PKU TRUE

Understanding the lived experience with phenylketonuria

Organized & Hosted By:

NPKUA

national PKU alliance

Voice of the Patient

Report on the Externally-Led Patient-Focused Drug Development Meeting for Phenylketonuria (PKU)

Held May 8, 2025

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View the meeting recording on-demand at bit.ly/TruePKU-ondemand

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AN INTRODUCTION TO THE TruePKU INITIATIVE

When speaking to people who are aware of phenylketonuria (PKU), but not personally affected by it, we often hear, "PKU has newborn screening, medical food and formula, dietary guidelines and prescription treatments. Isn't it one of the diseases that's been solved?" Sentiments like this one, in part, motivated National PKU Alliance (NPKUA) to spearhead the TruePKU initiative. We recognize that even with all the progress that's been made, the daily burden of PKU remains heavy, and people with PKU of all ages have many unmet medical needs.

Hosting the TruePKU meeting as a parallel effort to the U.S. Food and Drug Administration (FDA) patient-focused drug development (PFDD) initiative provided the opportunity to share the perspectives and priorities of PKU community members directly with FDA staff, researchers and therapy developers. Partnership with 14 PKU and related organizations around the globe helped expand our reach. Unrestricted grants from seven life-science-company sponsors provided essential resources to support two years of intensive planning and execution. (See Acknowledgements on page 34.)

In these pages, we hear directly from a wide range of people affected by PKU – from parents of babies navigating the early stages of life with a rigorous and dynamic daily regimen, to pioneers in our community who were on the leading edge of early detection and treatment in the 1960s and now face new unknowns as some of the longest-living adults with PKU. Direct quotes woven throughout the report preserve the authenticity of perspectives gathered through pre-meeting interviews, testimony and discussion during the meeting and written comments submitted before, during and after the meeting.

TruePKU has spurred new conversations, plans and activities. With the publication of this "Voice of the Patient" report, the PKU community has another powerful tool to align action with what matters most to people affected by PKU. We are proud to have hosted this forum and issue this "Voice of the Patient" report with hopes of accelerating further progress for the PKU community.

With deep gratitude,

Catherine Warren

Catherine Warren
Executive Director
National PKU Alliance

EXECUTIVE SUMMARY

Individuals with PKU and their caregivers are **the experts** on what it's really like to live with PKU. The TruePKU externally-led patient-focused drug development (EL-PFDD) initiative was designed to convey lived experience in a manner that informs the development, regulation and use of new treatments and disease management tools. Key learnings of the TruePKU initiative include:

GREATEST BURDENS

Symptoms Persist: Without question, newborn screening and early intervention with dietary management have changed the trajectory for people affected by PKU. Many meeting participants described benefits related to one or more of the three[1] FDA-approved treatments for PKU. However, even those who maintain good control over blood levels of phenylalanine (Phe) can experience symptoms from the effects of Phe on their bodies and brain. Commonly noted symptoms included challenges with executive functioning, attention, fatigue, emotional regulation, anxiety, depression, headaches, joint pain and sleep disturbance. Participants related how these symptoms can interfere with daily functioning, interpersonal and family relationships, school and work performance, overall well-being, physical activity and autonomy.

Mental and Emotional Toll of PKU: In addition to the symptom burden of PKU, participants spoke about the heavy weight of the continuous mental effort related to keeping Phe levels controlled. They shared the constant focus and planning needed to track and prepare low-protein foods and formula, adhere to a high-count pill regimen, maintain an injection schedule or manage a combination of these interventions. The nature of disease management exacts a major mental toll on people with PKU and their caregivers, as it requires constant daily effort with no days off and little room for error. Individuals relayed that failure to stay in range contributed to added worry, guilt and shame. Participants identified periods of high stress during puberty, pregnancy and postpartum due to biological changes that affected Phe levels in unpredictable ways.

Diminished Social Connections and Joy Related to Food Intake: Participants noted the loss of opportunities at every stage of life to take part in common, daily rituals and celebrations that center on food. Several people reported grieving these cultural touchstones and feelings of being different from their peers, especially during formative teen and young adult years. Many people noted that food was a source of anxiety, rather than enjoyment and healthy sustenance.

EXPERIENCE WITH CURRENTLY AVAILABLE THERAPIES

Control of Blood Phe Levels: Participants expressed gratitude for advances that have enabled most to avoid the severely disabling and life-limiting consequences of untreated PKU. Most cited relying on a combination of medical formula, special modified low-protein foods, foods that are naturally low in protein and/or medications to keep blood Phe levels close to or within the recommended range. Some adults reported that their regimen and degree of adherence changed over the course of their lifespan, as management guidelines evolved, access to care changed due to life circumstances or new awareness of long-term impacts and as new treatment options became available.

With Current Treatments, Unmet Needs Remain: Participants described variations in the adequacy and effectiveness of available therapies based on PKU severity, age, tolerability of side effects and other medical or lifestyle factors. Others expressed that the risks or concerns about some options outweighed potential benefits and limited their interest in pursuing them. Many participants said that even with current treatments, they must restrict protein intake to stay in range, while others noted that current therapies do not fully resolve symptoms that may appear, even when blood Phe levels are within the recommended range.

[1]KUVAN (sapropterin dihydrochloride), approved in 2008; PALYNZIQ (pegvaliase-pqpz), approved in 2018; SEPHIENCE (sepiaterin), approved on July 28, 2025.

ASPIRATIONS FOR FUTURE DISEASE MANAGEMENT

Diet Normalization is a Top Priority: Participants placed a high value on the ability to eat a wider variety of natural foods, reduce reliance on medical foods and foods with high carbohydrate counts, decrease food and Phe level tracking and participate more fully in social activities with fewer dietary concerns and restrictions. Those who achieved a more normalized diet with response to approved treatments or participation in clinical trials noted significant mental relief from food-related stress. They enjoyed feeling satiated. Others described a transition period as they became comfortable eating formerly forbidden foods and adjusting to new dietary allowances. Caregivers described their hopes for options that would allow their children to manage their diets more independently as they got older. Several participants noted that they would not pursue or continue a treatment unless it enabled this level of dietary freedom, underscoring how strongly this goal shapes decision-making about available therapies.

Strong Desire for Home Phe Monitors: Nearly every participant noted that lengthy turnaround times for receiving blood Phe level results complicates management by preventing timely adjustments to diet, activity or treatment. There were repeated calls for development of at-home monitors that could allow for more frequent testing and provide real-time results to guide self-management. These were also viewed as useful to aid research and therapy development that would benefit the PKU community.

SECTION 1:
SETTING THE STAGE


Catherine Warren

"Today's meeting is a landmark event for the PKU community, and it is a true expression of NPKUA's mission to improve the lives of individuals with PKU, pursue a cure by expanding research and provide education and support to individuals living with PKU and their caregivers. We hope today's meeting serves all three of these important aims," stated **Catherine Warren** in opening remarks.

Jamie Rosenthal, MD, provided an introduction on behalf of the U.S. Food and Drug Administration (FDA). "EL-PFDD meetings provide an important opportunity for the FDA and other stakeholders to hear directly from patients and their families about the symptoms that matter most to them, the impact that the disease has on their daily lives and their experiences with currently available treatments." Dr. Rosenthal presented an overview of the life cycle approach to drug development and ways PFDD meetings can inform the FDA's review process. She concluded, "While there are currently two approved treatments for PKU, we recognize that there is more progress to be made and more work to be done to further advance treatment and management of the disease."


Dr. Harding

A clinical overview of PKU symptoms and treatments was presented by **Cary Harding, MD,** professor of Molecular and Medical Genetics and Pediatrics at Oregon Health & Science University. He provided context for the daily impacts patients and caregivers would describe in greater detail. “The main biochemical phenotype and the cause of most of the symptoms in PKU is elevated blood and tissue levels of phenylalanine (Phe), but the disease gets its name from the presence of phenylketones in urine, therefore, phenylketonuria.” Dr. Harding explained that the missing enzymatic action in the liver leads to a buildup of Phe in the blood, which crosses into the brain and disrupts its development and function. He emphasized the importance of newborn screening for early detection, noting that confirmation requires both a plasma amino acid analysis and genetic sequencing. “A child’s phenotype helps determine their PKU subtype while their genotype may predict responsiveness to sapropterin dihydrochloride, one of two treatments approved by FDA as of the meeting date,” he noted. (See sidebar on page 17.)

Dr. Harding discussed the current treatment landscape for PKU, emphasizing the guidance for dietary Phe restriction and approved medications. In the decades since dietary restriction and protein substitutes were introduced in the 1950s, the recommended duration of dietary management increased from early childhood to pre-teens, and ultimately to the current practice of maintaining a low-Phe “diet for life,” following guidelines published in 2001. (See also page 7.) He explained that while a low-Phe diet supports healthy intellectual development in children, it becomes harder to maintain with age and doesn't fully eliminate PKU-related symptoms, even with good blood Phe control.

“We recruited a [longitudinal natural history study] cohort of individuals with relatively good overall blood Phe control, yet, we have measured impaired cognition and executive function in this group of people who are now nearly three decades beyond that study. This suggests that we still have outcomes that are imperfect. This is in the context of using a treatment, dietary food restriction, that you'll hear from the patients themselves, is difficult, socially isolating and frequently very unsuccessful in the adolescents and adults.” In closing, Dr. Harding stated, “Emerging data suggests that reducing Phe into the normal physiologic range with the ability to consume intact dietary protein is a goal that will require the development of novel treatments, and one that may improve global outcomes.”

Moderator **Kim McCleary** concluded the opening session with an explanation of the meeting format, which consisted of three sessions. Each session began with pre-recorded statements provided by PKU community members about their experiences, followed by a discussion featuring additional community members who joined live via video conference, telephone or through written comments submitted in advance or during the meeting. The first session was dedicated to symptoms and daily impacts of PKU, the second session focused on approaches to managing PKU and the third discussed treatment aspirations and clinical trial experiences. Panelists and discussion starters were carefully selected to reflect the array of experiences living with PKU, depending on the age at diagnosis, PKU severity and consistency of adherence to a low-protein diet across the lifespan.


Dr. Rosenthal

“EL-PFDD meetings provide an important opportunity for the FDA and other stakeholders to hear directly from patients and their families about the symptoms that matter most to them, the impact that the disease has on their daily lives and their experiences with currently available treatments.” – Dr. Rosenthal

SECTION 2:

SYMPTOMS AND DAILY IMPACTS

AN EVOLVING EXPERIENCE OF PKU

"In the lifetimes of most of gathered today, the outlook for children and adults with PKU has changed dramatically, thanks to the advances described by Dr. Harding," noted moderator Kim McCleary. Symptom descriptions shared by speakers with the longest-lived experience highlighted the impact of the timing of diagnosis and continuity of management on the severity and impact of symptoms individuals with PKU experience. Prior to widespread adoption of newborn screening for PKU that began in the 1960s, diagnosis was often delayed and individuals experienced severe intellectual disability, frequently requiring long-term inpatient care.

Dianne Obert, age 59, was the first baby in San Diego County to be diagnosed with PKU through newborn screening. "My parents and I had no other families for support because all the other children with PKU were intellectually delayed, some severely. PKU adults were in state hospitals. The diet was brand new to everyone. When I was 5, they did a protein challenge to see how much Phe my body could tolerate. There's a videotape of me. I was not able to walk straight. I wrote the alphabet backwards, and I was emotional. I acted like a 5-year-old drunk," she recalled.

In a pre-meeting interview, **Paul B.**, age 58, described the effects of being untreated for most of his life since age 8. "The symptoms can be very serious, and they wreak havoc on my life and self-confidence. Body odor is prevalent in patients with high Phe. It affects you socially and financially, because it's hard to get work. Constipation has been a big problem all my life. I was hospitalized in the 1990s for inflammation of the intestinal tract and the pain it caused. Doctors were dumbfounded that my intestines had not ruptured. I can't think straight, can't remember things and I'm depressed. My mother died recently and I'm on my own, but I can't handle life completely by myself. I'm worried about my ability to live. I worry about ending up in a shelter."

Saeed Purcell, age 55, was taken off a low-protein diet at age 8, based on clinical recommendations at the time, and later encountered challenges he didn't know were connected to PKU. "In high school, I had significant mental health struggles. Unfortunately, my mother attributed these issues to the vegetarian diet I had adopted and discouraged me from continuing it. Going forward, I followed a standard American diet. In college, I faced issues with emotional control, maintaining focus and managing relationships. These problems followed me into adulthood." **Dianne Obert** reported a similar experience with increasing symptoms after her doctors took her off diet at age 8. "Immediately I began struggling emotionally. In high school I noticed that when I ate meat and cheese, I got a headache that only time could take away. My grades were As to Ds, and I was struggling. The clinic said the headaches were unrelated to PKU and I wasn't assertive enough to challenge them. I wanted to go back on diet, but I was in the minority with that viewpoint. Finally, at age 21, I got to go back on diet."

SYMPTOMS WITH THE GREATEST IMPACTS

Symptoms and their impacts on daily functioning can vary over time and by person, as **Kristi Smith**, age 42, described for herself and her four adopted sons with PKU, who range in age from 6 to 21. "Some days we have amazing blood levels and are on our 'A-game' with regards to being on task with work, chores and studies, managing our time and controlling our emotions. Other days, one or more of us are just 'off.' Our levels fluctuate not only because of the protein we eat, but also the number of calories we do or don't consume, illness, activity level, growth spurts and hormone fluctuations. There's never a dull moment in our household."

Cognitive and Executive Functioning Impairments

Among the most persistent and challenging aspects of living with PKU cited by participants is the impairment of cognitive and executive functioning. They described symptoms of brain fog, problems maintaining focus, attention and concentration, forgetfulness and a diminished self-awareness of fluctuating Phe levels.

Les Clark, age 46, stated, "I try to keep my levels in the treatment range, which can be very difficult. When I do have too much protein, my attention span is limited, and my thoughts are all over the place with brain fog. It's difficult to realize you're slipping into some of the symptoms of high Phe because when we have bad days, we don't sleep well."

Individuals noted that these symptoms are not exclusive to adults, as changes in environment, routine and stressors can also trigger disturbances in neurocognitive and executive functioning in children. **Kala McWain** described her 5-year-old son **Braxton's** experience in preschool. "As soon as school begins, his levels go up, and they're harder for us to manage. We know when levels are up, he can experience brain fog, emotional ups and downs and trouble focusing, making it harder for him to concentrate in school and get the best out of his experience."

> *"Mental acuity - having clear focus, concentration, productivity and general desire to perform better [are among the most burdensome symptoms]. There are so many challenges for a person with PKU when [they get] older. I am not sure non-PKU people really understand all the complex challenges and how they relate to each other." – Written comment from Chad A., Texas*

Others noted this symptom pattern ramping up in adolescence, as **Jill Pickard** recounted with her son **Eliot**, age 15. "This past year has been especially tough with heightened struggles in keeping his levels, diet and emotions balanced. In high school, he has a 504-accommodation plan, but with so many teachers and students, it's challenging to maintain the same level of monitoring and communication that we once relied on. When his

Key Events Contributing to Evolving Patient Experiences with PKU

1951: Sheila Jones becomes the first child in the world to benefit from treatment with a Phe-free dietary formula, based on research conducted at Birmingham Children's Hospital in England, paving the way for dietary management guidance for young children with PKU

1960s: Broad adoption of newborn screening protocols for PKU enables early diagnosis and initiation of dietary management

1962-1990: Patients advised to follow dietary treatment until age 6 when it could be safely stopped based on prevailing understanding of Phe on brain development

1991: The recommendation to extend dietary restrictions through adolescence is published

2001: "Diet for life" guidelines established in the U.S.

2008: The first treatment for PKU, sapropterin dihydrochloride, an oral medication, is approved by the FDA

2018: Injectable medication pegvaliase-pqpz receives FDA approval, expanding treatment options for adults with PKU

2025: Oral powder sepiapterin is approved by the FDA for treatment of hyperphenylalaninemia in adults and children one month of age and older with sepiapterin-responsive PKU

levels are off, the first things to deteriorate are his executive functioning and emotional regulation – the very behaviors required to manage PKU. When we have to pull him out of school for clinic appointments, he falls further behind in school, compounding the cycle. Advocating for him has become a constant, as he isn't always able to advocate for himself when his levels are high."


Elizabeth Roper

Mood, Emotional Regulation, Depression and Anxiety

In addition to cognitive impacts, individuals associate high Phe levels with changes to their mood, ability to regulate their emotions and their overall mental health. **Elizabeth Roper**, age 49, described recurring mental health challenges from an early age. She reflected, "No one had ever explained to me the impact of high Phe on the brain. I thought you were either fine or unable to walk. I didn't know there was a huge set of in-between symptoms of altered brain chemistry and mental health problems. I became agitated and forgetful. I couldn't catch the bus on time. I felt paranoid about friendships. At my waitressing job, I once kicked a pedal bin across the kitchen because I just felt so randomly angry."

> *"My son struggles with big feelings of anger. His teachers have asked, 'Is it due to his PKU?'" – Written comment from Larisa D., New Jersey*

Kristi Smith recalled rough periods in middle- and high-school years when her Phe levels would fluctuate. "I describe the feeling of being possessed by rage. I was having headaches, anxiety, poor sleep and overall executive functioning issues. I could sleep 12 hours and still wake up exhausted because my sleep was so restless."

Emotional control issues and irritability were reported to be the most recognizable potential indicators of high Phe levels from infancy on. **Eugene Lubliner** shared how he and his wife, Kristen, recognize behavioral changes in their daughter **Adelaide**, age 9. "Over time, we've become attuned to the signs of Addie's Phe levels when they're potentially high. When she's more irritable or has trouble focusing, we suspect it's a spike in her Phe levels. Now Addie is entering her adolescence, so as she's getting older, we find ourselves wondering how much of a mood issue is related to PKU symptomology and how much of it is just our daughter becoming a teenager."

> *"I have a ton of anxiety. I struggle with the mental challenges of the disease and many times feel hopeless due to the lack of care and support." – Written comment from Anonymous, Colorado*

Headaches

Jennifer Christenson, age 50, described a rise in symptoms during a period in early adulthood when she lost access to PKU care and medical foods she relied on. "I had migraines, and they increased a lot then. My executive functioning struggled, I had anxiety, emotional fragility, even some eczema and skin issues." In college, **Brittany Murray**, now 38, was on the tennis team, juggling a full academic load as a science major. "I was on the road a lot, and finding low protein foods at restaurants and rest stops was hard. I would struggle with headaches, focus, mood and anxiety. Everything took a lot more effort than it needed to."

Headaches **Dianne Obert** experienced in her teens persist today, "I still get headaches, and it can be hard to go through each day. I have to watch what I eat throughout the day, and there are times I haven't eaten, and it's hard to think. So, if you don't eat right, you can't think right." Others regarded headaches as a signal

that their Phe levels might be elevated. “When I have a headache, I usually take my Phe levels,” stated **Maridith Baker**, age 23.

IMPACTS OF SYMPTOMS ON DAILY LIVING

The symptoms of PKU and their impact on daily living is intertwined with, and compounded by, the ongoing demands related to dietary management, including consistent tracking and adherence to a low-protein diet. Individuals with PKU and their caregivers recounted a range of physical, cognitive and emotional effects. Over time, these effects appear to vary across individuals, reflecting a spectrum of lived experiences. **Rhonda Connolly** summarized this by stating, “There are so many variations on how [people] feel and what they feel when their levels are high, from just feeling ‘off,’ to being in bed and being in full-blown depression.”

> *“There is a vast range of PKU severity and thus a wide variety of ways people manage living with PKU. Everyone is very different when dealing with this disease. There is no one management method that fits all, which leads to everyone have different strengths and different struggles.” – Written comment from Stephanie F., California*

Impacts on Individuals Living With PKU


Bianca Albanese

Bianca Albanese, age 34, described the ongoing demands of managing life with PKU. “I’ve experienced digestive issues related to formula and the medical low-protein foods that I rely on. I’m constantly hungry, and I struggle with energy. I feel as though I operate with limited resources. I carefully select my activities knowing I’ll tire faster. I plan, think and manage my rigid medical routine. But naturally, when that perfection breaks, guilt follows. How does that affect my brain? To me, fluctuating high or low Phe levels give me headaches, sore joints and a feeling of overwhelm and sadness, like a black cloud is over me. Unfortunately, this is an unseen burden by many.” Bianca continues, “Just because I carry it well doesn’t mean it isn’t heavy. From the outside, I may look like a successful adult. I have two degrees, a PhD and a good career, but it is really only a select group of people who truly understand my day-to-day life with PKU. Many of my struggles feel minimized as my Phe levels are good, so there ‘isn’t an issue.’”

Casey Connolly, echoed these sentiments, sharing his experience growing up. “Physically I looked normal, but mentally, emotionally, I was struggling on a regular basis – not just for that meal, but in the morning before school, I was already anticipating lunch, anticipating going to a friend’s house, not excited about the after-school events, but anxious at 10 years old because I had to approach the subject of what foods I can and cannot eat.” Now, at age 32, some of the same feelings and burdens continue. “If I can’t find a substitute that works for my diet, my options are limited. They’re ‘don’t eat’ or ‘eat.’ If I eat, I physiologically hurt myself with every bite, which then wears into the guilt of the next choice. With the next meal, you feel the same guilt that you felt with the previous one,” he said.

Individuals frequently noted how waiting days or weeks to receive Phe level testing results adds to the level of anxiety they experience, and the way this compromises appropriate self-management. **Karlye Vonderwell**, age 26, recounted, “I submitted a blood Phe level three and a half weeks ago, and I still don’t have the lab report back. While I can say I think I’m fine, sometimes you look back and recognize how the symptoms and side effects of high Phe levels are slow to become noticeable. We’ve heard many times today, ‘I had no idea what I was experiencing until I was adequately treated.’” **Jill Pickard** related her son’s experience, “**Eliot** has told us that he notices the impact of high levels, but only once we get his levels back down. He doesn’t notice in the moment, which makes it harder to course correct.”

Many participants described feelings of isolation and disconnection as a consequence of dietary restrictions. **Amy Oliver** stated, "Our kids miss out on the simple enjoyment of food as a social experience, and we do too as a family. Unfortunately for them, that's a really important way to connect with others."

Kelly called into the meeting to share the recent experience of her 6-year-old daughter being invited to join a friend's family at a restaurant. "I looked up the menu and, unfortunately, there was nothing that would be suitable for her and I just didn't have the time to be able to prepare something to send with her to eat there. I had to tell her, 'You will just eat dinner at home, and you can go to your friend's house afterwards.' It's just a small thing, but I do feel that effect of PKU adding up over time. She's going to miss out on some experiences that her classmates get to have or have fewer chances to bond with her friends."

Adelaide Lubliner, age 9, described a recent experience at school that made her feel different from her peers. "True story, this happened a couple days ago. I dropped my lunch tray on the floor and had to wait 20 minutes to have my food made again. I wish it could happen faster, but it's special food, so it takes longer to make." **Sarah Gallagher** reported, "By second grade, my daughter **Maeve** started coming home reporting that kids at school were making fun of the food that looked different or her smelly formula. So, she chose not to drink her formula at school. She's 15 now and still doesn't drink formula at school, which impacts how we spread her protein intake throughout the day."

Eighteen-year-old **Claire Oliver** described her family's approach to social engagements involving food. "My younger brother, Seth, also has PKU, but my older brother does not. As soon as I was diagnosed, my parents made sure I followed the strict PKU diet. Growing up, that was all I knew. I got used to eating before going out to restaurants and bringing my own food to birthday parties. That singled me out, but I also learned to be more independent and better able to speak for myself at a young age."

> *"As a teenager there were feelings of anger and resentment at not being able to just eat whatever I felt like, as my friends did." – Written comment from Karen D., Pennsylvania*


Jill Pickard

Physically active members of the PKU community reported the challenge of meeting caloric demands and feeling full on a low-protein diet. **Jill Pickard**'s son, **Eliot**, struggles with this as a competitive swimmer. "He's now 5'11" and active on multiple swim teams, so he needs a significant calorie intake to fuel his athletic life. Yet, his swim coaches don't know how to offer dietary guidance for someone with PKU, and his clinical team doesn't quite know how to offer guidance to someone swimming at the performance level he does. His doctor tells us there's no one else in their clinic quite like him. It's hard to be an 'n' of one in an already very small, rare disease population."

Knowing that consuming protein is harmful to the brain, participants noted the heavy stress of relying on the accuracy of food labeling and restaurant menu descriptions to guide meal planning and intake. **Kelci** and **Jared Bleasdale**, parents of two children with PKU, **Theo** (age 3) and **Hadley** (19 months), noted, "Labels aren't often accurate as far as how much protein the food contains or marked as no protein. They can still have traces of phenylalanine, which can be dangerous unless we have the time or tools to double-check the actual Phe content." **Karlye Vonderwell** studied abroad during college and must frequently travel to Asia for her job. "It's so hard to know what you might be consuming when you can't fully understand the menu. Even vegetarian options can include beans and other high-protein foods."

Women with PKU are warned from a young age about the risks of pregnancy, especially if Phe levels are not well-controlled. This affected family planning and other aspects of life. **Dianne Obert** recalled going to a

special camp for young women with PKU, hosted by the State of California. "I was 21. All eight of us who attended were off diet and we all had blonde hair. This happens when you go off diet for a long period of time. We learned about the PKU diet and the consequences of having a baby when you're off diet. The baby would have heart problems, a small head and other things. I stayed on diet since that camp. Doing so enabled me to complete my master's degree with a 4.0. I haven't married and I wanted to be a parent, so at 39 I adopted my first child, Tasha, then Isaac at 41, and Noah, when I was 50 years old."

"I remember in my teens going to clinic appointments and being grilled," reported **Jennifer Christenson**. "They'd ask, 'Are you sure you're not having sex?' and they told me, 'The baby could be very much harmed by high Phe levels.' It just created this anxiety of a future, a family that I wanted to have." As Jennifer reached that stage of life of starting her family, she had to make decisions about how to stay in good control to protect her baby's health and her own. She underwent a lot of extra testing and had to manage morning sickness and other aspects of pregnancy differently. She described the physical changes she experienced during pregnancy. "It's hard to keep calories up while keeping protein down, so I ended up with a lot of foods that were high in sugar and that just caused a lot of swelling, fatigue, joint pain and other things. I was tested for gestational diabetes and my level was just below the clinical threshold." She shared the outcome, "I made it through two pregnancies with my levels intact the whole time, and my boys are now 10 and 8 and are doing great. They're at grade level, involved in sports and have lots of good friends. They're amazing. My 10-year-old has ADHD, dyslexia and anxiety, and my 8-year-old is a gifted learner that has some anxiety and OCD as well. I would definitely do it again in a heartbeat, but it was physically hard on my body."

Maternal PKU syndrome is a pregnancy-related risk women with PKU may experience if elevated levels of Phe in the mother's blood cross the placenta and harm the developing baby. Due to this potential risk, women with PKU who become pregnant must be closely monitored and must tightly follow Phe-restricted diet and other treatment guidance.

Jennifer Christenson and the birth of her son Owen

Melissa Bernzen Goulart described how pregnancy with PKU affected her, "By my second trimester, I was steadily increasing my protein intake and my tolerance went from 7 grams of protein per day to 30 to 35 per day. This invited more stress and anxiety in my regimen as I was trying to navigate my rising tolerance, the mental toll of eating foods I've never been allowed before and the caution in choosing which foods to include in my diet because I knew this was short-term. I was worried that becoming too liberal with my food choices would make it harder to transition back to a lower protein diet, and I later learned that this concern was correct."

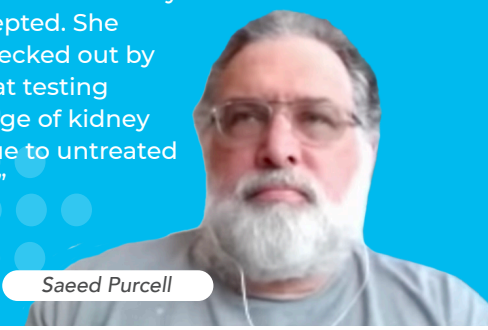
Bianca Albanese summarized the complexity of living with PKU and how challenges in one area can affect other aspects of managing the condition. "Some days I manage to keep all the balls moving: PKU, career, health, social life, energy and my mental well-being, but it is never effortless. It's also fragile. It only takes a slight disruption, sickness, stress hormones or a natural lapse in willpower to send everything crashing down, and the consequences aren't subtle. When one PKU ball drops, it creates a ripple effect. Energy plummets, cognitive function falters, my mood becomes low and I have a feeling of absolute overwhelm. Everything feels impossible at that moment. Unlike the clown who can pick up the ball and carry on, for me, restoring balance takes time, effort and sometimes the ability to just accept that some balls won't stay in the air at all. The constant juggling is exhausting."

> *"PKU isn't just a diet. It's more than just measuring food – it's our whole life and takes a lot of time, dedication, resources and commitment." – Written comment from Pamela K., Illinois*

The Role of the Spouse in Recognizing Ongoing Consequences of PKU

Some adults shared that they stopped following the low-protein diet when they were younger, based on then-current guidance from their doctor, with consequences to their health. **Steve Scott**, age 51, credits his wife, Beth, for identifying symptoms he had come to accept as normal for himself. When they were dating, Steve told her that PKU was something he suffered from in the past, "as a child." Steve recalled, "Beth is a nurse, and she started to pick up on behaviors she felt were kind of abnormal as we got further along in our marriage. She was concerned about my constant fatigue, frequent headaches and trouble following conversations, especially after meals. For me, that was my usual pattern, so it didn't feel different to me." After seeking medical guidance at her urging, Steve's provider confirmed that his symptoms were likely a result of high blood Phe levels.

Saeed Purcell described a similar experience. In a pre-meeting interview, Saeed's wife **Hannah** shared, "Saeed is a very gentle and intellectual person. I recognized a pattern in his anger and concentration issues that were out of character. It occurred to me that it could be related to PKU." Saeed affirmed, "Hannah brought a new focus on the moments of emotional instability and work difficulties that I had accepted. She encouraged me to get checked out by a primary care doctor. That testing indicated I was on the verge of kidney disease, at least in part due to untreated PKU since late childhood."



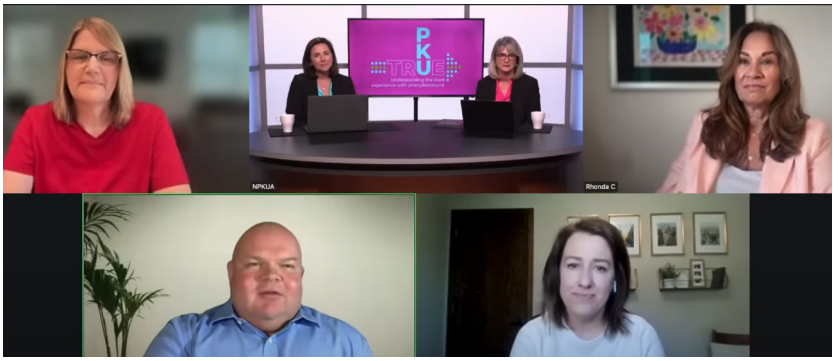
Saeed Purcell

Impacts of PKU on Caregivers

Caregivers reported the additional demands that PKU imposes, including more time and attention dedicated to obtaining appropriate foods and ingredients, managing meals, coordinating medical appointments and monitoring behavior to guide at-home disease management and help their loved one(s) live a healthy and fulfilling life.

For parents, the caregiver journey begins with out-of-range results from newborn screening and then a confirmed diagnosis. Many parents reported that the shock of the news compounds the overwhelming emotions and lifestyle changes that come with having a new baby. **Anna Phillips** recounted her family's immediate reaction to learning about her daughter **Ada**'s positive screen. "I was a second-time mom. Nobody in our family has PKU or any genetic disorders, so this wasn't on our radar at all, and we didn't do any extra genetic testing. We got a clean bill of health from Ada's pediatrician at her three-day-old check-up. Later that afternoon, I received a call from the chief pediatrician that he had just gotten word that her newborn screening test came back abnormal for PKU. Of course, we immediately freaked out and were super upset. He tried to reassure us, citing the possibility of false positives. To be safe, he got us an appointment with a pediatric geneticist for the following day." Several other parents recalled being told by their pediatric teams that false positives were common. This was described as challenging to process once they received confirmation of their child's diagnosis. Anna continued, "That evening, my family and I were on the internet, Googling, trying to still hold on to that hope, 'Maybe it's a false positive,' but you're starting to see upsetting stuff, what it means to live with a rare disease. The images of people with untreated PKU are really scary."

Kelci and **Jared Bleasdale** spoke about feeling unprepared to learn that their oldest child, **Theo**, had PKU. "[Our pediatrician] told us that Theo wouldn't be able to process protein, and that he would need a special formula, but gave us little information about how to feed our newborn. We rushed to local grocery stores and could not find anything. We had no guidance, and we had no idea what lay ahead in terms of sourcing products that would be healthy and safe for Theo to consume."



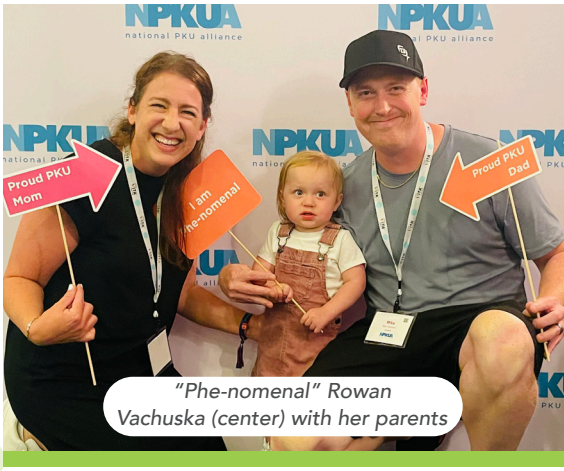
Panelists for the discussion about symptoms and daily impacts (clockwise from top left): Dianne Obert, Rhonda Connolly, Melissa Vachuska and Les Clark

Adapting to news of a PKU diagnosis can bring grief over the loss of certain aspects of parenting and family life that are simply more challenging. Several moms reported difficulties associated with breastfeeding a newborn with PKU led them to discontinue it before they wanted to. Thirty years ago, when she received her son Casey's diagnosis, **Rhonda Connolly** was told, "'Stop nursing and come meet with the geneticist and dietitian immediately, or it will cause permanent brain damage.' This was the beginning of our life with PKU and everything we knew would be different." **Kala McWain** recalled, "We couldn't manage Braxton's Phe levels with free breastfeeding, so I tried pumping and measuring. It was the start of the pandemic and navigating that, while learning about PKU and trying to safely feed my son, became overwhelming. I had to give up breastfeeding for my own mental health."

The moment of diagnosis was the start of a significant mental load caregivers reported experiencing. **Amy Oliver** is the mother of **Claire**, age 18, and **Seth**, age 15. She remarked, "For 18 years, I've thought about every single bite of food Claire and Seth have eaten every single day. The calculations, the planning, the extra steps for shopping, ordering formula and medical foods, tracking – those details are constantly running through my brain. There's no time off, there is no period when I can relax. There's no vacation from this responsibility of doing everything I can and, in turn, helping them each do everything they can to make sure that every Phe level is within the range for their immediate and long-term health of both their brains and their bodies." **Melissa Vachuska** was one of the parents who had to adjust work schedules to accommodate caregiving.

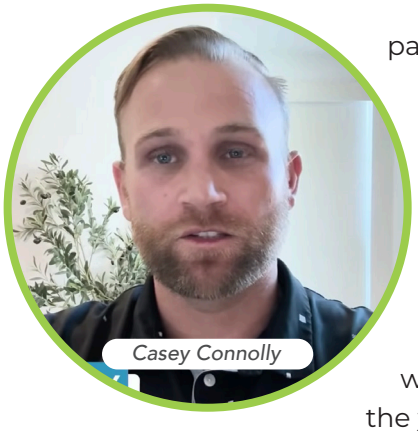
Caregivers reported how much additional preparation and stress is involved when leaving the controlled environment of their homes with their children or preparing others to help care for them. **Anna Phillips** spoke about her intention to send Ada to preschool in the fall. "It's anxiety-inducing. When you think about impromptu class parties, the snacks, all the little things that little kids love, you don't want your child to be different or miss out. There are lots of fears about the future and what that looks like for her. We're just taking it day by day." **Dianne Obert**'s 10-year-old son, **Noah**, has PKU. "My parents take each grandchild on a special trip and Noah's turn is coming up. There is a big discussion about whether my parents can, or are willing to, take on the diet for a week or two. My mom managed my PKU diet when I was a kid, so she knows it, but they are worried. Right now, the plan is for me to go on the trip with them because of the diet. One of Noah's cousins told him, 'No way. You can't take your mom because it will be a different trip.'"

Melissa Vachuska is the mom of 2-year-old **Rowan**. She noted, "One thing I've come to realize over the past two years is just how much society revolves around food, and that's been tough. I look at birthdays, family vacations and even getting a small order of McDonald's fries through the drive-thru as tasks that require so much planning. We enjoy traveling, and while PKU has not stopped us from doing that, it certainly has changed how we are doing it. It requires a lot more planning and a lot more just mental preparation to do anything these days."



"Phe-nomenal" Rowan Vachuska (center) with her parents

Transitioning care from the caregiver to the adolescent or young adult with PKU presents new challenges, stressors and tensions. Parents expressed concerns about letting go of hands-on management, while questioning whether their child could advocate for themselves when needed and independently manage their PKU regimen. Several


Casey Connolly

parents commented on how they incorporated their children into meal planning, beginning very young to help build skills and confidence. **Adelaide Lubliner**, age 9, and her mom, Kristen, prepared a snack together on screen. Several participants shared photos of young chefs learning to make their own low-protein meals.

Jill Pickard expressed the relief she felt from the burdens of managing her son **Eliot**'s care while he was attending sleepaway camp. "Even though I had done all the prep to send him off to camp, that first morning when I did not have to wake up and make his formula, I felt the release of all I had been carrying over the years. Summer camp is a chance for Eliot to learn how to manage his diet and advocate for himself away from my protection and influence."

College presents a crucial point in this transition of responsibility. **Rhonda Connolly** has two sons with PKU. She noted, "Sending the boys to college was a proud moment, although one compounded by fear about whether they would be able to stick with their diet away from home with all the wonderful distractions and temptations of college life. When talking by phone or during visits, we tried hard to balance our concern about PKU-related issues with other topics. At times, we could tell when they were more anxious than usual. I hated to keep bugging them about their diets and whether they were taking their formula and eating good foods. But, as a mom, I was worried about their health, and I just couldn't help it. Even though I recognized they were adults, and they would need to take ownership of managing their PKU diet to be successful in adulthood, I was then and always will be worried." **Casey Connolly** confirmed that his mom had reason to worry about the college transition period. "I played baseball and team road trips made eating out tough. We'd often stop at a steakhouse or a barbecue joint, which didn't provide many options for my diet. It wasn't trendy then to be a vegetarian and my friends didn't understand my strict diet, so I strayed from my diet and drank plenty of alcohol, causing an onslaught of symptoms I didn't immediately recognize."

> *"My son has a twin brother who is not a PKU patient. Managing their diets in a way that he doesn't feel different or see himself as having a disability, especially compared to his twin brother, is one of the hardest things in the world."*
> *– Written comment from Anonymous, Canada*

GREATEST WORRIES

The topics that worry people affected by PKU as patients or caregivers shift in response to different stages and ages. **Amy Oliver** shared her perspective on the shifts that occur. "The first few years of life are particularly challenging. There is a massive learning curve, and the pressure to be perfect as the parent of an infant, then toddler, then young child is intense and can't be overstated. In fact, their brain is at risk if you make one misstep! It gets better as the child reaches elementary school and early into middle school, as the family unit has adapted to address the daily challenges. But then come the teenage years, and it is like starting over. The desire of the teens to 'fit in' and not be different is intense. They don't want anyone to know about PKU, so they hide it and make decisions about food based on social pressure. They get defensive, and it can easily be a source of tension between parents and teens."


Amy Oliver

Some speakers noted that in adulthood, the impact of maintaining a strictly managed diet for so many years affects their relationship with food, and could

have negative physical effects, too. As **Les Clark** described, "My Phe levels remain 'in range,' but maintaining this has essentially resulted in giving myself an eating disorder. I'm constantly planning, tracking, accounting for everything I eat and am still wondering if I'm doing it right. The low protein diet is high in carbs, sugars and calories, which causes weight management issues, especially with the sedentary work I do. It could also contribute to other metabolic issues like diabetes later in life."

Casey Connolly questioned this too, "How is my body reacting to not eating foods from the earth for the majority of my life? Protein is essential for the body, and I fear that without enough natural protein sources, my body will continue to deteriorate as I get older. I worry about the lifelong impact of relying on medication and synthetic foods."

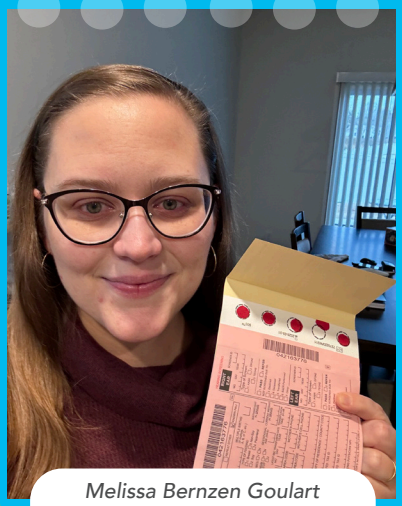
Several people aging with PKU remarked on the fact that research on PKU and its long-term effects is a relatively new topic, with many unanswered questions about the effects of aging and progression of symptoms in later life. **Dianne Obert** noted, "As far as aging, I have no idea what to expect as an older person with PKU. I had breast cancer in 2020. It was caught early and treated. My family history includes heart disease. I'm at the forefront of PKU patients working to coordinate multiple doctors." Les mentioned, "Nobody knows what happens as you get older with PKU, if you're at higher risk of things like dementia, Parkinson's or Alzheimer's because of the changes in the brain that even with well-treated PKU are still there. Like Dianne said, we don't know what's in store."

> *"As a more mature adult, the consequences of aging with the PKU diet are challenging in and of themselves. A heart-healthy diet is typically categorized as being high protein, high fiber and low carb. This is the opposite of the PKU diet out of the necessity to keep Phe levels low. Frankly, I did not see a viable path forward to aging healthily while continuing to manage my PKU with metabolic formula and low-protein foods." – Written comment from Karen D., Pennsylvania*

> *"I also have had increased GI and weight issues as I have gotten older, and I wonder how much of those issues have to do with indirect or direct side effects of PKU." – Written comment from Tricia J., North Carolina*

Women with PKU who are planning for future pregnancy expressed concern about how the condition can affect their body and their children's. **Melissa Bernzen Goulart** explained, "By the time I started my family planning, I had so much fear and anxiety about diet management despite having consistent normal Phe levels. During pregnancy, there are so many hormonal and diet changes that it's very hard to know what is pregnancy-related versus rising or falling Phe levels."

"At the age of 12, my PKU clinician told me about risks related to having children because of my PKU. The emotional challenge this presented in my early and mid-30s was not something I was prepared for despite having been warned. At 12, the concept is abstract at best. At 32, when women your contemporaries are pregnant or planning to become pregnant, it is difficult to handle." – Written comment from Karen D., Pennsylvania



Melissa Bernzen Goulart described fears about managing PKU during pregnancy

SECTION 3:
PERSPECTIVES ON CURRENT APPROACHES TO MANAGEMENT AND TREATMENT

CHANGING GUIDEPOSTS FOR MANAGING PKU

Speaker Kathleen Gonzales, age 61, and four of her older siblings have PKU. Their experiences reflect the changing management of PKU that followed research initiated by a team at Birmingham Children's Hospital in 1951. (See "Key Events" on page 7.) Kathleen shared, "My oldest sister, Terri, was born in the late 1940s before much was known about PKU or how to manage it. She had severe intellectual disabilities and couldn't sit up, speak or do anything independently." Kathleen said that Terri was placed in long-term care until her death at age 7, despite efforts by her family to care for her at home. Speaking about her other siblings with PKU, Kathleen stated, "When I was 8, my mom took all of us off diet at the same time. Today, each of us faces our own health challenges. My sister is now in an assisted living facility and struggles with memory loss. One of my brothers needs daily support from his wife. PKU has really affected my physical health, especially with vertigo and blackouts that started around age 20." During periods when she wasn't following dietary guidelines, Kathleen had many medical emergencies. "I started rapidly losing weight until I was skin and bones. No one could figure out what was going on with me," she said.

Kathleen Gonzales (left) with her mom and three of her older siblings with PKU in the 1960s

Saeed Purcell, age 55, was also in this cohort of short-duration dietary management. "Even under the care of Dr. Robert Fisch, a leading PKU researcher, the belief at the time was that brain development was complete by age 7 or 8. My mother kept me on a strict diet until that age, and then my diet became more typical, although my mother made sure I was monitored. In high school, I [voluntarily] started eating more of a vegetarian diet. Around the same time, I encountered some significant mental health struggles" (described on pages 6 and 12).

As evidence accumulated that early discontinuation of the diet was not adequate to control symptoms, guidance shifted toward continuing low-protein management through early adolescence (ages 12-14). **Les Clark**, age 46, was among the children affected by the recognition that dietary management should be sustained. He recounts, "As I got closer to age 6, there was more research, and the milestone for removing dietary restrictions moved to age 8. About the time I turned 8, they said, 'Well, maybe the brain isn't done developing until age 12.' By the time I got to 12, the research was supporting a 'diet for life' approach. I wasn't counting down until my 12th birthday so I could eat whatever I wanted, but I'm sure my parents were looking forward to not having to deal with special foods and medical formulas."

For **Steve Scott**, 51, the end of dietary restrictions marked the end of PKU treatment until much later in life. "My parents were told that I could start eating typical foods after late childhood, so I discontinued the low-

protein diet around age 12. From that time until now, I've just been off diet. Through adolescence [and] early adulthood, I didn't really identify as someone with PKU. When I met my wife in my early 20s, I told her that I used to have PKU; it was something that I experienced as a child. At that time, it certainly felt like PKU was just something of my past."

CURRENT THERAPY LANDSCAPE

Two FDA-approved pharmacologic treatments[2] now complement the prevailing guidance for dietary management for life, along with a variety of medical formulas and foods. Most participants reported they rely on a combination of approaches to achieve and maintain target blood Phe levels. However, the complexity and time-intensity of daily regimens, side effects associated with existing therapies and remaining unmet needs for achieving optimal health and wellness in the face of PKU underscore the need for more treatment options.

Prescription Medications

Throughout the meeting, participants shared their experiences with and considerations for both approved prescription treatments for PKU. Factors such as age, PKU severity (see sidebar, at right) and willingness to accept potential side effects influenced interest in these treatments. Treatment advances have been associated with reduced symptoms and fewer instances of disability compared with untreated or inadequately treated individuals.

Sapropterin Dihydrochloride

Many participants noted familiarity with sapropterin dihydrochloride, the first medication approved for PKU and now approved for individuals one month of age and older. This medication is taken orally to help minimize buildup of Phe in the blood, although it doesn't fully eliminate the need for diet restrictions for most responders. While specific genetic variants can sometimes predict responsiveness to sapropterin (see sidebar, at right), the only way to find out if an individual will respond is to go on the medication for a trial period. **Melissa Vachuska** was preparing her 2-year-old daughter for this trial period. "Based on **Rowan**'s mutation, she is expected to respond, and we're gearing up for that now. While we're hopeful it will increase her Phe tolerance, the preparation has been stressful. We've increased her protein to test her tolerance and are reverting back to weekly blood draws. All of this on top of navigating toddlerhood has been a lot to handle."

Karlye Vonderwell and her brother participated in a clinical trial for sapropterin dihydrochloride when they were in grade school. "We both responded relatively well; I responded more than he did, although it was not without its challenges." (See page 22.) **Owen Maxfield** didn't respond at age 6, but a family move and new provider led them to try it again at age 8. His mother, **Heidi**, recalled, "He had a better response than he did the first time, which allowed him to go from 7 grams of protein to 17 grams per day. Almost tripling your protein allowance at that stage was life-changing for us."

[2]*Since the meeting date, SEPHIENCE (sepiapterin) was granted marketing approval by the FDA for the treatment of PKU on July 28, 2025.*

PKU Disease Severity and Treatment Responsiveness

The specific severity of an individual's PKU depends on the PAH function. Treatment decisions are often informed by disease severity.

Classical PKU is characterized by little to no PAH enzyme activity. Individuals with classical PKU are generally considered poor responders to sapropterin dihydrochloride.

Moderate PKU is typically less severe, and individuals are typically responsive to a wider range of treatment options, including sapropterin dihydrochloride.

Hyperphenylalaninemia ("Hyperphe") is the mildest form of PKU, although individuals still face the challenges of living with and managing the condition.

Variant PKU describes a gene mutation resulting in slightly elevated blood phenylalanine levels. It is sometimes referred to as non-PKU hyperphenylalaninemia.

Before sufficient studies were done to support use during pregnancy, women would have to discontinue use before conception and during pregnancy. **Jennifer Christenson** described her experience: "In 2008, I was able to trial sapropterin, and I was a responder. I was able to double my Phe tolerance, and it allowed me to introduce a whole lot of foods instead of synthetic proteins in the medical foods. In 2012, my husband and I were planning to start a family, so I went off medication and back to just the diet and medical foods. [After two pregnancies,] I'm back on it now and am able to eat a lot more whole foods and less medical foods, and it's really been great to be back on that treatment."

Pegvaliase-pqpz

In 2018, pegvaliase-pqpz was approved by FDA as an injectable medication to treat people over the age of 18 with uncontrolled Phe levels greater than 600 micromol/L despite current therapies. It works by breaking down Phe in the blood and offers an option for those who didn't respond to sapropterin dihydrochloride or wanted more freedom from diet. "When I got back into care after 40 years without treatment, I tried sapropterin, but my levels didn't shift much; I wasn't a responder," reported **Saeed Purcell**. "I was eager to get my health on track and try other avenues that wouldn't require me to make huge alterations to my diet. Despite my fear of needles and concerns about potential side effects (see page 22), I decided to try pegvaliase in 2021. With my wife's support and guidance from the manufacturer's patient support team, it has been transformative and has significantly lowered my Phe levels – and it has given me dietary freedom."

Caller Alexia shared her experience with this treatment. "I was a responder to sapropterin, but as a teenager I was active in school, and I just wanted to eat everything. I tried pegvaliase. I responded pretty quickly. Now I don't take any formula, and it's really changed my life – my food life and not having to worry about all the extra challenges of PKU."

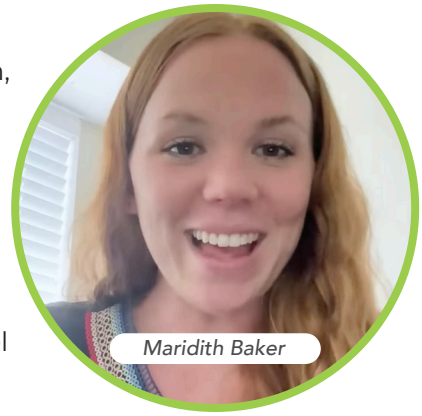
Brittany Murray also responded to pegvaliase, although she discontinued treatment for a period to enroll in a clinical trial. "I restarted last year since it's currently the best treatment option I have available. It has at least alleviated most of the burden of the PKU diet in the sense that I've been able to have lower, even normal Phe levels without following a restricted diet, which no other therapy can do for me at this time." She also related to drawbacks mentioned by others, as described on pages 22-23.

For some caregivers of young children, pegvaliase offers a hopeful option for the future. **Anna Phillips** described her daughter **Ada**'s future severity-based options. "She has a gene variant that leans towards classical PKU, and the data suggests that she wouldn't be a great responder to sapropterin. However, her care team is hopeful that in the future she could be a good candidate for something like pegvaliase, or some of the new treatment modalities that may be coming out. So, we remain hopeful."

Anna Phillips draws blood from her daughter Ada for Phe level testing

> *"Naturally, I can have 5 grams of protein per day. On sapropterin, I was at 10 grams a day. And now on pegvaliase, I'm at 60 grams a day, and I'm not on any formula." – Written comment from Samantha F., Washington*

Medical Formula and Foods



Medical formula remains a cornerstone of PKU management across the lifespan, and many participants emphasized its essential role in maintaining stable Phe levels. **Maridith Baker** shared, "I've been on formula and a low-protein diet my whole life. With two formulas as part of my regimen, I'm able to maintain a healthy Phe level." Similarly, **Melissa Bernzen Goulart** described formula as an ingrained part of her daily routine. "For a long time, I have been in the group of people who would rather not take medication for now and have been content with my diet. Drinking my formula is such a constant part of my life, it would feel odd for me not to have it."

> *"Currently, I medically rely on my formula. For my lifetime, formula has been the utmost important part of my treatment." – Written comment from Anonymous, Kansas*

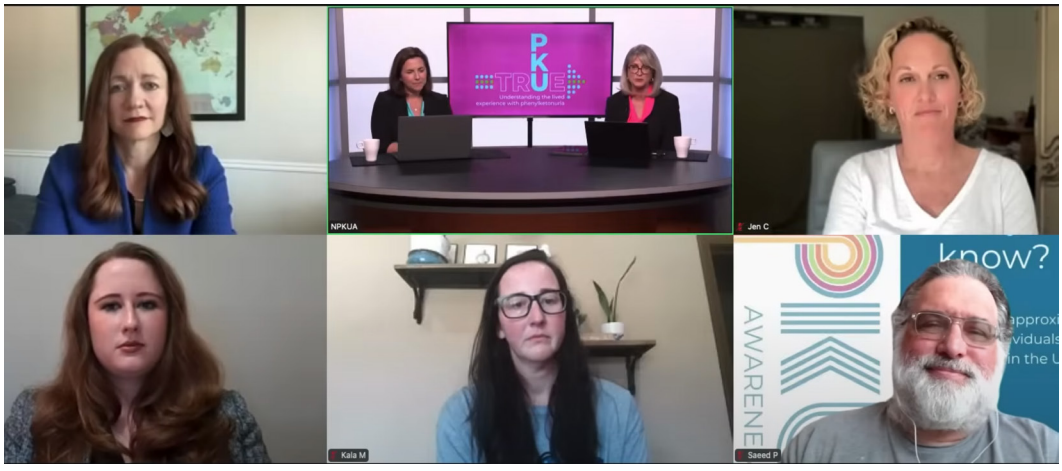
Low-protein foods are crucial to obtaining adequate nutrients. Participants cited various fruit and vegetable dietary mainstays with naturally low protein content, including potatoes and potato-based dishes, which require careful monitoring to maintain safe intake levels. **Kathleen Gonzales** noted another vegetable she has to limit. "I have been good about incorporating more vegetables into my diet, my favorite is artichokes. They're higher in Phe, so I have to use a scale to make sure I'm not overdoing it." Prepackaged, specially formulated low-protein options, such as breads, pastas and grains, were also referenced as supplemental sources.

Several participants mentioned learning how to prepare low-protein foods and snacks from a young age, including **Melissa Bernzen Goulart**. "My parents involved me in my diet management as young as age 6. This included making my own formula, baking my low-protein foods and tracking my food and Phe levels."

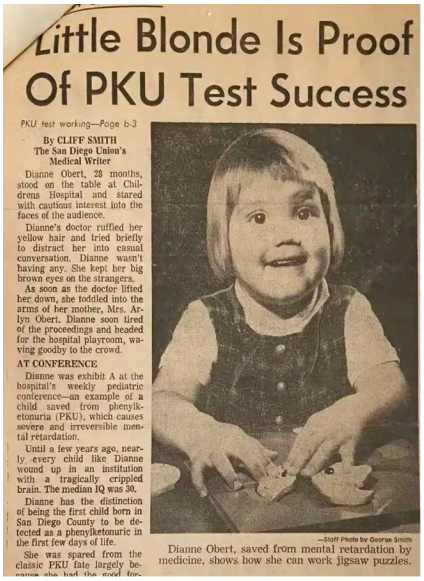
Other Treatments

A few participants referenced taking large neutral amino acids (LNAAs) alongside other therapies to help manage blood Phe concentrations, including **Casey Connolly** (see page 22) and people submitting written comments.

Elizabeth Roper spoke about the benefits of adding an antidepressant to her regimen. "A new PKU consultant saw me crying in clinic and explained how poorly managed Phe could cause depression. I read an article about how PKU patients can only access 30 percent of the dopamine that normal people can. My medical team reviewed my Phe levels, and we cut my protein allowance and started antidepressants. Within two weeks, I felt like a whole new part of my brain had come alive. For the past 11 years on this regimen, I've stopped making self-destructive decisions and I made it through COVID without a single obsessive thought," she said. "I wish when I was younger someone had looked past my diet and put my mental health into the bigger picture."



Panelists for discussion of current approaches to treatment and management (clockwise from left): Amy Oliver, Jennifer Christenson, Saeed Purcell, Kala McWain and Karlye Vonderwell



Little Blonde Is Proof Of PKU Test Success

PKU test working—Page b-3

By CLIFF SMITH
The San Diego Union's Medical Writer

Dianne Obert, 23 months, stood on the table at Childrens Hospital and stared with cautious interest into the faces of the audience.

Dianne's doctor ruffled her yellow hair and tried briefly to distract her into casual conversation. Dianne wasn't having any. She kept her big brown eyes on the strangers.

As soon as the doctor lifted her down, she toddled into the arms of her mother, Mrs. Arlyn Obert. Dianne soon tired of the proceedings and headed for the hospital playroom, waving goodby to the crowd.

AT CONFERENCE

Dianne was exhibit A at the hospital's weekly pediatric conference—an example of a child saved from phenylketonuria (PKU), which causes severe and irreversible mental retardation.

Until a few years ago, nearly every child like Dianne wound up in an institution with a tragically crippled brain. The median IQ was 30.

Dianne has the distinction of being the first child born in San Diego County to be detected as a phenylketonuric in the first few days of life.

She was spared from the classic PKU fate largely be-

—Staff Photo by George Smith

Dianne Obert, saved from mental retardation by medicine, shows how she can work jigsaw puzzles.

The Trustees of the California State University
on Recommendation of the Faculty of
California State University, Fresno
Have Conferred upon
Dianne Elizabeth Obert
the degree of
Master of Arts
in
Special Education

Dianne with her family

OTHER BENEFITS DERIVED FROM CURRENT MANAGEMENT AND TREATMENT APPROACHES

In addition to lowering blood Phe levels, participants spoke to a variety of other benefits they valued from current therapies. Meeting speaker **Dianne Obert** was herself a notable example of the transformative benefits of early detection and treatment. Moderator **Kim McCleary** introduced her, noting: "[Dianne's] presence here today is rooted in the fact that at 23 months old, Dianne was 'Exhibit A' at a weekly pediatric conference at San Diego's Children's Hospital after being the county's first child to be detected as having PKU by newborn screening in 1965. A newspaper headline states, 'Dianne Obert, saved from mental retardation by medicine, shows that she can work a jigsaw puzzle.'" Kim also highlighted a photo of Dianne as an adult, receiving her master's degree, a milestone possible for few people of her age living with PKU.

Improved Cognitive Functioning, Emotional Control and Temperament

Treated PKU has been associated with improvements in cognitive functioning and intellectual ability. **Kristi Smith**'s oldest son, **Ben**, was 14 when they adopted him from an orphanage in China that did not treat PKU. "He barely spoke. He couldn't bathe himself. He had no sense of safety. He has had seven years of great PKU treatment now, but still has, and always will, have a moderate level of intellectual disability. But Ben has accomplished many amazing things. He reads [English] at a second-grade level, and he can hold a conversation when he's in a familiar setting. He has a best friend, and he understands the basics of keeping himself safe in a kitchen or walking alongside a road. He has a hilarious sense of humor," she reported. Her other three adopted sons, ages 6, 11 and 12, were provided PKU formula and low-protein specialty food in the orphanage they lived in before adoption. Now the three younger boys are taking sapropterin, too. "They have their struggles, but they are now intellectually on par with their peers. They play sports, musical instruments, have friends and are caring and compassionate people."

Several participants reported improvements in emotional regulation after finding an effective treatment regimen. **Kala McWain** shared her son **Braxton**'s experience. "With sapropterin, symptoms of brain fog and emotional ups and downs improved. It's not a miracle fix. He's not a typical responder, as he does not get more protein tolerance from taking it, but even small gains in cognition and emotional control make a big difference, especially now that he's school aged." In a pre-meeting interview, **Hannah Purcell**, observed the

change in husband Saeed after he was treated with pegvaliase, “It seems to calm him down and mellow him out. He is more at ease. It’s done him good, and I see a difference in his behavior. He’s more relaxed than before.”

Steve Scott described global improvements with a drug he was given in a clinical trial, “The headaches stopped, and energy returned. I felt more present. Friends and family noticed a difference. For the first time in decades, I experienced what it was like to truly feel good, truly feel normal.”

> *“When I was in college learning to balance diet with newfound freedom, high Phe would show up as mood instability, slurred speech, lowered working memory and poor word recall. Now since [taking] sapropterin, it seems like I have more cognitive space to think before I act or speak and to solve all sides of a problem.” – Written comment from Leah C., Illinois*

Greater Flexibility in Diet and Socialization

Relief from some of the burdens of living with PKU described in pages 9-11 were huge benefits of more effective treatment. For **Heidi Maxfield**, whose 17-year-old son **Owen** participated in a clinical trial for sepiapterin, treatment positively affected his nutrition, energy and ease with food.[3] “He has gained over 20 pounds, and he feels better. He has more energy, and not having to track so much of his food really was just such a big deal for our family.” She also highlighted the social benefits Owen experienced once he could eat a diversity of foods. “Last summer, he was able to try his first hamburger, which sounds silly, but was a really big deal for our family. He’s able to go to eat with friends – a really remarkable thing that we didn’t know would happen in his lifetime.”

Owen Maxfield’s first hamburger was a major event for him and his family

Looking ahead, Heidi reflected on the potential for Owen’s future independence. “He wants to go to college. Just having the freedom to do those things without the restrictions of food and formula being a big problem gives us a lot of hope that the rest of his life will be a lot easier than we thought it was going to be.”

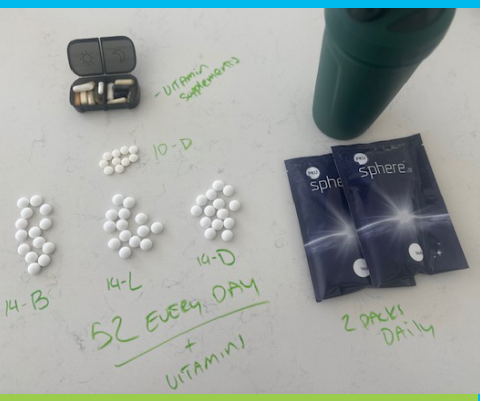
Other caregivers shared similar experiences once their children adapted to treatments that alleviated their PKU symptoms. **Sarah Gallagher**, mother to 15-year-old **Maeve**, described the impact of pegvaliase on managing food in social settings: “She recently went on a multi-day field trip, and it was the first time she could order off menus with her friends. It was the first time we didn’t have to prepare and pre-pack her food other than her formula, which felt huge for all of us.”

Bianca Albanese shared a similar sentiment following her experience when enrolled in a clinical trial for sepiapterin. “Coming from such a food-centered Italian family, it was really meaningful to enjoy the meals they love. For the first time, I felt truly satiated and free from the constant hunger that had often accompanied my low-protein diet.”

Andrew called into the meeting to share his experience getting on treatment with pegvaliase when he was first diagnosed with cancer. “The hospital treating my cancer wasn’t able to meet my dietary needs, because I also have diabetes. Pegvaliase allowed me to work on my diet and manage it very well.”

[3]*Sepiapterin (SEPHIENCE) was granted marketing approval as a treatment for PKU by the FDA on July 28, 2025.*

"I still take medical formula twice a day, 10 Kuvan pills every single day and then 14 large neutral amino acid tablets with every single meal. That adds up to 52 pills a day that I need to take to sustain a limited diet of medical foods." – Casey Connolly



BURDENS OF CURRENTLY AVAILABLE THERAPIES

Despite the benefits of treatment for some members of the PKU community, most participants noted challenges and downsides related to modes of administration, side effects and the routines required to achieve successful outcomes. There were also practical issues that acted as barriers to treatment.

Formulation and Administration of Prescription Treatments

Participants shared that taking sapropterin can involve an extensive medication regimen that requires counting, scheduling, ingesting and tracking many pills each day. **Casey Connolly** described the ongoing burden of his treatment. "I still take medical formula twice a day, 10 Kuvan pills every single day and then 14 large neutral amino acid tablets with every single meal. That adds up to 52 pills a day that I need to take to sustain a limited diet of medical foods. Some days I eat less than I should because eating right is such a hassle. I'd rather not eat anything than sacrifice my levels or ingest the medical foods that I should eat. How is my body doing digesting 52 pills a day? How is my body holding up if I miss any of those 52 pills? I supplement with formula and eat as many natural foods from the earth as my diet allows."

Karlye Vonderwell reported being a responder during the clinical trial of sapropterin, but also experienced challenges. "My dosage was 12 uncoated tablets every single morning. They would get stuck in my throat, so we tried crushing the pills and putting them in pudding. We tried taking them in the morning, in the evening, just about everything you could imagine. It was a really challenging experience, particularly with me being in third grade. It created a cycle of decline. When the medication got stuck in my throat, I would [vomit], which meant I didn't get my full dose for the day. Then my Phe level would increase, and I would have symptoms and feel guilty about not getting my medication, which made me unmotivated to continue taking it. That furthered the cycle of decline and made it seemingly impossible to break."

Some participants mentioned difficulties with decreasing efficacy of sapropterin over time, as experienced by **Jill Pickard**'s son **Eliot**. "The initial effectiveness seems to be waning, and so he's excited to try pegvaliase as soon as he is able. We're hopeful that he'll be a responder. The potential to liberalize his diet would mean the ability to eat what he needs to excel in swimming and academics, maintain emotional stability and finally feel full. We're especially eager to start this treatment before college so we can find his optimal dose and be comfortable with self-injecting before leaving home."

Participants described other challenges taking pegvaliase, including a fear of needles, injection fatigue, formation of scar tissue requiring frequent rotation of injection sites and the burden of daily or near-daily injections. "I overcame my fear of needles, and my wife has been crucial in getting my regimen under control and rotating the injections. I recently backed down to one injection per day from two daily injections. I can't even begin to imagine finding space on your body for more than that," observed **Saeed Purcell**.

Several people noted that the process of finding an optimal dosing schedule for pegvaliase to minimize side effects and maximize efficacy can be lengthy, and response varies greatly between individuals. For some

with severe disease, it may not be an effective option. **Meaghan Rogers** reported that it took two years to see any change in her levels. "It was really only my commitment to helping others in the PKU community and wanting to make history that caused me to stick with it for so long," she said. **Karlye Vonderwell** shared her and her brother's contrasting experiences. "I take three injections every single day, seven days a week. He takes one injection per day on six days a week, and his diet is completely liberalized. He has no concern with his diet and doesn't track protein intake at all. While I am valid in my struggle and my fight to make pegvaliase work as the best treatment for me right now, he is also valid in thinking, 'I love pegvaliase because I only take one injection not even every day of the week, and I basically don't have to think about PKU anymore.'"

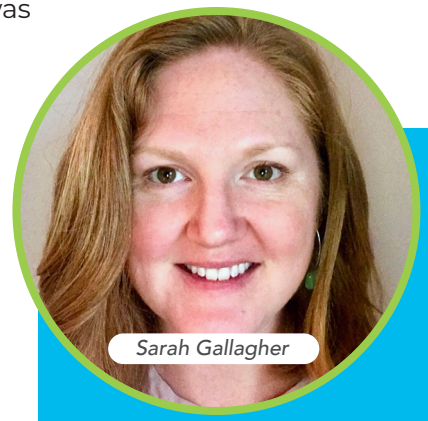
> *"I'm too young to start pegvaliase, and I'm scared of the side effects and giving myself shots every day." – Written comment from Caleb S., Arizona*

Side Effects

Participants described a wide range of side effects associated with pegvaliase, including injection site reactions, moderate to severe joint pain and more serious immune responses such as anaphylaxis. Experiences varied in both severity and duration. For others, concerns about these possibilities kept them from exploring this treatment option.

Kathleen Gonzales reflected on her reaction to pegvaliase. "After my third injection, I experienced injection site reactions, severe itchiness and flu-like symptoms. I figured out a cold shower would help with that. However, after 18 months of treatment, I had an intense anaphylactic reaction that led to two days in the hospital. I was angry that the treatment I had put so much hope into had failed me. I decided not to continue it. I do not plan to try other treatments unless severe side effects are ruled out."

Sarah Gallagher's daughter, **Maeve**, took sapropterin from age 8 until she was ready to try pegvaliase, with the hope that she'll someday be able to enjoy a fully normalized diet. "She's up to 30 grams of protein a day from 7. She currently injects 11 times a week and has experienced significant side effects. Those have included joint pain so intense that she could not use her hands at times. There have been days when we had to carry her around the house because it was too painful to walk. She's experienced redness and swelling at the injection site, and she still has to carry an EpiPen at all times. The uncertainty of the long-term impacts of frequent injections weighs on us, especially since she hasn't yet reached the goal of a normalized diet," Sarah stated. **Karlye Vonderwell** spoke about similar experiences with joint pain and injection reactions.


Sarah Gallagher

"There have been days when we had to carry her around the house because it was too painful to walk. She's experienced redness and swelling at the injection site, and she still has to carry an EpiPen at all times."

Some participants described pushing forward despite these risks, underscoring the limited treatment options available. In a written comment, **Jennifer P.** from Maryland shared: "I am doing my best to manage PKU in trying a re-challenge to an injectable that landed me in the ER previously with a severe adverse drug reaction. There is no reward without risk, and I am taking that road because I am in survival mode with no other recourse."

While medical formula is often essential to managing PKU, a few individuals highlighted side effects related to digestive or dental health.

Kala McWain described the challenges her family experienced in finding a tolerable formula for **Braxton**, now 5 years old. "The formulas are often unpleasant in taste and smell and can even upset their stomachs. We went through quite a gamut with Braxton in finding a formula that didn't upset his stomach and cause severe diarrhea when he was one or two years old. Even now, a large part of my day is spent reminding him to drink his formula and worrying about whether or not he did or will finish it, which is a whole other battle. On days when he is sick, it's harder to get down. There are some days he doesn't get it all down, which leads to a lot of worry about his brain."

"Powdered formulas were messy to prepare and had a really pungent odor. Unfortunately for me, they caused significant cavities, and I've had multiple root canals in my life due to their high sugar content," stated **Meaghan Rogers**.

Richard Farquhar had to learn how to eat new foods, like an egg, when his Phe tolerance expanded after treatment.

Psychological Challenges of Expanding Dietary Options

Participants who have achieved greater Phe tolerance through medication reported that incorporating higher-protein foods into their diets can present a significant learning curve. **Richard Farquhar**, age 44, described the experience of re-learning how to approach food after being treated with sapropterin. "I remember walking into a store numerous times and just staring at the shelves for a while thinking, 'Where do I actually start here?' It was like learning food all over again. Actually, I hadn't ever gone through that learning process, so I was starting completely fresh. The egg was one food that I decided that I wanted to try, but I wasn't even sure how to crack it or cook it because I had been taught to avoid eggs for so much of my life. My wife had to show me how the first time. The psychological effect on an individual as they're trying to unwrap that process probably sounds silly, but I had mental padlocks on foods that I had to release over time. I had to keep in mind, it's just a silly egg."

Brittany Murray shared her a similar experience after treatment with pegvaliase alleviated most of the burden of the PKU diet. "It's a good problem to have, to have a treatment that allows me to have a normal diet, but being intentional with food was ingrained in me for 25 years. Food was always at the top of our minds, and it was a constant worry. After doing that for 25 years, it doesn't just go away."

The psychological challenges of expanding options, and then potentially having to contract them if a treatment lost effectiveness keeps some from trying new therapies. **Melissa Bernzen Goulart** described this uncertainty. "Sapropterin became available when I was in high school and was often discussed at clinic appointments. However, I was told that individuals with classical PKU are less likely to be responders, and this concerned me because I was fearful about eating new foods I may like and then being told I could not eat them anymore [if the treatment didn't work]. Trying this medication felt like opening Pandora's box with no guarantee that I'd be able to enjoy a liberalized diet."

Exacting, Multi-Component Regimens

Many participants described the tight coordination required for managing dietary, prescription and formula therapies, including advanced planning for outings and required use of equipment such as refrigeration and heating devices for storage and preparation and scales for accurate measurement. **Melissa Bernzen Goulart** faced difficulties with this in college. "The college I attended didn't have a program to accommodate special dietary needs, so I snuck a toaster into my room so I could cook my medical foods. I worked in the dining hall and made friends with the chef so I could make my low-protein pasta. When I joined a sorority and moved into the house, my medical food had to be stored in the kitchen, which was locked between meals and on weekends. This was the first time I experienced being off diet in

my entire life." **Dianne Obert** is experiencing the challenges with her increasingly active 10-year-old son, **Noah**. "He's right at the age where there are a lot of events. Our work and school are a half-hour from home, so we usually carry food in the car. But, at times he needs low-protein food, and it's hard to carry cooked low-protein pasta in the car in case you need it," she said.

Kristen Lubliner, speaking with her daughter, **Adelaide**, on camera shared: "It takes a lot of extra time and preparation. The last time that we went on vacation, we were going on a cruise ship, and we had to call a month in advance to make sure that we could bring your special foods onto the ship and that the ship had the ability to cook your special foods." **Melissa Vachuska** highlighted the daily effort required to track intake and manage meals in a written comment: "As a parent, I carry the weight of every formula bottle she refuses, track every gram of food I prepare to then weigh what she didn't eat, and then log it for every single meal – snacks included. The daily management is exhausting while juggling working full-time."

Kristen and Adelaide Lubliner

"Being away from home requires a lot of extra time and preparation."

For people with PKU, sticking with complex regimens requires skills that get dull as Phe levels rise. As **Melissa Bernzen Goulart** explained, "[When I didn't have full access to my medical foods], it was hard to notice the impacts on my own. My parents recognized subtle changes in my mood and attitude and asked me about diet management." She continued, "The self-awareness and discipline of checking Phe levels and planning and preparing meals require executive functioning skills, which are often the first thing to slip when Phe rises. It honestly takes so much support, discipline and, frankly, extra financial investment to get back on track and stay on track with diet." **Les Clark** echoed this observation. "When you have the impaired thinking and focus due to high Phe levels, it's even harder to get back on track to plan and manage food and formula. That's probably why people go off diet, they just slip off. So, it really does impact your entire life when your Phe levels are too high."

> *"It's a vicious cycle of being 'off diet'/high Phe levels, leading to brain damage, emotional stress, anxiety and depression and lack of executive functioning which are all needed to support yourself in getting back to care or on diet or other treatment to feel your best and manage your PKU." – Written comment from Denise Q., Massachusetts*

Practical Challenges Adhering to a Low-Protein Diet

Participants cited various difficulties obtaining medical formula and low-protein foods and how changing formulations and recipes affect dietary management. Formula shortages, common during the pandemic, were an issue mentioned by several participants in pre-meeting interviews. **Les Clark** spoke about challenges with medical foods he relies on. "Suppliers are reluctant to invest in inventory, resulting in frequent outages and supply chain issues." For participants living in rural areas, access can be even more constrained. "We live in the second-largest city in Wyoming," said **Kala McWain**. "Grocery store chains are limited here. Sometimes we request certain items, but we're often dismissed due to there being low demand."

> *"I was fearful about eating new foods I may like and then being told I could not eat them anymore if the treatment didn't work." – Melissa Bernzen Goulart*

Challenges with Food Labeling

Kelci and Jared Bleasdale highlighted how crucial accurate nutrition labeling is to effectively manage PKU for their children. Both are science teachers and recognize that even small differences in protein content can affect daily dietary allowances. Kelci explained, "Labeling is deceptive. Our kids' diet requires more than simply eating foods labeled as 'low protein foods' – we still have to weigh and count even those foods. 'No protein' labeling isn't accurate either. It's a complicated balance that's different every day. I'd love for people to understand that foods considered to be 'healthy' doesn't mean the same thing for my family as it does for theirs. What's healthy for your kids could really harm my kids. And they will not grow out of it."

She expressed a desire for more precise labeling: "One change that would make PKU management significantly easier is greater precision in food labeling. In many countries, protein content is listed to the decimal point. Since every fraction of a gram of protein matters for PKU, this level of detail would be life-changing for families like ours. Meeting our kids' nutritional needs and keeping them feeling full as they grow is already a challenge. Accurate labeling would at least take the guesswork out of it."

Theo Bleasdale shows how young children with PKU learn to weigh food and measure formula.

Caregiver **Jared Bleasdale** described the impact of changes in food products. "One of our biggest frustrations is when brands change their ingredients or their formulas without any clear labeling or notification. For example, Veggie Straws are a staple in our house because they are fairly filling for our kids and fit well within our kids' protein limits. However, recently we noticed that Veggie Straws looked a little different. When we looked closer at the package, we noticed that the ingredients had changed without any other indication. Looking at the recipe, it had changed as well. A particular ingredient that changed caused a reduction of the amount that our kids can safely have each day." His wife, **Kelci**, continued, "Simply changing cassava flour out for sorghum flour or adding pea protein dramatically changes the amount that our kids can have in a day and may even lead to them not having it [in their diet] anymore. With so few convenient and affordable food options for PKU families, these unexpected changes are quite disruptive. It causes us to stock up on supplies of food that have the recipe that our kids can have instead of purchasing the new version with higher Phe amounts."

> *"My PKU milk keeps changing. I get used to the taste, and the company keeps changing the recipe, which changes the flavor. When a person with PKU finds a formula we like, it's hard to find a new one." – Written comment from Caleb S., Arizona*

Several participants described the challenges of traveling with medical formula, noting that sealed packaging often creates issues when passing through airport security. In a pre-meeting interview, **Jill Pickard** reflected on her family's recent air travel experiences. "Going through airport security with formula, TSA wanted to open the formula. They called it 'inorganic material' and said they had to open it. We were only carrying the bare minimum Eliot needed, so there was no room for error. We even had a letter from our clinic, but it didn't state that the formula couldn't be opened. On a trip last summer, we put the formula in our checked luggage to avoid these problems. Our flight was rerouted and our bags ended up at another airport. It makes you not want to leave home."

SECTION 4:
PERSPECTIVES ON TREATMENT ASPIRATIONS, MONITORING AND CLINICAL TRIALS

TREATMENT ASPIRATIONS

Participants expressed a range of unmet medical needs and priorities for improving existing treatments and regimens.

Key aspirations included treatments that enable higher dietary Phe tolerance, reduce the burdens of daily management and pose fewer long-term potential health risks. Participants also highlighted the need for tools to support more convenient and timely detection of elevated Phe levels, as well as ways to monitor ongoing dynamic Phe levels to guide management. Dr. Harding and community participants emphasized that the current target for blood Phe levels for children and adults are above those that a healthy person who does not have PKU would exhibit, reflecting ongoing potential health risks even for individuals with PKU who are considered to be "well-controlled." These aspirations and realities underscore the continued need for novel treatments and management supports.

Key aspirations included treatments that enable higher dietary Phe tolerance, reduce the burdens of daily management and pose fewer long-term potential health risks.

Desire for "Normalcy"

Throughout the meeting, participants who had not yet found a fully effective treatment returned to a shared treatment aspiration: the wish for a diet and lifestyle that felt "normal."

As caregiver to two teenagers with PKU, **Amy Oliver** noted that expanded dietary Phe allowance (without harm) represents an important goal for her family. "Both of my kids are very interested in normalizing their diets and being able to eat more nutrient-rich foods, especially since they are both very physically active. I use the term 'normalizing' intentionally. I feel the term 'liberalizing' conveys a certain judgment with it, that you're not strong enough or you simply don't have the willpower to stay on a restrictive diet." Amy continued, "Both of my children started sapropterin very young and responded well to the drug, but it didn't give them a normal diet. We find ourselves stuck in this middle ground where medical foods are too low in protein for their tolerance, and things like meat and legumes are still too high. We still have restrictions that we deal with every day. Until you have a normalized diet, you still bear that burden regardless of what your Phe tolerance is."

Additionally, participants expressed that being able to tolerate a higher Phe allowance could reduce dietary limitations they face in their daily routines, social settings and travel. **Melissa Vachuska** shared hopes for her 2-year-old daughter **Rowan**. "An ideal treatment would give my daughter freedom, stability and simplicity – allowing her to live without constant restrictions. She should be able to eat a variety of foods without tracking every bite or worrying about spikes in blood Phe levels. Eliminating her dependence on medical formula would also ease this daily struggle." **Kristi Smith** tracks five different regimens and tolerances for

Kristi Smith tracks 5 different regimens for herself and her four sons with PKU.

herself and her four sons with PKU. "Each of us has separate section in the refrigerator for what we can eat, and I'm trying to get the boys to track their own food. One is prone to eating high Phe foods and then lying about it. My dream for each of us is to have normalized diets and be able to gorge on healthy foods like broccoli, instead of relying on so many processed foods. I want them to feel like they 'fit in' with their friends," she said in a pre-meeting interview.

The desire to have a treatment that would restore a sense of normalcy was often rooted in childhood experiences. "We ate different, which meant we were different, which meant we were 'weird.' That was a really isolating experience for both of us," explained **Karlye Vonderwell** about what she and her brother experienced in school. **Jill Pickard** echoed those feelings of isolation as she described her son Eliot's current experience navigating PKU in high school. "Ultimately, **Eliot**'s biggest wish is to enjoy real food, succeed in swimming and in school and feel like any other teenager."

"Pretty much everything has protein in it. For those of us with classic PKU, we are extremely limited in the foods we can eat. We need new medical help to allow us the freedom to eat." – Written comment from Anonymous, North Carolina

> *"Day-to-day management can be draining, but traveling and prepping is the most taxing." – Written comment from Jewelia B., Washington*

> *"I'd like a medication that can be taken orally before meals to metabolize the Phe." – Written comment from JoAnn A., Kentucky*

> *"I would like to eat normal foods, such as no more low-protein foods – being able to eat meat or even just going out to eat and be able to order more than just French fries." – Written comment from Anonymous, Indiana*

Relief From Effects of Fluctuating Blood Phe Levels

Others' aspirations centered on freedom from the symptoms linked to high Phe levels. **Paul B.**, age 58, attributes high Phe levels to job insecurity he experiences. "I was let go from a catering job because of my body odor. I can't think straight or remember things. I really wish I had a stable treatment to help me get back on track." **Les Clark** stated, "I'd like relief from the irritability. Sometimes I have this 'road rage' feeling of staying angry all day when my levels are higher. It also affects my focus and executive functioning." Similar aspirations were cited by caregivers of children with PKU. "I want **Braxton** to experience learning with as much clarity as possible without brain fog and emotional instability," stated **Kala McWain** of her 5-year-old son.

Bianca Albanese notes that although her Phe levels are always in range, she struggles with peaks and troughs. "I get headaches, feel 'black cloud sad' for no reason and experience post-exertion fatigue. It's scary to think about managing pregnancy, and then caring for a child, when I'm not feeling my best now. The doctors see brain matter changes on my scans. A better treatment would help with all these effects."

Ultimate Treatment Goals

While many participants expressed hope for a definitive cure for PKU, others shared that they are not seeking a treatment that would eliminate the condition. They noted that PKU has become an integral part of their identity, shaping their sense of self and community. "No drug or 'cure' will ever change the fact that I have PKU. There is more to PKU than the actual method of treatment," reflected Sarah F. in Massachusetts through a written comment.

Meaghan Rogers and others emphasized that they are looking for innovations that make day-to-day management easier, safer and more flexible. "I am not interested in a cure. An ideal treatment for PKU would be convenient, odorless and easy to travel with. A bonus would be if it were available in several different forms (pill, powder, injectable) and without potentially life-threatening side effects."

These perspectives highlight the importance of broadening how "success" is defined in treatment innovation for PKU. While a cure remains a worthy goal, participants demonstrated that treatments that offer meaningful improvements in quality of life are equally valuable.

> *"Ideally, treatment for PKU is more holistic – not just calculating Phe levels but tracking and supporting mental health. The PKU population is at an elevated risk for anxiety, depression, OCD, etc. We need more support and study of this area of health. Treat the whole body, not just the Phe levels." – Written comment from Lillian R., New York*

Relief From Abdominal Discomfort and Hunger

Many participants sought relief from the way that current formulas and dietary measures affect their body's experience of fullness, either feeling bloated or perpetually hungry because of disproportionate volume, calorie count and nutritional value. **Claire Oliver** noted that both she and her brother have active, athletic lifestyles that make it difficult to achieve feelings of fullness. "**Seth** and I have always carefully followed this diet, which is even harder now that we're older and we're active, since it can be really hard to get enough protein and nutrients to sustain our body's needs. Seth is a tennis player and I can tell you, he's hungry all the time." **Bianca Albanese** hopes to again "go the whole day not feeling hungry and feeling happily full, from eating nutritionally dense food," like she did during her participation in a clinical trial.

> *"I would love to see a formula that did not require such large volumes and cause stomach upset." – Written comment from Anonymous, Illinois*

Treatments That Are Easier to Administer With Fewer Side Effects

Sydney D. in Kentucky and other participants shared a wish for medications that are easier to manage, such as simpler forms or smaller, more manageable doses. "It would be amazing if there was a way to turn the injection into a pill," she wrote in a comment. "But, I would not want the pill solution to be like sapropterin, where you have to take X number of pills depending on your body weight." A written comment from an anonymous contributor in Kansas expanded on these aspirations. "I desire something that is similar to pegvaliase in terms of outcomes (no need for formula, unrestricted diet, etc.) but is more easily taken (like a pill or powder vs injection), with less or more easily manageable side effects and a quicker response time." Ten-year-old **Noah Obert** shared a similar wish via his mom, **Dianne**, for a treatment that offered him the opportunity to eat a wider variety of foods, without the prospect of having to take regular injections.

Multiple community members expressed a desire for treatments that did not carry risks associated with injectable medications. **Casey Connolly** shared, "I decided against pegvaliase due to the continuous injections

Panelists for the discussion of treatment aspirations, monitoring and clinical trials (clockwise from top left): Sarah Gallagher, Brittany Murray, Steve Scott, Meaghan Rogers and Eugene Lubliner

and risk of anaphylactic shock and other side effects. This option just traded one fear for another. In my eyes, that did not increase my quality of life." **Jennifer Christenson** explained her weighing of potential risks and benefits. "I listen to the side effects people have experienced, knowing I have two children who count on me every day. I can't have debilitating joint pain. I can't risk anaphylaxis. I live in a rural town, hours away from my clinic. I simply can't risk these side effects based on the life I have right now."

> *"While I have found a treatment option that works for me, it's still not perfect. I have developed injection fatigue and having more alternative therapies would promote better compliance, higher patient satisfaction and better quality of life." – Written comment from Page M., Texas*

Safe and Effective Treatments for a Broader Array of Children and Adults With PKU

Differences in responses to current approved medications have left many community members hoping for therapies that are effective across all PKU severities, and safe for teens and children as well. "Despite advancements in treatment options, minimum age requirements and difficulty in (or not) responding to these available options, it circles the PKU patient right back to metabolic formulas and low-protein foods," shared **Karen D**. from Pennsylvania in a written comment. **Eugene Lubliner** expressed his optimism for his 9-year-old daughter **Adelaide**'s treatment outlook. "We're also very excited about new treatments that are on the horizon that have better bioavailability for her, especially since she has limited response to sapropterin. Therapies with new mechanisms of action and the promise of gene therapy or gene editing – those give us real hope."

> *"There is no medicine that works for me. I had anaphylaxis from pegvaliase. I am not a responder to sapropterin." – Written comment from Anonymous, North Carolina*

Several participants described aspirations for treatments that would be safe to use by women with PKU before and during pregnancy. **Jennifer Christenson** described her struggle to maintain her wellbeing during both of her pregnancies. "In 2012, there weren't a lot of known cases of women staying on sapropterin during pregnancy, so we just didn't want to risk it. It was considered a Class C drug, and we didn't know what would happen, so I went off the medication." She continued, "It's hard to keep calories up while keeping protein down, so I ended up with a lot of foods that were high in sugar, and that just caused a lot of swelling, a lot of fatigue, joint pain and all kinds of things. I was tested for gestational diabetes. I remember feeling anxiety and just sort of a cloud of, 'I have to manage all these things, and I don't get to enjoy my pregnancy.'" **Karlye Vonderwell** shared her concerns about family planning with PKU. "I'm also thinking ahead to starting a family and would love a better understanding of the effects of PKU, its treatment in pregnancy and what impact that holistically has on my body (as well as my baby's) during both pregnancy and breastfeeding."

Home Phe Monitoring

One of the most often cited aspirations was for the development of faster, more convenient methods for monitoring blood Phe levels, particularly through a personal, at-home device. Participants noted that more responsive Phe monitoring would enable them to adjust their eating habits before adverse effects set in.
"If I had a monitor at home to track my Phe, I would definitely use that to establish a baseline of what I'm doing on a daily basis," stated **Casey Connolly**. A written comment from **Rebecca J**. in North Carolina emphasized a similar request. "It would be great to have a quicker turnaround on levels so we can more closely monitor and control levels. A week is too long and prohibits almost any definitive cause-and-effect relationship from being identified."

Maridith Baker, as a child

Maridith Baker has been a champion of regular Phe testing from a young age. Today she wishes there were better ways to track how food, behavior and mood affect Phe levels.

Maridith Baker described a desire to reduce the level of effort involved in tracking how her behaviors affect blood Phe levels. "Now I have to track my food and how I feel through an app or with a paper and pen. I keep notes on how I'm feeling and what I'm taking in formula-wise and food-wise. It can take two weeks to get results from my blood spot tests. By the time I receive my results, I have to look back at my notes and figure out what might have caused any spikes. If we had a home Phe monitor, we would be able to have instant results, adjust our regimen in the moment, rather than having to wait and reflect back on what has happened in that time."

Others observed that a single Phe level result provides an incomplete view of a person's health, while more frequent monitoring could reflect the natural fluctuations that occur throughout each day. **Kristi Smith** described the physical impact of lacking real-time Phe level data. "As an adult whose blood levels have been in range for years, even a slight change or increase in my level, even if it's still in the therapeutic range, will throw me into these symptoms. There's no correction dose like a diabetic – only diet changes and time will fix a high blood Phe level."

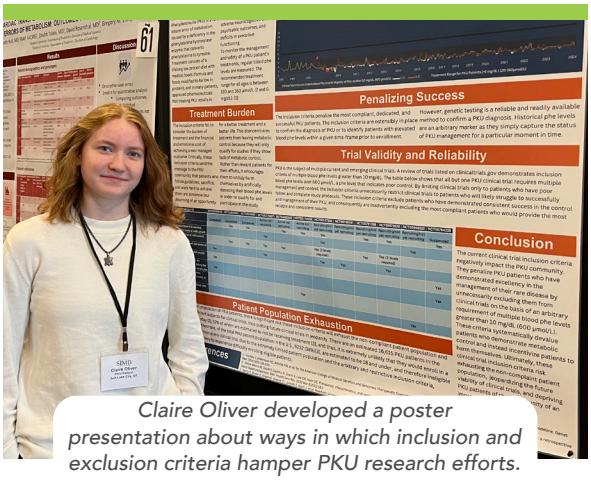
> *"With ways to monitor Phe levels at home, with immediate results, I could then alter my food choices as needed." – Written comment from Tricia J., North Carolina*

CLINICAL TRIAL EXPERIENCES

Members of the PKU community shared a range of experiences with qualifying for and participating in clinical trials, both for treatments that are now approved and those still in development. Common themes that emerged included the challenges of meeting inclusion criteria and the persistence required to stay in the trial while navigating complex study protocols.

Inclusion Criteria Challenges

Several participants noted that trial entry criteria prevented their participation, based on their age or diligent management of blood Phe levels. **Claire Oliver**, age 18, spoke about her and her 15-year-old brother **Seth**'s experience being denied participation despite being willing participants. "We were all excited about the possibility even though we knew being in a study would require a lot more clinic visits, time out from school and other activities, more blood draws and extra work to keep track of everything. It was very upsetting to



Claire Oliver developed a poster presentation about ways in which inclusion and exclusion criteria hamper PKU research efforts.

learn that neither Seth nor I had qualified for the trial because we had never had a Phe level higher than 600 micromoles per liter (µmol/L), which was a study requirement. I was angry that the chance to try a new treatment option was off the table for us because we had done too good a job managing our diet." Claire shared the response her family received from the clinic when study staff conveyed the news. "They told us if we could get our levels up to 600 µmol/L, we would qualify for the study, but doing harm to ourselves to get into this study was not a choice we were willing to make." **Kristi Smith** also emphasized that the structure of some clinical trials excludes individuals who maintain lower Phe levels, despite their ability and commitment to stay in good control. "I've had a clinician say they wish I could do the trial because they know I communicate, I'm compliant and honest."

Heidi Maxfield and her son, **Owen**, age 17, faced a similar rejection until the clinic adjusted its requirements. "When the trial started, you had to have a higher Phe level, so Owen didn't meet it. Eventually, the clinic changed the criteria to allow the use of all his levels across his lifetime. We had documentation of one high Phe level when he was born and three other cases at very young ages due to acute illnesses. These were just enough to get him enrolled."

Age limits for clinical trials posed a barrier for several participants and their children, much like the restrictions that exist for certain approved PKU medications. **Keri W**. in New York stated, "The age restrictions don't allow anyone under 18. My son is 15. I think he would love any opportunity to help him have a less restricted diet." Some trials exclude members of the community who are beyond the upper age limit, as **Annaliese M**. in Texas wrote, "The only barrier that has excluded me from a study was capping the age limit at 40."

Experiences With Study Participation

Meeting participants shared various experiences with clinical trials and noted that study design frequently influenced their ability to enroll and remain in the trial, or to have to drop out. "Clinical trials are no joke – they're so time-intensive. For a 17-year-old who wants to feel normal, it takes away their freedom. We take diet records every day and have lots of clinic visits. The first 10 visits at the clinic were all day, and there was a lot of waiting and bloodwork," reported **Heidi Maxfield** during a pre-meeting interview.

Bianca Albanese spoke about the difficulty she had controlling her Phe levels while adhering to the study protocols. "I found fluctuations or holding prolonged high or low Phe levels to be debilitating. Protocols would benefit from being responsive in these instances to account for the significant impact on participants' wellbeing." **Meaghan Rogers** highlighted the psychological impacts of her trial experience. "There were two things that were always drilled into us during the study: that we had to carry an EpiPen because we might go into anaphylactic shock (which was really scary to think about), and we couldn't get pregnant. That really added to the emotional load – another thing that needed to be controlled in our lives when we're already used to controlling so many other aspects."

In several cases, participants expressed that the potential benefits of enrolling in a trial were outweighed by the nature of the study protocols or the distance to the site. **Michael F**. from Michigan stated in a written comment, "I have considered joining a clinical trial for gene therapy, but the risk that exposure to AAV would prevent me from obtaining future AAV-related therapeutics or perhaps preclude me from future trials led me to decide not to participate." "I haven't had any barriers other than wanting to eventually have children and not wanting anything to impact that. I've chosen not to participate until something is better researched long-term," an anonymous contributor in Kansas wrote. In a pre-meeting interview, **Steve Scott** discussed that

his location in Yukon, Oklahoma, required time and a willingness to travel frequently to participate in a trial. "There were only two trial sites in the state, and those sites had long waiting lists. I was able to get into a study site in Dallas immediately, although that required me to drive more than three hours each way every other week."

Some participants decided to discontinue their trial due to unanticipated symptoms, side effects and the consequences of variable Phe levels that emerged. **Bianca Albanese** explained her decision to withdraw from a trial in a pre-meeting interview, despite the expanded dietary Phe allowance it offered her. "Initially, I was feeling good. Over time, I started feeling lethargic. I couldn't get up in the morning, and I used to be able to go to the gym at 6 a.m. I was very sore, and I put on a lot of weight even though I was tracking calories and eating healthy. I decided to withdraw to give my body a break." **D.R.** shared his son's experience in a written comment. "We started a trial about 15 months ago, but we had to end the study early because of adverse side effects on our child."


Steve Scott

"When you experience something new that's so much better than what you have been used to for decades, you feel lucky. It's made me excited to participate in another study."

Additionally, some community members expressed concerns about discontinuing current treatment regimens to be eligible for study protocols. **Leah C**. from Illinois recounted her experience of encountering new symptoms as a result of participating in the trial. "I was involved in the beginning steps of a clinical trial. However, I was not able to keep my blood Phe levels high enough without having life-altering symptoms. The testing team wanted me to eat more protein than had originally been recommended so they could monitor changes when I started the study medication." **Page M**. from Texas shared her perspective, "My concern is coming off my medication that is working and having unstable levels [during a study]. As a health care professional, I want to be functioning at my highest potential for my patients."

Despite the rigorous protocols of many studies, several participants reported achieving their hoped-for outcomes. **Owen Maxfield** was among those whose participation yielded better management. His mother, **Heidi**, reported, "We waited 17 years for this. We feel we have found the ideal treatment. The only thing that would make it better would be a one-shot cure, so he doesn't have to take medication anymore." **Steve Scott** had a similar experience, although the experimental treatment that benefited him hasn't yet reached the market. "When you experience something new that's so much better than what you have been used to for decades, you feel lucky. It's made me excited to participate in another study."

> *"Managing PKU already takes up so much of my life, I don't really feel I want to put a ton of time and energy into a clinical trial. I don't feel comfortable being a guinea pig and trying things that aren't for sure safe." – Written comment from Anonymous, Colorado*

CLOSING REMARKS

Catherine Warren remarked at how quickly the meeting and conversation flew by, recognizing the "compelling and actionable insights and information heard from so many members of the PKU community." She acknowledged all the speakers, meeting participants, partner organizations and sponsors. (See Acknowledgements, page 34.) "This is an exciting time for the PKU community, and I could not be more proud of all you've done today to illustrate and elevate patients' and caregivers' experiences, perspectives and aspirations. You truly helped to describe 'TruePKU,'" Catherine stated in closing.

ACKNOWLEDGEMENTS

National PKU Alliance expresses its gratitude to all who have enhanced the TruePKU initiative, especially the hundreds of PKU community members who participated in the meeting and/or submitted written comments.

MEETING SPEAKERS

Presenters and Discussion Starters *(listed in alphabetical order)*

Community-member presenters and "discussion starters" dedicated considerable time to reflect and prepare to speak to the challenges, expectations and hopes of the PKU community as a way of inviting an even broader range of experiences through the moderated discussion at the May 8, 2025, EL-PFDD meeting. We deeply appreciate their contributions, courage and commitment to the success of this initiative.

Bianca Albanese Sydney, Australia
Maridith Baker Dallas, TX
Melissa Bernzen Goulart High Point, NC
Kelci & Jared Bleasdale Buckley, WA
Jennifer Christenson Lebanon, OR
Les Clark Fort Worth, TX
Casey Connolly Encinitas, CA
Rhonda Connolly Encinitas, CA
Richard Farquhar United Kingdom
Sarah Gallagher San Antonio, TX
Kathleen Gonzales San Jose, CA
Adelaide, Eugene and **Kristen Lubliner** Mount Sinai, NY
Heidi & Owen Maxfield Salt Lake City, UT
Kala McWain Casper, WY
Brittany Murray Boston, MA
Dianne Obert Clovis, CA
Amy Oliver Salt Lake City, UT
Claire Oliver Salt Lake City, UT
Anna Phillips Salem, VA
Jill Pickard Basking Ridge, NJ
Saeed Purcell Irving, TX
Meaghan Rogers Pittsfield, MA
Elizabeth Roper Great Britain
Steve Scott Yukon, OK
Kristi Smith Tucson, AZ
Melissa Vachuska Minneapolis, MN
Karlye Vonderwell Indianapolis, IN

Introductory Speakers and Moderators

Thank you to these individuals for providing important context at the beginning of the EL-PFDD meeting and for guiding the conversation, incorporating perspectives from those calling in during the meeting and from written comments submitted in advance of and during the meeting.

FDA Perspective: **Jamie Rosenthal, MD,** Medical Officer, Division of Rare Diseases and Medical Genetics, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)

Clinical Overview: **Cary Harding, MD, FACMG,** Professor of Molecular and Medical Genetics and Pediatrics, Oregon Health & Science University

Moderators: **Catherine Warren**, Executive Director, National PKU Alliance (NPKUA), and **K. Kimberly McCleary**, Founder and CEO, The Kith Collective

INITIATIVE PARTNERS

National PKU Alliance thanks these partners of the TruePKU initiative for their enthusiastic and active support with community outreach:

CORPORATE SPONSORS

With thanks to these generous sponsors for unrestricted educational grants in support of the TruePKU initiative:

FURTHER ACKNOWLEDGEMENTS

National PKU Alliance is grateful for the following contributors to the execution of the TruePKU initiative.

NPKUA Planning Committee, including **Beth Aselage** (Member, Board of Directors), **Chuck Bucklar** (Member, Board of Directors), **Rhonda Connolly** (Board President), **Sarah Gallgher** (Director of Community Engagement), **Elaina Jurecki, MS, RD**, (Director of Research Development), **Kelsey McQueen, MS, CGC** (Associate Director of Research Development) and **Catherine Warren** (Executive Director) for guiding planning, outreach and communications for this initiative.

John Dudley and his team at **Dudley Digital Works** for creative and technical services to broadcast the meeting and preserve it for on-demand viewing.

Ethan Gabbour, Patient-Focused Drug Development Program Staff, Center for Drug Evaluation and Research, **U.S. Food and Drug Administration**, for providing guidance, counsel and encouragement through the entire planning process, including review of the meeting report.

Lauren Kenney, **Samantha Mayberry** and **Kim McCleary** at **The Kith Collective** for strategic counsel, program management, meeting content development, initiative communications and primary authorship of this report.

Julie Rathjens of **Hello Brand** for design of the TruePKU logo, production of creative materials and layout and graphic design of this report.

NPKUA
national PKU alliance

National PKU Alliance (NPKUA)

National PKU Alliance (NPKUA) is a registered not-for-profit (501(c)(3)) organization that was founded in 2008 after parents and grandparents formed a working group to create the beginnings of NPKUA to unite local and regional groups. In the 15+ years since the inception, NPKUA remains steadfast in its support of research endeavors through regular communications with emerging industry and academic leaders at the forefront of PKU research and investing in the NPKUA Grant Program and PKU Patient Registry. The organization has supported numerous fundraising events, conferences, community programs and affiliate organizations across the United States.

OUR MISSION

Our mission is to improve the lives of individuals with PKU, pursue a cure by expanding research and provide education and support to individuals living with PKU and their caregivers.

Our goal is to serve as the go-to resource for all PKU needs at all life stages.

Together we're understood.

Together we're strong.

Together we'll fund and find a cure.

STAY IN TOUCH

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