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HCU NETWORK AMERICA

VOICE OF THE PATIENT REPORT

Classical HCU Externally Led Patient-Focused Drug Development (EL-PFDD) Meeting

Meeting date: October 27, 2023
Report date: May 2, 2024

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Meeting sponsors

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Classical Homocystinuria (HCU) Voice of the Patient Report

HCU Network America strives to inform and provide resources for patients and families, create connections, influence state and federal policy, and support the advancement of diagnosis and treatment for HCU and related disorders. This *Voice of the Patient* report was prepared on behalf of HCU Network America as a summary of the input shared by families and caregivers living with Classical Homocystinuria (HCU) during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, conducted virtually on October 27, 2023.

Authors and Collaborators: This report was prepared and submitted on behalf of HCU Network America by Danaé Bartke, Co-founder and Executive Director, HCU Network America, Margie McGlynn, R.Ph., Hon DSci, President, HCU Network America and Liz Carter, Communications Manager, HCU Network America and by Chrystal Palaty, medical writer.

Consulting Partners include Larry Bauer, RN, MA, and James Valentine, JD, MHS. and from Hyman, Phelps & McNamara, P.C.

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James Valentine, JD, MHS. and Larry Bauer, RN, MA are employed by Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health.

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Point of Contact: Please contact Danaé Bartke, Cofounder and Executive Director of HCU Network America (info@hcunetworkamerica.org) for questions related to this report.

Contents

Classical Homocystinuria (HCU) Insights from the EL-PFDD Meeting

1. **Classical homocystinuria (HCU) is a rare and chronic disease.** Processing of the amino acid homocysteine is affected, leading to harmful buildup of homocysteine in the blood and urine. Approximately half of those living with classical HCU are missed by newborn screening: the delayed diagnosis and delayed treatment initiation leads to more severe disease manifestations.
2. **Classical HCU is a multisystem disease with a wide range of manifestations**. Most patients experience a high number of health concerns. Disease presentation can vary from one patient to the next. The most troublesome classical HCU manifestations include potentially life-threatening blood clots, strokes, pulmonary embolism, and optic lens dislocation. According to poll data, anxiety and/or depression were the most universally experienced. Additional health concerns include skeletal issues such as scoliosis and osteoporosis, pain, cognitive issues and learning problems, myopia as well as other optical issues. Caregivers can sometimes recognize uncontrolled homocysteine levels based on mood and behavior.
3. **Classical HCU impacts all aspects of daily life.** The restricted diet profoundly impacts school and social lives, and many feel like outsiders. Some are stigmatized because of their behavior, clumsiness, and intellectual disabilities. Some living with classical HCU face unemployment and are unable to financially support themselves, while others are completely dependent on their caregivers and will never be able to live independently.
4. **Individuals living with classical HCU and their caregivers have many worries.** They worry about potential thromboembolic events, symptoms worsening, and premature death. Parents worry about what level of independence their children will be able to achieve and whether they will adhere to their medications as they get older.
5. **Classical HCU is not just a children's disease**. Many adults living with classical HCU suffer from comorbid conditions that can profoundly complicate treatment adherence.
6. **The classical HCU community has tremendous unmet medical needs; betaine anhydrous is the only FDA-approved product to lower homocysteine.** Treatment includes a combination approach of a low protein diet, medical foods including formula, betaine anhydrous, folic acid (vitamin B9), B6 and B12

supplements, blood thinners, and antidepressants. Other approaches include frequent homocysteine monitoring, counseling, psychotherapy, and physical or occupational therapy.

7. **None of these medical treatments or approaches address the underlying disease itself, nor can they reverse the damage that has already accumulated**. The treatments require a great deal of effort, adherence is extremely challenging, and there is no guarantee that homocysteine levels will/can be controlled consistently and in all patients.
8. **Those living with classical HCU hope for new treatments to eliminate the need for the special diet and formula, to prevent disease progression, and to prevent blood clots and other catastrophic medical events**. They would like medications that ensure consistent homocysteine levels, to prevent the build-up of methionine, and with better administration options. They also identified other important needs: the need for home monitoring of homocysteine levels, more research about aging with the disease, and the need for deeper understanding of classical HCU**.**

Meeting Summary

The Classical Homocystinuria (HCU) Externally-Led Patient Focused Drug Development (EL-PFDD) was held virtually on October 27, 2023. The meeting was an important opportunity for HCU Network America and the HCU community to share patient perspectives regarding the symptoms and daily impact of HCU, as well as current and future approaches to therapies.

HCU Network America wishes to acknowledge that not all members of our socioeconomically diverse community had the technology to support their participation, so the assistance of Liz Carter from HCU Network America was invaluable. Liz aided in technological assistance, providing transcriptions, and the implementation of other accommodations to ensure access to all community members interested in participating. She was also instrumental in the preparation of panelists' speeches, assisting them through the process of drafting and rehearsing for the event. Some panelists required extra accommodation in this multistep process and Liz helped to ensure that each panelist had the support that they needed. For these reasons, not all symptoms or impacts of the classical HCU patient experience may be fully represented by this report.

Over 120 unique viewers attended the livestream. This included 22 individuals living with classical HCU, 12 family members, 31 parents/caregivers, 12 from the government, nine scientists and researchers, 23 from healthcare industries, 3 healthcare providers, 7 from nonprofit organizations, and 2 consultants. Results of demographic polling are shown in **Appendix 1.**

The classical HCU EL-PFDD meeting was structured around two key topics. The morning session focused on *Classical HCU: Symptoms and Daily Impacts,* and the afternoon session focused on *Current and Future Treatments for Classical HCU.* The meeting agenda is in **Appendix 2**. Meeting panelists and callers are listed in **Appendix 3.** An online comment submission portal was open for four weeks after the meeting to include as many patient and caregiver voices as possible. All submitted patient and caregiver comments are included in a separate PDF document, with selected comments included in the body of this report.

The Classical HCU *Voice of the Patient* Report Distribution

This *Voice of the Patient* report with the accompanying document containing the submitted comments, and the video recording of the meeting, are available on the HCU Network America website at http://hcunetworkamerica.org, and hyperlinked to the FDA's website. This report is provided for all classical HCU community supporters including the US FDA, other government agencies, regulatory authorities, medical products developers, academics, clinicians, and all other interested individuals.

Clinical Summary of Classical Homocystinuria

This clinical summary is based on the October 27, 2023 presentations of Kimberly Chapman, MD, PhD, Attending Physician in Genetics and Metabolism at Children's National and Assistant Professor of Pediatrics and Integrated System Biology at George Washington University and Margie McGlynn, R.Ph., Hon DSci, President HCU Network America.

Classical HCU background

Homocystinuria (HCU) is a group of rare inherited metabolic disorders denoted by the harmful elevation of homocysteine in the blood and urine. The three main subtypes of HCU include classical homocystinuria, cobalamin disorders with high homocysteine and severe methylenetetrahydrofolate reductase (MTHFR). Each subtype has a different genetic origin and requires different therapies and management strategies. The October 27th Externally-Led Patient Focused Drug Development meeting (EL-PFDD) focused on **classical homocystinuria** or classical HCU and includes those with homocystinuria due to cystathionine beta-synthase (CBS) deficiency.

The worldwide estimate of prevalence for classical HCU is 1 in 200,000 -335,000.[1] Some populations have a higher prevalence, for example, the USA has a prevalence of 1:100,000. Due to a founder effect, Qatar has a frequency of 1:1800.

HCU is caused by several different genetic variations. Half of those with HCU have a genetic variation that prevents a methyl group from being added to homocysteine to convert it to methionine; this results in an accumulation of homocysteine in the blood and urine. The other half of individuals have a variation in the gene that encodes CBS, so they are unable to convert homocysteine to cystathionine, leading to elevated levels of both homocysteine and methionine. Depending on the specific gene variant, people with the CBS

[1] Sellos-Moura M, Glavin F, Lapidus D, Evans K, Lew CR, Irwin DE. Prevalence, characteristics, and costs of diagnosed homocystinuria, elevated homocysteine, and phenylketonuria in the United States: a retrospective claims-based comparison. BMC Health Serv Res. 2020;20(1):183.

enzyme deficiency can be responsive, partially responsive, or nonresponsive to vitamin B6 (pyridoxine), a cofactor for the CBS enzyme. Those who are B6 responsive or partially responsive can experience more success in lowering their levels of methionine with vitamin B6.

Diagnosis of classical HCU

Newborn screening for classical HCU is available, but not always successful in identifying affected individuals. All US states screen for elevated methionine levels as part of newborn screening. Unfortunately for many with HCU, their methionine levels are lower than their state's newborn screening cut-off, thus approximately 50% are missed. States who have a lower methionine cut off, are more likely to diagnose patients at birth. In Qatar, where the carrier frequency is high, newborn screening focuses on elevations in total homocysteine as opposed to methionine, so more individuals are identified by this method. Several US states are now piloting other newborn screening approaches including a stepwise testing approach that uses lower methionine thresholds and measures total homocysteine as a second-tier test. Some states are also piloting a first-tier test, that would allow homocysteine to be used as the primary marker.

Those who have a delayed diagnosis usually present symptomatically. Individuals with classical HCU have several very common disease manifestations that can affect multiple body systems. These fall into four major categories:

- **Central nervous system** (CNS) manifestations can include anxiety, depression, OCD, intellectual disability and learning challenges, movement disorders, psychosis, mental health difficulties, and age-related white matter changes.
- **Eye manifestations** include optic lens dislocation (*Ectopia lentis*). Many individuals have severe myopia (nearsightedness).
- **Skeletal abnormalities** can include scoliosis, osteoporosis, and bone deformities. Some have excessive height and long limbs leading to a Marfan Syndrome misdiagnosis.
- **Vascular system defects** are the most life-threatening manifestation. These can include blood clots, deep vein thrombosis, pulmonary embolism, or stroke.

There is a correlation between overall homocysteine levels and thromboembolic effects; homocysteine levels greater than 100 - 120 micromole per litre put

patients at risk for spontaneous thrombosis. In contrast, the biochemical cause of cognitive deficits, ophthalmic issues, and skeletal issues have not yet been determined.

Classical HCU treatment options

Dietary approaches are a treatment mainstay for those with classical HCU who are not B6-responsive. Non-B6 responsive patients are prescribed a low protein or, in some cases a low-methionine diet. The intent of the diet is to decrease the levels of methionine so that it can't be converted to homocysteine. Patients prescribed a low methionine/low protein diet also require medical formula, consisting of methionine-free amino acids to support their growth. Most also take betaine anhydrous, to help convert homocysteine back to methionine. In addition, many patients take pyridoxine (vitamin B6) to support the CBS enzyme as well as folic acid (B9) and cobalamin (B12), which are both important for the methionine metabolic pathway. Patients with low cystine levels may also receive cystine supplements. Many patients are also prescribed blood thinners to help prevent thromboembolic events.

New treatment approaches are currently in development. The new approaches being explored include: (1) replacing CBS enzyme with systemic enzyme or gene therapy, or enhancing the enzyme with chaperone therapy; (2) oral therapies to prevent methionine absorption so that it cannot be converted in the body to homocysteine; (3) modification of the metabolic pathway to help lower homocysteine levels. These approaches could potentially provide greater control of homocysteine levels, possibly even allowing relaxation or mitigation of dietary treatment.

Topic 1 – Classical HCU Symptoms and Daily Impacts

Patients and caregivers shared their perspectives and experiences of living with classical HCU through stories, online polling, moderated discussion and submitted comments. They described the classical HCU-related health effects that they experienced, impacts on activities of daily living, and their worries and fears for the future. Many shared powerful stories about diagnosis: while many were diagnosed prenatally or at birth, others were missed by newborn screening. Those patients who were born before newborn screening was implemented were often initially misdiagnosed or not diagnosed until later in life.

An important theme emerged during the meeting that was not captured in the polls:

Delayed diagnosis and/or delayed treatment initiation results in more severe disease manifestations. However, even those diagnosed and treated from birth are affected.

> *"Doctors always say, 'If you're caught at birth, follow the diet and take your formula, you'll be okay.' I was diagnosed pre-birth, maintained a strict diet throughout my life, and HCU still affects my quality of life every single day, and I fear will continue to take away the life moments I have dreamed my entire life about."* - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

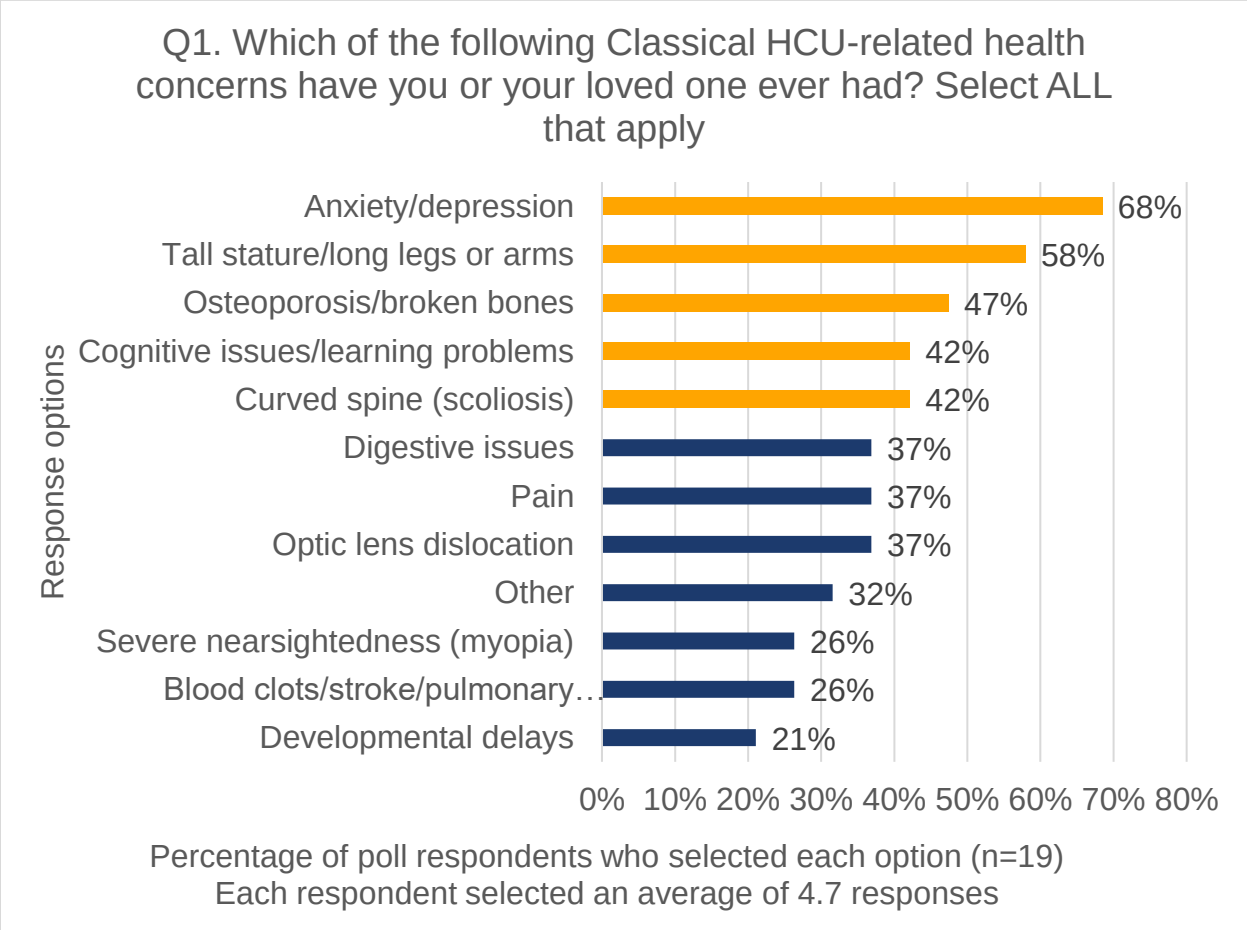
> *"I was diagnosed with classical homocystinuria at the age of five. My delayed diagnosis resulted in life-changing complications like dislocation of my lenses in my eyes, debilitating joint pain and stiffness and low range of motion."* - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

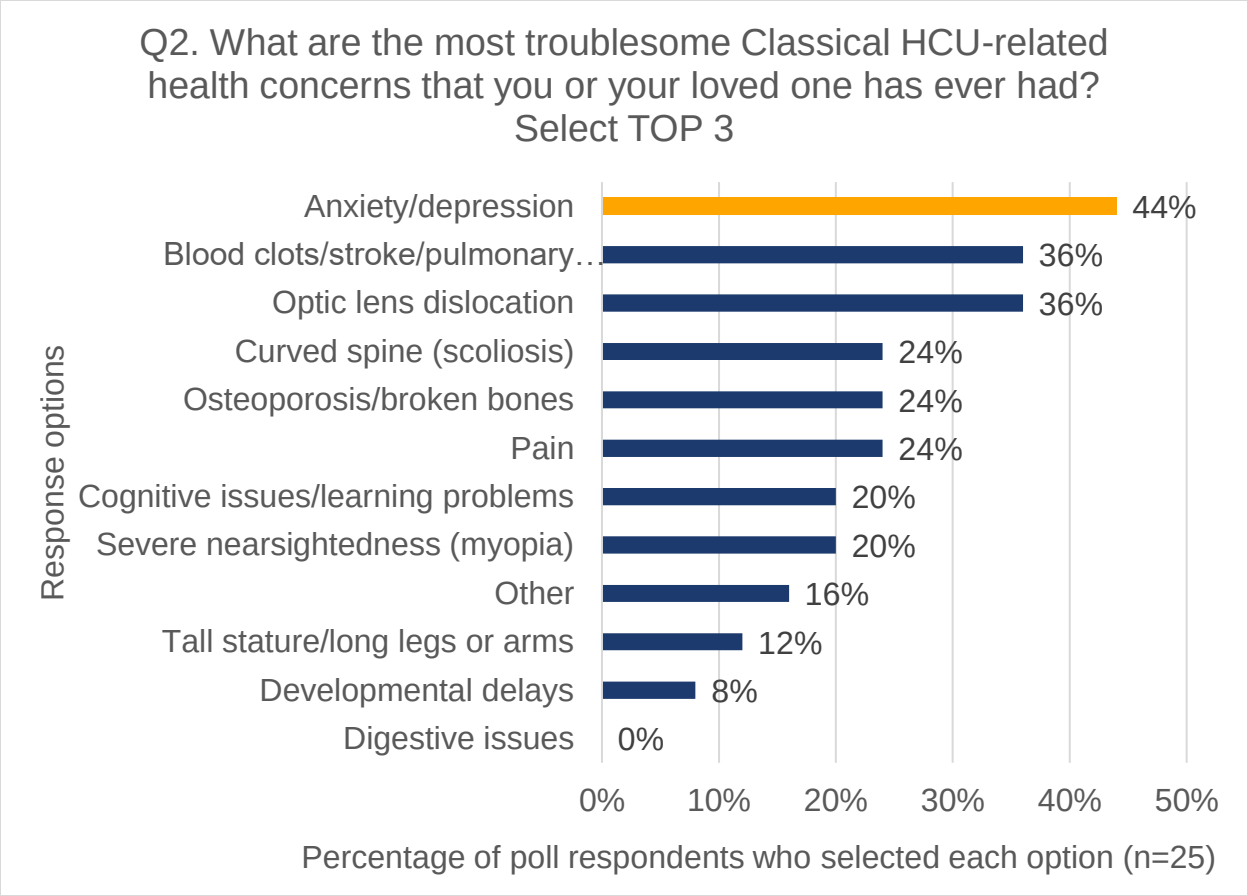
> A stroke and blood clots at the age of 46 led to Pamela's diagnosis. *"Although I have had homocystinuria my entire life, I wasn't diagnosed with classical homocystinuria until the age of 54. Currently, I am one of the oldest living patients with this disease."* - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

Poll Q1 & Q2

Classical HCU manifestations include potentially life-threatening blood clots, strokes, pulmonary embolism. According to poll data, anxiety and/or depression were the most universally experienced.

Meeting respondents used online polling to first identify which HCU-related health concerns that they or their loved one ever had (**Q1**), and then were asked to select their top three most troublesome (**Q2**). Those living with classical HCU experience many symptoms and each poll respondent selected an average of 4.7 different ones. The symptoms can be different from one patient to the next. Poll results are shown in the graphs and are described with patient quotes below.





Poll Q1 &Q2: These graphs include patients and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below the X axis (n=x). The responses for these polling questions are not considered scientific data. These are intended to complement the patient comments made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Classical HCU related health effects are listed below and illustrated with selected patient quotes. Patients and caregivers made many important comments throughout the meeting, but only a very select few are included in the report.

Blood clots/stroke/pulmonary embolism

Blood clots, stroke and pulmonary embolism were selected as some of the most troublesome symptoms in the polls. High homocysteine can lead to blood clots, strokes and pulmonary embolisms and the consequences can be tragic.

"In the mid-60s, I had two sisters diagnosed with classical HCU. One passed away at age 14 of a stroke, and one at age 9 of a pulmonary embolism. I vowed that someday I'd do something about it." - Margie McGlynn, R.Ph., Hon DSci, President HCU Network America

"I developed a deep vein thrombosis in my left hand. As a result, I lost 60% of my arm function." - Janet, 31-year-old living with classical HCU, diagnosed at 10 years of age

Christa's blood clot was first dismissed in the emergency room as, "*A holiday stress-induced panic attack, but the doctors and his team quickly went into high alert after my EKG showed heart attack. I coded immediately afterwards and several more times again. … It turns out I had a blood clot in the lower left ventricle of the heart or what they call the 'widowmaker' due to the severity and often difficult location it is to get in and repair it. This was a result of high homocysteine levels."* - Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age

Anxiety and depression

Poll respondents selected anxiety and depression as the most universally experienced classical HCU-related health concerns. For many, anxiety and depression started early in life. Some experience severe mental health challenges such as post-traumatic stress disorder as a result of their disease, the negative impacts of the treatment or medical procedures, and/or diagnostic odyssey.

"I had to worry about things a young child should never have to worry about. Social events brought immense anxiety, whether that be birthday parties or in-class events. I was often left isolated from my peers due to homocystinuria. All while, the looming worry of blood clots, strokes, and heart attacks took over my mind while my peers worried about their birthdays or elementary school." - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

"I didn't know at the time, but age eight, I was starting to develop anxiety. My friends remember me being angry at the strict dietary regimen. I wonder now if part of my anxiety was due to my elevated homocysteine levels." - Brooklyn, 37-year-old living with classical HCU, diagnosed at eight years

> *"He was anxious about his diet and how that was perceived by his friends and family members. …The anxiety would increase as he would enter a new situation like college, like he's doing right now. When he would go from elementary school, where he was with the same kids for five years, then he goes to middle school and now he meets new people and has to re-explain everything and get the looks and all of that. I think that's where it is. It's those new situations that you have to re-explain yourself with."* - Chris, parent of an 18-year-old son living with classical HCU, diagnosed by newborn screening

Optic lens dislocation, severe nearsightedness (myopia), and other vision issues

Optic lens dislocation was selected in the polls as one of the most troublesome symptoms by poll respondents and is often the first symptom experienced. Many described nearsightedness and other vision challenges such as lazy eye, double vision, glaucoma, myopic degeneration, peripheral vision, and color and depth perception issues.

> *"Our journey with homocystinuria began when our daughter, Clara, began struggling with her vision around the age of three. Eventually, we discovered that her lenses were detaching and after a long list of medical tests …we were told that she had classical homocystinuria."* - Breun, parent of 11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age

> *"His eyes - that's what affects us the most and that's also how we got our diagnosis. Mason had his lenses very close to dislocating, the eye doctor caught it and he had to have two surgeries on each of his eyes and now he sees with his contact lenses."* - Melanie, parent of a 10-year-old son living with classical HCU, diagnosed at 8 years of age

> "*My eyesight has been affected. My prescription is currently 10.5 and negative 12.5. I have had two sets of surgeries in my lifetime to correct lazy eye when I was younger. And then from that correction, it led me with double vision, which I got corrected in April of 2020. I'm happy to report that has since completely subsided, which is extremely exciting. Vision problems are terrifying."* - Samantha, 26-year-old living with classical HCU, diagnosed at 2 years of age

Curved spine (scoliosis), osteoporosis and broken bones

Many individuals living with classical HCU experience scoliosis and osteoporosis as well as other bone issues including brittle or broken bones and other bone malformations. Some are told that they will grow out of scoliosis, but for some, extreme treatment measures including spinal fusion surgery are required.

> *"Garrett and I have had quite the journey with HCU, both experiencing scoliosis, osteoporosis, anxiety, depression, OCD, learning difficulties and more."* - Danaé, 38-year-old living with classical HCU, diagnosed at 10 years of age

> *"At the young age of eight, I was diagnosed with scoliosis as a result of HCU. I was immediately put into a restrictive back brace for the next six years of my life. … On top of [scoliosis], I was dealing with osteoporosis and soon had to stop all contact sports due to the risks of my weak bones."* - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

> *"I was told once I stopped growing, my scoliosis would be taken care of, and for a long time, it was. … My scoliosis has returned, causing pain and trouble with mobility. … Because of my history of blood clots and my advancing age, doctors have advised me against surgery."* - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

Pain

Many individuals living with classical HCU experience a great deal of pain from bone issues such as scoliosis, osteoporosis, broken bones, joint pain, sore muscles, migraines, and fibromyalgia.

> *"My delayed diagnosis resulted in life-changing complications like dislocation of my lenses in my eyes, debilitating joint pain and stiffness and low range of motion."*- Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

> *"Navigating high school as a teenager with a rare metabolic condition and chronic pain made normalcy almost impossible."* - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

Cognitive Impairment/learning problems

Many living with classical HCU experience cognitive impairment, including memory issues, attention deficits, and "brain fog". These manifestations can make concentration and learning difficult and can, at times, lead to anger outbursts and behavior issues. Many patients and caregivers felt that worsening cognitive and behavioral issues correlated with high homocysteine levels.

> *"During the time in school, I struggled to hide frustration as I barely managed math, test taking, and multi-step assignments due to the significant executive function challenges that I had. …I skirted under the radar of struggling behind my peers until it was advised to my parents during my senior year that if I wanted to make it through college, I should have a cognitive neuropsychological evaluation for possible learning disabilities. This evaluation confirmed a diagnosis of ADHD and math learning disability."* - Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age

> *"One of the biggest impacts that has affected my day-to-day functioning has been brain fog. I often have brain fog associated with having trouble recalling words. Brain fog compounds these disabilities, increases my anxiety, and is one trigger for my migraines. I have to focus to find the right words, and something as simple as a daily conversation often leaves me exhausted."* - Brooklyn, 37-year-old living with classical HCU, diagnosed at 8 years of age

> *"She also has behavioral issues and learning difficulties, which drives an even bigger wedge between her and her peers. ... It has been an immense struggle to navigate this part of her disease, which has not only caused problems at an academic level, but even among friends and family. … In theory, everyone can understand she has a condition and needs special requirements, but most times what other people see is a child that doesn't follow rules and is disruptive."* - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

Other Classical HCU-related health concerns identified in the polls

Individuals living with classical HCU and their caregivers selected many other classical HCU-related health concerns in the online polls, including **tall stature/long legs or arms, developmental delay,** and **digestive issues.**

Tall stature/long legs or arms led many to be misdiagnosed with Marfan syndrome.

> *"I was also diagnosed with Marfan syndrome. Marfan syndrome and homocystinuria share a lot of commonalities."* - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

Developmental delays and missed milestones are experienced by many living with classical HCU.

> *"At the time of diagnosis, I was what they considered asymptomatic, but Garrett had many telltale signs. Garrett missed every single milestone, sitting up, crawling, walking, and talking. When our mother voiced her concerns to the pediatrician, they were dismissed. When we got the diagnosis, just shy of his fifth birthday, it helped connect many of the missing pieces."* - Danaé, 38-year-old living with classical HCU, diagnosed at 10 years of age

> *"Despite being diagnosed at birth, Ava has faced developmental delays. She did not walk until she was 18 months old, and her speech is delayed as well. … As of five years old, she still is in the bottom 3% of the growth chart and only has a 50-word vocabulary."* - Melissa, caregiver of 5-year-old Ava, diagnosed with classical HCU at birth

Digestive issues include digestive discomfort, acid reflux, vomiting, and constipation.

> *"On her worst day, Ava suffers from acid reflux from the medication and formulas and has constipation due to liquid aversion."* - Melissa, caregiver of 5-year-old Ava, diagnosed with classical HCU at birth

Other HCU-related health concerns not included in the polls

During the EL-PFDD meeting and in the comments, individuals living with classical HCU and their caregivers described several other health concerns that were not captured in the online polls. These include seizures, skin issues, motor issues, sensory processing disorders, muscle tone issues, poor teeth, connective tissue disorders, circulatory issues, pancreatitis, and heart issues. Some mentioned slow healing, as sores and wounds may take a longer time to heal on a low protein diet. A number of adult patients experience co-morbid conditions, including rheumatoid arthritis, diabetes, immune issues such as mast cell activation syndrome (MCAS) and rare cancers.

> *"My son, who was not diagnosed until age two, presented with seizures, blood clots in the brain and a stroke. He was put in a medically induced coma to give his brain a chance to recover. … The initial clotting that happened in his brain created a seizure focal point. ... Today, he still has random seizures. …They're not super frequent, but it seems like the moment we get kind of comfortable in a routine and thinking that we're no longer having them, he has another one that fires off that is really unexplained."* - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

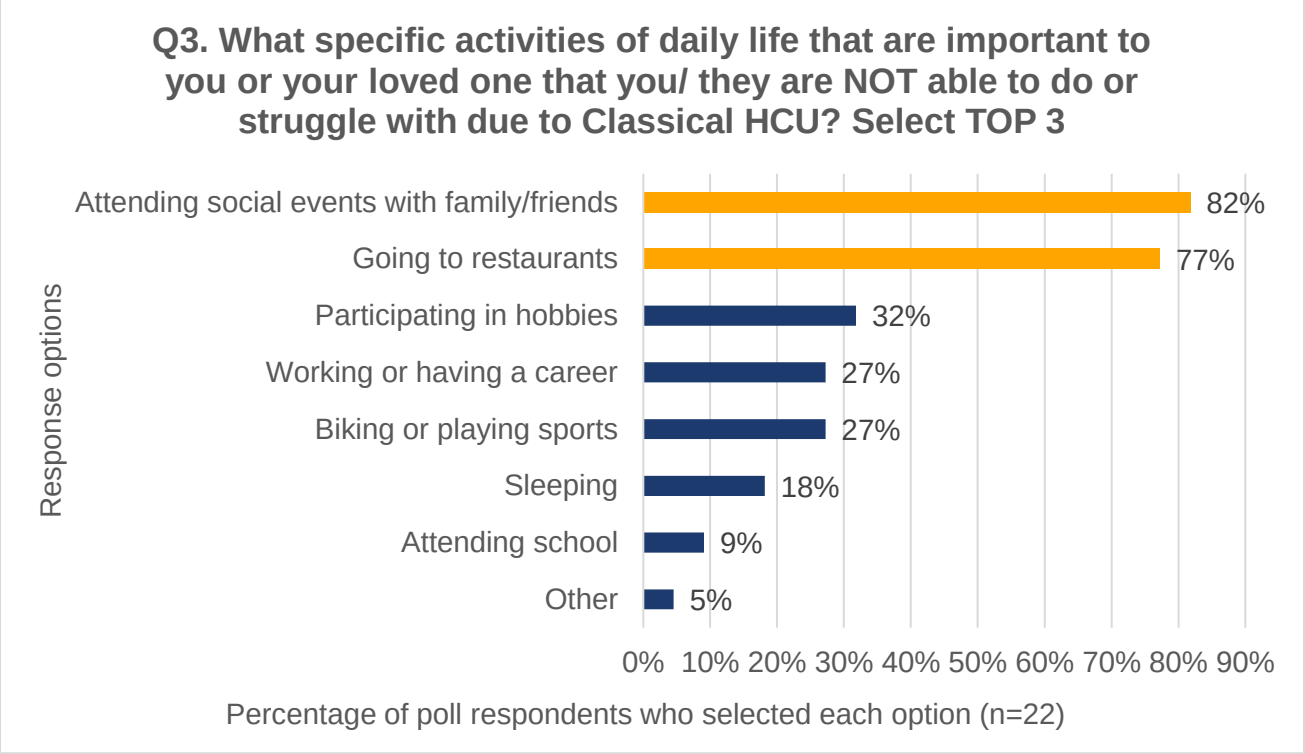
> *"Other symptoms Juana has developed throughout her life are behavioral issues, learning difficulties, bone issues in her feet, legs, and chest, and heart disease, all of them because of HCU. Each of these symptoms has affected Juana in different ways, but some of them have made her life a lot harder than it should be for any child."* - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

> Kelly listed some of her HCU-related health concerns including *"brain chemistry, drastic changes in vision, teeth not coming in correctly, weight issues, memory issues, learning disabilities, circulation issues, mental health issues, and loose ligaments in my back, which cause intense pain."* - Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

Poll Q3

Classical HCU-related health concerns, as well as having to rigidly adhere to a low-protein diet, have a daily negative impact.

Poll respondents selected the top three specific activities of daily life that are important to them or their loved one that they are unable to do or struggle with due to classical HCU. The top selected impacts were attending social events with family and friends and going to restaurants. Poll results are shown in the graph and are described with patient quotes below.



Poll Q3: This graph includes patients and caregivers who chose to participate in online polling. The number of individuals who responded to the polling question is shown below the X axis (n=x). The responses for this polling question is not considered scientific data, but is intended to complement the patient comments made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Attending social events with family/friends

Those living with classical HCU miss out on so much. Their restricted diet and treatment regimen limits social activities and negatively impacts relationships. Some are unable to fully participate in family activities, which is especially hard for those whose family culture is focused on sharing food. Many children miss birthday parties and sleepovers. As a result, many children and adolescents feel socially isolated and are stigmatized.

> *"For Latinos, food and social gatherings are a core part of our culture. … In the Hispanic household, food means love, family, and togetherness. If you don't eat what is prepared, it could be taken as a sign of disrespect to whoever made the food. … I felt like an outsider in my own family. While everyone was enjoying their 'bistec con arroz', I was stuck eating salads."* - Janet, 31-year-old living with classical HCU, diagnosed at 10 years of age

> *"I missed out on countless social opportunities and events due to my homocystinuria. … Everything from exciting life events to simple situations have been ripped away from me, from my first day of freshman year, senior year of high school experiences, college, to sleepovers, birthday parties, and class field trips. … Being left out of friend groups became the norm."* - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

> *"Something as simple as having [my grandson] over to spend the night makes me SO nervous; making sure that I count his protein correctly, giving him all of his formula and medication at the right times. It takes away from just being able to enjoy him. It makes me sad that he can't go to sleepovers with friends because of how complicated his treatment is."* - Nancy, grandmother of a 7-year-old grandson living with classical HCU

Going to restaurants

The food in many restaurants – and even school and college campus cafeterias – has too much protein for those living with classical HCU. This often means missing out on dinners with loved ones and friends.

> *"The biggest impact that I see now as an adult, it's very difficult to plan going out to eat, a date with my wife because restaurants don't often cater to low protein options. … We are having to scour menus online …it's a*

constant struggle trying to see the things that we can eat. And it causes a lot of frustration." - Ben M, 34-year-old living with classical HCU, diagnosed by newborn screening

"Maybe we want to go out for dinner or friends invite us to do something or he plays hockey or maybe his hockey team is going to have some sort of a dinner." If her son has already met his protein allotment for the day, *"he can't go and enjoy those types of things with his friends. He does his best to cope with these types of disappointments. It's just part of what he has to deal with and it's really unfair and it's really sad."* - Melanie, parent of a 10-year-old son living with classical HCU, diagnosed at 8 years of age

College dining halls can present food and social challenges. *"[My daughter] would have to plan her meals in the morning of what she wanted to have a dinner, and then she would have to let [the dining hall kitchen] know. By the time she would get there with her friends, her food usually wasn't cooked yet. .... By the time her food was prepared, her friends had already eaten, so she would eat alone."* - Karen, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

Participating in hobbies including travel, biking, or playing sports

Many living with classical HCU avoid playing sports because of the risk of lens detachment or of injury due to osteoporosis, nearsightedness, and clumsiness. Travel is particularly affected because of the large amounts of formula that they need to take with them which can cause problems going through security. Mobility can be limited due to scoliosis, pain, and poor eyesight.

Due to the risk of lens detachment, "Juana cannot participate in any sports or activities that can cause direct or indirect impact to her eyes. Juana's not been allowed to run, jump, play with a ball, or dive in a pool since she was five. So, most days she sits through PE classes watching the other kids play." - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

"During physical education I was slower than my peers. They teased me and made fun of me." - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

"My husband and I would like to be traveling and enjoying retirement, but I find homocystinuria often gets in the way. My diet is difficult to explain to others, and my medical formulas are a hassle at TSA checkpoints." - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

Working or having a career

Classical HCU impacts employment so many ways. Cognitive issues and high anxiety levels are barriers to finding and managing jobs. Some select jobs based on the level of medical coverage rather than potential job satisfaction. Many find the questions from employers and coworkers about their diet and medications challenging, and it can be difficult to take medication on time, especially when work doesn't permit regular breaks. Some find it hard to focus on work when they feel hungry. Unfortunately, many with classical HCU are unemployed and struggling to support themselves.

"Multi-step processes such as finding a job are really hard. There are steps, creating the right kind of resume, reading through job description, the job search, cover letter, an interview. Anyone who has applied for a job before knows how overwhelming that can be, but now add processing issues, brain fog, difficulty learning, finding words, plus anxiety, and it seems overwhelming. … If I do find a job, how am I supposed to retain it with these issues?" - Brooklyn, 37-year-old living with classical HCU, diagnosed at 8 years of age

"Other patients and myself are in the unfortunate position of having to include the possibility of proper insurance coverage as a make-or- break aspect in decisions around job changes and career opportunities, which states to live in given variation in applicable, patient-friendly state laws, and life choices that impact obtaining insurance coverage." - Ben L, 32-year-old living with classical HCU, diagnosed by newborn screening

"My daughter does work eight hours a week, but her greatest income is through Social Security benefits, truly not enough to sustain her livelihood for the future. My daughter lives at home and is able to afford more this way, but I have strong concerns for her future livelihood."- Joy, parent of a 26-year-old daughter living with classical HCU, diagnosed at 12 years of age

Attending school

Many individuals living with classical HCU start school well behind other students. Many struggle and have to work much harder than their peers, even with supports in place. Even if they are successful, individuals still struggle with anxiety and frustration.

> *"In preschool, she really struggled with pretty much anything: letters, numbers, vowel sounds, rhyming, you name it. … they thought she had had some type of learning disability. Well, it turns out it was [HCU]."*- Ruth, parent of a 12-year-old daughter living with classical HCU, diagnosed at 6 years of age

> *"I was unable to go to preschool because I was so far behind the other kids. … As I entered school, I was often taken out of my classes to do occupational therapy to try to close some gaps. As I continued on, I struggled with learning disabilities and needed an individual education plan or IEP in school in order to provide more time and assistance to complete my work, even though I was going to a special education school."* - Brooklyn, 37-year-old living with classical HCU, diagnosed at 8 years of age

> *"Entering college, I had constant anxiety about my HCU and being on my own. …In a new environment with roommates, hard classes, and a school that doesn't assist with sufficient accommodations, I felt frustrated and alone at a stage in my life that was supposed to be the time of my life. …In terms of my future, life looks scary."* - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

Other activities of daily life that are impacted by classical HCU

In the online poll, many chose **sleeping** as an activity of daily life impacted by classical HCU, but it did not generate discussion or comments.

Other important daily impacts that were discussed at the meeting but not captured in the polls include a **lack of independence** and **impacts on caregivers**.

Lack of independence. Many of those living with classical HCU depend on their parents and caregivers for their everyday care and some will never live

independently. Unfortunately, many of these individuals were not represented during the meeting, as their caregivers were too busy to join the meeting. Some older adults find themselves increasingly dependent on others.

> *"First thing in the morning, I put in her contact lenses because she can't see well enough to do it on her own. … Because of the impact homocystinuria has had on her, she relies on me always and completely for everyday care. And the fact that she cannot achieve the same level of independence as another 11-year-old has taken a great toll on her."* - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

> *Because of these [vision] issues, I can no longer drive, and I'm dependent on others for transportation."* - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

Impacts on caregivers. For some, the worries and fears of diagnosis and the burdens of caring for a child with classical HCU overshadowed the joys of parenthood.

> "*As a new parent rather than enjoying our daughter's newborn phrase, we were laden with worry about how she will be in later life and what it means for us."* - Aoibhinn, parent of a 1-year-old daughter living with classical HCU, diagnosed by newborn screening

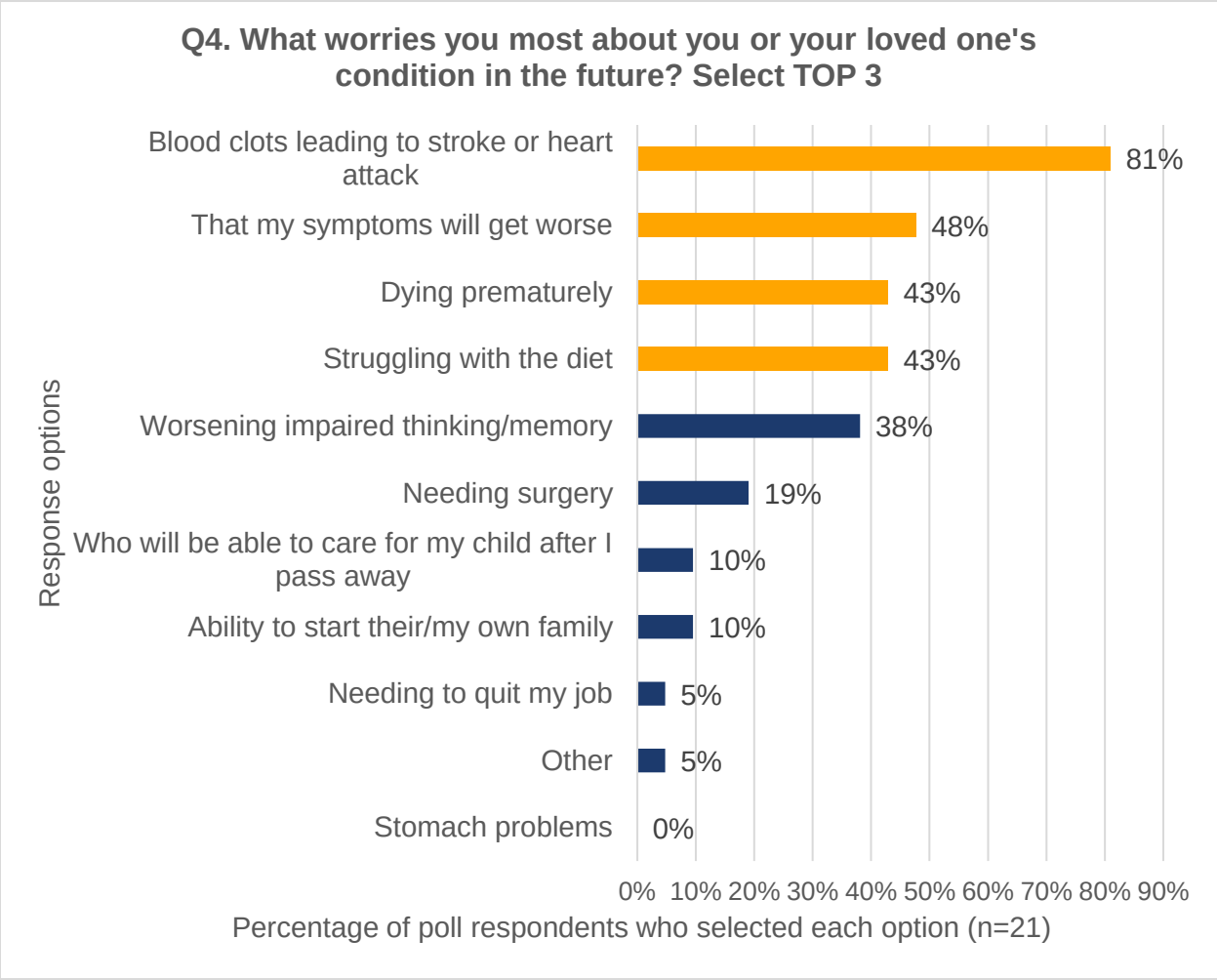
> *"As her mom, my heart breaks for her struggles, the ones she's had, and the ones to come. It hurts to know that life will always be difficult for her, that HCU has stolen so many opportunities from her and will continue to do so. … So much of our time and energy is spent on making sure that Juana's homocysteine levels are within a safe range, and as a result, I feel I'm missing out on being her mom."* - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

Poll Q4

Those living with classical HCU and their caregivers worry that high homocysteine levels will lead to blood clots, disease progression and premature death.

Poll respondents selected the top three things that worried them most about their or their loved one's condition in the future. Although a catastrophic blood clot

leading to stroke or a heart attack is the top worry, those living with classical HCU and their caregivers also worry that symptoms will get worse, fear premature death, and worry about struggles with the diet. Poll results are shown in the graph and are described with patient quotes below.



Poll Q4: This graph includes patients and caregivers who chose to participate in online polling. The number of individuals who responded to the polling question is shown below the X axis (n=x). The responses for this polling question is not considered scientific data, but is intended to complement the patient comments made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Worry about blood clots leading to stroke or heart attack

Suffering a catastrophic, potentially fatal event is the top worry of those living with classical HCU and their caregivers.

> *"My greatest fear is that even working collaboratively with a complex medical team and having blood check-ins every few weeks, I will not catch a too high level of homocysteine in enough time, and it will cause sudden catastrophic, irreversible damage, adding to the significant amount of trauma that my husband has [already] endured."* - Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age

> *"My son, who was not diagnosed until age two, presented with blood clots in the brain and a stroke. With treatment, he has not had any further serious complications, but we live in fear every day of what could happen."* - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

> *"Just the worry - and it's probably me worrying more than my children - of strokes, blood clots. I think it gets worse as a caregiver the older your children get, because they eventually aren't living with you anymore and they're on their own, and it can be a scary thing. That worry never goes away. ... Even though you're diagnosed early, it's still a possibility forever."* - Karen, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

Worry that symptoms will get worse

Many worry that the inability to control homocysteine levels will result in disease progression and new symptoms appearing. Many worry about the longer-term impacts of aging with a chronic disease and how they will be impacted as they age.

> *"I constantly worry that the possible side effects of HCU will happen to my child (even though we follow a low-protein diet and take her medication). I also do not want her to be on medication for her lifetime, but I appreciate that is just part of what we have to do. I am scared that later symptoms will affect her."* - Aoibhinn, parent of a 1-year-old daughter living with classical HCU, diagnosed by newborn screening

"It's something that is acutely on my mind to try to differentiate the normal signs of aging through the lifespan from the signs of aging that are compounded by HCU, whether the HCU is controlled or uncontrolled."- Jamela, 35-year-old living with classical HCU, diagnosed by newborn screening

"One of the things I fear most as an older patient is not having answers to my visual problems. I'm losing my vision rapidly and no one seems to be able to give me specifics as to why my retinas are deteriorating. … It is terrifying to think I may lose my vision due to the complications of this disease." - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

Worry about premature death

Many expressed worries about dying young because of classical HCU.

"How long am I going to live? What does the adult version of this [disease] look like? And is it riddled with all these horrible medical problems? You're just kind of a test. You just kind of have to wait and see, which is nerve wracking in a different way." - Alex, 36-year-old living with classical HCU, diagnosed by newborn screening

"When I was 16 years old, [I heard] a statistic from the 1980s stating that undiagnosed patients will die before reaching [the age of] 30. So, for 14 years, I woke up every day wondering if I'd make it to tomorrow. This created a toxic relationship with food, my homocysteine levels, my mental health, my weight, my perception of myself in general." - Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

Worry about struggling with the diet

Being able to maintain the low protein diet is an enormous worry for many. Adhering to the low protein diet takes a great deal of work, and low homocysteine levels are difficult to achieve and maintain.

"I constantly have to think about the future, the diet, the next meal. If I'm living in the present, I'm already too late because the choices I make today will have a lasting effect on the rest of my days. … Homocystinuria is still considered a child's disease, yet it is a full-time job that is mentally and

physically exhausting." - Brooklyn, 37-year-old living with classical HCU, diagnosed at 8 years of age

"Living on 11 grams of protein a day is incredibly challenging. Unlike other diets, there are no 'cheat days' - it's a life sentence. The mental gymnastics that it requires to make sure that your child is never exceeding what is considered a 'safe amount' of protein is exhausting. Tracking his food intake, administering formula and medications...it's a full-time job." - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

Worry about worsening or impaired thinking/memory

Many worried about worsening or impaired cognition and thinking, losing their memories and sense of self.

"Although my daughter has suffered many effects, my greatest concern is the effect that HCU has had on her cognitive functions. She was unable to get a regular high school diploma. She did receive an IEP diploma, but this is not acceptable to many employers." - Joy, parent of a 26-year-old daughter living with classical HCU, diagnosed at 12 years of age

"Because I've seen people struggle with Alzheimer's and memory loss in my family, I don't want to forget my daughter and all the good times that I've had, I don't want to forget those things." - Ben M, 34-year-old living with classical HCU, diagnosed by newborn screening

Worry about who will be able to care for my child after I pass away

This is closely related to worries about their child's future independence. Some living with classical HCU worry about what will happen to them if something were to happen to their family.

"I worry about her future; about what level of independence she will be able to reach and if she will be able to work and maintain a job. I also worry and wonder if she will be able to form healthy relationships where people respect and listen to her, regardless of her struggles." - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

> *"I worry about insurance and the cost of living with HCU if anything was to happen to my family."* - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

Worry about the ability to start their/my own family

Several women in the classical HCU community expressed their worries about whether they would be able to start their own families and if their medication would interfere with conception and pregnancy.

> *"I worry about having children and how that could affect my body."* **-** Samantha, 26-year-old living with classical HCU, diagnosed at 2 years of age

> *"I'm terrified of when [my daughter] wants to become a mom and she wants to have a baby. What does that look like for her?? … I would love for her to be able to have a pregnancy journey without these risks and complications."* - Breun, parent of 11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age

Other worries selected in the polls

Other worries selected in the polls included the **worry about needing surgery**, the **worry about needing to quit my job,** and the **worry about stomach problems**, however, these worries did not generate discussion or comments.

A worry mentioned throughout the meeting but not captured in the polls was **whether children will continue to follow the prescribed diet and take their medications**, especially when they are no longer under parental care. Others worry whether their child's ability to obtain insurance coverage will impact their future adherence.

> *"The consequences of them deciding to not stay on diet, not drink their formula or forgetting their medications is quite frankly terrifying. Blood clots, stroke, bone density issues, progression of scoliosis, depression, increases in mental deficits and cognitive abilities, not to mention the risk of our son also losing the lenses in his eyes like our daughter."* - Breun, parent of 11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age

"There aren't any guarantees for what's going to happen in the future. Our biggest concern is that he eats something wrong or gets off diet or whatever, and just all that hard work that he's put in for 18 years can change very quickly. … As your kid gets older, you've lost control over what they do. The fear is there that symptoms that he may not have had earlier in life will now manifest themselves because we don't watch him as closely as we used to." - Chris, parent of an 18-year-old son living with classical HCU, diagnosed by newborn screening

"What you want ultimately for your child is for them to grow up and go out into the world and you want them to have that freedom of choice and to be able to make mistakes because every child and young adult and teenager, they're all going to make mistakes. That is a guarantee. But when they make mistakes with their diet …they're at risk of making a very big mistake every single day. As a parent, that's a huge worry to think about." - Melanie, parent of a 10-year-old son living with classical HCU, diagnosed at 8 years of age

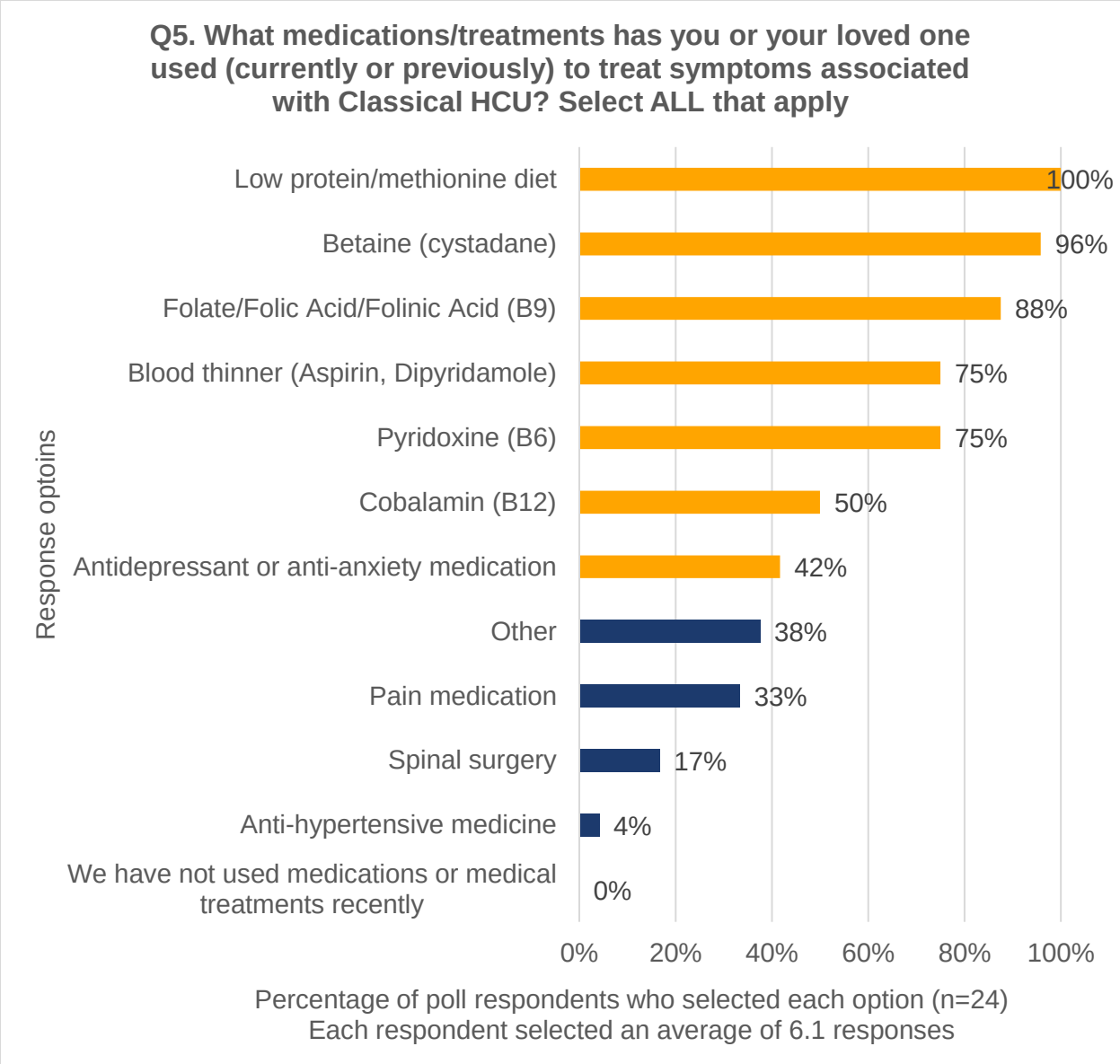
Topic 2- Current and Future Treatments for Classical HCU

Through online polling, moderated discussion and submitted comments, patients and caregivers described all the different medical treatments used to manage classical HCU-related symptoms, as well as non-medical approaches. They described the most significant drawbacks associated with each approach and articulated their hopes for a future of ideal classical HCU treatments.

Poll Q5

Individuals living with classical HCU require a large number of medications and treatments.

Individuals living with classical HCU and their caregivers used online polling to select all the medications or medical treatments that they or their loved ones used (currently or previously) to treat symptoms associated with classical HCU. Each respondent selected an average of 6.1 responses, which reflects the high number of different medications required. Not one person indicated that they have not used medications or medical treatments recently. Poll results are shown in the graph and are described with patient quotes below.



Poll Q5: This graph includes patients and caregivers who chose to participate in online polling. The number of individuals who responded to the polling question is shown below the X axis (n=x). The responses for this polling question is not considered scientific data, but is intended to complement the patient comments made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Low protein/methionine diet

Approximately half of individuals living with classical HCU must comply with a low protein/methionine diet (which is required for those living with B6 non-responsive HCU). The diet often includes a methionine-free amino acid supplement, most often consumed as a medical formula, which is meant to replace the nutrition missed on a low protein diet. Many living with classical HCU described how treatment helped improve coordination, cognitive abilities, and social engagement.

> *"I count my proteins every meal, so I do not go over my allotment. …These days I am on vitamin B6, B12, folic acid and Cystadane as well as a low-protein diet. My protein allowance is enough, so I don't need medical formula."* - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

> *"There are the protein formulas to offset essentially the lack of whole protein intake. And there's the limited, very limited, whole protein intakes that have to be balanced through all the social and all the other complexities of life. And that's what you do. That's how you manage it. That's what you need to do. These are the therapies available to us."* - Mark, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

> *"When he was a little kid, he could have 10 McDonald's French fries and that was it for his protein. The rest was supplemented with low-protein foods, which he disliked. And vegetables and fruits, some vegetables, some are high in protein. The diet is a burden. … It's not just a vegan diet. You can't have any grains, nuts or any beans. So, it's difficult. But he was on it and his [homocysteine] levels still fluctuated."* - Barbara, parent of a 36-year-old son living with classical HCU, diagnosed by newborn screening

The low protein/methionine diet has many downsides. Maintaining a low protein diet is very challenging and many struggle to achieve their specific protein target. Individuals living with classical HCU are often hungry. The formula tastes terrible, making adherence an issue. Many are unable to achieve consistently low homocysteine levels, even when they stick to their prescribed diet.

"The formula is a struggle for almost every patient or child that I've met. I know from my own two children now adults, it is an issue daily. The taste of it, the consistency, having to drink your formula in front of other people [when] bringing it to work or college. Also having to travel with it. It is a struggle. Companies discontinue it and you have to try a new one, which is a nightmare for any parent to have their child switch to a different formula." - Karen, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

"A big drawback definitely is the limited diet. It's hard to explain to people. They don't often understand. They think it's just an allergy, when really it's something that for us could be life-threatening, strokes, blood clots. That's definitely been a big disadvantage." - Landon, 17-year-old living with classical HCU, diagnosed at 4 years of age

"Ellie is growing and hungry. We calculate the methionine content in every meal and snack she has, and she is always hungry at the end of her day. As a parent telling your child you can't help their hunger is a terrible feeling." - Jeannie, parent of a five-year-old daughter living with classical HCU, diagnosed by newborn screening

Betaine anhydrous for oral solution (Cystadane®)

Betaine anhydrous is an amino acid derivative that may be consumed by individuals with classical HCU along with the low protein diet and supplements including folic acid, vitamin B6, and/or vitamin B12. Many reported that the betaine anhydrous works very well to help lower homocysteine levels. The most common downsides of betaine anhydrous include the extremely bitter taste, some experience upset stomach, and a few are even allergic.

"When he got into middle school, he obviously went off his diet somewhat. … I think he ate pizza and bologna sandwiches. …His [homocysteine] levels were very, very high. We put him on Cystadane, which was helpful at the time. …It decreased his anxiety about his condition, because had a lot of anxiety about his condition, even from a young age." - Barbara, parent of a 36-year-old son living with classical HCU, diagnosed by newborn screening

"The current options for HCU patients simply do not work well for me. Cystadane, which I take twice a day, is the only real option to combat high protein. I need to mask it with either applesauce or pudding. Current treatments cause stomach upset and are unpleasant to taste and smell. This does not encourage me to want to take it. I wish there were better options or better alternatives for me." - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

"Betaine has been critical to help lower levels of homocysteine but it comes with stomach upset and pain. It makes it difficult to take each day even though my kids still do because they know the consequences if they don't. My daughter goes to bed nauseous every night." - Karen, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

Folate/Folic Acid/Folinic Acid (B9), Pyridoxine (B6) and Cobalamin (B12)

These vitamins are taken in addition to the low protein diet and betaine anhydrous. Although some patients have only limited responsiveness to pyridoxine (vitamin B6), some continue to take this as it could have some effect along with other therapies.

Aoibhinn described her child's regimen. *"Low protein diet, a dose of pyridoxine (even though she is unresponsive to it), synthetic protein, weekly/bi-weekly blood tests in hospital, regular checks up in the hospital."* - Aoibhinn, parent of a 1-year-old daughter living with classical HCU, diagnosed by newborn screening

"His current treatment consists of vitamin B6, B12, folic acid, betaine, and of course the low protein diet." - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

"The B12 injections were prescribed to be administered at home intramuscularly. … It was very traumatic. Our daughter, Clara, still struggles with getting shots to this day. Recently, she actually had a panic attack at a doctor's office just getting a routine vaccination, and I remember clearly my son asking why we were doing this to them. It was absolutely heartbreaking and definitely not a position any parent should be put in." - Breun, parent of

11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age

Blood thinners (Aspirin, Dipyridamole)

Blood thinners help manage the cardiovascular risk associated with high homocysteine levels, but it can be challenging to determine the correct dose.

Despite being on blood thinners, Christa experienced a stroke. *"I had a massive stroke resulting from two blockages, one in my carotid artery, and another at the cross of my basal ganglia and frontal cortex. However, thanks to the preparation, my husband quickly identified the signs of the stroke. …His fast response we were told is what got me this assistance I needed within the golden hour, as they say, which allowed them to rush me to surgery and remove the clots in enough time to allow 90% of my damage from the stroke as of today to be reversed."* - Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age

Spinal surgery for scoliosis

Some individuals require spinal fusion surgery for severe scoliosis. Unfortunately, surgery is very dangerous due to the clotting risk associated with high homocysteine levels, and many have to reduce their blood thinners in advance of surgery.

Karen's daughter underwent two scoliosis surgeries, "*Which were probably one of the most traumatic things we've ever experienced as a family. … She was in ICU for eight days with each surgery, because after her surgery she wasn't able to really keep down any formula, wasn't eating. Her homocysteine levels were very high."* - Karen, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

Gabbi was allergic to the hardware used in her scoliosis surgery. *"My post-surgery pain was not only not subsiding but getting much worse. … Ultimately, I had to decide to redo the surgery and was admitted in the middle of my senior year of high school for an eight-hour-long procedure where they removed the metal hardware, extended my fusion, and then put in 26 screws and two titanium rods. With another eight days in the intensive*

care unit, my HCU was a constant risk." - Gabbi, 21-year-old living with classical HCU, diagnosed prenatally

Other medications and medical treatments being taken

Individuals living with classical HCU and their caregivers selected **antidepressants or anti-anxiety medications**, **pain medications**, and **antihypertensive** medications being taken in the online polling, however, there were very few associated comments provided.

Other medications and medical treatments not selected in the polls but described at the meeting and in the submitted comments include **ADHD medications**, **surgeries for ocular detachments and bone issues** (besides scoliosis), **g-tubes**, and **clinical trial participation**.

"I started on ADHD medication, which was a game changer in my ability to focus and complete tasks, manage my class requirements, and multi-step projects." - Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age

"My son's classical HCU symptom that has had the most significant impact on his life was his double eye surgery for Ectopia lentis. He had lensectomies in both eyes. Without his special contact lenses, it's like having your eyes open underwater. Very blurry." - Melanie, parent of a 10-year-old son living with classical HCU, diagnosed at 8 years of age

"As an infant, Ava experienced extreme difficulty tolerating the medical formula…. It caused acid reflux so severe … the pain caused her to stop eating much at all. At one point, a G-tube was inserted and we began administering her feeds in this way, but she would vomit most everything back up." - Melissa, caregiver of five-year-old Ava, diagnosed with classical HCU at birth

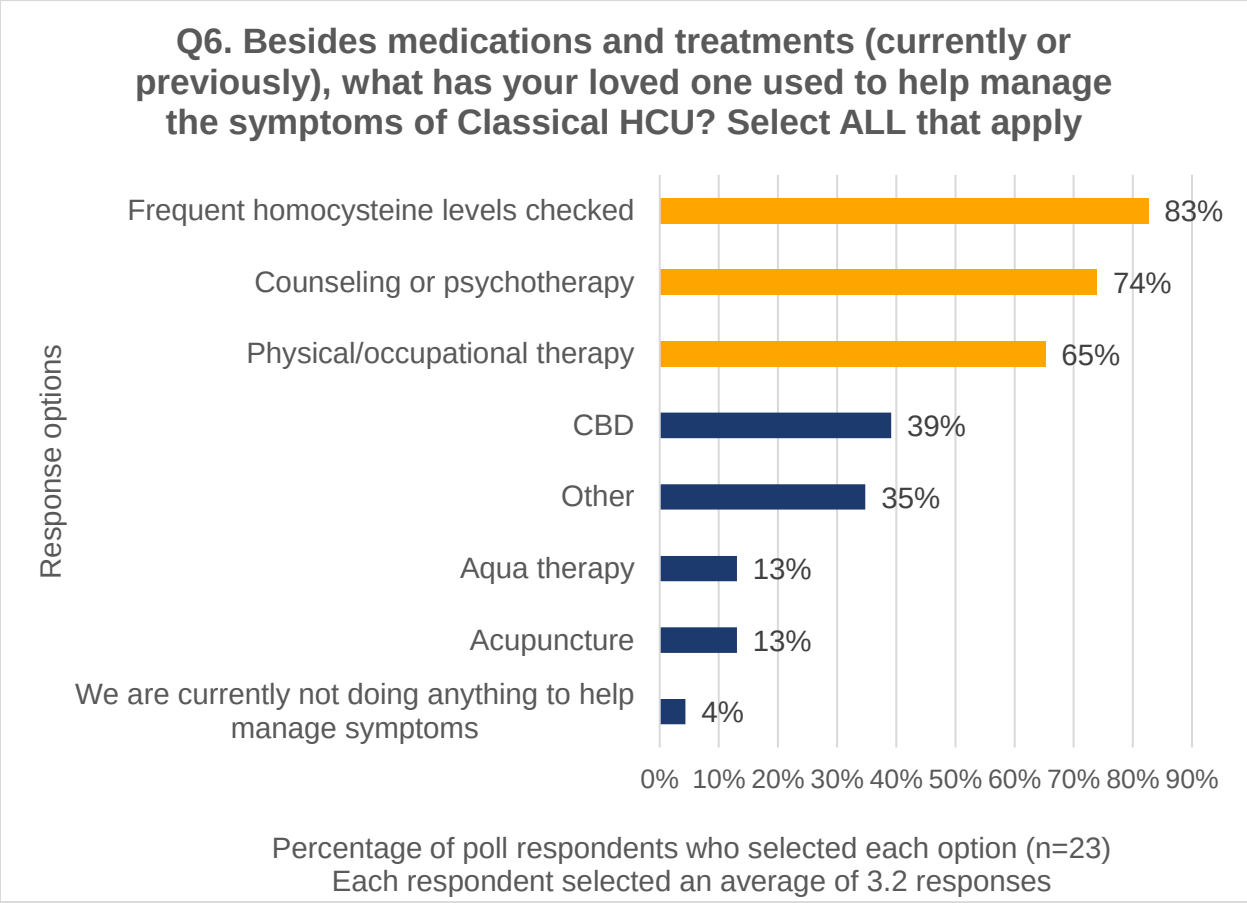
"Currently, I'm participating in a clinical trial in the open label portion, so I know I'm getting the drug. My homocysteine levels have been the lowest they've been since I was a child. They're now under 100, whereas previously they were in the 200s. I feel like a new person: more energy, less fatigue,

and much more able to manage my anxiety." - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

Poll Q6

Other approaches to help manage classical HCU symptoms include frequent monitoring, counseling, psychotherapy and physical or occupational therapy.

Using online polling, individuals living with classical HCU and their caregivers selected all the approaches that they or their loved ones (currently or previously) used besides medications and treatments, to treat symptoms associated with classical HCU. Each respondent selected an average of 3.2 responses. Poll results are shown in the graph and are described with patient quotes below.



Poll Q6: This graph includes patients and caregivers who chose to participate in online polling. The number of individuals who responded to the polling question is shown below the X axis (n=x). The responses for this polling question is not considered scientific data, but is intended to complement the patient comments

made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Frequent homocysteine levels checked

Currently there is no data to support how long it takes for homocysteine levels to rise or fall and how that directly correlates to protein intake and other factors. Despite this, those living with classical HCU need to have regular blood draws to check their homocysteine levels. However, downsides include the fact that blood draws are traumatic, and by the time the results are reported the information it provides is hard to put into context.

> *During his first year of life, he had to get his blood drawn every week for 50 weeks, 52 weeks, and that was really horrible."* - Barbara, parent of a 36-year-old son living with classical HCU, diagnosed by newborn screening

> *"One of the difficult sides of treatment is having to go to a lab and get blood drawn regularly. It varies for different individuals, but my 10-year-old goes every 4 weeks. Some might think "oh well, he will adapt", and in a way, sure he has. But that is not okay or acceptable. Nobody should have to adapt to being poked and hurt on a regular basis. It's a very difficult and sad effect."* - Melanie, parent of a 10-year-old son living with classical HCU, diagnosed at 8 years of age

> *"I can tell her homocysteine levels are not what they should be. I can see changes in her behavior, but it's not realistic to get her tested every time, considering the results would take time to come back to us and the fact that she would have to stop her regular routine for yet another medical procedure. Other children get ice cream and visit museums. Juana gets blood work done and visits her doctors and dieticians."* - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

Counseling or psychotherapy

Many require extra support to manage the anxiety and depression associated with classical HCU.

> *"We are living our lives in a long-term, heightened state of survival mode. It has taken me years of hard work and therapy to even begin to understand what's happened to me as a person and how it's impacted my mental*

health. Currently, I am diagnosed with anxiety, depression, OCD and CPTSD [complex post-traumatic stress disorder] from enduring everything I've had to." - Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

"I see a therapist to help try to manage my anxiety, but I've not been able to find a medication for my anxiety that I haven't been allergic to." - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

Physical/occupational therapy

Many reported successes with both physical (PT), occupational (OT) and other types of therapies to help them address primary challenges of developmental delays, osteoporosis as well as the results of strokes.

"With physical, occupational and speech therapy, we have been able to see some improvement, but we are still working hard to try to help Ava 'catch up' in terms of development." - Melissa, caregiver of five-year-old Ava, diagnosed with classical HCU at birth

Joanna experienced a major stroke, "*which paralyzed my left side. And currently I have everything back again, thanks to a lot of physical therapy, occupational therapy. … And so, it is through sheer persistence that I am able to walk.*" - Joanna, 53-year-old living with classical HCU, diagnosed at 3 years of age

"Elliott went through a lot of physical and occupational therapy to overcome some of the challenges initially that [blood clots, seizures and a medically-induced coma] presented. … the PT and OT helped to get him walking normally again and talking and using his fine motor skills and things like that, that were a result of just being immobile for a long period of time." - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

Other symptom management approaches

Those living with classical HCU and their caregivers selected **CBD (cannabidiol), aqua therapy** and **acupuncture** in the online polls as approaches they used to manage symptoms.

"During my last year of college, I developed a severe back pain. This resulted in several months at home, was treated with exercises, swimming, heating

pads, and relaxing. These days I still have back pains with flare-ups." - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

"As a teen I had a horrible time with my posture and struggled greatly to sit or stand up straight. It was discovered I had scoliosis. For several years my mother took me to a chiropractor who performed adjustments, acupuncture and cupping. For a long time, this worked, however about two decades later I still struggle quite a bit and can see that my shoulder blades sit differently as a result of the scoliosis." - Danaé, 38-year-old living with classical HCU, diagnosed at 10 years of age

Other symptom management approaches that were not captured in the polls but mentioned throughout the meeting include **back braces for scoliosis**, **ankle-foot orthoses (AFOs)**, **glasses**, **contact lenses** and **exercise**.

"In my teens, I was also diagnosed with scoliosis. I tried physical therapy and chiropractic adjustments, but in the end, I needed to wear a back brace for two and a half years. At a time when most kids are self-conscious about their looks, I was needing to wear a back brace 23 hours a day, even to sleep." - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

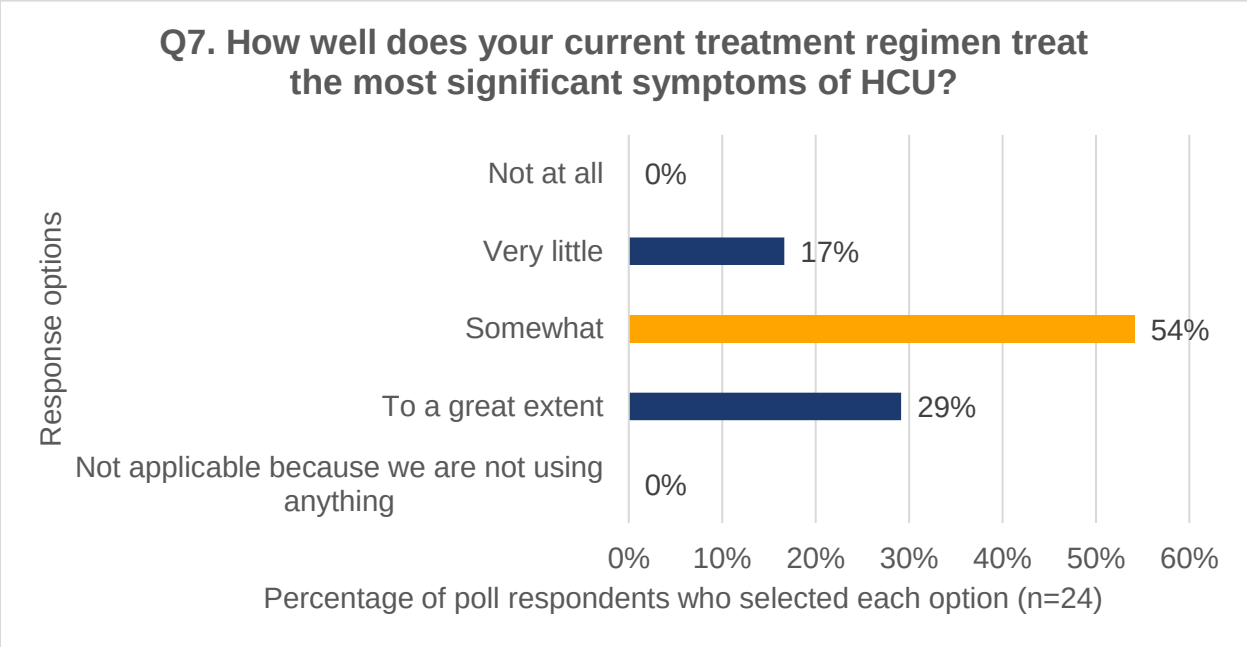
"Due to the removal of my lenses, I needed to wear thick glasses. In those days, teasing and being made fun of by my peers was part of the course. I tried contact lenses, but it did not work as my eyes were very, very sensitive, especially to sunlight." - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

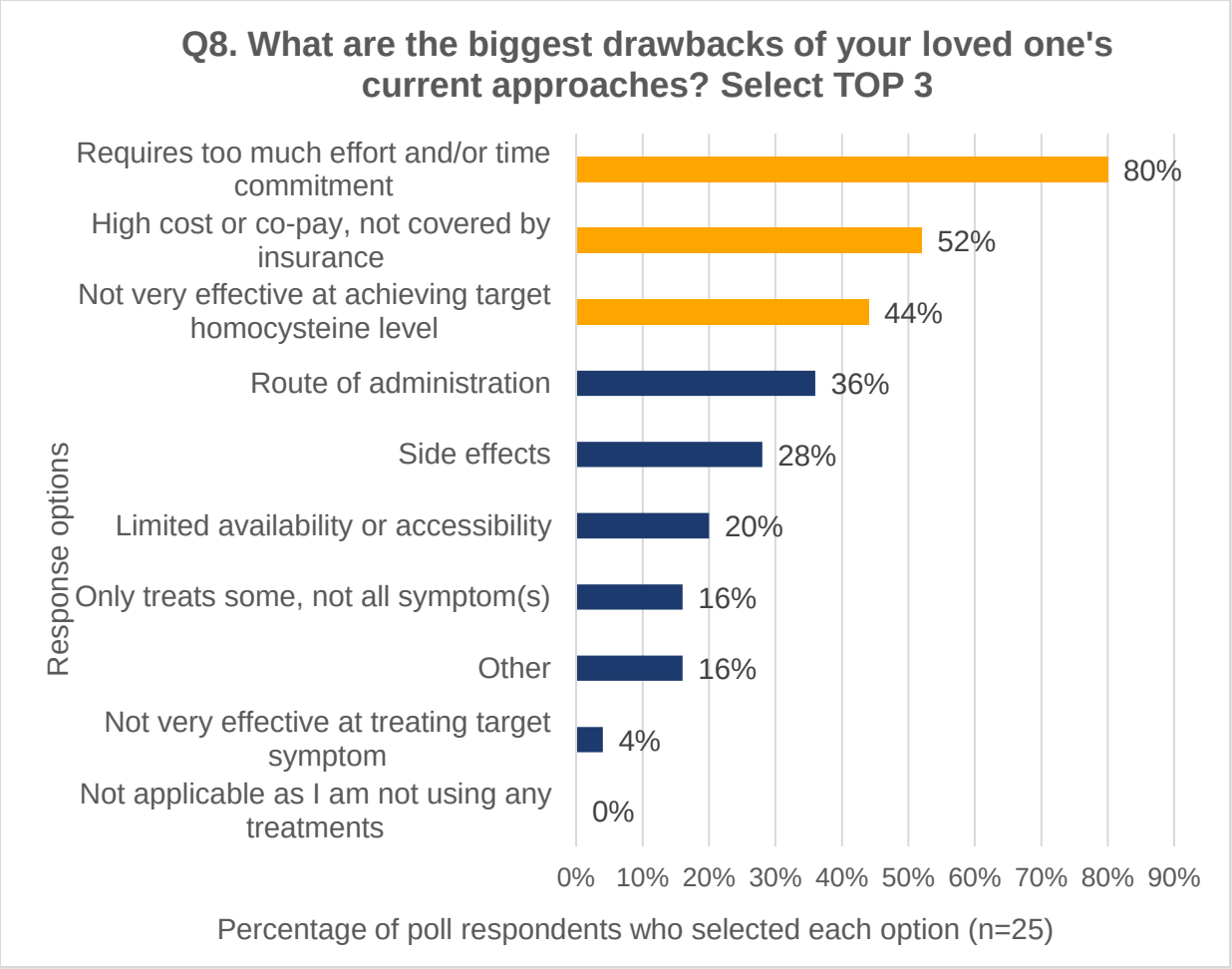
I have been doing CrossFit for a year now with a personal trainer and commit to it two times a week. This is important to me to hopefully not develop osteoporosis until much later in life, keep it from creeping up sooner in life." - Samantha, 26-year-old living with classical HCU, diagnosed at 2 years of age

Poll Q7 & Q8

Medical treatments and other approaches required to manage classical HCU symptoms work "somewhat" or "to a great extent". However, none of these treatments actually address the disease itself, and all treatments have downsides.

Using online polling, individuals living with classical HCU and their caregivers indicated how well their current treatment regimen treats the most significant symptoms of HCU (**Q7**). They then used online polling to select the biggest drawbacks of their or their loved one's current approaches (**Q8**). Most described that their medical treatments helped "somewhat" or "to a great" extent. The top selected downsides include treatments require a great deal of effort/time commitment, can be costly, and are not always effective at achieving target homocysteine levels. Poll results are shown in the graphs and are described with patient quotes below.





Polls Q7 &Q8: These graphs include patients and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below the X axis (n=x). The responses for these polling questions are not considered scientific data. These are intended to complement the patient comments made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Important themes that emerged during the meeting but were not captured in the polls are highlighted in blue.

Classical HCU treatments only help manage symptoms. None actually treat the underlying cause of the disease.

"Most of the treatments that we do go through, it's just because the benefit outweighs the risk. … I personally don't find any of these treatments as true

treatments. They're just maintenance." – Danielle, 33-year-old living with classical HCU, diagnosed by newborn screening

None of these treatments can reverse or address the accumulated damage from high homocysteine levels.

"I don't believe she'll ever be at the level of her older siblings - who do not have homocystinuria - as far as coordination and athletic ability. But she has come such a long way."- Ruth, parent of a 12-year-old daughter living with classical HCU, diagnosed at 6 years of age

Requires too much effort and/or time commitment

Throughout the meeting, patients and their caregivers emphasized how much hard work is required to adhere to a low protein diet. They described consuming large numbers of pills and enormous volumes of terrible tasting formula, which can negatively affect adherence. As described earlier, those living with classical HCU require regular blood tests to monitor homocysteine levels.

"It's a lot more work to prepare low protein diet as everything has to be weighed and you can't just eat things 'on the fly' – everything has to be carefully considered. It is a huge mental load. This affects my daily life as it means my sole focus a lot of the time is on my daughter's meals rather than her! I am more concerned about keeping her healthy, rather than happy (in a way). Because sometimes I feel I am not present and don't enjoy mealtimes as I am stressing to see if she is eating all of her meal. It also is difficult to get food/medicines into her and this is a big mental burden." - Aoibhinn, parent of a 1-year-old daughter living with classical HCU, diagnosed by newborn screening

"Counting the protein for the meals and snacks that I give him also takes a lot of focus and mental energy. I can't imagine having to do this every single day for every single meal and snack. To be completely transparent, it's exhausting just doing it for one overnight visit! I love my grandson, and wouldn't trade time with him for the world, but I just wish that there were a treatment that would allow me to spend less time planning, and more

quality time with him." - Nancy, grandmother of a 7-year-old grandson living with classical HCU

"For me personally, I take over a hundred pills a day, so traveling with that is a big downside. I currently take 80 HCU pills. I get my Cystadane, my betaine, in tablet form, so that's another 18. Then I am on antidepressants for the anxiety that this disease induces, vitamins B6. … Definitely managing taking all of them in one day and taking them on time. Definitely compliance has been a very big issue in my life." - Landon, 17-year-old living with classical HCU, diagnosed at 4 years of age

Not very effective at achieving target homocysteine level and only treats some, not all symptom(s)

Homocysteine levels are unpredictable and can fluctuate. Despite all the time and effort devoted to maintaining a low protein diet, individuals with classical HCU don't always achieve target homocysteine levels.

"While the low protein diet can certainly help to keep homocysteine levels regulated, it's not an exact science. For my son, we count every bite of food that goes into his mouth, and he never exceeds his daily allotment. Month to month, his homocysteine levels fluctuate, even with no changes made to his treatment. Even with restricting his diet with a great deal of consistency, we can't be sure that he's not in danger." - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

"Even though Juana is super compliant with her treatment plan, her levels still fluctuate, we can't count on her treatment to keep her homocysteine levels within a safe range. As a result, she has frequently experienced regular fatigue, difficulty concentrating, irritability, and has gotten ill frequently." - Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

"*My boys' levels are currently being treated with medications, but it's frightening as a parent to see all of the things they go through: skin issues, emotional dysregulation, vision and hearing issues, poor growth, and to wonder if our treatment course is the right one... will symptoms get worse...*

are they all related? Is this just the calm before the storm?" - Angela, parent of 6-year-old and 3-year-old sons living with classical HCU, diagnosed at 3 and 1 years of age)

Route of administration

Many individuals living with classical HCU are required to take so many pills and medications. Many described how awkward it is to take medications in front of their peers and coworkers, which can impact adherence.

> *"Currently I'm supposed to take 24 formula pills a day. However, I have acid reflux, which makes taking these pills very difficult. The liquid formulas are also a challenge. I have tried them all, and the texture and the horrible taste. It doesn't matter how much you try and mask it, it's still there."* - Samantha, 26-year-old living with classical HCU, diagnosed at 2 years of age

> *"I'm supposed to take 45 tablets a day, but most days I struggle to get them down. When I can't take a sufficient amount of formula, it leaves me feeling anxious and worn out."* - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

> *"Definitely organization is key for me in taking my medications, but sometimes it's very embarrassing or odd to take medications in front of my peers. Definitely that is a challenge."* - Landon, 17-year-old living with classical HCU, diagnosed at 4 years of age

Side effects

Many individuals living with classical HCU experience nausea, heartburn, or acid reflux from their medications, and this can result in eating aversions. Some have developed allergies to their medications. Many individuals worry about the longer-term side-effects of high methionine levels.

> *"We're on Cystadane, which is betaine. This lowers our homocysteine level and raises our methionine level very drastically. We don't know the long-term implications of that. We don't know what that's going to do."* - Alex, 36-year-old living with classical HCU, diagnosed by newborn screening

> *"We have spoken extensively about the beauty of betaine, but it was many years before the downside of having high methionine surfaced to a public*

level where we could all come together as a community and openly speak about it." - Danielle, 33-year-old living with classical HCU, diagnosed by newborn screening

Barbara wonders if her son's rare cancer was a side effect of his classical HCU treatments. *"We don't really know what the homocysteine, the methionine levels do, the treatment does. We don't know what betaine does. We're not sure if this is related to his cancer."* - Barbara, parent of a 36-year-old son living with classical HCU, diagnosed by newborn screening

High cost or co-pay, not covered by insurance

Many patients and caregivers described the high costs of their treatment and challenges in paying for their medications and medical foods.

"Obtaining affordable and affirmative coverage for HCU treatments - given it is a rare, unfamiliar disorder for insurers and involves only a limited number of available treatments that are exceedingly expensive in the absence of adequate coverage or assistance plans - is a major challenge and impact for patients and it influences patients' major life choices in negative ways." - Ben L, 32-year-old living with classical HCU, diagnosed by newborn screening

"Dealing with insurance companies to obtain medication, food, and supplies is definitely a challenge. I have advocated strongly to get what is needed for my daughter. I have been declined numerous times and it is beyond frustrating." - Joy, parent of a 26-year-old daughter living with classical HCU, diagnosed at 12 years of age

"I had to switch away from the brand name Cystadane to the older of two generics. I have seen a rise in my [homocysteine] levels. My insurance has raised the cost of the brand name Cystadane." - Joanna, 53-year-old living with classical HCU, diagnosed at 3 years of age

Limited availability or accessibility

For many patients with classical HCU, travel to medical appointments and participation in clinical trials are a burden. This is especially experienced by those with visual impairments that may rely on others for transportation, as well as

individuals on fixed income. Some individuals live in countries where medical food and formula for those with classical HCU is unavailable.

> *"There are so few clinical research sites in the United States. And if the majority of us have vision issues and we're unable to drive, going to a place would be - unless you live within a couple of hours - is going to be astronomically impossible, both for visual reasons and also for financial reasons. … There needs to be more clinical research trial sites in every state in the country, so that every patient who wants to participate can participate."* - Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

> *"My clinical trial went from being completely in person to virtual and this has presented some challenges, especially considering my visual impairments. Appointments that were supposed to last one to two hours have lasted closer to seven to 10. Despite these challenges, I participate because I want to see a new drug approved and become available for the HCU community."* - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

Other medication downsides: challenges with comorbid conditions

Throughout the EL-PFDD meeting, many individuals living with classical HCU raised an additional medication downside, that they have comorbid conditions that complicate or are incompatible with their classical HCU treatments. These include diabetes, rheumatoid arthritis, and immune syndromes. Medical treatments such as surgery or chemotherapy can cause issues with classical HCU medication adherence. This becomes an even bigger challenge as individuals age.

> *"Managing homocystinuria is complicated by the fact that I had been diagnosed with …diabetes as well as mast cell activation syndrome (MCAS). Both conditions have made compliance with my current treatment incredibly complicated. … Sticking to a low-protein diet is an impossible task [for diabetics]. The medical foods that I eat to allow me to stay within my protein allotment also tend to be very carb and calorie heavy. Trying to maintain a healthy blood sugar that's not going to make me pass out and stay within the restrictions of the diet is a constant struggle."* - Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

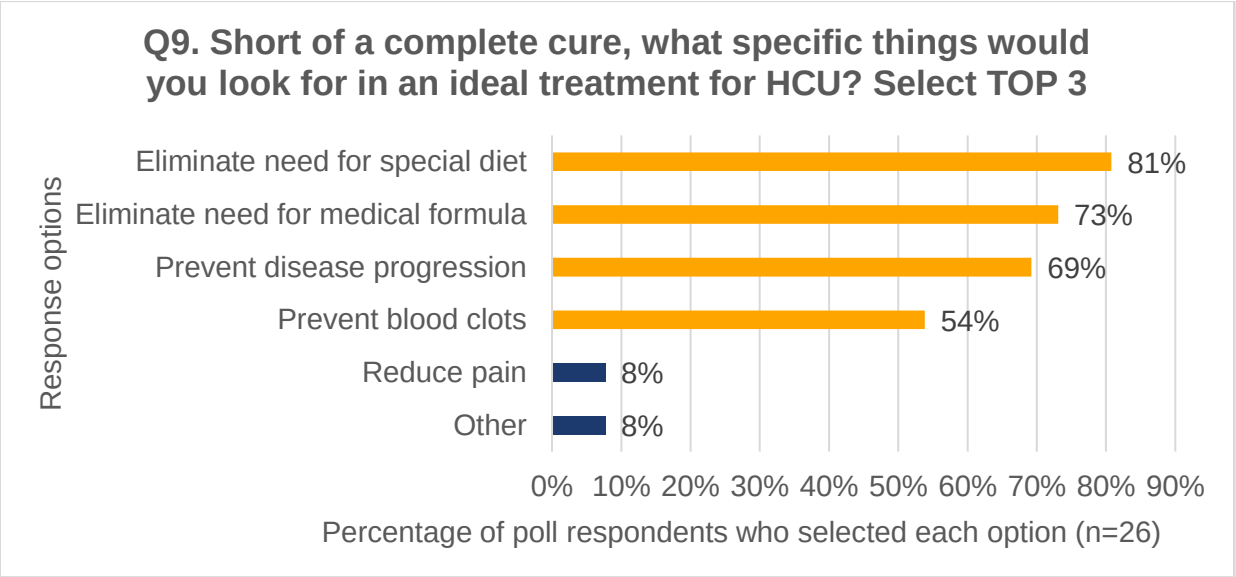
Barbara's son has a rare cancer. *"He's being treated with radiation treatment and his homocysteine levels are sky high. They're above a hundred. And there's no way to lower them quickly, so there's no treatment option for him right now. …He's not even eating. So, Cystadane is not going to really lower them quickly. There's really very, very little as far as treatment options for these very high levels of homocysteine."* - Barbara, parent of a 36-year-old son living with classical HCU, diagnosed by newborn screening

"What about the flu or the other medical events that you have that you can't ingest your formula? … There's really nothing you can do other than to hope that illness subsides and that you can get them back into their diet and complexities." - Mark, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

Poll Q9

Individuals living with classical HCU would prefer a treatment that would eliminate the need for special diets and/or medical formula and would prevent both disease progression and blood clots.

Using online polling, individuals living with classical HCU and their caregivers chose the top three specific things that they would look for in an ideal treatment for classical HCU, short of a complete cure. Poll results are shown in the graph and are described with patient quotes below.



Poll Q9: This graph includes patients and caregivers who chose to participate in online polling. The number of individuals who responded to the polling question is shown below the X axis (n=x). The responses for this polling question is not considered scientific data, but is intended to complement the patient comments made during and after the meeting. Poll responses selected by more than 40% of poll respondents are shown in **orange**.

Eliminate need for a special diet and medical formula

These were the top two poll responses selected. Many would be willing to maintain other treatments if only they could have a normal diet.

> *"I long for the day when I'm not consuming 33 pills a day, but my biggest wish is to one day have a better treatment for HCU, one that will allow me to eat a less restricted diet so that I can stop seeing food as the enemy and truly feel part of my family's celebrations again."* - Janet, 31-year-old living with classical HCU, diagnosed at 10 years of age

> *"Regarding future treatments, there aren't many options that I wouldn't consider. Pills, yes. Weekly shots, definitely. Daily shots, sure. Infusions at the hospital, sign me up. The value of lifting the burden of a low protein diet far outweighs the difficulty I might experience from any of the treatments that have been in development. If we can ditch the disgusting metabolic formula in addition to dropping the diet, that's even better."* - Ben M, 34-year-old living with classical HCU, diagnosed by newborn screening

> *"[My daughter] would want something to where she can have a meal other than french fries and salad at a restaurant and have some experiences that other kids her age take for granted every day."* - Ruth, parent of a 12-year-old daughter living with classical HCU, diagnosed at 6 years of age

Prevent disease progression

Many would like to prevent disease progression to maintain a good quality of life, especially as they age.

> *"Short of a cure we need medication that will stop the degeneration of the disease."* -Brooklyn, 37-year-old living with classical HCU, diagnosed at 8 years of age

"Long-term progression is certainly a concern. We've heard about that by some of the other community here. The "What ifs". My children were diagnosed at birth, they have hopefully a long life ahead of them. … But what does that look like? Because even though you do as good as you can, there's still the complications." - Mark, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening

Prevent blood clots and reduce the chance of catastrophic medical events

Many emphasized that they wanted classical HCU treatments to reduce the risk of blood clots and other catastrophic medical events.

"I would love to see the lowering of risk factors for serious complications and …a safer and healthier future." - Breun, parent of 11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age

"Definitely a lesser risk of blood clots and stroke and all of those not so fun things."- Landon, 17-year-old living with classical HCU, diagnosed at 4 years of age

"It is important to mention that access to a diverse array of medical treatments is not solely related to relaxing diet and lifestyle modifications, it is a matter of a reduction in catastrophic medical events. Prevention and management are key. Additionally, access to treatment and ease of use/integration for a wide spectrum of patients faced with varying symptoms must be taken into consideration." - Jamela, 35-year-old living with classical HCU, diagnosed by newborn screening

Other features of an ideal future classical HCU treatment

In online polls, those living with classical HCU and their caregivers selected **reduce pain** as a specific feature that they would look for in an ideal treatment for classical HCU, however there were few comments provided.

During the meeting, individuals living with classical HCU identified other important treatment goals, many reflecting the medication downsides that they identified earlier. These include **treatments that ensure more consistent homocysteine levels**, **better administration options, and medication that would**

prevent the buildup of methionine. These are described below with patient quotes.

Treatment that ensures more consistent homocysteine levels. This would lead to greater peace of mind and an improved quality of life.

> *"We'd really like a treatment that not only frees him up and gives him a more normal lifestyle, but also results in a much more predictable, consistent, and safe homocysteine level. I think that's key because as so many people have pointed out today, the current treatments are symptom management, but we want to be sure that the underlying condition and the homocysteine levels and everything, he's kept safe essentially."* - Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age

Better administration options. Many wish for a once-a-day pill or an injection to mitigate the need for the low protein diet. Some would just like formula with a better taste or even less added sugar.

> *My hope for the future is that there are better options such as pills, shots, or perhaps an inhaler for people like myself who live with HCU as well as the next generation to come."* - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

> *"Well, it's really heart-wrenching for … Mason having to take the formulas and the pills and everything as a little boy. If the taste could be better, … it would be so much better and easier for young people. It's hard for everybody."* - Dave, caregiver of a ten-year-old grandson living with classical HCU, diagnosed at 8 years of age

> *"A lot of the formulas, with the exception of one company that makes an unflavored formula, just have an excess of sugar. And an excess of processed ingredients in the food. … I think that there needs to be a real switch in the pharmaceutical approach to this in terms of creating healthy treatments."* - Alex, 36-year-old living with classical HCU, diagnosed by newborn screening

Medication that would prevent the buildup of methionine.

> *"If there was a medicine that dissolved the excess methionine in their systems before a buildup occurred. This makes the most sense, but I*

appreciate it is not as simple as that!" – Aoibhinn, parent of a 1-year-old daughter living with classical HCU, diagnosed by newborn screening

Additional gaps identified by the classical HCU community

Individuals living with classical HCU and their caregivers identified important needs within their community including the need for **home monitoring for homocysteine levels**, the need for **additional research regarding aging and pregnancy with classical HCU**, the need for **more awareness and a deeper understanding about classical HCU.** These are described below with patient quotes.

The need for home monitoring of homocysteine levels. Many individuals within the classical HCU community identified this gap during the EL-PFDD meeting and in submitted comments. One also suggested home monitoring for methionine levels.

> *"A caller earlier this morning mentioned that the blood levels of her kids are only taken every 4-6 weeks. My son's are only taken every 3-6 months, which is very stressful. If there was a way to check them at home every day or week (like diabetes), it would be much easier to reduce stress, change course of treatment if levels are high."* - Chris, parent of an 18-year-old son living with classical HCU, diagnosed by newborn screening

> *"Definitely a home monitoring system to measure those homocysteine levels and not be in the dark every day."* - Landon, 17-year-old living with classical HCU, diagnosed at 4 years of age

> *"We desperately need a way to monitor [homocysteine] at home through blood testing! … We shouldn't just be 'guessing' on allowable protein dosages of our next meals or treatments, … too many major life altering [events] are being gambled with as we await our next blood tests. We deserve access to at home testing and affordable medical treatments."* – Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age

The need for additional research with classical HCU. Two research areas highlighted during the meeting include aging and pregnancy. Many shared worries about starting their own families despite having HCU. Many individuals who are

aging with classical HCU described their concerns about an unknown future, including the emergency of additional side effects.

> *"As I get older, I find very little knowledge of what my future might look like. We need to better understand older adults living with classical HCU and find better options for them."* - Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age

> *"More research needs to be done on aging with HCU."* - Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age

> *"What does the future look like for adults? ……It sometimes feels like there is no system in place because we are kind of writing history as we go."* - Alex, 36-year-old living with classical HCU, diagnosed by newborn screening

The need for more awareness and a deeper understanding of classical HCU. Many in the community wished for greater awareness about classical HCU in the medical community as well as in society in general. Caregivers and patients even wished for more evidence-based information to guide their own treatment decisions.

> *"Since the diagnosis [of classical HCU] was rare, many doctors didn't know how to explain it, and there were even less people who knew how to interpret my disease in my parents' native tongue. So, there I was, a scared 10-year-old girl having to translate my disease that I knew nothing about to my parents."* – Janet, 31-year-old living with classical HCU, diagnosed at 10 years of age

> Kelly specifically wants more information for employers. *"Part of moving forward with treatments is also just educating, I feel like employers - so that when they have employees who have this - they understand a little bit better about what that is."* - Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

> *"I can't even find educational resources related to my boys' situations and gene mutations. Why don't we know more?"*- Angela, parent of 6-year-old and 3-year-old sons living with classical HCU, diagnosed at 3 and 1 years of age

Conclusion: Incorporating Patient Input into a Benefit-Risk Assessment Framework

The classical homocystinuria (HCU) EL-PFDD meeting helped to increase the understanding of how classical HCU impacts patients and their loved ones. The meeting also reinforced the urgent need for effective therapeutics for this disorder. **Table 1** speaks to the challenges and morbidities that patients living with classical HCU endure. It serves as the proposed introductory framework for the **Analysis of Condition** and **Current Treatment Options** to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of these disorders for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for classical HCU. The data resulting from this meeting may help inform the development of classical HCU-specific, clinically meaningful endpoints for current and future clinical trials, as well as encourage researchers and industry to investigate better treatment.

The information presented captures the perspectives of patients and families living with classical HCU presented at the October 27, 2023 EL-PFDD meeting. The collective hope of HCU patients, caregivers and families is that the information gathered at this meeting will encourage future research and support successful new product development for people living with classical HCU who urgently need treatment options. Note that the information in this sample framework is likely to evolve over time.

> *"There is a misconception that 'what doesn't kill you makes you stronger'. As someone who's had to be strong just to survive, I strongly disagree with that statement. What doesn't kill you does not make you stronger, it gives you trauma. After a lifetime of trauma, I am tired of being strong."* - Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

TABLE 1: Benefit-Risk Table for Classical HCU

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING	**Classical homocystinuria (HCU) is a rare and chronic disease.** Processing of the amino acid homocysteine is affected, leading to harmful buildup of homocysteine in the blood and urine. Approximately half of those living with classical HCU are missed by newborn screening: delayed diagnosis and delayed treatment initiation leads to more severe disease manifestations. **Classical HCU is a multisystem disease with a wide range of manifestations**. Most have a high number of health concerns. Classical HCU manifestations include potentially life-threatening blood clots, strokes, pulmonary embolism, and optic lens dislocation. According to poll data, most experience anxiety and/or depression. Other symptoms include skeletal issues, pain, cognitive issues and learning problems, myopia and as other optical issues. Caregivers can sometimes recognize uncontrolled homocysteine levels based on mood and behavior.	**Classical HCU impacts all aspects of daily life.** The restricted diet profoundly impacts school and social lives. Many feel like outsiders and are stigmatized because of their behavior, clumsiness, and intellectual disabilities. Some are unemployed and are unable to financially support themselves, while others are completely dependent on their caregivers. **Individuals living with classical HCU and their caregivers have many worries:** potential thromboembolic events, symptoms worsening, and premature death. Parents worry about what level of independence their children will be able to achieve and if they will adhere to their medications as they get older. **Classical HCU is not just a children's disease**. Many adults living with classical HCU suffer from comorbid conditions that can profoundly complicate treatment adherence.

CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	**The classical HCU community has tremendous unmet medical needs.** Betaine anhydrous is the only FDA-approved product to lower homocysteine. Treatment includes a combination of a low protein diet, medical foods including formula, betaine anhydrous, folic acid, supplements, blood thinners, antidepressants. Frequent monitoring, counseling, psychotherapy, and physical or occupational therapy are often required. **Medical treatments do not address the underlying disease, nor can they reverse or the damage that has already accumulated**. Treatments require a great deal of effort, adherence is challenging, and there is no guarantee that homocysteine levels will/can be controlled consistently and in all patients.	**Those living with classical HCU hope for new treatments to eliminate the need for the special diet and formula, to prevent disease progression, and to prevent blood clots and other catastrophic medical events**. They want medications that ensure consistent homocysteine levels, prevent the build-up of methionine, and with better administration options. They also identified the need for home monitoring of homocysteine levels, more research about aging with the disease, and the need for deeper understanding of classical HCU.
	See the Voice of the Patient report for a more detailed narrative.	

Acknowledgements

On behalf of the entire Classical HCU community, HCU Network America would like to thank the many individuals and organizations who helped make the Classical HCU Externally-led Patient-Focused Drug Development (EL-PFDD) Meeting a success.

Thank you to the many US Food and Drug Administration (FDA) staff members who took the time to attend our meeting and to read this *Voice of the Patient* report. A special thanks to Will Lewallen, Ethan Gabbour, Lyna Merzoug and Karen Jackler from the FDA's Patient-Focused Drug Development Staff for guiding us through this process.

Thank you to Dr. Mehul Desai, Dr. Kimberly Chapman, and Margie McGlynn for taking the time out of their busy schedules to speak at our EL-PFDD meeting.

Thank you to James Valentine and Larry Bauer from Hyman, Phelps & McNamara, whose assistance of planning and moderating our EL-PFDD meeting was invaluable. Thank you to the Dudley Digital Works media team for the production planning and all the behind the scenes work to ensure that our meeting was a success.

Thank you to our generous sponsors for their support, including Aeglea BioTherapeutics, EveryLife Foundation, Travere Therapeutics and Synlogic. Thank you to our partners, Ajinomoto Cambrooke, CanPKU, Compassion Works Medical LLC, Global Genes, GMDI, HCU Network Australia, the Mississippi Metabolics Foundation, Patient Worthy, RARE-X, and the ThinkGenetic Foundation who helped immensely in the planning and promotion of this meeting.

Thank you to all the representatives from advocacy and professional organizations, pharmaceutical companies, federal agencies, and research centers worldwide for attending our meeting or watching the recording afterward. We also want to express our deep appreciation for the dedicated physicians and researchers working tirelessly in hospitals and labs all around the world to help our HCU community.

Our EL-PFDD meeting was the result of months of planning and people working together behind the scenes. We send our deep gratitude to HCU Network America Board members and volunteers, including Kristin Rapp, Margie McGlynn, and

Danielle Benton. A special thanks to Danaé Bartke for moderating the meeting and to Liz Carter for providing the pre-recorded meeting panelists with assistance and support in preparing their comments.

Most importantly, thank you to the entire Classical HCU community: patients, caregivers, family members, and friends. Thank you for so honestly sharing the lived experience of HCU and for ensuring your voices were heard; our meeting could not have been as impactful or enlightening without each of you. We also acknowledge those who were unable to participate because the burden of care that inhibited their participation. We hope that this meeting will encourage future research and successful new drug development leading to urgently needed treatment options for the benefit of people living with classical HCU.

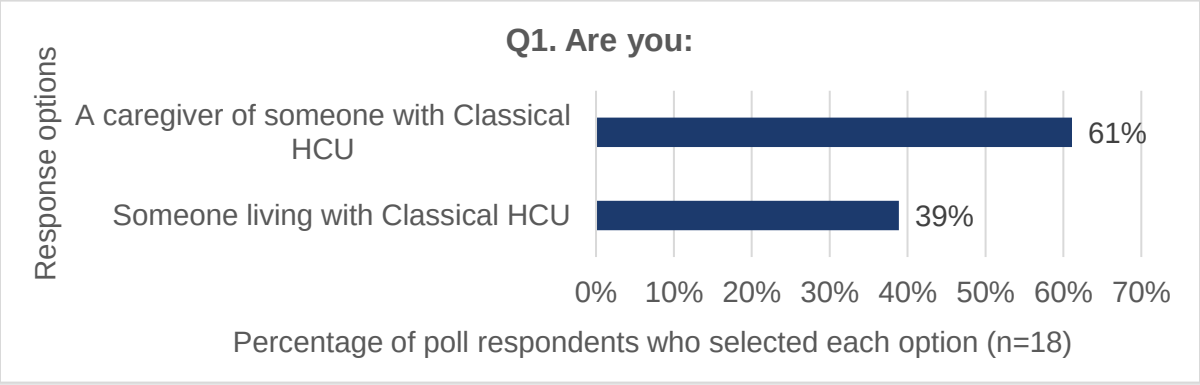
Appendix 1: EL-PFDD Meeting Demographics

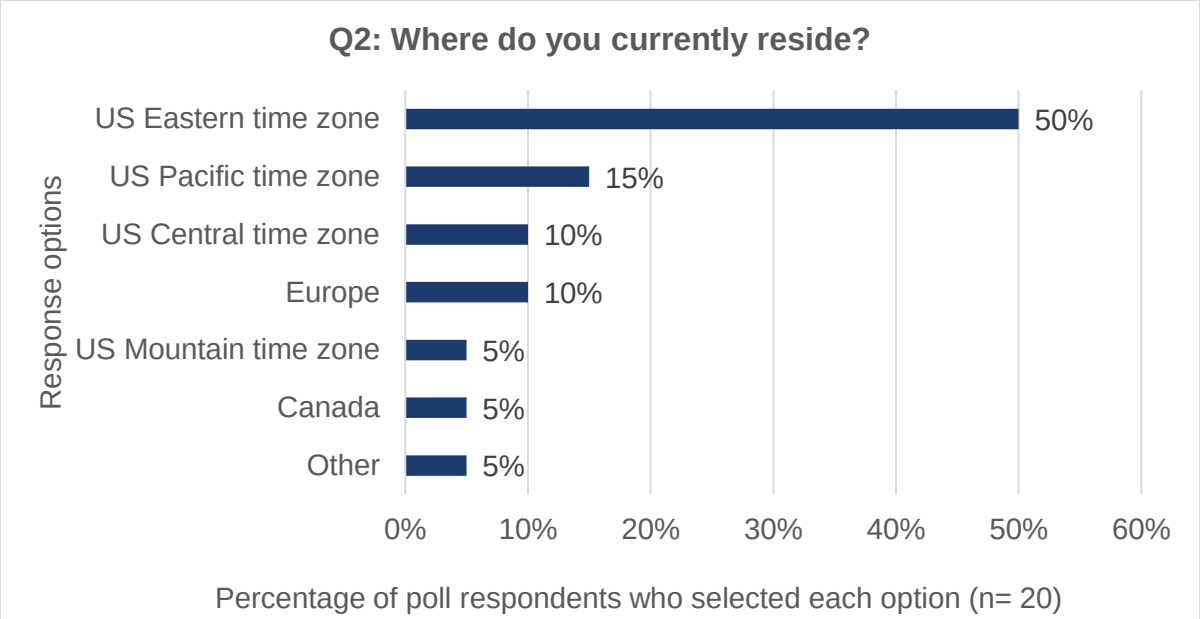
The graphs below include patients, parents and caregivers who chose to participate in online polling at the October 27th meeting. Online polling was restricted to people living with classical HCU and their caregivers. The number of individuals who responded to each polling question is shown below the X axis (N=x).

Most of those participating in polling were caregivers (61%) and the rest were individuals living with classical HCU (39%). Most were from the United States (80%), with representation from the Eastern, Pacific, Central and Mountain time zones. Community members from Europe (10%), Canada (5%) and other countries (5%) also participated.

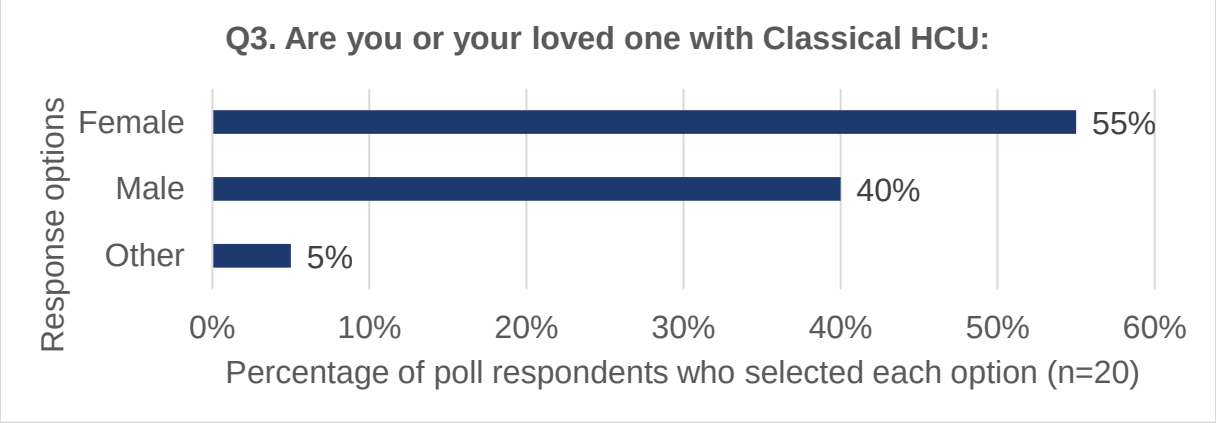
Females living with classical HCU had a slightly higher representation (55%) than males (40%) and others (5%). Similar percentages of individuals in the six to 18 years (34%), and 19 – 35 years of age (33%) were represented, with less representation from individuals in the ranges of 36 – 50 years (19%), 0-5 years (10%), and over 61 years of age (5%). While 10% of the individuals with classical HCU represented at the meeting were diagnosed prenatally, and 38% at birth, another 14% were diagnosed at the age of one to five years of age, 29% were diagnosed at six to ten years of age, and the remaining 10% were diagnosed at 11 years and older.

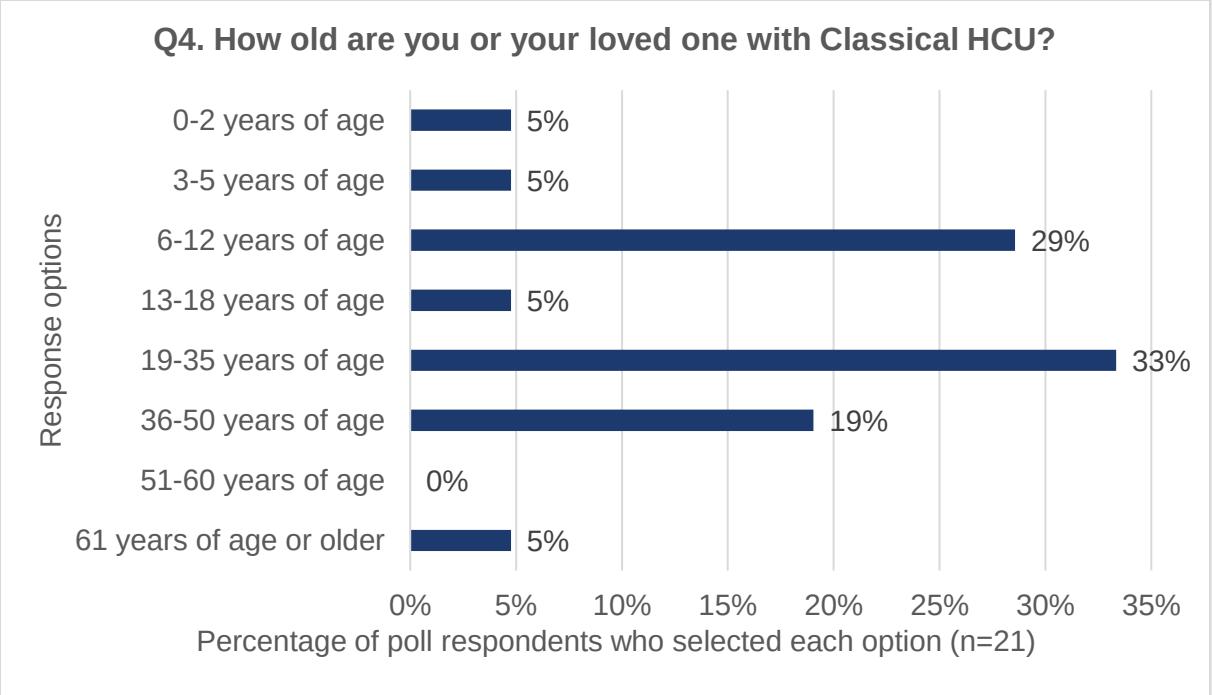
While the responses gathered in these polling questions are not considered scientific data with statistical significance, they provide a snapshot of the experiences and hopes of those who participated in the classical HCU EL-PFDD meeting. Note that meeting demographics are dynamic and may have changed as more individuals joined the meeting.

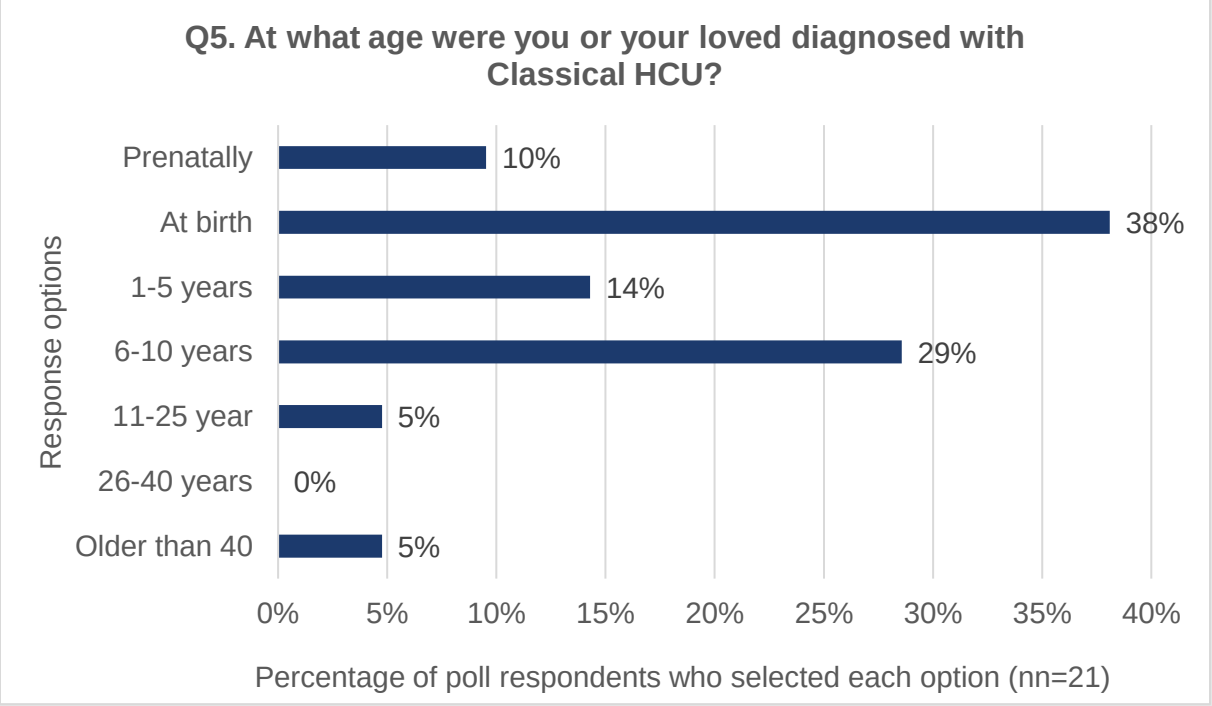




*Please note that at the time that the poll was conducted, there were no responses from US Alaska and Hawaiian time zones, Mexico, Asia, or the Middle east, but individuals from these time zones may have joined during the meeting.




Q4. How old are you or your loved one with Classical HCU?
Response options
0-2 years of age
3-5 years of age
6-12 years of age
13-18 years of age
19-35 years of age
36-50 years of age
51-60 years of age
61 years of age or older
5%
5%
29%
5%
33%
19%
0%
5%
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of poll respondents who selected each option (n=21)


Q5. At what age were you or your loved diagnosed with Classical HCU?
Response options
Prenatally
At birth
1-5 years
6-10 years
11-25 year
26-40 years
Older than 40
10%
38%
14%
29%
5%
0%
5%
0%
5%
10%
15%
20%
25%
30%
35%
40%
Percentage of poll respondents who selected each option (nn=21)

Appendix 2: Classical Homocystinuria (HCU) EL-PFDD Meeting Agenda

October 27, 2023, 10:00am-3pm ET

10:00 am- 10:05 am	Welcome (5 mins) *Danaé Bartke, Executive Director, HCU Network America*
10:05 am-10:15 am	FDA Opening Remarks *Dr. Mehul Desai, DRDMG, CDER, FDA*
10:15 am-10:30 am	HCU Clinical Overview *Dr. Kimberly Chapman, Children's National DC*
10:30 am-10:35 am	Introduction and Meeting Overview *James Valentine, JD, MHS, from Hyman, Phelps & McNamara, P.C., Meeting and Panel Moderator*
10:35 am-10:45 am	Demographic Polling

Session 1 – Classical HCU Symptoms and Daily Impact

10:45 am-11:10 am panelists	Patient/Caregiver Panel 1 - Five patient/caregiver
11:10-12:30	Audience polling & moderated discussion, including five patient/caregiver discussion starters, telephone call-ins, written comments read aloud
12:30pm- 1:00 pm	Lunch

Session 2 – Current and Future Treatments for Classical HCU

1:00 pm-1:10 PM	*Margie McGlynn, R.Ph., Hon DSci, President, HCU Network America*
1:10 pm-1:35 PM	Patient/Caregiver Panel – Five patient/caregiver panelists
1:35 pm-2:40 PM	Audience polling & moderated discussion, including five patient/caregiver discussion starters, telephone call-ins, written comments read aloud

2:40 pm-2:50 PM	Summary Remarks *Larry Bauer, RN, MA, from Hyman, Phelps & McNamara, P.C.*
2:50 pm- 3:00 pm	Closing Remarks *Danaé Bartke, Executive Director, HCU Network America*

Meeting Adjourned

Appendix 3: Meeting Panelists and Callers

Session 1: Classical HCU Symptoms and Daily Impacts

Pre-recorded panelists

- Gabbi, 21-year-old living with classical HCU, diagnosed prenatally
- Christa, 38-year-old living with classical HCU, diagnosed at 3 months of age
- Pamela P, 66-year-old living with classical HCU, diagnosed at 54 years of age
- Brooklyn, 37-year-old living with classical HCU, diagnosed at 8 years of age
- Anna, parent of an 11-year-old daughter living with classical HCU, diagnosed at 6 years of age

Zoom discussion starters

- Pam S, parent of a 31-year-old daughter living with classical HCU, diagnosed at 23 years of age
- Karen, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening
- Melanie, parent of a 10-year-old son living with classical HCU, diagnosed at 8 years of age
- Ben M, 34-year-old living with classical HCU, diagnosed by newborn screening
- Chris, parent of an 18-year-old son living with classical HCU, diagnosed by newborn screening

Telephone callers

- Joanna, 53-year-old living with classical HCU, diagnosed at 3 years of age
- Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age
- Jamela, 35-year-old living with classical HCU, diagnosed by newborn screening
- Breun, parent of 11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age
- Alex, 36-year-old living with classical HCU, diagnosed by newborn screening

Session 2: Current and Future Treatments for Classical HCU

Pre-recorded panelists

- Janet, 31-year-old living with classical HCU, diagnosed at 10 years of age
- Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age

- Judah, 59-year-old living with B6-responsive classical HCU, diagnosed at 7 years of age
- Breun, parent of 11- and 9 -year-olds living with classical HCU, diagnosed at 6 and 4 years of age
- Jessica, 32-year-old living with classical HCU, diagnosed at 5 years of age

Zoom discussion starters

- Ruth, parent of a 12-year-old daughter living with classical HCU, diagnosed at 6 years of age
- Barbara, parent of a 36-year-old son living with classical HCU, diagnosed by newborn screening
- Mark, parent of 32- and 22-year-olds living with classical HCU, diagnosed by newborn and prenatal screening
- Landon, 17-year-old living with classical HCU, diagnosed at 4 years of age
- Danielle, 33-year-old living with classical HCU, diagnosed by newborn screening

Telephone callers

- Dave, caregiver of a 10-year-old grandson living with classical HCU, diagnosed at 8 years of age
- Kelly, 34-year-old living with classical HCU, diagnosed at 5 years of age
- Alex, 36-year-old living with classical HCU, diagnosed by newborn screening
- Liz, parent of a 7-year-old son living with classical HCU, diagnosed at 2 years of age