

THE VOICE OF THE PATIENT REPORT: **PRIMARY HYPEROXALURIA**



Oxalosis &
Hyperoxaluria
Foundation

STEPPING STONES TO A CURE

THE VOICE OF THE PATIENT REPORT PRIMARY HYPEROXALURIA

A Report on the Externally Led Patient-Focused
Drug Development Meeting, Corresponding to FDA's
Patient-Focused Drug Development Initiative

Externally Led Public Meeting **Report Date: October 5, 2020**

Hosted by: The Oxalosis & Hyperoxaluria Foundation

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Center for Biologic Evaluation and Research (CBER)
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This document represents a comprehensive summary report composed by a patient advocacy organization as a result of an externally led patient-focused drug development meeting; a parallel effort to FDA's Patient-Focused Drug Development Initiative. This report reflects the organization's account of the perspectives of patients and caregivers who participated in the public meeting.

Submitted to Center for Drug Evaluation and Research (CDER); Center for Biologic Evaluation and Research (CBER); U.S. Food and Drug Administration (FDA)

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“It is not enough to be able to diagnose a disease, to be able to tell someone the cause of their suffering, we need to be able to treat it. Successful drug development takes a village, and you, the patient, need to be at the center of that village.”

Aliza Thompson, MD, MS

Deputy Director of the Division of Cardiology and Nephrology
in the Center for Drug Evaluation and Research at the FDA

Introduction

On October 5, 2020, the Oxalosis & Hyperoxaluria Foundation (OHF) hosted an externally led patient---focused drug development (EL-PFDD) meeting, held virtually, to share the perspectives of people living with primary hyperoxaluria (PH) and their caregivers on the rare disorder's impact on their daily lives, the shortcomings of current management approaches and their expectations and priorities for future treatments. Among the participants were senior officials at the U.S. Food and Drug Administration (FDA), the pharmaceutical industry, academia, and research institutions. The meeting was conducted in accordance with the agency's Patient---Focused Drug Development initiative to more systematically gather the perspectives of patients on their condition and available approaches to manage their condition. In addition, the 21st Century Cures Act has emphasized the importance of patient input in the regulatory process, mandating that regulators learn about which outcome measures matter to patients and to consider how patients weigh the balance of risks and benefits of a particular treatment. (More information on the FDA Patient-Focused Drug Development meetings can be found at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm>.)

This meeting came at a good time, according to Kim Hollander of OHF, because efforts to develop treatments for this severe rare disease were finally reaching fruition, with several research studies and clinical trials already in progress and more planned for the future. Addressing “the unmet medical need of treatments and an eventually a cure for primary hyperoxaluria is no longer just a vague hope,” she said.

Overview of Primary Hyperoxaluria

PH is a rare and debilitating recessively inherited metabolic disorder that occurs when the body (specifically the liver) produces a marked excess of oxalate. Oxalate cannot be broken down in humans, and must be eliminated primarily by the kidneys where it can cause harm, leading to severe chronic kidney disease (CKD) and other complications. Oxalate in the kidneys or in urine can combine with calcium to form calcium oxalate crystals that may cause cellular and tissue damage in the kidney (nephrocalcinosis) and aggregate into stones in the urinary tract. Stones can cause pain, blood in the urine (hematuria), can obstruct the flow of urine, and may be complicated by secondary infections that can further compromise kidney function. The stones may small or large, and form throughout life in persons with PH. Large stones can be difficult if not impossible to pass, causing pain that may be severe. Surgical removal is often necessary. Damage to the kidneys is progressive, irreparable and may lead to kidney failure and end stage renal disease (ESRD) requiring dialysis and/or transplantation. In addition, as kidney function becomes increasingly impaired, blood levels of oxalate increase, with crystals forming in the bloodstream and being deposited in multiple body tissues (oxalosis) including blood vessels, bone, heart, skin, and eyes. Finally, in the absence of timely dialysis or transplantation, worsening oxalosis in ESKD may lead to multiple organ dysfunction and even premature death, even sometimes in childhood.

There are three known types of PH due to different genetically determined enzymatic defects or deficiencies that result in the excess production of oxalate. PH type 1, which accounts for almost three quarters of people diagnosed with PH, is due to mutations in the AGXT gene. Errors in the genetic code of the GRHPR gene lead to PH type 2, which accounts for approximately 10% of PH diagnoses. A similar proportion of the population living with PH have type 3, which is due to mutations in the HOGA1 gene. The cause of the remainder, referred to as idiopathic PH or no mutation detected (NMD) PH, remains to be determined.

In the United States and much of Europe, the estimated prevalence of primary hyperoxaluria is 1-3 per million individuals, though it may be slightly higher from other parts of the world. The incidence has been estimated to be 1 person with PH for every 120,000 live births.

Etiology of PH

Recent advances in genetics and molecular biology have provided insight into the cause of the disorder—and potential targets for therapeutics. In PH1, there are a large number of mutations in the AGXT gene that can lead to reduced or absent activity of the liver enzyme alanine-glyoxylate aminotransferase (AGT), which catalyzes the transamination of glyoxylate to glycine. The mutations may lead to an absence or truncation of AGT, mistargeting of AGT to the mitochondria, amino acid substitutions or improper protein folding that impair the enzyme function. In a small number of mutations, the enzymatic activity of defective AGT can be increased with pyridoxine (Vitamin B6) supplementation. However, in the absence of adequate AGT activity in the peroxisomes, glyoxylate accumulates, providing an increased amount of substrate that lactate dehydrogenase (LDH) or glycolate oxidase (GO) can convert into oxalate.

A similar process occurs in PH2, where mutations in the GRHPR gene lead to impairment of glyoxylate reductase (GR)/hydroxypyruvate reductase (HPR), an enzyme that would normally convert glyoxylate into glycolate in the cytosol and mitochondria. Again, the more that glyoxylate accumulates, the more it is metabolized into the end product oxalate.

In PH3, mutations in the HOGA1 gene lead to deficiencies in 4-hydroxy-2-oxoglutarate aldolase (HOGA) in hepatic mitochondria. HOGA catalyzes the transamination of 4-hydroxy-2-oxoglutarate (HOG) to glyoxylate and pyruvate. The cause of increased oxalate production when HOGA is deficient is not yet fully understood. It has been suggested that though defective HOGA could reduce levels of glyoxylate in the mitochondria, it also leads to an abundance of HOG, much of which is transported to the cytosol, where it can inhibit GR activity, potentially leading to an increase in glyoxylate. HOG might also be broken down into glyoxylate.

The clinical manifestations of PH

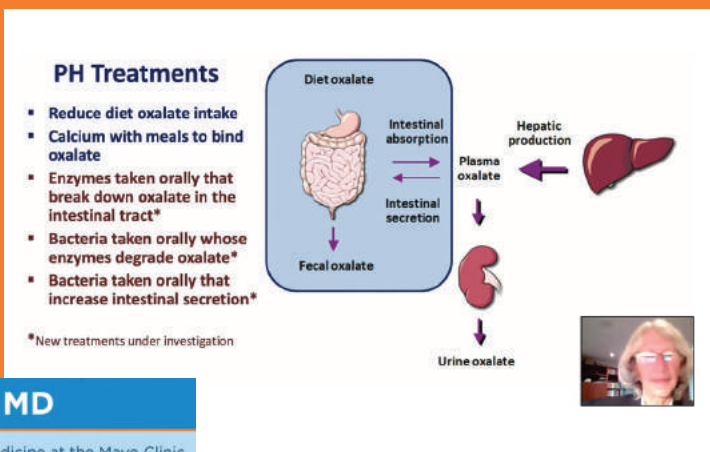
These different pathways to oxalate production lead to some clinical differences between the types of PH, but there are more similarities than differences. Each type of PH is characterized by marked overproduction of oxalate by the liver, with increased urine oxalate present from shortly after birth and over the course of life. The earliest symptoms, most of related to kidney stones, usually first occur in childhood, but may develop at any age and recur throughout. Most people with PH are first diagnosed in childhood or adolescence; though diagnosis may occur at any age, even in older individuals if the symptoms are mild, or if the symptoms are not recognized as being due to PH.

There is wide variability in the course of the disorder from one person to another in all PH types. Severe disease in infancy and childhood is encountered in PH type 1 more often than other types and may be associated with nephrocalcinosis, failure to thrive due to impaired kidney function, or even ESKD. Other individuals may only develop occasional kidney stones in adulthood. However, a substantial proportion of people, especially with PH1, are not recognized to have PH until after advanced kidney damage or even ESKD. Some people with PH are only diagnosed after transplantation, when disease recurs in their new kidneys.



Dawn Milliner, MD

Professor of Pediatrics and Medicine at the Mayo Clinic



Deposits of calcium oxalate crystals in multiple body tissues (systemic oxalosis) develop after kidney function deteriorates to CKD stage 4/5, when blood oxalate levels increase markedly. Crystal deposits in bone can lead to metabolic bone disease characterized by fractures, bone marrow deposits can result in anemia, and deposits in heart muscle and the cardiac conduction system can lead to cardiomyopathy, arrhythmias and death. Crystal deposits can also affect the joints, retina, and nervous system.

The clinical course tends to be more severe in PH1. PH1 generally leads to higher oxalate levels, while PH3 seems to generate oxalate levels in the lower range. Nephrocalcinosis more commonly occurs in PH1, as does earlier onset and greater loss of kidney function over time. A wide range of severity can be seen in PH2, with some reaching ESKD at a young age, while others have preservation of kidney function into late adulthood. The course of PH3 appears to be the least severe with better preservation of kidney function. PH3 is thus much less likely to lead to dialysis, transplants or systemic oxalosis. However, individuals with PH3 may have onset of kidney stones in infancy or early childhood similar to what is seen in PH1 and PH2.

Overview of PH management

Once diagnosed, supportive measures are recommended to protect the kidneys from calcium oxalate injury and stone formation. The mainstays of supportive care are high fluid intake to dilute oxalate and calcium in the urine so that crystals do not form as readily, and oral medications, such as diuretics and citrates that can reduce crystal and stone formation even oxalate is present in excess. In addition, in some individuals with PH1 (those with the Gly170Arg, Phe-152Ile and Ile244Thr genotypes) pyridoxine supplementation may partially restore AGT function and reduce oxalate levels. However, individuals with PH2, PH3 and other PH1 genotypes do not benefit from pyridoxine supplementation.

Management of all PH types includes routine monitoring of stone formation with regular ultrasound or other imaging. Stones that cause pain, obstruction or infections may require fragmentation by lithotripsy or removal by a urologist. Kidney function also needs to be routinely monitored with regular blood and urine tests, and as kidney function becomes significantly impaired, the blood oxalate level should be monitored closely. If kidney failure ensues, kidney replacement in the form of dialysis and transplantation should be initiated as soon as possible to reduce development of systemic oxalosis.

Other management approaches focus on reducing the accumulation of excess oxalate from and/or eliminating the oxalate. For example, a few experimental treatments currently under study include the oral administration of enzymes or whole bacteria to break down oxalate within the intestinal tract. Also in clinical trials, is oral administration of bacteria that increase intestinal secretion of oxalate (transporting oxalate from the blood into the intestine to be passed within stool).

Another strategy would be to directly target the errors in metabolism in the liver that cause excess oxalate production. Liver transplantation, which can restore normal liver metabolism, has been shown to be effective for PH1 and PH2, though with significant risks. Among them are the

need for Individuals who have a liver transplant to take immune suppressants to reduce the risk of organ rejection; and medical monitoring is required for the rest of their lives.

People with PH urgently need less invasive measures that can modify liver enzyme activity to produce less oxalate. Though people with some of the genotypes that lead to PH1 can reduce oxalate produce with pyridoxine supplementation, which increases AGT enzyme activity, most people with PH do not have this option. However, there are a number of investigational agents, some under development and others in clinical trials, targeting other parts of the enzyme pathway to oxalate production. Among them are, reduction of GO enzyme activity in PH1 and LDH enzyme activity in all PH types.

Some of these were in advanced clinical trials at the time of the PFDD meeting. One, lumasiran, has since received FDA approval for PH1.

At the conclusion of a scientific overview presented at the EL-PFDD meeting, Dr Dawn Milliner, Professor of Pediatrics and Medicine at the Mayo Clinic stressed that although management of PH has improved it is still inadequate. “High fluid intake and medications are a daily burden. Kidney stones are painful, unpredictable; they may need surgery and they interrupt your life at the most inconvenient times. Loss of kidney function and kidney failure can occur despite your best efforts and our best efforts as clinicians. And if kidney failure develops, and dialysis is needed, it's intense and it's very burdensome. Transplantation has long-term consequences, so it too is not a perfect solution. We must do better.”

Meeting overview

The EL-PFDD meeting was held in order to improve PH treatment options and outcomes by sharing the experiences of those with PH and their caregivers with industry and the FDA to inform drug development and review. “Your story, the stories that we hear at these meetings are a powerful,” said Dr. Aliza Thompson, the Deputy Director of the Division of Cardiology and Nephrology in the Center for Drug Evaluation and Research (CDER) at the FDA, at the start of the meeting. “We connect with your stories on a very personal level. Your stories remind us of the urgency with which we must act to address the obstacles to drug development; and they inspire us to do better.”

More than 300 individuals registered for the virtual meeting. In addition to Dr Thompson, these included several other members of the FDA including Rebecca Reindel, MD, Michael Monteleone, Andrea Hulse, MD of the Center of Biologics Evaluation and Research (CBER), Julianne Vaillancourt, Rare Disease Liaison at CBER, Karen Jackler, Patient Engagement Program Manager at CBER, Kirtida Mistry, MD, of CDER, and Shannon Cole of CDER.

Close to half of the people who registered to participate in the meeting were people with PH or their caregiver, parent or other family member. In addition, friends of people with PH and a broad cross-section of representatives from the pharmaceutical industry, academia, and patient advocacy organizations also participated in the meeting.

After presentations by Dr Thompson and Dr Milliner, the meeting was divided into two sessions that focused on different aspects of the patient and caregiver experience. The first session was on the burden of disease—including which symptoms or impacts of the disease had the greatest impact on the daily lives of people with PH. The second meeting session explored patient perspectives on current treatment, the unmet needs in PH management, and expectations regarding future treatments. This included treatment benefits they considered clinically meaningful and perspectives on how they would balance the benefits versus risks of current and potential treatment options.

CHALLENGE

- Participate in PH Registries
- Participate in clinical trials
- Help scientists, clinicians, the OHF, and FDA understand what you need
- Educate your families, friends, care providers
- Support each other



Solid progress:

Defining the genetics, errors in oxalate pathway, and causes of kidney damage in PH

Understanding disease expression over lifetimes of PH patients

Improving outcomes with current treatments



Yet:

High fluid intake and medications a daily burden

Kidney stones painful, unpredictable, surgery often needed

Loss of kidney function and kidney failure can occur despite our best efforts

Intensive dialysis extremely burdensome.

Transplantation has long term consequences

We must do better



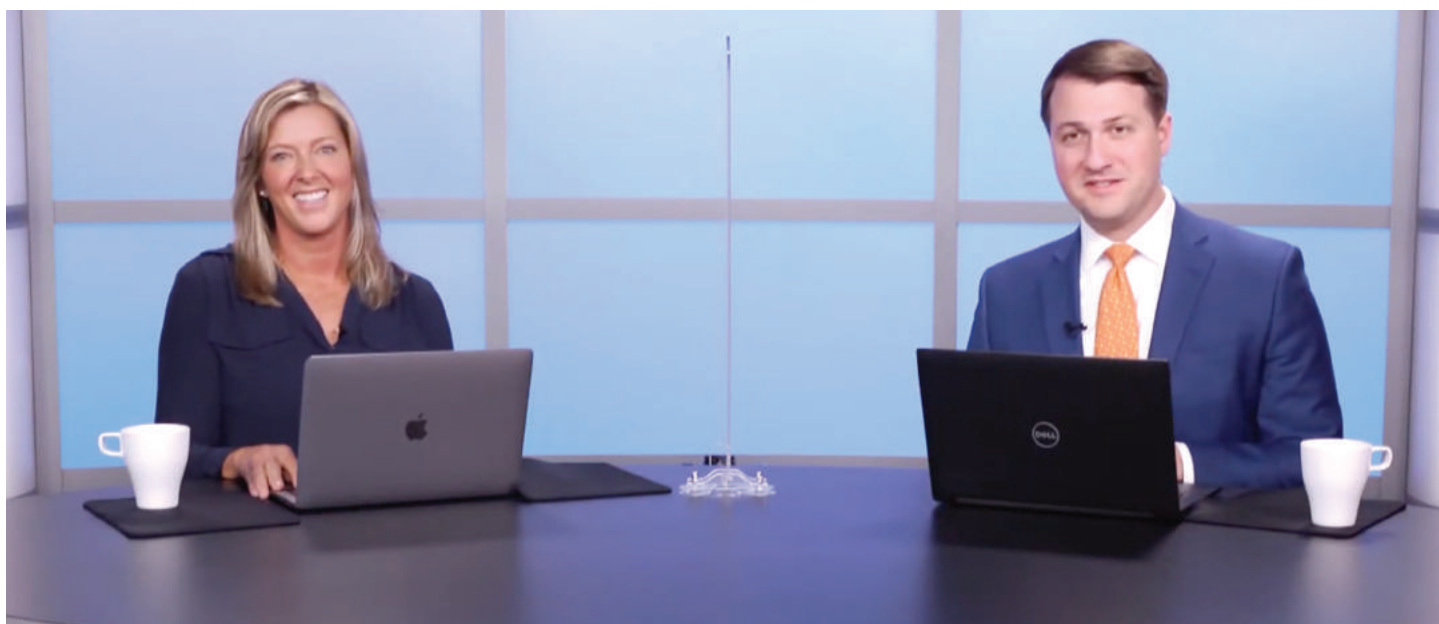
Each session began with a panel of five patients and/or caregivers representing each PH type, across the spectrum of life stages and disease severities. These individuals brought their voices through stories and photographs to depict the debilitating impact of PH upon their lives. In addition, the organizers played a short video sharing a glimpse into the life of three families living with PH at the start of the second session.

At various points of the meeting, the meeting's moderator, James Valentine of Hyman, Phelps & McNamara (who had also helped organize the meeting) posed poll questions to those watching the live webcast, followed by a period of facilitated discussion. Participation in each polling question was voluntary (depending on the question, there were between 49 and 83 respondents). Note that the results were used as a discussion aid, but the poll should not be considered as a statistical survey of a representative sample.

The first series of polling questions provided demographic information about the respondents and the individuals with PH who they were or represented. According to the results, 25% of the respondents were people living with PH, and 75% were parents or caregivers to someone with PH. The majority of participants were residents of the US, 16% were in England or the European Union, 5% in Asia, 3% in Canada, 3% were in New Zealand/Australia, and 1% lived elsewhere. Nearly a third (33%) of the people with PH or represented by polling respondents were younger than 12 years of age, 24% were 12-17 years of age, and the remainder were aged 18 years or older. Most (61%) identified as male, and 39% as female.

Consistent with the data presented by Dr Milliner, the majority of respondents were or represented someone diagnosed with PH1 (64%); while PH2 and PH3 were less common (15% and 17% respectively), and the remainder 4% either didn't know or had NMD PH. More than half (53%) had been diagnosed when before they were 3 years old, and most of the rest (37%) during childhood/adolescence, with approximately 9% diagnosed after they turned 19 years old. The vast majority had their first kidney stone when they were young: more than half (51%) first had kidney stones in the earliest years of life (younger than 4 years of age); 22% when they 4-10 years of age; 11% when they were 11-18 years of age. Only 2% reported detecting their first kidney stone during adulthood (age 19 years or older).

Valentine used the polling responses throughout the meeting to facilitate an interactive discussion which allowed people with PH or their caregivers opportunities to share their experiences. The meeting provided a number of ways to participate in the discussion. First, Valentine asked PH community members (five per session) who took part in a zoom panel to provide their experiences relating to issues raised in the polling responses. In addition, participants could call in to a phone number to provide their comments or send in written comments using the comment feature on the OHF webpage for the meeting. Community members could also send in comments up to 30 days after the meeting.



Report overview and key themes

This report summarizes the panelist testimonies, and reflects the discussions and the comments made or submitted during and after the meeting. To the extent possible, the terms used in this report to describe specific symptoms and treatment experiences come directly from the words used by the meeting participants. Note that there could be symptoms, impacts, treatments, or other aspects of PH that are not included in the document. While the subsection below presents a high-level overview of the meeting's key findings, a more granular description of the meeting's discussions can be found later in the report.

Topic 1: Burden of disease

During the first topic, meeting participants with PH and their caregivers described the burden of living with a very rare, often debilitating disorder in which overproduction of oxalate reaches toxic levels that cause progressive and irreparable damage to the kidney and, as kidney function declines, lead to complications involving other organ systems. They spoke about the most common manifestation of the disorder, kidney stones that cause obstructions, that may require surgical interventions or cause extreme pain as they are passed, and which may be preceded or accompanied by recurrent urinary tract infections. These events can strike repeatedly with little warning, often presenting in infancy, although in some they are only detected later in life. The severity of the disorder ranges with type and from person to person, with progression to ESRD, and in some cases, death, mostly occurring in those with PH1, though, as kidney damage progresses with age, stones and oxalosis, those with or caring for someone with each type of PH expressed anxiety about what the disorder had in store for them or their loved ones as they grow older.

Key voice of the patient insights in the burden of disease in PH:

- Kidney stones are ubiquitous and have the greatest impact. Regardless of PH type, caregivers described shock when ultrasound findings showed that their *"crying and moaning"* infants' and young children's *"kidneys were completely filled, both kidneys completely blocked off,"* and *"stones stuck in [their child's] ureter."* *"Loss of kidney function"* begins early in many, some reported *"my kidney didn't develop fully after that."* Others reported only detecting stones later in life when other symptoms led to the detection of *"hundreds of stones."* Some children or adults develop very large or *"staghorn stones"* that *"cannot be passed."* Many require surgical intervention. Stones recur *"constantly"* through life, even in transplanted kidneys, unless there is also a liver transplant.

- Approximately half, especially those with PH1, chose kidney failure/ESRD as one of the top three most impactful symptoms. Many had experienced it. Some *“almost died.”* For others: *“Each year we lose more kidney function and hype ourselves up to prepare for the inevitable dialysis and organ hunt.”*
- Pain was the second most common symptom, and it ranked third among the top three symptoms that mattered most to caregivers/individuals with PH, many of whom described being *“constantly in pain”* or having recurrent *“extreme pain episodes,” “traumatic pain,” “sudden agony,” “pain that would cause nausea and vomiting. It’s very, very intense and... no medication that can treat it.”* Pain is usually due to kidney stones, but as kidney function declines damage to bones and other organs contribute. A similar percentage of respondents selected the psychological impact of having PH (anxiety/depression) as one of their top symptoms. Many described having *“anxiety” “because of the unpredictability of the disease and the inevitability of disease progression”* including *“fears”* of having another *“painful kidney stone,” “progressing to kidney failure”* or because *“[PH] threatens to take away my future.”* Others were depressed because of the *“emotional toll of being different”* or even *suicidal due to the anguish of their pain: “I can’t live this way.”*
- Participants discussed many other impactful symptoms including recurrent UTIs and pain on urination that often preceded PH diagnosis: *“she had her second and third and fourth UTI in a span of two months;”* nausea and vomiting (often due to *intense pain*): *“months of vomiting seizures;”* blood in the urine: *“[he] has had sharp crystals in his urine, and... sees blood;”* failure to thrive, fatigue: *“limp”* and *“incredibly lethargic;”* and finally, those with advanced disease and systemic oxalosis develop grave symptoms such as *“damage to vision,” “brittle bones”* and *“fractures,”* cardiomyopathy and skin ulcers due to oxalate deposits in their eyes, heart, skin and bones.
- These symptoms (and their treatments) have a dramatic impact upon the daily life of children and adults with PH, forcing many to miss many days of school/or work in fulfilling job as well as miss out going out/have a social life/travel, which might be interrupted an emergency: *“what...if he begins to pass a stone or has another medical issue related to his disorder.”* Participating in sports was also seen as risky by many caregivers, given the need to maintain hydration and risk of dislodging stones that might *“get stuck in your ureter.”* Sadly, some individuals said that PH was a factor in their ability or choice to have/care for a family.
- People with PH and their caregivers are worried about their future with the disease as they age. The majority said they were stressed from not knowing how the disease will progress: *“We live in constant fear that something could go wrong again.”* Half, including some children, indicated that they afraid of dying at a younger age because of PH, and only slightly fewer were worried most that their disease would worsen, or that they might need dialysis. Others worried that they would never be free to live as they wanted to: *“I have to continue to consider PH in all that I do;”* or that they may progress to the point would become a burden to their family/unable to support themselves.

Topic 2: Patient perspectives on treatment options

The second meeting session focused on the medical and nonmedical management approaches that people living with PH and their caregivers use to try to manage their symptoms and prevent progression of the disorder. This included how they try to reduce oxalate levels and prevent kidney stones from developing, how they manage them and the related pain and other complications when they occur and how they try to deal with ESRD. Many of their needs remain unmet, so participants expressed their interest in engaging in clinical research, and how they would weigh risks versus the potential benefits of new treatments.

Key voice of the patient insights about the unmet needs in the management of PH:

- The most commonly used medical and supportive care approaches are used as parts of a preventive or secondary maintenance regimen to reduce oxalate in the body, whether by trying to reduce its production, accumulation, or by diluting or expelling it before it can form stones and damage organs.

- o Drinking large volumes of fluid, ranging from 3-6 liters a day is “a constant,” that daily life must be structured around. *“Every ounce of water”* must be tracked, because *“if you get behind, it’s hard to catch up.”* Sports or exercise increase the *“water requirement.”* The biggest downside is *“the constant need to urinate,”* which *“which interrupts days at school,”* and leads to embarrassment in children when there are accidents. Even for adults, *“the need to take frequent bathroom breaks can be very disrupting for many aspects of life, including time-consuming jobs, travel”* and *“sleep,”* which can interfere with work performance.
- o Prescription medications (such as vitamin B-6 and diuretics) and supplements such as citrates are also very commonly used.
 - About one third of individuals with PH1 are *“responsive to”* vitamin B6, however, the rest are not, and it doesn’t help those with other types of PH at all.
 - Many mentioned taking thiazide diuretics, or as one caregiver called them *“pee pills”* but, as the name implies, it increases the urge to *“urinate more frequently.”* These are not always tolerated, and there were mixed opinions about how well they work.
 - Participants across all types of PH described using multiple supplements such as potassium citrate (Cytra-K), Polycitra, potassium phosphate (PHOS-NaK) and magnesium-based supplements as part of their preventive regimen. One downside is that the supplements may not be *“covered by insurance.”* Another is that many children and adults do not tolerate them well. Participants described how some of the supplements were *“upsetting”* to their stomachs, causing *“constant acid reflux,” “nausea,”* and *“constantly throwing up.”*
- o After drinking extra fluids, diet-based approaches, cutting down on foods high in oxalates and reduce the burden on the kidneys were the most common nonmedical approaches used to manage PH. However, *“following the strict diet”* and *“constantly monitoring”* intake can be challenging. Also, participants complained there is *“a lot of conflicting information about diet,”* and *“it’s not a healthy diet,”* that could make one *“very lethargic.”*
- Many children and adults with PH require *“procedures to remove kidney stones”* on multiple occasions. Close to half (47% or 24 out of 51) of poll participants selected at least one of the three procedures for kidney stone removal as a medical approach that they or their loved one with PH were currently using. Extracorporeal shock wave lithotripsy (ESWL) is the least invasive but also the least commonly used—comments suggested that it may not work on PH-related stones. Ureteroscopy with stent placement was the most commonly used procedure to remove kidney stones. It is less invasive, but also *“less efficient and effective,”* than percutaneous nephrolithotomy (PCNL) which is needed by many because of the large size, complexity or position of PH-related stones. Aside from the multiple hospital stays, pain, and trauma associated with PCNL, the surgeries also cause scarring: *“His body is covered in scars”* and there is a risk of permanent injury to the kidneys. There can be complications with any procedure, including with stent placement.
- In almost one out of five of the children and adults with PH (usually though not always PH1) represented in the poll, kidney function had deteriorated to the point where they currently required dialysis, and a number of other participants in the meeting indicated that they been on dialysis before going on to have *single or double organ transplants* (including a liver transplant).
 - o The dialysis regimens—hemodialysis, sometimes peritoneal dialysis, and, in some cases, both—required to remove oxalate are *“extremely grueling”* and can be particularly long: *“She endured 4 hours of hemodialysis each day at the hospital and 10 hours of peritoneal dialysis each night at home.” “Dialysis is very invasive”* and takes a tremendous toll on the body, with many complications including *“exhaustion,” “congestive heart failure,” “peritoneal infections”* and *“bone wasting.”* Moreover, the risk of mortality over time is high.
 - o Several meeting participants described their or their children’s organ transplants to *“save [their] life,”* but kidney transplants on their own cannot prevent progression because stones will develop in the new kidney unless a liver is also transplanted. Other downsides include long waits to receive a double organ transplant, and a lifelong course of immunosuppressants and other medications, there may be *“multiple complications,”* including organ rejection.

- People with PH also use a variety of other medications and therapies to try to preserve their health, manage other symptoms, such as pain, depression and anxiety and improve their quality of life.

Overall, there is a great remaining unmet need for less disruptive, and more effective treatments for PH. As one woman with PH said, *“The treatments that are available now? There’s not a great one.”*

- In one polling question, when asked what individuals with PH and their caregivers most wanted from a future treatment, the two options most commonly chosen were *“completely stopping the formation of kidney stones,”* and *“stopping disease progression.”* In the discussion, participants expanded on these themes and described wanting more than one thing from a future treatment:
 - o Treatments are needed that prevent kidney stones and the progression of kidney disease to dialysis and organ transplantation. One caregiver said he wanted treatments that would remove *“the fear of kidney stones or fear of kidney transplant,”* and another said they wanted *“a medication to help preserve his kidney function, avoid oxalosis and transplant requirement.”*
 - o Treatments are needed that address the underlying cause of the disease to reduce oxalate levels: *“A treatment option that addresses the root cause of excess oxalate production would be a great benefit to the patients and families,”* wrote one caregiver.
 - o Treatments are needed that reduce the burden of the current preventive care regimens: *“A drug that would reduce a water drinking requirement and the frequency of taking a medication,”* said one teenager with PH.
- Several participants said they are willing to put a great deal of time and energy in clinical trials as well as put up with personal discomfort and inconvenience in order to find effective treatments: *“Finding a better treatment or medication that... would... give PH patients a genuine hope of leading a normal life has been [why] I endured the many x-rays, ultrasounds, CT and MRI scans, along with urine and plasma samples for research over the year,”* said one man with PH2. Many also said that they had chosen to take the risk of an experimental treatment, rather than accept an organ transplant that might cure the disorder (but which comes with its own downsides). While participants said they wanted safe options, some who faced life-threatening disease progression, said they would *“try anything”* given their desperate situation: *“We are also willing to risk side effects, including allergic reactions, paradoxical stone formation, and other intolerances if this medicine would lower oxalate production, help [him] preserve his kidney function and prevent oxalosis,”* one caregiver said.

Appendices

The appendices include the meeting agenda, polling questions and responses and submitted written comments. Additional information on the meeting has been posted online at www.ohf.org.

Benefit-Risk Framework

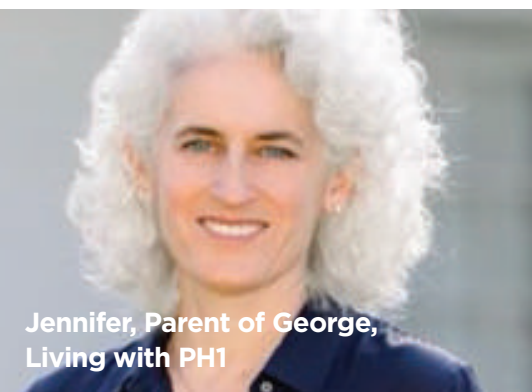
The patient input generated through this EL-PFDD meeting and post-meeting questionnaire is submitted to strengthen FDA’s understanding of the burden of PH on patients and their perspective on the treatments currently used to manage PH and its symptoms. It is our hope that FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. This input may also be of value to the drug development process more broadly. Specifically, it may be particularly useful to drug developers as they explore potential areas of unmet need for individuals with PH, for example with regards to reducing oxalate levels, kidney stones and overall symptom control—and reducing reliance on the existing regimens that are so disruptive to daily life.



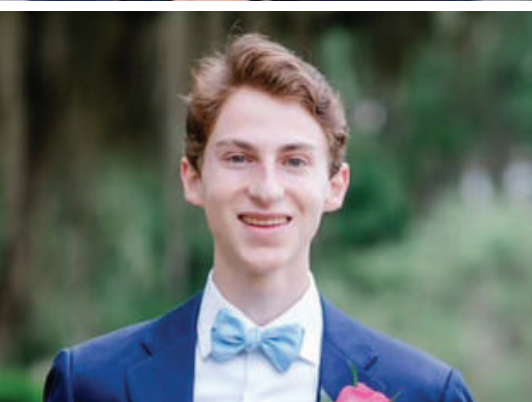
Amy, Parent of Owen,
Living with PH1



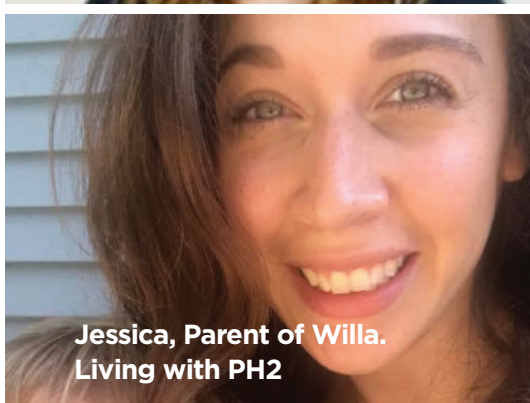
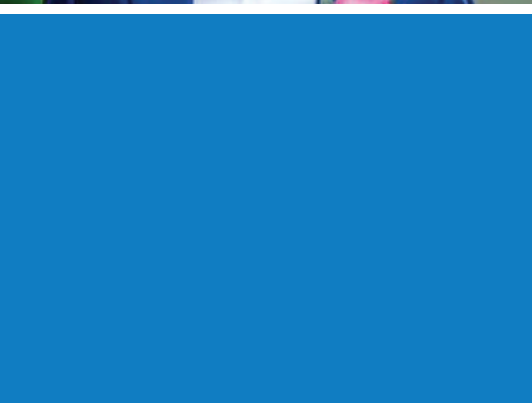
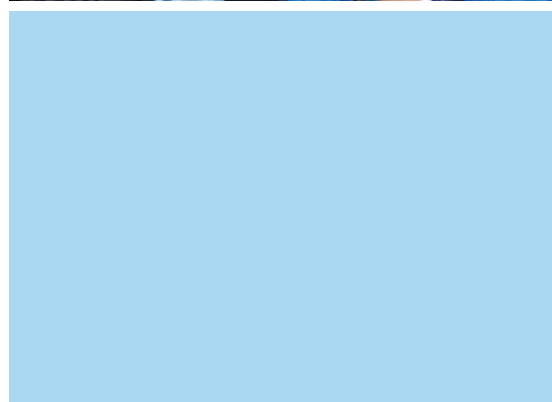
Kyle, Living with PH3



Jennifer, Parent of George,
Living with PH1



Natalie, Living with PH1



Jessica, Parent of Willa.
Living with PH2



Jamie, Parent of Alex
& Gunnar, Living with PH2



TOPIC

1

Most significant PH symptoms and their impact on daily life

The first discussion topic focused on the experiences of caregivers and the patients with the symptoms of PH as well as the impact and burden of the disease upon their daily lives. This section attempts to share a more complete picture of individual's lives across the spectrum of PH, beginning with a panel of patients and caregiver/parents to children with PH:

- *“Because of PH, [he] never feels well,”* said the first panelist, whose 12-year-old son “spent the first three years in and out of inpatient hospitals and long-term skilled stays” due “failure to thrive” and other grave health issues (described in more detail below). He suffered through his “first momentous kidney stone” at the age of 3 years. *“It would take two more years and a dozen more stones until we were able to receive his formal diagnosis,”* she said. She spoke about his severe pain, his many surgeries, frightening complications, and ever-declining kidney function. She also spoke of how much his PH had made him miss out in terms of social life and school. *“Our normal for [him] is never really being healthy in the way that we all take being healthy for granted... his ‘journey and progression slowly continues into deterioration. Each year we lose more kidney function and hype ourselves up to prepare for the inevitable dialysis and organ hunt with each blood test.”*
- *“As a young child, I often questioned why I was the one in a million to be diagnosed with this rare condition,”* said the second panelist, a 24-year-old man with PH3. He described how, as a boy, it was *“impossible to comprehend how the food I ate converted into kidney stones and having an unknown version of an invisible disease didn’t make it any easier. The emotional toll of trying to explain PH to my peers only made the suffering worse.”* Instead, he hid the pain as much as he could, but *“the surgeries have been constant,”* and interfered with his employment as an adult. Although researchers have now identified the cause of PH3, he said, *“the status of the disease has remained the same. It still impacts patients like myself; and remains largely ignored by the medical community because of the small patient sample size it impacts.”*
- *“We heard repeatedly that kids are not supposed to have kidney stones,”* said the third panelist, mother of four boys, two of whom have PH2. Her first son’s PH presented when he was 17 months old with *“uncontrollable vomiting, high fever, and with him acting very cranky.”* Scans showed that his *“kidneys were completely filled with kidney stones. Both of his little kidneys were completely blocked off.”* Genetic testing showed that her two oldest sons were genetic carriers, while her third son had the exact same mutation as his younger brother. The third brother’s symptoms have been mild—he hadn’t yet developed stones or require multiple invasive surgeries that have left his younger brother’s body covered in scars; however, she said, *“as they grow, this is reversing.”*
- *“It can be easy to see patients as just that, patients—so I first want to establish myself as a person. I’m a pediatric physical therapist. I’m a fiancé to my partner of nine and a half years. And last but not least, I’m a daughter, a sister, and a friend... PH1 has threatened to take all of these roles away from me,”* said the fourth panelist, a 30 year old woman who was diagnosed with PH1 after passing a stone at the age of five. As a young adult, she said *“after years of being compliant with my treatments, my yearly ultrasound showed stones that had been accumulating over the years and had more than multiplied.”* She described how some “mistakes” she said she made in getting prompt care led to a life-threatening situation and permanent kidney damage. *“I’ve always known I have PH, but I saw firsthand how fast it could change my life. It’s a sinking feeling to know that your whole life could be different from that moment forward... I hope you begin to understand that people with PH are fighting a daily emotional, financial, and physical battle for their lives and their futures,”* she said.

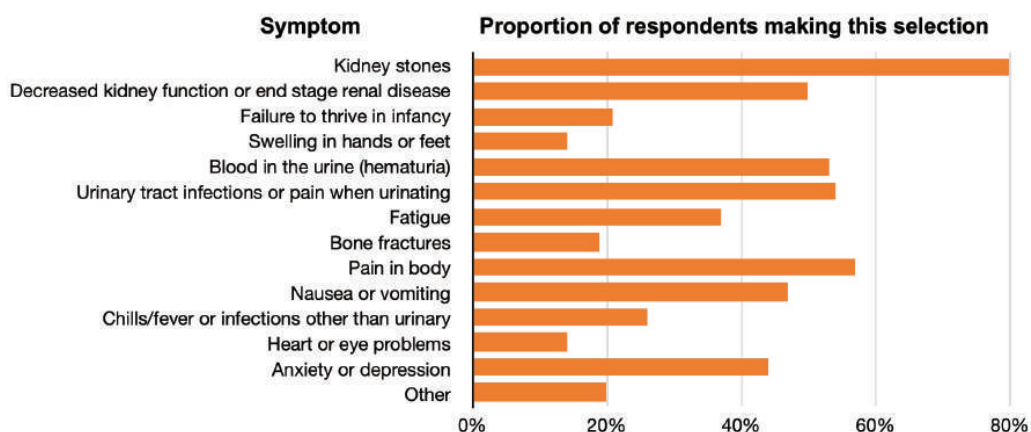
TOPIC 1

- The final panelist of the session had rushed her daughter to the hospital when she was four months old, “due to her uncontrollably vomiting and having diarrhea at the same time. She also went limp,” she said. At the time, the doctor gave her diagnosis for a UTI, but after a second, third, and fourth UTI diagnosis in the space of two months, she had an ultrasound on her kidneys. She had an 8 millimeter (mm) kidney stone in her right kidney and several small stones in the right [check] kidney as well. At 9, she was officially diagnosed with PH2. One day month later she had “completely stopped nursing. She didn’t have a single wet diaper. She vomited all she had left in her,” but she was unable to communicate the “pain that she was in.” That large kidney stone had become “stuck in her ureter and she had to have emergency surgery.” Now, four years old, the child is able to communicate her pain verbally, but her mother said she is “always... fearful” about what is next. “Could be the day another stone forms? Will she eventually need a liver and kidney transplant? This disease does not have a one size fits all plan.”

The symptoms that matter most to patients and their caregivers

Themes raised by the panelists were reiterated during the facilitated discussion (and in responses to the post-meeting questionnaire) by other meeting participants. During the facilitated discussion, the polling questions systematically explored a number of issues related to the symptoms, while the wider facilitated group discussion elicited further details about the impact of PH on people living with and affected by PH.

Before the discussion, four polling questions were posed on symptoms, disease impacts and the burden of disease. Note, the first of these revealed the breadth of complications experienced by individuals with PH. Out of fourteen options, participants were asked to select which symptoms and health effects that they, or the loved one with PH they represented, had recently experienced. Figure 1.1 shows the selections that 70 polling respondents made to the question:



When asked to choose the top three symptoms out of the same list that were most troublesome, however, it became clear that the majority of respondents were most concerned about stones and progression of kidney disease—however, the discussion made it clear many of the other complications were also cause for grave concern among some individuals. The symptoms below are ranked in the order based upon the percentages of responses to this question, although some related symptoms have been grouped together for the thematic review. After kidney stones and ESRD, responses were split among the other symptoms. Full polling results can be found in Appendix 2.

TOPIC 1

1. Kidney stones

"I've had, sporadically, a staghorn stone that was about the size of half of my fist... I will go through stable periods for a few years at a time. And then the stone just ends up getting a lot bigger. The stones...have been constant. I have them now."

Kidney stones are a hallmark of PH and 76% of the polling respondents chose them as one of the top three most distressing aspects of the disease—although in most (though not all) cases, the stones are paired with other downstream symptoms and complications. Many caregivers reported alarm when scans revealed their children not only had stones, but were “full of stones,” when, as one panelist said, “kids are not supposed to have kidney stones.” This was regardless of PH type.

"When he was 28 days old, an ultrasound showed he had both kidneys loaded with stones," one mother of two children with PH1 said. The panelist whose two sons have PH2 said that a scan showed one's “kidneys were completely filled with kidney stones. Both of his little kidneys were completely blocked off” when he was only 17 months old.

A zoom panelist said that when doctors were looking into the cause of a UTI in his 3-month-old daughter, they “couldn't quite believe,” her scan results. *"I saw a number of different kidney stones, including... one that was in her ureter causing a blockage and causing the infection."* They diagnosed her as having PH3.

One of the panelists said that doctors investigating other symptoms performed an ultrasound on her infant daughter's kidneys. *"She had an 8 millimeter (mm) kidney stone in her right kidney and several small stones in the right kidney as well. To say we, as her parents, were shocked is an understatement."* Diagnosed with PH2, her parents took their daughter to the hospital again months later, when *"the 8 mm stone [had become] stuck in her ureter and she had to have emergency surgery."*

"When I was 4 and was taken to the hospital because I had many UTI's and was in a lot of pain. After a few tests they realized I had a big kidney stone in my right kidney and after a day or two it came out with much pain, of course. Note that my right kidney didn't develop fully after that," wrote a woman with PH3.

In others, stones were only discovered much later. *"At the age of 19 with no prior symptoms... the CT scan revealed hundreds of stones in both her kidneys,"* the caregiver to one daughter with PH1 wrote.

Others described very large stones or “staghorn stones” that “could not be passed.”

"He had...a 3x1 centimeter kidney stone. Try to pass that. This had to be removed through his belly button," said the mother of one boy with PH1.

"My 16-year-old was diagnosed after having a 5 x 3 x 2 centimeter stone removed from her right kidney" said one caller. Another caller whose young daughter had PH3, said *"when we did accidentally find these kidney stones, there were so many... that they couldn't even count them at age three. There was just like little white dots all over the place on this image. And one of them was almost an inch big."*

TOPIC 1

Another aspect of the stones in PH is that they recur through life.

A 40-year-old woman with PH1 on the zoom panel described *“having had [kidney stones] my entire life constantly, maybe with a couple months gap somewhere around the age of 30.”*

The young man with PH3 on the topic 1 panel, described how, *“During the sonogram, I was told I would need a bilateral ureterostomy to remove eight kidney stones.”* Later in the meeting, during the video presentation, he said that he’d *“passed two or three kidney stones in the last year.”*

“I still get stones. I went four years without any stones. And then suddenly I had a kidney full of stones. It took three hospital admissions to remove them. Then within a year I was back with more stones,” said a 67-year-old woman with PH3 on the second zoom panel.

A mother of three children with PH1 who phoned in spoke of recurrence after a kidney transplant. Her 5 month old son was dying of kidney failure: *“They said his kidneys looked like walnuts. They were calcified. A year later he got his dad’s kidney and a few weeks later...it was full of stones already.”*

It is important to note that the kidney stones rarely occur in the absence of other downstream symptoms: *“vomiting seizures and intense pain,* and blockage of the urinary track leading to UTIs.

“Never would I have guessed this baby who was so ill was suffering from massive kidney stones that would eventually cause ureter blockages and hydronephrosis. Severe infections were to follow. Eventually 19 stones were removed from my 2 year old little girl,” said panelist on the second panel with two children with PH2. *“Sadly, more have reappeared and continue to build.”*

The stones, or procedures to remove them, can lead to permanent kidney damage. *“I had lost my right kidney...from stones just before my wedding,”* one woman with PH2 wrote.

TOPIC 1

2. Decreased kidney function or end stage renal disease

“We thought it was the flu, doctored him for the flu. And by the time we got to the hospital, his kidneys had already failed. He was full of stones... After the kidneys actually failed was the worst. That is the worst. It was constantly hospitalization. He required dialysis five days a week. I held him when he died.”

More than half (53%) of the polling respondents selected decreased kidney function, or ESRD as one of the top three most distressing aspects of the disease. Many, particularly those affected by PH1, described life-threatening events, and for some, during infancy.

“Around the age of one, I had bilateral obstructing stones and went into a complete renal failure and almost died,” one caller with PH1 said.

One mother wrote in that her daughter had a similar experience, *“My daughter was diagnosed with PH1 at 2 months old since she suddenly went into complete kidney failure, she almost died.”*

“He went into end stage renal failure at 5 months old and had to be rushed to [the] hospital. He spent two weeks inpatient getting stable and had a hemodialysis catheter placed to clean his blood of toxins and oxalate,” reported the mother of another young boy with PH1.

Not all children who experienced kidney failure survive: *“My sister, who was 2 years younger, was diagnosed when she was 2 ½ and her kidneys failed. [After years of dialysis], she passed away at age 11,”* wrote one woman. She herself was diagnosed with PH1 after she presented with ESRD at an older age. *“I did go... to the emergency room at 21 when I realized I was severely ill. My creatinine was 31 [milligrams (mg) per deciliter (dL)] and I was immediately told I had to go on dialysis,”* she wrote.

Others also reported ESRD presenting suddenly in adulthood. *“I was diagnosed at the age of 28 and the next day I went into renal failure,”* another woman texted in during the meeting.

Other participants described a gradual decline in kidney function to ESRD, and to dialysis or an organ transplant. Most of these had PH1, but at least a couple had PH2.

One of the zoom panelists, a 56-year-old man with PH2 said that despite remaining fairly stable with only one kidney for 20 years, eventually *“my remaining kidney was showing renal calculi again. And despite lithotripsy to break up the stones, which unfortunately, was unsuccessful due to their position, my renal function declined very quickly, and I had to receive emergency peritoneal dialysis to save my life. The next few months were a very traumatic time.”* After a kidney transplant, he did well for a time, *“but at the age of 47,”* he said, *“I was faced with end stage renal failure again.”*

TOPIC 1

3. Pain in body

“He has a constant level of pain that is never ending.”

Almost one quarter of the respondents, (24%) selected pain, often “*extreme pain episodes*” as the one of the top three most impactful symptoms of PH. However, it was one of the most mentioned symptoms during the discussion. Most commonly, the pain was due to having or passing kidney stones: “*The worst symptom was the pain of the kidney stones,*” wrote the woman who had ESRD at 28 years of age.

Descriptions of the pain ranged widely from “*common back pain,*” and “*considerable flank pain,*” One woman described “*a stabbing or hollow medium heavy pain. This type of pain usually lasts a few minutes but can return a number of times per day. [It] impacts my daily living and quality of life.*” Others described variations on “*severe burning pain.*”

“*Each time I drove over a bump in the road, I screamed out loud. I was admitted [to the hospital and] given intense pain medication,*” said one panelist with PH1. After a major surgery, she required two more hospitalizations since she “*had to pass stones.... The pain nearly made me pass out.*”

One mother described how her son with PH3 fainted from the pain of passing a stone. “*He said he felt some pain. We had him lie down, drink some water. And all of a sudden, he went white, and his eyes rolled to the back of his head. He went limp. He was out cold. We couldn’t get him up. We called 911 and they took him by ambulance to the hospital with lots of inconclusive tests to follow.*” Then the doctors found “*one less stone on ultrasound,*” and concluded “*he experienced traumatic pain and his body shut down.*”

One of the second zoom panelists, a 67-year-old woman with PH3 describing multiple episodes of acute pain that would come on without warning: “*I would just suddenly be in agony and I don’t even realize I have a stone. There’s nothing you can do except run for a doctor because you just can’t do anything else.*”

One mother described how her daughter with PH3, would “*experience pain episodes every day in school, and often would typically only make it about a half a day before the nurse would call and say that she needed to be picked up.*” Often this pain would make her vomit—and others had similar observations:

A phone caller with PH1 described “*severe kidney stone pain that would cause nausea and vomiting. It’s very, very intense and... there’s almost no medication that can treat it.*”

Others described having constant or recurring their entire lives. This included the young man with PH3 who said that during childhood, he was “*suffering from so much pain*” and that he had “*similar pain... throughout my life.*” A septuagenarian man who called in said “*he first started having a lot of kidney pain at the age of 14. Often a lot of pain, but I learned to live with the pain.*”

Some parents described the horror that their children with PH must have been in pain in infancy. One panelist said that there would be episodes her daughter with PH2 “*cried and moaned all day. This was one of my worst memories, as I now know what kind of pain she was in.*”

The mother of a boy with PH3 who wrote, “*he began having pain at 17 months but wasn’t yet talking so he couldn’t communicate what was wrong. He would just lay on the ground and cry and hit his penis.*”

TOPIC 1

"My daughter was diagnosed with PH 2 at age [year] after months of vomiting seizures and intense pain," one of the topic 2 panelists said.

Some of the pain participants described was more generalized, *"occasional joint pain,"* or due to other oxalosis symptoms, such as bone-related issues or was mixed with kidney stone-related pain. One mother described the tremendous pain her 12-year-old son with PH1 endured over the years. *"At the age of six, [he] began to wake up in the middle of the night with severe headaches,"* due to pressure on the brain caused by oxalosis. Later, she said *"he began to complain of severe stomach pains"* due to a huge stone that required surgical removal, and then just weeks later, *"[he] writhed in pain and in total hysteria,"* due to complications involving calcification of his first stent.

"Our fears include any pains, back pain, belly pain, or groin, and/or fevers that warrant a call or trip to our ER, which I do have those numbers on speed dial. I want to share that our life with PH is filled with constant pain," said the mother of two boys with PH2.

Finally, another caregiver described how after kidney failure and dialysis, there could be extreme and unbearable pain due to the cumulative damage wrought upon the body by PH and dialysis over the years, with broken bones and other injuries to an increasingly frail body: *"He hurt. He couldn't sleep. He'd cry from the pain,"* said the mother who held her 25-year-old son as he died from PH1. *"It was just constantly in and out of the hospital and pain. He suffered a lot of pain. That's the worst part, watching it."*

4. Anxiety or depression

"About a year ago roughly, [my teenage daughter] started suffering with extreme suicidal issues she started expressing to the social workers at the ERs when we would go. Her comment was that she doesn't want to wait to die. She feels like she never knows what's going to happen in surgery."

Approximately 23% of the polling participants indicated that the psychological and emotion impact of PH, symptoms such as anxiety or depression, were one of the top three most impactful symptoms.

As one of the zoom panelists, a 40-year-old woman with PH1, said she selected anxiety and depression as one of the top three impactful symptoms *"because of the unpredictability of the disease and the inevitability of disease progression."*

"The most debilitating thing growing up was just the psychiatric aspect to it. There wasn't a day that went by when I was in high school and college and didn't think about PH and how it could affect my life and maybe need a transplant, and those things are so scary," said one young man with PH1.

Another young man said he was so traumatized by severe pain (described above) that *"the worry of having"* a recurrence of intense *"kidney stone pain"* was something that was with him *"from day to day."*

"PH is more than a kidney stone disease. It impacts not only my body, but also my mind because each day it threatens to take away my future," said one of the panelists, a woman in her early 30's with PH1.

Another woman with PH1 wrote, *"I felt I was on a dark path and I started raving about life and thinking that I did not have much time left to live. Many times, I was depressed, but hid."*

TOPIC 1

“Our 6-year-old recently said to me when she went to do an MRI, ‘Mom, is this my life now? Do I always have to go to the hospital if I have the slightest pain and maybe stay there as well?’” wrote one mother.

Some spoke of the anguish of enduring ESRD and having to go on dialysis.

“After he started dialysis 6 hours a day, 6 days a week, [he] told me, ‘Mom, that’s it, I can’t wait for this transplant, I can’t live this way,’” the mother on one boy with PH1 who eventually passed away wrote.

Others spoke about the mental health impact of growing up wanting to hide their illness, when they *“looked completely normal outside”* but had a life-threatening rare disease. *“As a young child, I often questioned why I was the one in a million to be diagnosed with this rare condition,”* said the 24-year-old panelist with PH. *“The emotional toll of trying to explain PH to my peers only made the suffering worse.”*

One panelist with PH1 described *“coming home in tears because I was the only person in school with a water bottle on her desk. My mom sent separate treats to birthday parties because a low oxalate diet was required and, FYI, chocolate is not low oxalate. By the time I was a teenager, I was tired of being different.”*

Many of the caregivers also noted their own anxiety: *“We live with fear daily and wonder what will happen next. Recently, I noticed how I always make sure to have a full tank in the car because I never know when the next emergency will occur,”* one mother wrote.

Another woman who called in noted that *“there are so many unknowns with PH3,”* and said that her family not only had anxiety *“for our future”* but for *“future generations to come.”*

5. Urinary tract infections/pain when urinating

“I awoke in the middle of the night with the urgency to use the restroom and extreme pain when I did. I received a prescription for a UTI. With no reprieve for my symptoms, I found myself lying on the floor of my apartment, on the phone with my parents, who told me, ‘you have to go to the hospital now.’ I was... told my antibiotics were wrongly prescribed. I now had a very serious kidney infection. I was treated with IV antibiotics and sent home only to return days later with the same terrible symptoms, nausea, fever, chills, abdominal pain. This pattern continued for several weeks until I was septic.”

Selected by 22% as one of the top three most impactful symptoms, UTIs are often the first complication of PH, and because they often lead to a hospital visit, may be the first diagnosis some children with PH receive. The severity and refractory nature of the UTIs often lead to an eventual diagnosis with PH:

“Shortly after I was born, I had a fever and a urinary tract infection,” said the 24-year-old man with PH3.

“The doctors at our local hospital diagnosed her with a UTI. We didn’t think anything of it as we have dealt with our children having UTI’s in the past, but this started to get worrisome when she had her second and third and fourth UTI in a span of two months,” said the mother of the 4-year-old girl subsequently diagnosed with PH2.

TOPIC 1

One father on the first zoom panel said his daughter was diagnosed with PH3 when she was “an infant at around 3 months of age. She first had a urinary tract infection, which we thought was just going to be ordinary course type of thing. And then we learned that she has something called hydronephrosis, which effectively is when your kidneys swell because you can’t void the urine. And so, of course, the doctors [were] looking at that, that was something that is incredibly not typical for a 3-month-old child,” he said.

Another mother to a young girl with PH3 who called in said that her daughter “first showed her symptoms at age 3. However, the symptoms, which was a UTI to begin with, was found to be from urine reflux.”

[Our daughter] was seven months old in the fall of 2014, when she was hospitalized for a week with a severe UTI. Recognizing the severity of her infection and questioning why a baby would have a UTI and show so many shadows on an ultrasound, we were immediately referred to see a urologist. It took a year to confirm that [she] in fact, had PH3, the rarest type of a rare disease,” said another panelist.

Some of the pain described earlier may have been associated with urinary tract infections, or at least with blockages, but a few participants also noted pain upon urination or due to UTIs explicitly.

The 40-year-old woman with PH1 *on the first zoom panel selected “pain while urinating” as her second most impactful symptom. “It’s actually both pain and difficulty urinating, and that’s been something that’s changed over the years.”* At times when she had particularly large stones, there was “a lot more pain... maybe seven months of consistent pain whenever going to the bathroom.”

The mother of two boys with PH2 described how her first son to be diagnosed had symptoms that included “the pain that comes with a UTI, which also presented with a lack of urination and belly pain.”

6. Nausea or vomiting

“We rushed [her] to the hospital at four months old due to her uncontrollably vomiting and having diarrhea at the same time. [Then] just before her first birthday, she got very sick. One day she completely stopped nursing. She didn’t have a single wet diaper. She vomited all she had left in her... This past week, she had a stomachache and a fever. This happens every few months where bouts of vomiting and fever happen.”

Approximately 13% selected nausea and vomiting as one of the top three most impactful symptoms. (Note that nausea/vomiting due to a side effect of treatment is covered in the Topic 2 section.)

“Nausea is another huge thing for her. She’ll just run out of class and start throwing up,” said the mother of one teenage girl with PH3. As noted earlier, this was due to pain, and this was mentioned by others as well: *“The vomiting, and that’s a new sign. This has only been going on in the past year, that I would actually vomit with the pain,”* said the 67-year-old woman with PH3.

Vomiting is the presenting symptom for some, as one mother to one infant with PH2 described “months of vomiting seizures.” One infant girl with diagnosed with PH1 when she was taken to the hospital “after vomiting blood” according to her father, who served on the second zoom panel.

TOPIC 1

7. Blood in the urine (hematuria)

“Blood was in [my daughter’s] urine and she was in pain. Sure enough, after a visit to Children’s Hospital, our strong girl had a stone that was passing.”

Blood in the urine was selected as one of the top three impactful symptoms by 11% of the polling participants, usually due to passing crystals or stones.

“He actually was diagnosed when he was seven months old. He was playing one day, and we looked and there was blood in his diaper,” said the mother of the man who died of PH1 in his twenties.

“[My son], now 9 [years old], has had sharp crystals in his urine, and when he sees blood, we know it’s time to increase his fluids,” said the mother of two children with PH2.

“One summer at camp, I began noticing blood in my urine,” said the 24-year-old panelist with PH3, who described how he proceeded to pass the stone without telling anyone.

One caregiver to a teenager with PH1, described how her daughter’s *“Coca-Cola colored urine episodes.”* A mother to young boy with PH3 wrote that without *“enough hydration, his urine will become tea colored.”*

8. Failure to thrive in infancy

“He suffered from failure to thrive and was only in the third percentile for growth and development. He suffers from renal tubular acidosis, which aided in his inability to gain weight.”

A similar percentage of respondents (11%) selected failure to thrive in infancy as one of the most impactful symptoms. A couple parents mentioned this during their presentations. One was father to a 7-year-old PH1 girl with PH1, who said *“We were diagnosed at six months with a failure to thrive and taking her repeatedly to pediatricians and emergency rooms.”*

9. Fatigue

“He is quick to fatigue and lacks the stamina to play and be a normal 12-year-old boy.”

Another 10% of the respondents selected fatigue as one of the three most impactful symptoms. The fatigue may be linked to other symptoms.

“My kidney sometimes swells, and I generally have low energy and feel crummy for about a week. It can really slow me down, and I’ve had to take some days off of work to rest. I have other days where my kidneys, particularly my left side, just feels off and I have some discomfort and feel more worn out,” wrote one 31-year-old woman with PH1.

The father of a 9-year-old girl with PH3 mentioned this was a presenting symptom in his child: *“At 3 months old, [she] had... fatigue... just was incredibly lethargic,”* he said.

“She’s very tired, which affects her state of mind and wellbeing,” one mother wrote a daughter with PH1.

The mother of a 12 year old girl with PH3 said that her child has this symptom now: *“She sleeps an extreme amount. I mean, I thought for a while it was like teenage years or something, but no, no. She just would sleep for days if she could.”*

TOPIC 1

10. Heart or eye problems, and bone fractures

“My 13-year-old girl is also dealing with the effects of permanent significant oxalate deposits in the retinas or her eyes. No glasses or operation will ever fix the damage that has been done due to the overproduction of oxalate she experienced at a young age. She now has to sit at the front of the classroom at school and read within large print. She has to keep finding new ways to compensate for her vision loss. Doctors are unsure if she will ever qualify for a driver’s license.”

As they all caused by oxalosis, it is worth noting that “heart or eye problems” and “bone fractures” were selected by the same percentage of respondents (7%) as one of the top three symptoms that had most impact on their lives. (Note that dialysis-related effects on the heart and bones are covered in Topic 2.)

A few parents spoke about loss of vision due to “stones in their child’s eyes on their optic nerve.”

“That is something that my daughter is currently suffering from and I’ve been told that there is no operation to correct it and that it will probably eventually take her vision,” said one of the zoom panelists, whose teenage daughter has PH3. *“I feel like it has a huge effect on her. Like my daughter’s getting ready to go in for another percutaneous surgery and she can’t be laid flat anymore because of the stones on her optic nerves that may make her start stroking out during surgery.”*

The first topic 1 panelist mentioned that her 12-year-old with PH1 “has broken many bones due to the brittle nature of them.”

“She has broken maybe eight bones and will have eye damage for the rest of her life,” one mother of a daughter with PH1 who has had organ transplants. The damage occurred while she was still a toddler.

One woman with PH1 had bone problems though she eventually had kidney transplants, *“my joints and bones went through a lot until I started getting the oxalate out of my body. I fractured a rib when I was about 22 and will get a stress fracture or arthritis if I ramp up my activity too quickly,”* she wrote.

For others, the oxalate has caused life-threatening heart problems such as cardiomyopathy. *“At 14 months old, [he] received his first pacemaker. We’ve had two more since then. As a result of low heart rate, lethargy, and blue episodes from calcium deposits in [his heart],”* said the mother of one boy with PH1.

Others and chills/fever or infections other than urinary

Approximately 10 (12%) respondents selected some other notable symptoms as being in the top three great impacts. During the discussion, caregivers mentioned a number of these.

“Oxalate is still detected in blood tests, and his teeth are weaker than other places, and it seems that it is affecting the jaw and permanent teeth,” wrote the mother of a 6-year-old boy with PH1, despite his having a liver transplant.

The 12-year-old boy with PH1 had *“two brain malformations because of primary hyperoxaluria. His soft spots fused together too soon from the overproduction in oxalate. As a result, he had to have a cranial vault to alleviate the increased pressure on his brain,”* said his mother.

TOPIC 1

One mother mentioned her son with PH1 had episodes of extremely high blood pressure due to a urinary obstruction, “with systolic blood pressures in the 210 range, and diastolic pressures in the 110 range.”

Two respondents (2%) selected fevers or infections other than urinary as one of the top three most impactful symptoms. Some of these were related to peritoneal dialysis and are covered in Topic 2. Similarly, skin ulcers were also mentioned, although these may have been dialysis related.

Activities of daily life that one is less able or unable as fully due to PH

The impact of the disease is not limited to its symptoms, but also includes how it keeps one from living one’s life to the fullest or achieving one full potential. Consequently, another multiple choice polling question asked participants to select the top three specific activities of daily life most important to them that they or their child were less able or unable to do because of PH. Throughout the session, participants described how disruptive kidney stones and surgeries, frequent clinic visits, and the need for constant super hydration as a preventive are to every aspect of their daily routine and their goals in life.

A high and equal proportion (72%) of polling participants indicated that the impact of PH on “attending school or work,” and the limits it placed on ‘going out, socializing or traveling” were among the top three most significant impacts PH had on their own or their children’s lives. After these two selections, polling participants focused on other activities that bring joy and meaning to life, based upon their own interests. Note that although preventive and post-ESRD treatments have profound impact on the daily lives of people with PH, this report explores their impact in the Topic 2 section.

1. Attending school or working

“In first grade, [he] was not allowed to go on a field trip without me because his medical condition was so complex, they were admittedly scared of him. That school year, he missed 108 days of school due to his disease, which is a pattern for him every year. He misses a significant amount of school. Do you have any idea of the impact that has on the coming years for cumulative education? He has gaps by no fault of his own.”

For children, the impact of PH on schooling can be tremendous—beginning with the time missed from classes.

“The greatest limitations I felt was, during my junior year of high school, I missed quite a bit of school... because I just wasn’t feeling good with the pain, until after that first surgery,” said a man with PH1 who called in his comments.

“I am worried about school and having to miss school for doctor appoints and also having people ask about where I was. Also missing some school in the morning when I have to do bloodwork,” one 13-year-old girl with PH1 wrote.

The mother of a teenaged girl with PH3 said that school was the activity had most been impacted by PH: *“She’s just always so sick or in so much pain. So many appointments. Her freshman year, she averaged going to school one day a week. She definitely missed way more than she attended. She tends to fall asleep in class and has extreme pain episodes. She’d typically only make it about a half a day before the nurse would call and say that she needed to be picked up.”*

TOPIC 1

Other caregivers reported that either the symptoms or management of PH have reduced how their experience at school. The mother of a 13-year-old girl with PH1-related vision problem said *“she now has to sit at the front of the classroom at school and read within large print. She has to keep finding new ways to compensate for her vision loss.”*

According to one mother, one of the challenges at school was that people may not believe that children with PH are ill: *“It was really difficult when he was little and he looked completely normal, was physically very active. People don’t recognize that there really is an issue. He really has a health issue. He really is in pain; he really needs to miss school. I remember, teachers, if he missed a class, it was like, really? Does he have another kidney stone?”*

“Even with a milder form of PH,” one mother wrote, “every appointment with a specialist is on a weekday, every scheduled surgery is on a weekday. And because we travel to another state, we need to take off of school and work for days at a time. I even had an attendance officer from the school threaten to call child services on me when my daughter was in Pre-K, because she had missed so much school even though we had notes from doctors and hospitals.”

One young man with PH3 said described the psychological impact: *“In addition to taking multiple days off of school for my biannual trip to the clinic, everything began to seem less and less normal.”*

Meanwhile, a mother on the topic 2 panel said that although they had worked *“closely with guidance counselors, school nurses, and teachers in the building to ensure that everyone’s aware”* that her daughter and son have PH3, *“like most kids with a disorder, [he] and [she] don’t want to be called out or feel differently about the disorder.”*

As several participants mentioned, the PH-related disruptions experienced in grade and high school continue as they grow older and affects their work life.

“I’m currently living on my own and working in an industry that does not look lightly on taking days off from work,” said the 24-year-old panelist with PH3. *“Within the first six months on the job, I began experiencing a similar pain I had throughout my life... I would need a bilateral ureterostomy to remove eight kidney stones... I was forced to take a week off from work to recover from the surgery and explained to my bosses why I could not fulfill the duties of my job.”*

One zoom panelist described how knowing that her kidney stones could require surgery at any time has had a profound effect on her career choice: *“My childhood dream was to be a diplomat and I was denied the medical clearance to take that position because of the primary hyperoxaluria and the frequency of the surgeries from the state department’s perspective.”*

Another woman with PH1 wrote, *“my life has been impacted with regards to... career choices. I haven’t taken any risks with my career or attempted ventures that interest me because the health insurance is so vital. To maintain health insurance, I’ve worked for the same company for 21 years.”*

TOPIC 1

2. Going out, socializing, traveling

“He has missed many sleepovers and birthday parties. Who wants to send their kid to a sleep over when the parents are unsure of how to handle him if he begins to pass a stone or has another medical issue related to his disorder? What parent wants the responsibility of a kid who has these issues when it’s not yours? What kid feels comfortable enough to tell somebody else’s parents, ‘I’m peeing blood. I’m in pain and I need my mom to come and pick me up. He was not allowed to go on a field trip without me because his medical condition was so complex, they were admittedly scared of him.’”

For many children with PH, missing school, or just being different was the start of socialization problems.

“I missed school so often that I found it difficult to make and maintain friendships,” one adult woman with PH1 wrote.

“Making friends has had a severe impact on [her]. Bullying was a big issue in school. She felt different,” the mother of a daughter with PH1 wrote.

“She was in the Girl Scouts and they would do things like go hiking or go overnight camping. And that was just like a no-no. I was so worried about her overdoing it and just needing the extra water and what if I wasn’t around? And then how would they deal with this? And we just weren’t prepared for that...” said one caller whose 9-year-old daughter has PH3.

“Should your child go to that party where some of the kids might be sick and you might be exposed in one way or another. It always informs your judgment and potential fears of what might come to pass. Knowing that just literally one screw up, one dehydration event could lead to a stone event, which in turn could mean a kidney stone, a blockage, a surgery, and so this constant sword of Damocles hanging over your head based on those really bad outcomes,” said one father of two children with PH3. He added that there have been “multiple times in the social realm” that their limited his children’s social lives. *“This was pre-COVID... one of [my 9 year old daughter’s] friends had a birthday party and the extreme caution that we felt like we had to take. Choosing to remove her from that social situation and avoid all those bad things, those are real things that happen all the time.”*

“I was scared to death to let them go for sleepovers,” said the mother of twin boys with PH2. *“Especially, there’s no way they were going if I didn’t know the parents at all. Worried that they would get their amount of drinking that they needed.”*

“We no longer have holidays abroad because we don’t know what medical facilities are available, but we do know what kind of care our children need in an emergency. And this knowledge and fear control our lives,” wrote one mother of two children with PH1.

One of the panelists, the mother of two children with PH1 echoed these concerns: *“We rarely traveled. But when we did, we always stayed near to hospital and we carried her medical information with us since most people did not know what PH one was or how to treat it.”*

TOPIC 1

3. Participating in sports, and other activities or hobbies

“My boys are required to drink three liters of water a day. If they exercise, play sports or do anything out of the ordinary, that water requirement increases. We also had multiple instances where they were at friend’s houses or in the middle of a sporting event, when the pain strikes.”

The impact of PH upon participating in sports was highlighted by 29% as one of the top three impacts of PH on daily life, while another 17% of the polling participants

“Should your child participate in sports? Is it going to be okay to be outside playing tennis in warm weather and things? Some parents come out at different ends of that spectrum,” said the father of two children with PH2, illustrating the doubts that plague parents of children with PH of all types. *“We’ve kind of steered [my older daughter] towards those activities where we feel like she’ll be much safer and avoid those bigger issues and just not putting her in that position.”*

“He has had to forgo sports, which he would love to participate in,” said the mother of a 12-year-old boy with PH1.

Other parents have tried to make compromises so that their children do not feel left out of activities.

“We always try to much as possible participate in what we can. It might be modified. Like a hike or something, we might not just do the full hike. We do part of the hike,” said the mother of a young girl and boy with PH2.

“We also had multiple instances where they were at friend’s houses or in the middle of a sporting event, when the pain strikes,” said the mother of two boys with PH2.

“We have allowed our kids to participate in the sports, but you will often hear us from the sidelines, Drink! You got to drink when you’re on the bench!!” said the mother of twin boys with PH2.

Others said that they would not allow their PH to prevent them from participating in sports, but that afterwards, they always had to watch for other symptoms that might worsen as a result of the activity.

“I was very active, playing soccer—drinking lots of water—growing up... I was a very hyperactive kid. But it was very unfortunate. I always had to watch out after a lot of physical activity. If there’s any kidney stones that were sitting in my kidneys, I had to be careful. They could always move around and then before you know it, one of them could move and get stuck in your ureter and then that would be a cause for treatment,” said one man with PH1 who called into the meeting.

“She doesn’t get to participate in sports like, I hate to say, ‘normal kids,’ but she doesn’t,” said one of the zoom panelists about her daughter with PH3. *“Anything that takes the chance of her landing on her back or causing any damage to her kidney is a definite no for us. She’s huge in cheerleading but is limited on what she’s allowed to do because she can’t take any chances of damage to the kidneys.”*

TOPIC 1

4. Participating in family care

"I have anxiety about my daily routines but also about my future. I hope to expand my life roles to include those of wife and maybe even mother someday. However, I could become very sick before my wedding or worst of all, I could discover that my future children have PH too. My heart sinks each time I consider that real possibility."

Having a family and participate in caring duties was selected by 19% of the polling participants. Several adult meeting participants living with PH expressed concerns about how their declining health might affect their children repeatedly in pain, needing multiple surgeries and having little idea what the future might bring.

One of the panelists, a woman of about 40 with PH1 said that PH has affected her plans to have a family: *"When my husband and I started to want to start a family, I had a miscarriage and then the urologists said that I had to delay starting the family in order to process some of the stones that were had been stable in my kidneys, but the fear there was that I would have trouble during the pregnancy. So again, it's this negotiation with the urologist who has to care for me if something were to happen during the pregnancy."*

"Some years ago, my husband and I decided not to have kids. The decision is directly related to having PH1. Because my future is uncertain, along with the complications of carrying a child in my particular circumstances after transplant, we decided to not risk it. Burdening him with having to take care of both me and a child worried me too much," one woman wrote.

For some women, the possibility of passing on PH has been a factor in whether or not they become pregnant, or continue their pregnancy. One woman who had been diagnosed with PH1 when she was 18 months old wrote that *"My husband and I undertook genetic testing prior to planning a family because I couldn't fathom passing on my disease to another person."* Another woman wrote, *"I had to abort 2 pregnancies at 13 weeks since both of the babies inherited both mutations... hard choices to make. I do not wish any child the pain that my daughter had to go through."*

For others, dealing with their PH has interfered with their own family caregiving. One 67-year-old woman with PH3 described how, rather than caring for her husband whose *"been very unwell, I actually have to drag him out of bed at 7:00 in the morning to take me to the emergency room."*

5. Activities of daily living

Less commonly, polling respondents mentioned that they were unable or less able to perform activities of daily living, such as attending to personal hygiene (9%), performing household tasks (5%) or driving a vehicle (3%).

TOPIC 1

Greatest worries as one grows older with PH

The final polling question of session one asked participants to select up to three fears or worries related to PH that they were most concerned about, or abilities that they feared they or their child might lose as they grew older with PH.

6. The stress of not knowing how the disease will progress

“There’s always that constant stress and worry that, despite drinking 3-4 liters a day, being careful with diet, being careful with activity, being compliant with medication, that things could go very wrong.”

The most common worry, selected by 61% of the poll respondents across types, was the uncertainty about what further damage PH might cause in their lives, not knowing how they or their child might progress.

“The fear: ‘Am I going to get smacked with a kidney stone tomorrow?’ I missed my sister’s wedding,” one zoom panelist with PH1 said. “I had to suffer through exams when I was in college in law school, worrying about, “Am I going to get through without it all of a sudden interrupting those kinds of things?”

Many of the fears were expressed by caregivers worried about their child’s future clinical course, and the strain that it put on the caregivers and other family member lives.

“All the anxiety as a parent about the future and what may come to pass when there’s really no very good natural history of PH3 in particular. We don’t know a lot about the disease and the progression that it’s going to take,” said the father of a 9-year-old girl with PH3. This concern was echoed by a father of a 13-year-old boy with PH3, who wrote his “main concern is the unknown prognosis and future.”

After her daughter almost died of PH1 at the age of 2 years, one mother wrote “we live in constant fear that something could go wrong again with our daughter or that she will reject her liver.”

“For us, there will always be the lingering question about the slow, but certain impact of oxalosis and the invisible attack on its victims over time,” said the mother of two young children with PH2.

“We are constantly watching for signs and symptoms that something has changed, knowing that it can do that very rapidly,” said another mother of a child with PH2, who called in to share her experiences.

“It is also very challenging to do everything in your ability to get the best possible care for your child and stay on top of their care being very proactive and still watch your child decline despite everyone’s best efforts,” wrote one mother of two children with PH1.

As already mentioned, another mother worried the emotional toll of PH and many surgeries had had on her daughter might lead her to take her own life. *“That’s a huge fear for me as a mom. Now I’m afraid to leave her alone and really watch who she’s around and what their influence is and things like that.”*

TOPIC 1

2. Dying at a younger age

“One of the things that bothered me quite a bit was with the death of my sister, I had the perception, I would not live to be very old. And I had to deal with that as I entered into marriage and told my wife-to-be, I may not live to be very many years old.”

The second most commonly selected option for top three greatest worries among those with PH, chosen by 45% polling respondents, was that they would die at an early age—though only a few spoke about it.

One adult woman with PH1 wrote that when she was a child, *“my parents were told I would not live to see my teenage years.”*

According to the mother of a teenage girl with PH1, she was considering suicide at least in part, due to her fear that she might die on the operating table when her next kidney stone had to be removed.

One father said that his adult son with PH3 needed therapy for the mental anxiety experienced by when he was younger. *“He didn’t want to go to sleep at night because he thought he wouldn’t wake up because he was going to die,”* he said.

3. Worsening of severity and frequency of symptoms, and needing dialysis

“Even if he has a kidney transplant now, I am concerned that the remaining oxalate in his body will damage his kidneys.”

Roughly 39% of polling respondents selected worsening of severity and frequency of symptoms (essentially, disease progression) as one of their top three greatest worries as they grow older with PH. Note that this may overlapped with some other worries such as fears of unexpected emergency visits or surgeries for stones, which was selected by 8%. Additionally, 35% selected needing dialysis, which could be the outcome for disease progression for those with more severe cases of PH.

As one man with PH1 wrote *“The worry about future symptoms can be very debilitating. It can be hard at times to suppress those fears. Fear of the next stone or progressive decline in kidney function resulting in the need for dialysis or a transplant. I used to think about those possibilities every single day.”*

“Last year, I gave birth to my son. I could not love another person more. Now as a mom, I worry that my good health will not continue forever. I worry that I won’t get to watch him grow up. I worry that he will have to see me in pain and suffering,” one woman recently diagnosed with PH wrote.

“Once she gets older and goes to school and is required to drink water orally during the day, will she be susceptible to producing more stones? Will she eventually need a liver and kidney transplant? This disease does not have a one size fits all plan,” said the mother of a 4-year-old girl with PH2.”

One woman in her late 50’s with PH1 how had a *“double kidney transplant”* in 2019, without a liver transplant saw her kidney function improve but then *“gradually deteriorate to as low as 13% but over a year on it is now 18% so my worry would be that my function deteriorates further.”*

TOPIC 1

4. Not being able to live as I want to

“My life has been impacted with regards to where to live – I need to make sure I’m near a good medical system – and career choices.”

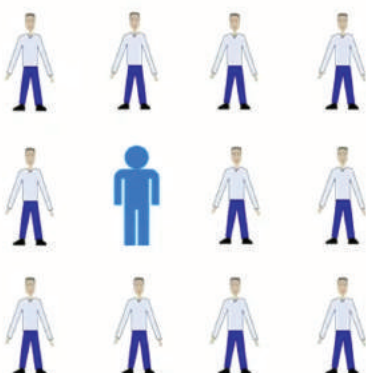
Approximately 31% of the polling participants selected not being able to live as they wanted to as being one of their top three fears as they grow older. As many noted, where they live (or possibly retire) is dictated by access to specialized care, and being able to make career changes was limited by the ability to maintain their insurance.

5. Not being able to support oneself/work/becoming a burden

The remaining categories could be seen as fears of loss of financial and physical independence, with 19% selecting “becoming a burden to my family,” 16% selected “not knowing if I can support myself/family financially,” and 3% selecting “not having energy to go to work.” Some of these fears were alluded to some comments sent in after the meeting, including the woman who chose not to risk having child due to fears of a poor outcome where her husband would wind up having to care for both of them, while the father mentioned his two children and his career and said, *“The rise of blood creatinine is terrifying me.”*

How many people have primary hyperoxaluria?

Kidney Stones



Primary Hyperoxaluria

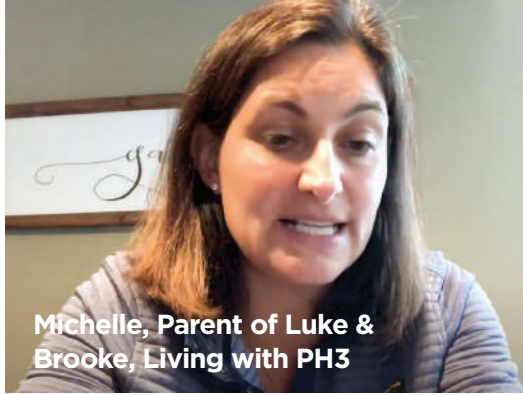


1 to 3 per million people

	Population	Kidney Stones	Primary Hyperoxaluria
Boston	4,309,000	360,000	4-13
Phoenix	5,050,500	419,000	5-15
San Francisco	3,314,000	275,000	3-10



Beth, Living with PH1



Michelle, Parent of Luke & Brooke, Living with PH3



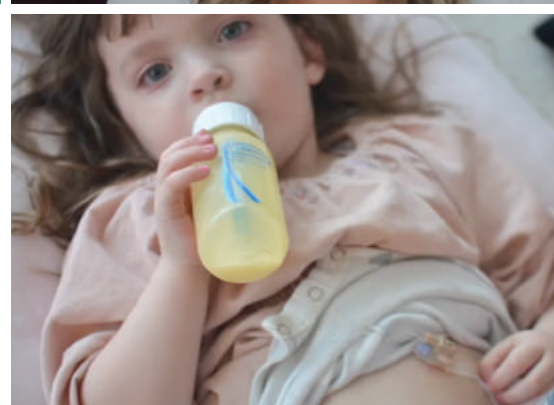
Carl & Jennifer, Parents of Jackson & Harrison, Living with PH2



Kristi, Parent of Molly & Matthew, Living with PH1



Sara, Parent of Jovanna & Logan, Living with PH2



Neil, Living with PH2



TOPIC 2

Patient and caregiver perspectives on treatment/management of PH

The second half of the meeting explored the medications and support therapeutic approaches individuals living with PH and their caregivers use to try to manage their symptoms and prevent progression of the disorder. This included how they try to reduce oxalate levels, how they try to prevent kidney stones from developing, how they manage them? How do people deal with pain and other complications when they occur? What has been their experience with dialysis and organ transplantation? Which of their needs remain unmet? What do they most want from new treatments, and how would they weigh risks versus the potential benefits of new treatments?

The following panel testimonies led off the session:

- *“My 17-year-old daughter and 9-year-old son have PH 1,”* said the first panelist. As a child, her daughter passed some stones on her own, *“but some were too large and needed surgery,”* usually a ureterostomy with a temporary stent placement. Years later, the mother said pregnancy screening revealed her son would also have PH1. At 28 days of age, an ultrasound showed his kidneys were already *“loaded with stones,”* and 4 months later, he went into ESRD. He went on dialysis and had a G-tube placed to help give medication and nutrition. His oxalate levels were so high that they had to give an adult kidney and liver transplant, but they first needed to use a catheter and fluids to stretch out his abdomen. He’s had many challenges since his transplant. *“We knew this was a possibility for [our daughter],”* said her mother and they looked for other options. Eventually she ended up on dialysis, but has since joined a research study which made it possible to cut down her dialysis frequency.
- *“When it comes to treatment for PH and oxalosis, I’ve been there done that,”* said the next panelist, a 56-year-old man with PH2. He said that for the 15 years of his life, they were unsure what was causing his kidney problems, but with a high fluid intake, and magnesium hydroxide, he said that he *“only needed two operations for kidney stones, plus a kidney removal.”* His remaining kidney was relatively stable *“on other medication, including different citrates”* for 20 years but then developed *“renal calculi.”* Lithotripsy to remove the stones was unsuccessful. He went into ESRD and needed to go on dialysis. He had a single kidney transplant and then *“was free to carry on as any normal person would”* but by the time he was 47 years old, he was again in ESRD, needing another kidney transplant. Over the years, he’s gained a wealth of experience with different dialysis techniques *“for oxalate removal.”* *“Despite this, the oxalosis continues to cause me many problems,”* so he eagerly participates in research for new treatments.
- *“Being the parent of a kid with even a moderate case of PH2 is waking up every day to kiss them and hand them a bottle of water at the same time,”* said the third panelist, mother to four children, two of whom have PH2. Her daughter was very sick in infancy, and required toxic antibiotics for UTIs and surgeries to remove 19 stones by the time she was 2 years old. When her son was then diagnosed at 1 month of age, *“I didn’t feel strong enough to watch another child go through this.”* She spoke of her constant struggle to keep her children hydrated, placing a G-tube and injecting fluids into her daughter until her stomach was full. Once when, after *“a cycle of vomiting and seizures,”* they rushed her daughter to the hospi-

TOPIC 2



Dr. Michelle Baum, MD

Co-Director, Kidney Stone Program: Attending Division of Nephrology;
Assistant Professor of pediatrics, Harvard Medical School

tal, “she was so dehydrated that it took 17 pokes, two hours and the life flight crew to eventually insert the IV into her foot. Her cries were soul piercing.” To keep up her son’s water intake, each night, she “would spend the last few hours of [my son’s] day offering bottle after bottle as he would begin to doze off.” She described how they have adjusted their children’s diets and other products to “help reduce the oxalates.” While she has fears about what next, her daughter has self-esteem issues because of the G-tube, “she sometimes feels broken and because of her disease, becomes sad,” she said.

- “When [my daughter] was seven months old, she was hospitalized for a week with a severe UTI,” said the next panelist. When an ultrasound showed “many shadows” she was referred to a specialist and eventually diagnosed with PH3. Her brother, three years older, had no symptoms at the time but an ultrasound found he had kidney stones. He was the boy previously described in this report who passed out from the traumatic pain of passing a stone. Both of her children take a manganate and a diuretic to keep the urine clean. The daughter also takes potassium citrate, but chokes on the large pills. “While they understand that these medications are a part of their daily routine, it’s always a worry,” however, “the hardest part was what I still to this day, call, excessive fluids,” she said.
- “I’m 16 years old. I was diagnosed with PH type 1 at age 8, when I presented with eight kidney stones,” said the final panelist, who allowed his mother to share the rest of his experience. “His first recognized kidney stone occurred when he was unable to urinate, as a stone was blocking his urethral meatus,” she said. He underwent his first extremely painful invasive surgery to remove it. Subsequent surgeries led to the placement of an adult size stent in his ureter that made it difficult to urinate without pain. Although he was able, with careful planning, to work his way up to drinking 3 liters of water a day, and he takes vitamin B6 and potassium citrate several times a day, his estimated glomerular filtration rate is under 60. He is now enrolled in a clinical trial of an experimental treatment that the family hopes will help him preserve his kidney function.

TOPIC 2

Before the facilitated discussion, which expanded upon the experience of the panelists, poll participants were asked to indicate all medical management and other therapeutic approaches for PH they were currently using. Figures 2.A and 2.B show the responses in the order in which they were selected.

Figure 2.A: Which of the following medical management approaches are you currently using for PH?

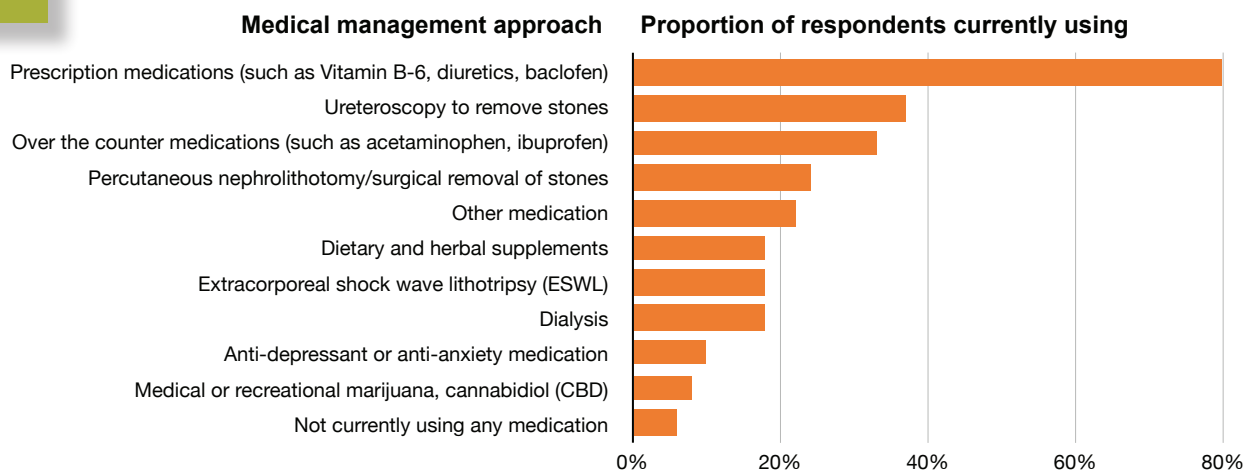
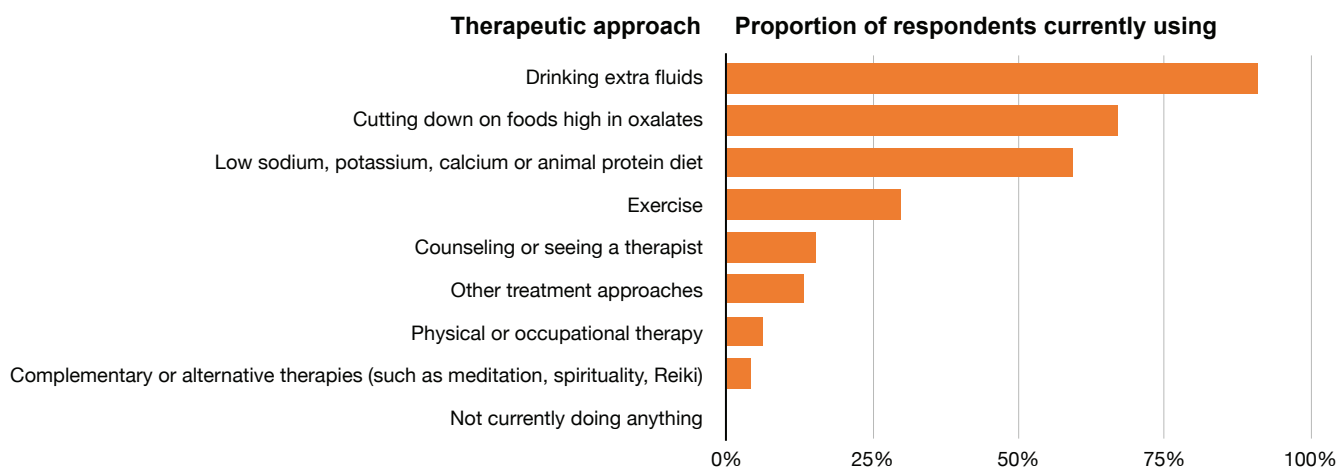


Figure 2.B Which of the following therapies are you currently using for PH?



TOPIC 2

While these responses provide a cross section of the medical and supportive care approaches participants were using at the time of the meeting, individuals with PH may require different types of therapies at different stages of their illness. It may therefore be useful to consider selections by their primary purpose in PH management. The most commonly used approaches, rarely used in isolation, are components of a preventive or secondary maintenance regimen to reduce oxalate in the body, whether by reducing its production, accumulation, or by diluting or expelling it before it can form stones and damage organs. Other treatments dealt with the direct outcome of the disease—removing kidney stones and providing a way for urine to be passed or voided. Less frequently utilized are the treatments of last resort required to deal the culmination of kidney disease progression—kidney failure and ESRD. The remaining choices can be viewed as therapies to mitigate other symptoms of the disease and/or complications of treatment, such as the nausea or unbearable pain, depression and anxiety, infections or nutritional deficiencies.

Two other polling questions asked participants about the effectiveness and drawbacks of their current regimen or treatment approach. More than half (54%) of the respondents indicated that their regimen had “*somewhat*” of an impact, 30% indicated that it helped to a great extent, while 14% selected “*very little*,” and 2%, “*not at all*.” Presumably, people perceive of their regimen as at least delaying progression of their condition, or else they would not adhere to it. However, when asked to select up to 3 drawbacks of their treatments, 40% responded that they were “*not very effective*” (other responses are discussed below).

The following section considers the benefits and downsides of different medical treatments and therapies at a more granular level, grouped together by the treatment purpose as described above.

Most commonly used preventive PH care components and their downsides

Virtually every person with PH uses treatments or therapies to try to reduce oxalate levels in the body and prevent stones, in most cases, a regimen or package of both medical and supportive therapies. These start with the most widespread activity, drinking “*an abundance of water*” and/or other liquids.

1. Drinking extra fluids

“He was able to get up to the initial three liter water drinking recommendations quickly. But drinking this amount of water every day is not easy. It took daily planning to help him reach his goals. If he struggled, we changed the water drinking plan to help him overcome the challenge.”

Drinking large volumes of fluid, usually at least 3, and in some cases, up to 6 liters a day to “*wash the excess oxalate out of [the] body*,” was chosen by 91% of the meeting participants as one of the top three therapeutic approaches to manage PH that were using. Perhaps the only meeting participants not currently drinking extra fluids were those on dialysis or who had had double organ (liver and kidney) transplants. For everyone else, “*knowing that just literally one screw up, one dehydration event could lead to a stone event*,” as father of a young girl with PH3 said, means that drinking extra fluids becomes “*a constant*,” an integral part of life with PH—one that daily life must be structured around.

TOPIC 2

"A typical day in our household is getting multiple drinks ready for the boys to take to school, 80 to 90 ounces a day," said the mother of twin boys with PH2 in a video played at the start of the second session of the meeting. "We have to drink..." one of her sons said, "every hour," his twin brother interjected, "milk in the morning," the first boy continued. "Then we have to drink... I drink lemonade. He likes apple juice." "Yeah, I like apple juice," the twin brother said in affirmation. "So, basically, we do that till the end of the day," continued the older brother. "And with dinner, we drink milk."

The challenges involved in maintaining what some called "hyperhydration," was mentioned as significant downside. "You have to plan all the drinks to take with you," said the mother of twin boys with PH2.

"It's tracking every ounce of water they drink because now they have to drink and it must start as soon as they wake up, because you know, if you get behind, it's hard to catch up," said the mother of a young girl and boy with PH2.

This becomes more difficult if when children and adults with PH engage in sports or exercise, because they need to take in even more water because of what they might sweat out.

"We have allowed our kids to participate in the sports, but you will often hear us from the sidelines, 'Drink! You got to drink when you're on the bench!!' My boys are required to drink 3 liters of water a day. If they exercise, play sports or do anything out of the ordinary, that water requirement increases," said the mother of two boys with PH2.

"When they play sports, they are likely to go through almost 48 ounces of water during a game," said the mother of a young boy and girl with PH3. "I feel like their body now craves the hydration."

It is also a tremendous challenge getting very young children to drink enough: "Getting a strong-willed child, like [my daughter], to drink average fluids is one thing, but having a target goal with a sippy cup and a toddler is another," said the mother of two children with PH3. In some cases, it simply is not possible to get a child to drink enough fluids, so some have surgeries to place a gastrostomy tube (G-tube) for fluids.

One mother described the placement of a G-tube to help her daughter, who has PH2, with hydration: "She gets over 2 liters of water through her G-tube daily." Another mother said her daughter with PH2 "had a G-tube placed so we could keep her hydrated by syringing water, into her little belly, every few hours. She would say, 'My tummy hurts, mommy. It's too full.' I recall worrying about water intoxication, but I was equally afraid of oxalosis and organ failure." But have been other drawbacks of this approach: "Because of her G-tube, [she] won't wear a two-piece swimsuit or do any activity that requires her to be on her stomach for fear her G-tube will catch on something and get pulled out. This has happened before. She doesn't like it when the tube is visible through her shirt."

Even the less invasive means of maintaining hyperhydration can make children with PH self-conscious.

"We bought every type of water bottle to convince me to drink water, the main treatment for PH. We experienced me coming home in tears because I was the only person in school with a water bottle on her desk," one woman with PH1 said, recalling her childhood.

TOPIC 2

"Every time she goes, even if she goes to a birthday party and she's dancing, she's got to carry that jug of water with her," said the mother of a daughter with PH3. "If they have a play date, she's carrying it around. But it's not the norm for a lot of kids; it is out of the ordinary."

"We had issues at the school where I had to get her a [Section] 504 because... she couldn't bring her water bottle to the gym class," said one caller said about her daughter with PH3, who also mentioned that, if her daughter had "a substitute teacher, several of them wouldn't let her use the bathroom often."

Which is perhaps the greatest drawback of hyperhydration: *"The constant need to urinate."* This was emphasized as one of the challenges of daily life with PH across types during the discussion, but it is really a complication of this preventive strategy.

"They need to go to the bathroom so often from all the fluid intake over the course of the day. Is there a bathroom that's accessible?" said the mother of twin boys with PH2, while another mother said her children with PH3 *"need frequent bathroom breaks because of the water and the volume that they intake."*

"[They] frequently have the urge to urinate, which interrupts their days at school; and when out playing with their friends, embarrassment when the urge to urinate comes over and over, and they end up going in their pants. That's hard on kids. My five-year-old is still not fully potty trained because she drinks so much water during the day and at night. So that means no sleepovers. In addition, with her recurring UTIs, her bladder hasn't been trained properly to let her know when it really is time to go. This is a struggle she deals with on a daily basis," wrote the mother of three children with PH1.

"Bathroom trips... affect their learning time in the classroom," said a mother a boy and girl with PH2. Taking lengthy exams, can be a challenge for children and people with PH and the need to urinate: *"I drink almost 6 liters of water a day because of PH1. Because I needed to use the toilet during a 3 hour exam, they forced me to redo the exam even though a teacher came with me to the toilet,"* one man wrote.

It also affects the ability to travel and go out: *"When we take road trips, we would leave in the middle of the night. Otherwise, you are stopping so much because they do need to go to the bathroom so often from all the fluid intake that they do over the course of the day,"* said the mother of twin boys with PH2.

As mentioned in the first session, this need to urinate also had an impact the social lives of children with PH, as accidents could happen if they don't get to the bathroom in time, or if they were sleeping over at someone else's house. *"I was unable to attend sleep overs from a young age because I continued to wet the bed until the age of 10,"* said the young man with PH3 on the topic 1 panel.

Bedwetting was a concern caregivers of children hydrated through G-tubes as well. *"[She] receives some of her water through her tube at night when she sleeps, which means for me, I get up every few hours to change her diaper,"* said the mother of a young girl with PH2. *There have been many accidents and many tears shed in frustration that I didn't do my job for her and wake up to prevent those accidents.*

Adults with PH also mentioned how *"the need to take frequent bathroom breaks can be very disrupting for many aspects of life, including time-consuming jobs, travel and road trips,"* one young man with PH1 wrote.

TOPIC 2

"I have a very demanding job yet I'm up all night, with having to go to the lady's room and having to keep hydrated, which doesn't seem like a huge deal until you're trying to struggle through something with no sleep," said one of the second zoom panelists, a woman living with PH1.

"One of my biggest fears right now is [when my kids are] in their teenage years, they are going to go to college at some point during that time, and I just fear that they're not going to drink the amount of fluids they need to every day," said one of the first zoom panelists whose two daughters have PH2. "And if there's not a medication that's truly going to help this disease, then I'm always going to have that fear."

2. Prescription medications (such as vitamin B6, diuretics, baclofen) and supplements ***"I'm constantly trying new medication regimens to control the production of stones."***

Of the medical management approaches, the one most commonly selected by polling participants, prescription medications for PH (such as vitamin B-6, diuretics, baclofen), encompass a range of drugs and therapeutic targets. Baclofen is prescribed as a treatment to help manage/pass kidney stones, and while it has been among the medications that meeting participants have been prescribed, it did not come up during the facilitated discussion at the meeting. Participants did, however, discuss over-the-counter or dietary supplements such as citrates to prevent stones. For the purposes of thematic analysis, this section focuses on the medications (prescription and non-prescription) used to reduce oxalate or prevent kidney stones, which fall loosely into three categories: a) vitamin B6 (pyridoxine), b) diuretics, and c) citrates and magnesium. However, meeting participants often mentioned using them together.

a. Vitamin B6 (pyridoxine)

"We have been fortunate as well to be B6 responsive with our daughter. We were diagnosed at six months with a failure to thrive. B6 was attempted, and she almost immediately started to regain and started to thrive again... almost immediately, upon starting B6 and Cytra-K combination started to thrive and regain, and started to regain kidney function. And her numbers went back to relatively normal where she is today."

As mentioned in the scientific overview, some individuals with PH1 are responsive to vitamin B6, although some with PH2 or 3 have been prescribed it before receiving a definitive diagnosis. *"Both of my children, both of my daughters are B6 responsive, approximately 30%, so we are very hopeful for the future,"* said a mother of two teenagers with PH1.

"I currently take B6 and am responsive to it, fortunately, and have not had any challenges taking it. This has reduced my stone formation greatly. So, most of my managing for my PH for the last few years has been managing periodic episodes and monitoring oxalate levels, blood pressure, kidney function," according to one woman with PH1 who sent in written comments.

Only "nausea" was mentioned as a possible side effect of high dose treatment. The greatest downside mentioned was that roughly only a third of those PH1 are very responsive to vitamin B6, however.

"B6 helped me a little, I was told, but my genetics were not fully responsive to it," one man wrote.

"Our daughter had two different kinds of mutations on the AGXT gene. One was known as being sensitive for pyridoxine treatment, the other one they did not know for if it would work or not. So, we tested it for a couple of months...it didn't work, so we lost time," wrote one caregiver.

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"My childhood was medication therapies, vitamin B6 (pyridoxine), magnesium, which unfortunately I didn't have actually really good results on," said one caller who went on to need double organ transplants.

b. Diuretics

"They also take hydrochlorothiazide, a medication often prescribed for high blood pressure, yet proves to keep our kid's urine clean. And we pray for no learn long-term side effects."

Thiazide diuretics, often called water pills, increase the amount of water and salt expelled from the body as urine, and have been shown to reduce calcium excretion in urine and reduce calcium-containing kidney stone recurrence. Several participants mentioned or wrote in that they or their children had taken them, at least for a period. This included a 15-year-old girl with PH2, who no longer takes hydrochlorothiazide, an adult man with PH1, whose kidney disease continued to progress to end stage renal disease and double organ transplantation, and a number of children and adults with PH3.

One downside of the treatment is that diuretics increase the need to urinate, already an issue for children and adults drinking 3-6 liters of water each day.

"I call the hydrochlorothiazide pill, a pee pill, which we make sure the kids take early in the morning because it does make them urinate more frequently. And if we take it too late, it'll just be disruptive to their day," said the mother of two children with PH3.

Not everyone tolerates the diuretics. The 67-year old with PH3 said that she had taken *diuretics*, *but I realized I was actually allergic to one of the ingredients, so I stopped taking those."*

The other downside is that some felt the benefits were limited. *"The medications that I'm taking, I switched from chlorothiazide to chlorthalidone, which is supposed to be a stronger pill, probably two or three years ago, and still haven't seen the efficacy,"* said young man with PH3 on the topic one panel.

c. Citrates and magnesium-based oral supplements

"We were prescribed a variety of different medication of which included... the Cytra-K, PHOS-NaK, as well as the hydrochlorothiazide. Today, she is considered very stable at the age of now 15 years old. She continues to take the PHOS-NaK."

A number of oral supplements are commonly prescribed for PH to reduce the formation calcium oxalate in the urine from forming into crystals and stones, including potassium citrate (Cytra-K), Polycitra (combination of citric acid, potassium citrate, and sodium citrate), potassium phosphate (PHOS-NaK) and magnesium-based supplements. Participants across all types of PH described using them.

One of the topic 2 panelists, the 56-year-old man with PH2 deemed his regimen, which included *"a high fluid intake i.e., four to five liters per day every day"* and, during his youth, *"magnesium hydroxide,"* and then, later in life, various citrates as a *"relative success"* that helped keep his kidney disease stable during long periods of his life, before diagnosis and after kidney transplants: *"This helped wash the excess oxalate out of my body instead of it depositing as renal calculi."* However, his disease progressed eventually to stones, ESRD, and he had to go on dialysis and undergo kidney transplants on more than one occasion.

TOPIC 2

Others were unsure whether the citrates help or not, though their children were not progressing rapidly.

"Since we got the diagnosis, he has only been on one particular treatment and that is potassium citrate," said one zoom panelist, the mother of a 12-year-old boy with PH2, diagnosed when he was 3 years old. He seems very stable at the moment, and hasn't needed surgery for the last few years despite the fact that: "He's never, ever been stone free. He's currently got two stones in each kidney and he has them for the last four or five years." But she thought he might be "one of those that may be suffers from PH2 mildly."

One caregiver, mother of a 3-year-old son with PH3 had similar concerns: *"At 4 months old, he began taking potassium citrate solution several times a day, when the ultrasound scans showed possible stones. We are trying to determine if the benefits of the citrate outweigh the negatives or if we are asymptomatic to PH3 to date. I don't think he tolerates the citrate well, but that is still undeterminable."*

Still others reported seeing no benefit at all, even when supplements were taken in combination. According to written comments from the mother of a 13-year-old with PH1: *[My son] is currently on potassium citrate 3 times a day, 500mg B6 and magnesium twice a day. 12 tablets a day. And around 3L water. They don't seem to be helping his stones at all and his renal function continues to decline."*

Aside from limited efficacy, these regimens add to the medication burden for children and adults.

Another issue, raised by the father of a young girl with PH3, is that the supplements are *"quote-unquote medication... The FDA actually regulates these as food, not drugs."* Consequently, some insurance companies do not reimburse for over-the-counter supplements, even if they are prescribed. *"PHOS-NaK is considered an over-the-counter medication. So even though we are prescribed that medication from her doctor's team, unfortunately, because of how it's classified, it is not covered by insurance,"* said the mother of the 15-year-old with PH2 who appears to be stable on the supplement.

Finally, many participants said that they do not tolerate the supplements well.

"The potassium citrate causes constant acid reflux for which he takes additional medication," said the mother of a teenage boy with PH1.

"The Polycitra really caused a lot of problems for him. He would constantly throw up and be in a lot of pain in his stomach. We stopped giving it to him about 8 months ago, and he hasn't had a hospitalization for dehydration since. It was making him so nauseous," wrote the mother of a 5-year old son with PH1.

"[My daughter] also takes a gigantic potassium citrate pill each morning. I remember it breaking my heart the first few times she could have choked on it, but the liquid was just not staying down and upsetting her stomach," said the mother of two children with PH3.

"The nausea of taking B6 or taking potassium citrate: In the middle of the day, I'd want to throw up, while I'm trying to be an attorney," said an adult woman who served on the topic 2 zoom panel. *"Since I've been on a medication and was diagnosed in 2003, it's really important that any therapy I use is a long-term therapy. So, I dropped off of the potassium citrate because it really was problematic for me."*

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3. Diet-based approaches

“The whole diet thing adds a whole other level with the sodium and the oxalate and how much we allow them to consume per day.”

After drinking extra fluids, two diet-based approaches, cutting down on foods high in oxalates and following a low sodium, potassium, calcium or animal protein diet, were by far the most common selections in the poll question about top three nonmedical approaches being used to manage PH.

“We modify their diet to reduce the oxalate in their urine. Excess oxalate will bind with calcium causing the kidney stones. Chocolate, rhubarb, spinach and nuts are all high in oxalate. It is hard to explain to a child why they can’t have chocolate cake or candy at a birthday party while their sisters can,” said the caregiver of two children with PH2.

A number of participants said that adherence to these diets or *“constantly monitoring his food to ensure it is low sodium”* can be extremely challenging.

“As I moved out of my parent’s home and into the adult world, it became increasingly more difficult to follow the strict diet and medical regimen I was accustomed to,” the young man with PH3 reported. Another issue he and others raised was that dietary advice seems to have evolved over the years.

“My diet and everything has changed, in terms of continuing to focus on low sodium. When I was a kid, I couldn’t eat chocolate, I couldn’t eat spinach and all those different items that people have listed. Then at a certain point during my journey with primary hyperoxaluria they thought that the diet wasn’t as important, and so a lot of those foods were introduced to my life. Now I’m starting to think that I need to go back to that stricter diet that I was following as a kid, in order to try and control the production more,” he said.

“We have quite a lot of conflicting information...about diet... we just get really confused on what’s best for [our son],” said the mother of a 12-year-old boy with PH2.

Another concern is that while these diets may reduce oxalate levels, and preserve kidney function, they may not provide adequate nutrition.

“The dietary restrictions, it’s not a healthy diet, you have to avoid green leafy vegetables. What is that? So, there are other effects of these dietary restrictions. When I was strictly following the diet, I found I was very lethargic,” said the lawyer with PH1 who served on the second zoom panel.

4. Existing combination preventive approaches

Each child and adult with PH, who are not yet on dialysis or had double organ transplants, tends to use an individualized combination of the various medical and supportive therapy approaches. These combination regimens may “help somewhat,” otherwise, no one continue to take them. But for most children and adults with PH, these preventive regimens are disruptive to daily life and not adequately effective.

As one mother whose child has PH3 wrote, *“extra hydration is hard to manage in my child, as well as constantly monitoring his food to ensure it is low sodium. My child currently takes high doses of HCTZ, low sodium, low oxalate diet and hyperhydration; however, his 24-hour urine still shows his oxalate very high.”*

TOPIC 2

"Taking medicine throughout the day and the scheduling around when you're taking your medicine is extremely difficult," said the young man with PH3 who was on the topic one panel. He added that he also thought "the medications and the regimens that people are taking often work for certain periods of time, and then their bodies change, and their experiences with the disease change. For me, that was certainly true," said the young man with PH3 from the first topic panel.

"I just drink water and I watch my oxalate level of the dark green leafy vegetables and cut down on meat, and that's basically it. And does what I do work? I don't know, actually, because I still get stones," said the 67-year-old woman with PH3 on the second zoom panel.

Most commonly used procedures to remove kidney stones in PH

"When you're dealing with stones, whether it's a percutaneous nephrolithotomy or a cystoscopy or lithotripsy, or getting stents put in: They're all painful, they're all invasive, and they all take a toll."

The clearest evidence of the poor efficacy of current preventive care for PH is the need for procedures to remove kidney stones (as well as the need for dialysis or organ transplantation in the most severe cases). Many participants indicated that they have had to have kidney stones removed *"many times."*

"I have had 20 surgeries to remove them," one woman with PH1 said. Another mother wrote that her little girl had had *"30 surgeries"* (although this included organ transplants).

"We've had double digit surgeries on a son, and it's just a major burden, not only on him, but the entire family, two working parents, the economic cost, the quality of life, the mental anxiety," said a caregiver whose son is now in his twenties has PH3.

"He had so much surgeries, like 17-hour surgeries and everything had to be redone. He kept continuing to make stones and they would try to bust them," said the mother whose son died of PH1 at age 25 years.

Although the 67-year-old zoom panelist with PH3 thought that her condition was mild compared to others, she had had at least 19 surgeries to remove her stones.

"[He] has endured 24 total surgeries," said the mother of one boy with PH2, who was only 13 years old at the time of the meeting.

According to the raw data (not shown) from the polling question, close to half (47% or 24 out of 51) of polling participants selected at least one of the three procedures for kidney stone removal as a medical approach they or their loved one with PH were currently using. Often, poll respondents indicated that they were using all three procedures. During the discussion, meeting participants indicated that the choice was determined by the position and size of the stones and the relative effectiveness of the approach. The least invasive method, extracorporeal shock wave lithotripsy (ESWL), was less commonly used according to the poll—although 18% of the poll respondents said that they were currently using ESWL, only a couple selected it without indicating they were also using other methods. The only references to ESWL during the discussion suggested it was not adequately effective: *"Lithotripsy, unfortunately, was unsuccessful due to their position,"* and *"he's had lithotripsy that doesn't work on his stones"* were some of the comments.

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Consequently, the following section will focus on the more invasive procedures that children and adults living with PH have to *repeatedly* endure: ureteroscopy (with stent placement) and percutaneous nephrolithotomy (PCNL) or surgical removal of stones.

1. Ureteroscopy to remove stones

“The first of several procedures, involve[ed] stents and laser lithotripsies to rid him of these stones. Stents were placed initially to open the ureters and allow passage of urine from the kidney to the bladder. After the stent placement then the following procedure involved using laser lithotripsy in which an adult size tube was placed through the penile urethra under video, and each stone was blasted. The lithotripsy procedures would last over a couple of hours each time.”

Ureteroscopy with stent placement was the most commonly used procedure to remove kidney stones. *“Most of her surgeries were by ureterostomy and a temporary stent was placed,”* said the mother of one 17-year-old girl with PH1. As one woman with PH1 said, this was *“much less invasive from my perspective [than PCNL, though] it may be as less efficient and effective from my doctor’s perspective.”*

One obvious downside is that, while providing some relief for a time, the kidney stones keep coming back.

“Both girls, basically every 18 months or so, have to undergo ureteroscopic lithotripsy,” said the mother of two girls with PH1. *“During the sonogram, I was told I would need a bilateral ureterostomy to remove eight kidney stones. At the time, this was the third surgery I would have in just over one and a half years,”* said the young man with PH3 on the topic one panel.

Although not as invasive as PCNL surgeries to remove stones, the procedures can have complications.

“I have had numerous ureteroscopies; We’ve lost count. Over time, these have caused me to become incontinent to a degree. Coughing and so on cause me to leak. My underwear, my pajamas, always smell of urine,” wrote the 67-year-old woman with PH3 in comments submitted after the meeting. In addition, she worried that she might be getting *“too old for anesthetic to be safe for me.”*

2. Percutaneous nephrolithotomy/surgical removal of stones

“I’ve been through PCNL surgeries, where they have to go through my back. The PCNLs really take a toll on me.”

Roughly half of the participants currently requiring stone removal indicated they were undergoing PCNL or other invasive surgeries to remove their kidney stones because of the large size, complexity or position of PH-related stones. When these procedures are performed on children, they are particularly harrowing.

One caregiver said that since her 6-year-old son could not pass a 3x1 centimeter stone, it *“had to be removed through his belly button.”* Another mother of a boy with PH1 said that *“his first treatment was a urethral myotomy performed under general anesthesia, which involves actually cutting the opening of the urethra to remove the kidney stone that was lodged at the tip of his penis. When the anesthesia wore off, it took two large physician assistants to hold [him] down and remove his hands, which were protecting a surgical site so that the urologist could apply some soothing lidocaine.”* He was 8 years old at the time.

TOPIC 2

"[She] was admitted to have two stones removed that were over an inch in size. The doctor operated through her back to get to them," said the mother of a teenage daughter.

One panelist said that his baby daughter with PH3 had to have a percutaneous stone removal procedure. *"We were just lapsing into a more normal cadence when bang the same exact thing happened again in the other kidney for her. By the time she was one years old, she had four different procedures to deal with these stones."* These procedures are not easy in an infant: *"The doctors delayed surgery as long as possible since the surgical tools they would use were bigger than her tiny little kidneys. Eventually 19 stones were removed from my 2-year-old little girl,"* one caregiver to two children with PH2 said.

Aside from the multiple hospital stays, pain, and trauma associated with the procedures, the surgeries also cause scaring: *"His body is covered in scars. He does look like he's a survivor of a shark attack and is often asked that by his friends,"* one mother said of her 13-year-old son with PH2 who has had many stones removed. Worse, there is a risk of permanent injury to the kidneys: *"The surgery damaged my kidneys, and they would never gain that function back,"* said one panelist with PH1. *"On my first surgery at [the age of 16], they removed about a third of my left kidney,"* one caller with PH1 said. Another woman with PH1 wrote that she has *"spasms in my kidneys and ureter that my nephrologist believes is due to scar tissues from multiple surgeries."*

The 56-year-old with PH2 said that in his youth, two operations for kidney stones plus a kidney removal *"were very invasive leaving two large scars on my abdomen and each time a several week stay in hospital."*

Stent placement is common in both ureteroscopy and surgical stone removal, but several caregivers said there can be complications. For instance, the boy who had a urethral myotomy later had an adult-sized stent placed in his ureter to allow for another procedure: *"The pediatric urologist told us that [he] would be very sore since she was inserting and passing tubes for imaging and for laser lithotripsy in and out of the small urethra recently cut from the first surgery. She told us that he would have pain with urination and would pass blood clots for several days. And as predicted after each ureteral procedure, the initial post-operative urination attempts were painful for him,"* his mother said. As a result, at school, he had to *"use the faculty bathroom because the blood might've been frightening to the other children to see."*

Another caregiver said that complications about one month after a stent placement in her young son were *"something that nightmares were made of. [He] writhed in pain and in total hysteria. When we went to remove his stent, we learned that in a very short time, the stent that was in place had encrusted itself to his kidney and had to be laser removed."*

Still other children required a more invasive method, a nephrostomy tube to prevent hydronephrosis. One mother said that after an *"emergency surgery"* to remove a large stone from the urethra of her 11-month-old daughter with PH2: *"She had to have a nephrostomy tube in for about a month to help her kidney drain excess fluids. She had a stent put in her ureter to help repair the damage the stone had caused."*

"We had to have an emergency procedure done called a nephrostomy, which is when you put a tube into the child's kidney directly so she can void the urine directly into a bag. Picture a 3-month-old child. This is not, obviously, typical. One of the typical interventions that would be done would be a stent would be inserted, but there was no such thing as a stent for a 3-month-old child having to have this type of procedure. This just doesn't exist. The tools don't exist. So very basic procedures, this nephrostomy tube where a small child, barely an infant, the bag was as big as she was," said the father of a girl with PH3.

TOPIC 2

Management of kidney failure and end-stage renal disease in PH

“I spent a year on dialysis, six days a week. Dialysis was extremely grueling... and... very rigorous. It takes a tremendous toll on your body. I received a liver and kidney transplant. That’s ultimately what it came to for me. I’m so grateful for my transplants, but it’s like trading one set of issues for another with the medications I have to take, and just worrying about: “Will I have to get another transplant?””

In CKD, when kidneys fail, dialysis is necessary for survival. In the absence of an effective treatment for PH, there is currently little chance of recovery without undergoing organ transplantation (though there can be recovery from acute kidney failure, as one caregiver described in his child who responded to vitamin B6).

Dialysis

My 2-month-old baby girl [was] in kidney failure due to PH1. From that moment on, nothing in our family would ever be the same. Dialysis began and we soon started a regime of doing hemodialysis for 3 hours a day, 6 days a week; and for a time added peritoneal dialysis for 12 hours every night while she slept. She did 15 hours a day of dialysis for 2 years until she was big enough to receive a lifesaving kidney/liver transplant.

Based upon the polling question responses, approximately 18% of the children and adults with PH were currently on dialysis. The proportion of the community who have needed dialysis due to kidney failure (usually due PH1, but in cases PH2) at some point in the course of their life (sometimes as early as infancy) would have been higher, as many meeting participants said that they or their loved one had gone on from dialysis to have double organ transplants.

The dialysis regimens—hemodialysis, sometimes peritoneal dialysis, and, in some cases, both—required to remove oxalate are particularly prolonged and arduous.

One mother wrote that her daughter, diagnosed with PH1 at 3 months of age, “lived a very challenging life for 1 1/2 years before her eventual combined kidney and liver transplant. She endured 4 hours of hemodialysis each day at the hospital and 10 hours of peritoneal dialysis each night at home. It was an incredibly stressful time for our entire family.”

Several caregivers reported that their infants with PH1 who went on emergency dialysis remained on it for years before receiving the correct diagnosis and could then receive a double organ transplant. One woman who sent in comments about how her sister was on dialysis for 9 years before she died. These young children could not share their experiences with dialysis at the meeting, but there were several who went on dialysis as adolescents or adults who could.

One of the topic 2 panelists, the 56-year-old man with PH2, shared his extensive experience with different forms of dialysis after more than one kidney episode of failure.

“I had to receive emergency peritoneal dialysis to save my life. The next few months were a very traumatic time as now we were no longer managing or treating PH. It was now all geared around managing and treating oxalosis. Within three months, I initially had continuous ambulatory peritoneal dialysis (CAPD); however, after just a short time, it proved to be inadequate at removing oxalate. At the age of 31, I was now looking at spending the rest of my life, relying on a machine to clean my blood in order to stay alive,” he said. He’s since had two single kidney transplants, though for the first 14 days after each transplant, he had 8 hour sessions of hemodialysis *“in order to get the kidney the best chance.”*

TOPIC 2

When he was 47 years old, he had ESRD again and went back on hemodialysis. He had determined that *"hemodiafiltration was better than the usual hemodialysis and that the longer sessions would be better for oxalate removal. However, these bring other complications which involve closer monitoring than usual."*

"Dialysis is very invasive and changes everything you've done previously to manage PH. For example, no more high fluid intake as the patient is often put on a fluid and dietary restriction to prevent fluid overload and the breathing implications that goes with it and to manage potassium, phosphates and other mineral levels, which often requires further medication to manage. Despite this, the oxalosis continues to cause me many problems," he added.

A few community members described about how exhausting dialysis can be. The woman who wrote about the experience her deceased sister had with PH1 and dialysis, later went on dialysis herself and reported that dialysis is *"really hard. I always tell people that they don't know true exhaustion until they have been on dialysis. I still recall moments lying down, expelling all the air out of my lungs, and trying to be as still like that as long as I could because I felt too tired to breathe. No exaggeration."*

One of the panelists had a 17-year-old daughter who, six months before the meeting, had to go on *"hemodialysis six days a week for three hours each day."* The girl sent her own comments to the meeting saying that while she was now stable on dialysis, *"it comes with the side effect of no life. No school, difficult schedule making it harder to see friends, and exhaustion taking up a majority of my days."*

The mother of another older adolescent girl who is also on hemodialysis, also commented on the time commitment accompanying her child: *"Having to be in California traffic with our daughter, going to dialysis, made things very challenging, especially with limiting who can be there, and who can be in the hospital. When our son [who had organ transplants] was in one wing of the hospital and our daughter was in the other, we couldn't go back and forth, we had to have one parent with each. It was very challenging. So, my husband left his work so that he can help me at home, care for the kids."*

Dialysis also takes a tremendous toll on the body.

One caregiver said her young son eventually received a double-organ transplant but *"before that, he got congestive heart failure because of a dialysis issue."*

Other participants reported *"many peritoneal infections from the catheter for peritoneal dialysis and frequently required blood transfusions."*

Many made reference to bone wasting and related complications that were likely to be at least partially due to dialysis-related renal osteodystrophy. One noted *"a risk of pelvic fracture on x-rays"* in her son. The woman who sent in comments and her and sister's experience, wrote, *"she had to switch to home tutoring when she broke her hip at age 7 and was in a half body cast for a year. It never healed and she never walked again. She was in constant pain. Her ankle bone totally deteriorated by the time she was 10. She had a large ulcer on her ankle from it not moving frequently enough. She was in constant pain."*

The zoom panelist whose son *"required dialysis five days a week,"* described how *"his bones broke, he twisted a leg, his heart... the food, he was on dialysis, certain foods he couldn't eat. He did five years on dialysis, but it was a hard 5 years. It was just constantly in and out of the hospital and pain."*

TOPIC 2

Over the long term, dialysis simply is not sustainable. 5-year mortality rates are extremely high.

"I held him when he died. And that's the impact. You never know when it's going to happen, and you face it daily with the pain and sickness and vomiting," a caregiver on the first zoom panelist said.

"Towards the end we had to keep the blinds and curtains shut because the light would hurt her eyes. I can't even imagine what it was like to suffer the way she did," recalling her sister's death almost 27 years earlier.

Another woman with PH1 wrote, *"I lost my older brother in 2008 due to PH. The claim was that, during dialysis, the oxalate went up to the heart and hurt him. He was 35 when he died in the operating room after the surgeons finished the transplant."*

Organ transplantation

"[He] got his kidney and liver transplant when he was 2 and a half years old. Due to life-threatening complications, he spent a lot of the next year in the hospital. Organ donation saved my son's life, and it is a beautiful gift that is never taken for granted. However, [he] has had a lot of transplant-related health issues and will continue to face many of these challenges the rest of his life... He recently had a biopsy of his kidney, which confirmed he has new complications and health issues, and he will need another kidney transplant in his future."

After ESRD, receiving a kidney transplant is the only way survive without dialysis. The 56-year-old man with PH2 described it as *"the ultimate gift one human can give to another. It is not a cure for PH and/or oxalosis, but it is the next best thing available right now. My first transplant plus a high fluid intake gave me the opportunity to do whatever I wanted, and I was free to carry on as any normal person would be."*

However, as he noted above, his PH proceeded to damage his new kidney, and eventually, he would go back on dialysis and seek another transplant. Without a treatment for the cause of PH, this cycle will repeat for most of those who have only have kidney transplants.

"My kidney function improved after the transplant to 50%, but gradually deteriorated to as low as 13%. But over a year on it, it is now at 18, so my worry would be that the function deteriorates further," wrote a woman who had a double kidney transplant when diagnosed in 2019 with PH1 at the age of 57 years.

One caregiver who phoned into the meeting, the mother of a boy who was 5-month-old when he developed ESRD and was put on peritoneal dialysis until he was large enough to receive *"his dad's kidney,"* described how *"a few weeks later, they went into biopsy the new kidney and it was full of stones already. That is when [he was diagnosed with] PH1."*

For this reason, guidance is that people with PH on dialysis receive a liver transplant along with at least one new kidney. It can be a challenge to get a double transplant at the same time, and it may be difficult to perform this surgery in young children.

"Because that kidney had already been damaged, we had to have a liver. But because he was so sick, he couldn't have another transplant. [We] waited until he was five and he got a liver," said the mother of the boy who had received a kidney from his dad.

TOPIC 2

One of the topic two panelists described her infant son's ordeal: "[He] was placed on the transplant waiting list for a liver and kidney. He also had a peritoneal dialysis catheter placed so that fluid would stretch his abdomen so that it could be large enough to receive adult size transplanted organs. Peritoneal dialysis was seven days a week at home for four-hour sessions. They explained that [he] needed adult organs because he had such a large oxalate burden that if he had pediatric organs transplanted into him, the oxalate would destroy those organs."

The persistence of oxalate has complicated transplantation for other children as well. One mother wrote that her 9-year-old son had a liver transplant three years ago, "and he has been on hemodialysis for three years after that. He was waiting, and still is waiting for a kidney transplant. Oxalate is still detected in his blood tests... Even if he has a kidney transplant now, I am concerned that the remaining oxalate in his body will damage his kidneys."

Another mother wrote that her young daughter, "had a liver transplant at the age of one and a kidney transplant at the age of two... If she had not received her double transplant, she would not have lived past two years of age." However, she added: "She had multiple complications."

One drawback is that in most cases, the transplanted organs eventually need to be replaced. The woman with PH1 whose sister who died on at the age of 11 years, went onto having dialysis and a liver and kidney transplant. "The kidney had some complications. I received a second kidney from my husband who I met in 2007, in 2008," she wrote. "I do face the reality I will need another kidney transplant or two in the future and possibly need on dialysis again for a period of time," she wrote.

In order to prevent organ rejection, people also have to live the rest of their lives on immunosuppressant medications and need to take others to prevent opportunistic infections and cancers due to their immune suppressed state. One woman credited a liver-kidney transplant with saving her brother's life: "Since then he is healthy, but every day, he takes a large amount of medication. He has difficulties of a different kind."

Other medications and supportive care that are used by people with PH

While preventive care to keep from developing kidney stones, procedures to remove kidney stones, and for those with ESRD, dialysis and organ transplants reflect the key interventions used along the course and severity of the disorder, people with PH also use a variety of other medications and therapies to try to preserve their health and improve their quality of life.

Supportive therapies: Since the polling question had asked participants to select their top three non-medical approaches, and most selected drinking extra fluids or dietary approaches, the poll results have under-represented how commonly people use other approaches such as exercise, counseling therapy, physical occupational therapy, complementary alternative and other approaches. Nevertheless, almost a third selected exercise and at least 2 to 8 respondents selected one of other approaches as something that they or their loved one were using to cope with PH. One mother said music therapy helped her son with painful urination: "We learned that playing Chopin Nocturnes would help [him] relax, which would help him urinate."

Over-the-counter medications: As for the medical approaches, according to the polling results, medications such as acetaminophen, ibuprofen were being used by about one-third of those represented in the poll, though as one man said of his kidney stone pain, "almost... no medication that can treat it."

TOPIC 2

Antibiotics: Participants also mentioned using medications antibiotics, such as, sometimes intravenously, which can have a number of downsides. *“I was septic. I ultimately received a medication that worked, but the infection was so bad it would take weeks of antibiotics. A PICC (peripherally inserted central catheter) line was inserted and home health care was set up,”* one of the panelists said after she developed a very serious kidney infection. One caregiver said her baby with PH2 and severe UTIs, *“had to be treated with an antibiotic that was so toxic it had to be injected slowly over several hours as not to poison her.”*

Immunosuppressant medications: As noted above, those who have had organ transplants, have other complications due to the medications they take to prevent organ rejection.

“He’s on dozens of medications and will continue to be on most of these medications for the rest of his life [He] had to be homeschooled due to severe weakened immune system,” one mother said whose son had had a double organ transplant.

“I do have to be very careful with the immune suppressant medication that I have to take. Everything [needs to be] extremely clean I have to be extremely, extremely cautious,” one man said, adding that this had become particularly difficult during the COVID-19 pandemic.

Another mother of a son with a double organ transplant agreed that the pandemic had *“made it a lot more challenging for us. With our son having his transplant seven years ago, he has a very complex medication regimen that he needs to be on and very immune compromised system, so his care is very specified with how we have to deal with things.”*

Antidepressants or anxiolytics and marijuana: Others polling respondents indicated using antidepressants or anxiolytics, while some used marijuana or cannabidiol products for symptoms of PH.

Other surgeries: In addition, severely ill individuals may need other surgeries for a range of complications: *“At four months old, he received his first of many surgeries to place a feeding G-Tube as he suffered from failure to thrive. At 14 months old, he received his first pacemaker. We’ve had two more since then. At the age of six, he had to have a cranial vault to alleviate the increased pressure on his brain,”* said the mother of one boy with severe PH1.

A number of others also reported surgeries for G-tube placement. *“He had a G-tube placed to help give medication and nutrition [Now], seven years post-transplant, he still relies on his G-tube for medication and to assist him in achieving his fluid goal of three liters a day,”* said one caregiver.

One downside, one caregiver noted, is that parents often have difficulty getting pharmaceutical companies to reimburse for such interventions. *“The same with my daughter’s G-tube to ensure she gets enough fluid. We’ve had to fight the insurance company to get a G-tube that they would cover. They still don’t. Because it’s not needed for food and just water and fluids, they do not cover that because it’s not considered necessary for life,”* said one of the topic 2 panelists who has two children with PH2.

TOPIC 2

There is a great remaining unmet need for less disruptive, more effective treatments

While these remaining medical and non-medical approaches may help to manage some PH symptoms and complications, participants stressed that they add to the overall expense and burden of care of an already demanding prevention, care and treatment regimen. As indicated by the responses to the penultimate polling question, 65% felt that the number of pills/medications needed per day is already too high, and 40% indicated that the treatment regimens are not very effective. Roughly a third of the respondents indicated either that the treatment required too much effort and/or time commitment, or had side effects, or a high cost or co-pay not covered by insurance, while approximately 14% responded that there was limited availability or accessibility to their treatment, or some other drawback.

"There is really no true cure right now, and nothing is really working, except for a select few with Vitamin B6 sensitivity," said the father whose son, now in his 20's, has PH3. "Obviously, we're keeping the urologists and the emergency rooms very busy, but the personal and economic costs are way too high. We just must get another treatment or a therapeutic of some sort to help more patients. We're not getting enough patients a better quality of life and a better treatment."

"The downsides to all of the therapies so far are just, it is incredibly disruptive to everyday life... and for people who haven't found a therapy that, at least, gets their oxalates down, it's terrifying," said the attorney with PH1. "What I want to make clear to the people who will be reviewing all of this is that: The treatments that are available now? There's not a great one."

Perspectives on future treatments and considerations in treatment decisions

Out of the chief outcomes of the patient-focused drug development meeting was to identify what the children and adults living with PH most need and want from future treatments and how they would make their treatment choices between existing management approaches and new treatments. Consequently, in the final polling question, meeting participants were asked what two outcomes, short of a cure, would be most meaningful to them in a future treatment. The two most popular choices were *"completely stopping the formation of kidney stones,"* and *"stopping disease progression,"* though there was clearly overlap in these two categories, while almost a third wanted to see something that might be a greater challenge: *"Improving kidney function."*

In the discussion, however, even though some participants mentioned preventing stone development, no one focused on it alone.

"I hope for a medication for [my daughter] so she will never have a kidney stone again," said the mother of a 4-year old girl with PH2. But then she added, *"so she's able to eat whatever she wants and live a life without worrying that she didn't drink enough that day."*

Indeed, most called for outcomes more holistic in scope. Participants wanted to avoid the worst outcomes, and said that they don't want to live in fear of a catastrophic stone event or kidney failure that leads to dialysis or transplants or an early death. They want a treatment that stops the underlying process of the disease, effectively interrupting oxalate production or accumulation. They expressed an expectation that such a treatment would reduce the burden of care compared to the current, inadequate management approaches—so the new treatment would mean that they wouldn't have to drink continually or take as many other medications.

TOPIC 2

Treatments are needed that effectively prevent kidney stones and the progression of kidney disease to dialysis and organ transplantation

“Being able to avoid dialysis and the need for transplant, and finding the miracle of having a donor, would be incredible. We desperately need drug treatments or even drug mitigation of PH1 symptoms.”

Many people with PH and their caregivers expressed a desire for treatments that would prevent kidney stones and other even more traumatic outcomes in PH such as dialysis and organ transplants. Some had already experienced such events.

“Transplantation is an archaic treatment. We are in 2020, the advances we have made in all aspects bring hope that we can find a medicine so we do not have to replace organs,” wrote the mother who credits organ transplant for saving her toddler's life. The woman who lost her sister on dialysis and later went on dialysis and had multiple organ transplants herself wrote about finding treatments that would give *“hope... so patients do not have to go through dialysis and transplant.”* She also expressed hope for an alternative organ supply via *“continued medical advances in kidney growing / procurement.”*

The risk of death is something that few want to consider, but some individuals with PH1 in resource-poor settings overseas sent in written comments that they only had access to dialysis and kidney transplants and that they needed to access treatments to give them *“a chance to live.”*

A young person who had had a double transplant said this broke his heart: *“In America, not too long ago, people with PH1 were getting kidney transplants, were not properly diagnosed, and their kidneys were failing, and they were passing away. To prevent having to go through that, I think would be invaluable.”*

People who had not yet suffered severe disease also want treatments that would prevent progression and relieve their anxiety. One mother of a 3-year-old boy with PH3 said that while his condition might be well-controlled at the moment, they were anxious that tomorrow, it might not be: *“Any future treatment, would really lower my anxiety and our family's anxiety for our future and future generations to come.”*

Many said that they also wanted the treatments that prevent the poor outcomes to have minimal side effects and reduce reliance on other medications. During the short video at the start of the second session, the mother of twin boys with PH2 said she was hoping for a medication that would *“work with very minimal side effects and help patients live a longer, healthier life and not have to worry about having a kidney or liver transplant.”* Her husband added he hoped for a treatment that would have *“more of a minimal effect on their life without the fear of kidney stones or fear of kidney transplant in the future.”*

The mother who was a co-panelist with her 16-year-old with PH1 said, *“We are concerned for his future and want to do what we can to help preserve his kidney function, avoid oxalosis and transplant requirement. We are hoping for a medication that can protect him from that course.”*

TOPIC 2

Treatments are needed that address the underlying cause of the disease to reduce oxalate levels

“My wish for new drug therapies would be those that help treat excess oxalate production so that I can maintain my kidney function. Those that improve my kidney function.”

While the participants who indicated they wanted treatments that would “control oxalate levels” were also seeking a treatment that would preserve kidney function and prevent stones, it is notable that they focused on oxalate as an outcome measure—and as part of the root cause of their symptoms.

One of the caregivers on the first zoom panel, the father of a young girl with PH3, sent in a written comment making this point: *“Other than for B6 responsive patients, the current treatment options don’t do anything to reduce oxalate in the urine or blood. Super hydration, Polycitra-K and Phos-NaK only try to neutralize the oxalate after it has been formed. A treatment option that addresses the root cause of excess oxalate production would be a great benefit to the patients and families,”* he wrote.

“Short of that cure, [I want] anything that can lower the production of oxalate, because ultimately that’s why I grow stones,” said the 67-year-old woman with PH3.

“We would love to see a miracle medication to help the kidney and liver break down the oxalate,” said a mother of two children with PH3.

Treatments that reduce the burden of preventive care for PH are needed

“Anything we can do to help reduce our fears for the future and frequency in intake of medicines, if we can reduce that. We’re worried about increased symptoms and... the chance of transplants.”

Again, participants asked for treatments that would reduce their or their children’s reliance on so many “over-the-counter vitamin type drugs” and “a drug that would reduce a water drinking requirement and the frequency of taking a medication.”

“The goal would be to reduce the need for daily medications that likely have long-term side effects we don’t even know about. We hope for a medication that is least invasive and something that could be giving at home. One pill that could do it all would be ideal,” said one of the mothers to children PH3.

One caregiver to two teenagers and a 5-year-old with PH1 called into the meeting to share what her children said they most wanted. *“For them, it was being able to decrease the hydration intake. It’s certainly a burden for them to have that constantly on their mind, as well as on mine, nagging them of what they’ve been able to drink and keeping track of that. And secondly, a simplified medication routine. With three kids with this disease, I have over 20 medications, two shots, and things that I’m trying to keep track of, of when’s it due at the pharmacy, and is that one out of refills, do I need to call the doctor and get them to refill that? It can definitely be a burden to try to keep track of all of those medication refills and keeping them dispensed correctly and all of that. But for me as a caregiver, having that simplified medication routine would certainly be a benefit to a future treatment.”*

TOPIC 2

Perspectives on clinical trials and benefit-risk analyses

“You are making all these risk assessments... it’s a long downward trajectory, unless there’s an actual treatment option here in one way, shape or form.”

Toward the end of the meeting, individuals with all types of PH and their caregivers also spoke about their eagerness to engage in clinical trials and about the risks that they would take in exchange for treatments that could prevent kidney stones, disease progression and simplify treatment. Individuals with PH are willing to put a great deal of time and energy in clinical trials in order to find effective treatments.

“Finding a better treatment or medication that truly would change everything and give PH patients a genuine hope of leading a normal life is something that has driven me for my entire life and has always been the main factor when I endured the many x-rays, ultrasounds, CT and MRI scans, along with urine and plasma samples for research over the years,” said the 56-year old man with PH2 on the topic 2 panel.

“Recently, he entered a drug research trial. For this study, we traveled monthly to our study center requiring one day of travel each way, such that [he] missed at least two days and sometimes three days of school every month for the initial six months of this trial. In addition, he collected monthly 24-hour urine collections and had monthly blood draws for the study and received the subcutaneous study drug. We’re very willing to travel, miss school or work, perform these evaluations for the chance to participate in a trial,” said the mother who served as a co-panelist with her 16-year-old son with PH1.

When the 67-year-old woman with PH3 heard about an experimental treatment that could reduce oxalate levels, she said she went to see a doctor about it. *“He actually asked me would I be interested in a clinical study, and I said, “Yes!” And so, I left there on cloud nine,”* she said.

“My son was diagnosed with PH1 when he was nine. I was offered the opportunity to get him into a clinical study and accepted. We travel quite a bit to participate, but his oxalate numbers have gone down tremendously. I see a look of relief across my son’s face. I also hear it in his words. I would do anything to keep my son from living a life with a double transplant,” one caregiver said.

A couple of caregivers said that they were willing to take great risks—even passing on hard-to-come-by organ transplants to take an experimental treatment. It was a choice that said they did not regret.

“We became aware of upcoming clinical trials which offered some hope for a pharma-based solution to PH1. About 5-6 months after [our son’s] diagnosis, we received a call at 3am to advise us that a liver was available for transplant and we had to make the agonizing decision to go ahead or to refuse the transplant. I will never forget the 30 minutes or so that we had to make up our mind. We decided not to go ahead with the transplant and put all our hope into the drug trials. Luckily for us, [he] remained stable enough through the period when we were waiting for the trials to commence. Fortunately, he was accepted onto the trial and has been on it since,” wrote the parents of one 12-year-old boy with PH1.

TOPIC 2

"In June, we were finally granted the opportunity to get an investigational medication. For the first time, we started to think we had options for [her] that we didn't have for [our son]. Was it possible to keep her liver if the medication continued to work? Then we received an offer of a liver and kidney for [her] after careful consideration and discussing with the doctors. Surprisingly, we chose to pass on those organs," said the mother of two children with PH1.

Caregivers and people with PH described routinely making benefit-risk calculations in day-to-day treatment decisions, taking therapies that disrupt their lives or have unknown long-term side effects, as well as to undergo invasive surgeries to remove kidney stones. Some said they had even, at times, decided to try to endure pain and pass stones rather than go in for surgery. Those with the most advanced disease demonstrated their willingness to go on dialysis, or to undergo organ transplants in order to stay alive. Some said they were willing to make similar calculations for an experimental treatment.

"I would try anything, provided it was safe. I would try anything because I'm desperate, because of my age," said the 67-year-old woman with PH3 who needs recurrent surgeries for kidney stones.

"We are also willing to risk side effects, including allergic reactions, paradoxical stone formation, and other intolerances if this medicine would lower oxalate production, help [him] preserve his kidney function and prevent oxalosis," said the mother who was a co-panelist with her 16-year-old son with PH1.



Incorporating patient input into a benefit-risk assessment framework for PH

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of PH and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the PH EL-PFDD meeting and docket comments will inform the understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the sample framework for PH, below, draws from various sources, including what was discussed at the PH EL-PFDD meeting held on October 5, 2020. This sample framework contains the kind of information that, it is anticipated, could be included in a framework completed for a drug under review for PH. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.



Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • PH is an extremely rare recessively inherited metabolic disorder characterized by a marked excess of oxalate. Excess oxalate accumulates in the urinary track and kidneys and forms calcium oxalate crystals that cause cellular and tissue damage in the kidney and multiple calculi in the bladder, urinary tract, ureter, or kidney. Damage to the kidneys is progressive, irreparable and, in the most severe cases, may lead to kidney failure and end stage renal disease (ESRD). In addition, as glomerular filtration rates decrease, blood level of oxalate increase, with crystals forming in the bloodstream and being deposited in multiple organs: blood vessels, bone, heart, skin, and eyes. In the absence of timely dialysis or double organ transplants (liver and kidney), multiple organ failure and premature death can occur, sometimes in infancy. 	<p>PH is an extremely rare, debilitating metabolic disorder causing recurrent kidney stones, urinary tract infections, chronic kidney disease, and in the most severe cases, kidney failure, oxalate toxicity in multiple organ systems and potentially death. It has wide-ranging complications and devastating impacts on the lives of people with the disorder and their families.</p>
	<ul style="list-style-type: none"> • Three types of PH due to different enzymatic deficiencies have been identified. The severity of disease ranges with type and from person to person. <ul style="list-style-type: none"> - PH1 is most common and most likely to cause severe disease leading to ESRD. - PH2 is on the middle of the spectrum but may also progress to ESRD with age. - While ESRD is uncommon in PH3, it is not as well characterized. - In addition, there are cases where genetic/enzymatic deficiency is unknown. 	<p>Although PH1 is most likely to cause severe disease and be life-threatening, PH2 and PH3 also cause frequent and traumatically painful medical emergencies often starting in infancy, and experience similar symptoms and complications.</p>
	<ul style="list-style-type: none"> • Regardless of PH type, the most common symptom is recurrent kidney stones that may be abundant, too large to be passed and that cause traumatic debilitating pain, often in infancy. Stones cause obstructions to the flow of urine, blood in the urine (hematuria), and may lead to secondary urinary tract infections that compromise kidney function. 	<p>Individuals with PH have complex treatment needs for therapies that address both the cause of the disease, and its many symptoms.</p>



Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Other PH symptoms include nausea and vomiting, failure to thrive in infancy, fatigue, and depression and anxiety. 	
	<ul style="list-style-type: none"> In severe disease, systemic oxalosis can cause damage to vision, renal osteodystrophy with fractures, cardiomyopathy and skin ulcers, concluding with ESRD. 	
	<ul style="list-style-type: none"> PH has a profound impact on the daily life, including disruptions to school and employment, limiting recreation, and family/social life. Patients and caregivers experience frequent medical emergencies, and fear when the next stone will occur and disease progression to the point of dialysis, organ transplantation or early death. 	
Current Treatment Options	<p>Existing management approaches of PH include:</p> <ul style="list-style-type: none"> Preventive care regimens to reduce oxalate levels including drinking extra fluids (3-6 L a day), vitamin B6, diuretics supplements, and diets. These are burdensome, disruptive (causing a constant need to urinate) and have limited efficacy. 	There is an unmet need for more effective and less complex disruptive FDA-approved therapies to prevent kidney stones and their recurrence, whether in PH1, PH2 or PH3.
	<ul style="list-style-type: none"> Surgeries, often invasive, to remove stones that frequently recur. 	
	<ul style="list-style-type: none"> In ESRD, grueling dialysis regimens and double organ transplants. 	Treatment options are needed that treat the root cause of the disease, reduce oxalate levels, and preserve kidney function that cause fewer complications than repeated surgeries in all types of PH, or dialysis or organ transplants in PH1 and severe cases of PH2.
	<ul style="list-style-type: none"> Participants desire treatments to prevent kidney stones and loss of kidney function leading to organ replacement. Prefer a simple therapy that reduces oxalate levels, as well as pill burden and the need for hyperhydration. 	
	<ul style="list-style-type: none"> There is a preference for safe, more tolerable preventive treatments. In severe disease, individuals are willing to risk side effects for treatments that have fewer complications than dialysis, organ transplants and repeated surgeries to remove stones. 	
	<ul style="list-style-type: none"> See the Voice of the Patient report for a more detailed narrative 	



Conclusion

This meeting provided the FDA with a unique opportunity to hear in great detail directly from people living with PH and their caregivers and to better appreciate the painful trauma of living with an extremely rare, often debilitating disorder characterized by kidney stones and progressive and irreparable damage to the kidney and, as kidney function declines, lead to complications involving other organ systems.

"PH is a very rare condition with only one to three people per million. On the rare disease spectrum, this is definitely at the low end of rare diseases," said Larry Bauer of Hyman, Phelps & McNamara, but who previously worked FDA where he co-founded the rare diseases program where he worked on drug development. He summarized the key themes at the end of the meeting, including:

- There are three types of PH with defined enzymatic deficiencies leading to the production of excess oxalate, as well as some cases where the cause has yet to be identified. The severity of the disorder ranges with type and from person to person within each type. The three types of PH have a lot of common and share most of the same symptoms, with the exception of the most severe symptoms associated with ESRD and early death, which occur most commonly in those with PH1.
- Each type of PH is characterized by the development of abundant or large kidney stones, often presenting in infancy, although in some they are only detected later in life. These stones can recur with little warning, cause debilitating pain, and obstructions that lead to frequent UTIs and other complications.
- Meeting participants wanted to make clear FDA and industry that there is a great unmet need for treatment that are safer and less burdensome than existing approaches to management.
- Children and adults with PH spoke about the multiple invasive surgeries and interventions to remove stones that require many visits to the hospital, and leave them scared.
- People spoke about *"the need to constantly worry about hydration, and always worrying about getting enough water intake."* This has some major downsides including the most disruptive to daily life: *"the constant need to urinate."*
- Short of a cure, people with PH expressed a desire for treatments that reduce oxalate levels, and prevent kidney stones, kidney disease progression and the need for dialysis or transplants.
- They also want effective treatments that reduce their fears of what might happen as they age.
- They want a simpler treatment that reduces the number of medications they have to take at different times of the day, that removes the requirement to drink so much water and the need for specialized diets.
- Finally, they want a treatment that is less invasive and grueling than the current surgical approaches, dialysis and double organ transplants and will risk some side effects and inconvenience to avoid surgeries.

Many individuals with PH and their caregivers expressed their eagerness to give their time and energy to engage in clinical trials of experimental medications that might give people with PH hope of leading a normal life, and one day, a cure.

OHF and the PH community is grateful to the patients and their representatives and to the physicians and scientific experts who participated, and to the FDA for their support, participation and for bringing this initiative to life. It is hoped that this information will be used to guide approvals of much needed therapies in PH.

APPENDIX 1

Appendix 1: Meeting Program

Externally-Led Patient Focused Drug Development Meeting on Primary Hyperoxaluria

- 9:45–10:00 **Log On**
<https://www.ohf.org/EL-PFDD-meeting>
- 10:00–10:05 **Welcome & Opening Remarks**
Kim Hollander, Executive Director, The Oxalosis & Hyperoxaluria Foundation
- 10:05–10:15 **FDA PFDD Overview**
Dr. Aliza Thompson, Deputy Director of the Division of Cardiology and Nephrology in the Center for Drug Evaluation and Research at the Food and Drug Administration
- 10:15–10:30 **Clinical Overview of Primary Hyperoxaluria**
Dr. Dawn Milliner, Professor of Pediatrics and Medicine, Mayo Clinic
- 10:30–10:40 **Introduction & Meeting Overview**
James Valentine, Meeting Moderator: JD, MHS, Hyman, Phelps & McNamara

Morning Session: Living with Primary Hyperoxaluria - Symptoms and Daily Impact

- 10:40–10:45 **Audience Demographic Polling**
- 10:45–11:10 **Panel 1: Patient & Caregiver Perspectives on Symptoms and Daily Impact**
- 11:10–12:30 **Audience Discussion and Remote Polling**
- 12:30–1:00 **Break**

Afternoon Session: Current & Future Approaches to Treatment for Primary Hyperoxaluria

- 1:00–1:05 **Journey For A Cure – Three Families Share Their Experiences**
- 1:05–1:30 **Panel 2: Patient & Caregiver Perspectives on Current & Future Treatments**
- 1:30–2:50 **Audience Discussion and Remote Polling**
- 2:50–2:55 **Meeting Summary**
Larry Bauer, RN, MA, Senior Regulatory Drug Expert, Hyman, Phelps & McNamara
- 2:55– 3:00 **Closing Remarks**
Kim Hollander, Executive Director, The Oxalosis & Hyperoxaluria Foundation

APPENDIX 2

Appendix 2: Polling questions and results

Demographic questions

1. Are you: (56 respondents/responses)

Response	Count (Responses)	Percentage
An individual living with PH	14	25%
A parent or caregiver of an individual with Primary Hyperoxaluria	42	75%

2. Where do you live? (74 respondents/responses)

Region	Count (Responses)	Percentage
US Northeast	20	27%
US Mid-Atlantic	5	7%
US Midwest	10	14%
US South	7	9%
US Mountain	2	3%
US West	9	12%
Canada	2	3%
Central or South America	0	0%
Europe or UK	12	16%
Asia	4	5%
Africa	0	0%
Australia or New Zealand	2	3%
Other	1	1%

3. What is your or the affected individual's age? (72 respondents/responses)

Age	Count (Responses)	Percentage
Younger than 12	24	33%
12-17 years	17	24%
18-29 years	11	15%
30-39 years	9	13%
40-49 years	3	4%
50-59 years	5	7%
60 or older	3	4%

APPENDIX 2

4. Do you/the affected individual identify as? (67 respondents/responses)

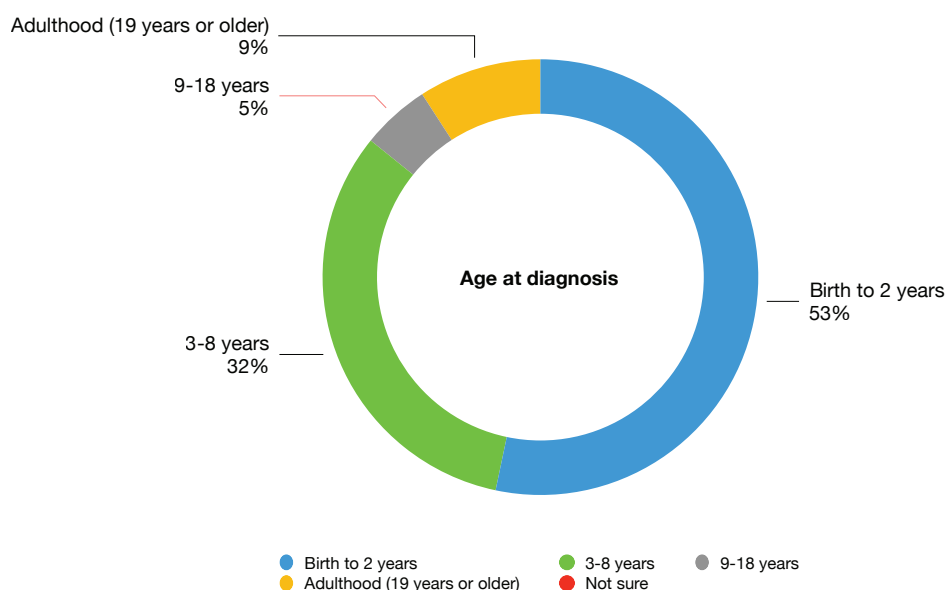
Options	Count (Responses)	Percentage
Male	41	61%
Female	26	39%
Non-binary/gender non-conforming	0	0%
Prefer not to say	0	0%

5. What type of Primary Hyperoxaluria have you been diagnosed with having? (75 respondents/responses)

Types	Count (Responses)	Percentage
Type 1	48	64%
Type 2	11	15%
Type 3	13	17%
Don't know	3	4%

6. At what age were you or the affected individual diagnosed with Primary Hyperoxaluria? (77 respondents/responses)

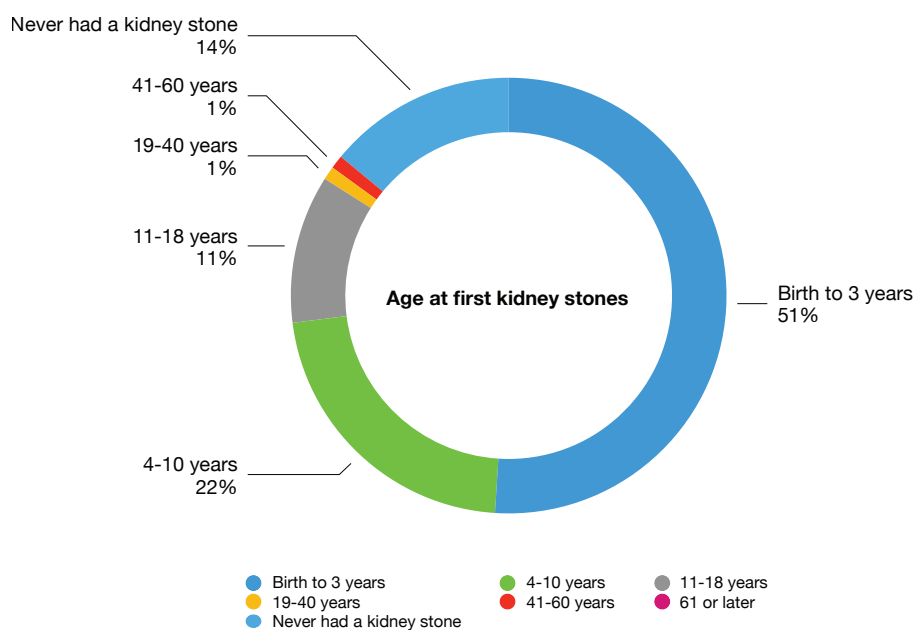
Age	Count (Responses)	Percentage
Birth to 2 years	41	53%
3-8 years	25	32%
9-18 years	4	5%
Adulthood (19 or older)	7	9%
Not sure	0	0%



APPENDIX 2

7. At what age did you have your first kidney stones? (81 respondents/responses)

Age	Count (Responses)	Percentage
Birth to 3 years	41	51%
4-10 years	18	22%
11-18 years	9	11%
19-40 years	1	1%
41-60 years	1	1%
61 or later	0	0%
Never had a kidney stone	11	14%

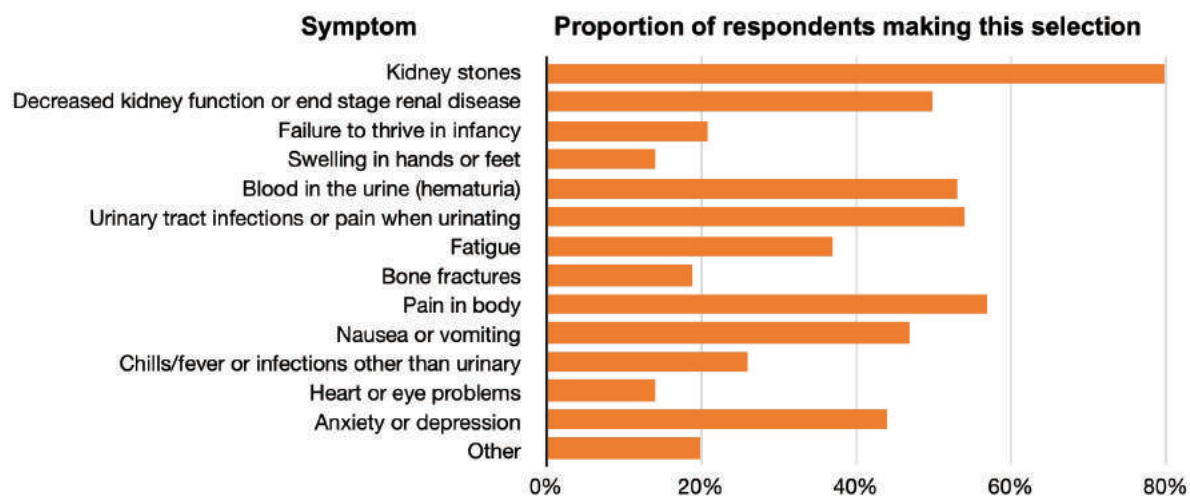


APPENDIX 2

Topic 1 Living With Primary Hyperoxaluria: Symptoms And Daily Impact

8. Which of the following Primary Hyperoxaluria-related health effects do you or your child have or recently had? Select ALL that apply (70 respondents/376 responses)

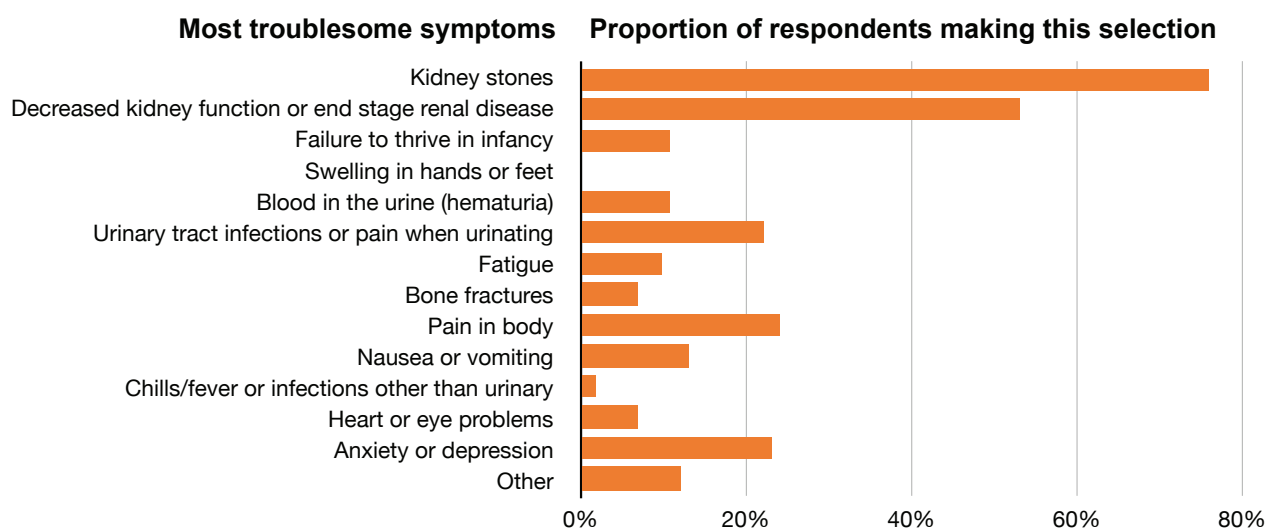
Symptoms/Health effects	Count (responses)	Proportion of respondents making this selection
Kidney stones	56	80%
Decreased kidney function or end stage renal disease	35	50%
Failure to thrive in infancy	15	21%
Swelling in hands or feet	10	14%
Blood in the urine (hematuria)	37	53%
Urinary tract infections or pain when urinating	38	54%
Fatigue	26	37%
Bone fractures	13	19%
Pain in body	40	57%
Nausea or vomiting	33	47%
Chills/fever or infections other than urinary	18	26%
Heart or eye problems	10	14%
Anxiety or depression	31	44%
Other	14	20%



APPENDIX 2

9. Select the most troublesome Primary Hyperoxaluria-related health effects that you or your child have: Select TOP 3 (83 respondents/225 responses)

Symptoms	Count (responses)	Proportion of respondents making this selection
Kidney stones	63	76%
Decreased kidney function or end stage renal disease	44	53%
Failure to thrive in infancy	9	11%
Swelling in hands or feet	0	0%
Blood in the urine (hematuria)	9	11%
Urinary tract infections or pain when urinating	18	22%
Fatigue	8	10%
Bone fractures	6	7%
Pain in body	20	24%
Nausea or vomiting	11	13%
Chills/fever or infections other than urinary	2	2%
Heart or eye problems	6	7%
Anxiety or depression	19	23%
Other	10	12%



APPENDIX 2

10. What specific activities of daily life are most important to you that you are less able or unable to do because of your or your child's Primary Hyperoxaluria? Select TOP 3 (75 respondents/185 responses)

Activities of daily life	Count (responses)	Proportion of respondents making this selection
Attending school or working	54	72%
Personal hygiene	7	9%
Driving a motor vehicle	2	3%
Participating in sports	22	29%
Participating in other hobbies	13	17%
Performing household tasks	4	5%
Participating in family care and activities	14	19%
Going out, socializing, traveling	54	72%
Other	15	5%

11. What do you fear or worries you the most as you get older for either yourself or for your child? What capabilities are most concerned about potentially losing as you grow older? Select up to three (62 respondents/167 responses)

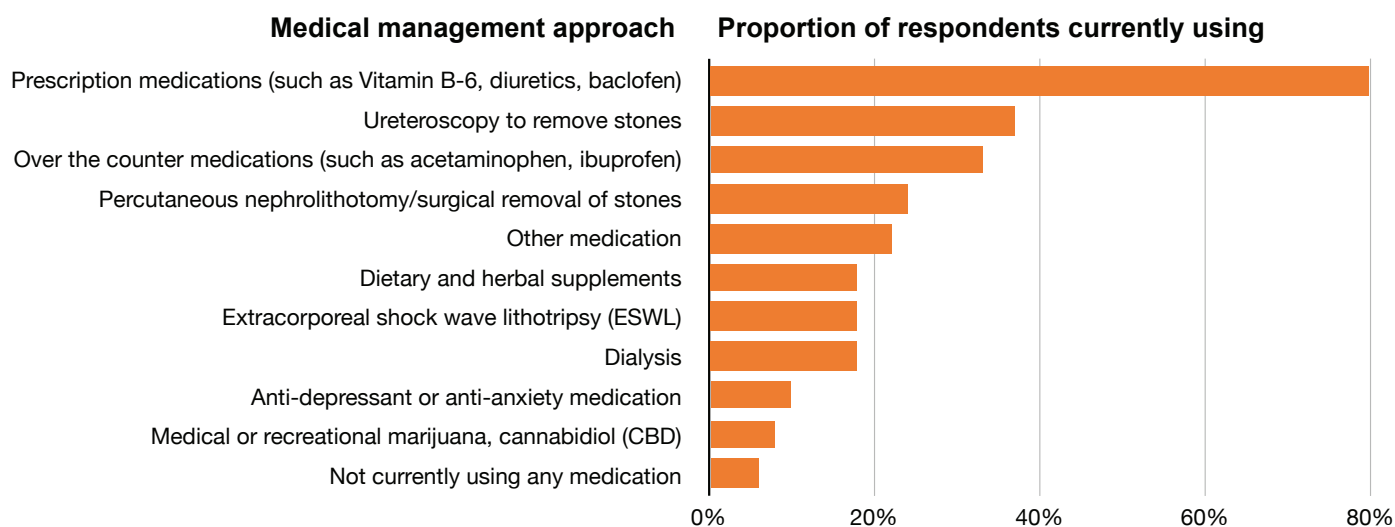
Worries about the future	Count (responses)	Proportion of respondents making this selection
The stress of not knowing how the disease will progress	38	61%
Worsening of severity and frequency of symptoms	24	39%
Unexpected emergency room visits or surgery for stones	5	8%
Needing dialysis	22	35%
Not having the energy to go to school or work	2	3%
Not being able to live as I want to	19	31%
Not knowing if I can support myself/family financially	10	16%
Becoming a burden to my family	12	19%
Dying at a younger age	28	45%
Other	7	11%

APPENDIX 2

Topic 2 - Perspective On Current And Future Approaches To Treatment

12. Are you using any of the following to manage Primary Hyperoxaluria? Select ALL that apply (51 respondents/139 responses)

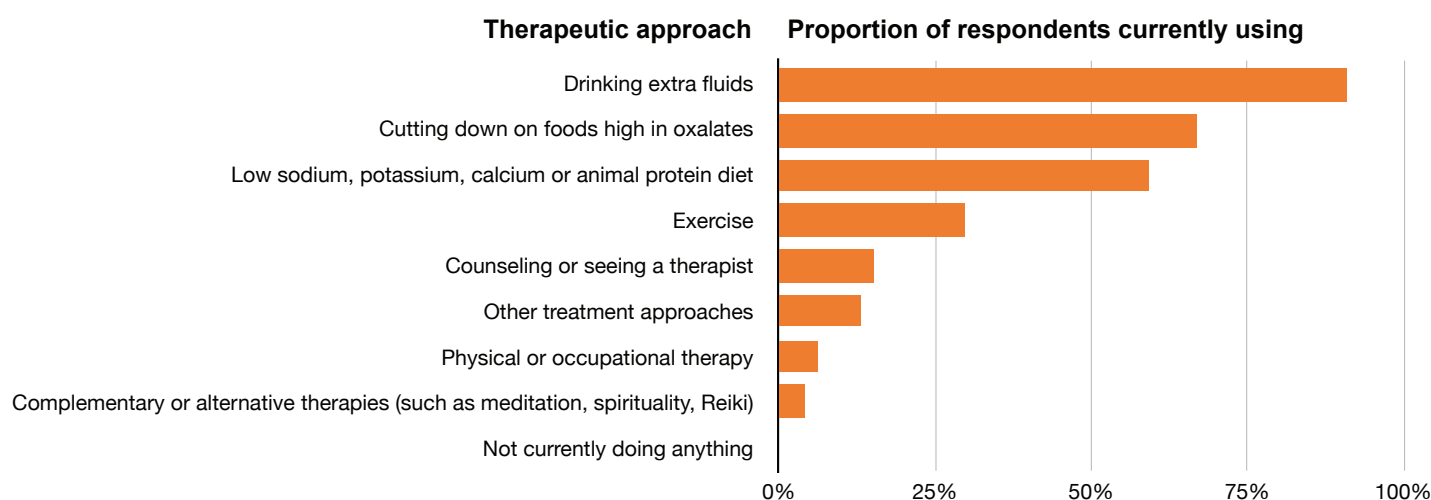
Medical management approaches	Count (responses)	Proportion of respondents making this selection
Prescription medications (such as Vitamin B-6, diuretics, baclofen)	41	80%
Ureteroscopy to remove stones	19	37%
Percutaneous nephrolithotomy/surgical removal of stones	12	24%
Extracorporeal shock wave lithotripsy (ESWL)	9	18%
Dialysis	9	18%
Over the counter medications (such as acetaminophen, ibuprofen)	17	33%
Medical or recreational marijuana, cannabidiol (CBD)	4	8%
Dietary and herbal supplements	9	18%
Anti-depressant or anti-anxiety medication	5	10%
Other medication	11	22%
Not currently using any medication	3	6%



APPENDIX 2

13. Beyond medications and supplements, are you using any of the following to manage Primary Hyperoxaluria? Select ALL that apply (54 respondents/153 responses)

Other therapeutic approaches	Count (responses)	Proportion of respondents making this selection
Exercise	16	30%
Physical or occupational therapy	3	6%
Drinking extra fluids	49	91%
Low sodium, potassium, calcium or animal protein diet	32	59%
Cutting down on foods high in oxalates	36	67%
Complementary or alternative therapies (such as meditation, spirituality, Reiki)	2	4%
Counseling or seeing a therapist	8	15%
Other treatment approaches	7	13%
Not currently doing anything	0	0%



14. How well does your current regimen control your condition overall (57 respondents/57 responses)

Impact of regimen	Count (responses)	Proportion of respondents making this selection
Not at all	1	2%
Very little	8	14%
Somewhat	31	54%
To a great extent	17	30%
Not applicable because I'm not using anything	0	0%

APPENDIX 2

15. What are the biggest drawbacks of your current treatment approaches? Select up to 3 (57 respondents/131 responses)

Therapeutic Approach	Count (responses)	Proportion of respondents making this selection
Not very effective	23	40%
High cost or co-pay, not covered by insurance	18	32%
Limited availability or accessibility	8	14%
Number of pills/medications needed per day	37	65%
Side effects	18	32%
Requires too much effort and/or time commitment	19	33%
Other	8	14%
Not applicable as I am not using any treatments	0	0%

16. Short of a cure, what outcomes are most meaningful to you in a future treatment? Select up to 2 (49 respondents/92 responses)

Therapeutic Approach	Count (responses)	Proportion of respondents making this selection
Slowing the formation of kidney stones	9	18%
Completely stopping the formation of kidney stones	30	61%
Regaining strength and energy	0	0%
Lessening pain	1	2%
Improving kidney function	14	29%
Decreasing need for super hydration	11	23%
Decreasing urinary tract problems	0	0%
Stopping disease progression	23	47%
Letting me be able to eat whatever I want	1	2%
Other	3	6%

APPENDIX 3

Appendix 3: Written comments

The following are the written comments and questions received during and after the meeting. Comments from the same respondents have been placed together; however, personal identifiers, such as names and email addresses have been removed. Please note that not all respondents are native English speakers but, with the exception of one translation, no one's comments have been edited for typos or punctuation. Please also note that some of the comments, submitted during the meeting, were in response to the discussion that was going on live at the time, and may seem incomplete outside of the meeting context.

Respondent #	Comment
1	<p>I'm 26 and I have PH3, One of my first memories was when I was 4 and was taken to the hospital because I had many UTI's and was in a lot of pain. After a few tests they realized I had a big kidney stone in my right kidney and after a day or two it came out with much pain of course. Note that my right kidney didn't develop fully after that. We didn't know much about HP back then, thanks to Professor YF who guided us and researched our case, we eventually got some clarity. Apparently, I had 4 more sisters (including my identical twin) who had PH3 (5 out of 10 kids). Two of them had kidney stones as well, including the youngest sister who had a stone at the age of 18 months.</p> <p>Ever since I had to make sure to drink a lot of water (which is not easy) and try not to eat foods high in oxalate.</p> <p>Furthermore, I have a yearly checkup including Ultrasound's, blood and urine tests since I have another kidney stone for the past 10 years that hasn't moved and I have no symptoms (besides worrying), hopefully it will be the last kidney stone I ever have.</p> <p>I would love to know more information regarding the clinical trial, what does it include? Can all types of HP participate? And does it include guidance by a nutritionist?</p> <p>Thanks for building such an important foundation that can help many people and children get the care and support they need.</p>
2	<p>I am a caregiver of my 13 years old son who has PH3.</p> <p>My main concern is the unknown prognosis and future.</p> <p>I would consider any clinical trial which could be tolerated both mentally and physically by a 13 years old boy.</p> <p>Thank you so much!</p>
3	<p>Comment 1: I am the caregiver of my patients we are from poor facility countries here is no available of any treatment for this disease so how can we get the medicine rid of from the disease.</p> <p>Comment 2: How will medication be made available for those who do not live in area that it is approved? How can I receive medical help when I live in a country that does not have treatment available? Is there anyone who can help me get medicine to me or get me to the medicine? I will do anything and go anywhere. I just need help.</p>

APPENDIX 3

Respondent #	Comment
4	<p>Comment 1: Thank you for organizing this. As a primary researcher on PH1, hearing from the patients, families, and caregivers has been very important for directing research and drug development</p> <p>Comment 2: As a researcher, it was great to hear from physicians, patients, and families about how they live with PH and the importance of technologies including drugs to develop treatments for this disease. I hope this will emphasize basic and translational research for generating new therapeutics and improved diagnostics</p>
5	<p>Comment 1: My story began with my second daughter when she diagnosed her with primary hyperoxaluria. she was 9 month. Know she has 12 years. these 12 years full of pain for my daughter and for me as mum. Im always worry about her future....</p> <p>Comment 2: I have 3 children with primary hyperoxaluria. they suffering from the abdomin pain special when stone go down. We force them to take their medication. I hope that one day my children will take the enzymes they need. I live all the time with fear about their future.</p> <p>Comment 3: Im always worry about the future for them. Im really tired. One of them reject to take the medicine. We force them to take it. They always complain from pain in their abdomin. I hope that pfd will find the enzymes that they need.</p>
6	<p>Thank you for organising the meeting with the FDA. I wanted to add our story to those who presented so bravely on the call.</p> <p>Our son, A. was diagnosed with PH1 aged 8. He had many UTI and stone events prior to diagnosis and thus, by the time of that diagnosis he was seriously ill with end stage kidney disease.</p> <p>He was transferred to a specialist hospital in London where we were told that a double transplant was the only cure for him - a very shocking and upsetting discussion but we agreed that he should be put onto the transplant waiting list asap.</p> <p>Over the next 4-5 months he was treated at the hospital and started a regimen of pyridoxine and water together with antibiotics. Very luckily for us, the pyridoxine seemed to work and his kidney function improved to the extent that he moved from critical transplant need to one of 'just' chronic kidney disease.</p> <p>During the same period we became aware of upcoming clinical trials which offered some hope for a Pharma-based solution to PH1.</p> <p>About 5-6 months after his diagnosis we received a call at 3am to advise us that a liver was available for transplant and we had to make the agonising decision to go ahead or to refuse the transplant. I will never forget the 30 minutes or so that we had to make up our mind.</p>

APPENDIX 3

Respondent #	Comment
6 (continues)	<p>We decided not to go ahead with the transplant and put all our hope into the drug trials. Luckily for us, A remained stable enough through the period when we were waiting for the trials to commence.</p> <p>About 24 months ago we started discussion with the hospital for A to commence one of the trials. Fortunately, he was accepted onto the trial and has been on it since.</p> <p>The results, both for A and the other participants of the trial are very encouraging and we hope beyond hope that the trial will lead to approval by the FDA and European agencies.</p> <p>We can't imagine what those families before us have gone through when having the deal with double organ transplants and we are desperate that no other family has to go through such an ordeal.</p> <p>We therefore can only encourage all those who have influence to push as hard as possible to get these new, amazing therapies approved and more widely available. No child deserves to be blighted by this terrible condition.</p> <p>Thank you AK & SM - Parents to AR, now 12 years old.</p>
7	<p>I have PH3. I have had numerous ureteroscopies; We've lost count. Over time, these have caused me to become incontinent to a degree. Coughing and so on cause me to leak. My underwear, my pyjamas, always smell of urine. It's rather ironic since I had a bladder repair back in 2007.</p> <p>This is a side effect of PH3 that probably no urologist would consider and I understand that there is medication available but that it can cause Dementia. I am already 67 years old. I pray help can be found before I become too old for anaesthetic to be safe for me.</p>
8	<p>Thank you for having this symposium. The suffering caused by this disease is significant, and our treatment options pale in comparison to the problems. We are excited about the possibilities of research with new therapies. We are willing to risk side effects to have these options. I am concerned about costs of these novel medications, but the costs of not having them is also tremendous. Thank you to the FDA, to the scientists, to the physicians, to the families, to the OHF and to supporting staff for all of your help.</p>

APPENDIX 3

Respondent #	Comment
9	<p>Comment 1: Go ahead, alot of people around the world waiting for your fruitful treatment, I'm a patient and parent of two kids hope to spend my time with my family in good health....alot of hope you gave to us... thank you very much</p> <p>Comment 2: Hi, waiting for this opportunity for long time, My creatinine is around 2 mg/ dl according to accumulation of calcium oxalate in the kidneys, unfortunately I don't know what is the type of my genetic disorder, I hope to find a treatment to reduce the oxalate and oxalate salts bad effect, my health is good generally but the rise of blood creatinine is terrifying me, I'm 30 years old and father of two kids, I'm ready to participate in any medical and clinical trials. I'm a civil engineer with master of environmental engineering with good background in the field of nano photo catalyst applications.</p> <p>Thank you very much for this given hope....with love</p> <p>Comment 3: I'm a patient of 30yo Actually, living with chronic disease wich has no tratment makes you live in horror, really hope to get the treatment</p> <p>Comment 4: I would like to know if there is another way than the genetic analysis to know the type of PH scince it's not avilable in my country.</p> <p>Comment 5: I know hundreds of patients with PH waiting for this medication... so give them the hope God bless you</p>
10	<p>Comment 1: Our daughter had 2 different kinds of mutations on the AGXT gene. 1 was known as being sensitive for Pyridoxine treatment, the other one they did not know for if it would work or not. So we tested it for a couple of months...it didn't work, so we lost time (damage). Can researchers share their experiences on this on a general platform or something, since it is a rare disease and so every info could be helpfull between experts.</p> <p>Comment 2: So nice to hear all these stories and feel related! Thanks for bringing us together.</p> <p>Comment 3: My daughter was diagnosed with PH1 at 2 months old since she suddenly went in complete kidney failure (she almost died). Followed by 2 years of hemodialyse and many months of hospitalisations and 30+ operations. She had a liver transplant at the age of 1 and kidney transplant at the age of 2. She had multiple complications, we often feared for her life. She has broken maybe 8 bones and will have eye damage for the rest of her live. It's been verry hard and she will need kidney transplantations in the future.</p>

APPENDIX 3

Respondent #	Comment
10 (continues)	<p>Once we knew she would survive this, we wanted a second baby. I had to abort 2 pregnancies at 13 weeks since both of the babies inherited both mutations... hard choices to make.</p> <p>We now have a baby boy who is a carrier both does not have PH1. We live in constant fear that something could go wrong again with our daughter or that she would reject her liver. Let's hope for the best and enjoy the time we have!</p> <p>Comment 4: Even after a kidney-liver transplant you are still limited to school and social things since you take immuno suppressive medication and so you are in high risk of getting infected. Also no sleepovers because of guarding her drinking water and giving her medication.</p> <p>Going on a holliday is also a risk; what if she rejects her kidney or liver transplant, what if she gets diarea/vomiting and she needs IV fluids...</p> <p>Also drinking liters of water does not stop (to guard your kidneys and try to keep them as long as possible).</p> <p>No school possible now because of COVID.</p> <p>Also difficulties in school developments because of bad eye sight (eye dammage) and she was motorically behind because of missing a lot of "normal" baby development because of all the hospitalisations and the yaers of daily dialysis between her 0 and 2 years of age</p> <p>Comment 5: what worries you most...</p> <p>At this time: rejecting the transplanted liver or kidney</p> <p>Comment 6: Daughter PH1 total renal faillure at 2 months old: regarding treatments; what was very frustrating is that you know that, despite dialysis 6/7 days, every day the oxalate is causing irreversible dammage to your body (bones, eyes, kidneys,...).</p> <p>Comment 7: PH is a non-dominant genetic disease, so theoretically you have 1 chance out of 4 to have a child with PH when both parents are only carriers.</p> <p>Yet it seems like there are a lot of people with multiple chilren with PH. I myself also had more pregnancies with doucle mutations then only 1 mutation.</p> <p>Has there ever been research done to see if there is indeed a higher prevelance then 1 out of 4?</p> <p>And what might be the reason for this (ex. faster sperm swimmers, certain protein surfaces/changes,...)</p> <p>Comment 8: Outcomes for a cure "other" = find a solution for the enzyme problem in the liver. Since the rest of the liver is "ok" and now we had to "throw away" a perfectly good liver aside from the enzyme problem... that's a pitty...and liver transplantation is very hard to go through...</p> <p>So yes of course stone formations decrease is a good outcome, but dealing with the original problem would even be better.</p>

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Respondent #	Comment
10 (continues)	<p>Comment 9: Important piece of the treatment is to share relevant info (medical data) about PH towards all professional doctors (nephrologists / liver doctors) around the world. Sharing this data openly will help the pharma industry/researchers but also doctors to quicker make the right diagnose and continuously be up-to-date about current treatments.</p> <p>Comment 10: About prenatal testing: you only know the result at about 12-13 weeks pregnancy... it's hard to be 3 months pregnant without knowing if you carry a child with PH and so might need to abort the pregnancy... I had to abort twice since i do not wish any child the pain that my daughter had to go through... Main reason to make this very difficult decision is the fact that there is NO cure...you can not avoid the permanent damage that will be done, not even if you know it from birth...</p>
11	<p>Thanks to the FDA, Sponsors, OHF and Kim and Jim for hosting. The mysterious progression of the disease is so concerning. The uncertainty about the quality of life to expect can be far more concerning than even know bad news. A drug to give patients some certainty for a healthy life is monumental to living a healthy life.</p>
12	<p>Comment 1: Thank you for listening. Our family is excited about potential new treatments. How soon do you think one will be on the market? What are the barriers that you see.</p> <p>Comment 2: Just to reiterate, mental health is just as important as physical health so proper mental health following and medication is very important !</p> <p>Comment 3: The psychological impact and on relationships is a challenge, the intense learning curve one overcomes with chronic illness, the need to advocate and navigate....these are beyond the meds, surgeries, procedures.</p>
13	<p>Comment 1: I have 2 children with PH1. They presented differently. Our son was an infant in kidney failure and our daughter struggled through years of painful kidney stones and a slow descent into kidney failure. It is a helpless feeling not being able to take away your child's pain and make things all better. It is also very challenging to do everything in your ability to get the best possible care for your child and stay on top of their care being very proactive and still watch your child decline despite everyone's best efforts. It is so important to stay on top of their mental and emotional health as well as their physical health. Even when the treatment options are limited, there is always hope.</p>

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Respondent #	Comment
13 (continues)	Comment 2: This disease has consumed our lives for so long. Our children trust that we are doing everything we can to get them a treatment and cure. We have been proactive since day one. We have been “too little too late” for so long now and the declined too fast to be saved from needing transplants. We question if we somehow failed them by not getting them treated before they declined into kidney failure and experiences so much pain. Please understand the urgency and desperation for so many patients that still have time to get treated before they decline. Please help get these investigational medications out to the patients ASAP. We have all held onto hope for so long, but we need action and we need it fast. If you need more patients to participate in studies, make it easier to get patients from other countries to participate. If you need us as patients and caregivers to do something, tell us what it is. We will do anything to prevent others from suffering from this horrible disease.
14	I worry about the future for my daughter all the time. Even though things are working today, we know tomorrow can be a completely different story. She never wants to have a stent placed ever again and fears the next time she will need surgery or have other complications. She has huge dreams for her future but I worry PH2 will stop those dreams. I hope for a better medication or treatment in the future that will allow all of those impacted by PH to have something that will work long term and will keep their disease stable so they can follow their dreams without all the burdens this disease brings.
15	We have a 3 year old son that was diagnosed with PH3 prenatally through a “standard genetic testing panel” given by my OB-Gyn when I was pregnant. Currently he has experienced no stones or symptoms, but we have been proactive in monitoring this extremely rare disease. We have had frequent ultrasounds (monthly when he was under 2 years old) to “try to find anything that even resembled a stone” before his kidneys get covered like some of the other stories we have heard. At 4 months old, he began taking potassium citrate solution several times a day, when the ultrasound scans showed possible stones. We are trying to determine if the benefits of the citrate outweigh the negatives or if we are asymptomatic to PH3 to date. I don’t think he tolerates the citrate well, but that is still undeterminable. It is a constant worry which leads to high anxiety as a parent and to our family for our current and future lives. Also, any doctor that sees my child automatically focuses their questions on this rare disease, questioning if my visit is really related to PH3, which they don’t know anything about. Because there are so many unknowns with PH3, most medical professionals can’t look at my son as a normal child. We have no idea what the future brings and hope that a treatment will solve for everyone.

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Respondent #	Comment
16	<p>Comment 1: I'm C in [a city in the US] and have PH1.</p> <p>I want to convey the importance of finding treatments for rare diseases and the hope it provides. I'm going to share part of my (and my sister's) story which I don't share often because it's quite sad (like so many other's sharing today) with the goal of helping to inspire future research.</p> <p>I was diagnosed at 21 when my kidneys failed. I passed kidney stones as a teenager, but didn't know what was going on at the time. My sister, who was 2 years younger, was diagnosed when she was 2 1/2 and her kidneys failed. It was 1984. Fortunately, the doctors identified what it was quickly. Unfortunately, they were not aware of any treatment options. They told my parents that she probably wouldn't live to be a teenager. She passed away at age 11.</p> <p>She suffered many peritoneal infections from the catheter for peritoneal dialysis and frequently required blood transfusions. We both missed a lot of school. She had to switch to home tutoring when she broke her hip at age 7 and was in a half body cast for a year. It never healed and she never walked again. She was in constant pain. Her ankle bone totally deteriorated by the time she was 10 and her foot had to be supported if she was moved at all because it would just flop around. She had a large ulcer on her ankle from it not moving frequently enough. She was in constant pain. I, as a night owl, would often respond to her requests for Tylenol in the middle of the night. Towards the end we had to keep the blinds and curtains shut because the light would hurt her eyes. It will be 27 years... since she passed away and I still miss her.</p> <p>I can't even imagine what it was like to suffer the way she did. Based on what I could imagine alone, it scared me and I knew I never wanted to go through it. As a child, they said I might have the same disease. I was strong and healthy though and believed that would not be the case. My Mom felt totally let down by the medical community and swore off all doctors after my sister passed away. I never went to the doctor as a teenager even though I did, in hindsight, pass kidney stones. I just endured the pain.</p> <p>I did go against my mother's wishes and go to the emergency room at 21 when I realized I was severely ill. My creatinine was 31 and I was immediately told I had to go on dialysis. Based on my sister's illness, I was told I had Primary Hyperoxaluria. This thought of receiving the diagnose had come to the back of my mind from time to time and I decided I would not do dialysis if that day ever came because there was NO WAY I would go through what she did just to suffer a long death. I didn't believe that there would be any hope. Why would anyone ever dedicate their time to studing such a rare disease? So, when I heard I had Primary Hyperoxaluria, I refused dialysis. Fortunately a nurse took the tiime to listen to me and convinced me that MAYBE there had been some advances.</p>

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Respondent #	Comment
16 (continues)	<p>A family friend brought some information she had found online (if I recall correctly) from the OHF showing that people had been studying it. It gave me hope. I continued dialysis, got in contact with Dr. Milliner, and the wonderful folks at the Mayo Clinic and had a kidney / liver transplant in 2004. The kidney had some complications. I received a second kidney from my husband, who I met in 2007, in 2008. I turned 40 this year, am happy, 99% healthy, and have a better life than I could have imagined. I have a few long standing problems, mainly with my joints and bones which went through a lot until I started getting the oxalate out of my body. I fractured a rib when I was about 22 and will get a stress fracture or arthritis if I ramp up my activity too quickly. With COVID, my life has been the most impacted. My husband and I haven't left home in about 7 months now. Overall, though, I have been able to do a lot including complete a triathlon and half marathon and look forward to a long, similarly healthy life. I only avoid contact sports to avoid any impact near my kidney transplant. I do face the reality I will need another kidney transplant or two in the future and possibly need on dialysis again for a period of time. Although, I desperately hope not. I hope there are continued medical advances in kidney growing / procurement. Other than these physical impacts, my life has been impacted with regards to where to live – I need to make sure I'm near a good medical system – and career choices. I haven't taken any risks with my career or attempted ventures that interest me because the health insurance is so vital. To maintain health insurance, I've worked for the same company for 21 years. (If you're doing the math I worked (and finished college) at the time of my diagnosis and while on dialysis out of necessity. It wasn't easy to say the least but was necessary.) Thank you for listening and your focus on continuing to improve the lives of those with Primary Hyperoxaluria. It's truly life saving and life changing!</p> <p>Comment 2: I didn't think to share this before and was just reminded by another's comment about becoming a mother. Some years ago, my husband and I decided not to have kids. The decision is directly related to having PH1. I plan to live a long and healthy life, but the reality is that we really don't know. Because my future is uncertain, along with the complications of carrying a child in my particular circumstances after transplant, we decided to not risk it. Burdening him with having to take care of both me and a child worried me too much.</p>

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Respondent #	Comment
16 (continues)	<p>Comment 3: I don't think about this often but hearing other's experiences I keep thinking about items regarding the impact of PH. The loss of my sister is a bigger impact to me than any other way PH1 has affected my own health including the transplants and the 3 1/2 years on dialysis 5 times week with many access issues. In addition, there is this looming survivor's guilt. Why did she have it worse than me? Why am I still here? It can be a motivator, but also a burden. This is true as someone who has PH1, but also true before I found out I had PH1, wondering why I didn't have it but she did.</p> <p>Comment 4: As a transplant recipient, improving kidney function is the top of my list. I would drink 10 liters of fluid a day, take 100 pills a day, eat whatever diet you wanted to throw at me if I could preserve and even better improve my kidney function throughout the rest of my life. Dialysis is life-saving but really hard. I always tell people that they don't know true exhaustion until they have been on dialysis. I still recall moments lying down, expelling all the air out of my lungs ,and trying to be as still like that as long as I could because I felt too tired to breathe. No exaggeration.</p>
17	<p>Comment 1: I live in a country that can't properly treatment my disease what should I do ?how can you help me get medication ?</p> <p>Comment 2: I am 33 years old and was diagnosed with PH1 this year after being in kidney failure and on dialysis. There is no good treatment or knowledge for PH here in Nepal. I can only have dialysis 2 days a week and there is no lab work to follow oxalate levels. They only do kidney transplant here and I cannot afford it. How can I get somewhere for treatment or participate in a clinical trial and have a chance to live? Here in Nepal I have no hope. Please help me.</p> <p>Comment 3: I am in Nepal on dialysis with PH1. I want to be in a clinical trial and I know clinics are looking for patients to participate. I want to participate but there is no clinic near me. I have family in USA and Australia who will let me stay with them if I can get there but Covid has borders closed. How can I get to USA if I am not a citizen and how can I get dialysis treatment while participating in the clinical trial? I am so thankful there is so many who are getting better care, but I do not want to be ignored or forgotten because I live in Nepal. I want to live. I will do anything. Please fight for us too. help us in poor countries get help, we do not want to die.</p>
18	<p>One medication- right now too many medications w/ unknown side effects.</p>

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Respondent #	Comment
19	<p>Comment 1: Thanks a lot. MY SON has been transplanted, so i chose the difficulties after transplantes 10 years</p> <p>Comment 2: my son diagnosed in age of 5 months as stones in kidney, and in age of 6 months diagnosed as ph1 . in age of 1 year and 6 months has been liver and kidney transplanted, i did spend kidney to him . He is now 10 years in the third class playing piano and mathatic boy! i think we need to share more details a very specific stories like what kind of food, what the symptoms before and after transplantations. I'm sorry you will find lots of grammar mistakes! we have to ask a very important question that what the differences between symptoms and the side effects of medicine ? There are lots of signals that are not clear</p>
20	<p>Our 7 years old daughter was diagnosed few months ago with PH1 after suffering from vomiting for a year.. we have been to doctors that they checked her for brain cancer and stomach problems. Always getting a diagnosis of sensitivity of her stomach. The last time that she was very unwell the current nephrologist visited us in the hospital and he talked to us about nephrocalcinosis that was found and that he believed that she has ph1. After that she had a surgery for stones removal. Her mutation is partially effected by B6we have no idea yet what this means and how well she will be in the future!! We hope for a treatment that will stop the reduction of her kidney function right there, to have a good quality of life with out dialysis and transplants.</p>
21	<p>As a grandparent of a boy with PH1 diagnosed at about age 8 (who has had multiple kidney stones/some with obstruction requiring surgery)- when visiting his family I try, in a very small way, to be helpful to the family by substituting for them- to awaken my grandson in the middle of the night to get him to the bathroom to empty and protect his bladder from the large amounts of urine (which is from his drinking 3-4 liters of fluid/.day) and to continue to drink water at that time, and then get him back to bed .</p> <p>As an aside, its may be not be so difficult to drink 3-4 liters of water a day-for a few days !!-BUT (wow)much more difficult for sure to drink that amount of water EVERY, every DAY to help- with in addition to all the other medications- to hopefully decrease the occurrence of oxalate stones and kidney function damage. I marvel at what PH patients have to endure to live with this very difficult disorder</p>

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Respondent #	Comment
22	My son, now 26, has PH 3. He had stone events in his teens. We did find that limiting the number of simple carbohydrates he consumed, we could keep his urinary oxalate levels in the normal range. He no longer follows this diet as it is limiting. He never did take any medications for his PH 3. He has had no stone events or issues since he was about 18.
23	Current treatment management is only somewhat effective; I have never been 100% stone free. It's just a matter of time until the next surgery, which I hope is only ureteroscopy, rather than PCNL. My oxalate levels remain high, leaving a question about when I may progress into kidney failure.
24	I had a double transplant in 1999 at the Mayo Clinic in [a town in the US]. I know it is a scary concept or many of you, and yes, spring of 99 was a bit touch and go, but 20 years later I'm strong and healthy, and have two teenage children who are healthy and do not have oxaluria. I work full time, coach soccer, participate in local theater and fish regularly. Stay positive !
25	<p>I have 2 sons who are diagnosed with PH1. One is 5 and he is currently B6 responsive for now. He was diagnosed shortly after -ruling out pyloric stenosis. He has had 4 kidney stone surgeries after the age of 1 year old. He currently has a stone in his right kidney that they are watching. We are currently dealing with a lot of bone pain and bone weakness, and another diagnosis of osteoporosis due to the PH1. He has had multiple hospitalizations and procedures. 1 failed stone removal event because he was too small. The poly cit really caused a lot of problems for him. He would constantly throw up and be in a lot of pain in his stomach. We stopped giving it to him about 8 months ago, and he hasn't had a hospitalization for dehydration since. It was making him so nauseous. His fluid intake is 2.5 liters a day, and it's challenging. We are hoping he continues to be B6 responsive.</p> <p>My other son, is 7 months old. We just received the diagnosis about a month ago. He is currently not stable as far as the disease. He just began B6 and Poly Cit a month ago, and we just checked labs again on Friday and we are waiting on results for both both. His kidneys didn't look great on the ultrasound - they lit up bright white and my husband and I knew right away. We should know really soon if it's working or not. We have no idea about his journey yet.</p>

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Respondent #	Comment
26	It's important to note that, other than for B6 responsive patients, the current treatment options don't do anything to reduce oxalate in the urine or blood. Super-hydration, Polycitra-K and Phos-NaK only try to neutralize the oxalate after it has been formed. A treatment option that addresses the root cause of excess oxalate production would be a great benefit to the patients and families.
27	I'm currently online live and am happy to answer any questions anyone has about my Video. [A panelist during session 2]
28	One of my biggest worries as a caregiver in our current state of research, is that even if drugs become available to all of us, our families affected, what guarantees will there be that they will be affordable or even accessible around the world?
29	Managing PH is feels pretty impossible. From years of water, and surgeries, and confused doctors, none of it was perfect. I'm now on dialysis and while my kidneys are 'happy' and I'm stable, it comes with the side effect of no life. No school, difficult schedule making it harder to see friends, and exhaustion taking up a majority of my days.
30	Can't figure out how to log in, from either your page or my email. Also, it appears this is about clinical trials, which I'm definitely not interested in when it comes to my son. Pretty disappointed about that part.
31	I have just been diagnosed with PH1. I am 62 years old. Only important question that I need answered is, have I passed on PH1 to my children? and is it true you need 2 parents with this gene to then pass PH1 on to their children.
32	My son is a PH3 patient. He began having pain at 17 months but wasn't yet talking so he couldn't communicate what was wrong. He would just lay on the ground and cry and hit his penis. This went on for weeks, back and forth to the pediatrician with them saying he is probably just discovering his privates, or giving us fungus cream, or sits baths. After multiple visits I finally said please refer me to a urologist. My son is a PH3 patient. He began having pain at 17 months but wasn't yet talking so he couldn't communicate what was wrong. He would just lay on the ground and cry and hit his penis. This went on for weeks, back and forth to the pediatrician with them saying he is probably just discovering his privates, or giving us fungus cream, or sits baths. After multiple visits I finally said please refer me to a urologist. The pediatric urologist all but dismissed me as well and I told him I was not leaving until you test his urine, which came back with blood in it. After a renal scan it showed stones in his bladder and kidney which were removed at 20 months. It took us more than 3 years to get an actual PH diagnosis.

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Respondent #	Comment
32 (continues)	He's now almost 8 and hasn't had an episode since then so doesn't understand the importance of his fluid intake or need to urinate more or why there are certain foods he can't really eat. He's on a low sodium diet and take tri-citrates twice a day. He can't swallow a pill and the fluid is horribly tart. We have finally found a yogurt mix that works, but it took a long time. As of this year our insurance no longer covers the medication because it is technically considered supplements. We have tried appealing this with no such luck. We feel very lucky that he hasn't had another episode but are nervous for what the future may have in store.
33	I am 13 and started middle school. I am worried about school and having to miss school for doctor appoints and also having people ask about where I was. Also missing some school in the morning when i have to do bloodwork.
34	I drink almost 6 liters of water a day because of ph1. because i needed to use the toilet during a 3 hour exam they forced me to redo the exam even tho a teacher came with me to the toilet.
35	<p>Comment 1: My daughter was born with a sever ecase of PH1. She was born in kidney failure. She is extremely lucky to have been diagnosed at 5 weeks old. The Dr's thought she would die. She was non b6 responsive. The only cure was a liver transplant. Weekly labs showed her kidney function improve up until her liver transplant at 10 months old. The wait for that liver was traumatic for our whole family. I would hold my infant child in my arms and wonder how far the monster (PH) had gone. Had it travelled to her heart or her bones. She would cry in pain. It was so hard to watch. After her liver transplant, at 4 yrs old she was diagnosed with de nova auto immune hepatitis. Transplant is not a cure. You only switch one set of problems for another. We knew one day she would need a kidney transplant. The harsh ant rejection medications contributed to the need for her kidney transplant at 14 yrs old. She is 19 now. Being immune suppressed during a pandemic as a teenager is very hard for her. Takes isolation to a whole new level. While I am extremely grateful and lucky to have my beautiful child alive I think transplantation is an archaic treatment. We are in 2020. The advancements we have made in all aspects brings hope that we can find a medicine so we do not have to replace organs.</p> <p>Comment 2: Polling question Other Making friends has had a severe impact on E. Bullying was a big issue in school. She felt different.</p>

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Respondent #	Comment
35 (continues)	<p>Comment 3: E was diagnosed at 5 weeks old. Having been diagnosed so early and not B6 responsive she had her liver transplant at 10 months old. Such an early diagnosis is absolutely critical with this disease. Before her liver transplant she was hospitalized 20 times. After liver tx only 2 and one was for her kidney transplant at 14 years old. Because of the early diagnosis she has had a minimally medically invasive life. She did everything and suffered minimally compared to everyone I have heard here. I always knew how lucky we are. But listening to these stories of later diagnosis is heartbreaking.</p>
36	<p>I have been diagnosed with PH2 since 1977. I had lost my right kidney in 1973 from stones just before my wedding. I have had one kidney stone incident since that time. I have gone to Mayo Clinic where my sister was diagnosed and had a transplant in 1977. That is when they told us that 3 of us in our family had PH2. I have not really suffered a great deal of problems with my kidney disease. I have lower kidney function but it has been stable for several years. I follow my medication and also drink a lot of water and other liquids. I also have been very careful to follow a low sodium diet and avoid some foods. I feel that at 67 years old I have lived a pretty good life. I have 5 children who are adults now and 17 grandchildren. I realize I have been very lucky with my condition. With the information I received over the years from research I have been able to manage my kidney problems with the help of my Dr. here in [a state in the US].</p>
37	<p>Even with a milder form of PH, every appointment with a specialist is on a weekday, every scheduled surgery is on a weekday. And because we travel to another state, we need to take off of school and work for days at a time. I had to take intermittent child care leave for whenever needed (without pay). I even had an attendance officer from the school threaten to call child services on me when my daughter was in Prek, because she had missed so much school even though we had notes from doctors and hospitals.</p>
38	<p>Comment 1: https://m.soundcloud.com/pappi-haze/snowball-story-of-my-life-feat My son SK wrote and sang it showing how it is to live with PH 1.</p> <p>Comment 2: My son SK, after he started dialyses 6 hours a day, 6 days a week told me mom I want to give all my organs to patients who need them, that's it I can't wait for this transplant, I can't live this way. He passed away four months after transplant come through. We waited almost four years for it to come.</p>

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Respondent #	Comment
39	<p>I was diagnosed with PH approx 18months, following a fit that took me to the hospital. My childhood was marked by kidney stones, pain, nausea, headaches, and fatigue. I missed school so often that I found it difficult to make and maintain friendships. My parents were told I would not live to see my teenage years. There were only 4 people diagnosed in Australia. Information and medical experts in my country were difficult to find. Reason unknown my health appeared to improve following age 12. I am now aged 36, and PH1 always lives in the shadows for me. My husband and I undertook genetic testing prior to planning a family, because I couldn't fathom passing on my disease to another person. Last year I gave birth to my son. I could not love another person more. Now as a Mum I worry that my good health will not continue forever. I worry that I won't get to watch him grow up. I worry that he will have to see me in pain and suffering. Regular testing, headaches, nausea and pain continue with occasion stone and crystal formation, but I count myself as exceptionally lucky. I hope and pray for a cure. I want to watch my little boy grow up to be a man.</p>
40	<p>Comment 1: The symptom that has had the most significant impact on our family is having my 2 month old baby girl in kidney failure due to Primary Hyperoxaluria Type 1. From that moment on, nothing in our family would ever be the same. Dialysis began and we soon started a regime of doing hemodialysis for 3 hours a day, 6 days a week; and for a time added peritoneal dialysis for 12 hours every night while she slept. She did 15 hours a day of dialysis for 2 years until she was big enough to receive a life saving kidney/liver transplant. Kidney failure is a symptom of PH1 I would not want anyone, let alone a baby, have to go through.</p> <p>Another symptom of this disease that we have to monitor on a daily basis is the healthy of the kidney. UTI's and often antibiotics for treatment are a common recurring symptom we deal with. The urge to frequently urinate interrupts my children's days at school and when out playing with friends. Embarrassment when that urge to urinate comes over and over and they end up going in their pants is hard on my kids. My 5 year old is still not fully potty trained because she drinks so much water during the day and at night. In addition, with her recurring UTI's, her bladder hasn't be trained properly to let her know when it really is time to go! This is a struggle she deals with on a daily basis.</p> <p>My 13 year old girl is also dealing with the effects of permanent significant oxalate deposits in the retina of her eyes. No glasses or operation will ever fix the damage that has been done, due to the overproduction of oxalate she experienced at a young age. She has to sit at the front of the classroom at school and read with enlarged print. She has to keep finding new ways to compensate for her vision loss.</p>

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Respondent #	Comment
40 (continues)	Comment 2: Don't forget the permanent impact PH1 has on the eyes! My daughter was in kidney failure at 2 months of age. Even though she received a kidney and liver transplant at 2 years of age, the overproduction of oxalate she experienced as an infant has caused permanent damage on her eyes. Doctors are unsure if she will be able to qualify for a drivers license. No glasses or operation will ever fix the damage that has been done. She has to sit at the front of the classroom at school and read with enlarged print. She is continually finding new ways to compensate for her vision loss.
41	I was diagnosis at the age of 28 and the next day went into renal failure. The worst symptoms was the pain of the kidney stones that lead to the many surgeries.
42	Can share perspective as caregiver to my son DX at age 11 PH1 non-B responder and TX are age 26. Dialysis 10 months and 3 TX offers before the 4th was the perfect match. He is 3 years post double transplant.
43	<p>Comment 1: My daughter was diagnosed with PH1 at 3 months of age. She lived a very challenging life for 1 1/2 years before her eventual combined kidney and liver transplant. During that time she struggled to gain weight and was fed only by a g-tube. She vomited 4-5 times daily because of her nausea. She endured 4 hours of hemodialysis each day at the hospital and 10 hours of peritoneal dialysis each night at home. It was an incredibly stressful time for our entire family. Thankfully, she is now 14 years old and post-transplant life is much better but she will be taking anti-rejection medications for the rest of her life. She has already had a few rejection episodes and we worry about how long these organs will last. It would have been so much better if a treatment had existed at the time she was diagnosed that could have prevented her transplants completely.</p> <p>Comment 2: My daughter's top 3 troublesome symptoms when she had PH1 were her end stage renal disease, nausea/vomiting and failure to thrive. She had to do both hemodialysis and peritoneal dialysis for over a year before receiving her combined kidney and liver transplant. If she had not received her double transplant she would not have lived past two years of age.</p>
44	As a research scientist working on PH and Hyperoxaluria, those personal stories from PH patients and parents are very moving and difficult to hear.

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Respondent #	Comment
45	<p>Comment 1: Hi, this is M. I am not good at English, so please excuse me There are two questions. first of all, How far is the drug development progressing? second of all, When will the market be released? If possible, I would like you to answer. Thank you.</p> <p>Comment 2: Hi, I'm an old lady with a grandson who is suffering as an oxalite in Korea. Please understand that I am not good at English. I have a question. First of all, how far is medical development going? When will it be on the market? What are the side effects of the drug? Please answer me if possible. Thank you.</p>
46	<p>Comment 1: A kidney/liver transplant is a cure for primary Hyperox- aloria. I have been on a regimen of meds for 17 years and have had only a few side effects. Sleep Insomnia can keep me from functioning normal throughout the day. hair loss is embarrassing and most resent gout from build up of uric acid in the blood. Very painful and its hard to keep on a specific diet.</p> <p>Comment 2: side effects: Hair loss and Insomnia</p>
47	<p>Hi, I'm SY from South Korea. In my country, there are not many patients suffering from oxalate-re- lated diseases. So this study will be great help to patients. I really hope that a treatment can be developed. I have two questions. first of all, How far is the drug development progressing? second of all, When will the market be released? If possible, I would like you to answer. Thank you.</p>
48	Phyox7 decerni
49	<p>Good evening from Australia! My name is VT and I'm 42 years old. I live a healthy lifestyle whilst suffering with PH1. I am also an RN and done alot if independent re- search into this disease. My question is, a rather important one, WHY can't patients with PH qualify for a dual transplant of both liver and kidney OR even a liver transplant? Or kidney? If I have managed to get 42 years from one diseased kidney, why can't we have a trans- plant and live a potential 20 plus years from a healthy kidney? I believe the disease process would be slow to effect the new kidney. It could extend many lives! Thankyou!</p>

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Respondent #	Comment
50	How can we get treatment of pH disease. we are from Nepal .Here is no any primary hyperoxaluria clinic
51	Hi, please can I ask what the probability is of kidney transplant and dialysis in type 2?
52	We're developing a new treatment for PH1 and are very interested in hearing, and getting feedback, fom the affected patients amd their families.
53	My son O. is 13, he is currently on potassium citrate 3 times a day 500mg b6 and magnesium twice a day. 12 tablets a day. And around 3L water. They dont seem to be helping his stones at all and his renal function continues to decline.
54	How does your child advocate their rare disease to their friends?
55	Being able to avoid dialysis for a year and a half would be worth a lot, and then add to that the need for a transplant, the removal of my old kidneys- the miracle of having a donor. That is how much drug treatment or even drug mitigation of PH1 symptoms is worth. B6 helped me a little, I was told, but my genetics were not fully responsive to it. SO grateful for you researchers. I have 6 brothers and sisters I am worried have PH1 and don't realize it yet.
56	<p>Comment 1: Our daughter has been living with this disease for 25 years. It changed all of our lives. 4-5 fundraisers per year with our daughter as the cover story. More attention than we ever wanted but knew we had to do something to make a difference for her and all PH patients. To finally have a potential treatment makes it all worthwhile. Thank you for hearing our story.</p> <p>Comment 2: Will a patient be able to take the drug if they are trying to get pregnant?</p>
57	<p>Hi hope your well,</p> <p>I just wondered if you had an answer to a question that I had in mind. I had no symptoms of this condition until I was nearly 25 years old but I can see some people have had symptoms from at a young age. I had never had the need to go to the doctors and I was perfectly a healthy person so I just wondered if there was any reason to why some people get symptoms quicker than others from having Primary Hyperoxaluria.</p> <p>Kind Regards,</p> <p>A.</p>

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Respondent #	Comment
58	<p>My son is now 9 years old (born in 2011) and was diagnosed with Primary hyperoxaluria Type 1 at 3 months of age.</p> <p>He had a liver transplant 3 years ago (when he was 6 years old), and he has been on hemodialysis for 3 years after that, and He was waiting for a brain death transplant.</p> <p>Oxalate is still detected in blood tests, and teeth are weaker than other places, and it seems that it is affecting the jaw and permanent teeth. He does not do vigorous exercise because there is a risk of pelvic fracture on x-rays.</p> <p>Fortunately, he is stably on hemodialysis, but it is questionable how much oxalate is reduced through hemodialysis. He can hardly urinate. I wonder if the remaining oxalate in his body can be discharged more properly through a new drug.</p> <p>Even if He has a kidney transplant now, I am concerned that the remaining oxalate in his body will damage his kidneys.</p> <p>In fact, I was afraid of having my son undergo two major surgeries, so I waited for a drug that could reduce the oxalate. Before the operation, he maintained less than 2.0 creatinine and was able to urinate well, but after twice liver transplant, The kidneys were damaged to require dialysis. [Surgical complications] My son struggled with biliary and ascites for almost two years after the liver transplant.</p> <p>The whole family suffered from various procedures and tests for a year. So, if a drug is developed to help break down oxalate even a little, I think it will be of great help to many patients, especially young children.</p> <p>In particular, some children suffer from fractures due to a lot of accumulation on the bones, and my son also has symptoms such as osteoporosis on x-rays.</p> <p>Each has a variety of problems. Prior to the liver transplant, it was said that it could accumulate in the bones and eyes, affecting the heart, and was tested several times.</p> <p>Young children do not have an appropriate catheter during hemodialysis, so they have several surgeries, and one boy has switched to peritoneal dialysis for blood vessel problems.</p> <p>In addition, it is known that there are also problems such as calcification of blood vessels, such as problems such as platelet reduction after surgery, during dialysis, and so on.</p> <p>If the oxalate remaining in the body can be properly discharged even after a liver transplant, I think the quality of life after that can be changed. We sincerely hope that the drug will be developed as soon as possible.</p>
59	<p>I don't have any symptoms since 2010. I don't even feel that I have Primary Hyperoxaluria!</p> <p>It's important to me to know about the clinical trial in general and the biological and chemical effects in my body.</p>

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Respondent #	Comment
60	<p>My son was diagnosed with Hyperoxaluria Type 1 when he was nine. His early to late teen years were spent at specialists appointments scanning for any damage that might have been occurring to any organ. I was offered the opportunity to get him into a clinical study using the drug Lumarisan. We travel quite a bit to participate but, his oxalate numbers have gone down tremendously. I see a look of relief across my son's face, I also hear it in his words. I would do anything to keep my son from living a life with a double transplant. The news of his oxalate numbers decreasing has been so welcoming and positive. It has been wonderful to have a small patch of hope since the study has shown these recent results. Please hear our voices. We have something to share.</p>
61	<p>סיבאכמ יתלהס, תוילכב תורחזח סינבאמ יתלבס הנחבהה תלבק ינפל סיתתנש קשמב דיחיה רבדה התייה יתניחבמ הפורתה, דיתעה יבגל תוששח טעמ אלו הבירצ, מיקזח ויה מג קא אפרה לש העצהה ירחא יוסינב פתתשהל יתיצר ככ לכו ילרוג תא תונשל לוכיש תוששח.</p> <p>תאצל הווקתל תוא יל הנתנו ייח תא התניש הפורתה נכאש דיגהל לוכי ינא ירחא יצחו הנש ילב סינבא ילב יצחו הנש, ומצע דעב רבדמ פרגהו תוניוצמ תואצותה. השק תואיתממ ם תוקוחר יד מיתעל סיבאכ מעו תוששח</p> <p>Translation</p> <p>For years before receiving the [treatment] I suffered from kidney stones, suffered from severe burning pain, and quite a few worries about the future, the drug for me was the only thing that could change my fate and so I wanted to participate in the experiment after the cure proposed but there were also concerns.</p> <p>A year and a half later I can say that indeed the drug changed my life and gave me a signal of hope to get out of a difficult wonder. The results are excellent, and the graph speaks for itself, a year and a half without stones without worries and with pain quite rarely</p>
62	<p>I am the mother of two PH1 adult children. Our daughter went into total kidney failure at 8 months of age, 35 years ago. She has had three kidney transplants, the last being a double kidney/liver five years ago. Her older brother was diagnosed in his late teens after multiple kidney stones and a previously incorrect diagnosis. He still has his own kidneys but continues to have stone problems. He takes B6 as his only treatment. All of our lives have been forever impacted by PH1, kidney failure and transplants being the most significant symptoms. Potential risks and side effects would be the primary concerns regarding participation in any trials. Thank you for this opportunity to share and learn more.</p>

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Respondent #	Comment
63	<p>My child is a patient and is currently being treated in South Korea. The doctor told me that the solution can only be solved by transplantation of liver and kidney. We have performed liver surgery in September last year. We are currently waiting for the transplantation of the kidney, but the operation is complete. The physical condition is very unstable, so I very much hope that you have other ways to solve this problem, or medicine can solve it, without transplantation surgery, thank you.</p>
64	<p>First of all I want to thank you for your efforts to develop this important research, for me it is life saving. I lost my older brother in 2008 due to this disease he was 35, he died in the operating room after the surgeons finished the transplant, his heart stopped working (the claim was that during dialysis, the oxalates went up to the heart and hurt him). In addition, I have another brother who went through a painful journey with the disease until he had surgery at Schneider Hospital in Israel, where he had a liver and kidney transplant and since then he is healthy, but every day he takes a large amount of medication, he has difficulties of a different kind ...</p> <p>Before the new treatment, I felt I was on a dark path, and I started raving about life and thinking that I did not have much time left to live, many times I was depressed but hid, and most of the time I tried to help myself by music, by the way I am a musician, singer and violinist. Now, and after the journey with the treatment for about a year and a quarter, I feel I am lucky and will not experience the tragedies I thought of before. I feel like I have found my health back and life of course.</p> <p>Regarding something that bothers me due to the treatment:</p> <p>- I wake up a lot from sleep to go to the bathroom and pee. Is it better not to drink before bed?</p> <p>And my question about the study:</p> <p>- Will kidney stones that appeared before the treatment be reduced due to the treatment? Or do they stay the way they are until I get over them and get rid of them?</p> <p>Thank you again Angles :)</p> <p>M</p>
65	<p>I was only diagnosed in 2019 with PH1 at the age of 57 after a double kidney transplant in May 2019. My kidney function improved after the transplant to 50% but gradually deteriorated to as low as 13% but over a year on it is now 18% so my worry would be that my function deteriorates further.</p> <p>At the moment I have no obvious symptoms except for occasional joint pain in my fingers although I had suffered kidney stones since the age of 43 which now looks as though it is linked to PH1 fortunately I had no pain with the kidney stones so was scanned every 6 months.</p> <p>I try not to let the worry of PH1 defeat me I remain positive and walk over 10000 steps daily, eat healthily as i enjoy cooking and follow to the letter the advice given by my doctors. I am determined to live life to the full. I actually feel fortunate and blessed that I did not develop PH1 until later in life and I have been able to have a healthy family and last week our first grandchild was born.</p>

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Respondent #	Comment
66	<p>Comment 1: The symptom of having pain in the kidney area. I especially feel it when I do not drink the amount of water I have to drink. It is a stabbing or hollow medium heavy pain. This type of pain usually lasts a few minutes but can return a number of times per day. This symptom impacts my daily living and quality of life because I am severely limited. It always reminds me of having a chronic disease which becomes extremely noticeable from time to time.</p> <p>Comment 2: When considering participation in a clinical trial, it is important for me to understand how much time has to be occupied (schedule), in how far I am going to be limited physically, and which secondary effects might occur. It is important for me that enough time is provided for the elucidation.</p>
67	<p>Our daughter was diagnosed with PH1 at the age of 19 after a CT scan revealed hundreds of stones in both her kidneys. She had no symptoms of PH during childhood, so this finding was a total shock. We were told there were only 3 doctors in the country who could do the surgery necessary to remove the stones. We were fortunate to be referred to Dr. JL in [a city in the US], where our daughter had 3 operations totaling 13 hours. Most of the stones were removed, but the damage to her kidneys was extensive, leaving her with out 50% function. Over the next 3 years, she experienced several serious kidney infections and 2 additional procedures to remove stones. Thanks to Dr. L, we were connected to Mayo Clinic's PH Clinic, which has been an incredible source of information and support over the past 12 years, as has the OHF.</p> <p>Soon after our daughter's surgeries, we learned that our son also has PH1, although he has been thankfully asymptomatic so far. Our children are now 31 and 37 and are doing well. They are both responsive to vitaminB6 which keeps their oxalate levels under control. We understand that PH can be an unpredictable disease, and that things could change for either or both of them at any time. But, we are immensely grateful for the help and support of their doctors, Mayo Clinic and the OHF. Without them, I know our journey would have been very different.</p>
68	<p>I was diagnosed with PH1 at 19. I am now 31. After several months of neck and back pain, imaging revealed that my kidneys were both full of stones. Within a few weeks I had three surgeries to remove most of the stones. I have since had two additional stone removal surgeries. I currently take B6 and am responsive to it fortunately and have not had any challenges taking it. This has reduced my stone formation greatly, so most of managing my PH for the last few years has been managing the periodic episodes and monitoring oxalate levels, blood pressure, kidney function, etc. I have also taken citrate before but have not found something I could take regularly as everything I tried caused stomach and gastrointestinal issues.</p>

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Respondent #	Comment
68 (continues)	<p>I was diagnosed with PH1 at 19. I am now 31. After several months of neck and back pain, imaging revealed that my kidneys were both full of stones. Within a few weeks I had three surgeries to remove most of the stones. I have since had two additional stone removal surgeries. I currently take B6 and am responsive to it fortunately and have not had any challenges taking it. This has reduced my stone formation greatly, so most of managing my PH for the last few years has been managing the periodic episodes and monitoring oxalate levels, blood pressure, kidney function, etc. I have also taken citrate before but have not found something I could take regularly as everything I tried caused stomach and gastrointestinal issues. I have a general rule with treatment that if there are side effects, I want to feel good, or at least okay, more days than not. Having regular stomach discomfort impacted my daily life and my doctor and I opted to not move forward with citrate unless it becomes more necessary. I also take medicine for blood pressure which began increasing a few years ago. We aren't sure how much family history and other factors play into that. I also drink a lot of water and generally try to manage my overall health through diet, exercise and sleep.</p> <p>The symptoms with the most significant impact to me are stone formation, and episodes of pain and spasms in my left kidney and ureter that my nephrologist believes is due to scar tissue from multiple surgeries. I usually have 1-3 episodes annually of having pain in my left kidney and along my side and around my ureter, with periodic spasms. My kidney sometimes swells and I generally have low energy and feel crummy for about a week. It can really slow me down, and I've had to take some days off of work to rest. I have other days where my kidneys, particularly my left side, just feels off and I have some discomfort and feel more worn out. I have also had two kidney infections, one of which resulted in an ER visit and was quite serious. I have learned to live with PH and consider myself quite lucky. That being said it does impact my daily life and I have had to be patient in finding the right treatments. The most important things for me in considering participation in a clinical trial are any risks it could pose to my health, the time commitment, any required travel and generally how participating would fit into my life. Additionally, potential COVID-19 exposure is a major concern right now. Essentially, I would have to really assess the balance of risk and potential benefit. I'd also want to know more about how the treatment is administered. For example, I'd prefer a pill over an injection.</p> <p>Thank you for the opportunity to share my story. Mine is one of many, and my family's experience is as unique as all other families navigating life with PH. I am extremely grateful to OHF and the PH community for the many opportunities to connect, learn from each other and help future patients.</p>

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Respondent #	Comment
69	<p>Comment 1: Hi, would like to ask you a Question, do you know if siblings could have a different type of PH, fraternal twins from different egg (IVF)? Thank you</p> <p>Comment 2: The question is this. 1 If for any reason kids with PH3 could have a kidney failure from causes other than Hyperoxaluria, are they still in danger of getting Oxalosis? Another words, what amount of oxalates (per graf) makes it a danger of getting oxalosis? (God forbid)</p>
70	<p>When we received our children's diagnosis three years ago, we were devastated. The future of our children suddenly looked different. I can still remember that feeling of hopelessness very well. That was awful. I cannot describe in words how I felt as a mother. Hope is our motivation to be able to look forward, to fight our fights. Actually, I'm a very positive person but at this point I felt lost. I remember telling my husband: we are lost, our children are lost, nobody will care about these few cases. No studies are funded, if at all! Those were my thoughts three years ago – and now! Thanks to the new medicines discovered, our children can have a future. I have hope again and that changes everything. Our family life has improved thanks to this prospect of hope. Hope gives courage and confidence. Our regular hospital visits become more bearable because there is a ray of hope for improvement.</p> <p>Our second daughter is often sick and has to go to the emergency room. She is also very tired, which affects her state of mind and well-being. We live with fear daily and wonder what will happen next. Recently, I noticed how I always make sure to have a full tank in the car because I never know when the next emergency will occur. The hospital stays are a test. Our family is pushed to the limits with fear, worry, fatigue, having to make decisions and handling every day life. Our 6 year old recently said to me when she had to do a MRI; "Mom, is this my life now? Do I always have to go to the hospital if I have the "slightest" pain and maybe stay there as well?"</p> <p>Our children stand out from their friends and peers again and again because they have a low-oxalate diet and have to drink a lot. They don't always like that. Sometimes, they just want to be normal. I'm always checking that they drink enough. Every day. The whole day. I am creative every day to animate them to drink. I often have to talk with the teachers, they forget to remind them to drink.</p> <p>Family life is organized so that they get enough sleep, and our excursions always take place near a university clinic. We no longer have holidays abroad because we don't know what medical facilities are available; but we do know what kind of care our children need in an emergency. And this knowledge and fear control our lives. We also realized that when we visit a general practitioner or family doctor, they don't like to treat our children because they are afraid. They don't know enough about the illness and refer us to someone else.</p>

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Respondent #	Comment
70 (continues)	<p>The eldest daughter suffers from anxiety and loss disorders. She had to watch how her sisters had to be picked up by the ambulance a few times. She shows a lot of empathy and supports her sisters whenever she can.</p> <p>The pandemic has made many people aware of what we have known and lived already for a long time: being there for each other, taking care of others and valuing our health! Thank you very much for listening!</p>
71	<p>The current treatments affect our lives the most. Extra hydration is hard to manage in my child as well as constantly monitoring his food to ensure it is low sodium. If he doesn't have enough hydration his urine will become tea colored and it worrisome. I would want to understand the risk/benefit of any clinical trial and what the time commitment would be. My child currently takes high doses of HCTZ, low sodium, low oxalate diet and hyperhydration. His 24 hr urine shows his oxalate is still very high. I want treatments available for PH3 patients to control the oxalate.</p>
72	<p>I may not be able to provide these comments live as I work in a hospital with an unpredictable schedule. To answer some of the above questions:</p> <ol style="list-style-type: none"> 1) The symptoms that have impacted me the most with PH include very painful and debilitating kidney stones and fear of the next stone or progressive decline in kidney function resulting in the need for dialysis or a transplant. I used to think about those possibilities every single day, and have learned to grow with the disease and think about them less. 2) The worry about future symptoms (see answer to question 1) can be very debilitating. It can be hard at times to suppress those fears. 3) For me, prior to enrolling in a study I want to know the potential side effects of the intervention. If potentially severe side effects, I would not be willing to take the risk. I also want to know about the proposed benefits to those with PH. I am less concerned with the amount of time or effort the study will take me as a PH patient we have all been through a lot usually starting in the first few years of life. 4) I am currently taking a medications 3 times daily, a study drug, avoiding certain high oxalate foods, and consuming around 5-6 liters of water per day. This seems to have been working well for me the past 5 or so years. 5) The downsides to the treatment include need for frequent bathroom breaks which can be very disrupting for many aspects of life including time consuming jobs, travel (ie road trips), etc.

