient Testimonies

The full testimonies from each patient can be found in Appendix 2. Here are some of the most impactful comments made by each.

Zach (caregiver for two children, four and six years old):

"Our concerns for the future include those for their quality of life (as far as energy and ability to thrive), the effects of lifetime iron overload on the organs, the potential for contracting disease through such frequent blood transfusions, our daughter becoming a mother and carrying children, and acute crises such as gallstones, and related issues."

Because our children's iron overload and other symptoms are currently fairly well-controlled, our greatest desire, medically, is for the successful discovery and availability of medicine that would safely activate the PK enzyme and elevate their hemoglobin to somewhat normal levels, therefore eliminating or reducing the need for frequent blood transfusions and pyruvate kinase deficiency's associated symptoms."

Libby (patient):

"At age 33, I got pregnant with my little boy, and required 10 blood transfusions throughout pregnancy, and three with delivery. Being pregnant was extremely tough on my body. Iron overload got worse after pregnancy because I wasn't able to be on any chelation drugs during pregnancy. I had increased iron in my heart and liver."

Obviously, having to receive blood transfusions requires an IV being placed. Because I developed so much scar tissue in my hands and arms, it was a struggle to find adequate veins. In 2016, my doctors needed to place a chest port to have easier access. Because of the chest port, I developed numerous DVT blood clots, and pulmonary embolisms two different times. My doctors learned patients with pyruvate kinase deficiency having a splenectomy at a young age were developing blood clots as adults.

My ideal treatment for pyruvate kinase deficiency would be successful gene therapy to replace the inactive PK enzyme, and get it functioning to prevent the hemolytic anemia. Also, I have learned to tolerate receiving blood transfusions, but the iron overload that comes with all the blood is horrible. If I didn't have to endure even more side effects of iron overload, I think it wouldn't be as bad."

Jennifer (caregiver for two children, six and eight years old):

"The doctors did a liver biopsy and more genetic testing to get a better understanding of the degree of damage, and also to rule out any possibility of other diseases. These tests have all come back negative for any other non-liver diseases. This damage is not from iron overload, which is more commonly seen with pyruvate kinase deficiency, but from the production of calculi and sludge, creating blockages. Even with her gallbladder being removed and daily antibiotics and many endoscopic retrograde cholangiopancreatography (ERCP) procedures, the calculi are still forming rapidly and causing continual damage."

The medications she is currently on are Ursodiol to help with bile duct flow, Cipro antibiotic to help prevent infections, Zofran for nausea, Clonidine to help with anxiety, photo light therapy to help with the itching and perforating collagenosis, ERCP as needed to clean out blockages in her bile ducts, and blood transfusions to help with the hemolysis. The treatments have not made a difference in stopping or preventing the continuing damage to her bile duct and liver."

The physical and psychological trauma of being stuck with needles and held down for sedation to perform procedures have been overwhelming. Anxiety and depression have been increasing with each appointment and procedure."

Tina (caregiver for two children, 31 and 11 years old):

"Molly had her spleen removed at age four and had few transfusions for several years afterwards. At age 10, her gallbladder was removed due to gallstones, and a subsequent liver biopsy showed that she had severe iron overload. She frequently presented with an enlarged liver. She had pituitary gland damage from the iron overload and didn't produce adequate growth hormone, so she took growth hormone shots for three years. The lack of spleen presented with extreme illness and hospitalizations, during one of which she was becoming septic.

So, with Adam, after consultation with a wonderful doctor, we did NOT have his spleen removed and we did NOT let his hemoglobin go below 9. Our rationale was that he would likely have to return to transfusions anyway as Molly had to do, and that he would still get iron overload from the red cell breakdown as Molly had. But, he would feel better with the higher hemoglobin and he would not be ill and hospitalized as much since the intact spleen would be able to help with that. All of this proved to be true, and he never had an enlarged spleen or liver.

Both children had iron overload and did well with subcutaneous desferoxamine. Neither were able to handle Exjade. Adam has done well on Jadenu, but Molly did not do well with any of the oral chelators. As far as meds, aside from RBC transfusions and chelation therapy, both children take ibuprofen to manage headaches, joint, and back pain from a low hemoglobin, as well as baby aspirin and folic acid."

Jonathan (15-year-old patient):

"My iron-chelation medicine keeps me from dying from a large buildup of iron in my vital organs, but at the same time, the iron chelator itself can greatly damage my organs. My blood transfusions also keep me alive from losing all my blood, but the blood transfusions also give a chance of contracting blood-borne illnesses through transfusions, and it also causes my liver/bone marrow to overwork, damaging them in the process. Not only that, but the blood transfusions cause my chronic iron overload.

An ideal treatment for me would be a simple pill that I could take over time, which over the course of a month would cure me of pyruvate kinase deficiency and slowly get rid of the extra illnesses and symptoms that come with it. This pill would have no chance, or at least an impossibly low chance of death. It would also require no surgery and it wouldn't take any of the time I need for school.

I would consider another clinical trial if it had little to no risks, but anything with a higher risk of something unfavorable is too risky for my age. The most important symptom I would like to see treated is the need for blood transfusions. The effects of chronic iron overload should also be the top priority."

Session 2: Moderated Audience Discussion

The following is a sampling of insightful comments that were made by the broader attendees during the moderated audience discussion. Some comments were also taken from the post-meeting 30-day open comment period.

Discussion Question 1: What are you currently doing to help treat your condition or its symptoms?

"Transfusions are expensive. It's about $5,000 to do a transfusion every month. The battle I had with the hospital was they wanted me to go to an outpatient lab to get a CBC to check whether my hemoglobin level was below a certain threshold that would then allow me to get type and crossed. So, I would have to get two sticks. I would have to basically get a CBC, make sure that it was below a certain threshold. If it was, I would go get another stick to basically do a type and cross. I said, 'This is ridiculous. Why don't we just assume it's where I think it is, and do all of the blood work up front?'"

"Erythropoietin is taking me from…between 6 to 7 to now 7 to 7.5, which I really appreciate your comment because 7.0-7.5 is just not a great quality of life."

"When my hemoglobin levels drop, I obviously get more fatigued. But it's hard because that'll even trigger a depression state and you have to be very, very careful. Especially when you're on medication for a long time. I know my husband said he's also worried about my liver and taking long-term medication, especially with the bipolar. I take two different medications, one to sleep and one to maintain my mood, so it's just really hard to try to balance everything with social life and work and everything like that."

"One thing that I find that actually does help me, which I cannot get my doctor to understand, is resting…I did take an extended time off of work, five weeks. Before I did, it was at that 6.8 level, and when I went back to work, which I was forced to go back to work because I was denied the FMLA while I was out, it had gone back up to a 7.1 on its own. I actually really feel that if I could get the proper rest, or maybe work part-time, or whatever it is I need…my hemoglobin would raise on its own. But I cannot get anybody to believe me."

"I became a vegetarian because of just trying to avoid iron. I don't know if it makes a huge difference, but I feel like it does."

"I just try and avoid anything acidic when I consume food. So, no sodas, no orange juice. I try and drink iced tea. I'm not convinced that dietary aspects help all that much, but I try and do my part as best as I can. I do avoid red meat."

"But what really can make you feel a little bit better is to have a more balanced diet instead of to have just vegetables, or just to get meat. It's to have a more balanced diet."

"The only thing that my hematologist has ever been given me is folic acid and I take two milligrams a day and that's it. That's my treatment and I don't feel any different. I don't have more energy."

Discussion Question 2: How has your treatment regimen changed over time and why?

"I was transfusion dependent until I had my spleen removed at age four or five. Post splenectomy, I was transfused on an as needed basis when I became ill. I had a hard time with illness and even became septic with one incident of illness in my later years. I was not doing well without transfusions so I went back to being transfusion dependent-ish. I received them but not on a regular basis. I began having issues with blood clots along with experiencing symptoms of low hemoglobin. It became evident my body needed the healthy cells, so my hematologist opted to make my transfusions regular to maintain a hemoglobin of 9.0."

"After my spleen was removed, I think I could probably count on one hand the number of transfusions I had until mid-30s. In my mid-30s, I think I was cursed with a narrow common bile duct, so I started to develop biliary sludge that would cause blockages, I would be prone to sepsis. I would have to have multiple ERCPs. I think I've probably had close to two dozen ERCP procedures."

"I think it's important to gain your hematologist's trust and help be the best advocate you can for your body because as you were saying earlier, you know your body the best. Sometimes that hemoglobin number is not a correlation of how you feel. There's been many times that the hemoglobin number, which also can be skewed if you're dehydrated, so if you're dehydrated, it's going to be a lot higher than what it actually is. So, trying to get yourself to drink enough water to go in and then not have a skewed hemoglobin so you can actually get a blood transfusion."

"As I found I've gotten older, I do work, I do have a family, to maintain those responsibilities I think it's like table stakes. I have to have a hemoglobin of 10, there's just no way I can function. I do have a brother that has the same condition, but he refuses to get blood transfusions, so he does not work. He is on disability. For me to function, that's the regimen that I have to go through."

"I am a caregiver of my son Travis, who's 12 he actually did not have exchange transfusions when he was younger. He actually has them now. That's his course of treatment…because then we would be removing some of that iron as we were transfusing him. He now gets exchange transfusions every four weeks. And his biggest side effect is raising his potassium level."

"He was in extreme pain…he was screaming and sweating and yellow and he was just terrible…So he had to be completely taken off the Jadenu, and he was never able to take it again…he's allergic to Jadenu and they had to restart the Ferriprox and Desferal for a while and start to go down. And right now, he's just on Ferriprox."

"I started on Desferal, and it kind of plateaued, but with a Desferal I did the subcutaneous pump. And that works pretty well. But I couldn't be on it for like more than three or four months at a time because it really started to fatigue me and then I would be off of it for a couple of months and then could go back on. But then my ferritin numbers just kind of flat lined and then got off of that and I started with

Jadenu…I haven't had any negative reactions from the Jadenu and it's worked really well. It's continued to drop my ferritin."

"I first started with Exjade oral, just dissolve it and then take it with water. I developed severe GI issues, so every bathroom was an emergency and I just couldn't tolerate that. So, they transitioned me to Desferal, which is the subcutaneous pump. The way I received it was anhydrous. I had to play chemist and mixed my own medicine and I would transfer, well, infuse myself overnight. And then it's a burning sensation at the site of injection. So, I'd overdose with Benadryl just so I could sleep at night and so I do that over eight hours and use that worked…I travel a lot for work so it's, I'm not going to drag all that's required. I started about two years ago, moved to Jadenu. The big challenge I had with Jadenu is it affects the kidney function, so I can't take the maximum dose."

"The final thing that evolved for me as I've gotten older is my anticoagulant therapy…clot formations while on an anticoagulant have caused concern for me with regard to pregnancy. I have an upcoming appointment with a maternal fetal medicine specialist who also specializes in genetics and clotting. I will be going in October to see an opinion regarding if it is advisable for me to become pregnant."

Discussion Question 3: How well does your current treatment regimen treat the most significant symptoms of your disease?

"There is a profound lack of a standard of care for how to treat the disease. I have advocated for that, and even willing to write one. I think it's one of the things I struggle is, every hematologist has a different opinion, which to me is unacceptable. I guess that's why they call it 'practicing medicine.'"

"It is such a balance, because clearly I don't want a blood transfusion because that means a lot more iron. But, when you are so sick and you can barely walk, and you are having trouble breathing, you have to have blood because that's what's going to make you feel better."

"Before I had my latest transfusion, my hemoglobin was at a 7.1. Which wasn't tolerating very well anyway, and I probably needed a transfusion before that, but I was having a hard time finding a doctor to believe I was even sick. It went down to a 6.8, and that's a big difference to me. It's even a large difference between a hemoglobin of 7.5, which I actually tolerate pretty well. I function pretty well at a 7.5, but when I went down to 7.1 I barely could function. A 6.8, of course, functioning even less. Finally, had the transfusion at a 6.4. I remember my hematologist saying to me, 'Well, that's such an insignificant range. I don't know how you could feel much worse or any worse than you do.' I was like, 'Well, I'm sorry you feel that way, but—' I was shocked, actually, and appalled really that he even said that to me. I didn't even have a reaction to him. I didn't even know what to say or what to do. It was just immediate anger and frustration."

"I just now got a doctor to believe me and understand that it's affecting me greatly from going from a hemoglobin of 7.5 to a 6.4. That's what my last blood test told me that. I finally did have a transfusion

last week, so I do feel a little bit better. It did not take me to the level that I thought I was going to be in energy, so I still have a very low energy level."

"I wish there were better iron chelators than what's available today. I think there's a lot that caused some measure of toxicity in the body, and not well-tolerated. I think my ideal treatment would be something that can stabilize my hemoglobin above 10 where I no longer had to have transfusions or worry about chelation therapy."

"We know that I cannot take that drug. Jadenu, if I go for what my body weight is, and the amount I'm supposed to have, I am so much worse than when I am when I have low blood. I cannot get out of bed. It is crazy, and that's happened three different times, so we've now just stuck to a lower dose of Jadenu. I feel like any dose of an iron chelation is better than no dose of an iron chelation."

"I think there might be, you know some way to test our hemoglobin at home ourselves which could be beneficial to us obviously. One thing that seems to be an issue and especially as you get older is just the accessibility of being able to actually access blood. So, for me there is nothing that you can actually get blood out of. You can poke, poke, poke, poke, poke, poke, poke, but there's no blood available and, I'm sure there's a name for it. Right now, all of my blood draws are out of either my hands or my feet."

"Assuming that there is no complete cure for pyruvate kinase deficiency, I hope that future research results in:

- A deep understanding of pyruvate kinase deficiency as a disorder—its natural history—in order to appropriately weigh the risks and benefits of any treatment, it's imperative to understand the consequences over time of the disease
- A medication that raises and stabilizes the hemoglobin of all PKD mutation combinations with minimal side effects
- Improved blood management practices for patients in need of transfusions
- Safer chelators
- Improved non-invasive imaging for iron overload
- Excellent standards of care and access to that care for all PKD patients"

Session 2: Polling Results

The following is a summary of the polling results from Session 2. For a full description of the polling questions, see Appendix 3.

What is your experience in, and perception of, clinical trials for a new pyruvate kinase deficiency treatment?

Twenty-six percent of respondents have not participated in a trial because they didn't know about the opportunity, 24% have not participated in a trial because they were not eligible, 24% have participated in a trial and would do so again, 12% are currently participating in a trial, 3% would never enroll in a clinical trial, and 12% were not sure of their answer.

Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating in a clinical trial.

The most common responses to this polling question included potential side effects from a new drug (100%), whether the drug is supposed to treat symptoms or the underlying cause of disease (67%), whether I need to stop my current disease management and treatment regimen (58%), how the drug is taken (50%), and whether I might get placebo (47%).

Select the medications or supportive treatments you use or have used for pyruvate kinase deficiency. Select ALL that apply.

The most common answers to this question included blood transfusions (100%), vitamins/folic acid (89%), full splenectomy (69%), cholecystectomy (gall bladder removal [63%]), iron chelation or phlebotomy therapy (63%), phototherapy (43%), exchange transfusion or pheresis (34%), and anti-depressant or anti-anxiety drugs (34%).

How well does your current treatment regimen reduce the most significant symptoms of your pyruvate kinase deficiency?

Fifty-eight percent responded that their treatments work moderately well, 14% responded that their treatments work poorly, 11% responded that their treatments work very well, and 8% responded that their treatment do not work at all. 8% do not currently take any treatments.

Which THREE factors are the most important to you when deciding to select a new treatment or drug for your pyruvate kinase deficiency?

Respondents ranked the following as most important to be addressed by a new drug treatment: evidence in pyruvate kinase deficiency patients that the drug improves specific symptoms that are the most bothersome (68%), severity of side effects (57%), whether drug will improve anemia or decrease transfusion needs (51%), whether drug is taken by mouth, IV or injection in muscle (41%), and cost and/or whether covered by insurance (35%). Only 3% considered what their physician recommends an important factor.

Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy for your pyruvate kinase deficiency?

In response to this polling question, 51% chose evidence that the drug will improve quality of life or prevent future reduction in quality of life as the most important. This was followed by evidence that the drug significantly decreases the complications of pyruvate kinase deficiency (iron overload, gallstones, pulmonary hypertension, etc. - 30%), and evidence that the drug will delay the need for transfusions or increase the time until next transfusion (16%).

Which of the following statements most closely reflects your physical symptoms and how related they are to your hemoglobin/hematocrit levels?

In response to this polling question, 49% replied that they can sometimes predict their hemoglobin test results based on how well/not well they are feeling, 43% replied that they can reliably predict their hemoglobin test results based on how well/not well they are feeling, and 9% replied that their hemoglobin test results do not reliably indicate how well/not well they are feeling.

SPECIAL EXTERNAL SESSION: INSIGHTS FROM THE AMISH COMMUNITY

While pyruvate kinase deficiency is very rare in the general population, there exists a community where it is not rare. An Amish community founded around 1791 in Belleville, Pennsylvania, has documented at least 50 cases of pyruvate kinase deficiency. Pyruvate kinase deficiency is more common in this community due to a founder effect resulting from the small size of a population with common ancestry, which leads to a higher frequency of disease manifestation for recessive genetic diseases. Since many of the Amish community do not access the types of technologies that were used to gain insights at the EL-PFDD meeting (e.g., emails, webcasts and computerized surveys), NORD brought the discussion to them. The FDA confirmed that this was the first time the Amish community has been included in a "Voice of the Patient" report.

To engage this community, Dr. Holmes Morton (who treats many Amish patients with pyruvate kinase deficiency) invited NORD representatives to speak to a group of 50 Amish patients and parents. They then asked similar survey and discussion questions to those considered at the EL-PFDD meeting. The average number of participants answering each of the polling questions was 17. Seventy-six percent of the Amish participants were pyruvate kinase deficiency patient caregivers and 24% were individuals living with pyruvate kinase deficiency, with 86% identifying as female and 14% identifying as male. Here are the key results from this engagement.

What is your age or the age of the person you are caring for?

There was a very broad range of ages in the Amish patients represented:

- 19% were 30–39 years old
- 14% were 5–11 years old
- 14% were 18–29 years old
- 14% were 40–49 years old
- 14% were 50–59 years old
- 10% were <5 years old
- 10% were 12–17 years old
- 5% were 60–69 years old.

At what age did you receive a diagnosis of pyruvate kinase deficiency?

95% of the Amish patients received a diagnosis of pyruvate kinase deficiency by the age of one. This differs from the general population surveyed during the EL-PFDD meeting, among whom many were diagnosed very young with anemia but received a specific pyruvate kinase deficiency diagnosis later in life.

Have you experienced any of the following difficulties because of your pyruvate kinase deficiency (select all that apply)?

This poll revealed that there is a wide range of very serious difficulties experienced by many of the Amish patients. Generally speaking, the difficulties experienced were at a lower rate than in the general population.

- 89% experience tiredness/exhaustion/fatigue, 67% have jaundice/yellow in eyes, 67% have anemia
- 39% have exercise intolerance, 33% have shortness of breath, 28% have heart racing
- 22% have iron overload, 22% have gallstones, 17% have abdominal pain, 11% have enlarged spleen

Which three of the following symptoms of your pyruvate kinase deficiency most negatively impact your daily life?

Similar to the general population, this poll showed that 83% of Amish patients feel that the tiredness/exhaustion/fatigue associated with pyruvate kinase deficiency most negatively impacts their daily life. 44% chose jaundice, 33% chose anemia and 28% chose shortness of breath in response to this question.

Which have you experienced [relating to emotional health and social life] while coping with your pyruvate kinase deficiency (select all that apply)?

The responses in the Amish population to this question included anxiety (44%) and depression (28%). These numbers were much lower than in the general population, and 39% did not experience any of the emotional/social issues listed.

What is your experience in, and perception of, clinical trials for a new pyruvate kinase deficiency treatment?

More of the Amish population (42% versus 12% in the general population) were unsure how to answer this question. Twenty-six percent have not participated in a trial because they were not eligible, 16% have not participated in a trial although they were aware of the opportunity and eligible, 11% have participated in a trial and would do so again, and 5% have participated and would not do so again.

Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating in a clinical trial.

Within the Amish population, the most common responses to this polling question included potential side effects from a new drug (85%), how the drug is taken (69%), and distance to the trial site (54%, which was significantly more than the general population). None of the participants cited whether or not they might get placebo as a response to this question, which was very different from in the general population (47%).

Select the medications or treatments you use or have used for pyruvate kinase deficiency. Select ALL that apply.

For the Amish population, the most common answers to this question included full splenectomy (95%, significantly higher than in the general population), blood transfusions (90%), vitamins (90%), and phototherapy (45%). Iron chelation therapy was not selected by any (versus 63% in the general population). Gall bladder removal was not listed as an option for this survey.

How well does your current treatment regimen reduce the most significant symptoms of your pyruvate kinase deficiency?

The Amish patients rated their current treatment regimens higher in reducing symptoms than the general population, with 30% responding "very well" and 30% responding "moderately well." Among the Amish, 30% of patients don't currently take any treatments (versus 8% in the general population).

Which THREE factors are the most important to you when deciding to select a new treatment or drug for your pyruvate kinase deficiency?

Amish respondents ranked the following as most important in selecting a new drug treatment: severity of side effects known for the drug (82%), number of side effects known for the drug (76%), and cost and/or whether covered by insurance (53%). The larger emphasis on side effects here differed from the general population.

Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy for your pyruvate kinase deficiency?

In response to this polling question, the Amish population chose evidence that the drug significantly improves symptoms (65%) and evidence that the drug will improve quality of life or prevent future reduction in quality of life (41%) as the most important factors.

PRELIMINARY BENEFIT-RISK FRAMEWORK PROPOSAL FOR PYRUVATE KINASE DEFICIENCY

Benefit-risk assessment is the foundation for the FDA's regulatory review of human drugs and biologics. These assessments capture the agency's evidence, uncertainties and reasoning used to arrive at its final determination for specific regulatory decisions. Additionally, they serve as a tool for communicating this information to those who wish to better understand the FDA's thinking. Background and guidance on benefit-risk assessments can be found at the following link:

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhancing-benefit-risk-assessment-regulatory-decision-making

The input provided by people with pyruvate kinase deficiency and their representatives at the EL-PFDD meeting was used to prepare the preliminary benefit-risk table on the next page. This is a sample framework that is intended to provide an understanding of the benefit-risk aspects for two of the key decision factors, analysis of condition and current treatment options, that factor into the benefit-risk assessment. This sample framework is likely to evolve over time and could be incorporated into a benefit-risk assessment framework for a drug under review.

Sample Benefit-Risk Framework for Pyruvate Kinase Deficiency

DIMENSION	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
Analysis of Condition	Patients continuously deal with difficult issues in daily living: • Tiredness/exhaustion/fatigue • Difficulty concentrating • Anemia Patients living with pyruvate kinase deficiency are most concerned about: • Iron overload caused by frequent blood transfusions • Worsening symptoms • The need for lifetime transfusions • Long-term risks of infection due to splenectomy • Not being able to parent or take care of a family • Looking different due to yellow skin/eyes Patient living with pyruvate kinase deficiency find that the disease limits them because: • Others don't know what it's like • They can't participate in sports/physical activities • They miss work or school too much • They have general daily function limitations Patients with pyruvate kinase deficiency experience a high level of emotional and social issues including: • Anxiety • Low self-esteem • Social isolation • Depression • Bullying	Pyruvate kinase deficiency is a genetic condition with variable manifestations and high unmet needs and has a particularly significant impact on children and women: • It appears with widely diverse and unpredictable symptoms that have a huge impact on quality of life • Many of the common manifestations of the disease and treatments are not commonly seen in children and thus can be easily misdiagnosed • Additional complications occur during pregnancy, and women often cannot take birth control pills because they have a higher risk of blood clots due to splenectomy Disease manifestations and benefit-risk profile of interventions change over time and thus are difficult to manage: • There are no standard care guidelines, perhaps due to the small size of the population, changes in disease manifestation over time, variable treatment courses prescribed and variability of patient responses to various interventions • Physician-determined targets for hemoglobin/hematocrit levels are not always in line with what targets patients feel are best for them • Hemoglobin/hematocrit levels are not always predictive of how patients are feeling and can vary depending on environmental factors • Temperature (too hot, too cold), hydration and illness can have a very significant impact on hemoglobin levels and on how patients are feeling
Current Treatment Options	Symptoms are managed largely by frequent blood transfusions, and no drugs are approved that target the specific causes of disease. The most common medications or supportive treatments for pyruvate kinase deficiency include: • Blood transfusions • Vitamins/folic acid • Full splenectomy • Cholecystectomy (gallbladder removal) • Iron chelation or phlebotomy therapy • Phototherapy • Exchange transfusion or pheresis • Antidepressant or antianxiety drugs	Only 11% of participants in the EL-PFDD meeting believe their current treatments work very well and 22% responded that they work poorly or not at all. New treatments should focus on these unmet needs: • Evidence the drug improves the worst symptoms • Severity of side effects • Improvements in anemia/reduction in transfusion Patients are also very interested in better ways to manage the complications caused by current interventions: • Iron overload caused by frequent blood transfusions • Long-term risks of infection and blood clot formation due to splenectomy • Side effects from iron chelation therapies

CONCLUSIONS

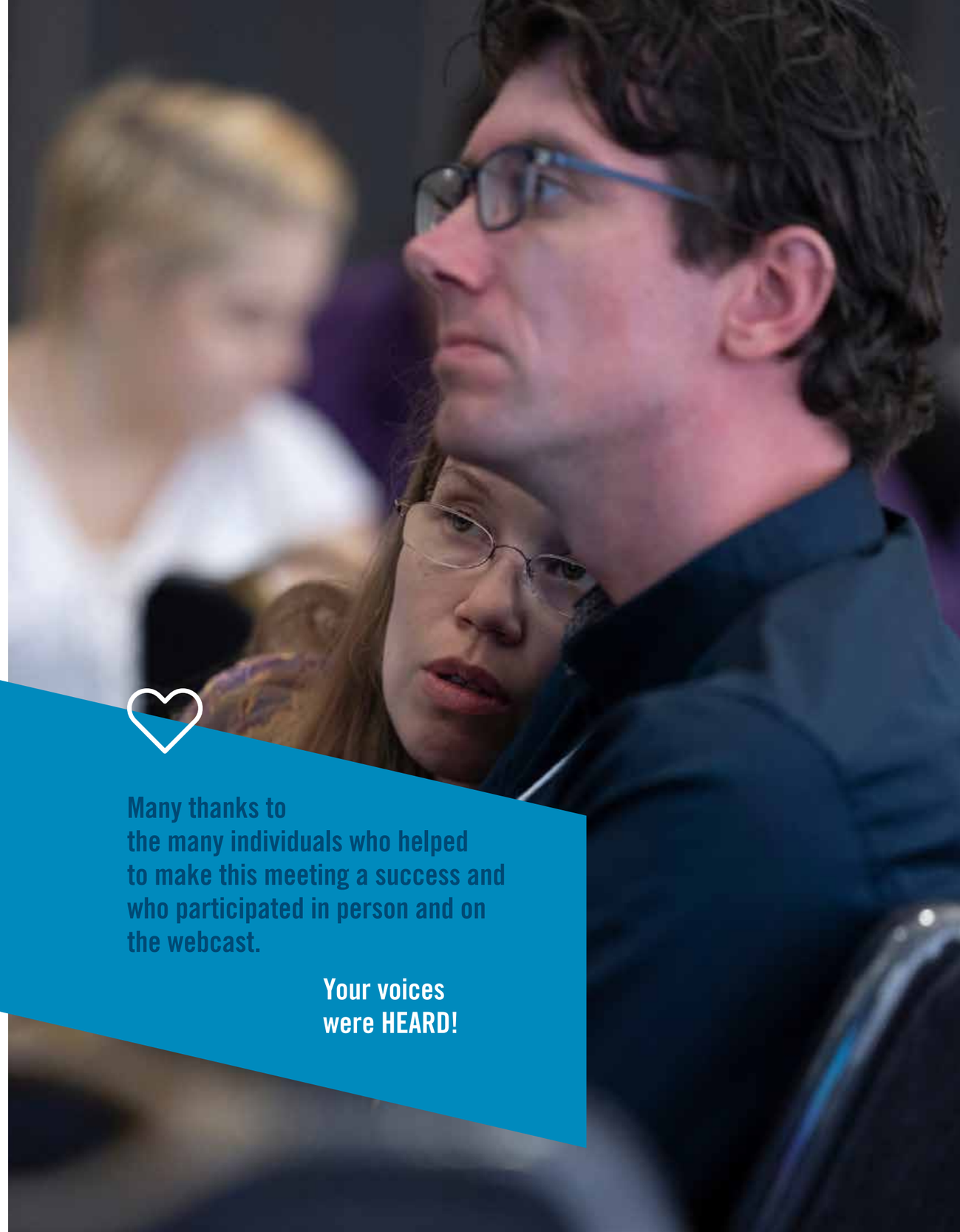
On September 20, 2019, NORD and SZB hosted an externally-led Patient-Focused Drug Development (EL-PFDD) meeting. In attendance were patients, caregivers, government officials, health care providers, industry representatives, patient advocates and others. The EL-PFDD meeting was an opportunity for patients and families to inform the FDA, drug developers and other key stakeholders on the true burdens of living with pyruvate kinase deficiency and how patients view the benefits and risks of treatments.

The meeting was successful in bringing the voices of patients and caregivers to the FDA and other stakeholders who are instrumental in bringing desperately needed medications to the market to treat the high unmet needs of patients with pyruvate kinase deficiency. At the conclusion of the meeting, Dr. Lucas Kempf aptly summarized the key patient voice messages. Here is one example of the insights he shared:

> *"It seemed like from what you're saying, the fatigue has profound effects on your ability to participate in your home, your work, and your socialization, which can be quite profound. So, when we look at the biggest concerns—which is important for folks to hear—it's iron overload, general worsening over time, and the concept that you're going to be transfusion-dependent for the most of your life. It seems like people are very used to having intensive interventions. Everybody seems to be taking some daily medicine, whether or not as vitamins or something else. But you're also having to take a lot of other interventions in order to decrease all the side effects of your interventions, all of which are sort of elements when we think about this in a clinical trial setting that people are going to need to control for."*
>
> LUCAS KEMPF, MD, MEDICAL OFFICER, RARE DISEASES PROGRAM, CENTER FOR DRUG EVALUATION AND RESEARCH, US FOOD AND DRUG ADMINISTRATION

One webinar participant summarized the impact of this meeting well in a follow-up email:

> *"The webinar was very interesting and informative for [my daughter and me]. As the rarity of the disease was brought to light, it gave us a new perspective on how important it is to participate with others who are affected by pyruvate kinase deficiency, both patients and caregivers. It was edifying to realize all the various mutations of pyruvate kinase deficiency, as well as other physical, mental and emotional complications that people encounter with this disease. It became very clear that everyone's case is unique, and how valuable it is to be able to relate to others with pyruvate kinase deficiency because our experience has been that people, including our peers and medical professionals, just don't understand the disease at all. There were some new aspects that we had not previously considered or thought much about such as birth control issues, blood clots and joint pain. We learned that there were more treatment plans out there than that of our own experience."*



APPENDIX 1: REFERENCES AND RESOURCE MATERIALS

The full recording of the pyruvate kinase deficiency externally-led Patient-Focused Drug Development meeting can be found at the following link to the NORD website:

https://rarediseases.org/pkdpfdd-watch/

This site also contains the meeting agenda and the following slide presentations:

Clinical Overview of Pyruvate Kinase Deficiency (Dr. Rachael Grace, Director, Hematology Clinic, Boston Children's Hospital)

For more information on pyruvate kinase deficiency, please see the information posted in the Rare Disease Database on the NORD website:

https://rarediseases.org/rare-diseases/pyruvate-kinase-deficiency/

A patient-oriented pamphlet authored by Dr. Rachael Grace ("Fast Facts for Patients and Supporters - Pyruvate Kinase Deficiency") can be found at the following link:

https://s3.amazonaws.com/knowpkdeficiency.com/03-5-19/FF-PKD-Patient+Booklet_final.pdf

APPENDIX 2: FULL PATIENT AND CAREGIVER TESTIMONIES

Session 1: Living with Pyruvate Kinase Deficiency—Burdens and Symptoms

Becky:

My name is Becky and I am from Billings, Montana. A little about us. I am a mother to a three-year-old named Remyton with pyruvate kinase deficiency. I am her primary caregiver. I am the one that is up with her all night, wipes away tears, sits at appointments and the one that sees her at her worst, but I see her at her best. I would not change it for the world. She was born on January 26, 2016, and spent three weeks in the hospital. We were life-flighted when she was two months old to Salt Lake. She was diagnosed with pyruvate kinase deficiency at three months. We didn't get a hematologist until two years ago in Montana.

Each case of pyruvate kinase deficiency is different. Each person handles it differently. Remyton does not sleep well. She is up late and wakes up early. This makes for one tired mom. When she gets symptomatic, she also gets crabbier. I really cannot wait until she gets older to tell me how she actually feels. Remy speaks with her eyes. She always tells me I feel better mom, but her eyes tell a different story.

Rem is super strong. Somedays she just wants to cuddle and have us rub her legs. The whites of her eyes turn yellow. This is usually the first symptom. Following is her yellow skin. She does get crabby, dizzy and has leg pains. We are doing transfusions every three and half weeks. Because of all the transfusions, Remy has PTSD. She gets really bad anxiety. It's hard to deal at times. She hates the pokes. Her team tries to make it fun for her while she gets her transfusions. She does not like going to her hematologist. Who can blame her? She also has iron overload which causes issues in her organs. Iron overload is when extra iron builds up in her organs and can cause cancer, irregular heartbeat and function not correctly. She is on 360 mg of Jadenu. Which is hard, she is three years old. Have you tried to give a pill to a toddler? The next step is the infusion pump hooked up for 12 hours. Once again, she is three and has PTSD about needles.

Remy is three. I don't work. I take care of her. It's hard to find a job that would understand why I need to take off time. We have a lot of help from the state. We are on SNAP, Section 8, and SSI. Without her disability status, we would not be able to get the help that we need. I would have to be able to work from home to still take care of her. Our family helps us out when they can. We also get help from the foundation at our local hospital.

As her caregiver, I am her voice. I have upset a lot of people saying "No, Remy can't do that," she is symptomatic. She can't be around other people when she is low. They do not understand she cannot do stuff. It has put a lot of stress on my relationship with her dad, my husband. We tend to be on the same page as everything now. It also puts stress on the extended family, when/if Rem gets her spleen removed she cannot be around her cousin, who is not vaccinated. I came from a medical field. I worked as certified nursing assistant for many years. I am also a medical nerd. I do understand a lot about this illness. We do not go out a lot when it's cold and flu season. Remy gets sick, her counts drop. We are isolated ourselves. We give Remy extra time. We just make sure she doesn't overdo it. Remy just gets sick easier. The heat makes her feel worse.

When thinking about her symptoms, on a scale of 1-10, I would say Remy is a 5. She is a normal kid, with not normal things on the inside. She is our first. We are one and done. We try not to define her by her pyruvate kinase deficiency. We are the pyruvate kinase deficiency family.

Cathy:

When I was born with pyruvate kinase deficiency, not much was known about this disorder. Within 12 hours after birth, my bilirubin was dangerously high. It was decided an exchange transfusion must be done, and quickly. Intensive phototherapy and other supportive therapies took care of the initial crisis followed by a regimen of lifesaving transfusions and frequent blood draws. Transfusions turned me into a bouncing, pink-cheeked healthy child, so different from my regular state that all the discomfort was worth it. At six months of age a move to a different state with all new doctors resulted in my diagnosis being changed to simply "hemolytic anemia." Pyruvate kinase deficiency wasn't mentioned again, and spherocytosis was listed in my medical records.

The transfusions ended at age five following splenectomy. All the usual childhood illnesses were weathered with the usual grit and determination of a child with pyruvate kinase deficiency who is determined to not be different from healthy peers and siblings. It is embarrassing to a teenager to walk out of a classroom early to leave for regular doctor's visits. To have to explain why I had to skip sleepovers or drag myself through classes the next day, half sick. And to explain why my skin was a different color.

At the age of 18 I experienced right upper quadrant pain with nausea, pronounced jaundice and fatigue. It was decided to do a cholecystectomy and exploratory surgery to solve the puzzle of an 18-year-old with gallbladder issues, not realizing these are typical pyruvate kinase deficiency symptoms. A liver biopsy was done during surgery due to the evident scarring which the surgical team tried to blame on me drinking too much alcohol, when I drank absolutely none.

The next hurdle came when I got married and gave birth to five healthy children. My obstetrician knew nothing about hemolytic anemia, and neither did the hematologist they sent me to. They did accept my refusal to take any vitamins containing iron. There were times when all the grit and determination in the world wasn't enough to keep me from crashing into bed, not being sure whether I'd ever be able to get up again. These crashes were the result of pushing myself hard to accomplish what healthy people could do easily. At its worst the bone deep fatigue would affect my memory and I remember not being able to recall my phone number to give to my sick child's pediatrician.

In 2012, I determined to find a hematologist and made an appointment with a specialist in a large city. He promptly informed me I did not have spherocytosis, which I expected to hear because of my macrocytic cells. Nonetheless, he was the first to notice spherocytosis is not compatible with microcytic cells. He also informed me I could not have pyruvate kinase deficiency, as "we only see that in textbooks". He Googled around until he decided I have CDA 11. I researched pyruvate kinase deficiency, found papers published connecting my family to the study. Then I contacted Dr. Morton whom I found to have published a paper on pyruvate kinase deficiency about his large group of pyruvate kinase deficiency patients. The first time I met Dr. Morton, I knew I had come home. For the first time ever, a doctor sat down with me and explained pyruvate kinase deficiency.

I've learned to avoid iron in my diet. My bone density tests show diffuse demineralization and bone density loss, unexpected for age. I take Advil to help with bone pain and have learned to be careful with my activities. I've learned a lot about pyruvate kinase deficiency, and I'm passionate about raising awareness within the medical world and the patient community. It is so unnecessary that preventable disabilities related to complications arising from pyruvate kinase deficiency are still happening today. Pyruvate kinase deficiency is a rare disorder, putting patients at risk for misdiagnosis, mistreatment and ego-related indifference. Life with pyruvate kinase deficiency is difficult enough without these misfortunes.

Ai Bee:

Hello! My name is Ai Bee and I live in Georgia with my husband, Alex, and our 15-year-old daughter, LynnAnn. When LynnAnn was born, she was admitted immediately to the NICU of Piedmont Hospital. Her hemoglobin was only 4.2 at that time and she was "coded blue" twice. After the rough beginning at birth, LynnAnn went through multiple blood transfusions, a heart surgery and a liver biopsy. Subsequently, she also had a bone marrow biopsy and a G tube placement during her 3-month stay at the Children's Healthcare of Atlanta NICU.

For many years, Dr. Boudreaux continued to find a diagnosis for LynnAnn. She sent LynnAnn's blood samples to many hospitals for all kinds of testing. We even visited John Hopkins Hospital but did not receive a diagnosis. At the age of three, LynnAnn's spleen was removed to reduce her blood transfusion needs. Then she went through a comprehensive bone marrow transplant workup including a chest port placement and a successful search for a donor's bone marrow. However, she did not qualify for the BMT due to her liver cirrhosis.

When LynnAnn was 12, she was formally diagnosed with pyruvate kinase deficiency through an unlisted molecular pathology procedure that has to overnight her blood sample to a lab service based out of Cincinnati. Currently, the symptoms that affect her the most are gallstone attacks, extreme fatigue, requiring blood transfusion every two months, and frequent hospital visits due to poor immune system.

The extreme fatigue affects LynnAnn's school performance. The yellowing of her eyes and skin also makes her schoolmates wonder about her health and if she is contagious. Some children at school avoid her because they had not seen anyone who could turn yellow. The fatigue also prevents her from participating in school sports. We needed a special accommodation plan for LynnAnn's school because of her low energy and frequent hospital visits. The school issues her a bookbag pass so she can avoid going back and forth from the school locker. The school also gives her an elevator key so she can cut down on climbing the stairs.

On the worst days, which are usually closer to the blood transfusion day, LynnAnn will have poor appetite and taking long naps. When she comes home from school, she will go straight to bed and not be able to complete her school homework or prepare for the quiz or tests on the next day. When LynnAnn is sick, she misses the school instructions, and the compounding effects of accumulating homework and tests are tremendous. She is always trying to play catch up whenever she gets well from her illness.

So, what kind of burdens do we have as a pyruvate kinase deficiency family? We do not expect LynnAnn to be married or have children. It would not be fair to expect another person to pick up this financial burden to care for our child. We do not expect LynnAnn to be able to live independently in the future. Her extreme fatigue may not allow her to secure a permanent job. We are constantly worrying about her future and how she could afford to support herself with all these expensive medical treatment and medicine.

As parents, this illness definitely puts a lot of strain in our marriage because we are constantly under a lot of pressure to provide for her. We must have good health insurance plans from our employers to cover for LynnAnn's monthly medication and hospital visits. Thank you for listening.

Tamara:

My name is Tamara and I am from Minneapolis, MN. I was born in Mandan, ND in 1969. Shortly after delivery I exhibited some unusual symptoms—jaundice, high bilirubin, and low hemoglobin. The doctor gave me a blood transfusion and a prescription for daily doses of iron and folic acid. I received a couple transfusions that year as it was a difficult time. My mother described me as a colicky, sick baby.

I wasn't diagnosed with pyruvate kinase deficiency until I was five years old when I got a viral infection and was unable to recover. I remember laying in the living room, conscious enough to hear my parents talking, but not able to open my eyes, move, or speak. My parents took me to the hospital, where I got a blood transfusion, and later, a diagnosis via the mail from the Mayo Medical Center.

The symptom that bothered me the most when I was a kid was not being able to keep up with other kids in games or activities that included running or sustained energy (i.e., tag, races, running in gym, basketball, riding bike). I hated being slow and being last when usually I was first or the smartest. But more than that, I hated being yellow. One time in fourth grade one of the kids told all my classmates to stay away from me because I had hepatitis. Even though none of the kids knew what that was, no one played with me for days. My parents and the teacher straightened up the rumor, but by that time, the damage was done and for the rest of fourth grade I didn't have any friends. I remember it hurt my feelings so badly I wanted to kill myself.

When I was 13, I had my gallbladder removed because of gallstones related to jaundice. The surgery went well, and I was back in school within a week. I was finally able to eat the peanuts served at school meals without getting a gallbladder attack.

High school and college came next. I never had a boyfriend during that time. I take it back. I had lots of guys who were my friends, but none of them wanted to date me and I knew it was because I was yellow. In public, random people would approach me about my jaundice with unsolicited advice—druggies wanted to know what drug I was using, law enforcement wanted to know the same thing, nurses begged me to "get help," and there was always the church lady offering her prayers. I hated the unwanted attention. Instead, I developed an eating disorder because I figured if I had to be yellow, I'd at least be thin. I had anorexia nervosa first, then bulimia.

Finally, when I was 22, a doctor told me about phenobarbital. If I took a small dose daily, it would help my jaundice go away. I also started going to tanning beds for about the next five to six years. My coloring went through a metamorphosis. All of a sudden, I was an attractive woman and guys liked me. It made me angry because I was the same person on the inside. At 26 my spleen was removed. There were complications and I developed a portal vein clot, esophageal varices, and bowel problems that plague me to this day. At age 35 I started having atrial fibrillation from possible iron overload, and last December I had a pacemaker installed.

Today I'm doing EPO shots every other week to keep my hemoglobin around 7.5 mg/dL. Without EPO, my hemoglobin is between 6-7.2 mg/dL. I struggle with depression, abdomen pain, esophageal varices, issues related to my pacemaker, PTSD from needles, and overall fatigue. I don't rely on transfusions because I hate needles. The symptoms (except jaundice) have gotten worse and more intense with age, but my perspective on life has gotten better. The hardest thing about pyruvate kinase deficiency is that my ambition is much greater than my energy level and this has caused me a lot of frustration.

A word about fatigue: Pyruvate kinase deficiency fatigue feels like a three-year-old's meltdown. It's both an emotional and physical breakdown. When I'm tired it means I'm dizzy and I need to hold on to steady surfaces, my brain is foggy and I can't focus, I can't remember words, I have a headache and my body is sore. It feels like I'm drunk. I shouldn't drive or make decisions. I require 9-10 hours of sleep/night. Short of a cure or bone marrow transfer, sleep is my medicine and I protect it above all else competing needs including work and family. I take Ambien on a nightly basis because I struggle with insomnia.

My symptoms are always with me, but I'd rather have this disease than any other simply because I'm familiar with it. Pyruvate kinase deficiency is a manageable disease if a patient has access to appropriate medical care and support from friends and family.

Alejandra:

My name is Alejandra. I am a mother of three boys and only one child with pyruvate kinase deficiency. We start our journey almost 15 years ago, on November 8th, 2004 and like many of you, Jonathan was admitted to NICU a few hours after birth. He was diagnosed with pyruvate kinase deficiency in February 2005 after a series of tests, including a bone marrow biopsy. After the diagnosis I decided to learn more about the disease by searching for people with the same disease. However, all I found was dogs with pyruvate kinase deficiency. After digging around the internet enough though, I found another patient, Dore Peereboom. You might know her as one of the administrators of the PK Deficiency Facebook group. Today, Jonathan, Dore and I are all working together towards finding a cure or treatment of pyruvate kinase deficiency. As a mother during the past 14 years, I had to learn to prioritize certain things in Jonathan's life and medical condition such as separating the urgent from the non-urgent symptoms, like pancreatitis or Jonathan having a stomachache, low oxygen desaturation or asthma. I don't think of all the possible symptoms that might crop up in the future, I just concentrate on what is important now.

I kept a journal where I documented the things that happened and the days they happened in order to help demonstrate when and how symptoms occurred. It also demonstrated that a symptom may be variable or difficult to detect. Years ago, when Jonathan was four or five years old, I noticed that he was having stomach aches very often which made him scream and cry from the pain. The doctors were reluctant to do something, though. So, I had to argue with the doctors for an ultrasound where it showed that Jonathan was having gallstones and biliary slush like I suspected since the beginning. When I requested to remove it, however, I had to argue with the doctors again, only to have Jonathan's spleen removed and, three months later, the gallbladder, since the doctor did not think it was important to remove it at the time of the surgery. The surgery was complicated since Jonathan had underlying problems with his lungs that were not previously detected because of that, he was in ICU as his lungs had collapsed during the surgery. Right after the surgery, the incisions started to show signs of infection due to the hospital reusing surgical instruments at the time.

Over time, we found many different symptoms that might've been difficult to identify, like his problems with his lungs, oxygen desaturations, hyper/hypoglycemia, congenital heart conditions, chronic illnesses, etc. Most patients with pyruvate kinase deficiency have complex issues, multiple symptoms, and/or variable presentation of the symptoms.

Even when Jonathan is living a more "normal" life now, he still has serious complications that are not allowing him to have the normal life he wishes for. Due to Jonathan's splenectomy, he's been experiencing other health problems like acute pancreatitis and inflammation of his lymph nodes. A year after his splenectomy he had a surgery in his neck to remove non-malignant tumors, then a year after that, he

had his tonsils removed. The specialist indicated that this was one of the splenectomy's "side effects," and these are just a few side effects. Regarding sports, he cannot participate in them because he gets tired much quicker than others, and most of the time, he is not able to finish any sports competitions. Living with pyruvate kinase deficiency can isolate you from the world, because the conventional treatment for pyruvate kinase deficiency prevents kids, teenagers, young adults, and adults to live a normal life, especially if you suffer from severe pyruvate kinase deficiency like Jonathan. Where his symptoms, amount of blood transfusions, and admissions to the hospital prevent him from having a normal social life. A lot of kids or teenagers don't like to hang out with guys that cannot keep up with them, or don't share the same interests. Jonathan usually shares the same interests as other teenagers but lacks the physical ability to keep up with them in games or sports.

Jonathan taught me that life is more than being social, having lots of friends, or feeling isolated and alone. He teaches me every day to see life in a more balanced and positive way, to enjoy the morning and the night, to believe in myself and stretch my hand to reach the stars. Jonathan can be very sick one day, but his optimism in life and strength lift him up the next day and prepares him to be stronger for the next fight. Life hasn't been easy, but it has been full of wonderful experiences that has been helping us overcome the challenge of a life filled with pain and unexpected illnesses.

Session 2: Current and Future Treatments

Zach:

Good afternoon! My name is Zach. My wife, Julie, and I are from the Gulf Coast of Alabama, and we are very thankful to be here with all of you today. Julie and I have four children: two girls and two boys. Of our four kids, two have pyruvate kinase deficiency, and were both diagnosed when they were newborns. These two are our daughter, Kennedy, who is six years old, and our son, Bennett, who is four. My wife and I were not aware of any genetic history of hemolytic anemia within our families, so it was all a complete surprise when Kennedy was born. She was our second child, and our first had been born completely healthy. A couple hours after Kennedy's birth, the nurses realized she was quite jaundiced, and not able to be soothed and calmed. After preliminary testing, she was transferred to a children's hospital, about 30 miles away.

We were fortunate to have very astute doctors, who quickly tested her blood, treated her anemia symptoms with a blood transfusion, and narrowed down the potential causes to only two or three. They told us they were confident it was pyruvate kinase deficiency. All of this happened in the first few days of her life. The pyruvate kinase deficiency diagnosis was confirmed after a visit to a hospital in Salt Lake City, Utah, four weeks later, where we did genetic testing. Kennedy received two blood transfusions in the first few days of life, spending about five days in the NICU under phototherapy, before coming home. Her brother, Bennett, was born next, also with pyruvate kinase deficiency.

Both Kennedy and Bennett's NICU stay, symptoms, need for transfusions, and rate of hemoglobin decline have been nearly identical throughout their lives. They are currently transfused every four weeks, as we aim to keep them at a hemoglobin of around 9 g/dL. They have never gone longer than six weeks without a transfusion. Kennedy and Bennett both still have their spleens, which have never been enlarged, that we know of. Although we are aware of potential reduction of transfusion dependence and frequency through spleen removal, we also know of many people for whom spleen removal was not helpful. And because the spleen is a major part of one's immune system, we are very hesitant to have theirs removed without strong clinical predictors that it would be helpful, specifically for them.

They both have the typical iron overload, but thankfully it has been controlled pretty well with the prescriptions, Exjade and Jadenu, both which they have tolerated without any perceivable side effects. In addition to our monthly care near home, we see a pediatric hematologist at Emory University's hospital in Atlanta, Georgia, once a year, which includes an annual FerriScan MRI to check for iron. Kennedy and Bennett tend to appear a bit jaundiced, but the yellow color is much more pronounced in their skin and their eyes when it's almost time for transfusions. Their urine is usually quite dark in color, which we understand to be, at least in part, due to the hemolysis happening in their bodies on a regular basis. Both kids are currently able to participate in most physical activities within the first three weeks or so following a transfusion. During the fourth week following a transfusion, they often experience body aches and irritability, as their hemoglobin drops to near its lowest point.

Although they are each transfused about 12 times each year, they often require blood from two separate donors, to receive the volume they need. Seemingly, this will continue, equating to donor exposure to blood from up to 24 different people each year. Our concerns for the future include those for their quality of life (as far as energy and ability to thrive), the effects of lifetime iron overload on the organs, the potential for contracting disease through such frequent blood transfusions, our daughter becoming a mother and carrying children, and acute crises such as gallstones, and related issues.

One of the most difficult parts of treating pyruvate kinase deficiency seems to be the variety of gene mutations, and trying to draw out correlations, patterns and prognoses among such variety, mixed with relatively limited data overall. For instance, my wife and I each have a different mutation on the PKLR gene, with one of ours being well documented and common, and the other one never having been documented prior to our case in 2013. Much is still being learned and recorded regarding pyruvate kinase deficiency. One of our children is enrolled in the official pyruvate kinase deficiency Natural History study, which is ongoing.

Concerning clinical trials, we are open to the possibility of our children being involved in such, as long as the associated risks are not significant. Because our children's iron overload and other symptoms are currently fairly well-controlled, our greatest desire, medically, is for the successful discovery and availability of medicine that would safely activate the PK enzyme and elevate their hemoglobin to somewhat normal levels, therefore eliminating or reducing the need for frequent blood transfusions and pyruvate kinase deficiency's associated symptoms.

Thank you again for the opportunity to speak to you today, and for the work so many of you are doing to help our children, and the pyruvate kinase deficiency community, across the world.

Libby:

My name is Libby and I was diagnosed with pyruvate kinase deficiency as an infant. Currently, to treat my condition, every three to six weeks, I receive two units of blood for blood transfusions in order to maintain a stable hemoglobin. I was one of the first patients to start on a drug clinical trial for transfusion dependent patients. I started the trial on December 28th, 2018.

Fatigue, stamina, shortness of breath, and brain fog are some of my main symptoms. I take folic acid to help make new red blood cells. I take a low dose of Adderall, an amphetamine, to help with energy levels. I take

a vitamin B complex to help with energy levels. I refrain from exercise and walking up a flight of stairs to conserve the little amount of energy I have. I rest in bed a good portion of the day.

My treatment has definitely changed over time. When I was first diagnosed as a baby, I received blood transfusions approximately every one to three months. I had my spleen removed at the age of eight and was on a penicillin antibiotic regimen every day for 10 years, then I didn't have to receive but one or two transfusions a year. It wasn't until after stopping the penicillin at age 18, that I would contract many viruses and infections, which caused my hemoglobin to drop. This resulted in more frequent blood transfusions.

Removing my tonsils while in college made a big difference in the number of infections I had. It wasn't until I graduated from college, and started working full-time, that my transfusion regimen restarted, and I had to receive blood every three to six months. The added blood meant the start of iron overload. At age 33, I got pregnant with my little boy, and required 10 blood transfusions throughout pregnancy, and three with delivery. Being pregnant was extremely tough on my body. Iron overload got worse after pregnancy because I wasn't able to be on any chelation drugs during pregnancy. I had increased iron in my heart and liver. My hematologist decided to only do one unit of blood each time I received blood the next year. They realized that wasn't helping so I went back to two units of blood. Having a baby definitely put a strain on my body, and since then I have required more frequent blood transfusions, ranging from every three to six weeks.

At the end of 2018, I started taking a clinical trial drug. Receiving frequent blood transfusions only treats my symptoms temporarily. When my hemoglobin is at a stable level after a blood transfusion, the fatigue, shortness of breath, and brain fog is not as prevalent. Taking Adderall and vitamin B daily provides a small increase in energy, but by late afternoon/early evening, I am very drained. I struggle most days taking care of myself, so it can be quite challenging also caring and trying to play with my four-year-old son. Unfortunately, the clinical trial drug has not made a difference in increasing my hemoglobin and decreasing my burden of frequent blood transfusions.

There have been some significant downsides to current treatments. Obviously, having to receive blood transfusions requires an IV being placed. Because I developed so much scar tissue in my hands and arms, it was a struggle to find adequate veins. In 2016, my doctors needed to place a chest port to have easier access. Because of the chest port, I developed numerous DVT blood clots, and pulmonary embolisms two different times. My doctors learned patients with pyruvate kinase deficiency having a splenectomy at a young age were developing blood clots as adults. In order to prevent more clots from forming, I have been on Lovenox blood thinner injections every 12 hours for the past three years. After enduring blood clots, I became very depressed and couldn't function well enough to continue working the career I had of 14 years. I currently take an antidepressant drug and it is an everyday battle to endure depression. Also, the blood clots caused damage to my lungs and caused me to have obstructive lung disease. I currently have to use two inhalers every day to help me to breathe better.

Iron overload is developed when you have frequent blood transfusions and can be toxic when iron is stored in your body. This can present an array of symptoms, but for me the main ones are fatigue, low sex-drive, and joint pain. Over the last 10 years, I have taken all four iron chelation drugs that are available. Some of the drugs I can't tolerate at all and make me sicker than what I already am. I currently take Jadenu but have to take a smaller dose than what is prescribed to keep the side effects tolerable.

Taking the clinical trial drug has had some tough side effects. I developed some serious nausea after taking it. After doing further tests, my doctors determined I had developed a stomach ulcer, and gastroparesis, which is paralysis of the stomach; it prevents you from being able to digest fat or fibrous foods. Also, it has caused significant insomnia, which I have to take OTC medicine to help me sleep at night and stay asleep.

My ideal treatment for pyruvate kinase deficiency would be successful gene therapy to replace the inactive PK enzyme, and get it functioning to prevent the hemolytic anemia. Also, I have learned to tolerate receiving blood transfusions, but the iron overload that comes with all the blood is horrible. If I didn't have to endure even more side effects of iron overload, I think it wouldn't be as bad.

Jennifer:

My name is Jennifer and I'm from Bono, Arkansas. I have two children with pyruvate kinase deficiency, William, currently six and Lillian who is eight. Their first symptoms were jaundice at birth, which required a blood transfusion and photo light therapy. William had to undergo a double exchange transfusion and at that time the doctors believed it to be spherocytosis. At five months old, William became jaundice again and had to receive a blood transfusion. They are monitored closely by their pediatrician, hematologist, GI specialist. When Lillian was four and William was two we were seen at Arkansas Children's Hospital by a new hematologist that felt the diagnosis of spherocytosis was incorrect and wanted to test them for pyruvate kinase deficiency. The results from that test were positive. William and Lillian both struggle with fatigue during times of illness, and it takes them longer to fully recover. But even with William's normal for him, levels of hemoglobin of seven most days, he has plenty of energy without the need of any blood transfusion.

Of my two children, Lillian has had the most difficult and challenging of symptoms. Starting in 2017, the hepatic panel for Lillian has been abnormal and she was referred to a GI specialist with multiple specialized MRIs showing extensive and continuing damage to her liver and bile ducts. The doctors did a liver biopsy and more genetic testing to get a better understanding of the degree of damage, and also to rule out any possibility of other diseases. These tests have all came back negative for any other non-liver diseases. This damage is not from iron overload, which is more commonly seen with pyruvate kinase deficiency, but from the production of calculi and sludge, creating blockages. Even with her gallbladder being removed and daily antibiotics and many endoscopic retrograde cholangiopancreatography (ERCP) procedures, the calculi are still forming rapidly and causing continual damage.

Without any other treatments available, a six-month test run of once a month blood transfusions were tried, in hopes of reducing the hemolysis that was causing the production of calculi. This was proven to be unsuccessful with the last lab results and recent imaging. Without a successful new treatment option available to her, we fear the clock is ticking down for her need of the liver transplant, with no guarantees of a repeated outcome of a new liver being damaged.

The medication she is currently on are Ursodiol to help with bile duct flow, Cipro antibiotic to help prevent infections, Zofran for nausea, Clonidine to help with anxiety, photo light therapy to help with the itching and perforating collagenosis, ERCP, as needed to clean out blockages in her bile ducts, and blood transfusions to help with the hemolysis. The treatments have not made a difference in stopping or preventing the continuing damage to her bile duct and liver. ERCPs are helpful in cleaning out the blockages but they continue to be recurring frequently. The blockages cause the bilirubin to rise which causes the itching, flare ups of perforating collagenosis and stomach pain when infection is present. The antibiotics have helped with preventing infection and the need for hospitalizations have lessened due to using them daily.

The physical and psychological trauma of being stuck with needles and sedated to perform procedures have been overwhelming. Anxiety and depression have been increasing with each appointment and procedure. An ideal drug for us would be a pediatric drug that can target and prevent the hemolysis. It would be great if it could prevent the production of calculi buildup in the bile ducts, and also current medications taste horrible to her and leave her with a very unpleasant aftertaste. A drug that is more palatable for a child, and one that could possibly be compounded to be more palatable to a child, is something we really need. The symptoms that would be most important to treat are the hemolysis. A way to help activate the pyruvate enzyme, a way to treat and prevent the calculi that causes the blockages and the liver damage. We would consider taking part in a clinical trial, and it would be important to us that a clinical drug would not cause any more anxiety in having to take because of taste. Also important is one that would not need to be injected to lessen the physical and psychological trauma of treatment.

Tina:

My name is Tina and I am happy for the opportunity to speak to you today. I have two children with pyruvate kinase deficiency. Molly is currently 31 and Adam is 11 years old; both were diagnosed while an infant. They share the exact same mutation constituting severe pyruvate kinase deficiency. The preferred protocol for severe pyruvate kinase deficiency seemed to be surgical removal of the spleen at an early age, transfusions as needed, and chelation for the resulting iron overload, with a hope that the spleen removal would cut the frequency and need for transfusions. This is the path we followed for Molly. We took a different path for Adam.

Molly had her spleen removed at age four and had few transfusions for several years afterwards. At age 10, her gall bladder was removed due to gallstones, and a subsequent liver biopsy showed that she had severe iron overload. She frequently presented with an enlarged liver. She had pituitary gland damage from the iron overload and didn't produce adequate growth hormone, so she took growth hormone shots for three years. The lack of spleen presented with extreme illness and hospitalizations, during one of which she was becoming septic. Molly was not transfused until her hemoglobin was around 6. She currently gets transfusions about every four weeks and has her iron overload under control with chelation therapy. But she has had several blood clots in the last couple of years and struggles whether to become pregnant. She is currently participating in a clinical trial to determine any relationship between pyruvate kinase deficiency and blood clots.

From Molly's journey, we wondered if that protocol was the best for our children. So, with Adam, after consultation with a wonderful doctor, we did NOT have his spleen removed and we did NOT let his hemoglobin go below 9. Our rationale was that he would likely have to return to transfusions anyway, as Molly had to do, and that he would still get iron overload from the red cell breakdown as Molly had. But, he would feel better with the higher hemoglobin and he would not be ill and hospitalized as much since the intact spleen would be able to help with that. All of this proved to be true, and he never had an enlarged spleen or liver.

Other than the different protocol we chose for Adam, both children have needed transfusions every three to four weeks; both try to keep a hemoglobin above 9; both have vein issues, with Molly having had several ports and Adam requiring several sticks to get his IV going. Both children had iron overload and did well with subcutaneous deferoxamine. Neither were able to handle Exjade. Adam has done well on Jadenu, but Molly did not do well with any of the oral chelators. As far as meds, aside from RBC transfusions and chelation therapy, both children take ibuprofen to manage headaches, joint, and back pain from a low hemoglobin, as well as baby aspirin and folic acid.

Emotional stress is one of the most significant downsides. Both children have struggled with school attendance due to illness. It makes it harder to keep up. Both have been asked by their peers about the yellow in their eyes and skin and the infusion pump they carried around. Both struggle with headaches and joint pain. Like most kids, mine are trying to deal with perceived inadequacies and lack of confidence. The effects of pyruvate kinase deficiency pile on to that struggle. With these commonalities, my children have different personalities and struggles as well. Adam has autoimmune encephalitis, which piles on many other social challenges, but he handles his pyruvate kinase deficiency with dignity and a quiet sadness and fatigue. Molly plows ahead and always has, working 50+ hours a week, seemingly having the need to compensate for the pyruvate kinase deficiency. But she has worries about blood clots and pregnancy.

I have been blessed with family support to help with the many trips for transfusions and related care, while my husband and I can maintain our much-needed jobs with medical insurance. But there is always the constant worry about the quality of donated blood. When Adam was five, his doctor got a letter from the blood services provider stating that the donor of a unit of blood that Adam had received had recently admitted to questionable life behaviors. Forgetting about the sick visit we were there for, Adam was immediately sent to the lab to be tested for HIV and hepatitis.

The pregnancy with Adam was stressful. Because of a lab error, we did not know that Adam had pyruvate kinase deficiency in utero. He appeared jaundiced at birth and didn't cry. I was extremely nervous about this, and within a couple of hours, my suspicions were confirmed. Adam was taken to the NICU with high bilirubin. I insisted they do a CBC, and he needed transfusions. I knew from experience to direct the NICU doctors to draw blood samples prior to the transfusion so that they could test HIS blood. I immediately cried in front of the NICU doctor. He hugged me and seemed confused as to why I was upset. I was 20 years older and I could not imagine doing it all over again. I dried my eyes and got back into the routine.

Jonathan:

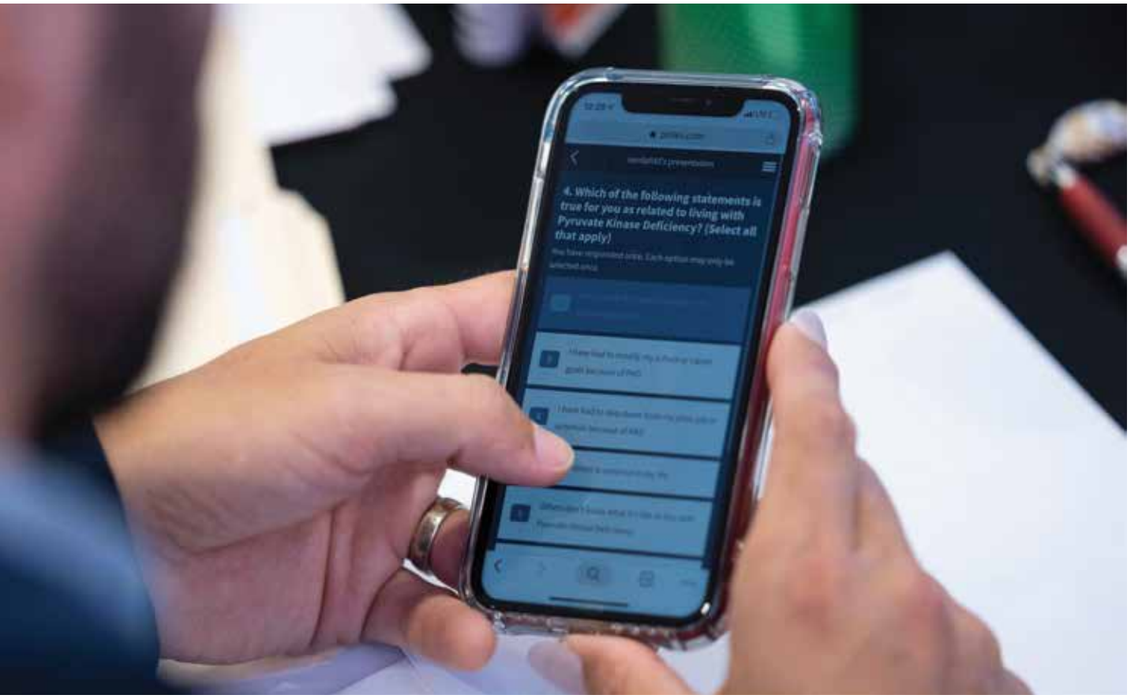
My name is Jonathan. In order to keep my body in close to normal shape, I get blood transfusions every two to three weeks. This usually keeps my hemoglobin at over 10, which keeps me from getting fatigued due to low blood, keeps my brain from getting foggy, keeps my bone-marrow from overworking itself, and keeps my lungs/heart functioning close to normal. I also have to take iron-chelation medicine for my chronic iron overload I get from constant transfusions. I also play the trombone in my school band as a sort-of therapeutic method to help my lungs work properly. My sugar levels will drop as well as rise due to beta-cell dysfunction, so in order to counteract the dropping of my sugar levels, I have to consume some kind of sweet food or beverage. Every year, I must get a bone-density test as well as an MRI and MRE to the heart and liver in order to evaluate the iron contents of my heart, liver, pancreas, and bone-marrow. Due to my chronic iron overload, I must also get eye-vision and hearing tests every year to make sure no iron has damaged these parts of the body. I also have to make sure that the amount of blood transfusions and overwork of the liver doesn't cause liver cirrhosis or cancer.

My iron-chelation medicine keeps me from dying to a large buildup of iron in my vital organs, but at the same time, the iron chelators itself can greatly damage my organs. My blood transfusions also keep me alive

from losing all my blood, but the blood transfusions also give a chance of contracting blood-borne illnesses through transfusions, and it also causes my liver/bone-marrow to overwork, damaging them in the process. Not only that, but the blood transfusions cause my chronic iron overload.

An ideal treatment for me would be a simple pill that I could take over time, which over the course of a month, would cure me of pyruvate kinase deficiency and slowly get rid of the extra illnesses and symptoms that come with it. This pill would have no chance, or at least an impossibly low chance of death. It would also require no surgery and it wouldn't take any of the time I need for school.

Regarding clinical trials, I have done a trial five years ago, and I was in the clinical trials for the MRE versus the liver biopsy 7seven years ago. Both clinical trials ended up going well and both are now available to everyone. I would consider another clinical trial if it had little to no risks, but anything with a higher risk of something unfavorable is too risky for my age. The most important symptom I would like to see treated is the need for blood transfusions. The effects of chronic iron overload should also be the top priority.



APPENDIX 3: DETAILS OF POLLING QUESTIONNAIRE

Demographic Polling Questions:

1. I am:
    a. An individual with pyruvate kinase deficiency
    b. A caregiver of someone with pyruvate kinase deficiency
2. Where do you live?
    a. East coast (Eastern time zone)
    b. Midwest (Central time zone)
    c. West (Mountain time zone)
    d. West coast (Pacific time zone)
    e. Canada
    f. Mexico, Caribbean Islands
    g. Outside of North America
3. What is your age or the age of the person you are caring for?
    a. Less than 5 years
    b. 5–11 years
    c. 12–17 years
    d. 18–29 years
    e. 30–39 years
    f. 40–49 years
    g. 50–59 years
    h. 60–69 years
    i. 70 or greater
4. Do you identify as:
    a. Male
    b. Female
5. At what age did you receive a diagnosis of anemia?
    a. 0–1 year
    b. 2–5 years
    c. 6–11 years
    d. 12–18 years
    e. 18–29 years
    f. 30–39 years
    g. 40–49 years
    h. 50–59 years
    i. 60–69 years
    j. 70 or greater

6. At what age did you receive a diagnosis of pyruvate kinase deficiency?
    a. 0–1 year
    b. 2–5 years
    c. 6–11 years
    d. 12–18 years
    e. 18–29 years
    f. 30–39 years
    g. 40–49 years
    h. 50–59 years
    i. 60–69 years
    j. 70 or greater

Topic 1 Polling Questions: Living with Pyruvate Kinase Deficiency: Disease Symptoms and Daily Impacts

7. Have you experienced any of the following difficulties because of your pyruvate kinase deficiency? (Select all that apply.)
    a. Anemia
    b. Shortness of breath (dyspnea)
    c. Being tired, exhausted, or fatigued
    d. Exercise intolerance
    e. Iron overload
    f. Jaundice/yellow in eyes
    g. Enlarged spleen
    h. Abdominal pain
    i. Gallstones
    j. Leg ulcers
    k. Pulmonary hypertension
    l. Low bone density
    m. Bone pain
    n. Pancreatitis
    o. Heart racing (tachycardia)

8. Which THREE of the following symptoms of your pyruvate kinase deficiency most negatively impact your daily life?
    a. Anemia
    b. Shortness of breath (dyspnea)
    c. Being tired, exhausted, or fatigued
    d. Difficulty concentrating
    e. Exercise intolerance
    f. Iron overload
    g. Jaundice/yellow in eyes
    h. Enlarged spleen
    i. Abdominal pain

    j. Gallstones
    k. Leg ulcers
    l. Pulmonary hypertension
    m. Bone pain
    n. Pancreatitis
    o. Heart racing (tachycardia)

9. Which have you experienced while coping with your pyruvate kinase deficiency? (Select all that apply.)
    a. Depression
    b. Anxiety
    c. Low self esteem
    d. Social isolation
    e. Bullying from others
    f. Unwanted attention based on your appearance
    g. Difficulty with relationships outside of family
    h. Hopelessness
    i. None of the above

10. Which of the following statements is true for you as related to living with pyruvate kinase deficiency? (Select all that apply.)
    a. I miss work or school more than I'm comfortable with
    b. I have to modify my school or career goals because of pyruvate kinase deficiency
    c. I have had to step down from my prior job or schedule because of pyruvate kinase deficiency
    d. Family stress is common in my life
    e. Others don't know what it's like to live with pyruvate kinase deficiency
    f. I cannot participate in sports or other physical activities I enjoy
    g. My general daily function is limited by pyruvate kinase deficiency
    h. None of the above

11. What are your biggest concerns about living with pyruvate kinase deficiency?
    a. Worsening symptoms
    b. Iron overload
    c. Needing transfusions forever
    d. Needing a splenectomy
    e. Long-term risk of infections due to splenectomy
    f. Yellow skin/eyes, looking "different"
    g. Ability to have a healthy pregnancy
    h. Not being able to be a parent or take care of my family
    i. Maintaining chelation therapy
    j. Explaining to or hiding my disease from relatives, friends, employers, co-workers, etc.
    k. Explaining or hiding my disease from a romantic partner
    l. Other

Topic 2 Polling Questions: Clinical Trials

12. What is your experience in, and perception of, clinical trials for a new pyruvate kinase deficiency drug?
    a. I am currently participating in a trial
    b. I have participated in a trial, and I would do so again
    c. I have participated in a trial, and I would not do so again
    d. I have not participated in a trial, because I didn't know about the opportunity
    e. I have not participated in a trial because I was not eligible
    f. I have not participated in a trial, although I was aware of the opportunity and eligible
    g. I would never enroll in a clinical trial
    h. Not sure

13. Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating in a clinical trial:
    a. Whether I might get placebo ("sugar pill")
    b. Whether I need to stop my current disease management and treatment regimen
    c. Potential side effects from a new drug
    d. How the drug is taken (by mouth, IV, injection in muscle)
    e. Whether the drug is supposed to treat symptoms or the underlying cause of my disease
    f. Unsure if I can make the commitment to participate in a clinical trial
    g. Frequency of exam appointments
    h. Distance to trial site
    i. Length of trial
    j. Negative things I have heard about clinical trials
    k. Other

Topic 3 Polling Questions: Current Challenges to Treating Pyruvate Kinase Deficiency

14. Select the medications or supportive treatments you use or have used for pyruvate kinase deficiency. (Select all that apply.)
    a. Blood transfusions
    b. An exchange transfusion or pheresis
    c. Full Splenectomy
    d. Partial Splenectomy
    e. Cholecystectomy (gall bladder removal)
    f. Iron chelation or phlebotomy therapy
    g. Statin (or other drug for cholesterol)
    h. Phototherapy (light therapy)
    i. Vitamins/Folic acid
    j. Aspirin
    k. Anticoagulant (blood thinner)
    l. Erythropoietin
    m. Antidepressant or antianxiety drug
    n. Research drug

15. How well does your current treatment regimen reduce the most significant symptoms of your pyruvate kinase deficiency?
    a. Very well
    b. Moderately well
    c. Poorly
    d. Not at all
    e. I do not currently take any treatments

16. Which THREE factors are the most important to you when deciding to select a new treatment or drug for your pyruvate kinase deficiency?
    a. Whether drug is taken by mouth, by IV, injection in muscle
    b. How often you have to take the drug
    c. Evidence in pyruvate kinase deficiency patients that drug improves specific symptoms most bothersome to you
    d. Whether the drug will improve my anemia or decrease my transfusion needs
    e. Number of side effects known for the drug
    f. Severity of side effects known for the drug
    g. Cost and/or whether covered by insurance
    h. What your physician recommends

17. Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy for your pyruvate kinase deficiency?
    a. Evidence that the drug will delay need for transfusions or decrease the time until next transfusion
    b. Evidence that the drug significantly decreases the complications of pyruvate kinase deficiency (iron overload, gallstones, pulmonary hypertension, etc.)
    c. Evidence that the drug will improve my quality of life or prevent future reduction in quality of life
    d. Evidence that the drug will help me avoid splenectomy
    e. Evidence that the drug will decrease jaundice

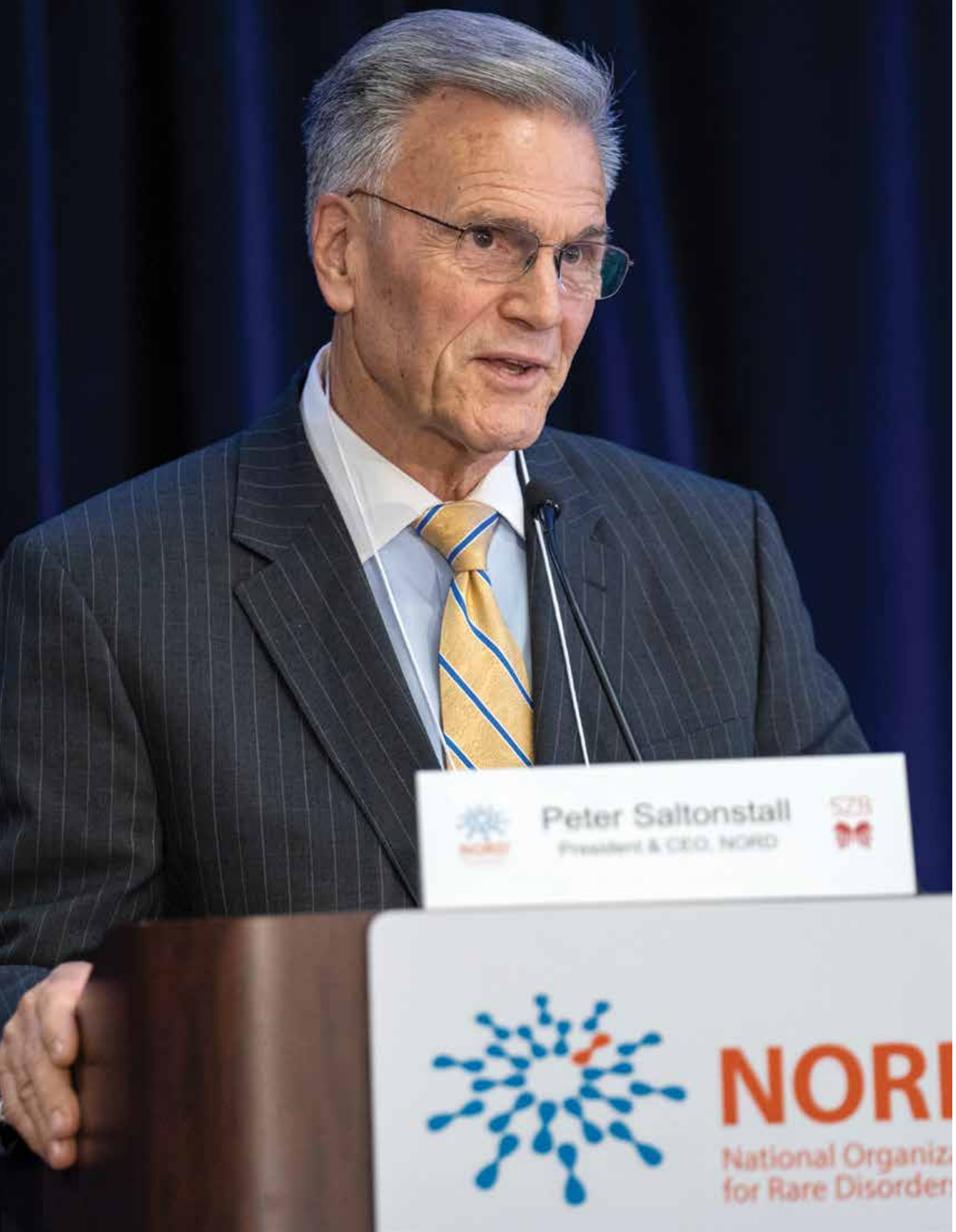
18. Which of the following statements most closely reflects your physical symptoms and how related they are to your hemoglobin/hematocrit levels:
    a. I can reliably predict my hemoglobin test result based on how well/not well I am feeling
    b. I can sometimes predict my hemoglobin test result based on how well/not well I am feeling
    c. My hemoglobin test results do not reliably indicate how well/not well I am feeling

APPENDIX 4: MEETING MATERIALS

Agenda

Externally-led Patient-Focused Drug Development Meeting for Pyruvate Kinase Deficiency
College Park Marriott Hotel and Conference Center, Hyattsville, Md.
Friday, September 20, 2019

9:30 am	**Registration and Light Continental Breakfast**
10:00 to 10:10	**Opening Remarks** Peter L. Saltonstall, President and CEO, NORD Dore Peereboom, Foundation for Rare Blood Diseases (SZB)
10:10 to 10:25	**Clinical Overview of Pyruvate Kinase Deficiency** Rachael Grace, MD, Hematologist/Oncologist, Boston Children's Hospital
10:25 to 10:45	**Welcome Remarks** Wilson Bryan, MD, Director, Office of Tissues and Advanced Therapies, CBER, FDA
10:45 to 10:55	**Introduction and Meeting Overview** Larry Bauer, Senior Regulatory Drug Expert, Hyman, Phelps, & McNamara, PC, Meeting Moderator
10:55 to 11:05	**Overview of Discussion Format and Demographic Polling Questions**
11:05 to 11:30	**Topic 1: Living with Pyruvate Kinase Deficiency — Burdens and Symptoms** Rebecca Herzog, Caregiver Katine "Cathy" Miller, Patient Ai Bee Poh, Caregiver Tamara Schryver, Patient Alejandra Watson, Caregiver
11:30 to 12:30	**Polling Questions and Facilitated Audience Discussion on Topic 1** Larry Bauer, Meeting Moderator
12:30 to 1:30	**Lunch**
1:30 to 1:55	**Topic 2: Current and Future Treatments** Zach Adamson, Caregiver Elizabeth "Libby" Garrett, Patient Jennifer King, Caregiver Tina Knapp, Caregiver Jonathan Watson, Pediatric Patient
1:55 to 2:55	**Polling Questions and Facilitated Audience Discussion on Topic 2** Larry Bauer, Meeting Moderator
2:55 to 3:15	**Closing Remarks** Lucas Kempf, MD, Medical Officer, Rare Diseases Program, CDER, FDA
3:15 to 3:20	**Farewell Remarks and Next Steps** Michelle Adams, Director of Federal Policy, NORD
	Adjourn
3:30 to 5:30	**Closing Reception** Sheppard's Art Gallery, College Park Marriott Hotel and Conference Center



Message from NORD's Leadership

Welcome to today's externally-led Patient-Focused Drug Development meeting on pyruvate kinase deficiency (PKD). On behalf of the National Organization for Rare Disorders® (NORD) and the Foundation for Rare Blood Diseases (SZB), we thank you for joining us. If you are a patient, family member or caregiver affected by PKD, this is an important opportunity to have your voice heard.

NORD and SZB believe that PKD is a disease with an unmet need, one that imposes a severe burden on patients, especially in the pediatric population. Through today's meeting, we will strive to provide researchers, drug developers and the US Food and Drug Administration with a robust understanding of patients' and caregivers' experiences with PKD. The ultimate goal of the PKD EL-PFDD is to produce a "Voice of the Patient" report that will help to inform the development of potential therapeutics that can improve the lives of patients living with PKD.

We appreciate your participation and valuable input on this rare, genetic hemolytic anemia disorder, and look forward to sharing the insights gathered from today's discussions.

We'd like to thank the representatives from the FDA for taking the time to be here today to hear from patients, whose lives they strive to improve.

We want to especially acknowledge the panelists for today's meeting. Thank you to our webcast audience, as well. Your remote participation and input are equally valuable.

We are grateful to our planning committee, whose collective expertise and guidance will be evident here today.

Finally, we are thankful to Rocket and Agios for sponsoring this meeting.

I know that all of you will make this an extraordinary meeting. Thank you all for your contributions today.

Sincerely,

Peter L. Saltonstall
President and CEO, NORD

About This Meeting

The patient perspective is critical in helping the US Food and Drug Administration (FDA) understand the context in which regulatory decisions are made for new drugs. Externally-led Patient-Focused Drug Development (EL-PFDD) meetings provide an opportunity for patients, their families and caregivers to share critical information about the impact of their disease on their daily lives and their experiences with currently available treatments. Patients' experiences provide valuable insight for FDA and other key stakeholders, including researchers, medical product developers and health care providers.

The National Organization for Rare Disorders® (NORD) and the Foundation for Rare Blood Diseases (SZB) have organized this EL-PFDD meeting on pyruvate kinase deficiency (PKD).

PKD is a rare condition with no targeted treatment currently available. Existing medical interventions (mainly routine transfusions and splenectomy) introduce significant risks and burdens to patients. NORD and SZB believe this rare, genetic hemolytic anemia disorder is one with an unmet need and a severe disease burden, especially in the pediatric population.

The goal of this EL-PFDD meeting is to provide researchers, drug developers and FDA with a robust understanding of patients' and caregivers' experiences with PKD, including how individuals with PKD view their quality of life, which aspects of the disease are most problematic for them and what actions they currently perform to treat and cope with this disease. The results of this meeting will be shared publicly in a "Voice of the Patient" report in an effort to inform the development of potential therapeutics that can improve the lives of patients living with pyruvate kinase deficiency.

Speakers

OPENING REMARKS

Peter L. Saltonstall
President and CEO, NORD

Peter L. Saltonstall is the President and CEO of the National Organization for Rare Disorders (NORD). He joined NORD in 2008 after having served for more than 30 years as a senior executive in both for-profit and not-for-profit health care environments.

Under his leadership, NORD has maintained the integrity of the Orphan Drug Act while forging new relationships between the patient community and the executive branch, Congress, HHS, FDA, NIH, Social Security Administration and CMS, as well as with drug and device companies and with the medical, academic and investment communities. His efforts to build collaborations stem from his view that advances for the rare disease patient can be achieved best through joint efforts. Today he continues to be one of the country's leading voices on rare disease issues to industry, FDA, Congress and the federal government.

Peter is also committed to globalization of the rare disease patient community, as diseases do not recognize geographical boundaries and research can be expedited when patients from many countries are involved. He has helped established collaborative programs with patient communities throughout Europe, Australia, Japan, Asia and South America.

Under Peter's leadership, NORD has grown to be the global reference site for the rare disease community, with NORD's website now receiving more than one million requests a month for information. He has also overseen the expansion of NORD's US-based Patient Assistance Network, which works with manufacturers and patients to provide assistance to patients in need of medications they cannot afford. He has also played a major role in building the NORD Longitudinal Natural History System, which is recognized by the FDA as one of the tools of choice for Patient Organizations collecting data on their disease.

Dore Peereboom
Foundation for Rare Blood Diseases (SZB)

Dore Peereboom, a patient and advocate for PKD from the Netherlands is one of the first advocates to create, organize and maintain a Facebook group that connects patients and families. Dore has studied law and works for the Dutch Provincial Government. She has studied with EURORDIS, the European Organization for Rare Diseases in Barcelona, Spain and Paris, France. Dore has been at the forefront of advocacy for SZB, an organization in the Netherlands created in 2005 to further research, education, patient and family services for patients of PKD.

CLINICAL OVERVIEW

Rachael Grace, MD
Director, Hematology Clinic, Boston Children's Hospital, and Assistant Professor of Pediatrics, Harvard Medical School

Dr. Rachael Grace is an experienced pediatric hematologist/oncologist and an instructor of pediatrics at Harvard Medical School. She has expertise in the treatment of bleeding and clotting disorders including ITP. Her clinical research interests include ITP, childhood cancer and thrombosis, and disorders of bleeding and clotting.

WELCOME REMARKS

Wilson Bryan, MD
Director, Office of Tissues and Advanced Therapies, CBER, FDA

Wilson Bryan is a board-certified neurologist who graduated from the University of Chicago Pritzker School of Medicine. He served on the neurology faculty of the University of Texas Southwestern Medical School for 13 years. He has been an investigator on clinical trials in cerebrovascular disease and neuromuscular disorders, particularly amyotrophic lateral sclerosis. Dr. Bryan joined the United States Food and Drug Administration (FDA) in 2000 and now serves as Director of the Office of Tissues and Advanced Therapies (OTAT) in the FDA's Center for Biologics Evaluation and Research.

MEETING MODERATOR

Larry Bauer
Senior Regulatory Drug Expert, Hyman, Phelps, & McNamara, PC

Larry Bauer is a Senior Regulatory Drug Expert with Hyman, Phelps, & McNamara, PC, and assists medical product industry and patient advocacy organization clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Prior to this position he worked at the FDA in CDER's Rare Diseases Program, working on policy, education and science related to rare disease drug development. He has expertise in Rare Pediatric Disease priority review vouchers and designations, expedited programs, and patient engagement including extensive experience guiding patient advocacy groups. He also serves on the National Organization for Rare Disorders (NORD) Advocacy Committee.

CLOSING REMARKS

Lucas Kempf, M.D.
Medical Officer, Rare Diseases Program, CDER, FDA

Prior to joining FDA in 2012, Lucas spent eight years at the NIH with a focus on neuroscience research, working to understand the genetics of neuropsychiatric disease and developing translational approaches and therapeutics to study these disorders. He did postgraduate training in psychiatry at Georgetown and Johns Hopkins before moving to the NIH for a fellowship.

FAREWELL REMARKS

Michelle Adams
Director of Federal Policy, NORD

Michelle has worked as a legislative assistant and legislative director for two US Representatives and a US Senator, as Director of Public Policy for the Friends of the Global Fight Against AIDS, Tuberculosis and Malaria, and most recently as Congressional Affairs Specialist for the FDA.

APPENDIX 5: ACKNOWLEDGEMENTS

Sponsors

Many thanks to our generous sponsors, including:

- Agios Pharmaceuticals
- Rocket Pharma

Authors

This "Voice of the Patient" report was written by Elizabeth White, President, White Biotech Solutions, LLC.

Contributors to the collection of the information and development of the document included Michelle Adams, Larry Bauer, Debbie Drell, Rachael Grace, MD, Carrie Lucas, Alexa Moore and Dore Peereboom.

About NORD

The National Organization for Rare Disorders, a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 300 patient organization members, is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services.

About SZB

The Foundation for Rare Blood Diseases is an organization based in the Netherlands and created in 2005 to further research, education, patient and family services for patients with pyruvate kinase deficiency.

Mission Statement

NORD, a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 300 patient organization members, is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient services.

NORD®
National Organization for Rare Disorders

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RAREDISEASES.ORG

NORD: Fighting for the rare community every day for more than 35 years. NORD is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and patient support services. NORD does not recommend or endorse any particular medical treatment but encourages patients to seek the advice of their clinicians. NORD is a registered 501(c)(3) charity organization.
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