James Valentine, JD, MHS (00:13:02):

Good morning. My name is James Valentine, and welcome to the Externally- Led Patient-Focused Drug Development meeting on classical homocystinuria. I'm here with my co-host, Danae Bartke, the Executive Director of the HCU Network America. We're coming to you live from the Washington DC metropolitan area, actually not too far from where the US Food and Drug Administration's headquarters are located. It's my pleasure to turn it over to Danae to provide some opening remarks. Danae.

Danae Bartke (00:13:30):

Yes. Thank you, James, and hello everyone. I'd like to thank you to the Externally-Led Patient-Focused Drug Development meeting on classical homocystinuria, or HCU. My name is Danae Bartke and I'm the co-founder and Executive Director of HCU Network America, as well as a person living with HCU.

(00:13:48):

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.

(00:14:03):

My diagnosis starts with the story of my brother, Garrett, when his lenses dislocated. 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.

(00:14:32):

Garrett and I have had quite the journey with HCU, both experiencing scoliosis, osteoporosis, anxiety, depression, OCD, learning difficulties and more. Unlike Garrett, though, I suffered a blood clot just after my 24th birthday. This led me to a journey of self-discovery and a mission to help others living with HCU.

(00:14:56):

Homocystinuria is a group of inherited metabolic disorders denoted by the elevation of homocysteine in the urine. It subdivides into three groups, classical homocystinuria, cobalamin disorders with high homocysteine and severe MTHFR. The focus of today's ELPFDD is specifically on classical homocystinuria, which may be referenced throughout today as classical HCU, HCU, homocystinuria due to Cystathionine Beta-Synthase Deficiency or CBS deficiency.

(00:15:29):

When we ask for polling responses, comments, or calls in participation, we kindly ask that this is limited to those living with classical HCU or their caregivers.

(00:15:41):

On behalf of the HCU community, I'd like to extend a special welcome to the Food and Drug Administration staff members. Thank you for taking the time to be with us today and for giving us permission to hold this meeting. We are excited to have you with us and hope that you'll learn a lot from our amazing patients and caregivers.

(00:16:02):

Thank you to our partners, Ajinomoto, Cambrooke, CanPKU, Compassion Works Medical LLC, Global Genes, GMDI, HCU Network Australia, the Mississippi Metabolics Foundation, Patientworthy, RareX, and

the ThinkGenetic Foundation who have helped immensely and helping promote this meeting. Thank you to our sponsors, Aeglea BioTherapeutics, EveryLife Foundation, Travere Therapeutics and Synlogic.

(00:16:33):

We'd also like to thank the representatives from advocacy and professional organizations, pharmaceutical companies, federal agencies, and research centers worldwide for taking the time to join us today. Today's meeting is a result of months of planning and people working together behind the scenes. I would like to express my deep gratitude to each of you who have worked so hard to make this meeting possible.

(00:16:57):

Most importantly, I want to thank the members of the audience whose lives have been directly impacted by HCU and you who are here to share your story. We are grateful to have this opportunity to ensure that patient and family perspectives are considered in the drug development and regulatory process. I want to express my deep appreciation for the physicians and researchers working tirelessly in hospitals and labs all around the world to help our community. Your work has led to a solid foundation of science resulting in clinical trials that are in process, with more being planned for the near future.

(00:17:37):

We hope that this meeting will encourage future research and successful new drug development for people living with classical HCU or urgently need treatment options. For our classical HCU families, we invite you and your loved ones to call or write in during the program and ask that you participate in remote polling as well. We want to hear as many perspectives as possible and we'll do our best to get to all of your comments. Please use your first name and state or country only. No other identifying information should be shared. The comments that we cannot get to are just as important because they will be collected and published in the Voice of the Patient report, a summary of this special day.

(00:18:23):

To begin today's meeting, I'm delighted to introduce Dr. Mehul Desai. Dr. Desai is a Medical Officer in the Division of Rare Diseases and Medical Genetics Center for Drug Evaluation Research at FDA. Dr. Desai has clinical development experience in both the pharmaceutical industry as well at the FDA. Dr. Desai will provide some opening remarks about the importance of patient-focused drug development. Dr. Desai, over to you.

Mehul Desai, MD (00:18:55):

Good morning and thank you so much for the kind introduction. I'd like to especially thank Danae Bartke and the HCU Network of America for inviting me today to provide opening remarks.

(00:19:09):

As you've heard, my name is Mehul Desai, and I'm a physician and Medical Reviewer in the Division of Rare Disease and Medical Genetics within the Center for Drug Evaluation and Research of the Food and Drug Administration. I'm very excited to participate in today's meeting and to learn from all of you. I'm happy to see so many patients as well as caregivers present at this meeting. Thank you all for sharing your experiences with us today.

(00:19:39):

Before I provide my opening remarks, I'd like to state that I'm a full-time employee of the Food and Drug Administration and do not have any conflicts to disclose.

(00:19:50):

Medical product development is a complex time and resource intensive effort. Although the FDA plays a critical role in medical product development, there are additional key stakeholders involved, including but not limited to medical product developers or sponsors, study investigators or study doctors and, of course, patients, families and caregivers such as yourselves. Drug development would not be possible without the contributions from each of these key stakeholders.

(00:20:29):

Sessions such as these provide an important opportunity for both the FDA as well as additional stakeholders, such as sponsors, to hear directly from patients and their families about symptoms that matter, most of them, the impact the disease has on patients' daily lives, as well as the patient's experience with currently available treatments.

(00:20:55):

At a high level, the process of drug development starts with a drug discovery, which is then followed by testing in animals or nonclinical research, which is then followed by testing in humans or what's called clinical research, which, when successful, ultimately leads to the FDA review of a new drug application, or NDA, or biologic application, or BLA.

(00:21:23):

Medical product developers or sponsors will often engage with the Food and Drug Administration very early on, oftentimes well before initiation of their first in human studies, and will also engage with FDA throughout their medical product development to ensure generation of high quality data as well as high quality study designs that'll ultimately inform decisions on benefit risk as well as approvability.

(00:21:52):

FDA has a talented group of cross-disciplinary reviewers, including clinical reviewers, nonclinical reviewers, biostatisticians, drug safety scientists, clinical pharmacologists, regulatory professionals, as well as the others. Equally important in the process of drug development, and particularly development of a rare disease drugs, is incorporating the patient perspective into medical product developers plans and study designs.

(00:22:26):

It's often important to obtain the patient perspective on what is meaningful to them well before the initiation of clinical trials that'll be used by FDA to assess benefits and risks. It's important to get feedback early on what is meaningful to patients because there are subsequent discussions that take place between medical product developers and FDA on translating patient feedback into endpoints that can easily be measured, that are reliable as well as reproducible.

(00:23:04):

Patient perspectives are important in a number of ways. For example, patient perspectives can help identify what outcomes are most meaningful to patients. For example, is it living longer? Is it having fewer dietary restrictions? Is it having fewer side effects? Patient perspectives can also help elucidate what motivates a patient to participate in a clinical trial in the first instance. For example, is it having assurance that the investigational treatment will be available not only during the randomized portion of the trial, but also after the randomized trial is complete, for example, the open-label extension? Or is it fear of side effects from approved currently available therapy?

(00:23:53):

Patient perspectives can also help elucidate what helps motivate patients to stay in a trial once they've signed up to participate. For example, is it limiting the number of burdensome procedures? Is it having

caring and engaging research or site staff? These are just a few examples of how incorporating patient feedback into the clinical development can favorably impact and increase the likelihood of success of medical product development.

(00:24:27):

The perspectives you'll provide today will help the FDA as well as medical product developers advance drug development and ensure that new medicines that will eventually come available will meet the needs of people living with homocystinuria. The output of this meeting will be summarized in a Voice of the Patient report, which will be a public document that will be available to the general public as well as the FDA for future reference.

(00:24:57):

Once again, we're here today to hear the voice of the patient, so thank you all for taking time out of your schedules to participate in today's meeting. We're grateful to each of you for being here and sharing your personal stories. Thank you. Now, back to the studio.

Danae Bartke (00:25:23):

Thank you, Dr. Desai. Next up is Dr. Kimberly Chapman, who will provide a clinical overview of classical homocystinuria. This will serve as a scientific foundation for this morning's discussion. Dr. Chapman is an Attending Physician in Genetics and Metabolism at Children's National and Assistant Professor of Pediatrics and Integrated System Biology at George Washington University. She specializes in taking care of all ages of individuals with defects of methylation, homocysteine, propionate metabolism. Dr. Chapman, over to you.

Kimberly Chapman, MD, PHD (00:26:00):

Thank you so much for that really nice introduction. Today, I'm going to talk about the homocystinurias. Where we're going to really focus on is Cystathionine Beta-Synthase Deficiency or CBS deficiency.

(00:26:13):

As you may know, there's a number of homocystinurias, and these all require different therapies, different management, are caused by different genetic disorders. Today, we're really going to focus on Cystathionine Beta-Synthase. Let me talk a little bit about my conflict of interest. I'm a Medical Advisor and Board Member for HCU Network America. I'm a Medical Advisor for Travere who currently has a therapeutic and clinical trial, as well as being a PI for the Travere CBS Natural History study, also known as Accapella.

(00:26:46):

The homocystinurias, there's basically three large categories of disorders that are included within the population of homocystinurias. There's the remethylation defects, the cobalamin defects, and then the CBS related defects.

(00:27:02):

And so, within the red circle is where our remethylation disorders are, and in these disorders, we accumulate homocysteine because we're unable to convert homocysteine to methionine. The cobalamin defects, as designated by the yellow arrow, are caused by the inability to process cobalamin or B12. Again, these are necessary for methylation and they're necessary to convert homocysteine to methionine, and are treated in a different way.

(00:27:35):

Finally, there is the CBS defects. These are caused by the inability of Cystathionine Beta-Synthase to convert homocysteine to cystathione. In this particular cycle, methionine that arises from the diet is converted to homocysteine. Homocysteine is then converted to cystathione, by CBS. CBS is a B6 or pyridoxiary responsive enzyme, and that is necessary for its metabolism.

(00:28:04):

Individuals with this type of homocystinuria not only accumulate homocysteine in their blood and urine, but also have elevations in methionine. Methionine is an essential amino acid and, typically, enters the cycle through the diet.

(00:28:21):

Individuals with Cystathionine Beta-Synthase Deficiency, but not necessarily all of the other homocysteine areas, have a number of very common disease manifestations. The four big categories that are involved here are the CNS, or the central nervous system, the eyes, the skeleton and the vascular system.

(00:28:43):

In the CNS, you can see psychosis, mental health difficulties, but you can also see intellectual disability in individuals that are adequately treated, and a number of folks will develop movement disorders or white matter changes with age.

(00:28:58):

The eyes. The classic presentation is a ectopic lenis, and many individuals have severe myopia. For those who are not identified by newborn screen in the United States, ophthalmology and optometry are usually the first touch base for a number of these complications. Because ectopic lentis is fairly rare, these individuals present, oftentimes, to optometry or ophthalmology.

(00:29:24):

The skeletal abnormalities are the things that most medical textbooks include, and these include excessive height, incredibly long limbs for the size of the thorax. And then, individuals often develop osteoporosis with age whether they're treated or not, and have a number of bone deformities. These things are often reflective of a different genetic disorder, which is called Marfan Syndrome. And so, some individuals with CBS deficiency are identified when they're being evaluated for a disorder like Marfan Syndrome. Finally, there's the vascular system. This is potentially, arguably, the most life-threatening system because we see a number of thromboembolisms. Anybody with an elevated total homocysteine greater than the 100 micromole to 120 micromole per liter level are at risk for having spontaneous thrombosis. These are mostly venous versus arterial, and so individuals can present with blood clots in their lower extremities as deep vein thrombosis. They can have pulmonary embolisms or the most frightening as stroke-like episodes. Individuals who have these types of strokes present like a stroke, they're often at earlier ages and can be life-threatening, impacting both morbidity and mortality.

(00:30:51):

We're talking predominantly about CBS and CBS deficiency. CBS deficiency is caused by dysfunction of the Cystathionine Beta-Synthase gene. This is usually a dimer and is illustrated here in the right side of your slide. It's encoded on chromosome 21 at q22.3 and has 23 exons, or coating regions, with intervening sequence between.

(00:31:17):

Mutations in CBS are seeing pan-ethnically, but there's certain locations that are more commonly represented because there's a higher carrier frequency. Two of the most common places for this are

within Qatar, where the carrier frequency is very high and, in fact, so high that the newborn screening does not look for elevation in methionine, but goes directly to elevations in total homocysteine, and then in a number of some of the Irish population.

(00:31:46):

As I said, Cystathionine Beta-Synthase is pyridoxine responsive. Pyridoxine is vitamin B6. There's a number of common mutations that are seen, such that approximately 50% of the population is estimated that has CBS has this B6 responsive type of thing. The pyridoxine responsiveness, probably the most common variant is this isoleucine 278 to threonine, although there's a number of other known pyridoxine responsive genes. Individuals who have are homozygous for those genes are almost always pyridoxine responsive. Those who are heterogeneous such that they have one of these pyridoxine responsive in one of the more severe mutations typically are either partially responsive or not responsive to pyridoxine.

(00:32:37):

Part of the reason that I am presenting this particular thing is because I sit on one of the major guideline groups that has produced recommendations for diagnostic and treatment for Cystathionine Beta-Synthase. And so, how do you diagnose this disorder within the US population specifically, but in the general population? Well, most states in the United States have newborn screening, or NBS, and most states in the United States, as their primary screen, looks for elevations in methionine. It is important to note that if you look predominantly to elevations in methionine in newborn screening cards, you're likely to miss the B6 responsive patients. In the US, the estimate is approximately 50% of individuals with CBS will be period pyridoxine responsive or partially responsive. The reason this is the case is because individuals with B6 responsiveness or partial responsive do not have elevations in methionine high enough above cutoff.

(00:33:42):

There are a few states which are either looking at whether they do dual testing for total homocysteine plus methionine or looking at serial testing. Individuals above a particular cutoff of methionine would then have a secondary screen using total homocysteine. In the state of Qatar, or the country of Qatar, their screen, because of how high and what a high frequency it is in the disease, is actually looking directly at total homocysteine.

(00:34:11):

Now, the vast majority of individuals within the United States are either older and were not newborn screened or are missed by the newborn screen, and those folks usually present in a symptomatic way. We talked a little bit about what the common disease manifestations are. And so, these individuals may present to their pediatrician or to a developmentalist with some intellectual challenges or learning challenges. They may present to psychiatry with some of their psychiatric disease. They may present to orthopedics. They may present to a geneticist with a rule out Marfan. They may present to ophthalmology. Typically, the way that you make the diagnosis, at least have the first hint that this is the diagnosis, is to look at somebody's total...

PART 1 OF 9 ENDS [00:35:04]

Kimberly Chapman, MD, PHD (00:35:03):

... This is the diagnosis is to look at somebody's total homocysteine. Individuals with total homocysteine greater than the normal range, and in most labs the normal range is approximately 12 to 15 micromole per liter, and many individuals with these disorders will be much higher than that. We talked a little bit

about epidemiology and that this is a panethnic thing. The epidemiology in Qatar has a very high frequency. We're seeing it about one in 1,800. This is because there's a high carrier frequency due to a founder effect, so an individual back in the past who had a mutation within this gene.

(00:35:41):

The estimate worldwide is about one in 900,000. If we start looking at the populations that we see within the United States, we generally say that those from the Asian continent have a fairly low frequency. Those of African descent also have a low frequency. Non-Finnish Europeans are about 0.82 per 100,000, and then some of the other estimates are about 0.39 per 100,000. Within the United States, we know that there's probably more individuals with homocysteine, ureas and CBS deficiency specifically, and part of this is because approximately 50% of individuals within the United States, knowing where our populations come from, are likely to be B6-responsive. And at this point, I'd like to thank HCU Network America for allowing me to do this talk and then our patients, faculty, and staff at the Children's National Rare Disease Institute. Thank you so much.

Danae Bartke (00:36:59):

Thank you, Dr. Chapman. I'd now like to welcome our moderator for today's meeting, James Valentine. James has worked the last 15 years as a champion for the patient voice as part of the regulatory process. He previously worked at FDA where he was a patient liaison, helping to incorporate the patient voice into medical product review across the FDA's various medical product centers and review divisions. There he helped to develop and launch the patient-focused drug development initiative. In private practice, James has worked with many patient organizations to ensure their community's voices were heard by decision makers. Relevant to our EL-PFDD meeting, he has been involved in helping plan and moderating three-fourths of the over 75 externally PFDD meetings. So we're in good hands with him. James.

James Valentine, JD, MHS (00:37:54):

Thank you so much, Danae, for that kind introduction and it's such a pleasure to be here with this classical HCU community today to hear your voices and bring that into the discussion with drug developers and the FDA. So, now that we've heard a clinical overview from a disease expert, we turn to the core of today's meeting, which is to hear from you, people living with classical HCU and their parents, spouses, and other direct caregivers. Patient-focused drug development is a more systematic way of gathering patient perspectives on their condition and on available treatments. As you heard from FDA's Dr. Desai, your input can help the agency's understanding of classical HCU to inform drug development and review. While FDA has held many of its own patient-focused drug development meetings, today marks the 80th externally led PFDD. As we heard from Dr. Chapman, classical HCU is rare, so with over 10,000 known rare conditions alone, this is such a unique and important opportunity for this community. Today's meeting is interactive, so let me tell you a bit about what we'll be asking of you and how today's meeting will be organized. First, the meeting is organized into two overall sessions and our first session, which will be this morning, we'll be exploring the patient and caregiver experience of living with classical HCU and its impacts on you and your loved ones' daily lives. In our second session this afternoon, we'll bring everyone back together to explore the various approaches to treatment, including participating in clinical trials, and we'll also be asking you for your preferences for future treatments. So, what will these two discussions look like? Well, today we'll primarily be using three different ways to bring your voices into the discussion. First, for each of our sessions, we'll be hearing from panels of patients and caregivers of individuals living with classical HCU. These panels will set a good foundation for our discussion and the individuals speaking reflect a range of experiences with

classical HCU. Although, we know that no set of individuals can reflect the full range of experience, so after the panels have an opportunity to speak, we'll be broadening the discussion and we'll have a facilitated audience discussion, which will be open to all of our patients and caregivers tuned in today. This discussion will build on that panel and I'll be asking questions and inviting you to state your name and provide a comment. This can be done in one of two ways. We want you to dial in by phone or provide written comments. You'll notice we'll also have a Zoom panel of patients and caregivers who will be sharing their stories throughout the program as well. Finally, we'll be asking you to participate in polling questions, which will broaden the discussion to all of our patients and caregivers in the audience. We do ask that only patients and caregivers of those living with classical HCU use your either phone or web browser to respond to those polling questions. And actually, we can go ahead and get into the polling system now because once you're in it, you'll be able to stay there throughout the entire day. So at this time, I ask that you pull out your phone, open up a browser or on your computer that you're following along on, open up a new tab, and go to www.pollev.com/hcupfdd. Again, feel free to go there now, www.pollev.com/hcupfdd, we'll be getting to polling very soon. These polling questions will, again, broaden the discussion to everyone, as well as help aid in the discussion. I want to mention we'll also have an opportunity for you to provide written comments for 30 days after today's meeting. So, whether you leave the meeting and think of something else that you didn't think to share over the course of today's proceedings or if you're watching this video on demand after the actual live meeting has happened, we welcome and encourage your feedback over the next 30 days.

(00:42:06):

All of today's input, as well as that additional written input, will be summarized in the Voice of the Patient report, which will be provided to the Food and Drug Administration and made available online for researchers and drug developers. One last thing before we get into our first set of polling questions, I want to cover a few ground rules for today's meeting. We encourage people living with classical HCU and their family members and other direct caregivers to contribute to the dialogue, again, through polling, calling in by phone and submitting written comments. Today's discussion is limited to patients and family members and other direct caregivers of those living with classical HCU. Meanwhile, our colleagues at the FDA, at drug development companies, and our clinician friends are here to listen. I also want to mention that views expressed today are inherently personal and the discussion may get emotional at times. So, respect for one another is paramount, and to that end, we ask that you try to be focused and concise in your comments, so that way we can hear as many voices as possible. So without further ado, let's get into our first set of polling questions. So again, for all of our patients and caregivers living with classical HCU, if you can go to www.pollev.com/hcupfdd. Go to this page, you can keep it up throughout the entire day. And as we go to different polling questions, the new questions will automatically appear there. You don't need to refresh or anything. So again, that's pollev.com/hcupfdd.

(00:43:44):

So, we're going to give everyone some time to get into this system, so that way you can record your responses to all of these questions that we have for you. However, our first question for the day is we want to know, are you someone living with classical HCU or are you a caregiver of someone with classical HCU? So, we'll give everyone a few moments here to make sure we get... While this is a very simple question, I promise these questions get a little harder to answer as the day goes on. We do want to give everyone a chance to get into the polling system, so that way we can track your responses throughout the day.

Danae Bartke (00:44:24):

Kind of interesting watching the numbers go back and forth with the options. We see a lot of engaged, both patients and caregivers in our community. So, it'll be interesting to see where it ends up.

James Valentine, JD, MHS (00:44:37):

Yes, we were pretty close to 50/50 for a while. It looks like we're leaning more towards having more caregivers than people living with classical HCU today, but for purposes of today's meeting, we want to hear from both of these groups. We want you to call in and write in throughout the program. So, we thank everyone who has joined us today. If we can move to our second polling question. So, here we want to know where you currently reside and if you're a caregiver, we are asking these questions about the person that lives with classical HCU that you care for. Most likely you live in the same area, but I do want to point that out. So the options here are A, the US Pacific Time Zone, B, US Mountain Time, C, US Central Time, D, US Eastern Time, E, US Alaska time, F, US Hawaii Time, G, Europe, H, Middle East, I, Asia, J, Canada, K, Mexico, or L, some other country or region not otherwise listed in the other response options.

Danae Bartke (00:45:45):

It would be a pretty amazing to me if someone from Asia, considering the time difference pops on, but that would be quite incredible too.

James Valentine, JD, MHS (00:45:54):

Yes, so we'll give everyone a few more moments to get your responses in. Perhaps not surprisingly, as this is a morning meeting starting in the morning time Eastern, we have the greatest participation from US Eastern Time zone, but I'm glad to see we do have good representation across the major US time zones as well, and perhaps we'll get some additional participation there as it gets a little later in the morning across the US. I see we do have some good representation from Europe, Canada, and others. So, we do welcome everyone from outside of the United States and we absolutely do want to hear from you throughout the course of today as well. If we go to our third polling question, so here we want to know are you, if you're a person living with classical HCU, or for the caregivers, is your loved one who's living with classical HCU, A, female, B, male, or C, other?

(00:46:54):

Again, these first sets of questions, we just want to get a sense of who's in our audience today, who living with classical HCU is represented here before we get into more of the meat of the program of hearing about your lived experiences with classical HCU. So again, we'll give everyone a few moments here to get your responses in. I see some responses are still trickling in. As it stands, it looks like we're seeing the greatest representation of those living with classical HCU being female, a little over half of our audience. We're seeing a little under a third of those that are represented being male, and we do have around 5% who identify as other.

Danae Bartke (00:47:42):

James, I have a question for you. So for those who are sending in their answers, if they have two children and one is a boy and one is a girl, what would you suggest? Are they able to answer both or what would be your suggestion in that case? I'm thinking about my own [inaudible 00:47:59]. She'd have to be torn. Which one is she going to claim?

James Valentine, JD, MHS (00:48:02):

Yes, what we recommend doing in that situation is selecting one of the people living with classical HCU that you care for to kind of respond on behalf of for these questions. And so, if there are perhaps multiple caregivers participating, you could each select one person to represent. So for purposes of polling, that's what we recommend. Once we get to actually calling and writing in, we encourage you to speak to both of your loved one's experiences. If we can go to our next question. So here we want to know, how old are you if you're living with HCU or your loved one who's living with HCU? The options are zero to two years of age, B, three to five years of age, C, six to 12 years of age, D, 13 to 18 years of age, E, 19 to 35 years of age, F, 36 to 50 years, G, 51 to 60 years, or H, 61 years of age or older. Again, this is the person that is living with classical HCU, whether that's you yourself or if you're a caregiver, your loved one. We'll give everyone-

Danae Bartke (00:49:18):

It's really interesting to see which categories are really... The 19 to 35 year old range is really holding strong. It's pretty impressive.

James Valentine, JD, MHS (00:49:32):

Yes, that continues to be kind of the top, a little over a third of our audience representing those who are living with HCU in those early adult years of ages 19 to 35, a little under 30% in kind of mid-childhood years of ages six to 12, but we are seeing representation across almost every age range, with the exception of ages 51 to 60, and we do want to hear about your HCU experiences across the lifespan over the course of years. So, whether that's your loved one or you or younger living with HCU, or for those of you who've been living with it for perhaps decades, we do want to hear about what those experiences have looked like, how they've shifted over time.

(00:50:21):

So, we have one more polling question for you here this morning to get started. So here we want to know now, we just asked about current age, but here we'd like to know, at what age were you or your loved one diagnosed with classical HCU? So the options are A, prenatally, B, at birth, C, one to five years, D, six to 10 years, E, 11 to 25 years, F, 26 to 40 years, or G, older than age 40. Again, this is the age of diagnosis with classical HCU.

Danae Bartke (00:51:01):

This is another one that I find very intriguing because we know, and Dr. Chapman shared this, that our newborn screening system, at least here in the US, does fail about 50% of the time to diagnose people. So, seeing that we have so many diagnosed at birth, that is very exciting for us to see. It gives us the best outcomes possible currently.

James Valentine, JD, MHS (00:51:24):

Yes, and given what we saw in the previous slide, we saw that there are a number of individuals that are even age 61 and older, so perhaps age of diagnosis might have been different for them, than individuals who might be younger with current day kind of diagnostic techniques. So, in terms of who we have represented, we're seeing about right at 40% represented being diagnosed at birth, 10% diagnosed prenatally, but then we do see quite a few that are diagnosed in the first two and a half decades of life, but we also have some that were diagnosed when they were older than age 40. So again, we are very interested. If you were diagnosed not at birth, what led to the diagnosis or diagnosis, what symptoms or

health effects perhaps maybe drove to lead to get a diagnosis would be very helpful to hear. So, I want to thank everybody for participating in this first set of polling questions.

(00:52:33):

At this point, we get to move into our first topical discussion for the day on what it is to live with classical HCU. So, if we can pull up our first set of discussion questions, we'll get a sense of some of the things we want to hear about as we get into this discussion. So, if you want to call in and write in on these topics, we encourage you to do so. So here in the morning, we want to understand, of all the different symptoms and health effects of HCU, which one to three of these have had the most significant impact on you or your loved one's life? We know that some of these symptoms and health effects can be variable for you, and so we want to know, how does your HCU affect you or your loved one, perhaps on a best day versus a worst day?

(00:53:19):

We also know that these things can shift over time, and so we want to know how your you or your loved one's symptoms have changed over time, whether that's over the course of weeks, months, or even years. And related to that, how has your ability to cope with those symptoms changed over time? We also, beyond wanting to hear about those direct symptoms and health effects, want to understand how they impact your daily life. And so we want to know, are there specific activities that are important to you or your loved one that either you or they are not able to do or do as fully because of HCU?

(00:53:53):

And finally, while we recognize that there's so much that people with HCU have already gone through and are living with, we also know that you're thinking about your futures or your loved one's futures, and so we want to know, what do you fear the most as you or your loved one gets older living with HCU, and what worries you the most about their condition or your condition? So, to get us started in exploring these different topics, it's my pleasure to introduce our first panel of the day. We have Gabbi, Christa, Pamela, Brooklyn, and Anna who will be sharing some of their and their loved one's experiences of what it is to live with HCU. So Gabbi, please take it away.

Gabbi L. (00:54:34):

My name is Gabbi. I'm 21 years old and have classical homocystinuria. I'm what's believed to be the first baby diagnosed pre-birth via amnio. This meant that I could start diet and medical formula instantly, but this did not spare me from the harsh realities of HCU. From a young age until now, I've always felt like I was living two lives, one where I would desperately try and appear normal, and another one where I was in and out of hospital appointments, taking lots of medication and restricting every aspect of my life due to not being able to eat more than eight grams of whole protein per day. 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.

(00:55:27):

All while the looming worry of blood clots, strokes, and heart attacks took over my mind while my peers worried about their birthdays of elementary school. 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. This method of treatment made it impossible to keep up with my large medication regimen, and I found myself skipping my brace to control my HCU. On top of this, I was dealing with osteoporosis and soon had to stop all contact sports due to the risks of my weak bones. All of this was happening while navigating elementary and middle school and grasping at any sense of normalcy I could get. As I entered

into middle school, I found myself feeling so isolated from my peers because no one could quite understand my situation.

(00:56:18):

The summer before my freshman year of high school, I was told my scoliosis was so severe that I had to have immediate spinal fusion surgery, which was scheduled just a month later. Due to HCU, the surgery was extremely dangerous and meant I had to reduce my whole protein to zero grams per day immediately and receive IV fluids 24 hours prior to the surgery. After the seven-hour surgery, fusing my entire spine and implanting two titanium rods and 24 screws, I spent eight days in the intensive care unit with life-threatening homocysteine levels. They used methods such as a feeding tube to try and combat the risks of blood clots. As the six-month and eventually one year mark passed, my post-surgery pain was not only not subsiding, but getting much worse. Navigating high school as a teenager with a rare metabolic condition and chronic pain made normalcy almost impossible.

(00:57:14):

Being left out of friend groups became the norm. While searching endlessly for an answer to my pain, it was found that I had a crushing disc and was allergic to the metal in my body. I was warned by my surgeon that another surgery had a good risk of not helping and had to weigh the risks. As an 18-year-old, I had to decide if it was worth redoing the most traumatic event of my life and dangerous event as well. 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. Recovery meant that I opened my college acceptance letters bedridden, missing the last months of my senior year.

(00:58:04):

Entering college, I had constant anxiety about my HCU and being on my own. My school attempted to help me in ways that they thought were suitable, but in reality, I was left eating alone, isolated from my friends, and often forced to make choices to eat unsafe foods. I realized then that even the people whose job it is to help you gain some normalcy couldn't understand. In a new environment with roommates, hard classes, and a school that doesn't assist with accommodations sufficiently, I felt frustrated and alone at a stage in my life that was supposed to be the time in my life. I woke up every day trying to figure out my dinner, so that I could simply just eat breakfast. I missed out on countless social opportunities and events due to my homocystinuria, and often had my needs severely undermet due to the staff not helping me in the ways that I needed. In terms of my future, life looks scary.

(00:58:58):

There aren't many early diagnosed patients aging with HCU and I don't know what my future holds, which is a very scary thing for a 21-year-old to grasp. I have all these dreams and aspirations, but I don't know how HCU will affect me in the future. I do know that HCU affects every second of every part of my day. Every phase of my life is impacted by this condition. 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. 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. Thank you.

Christa G. (01:00:00):

My name is Christa. I'm 38 years old and live in Marysville, Ohio. I was born prematurely, weighing just a little over three pounds and measuring 19 inches. My high markers on my newborn screening test prompted further investigation, leading to the discovery of classical homocystinuria at three months of age. Throughout my childhood, my most notable symptom was digestive discomfort, likely attributed to the formula. 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 always knew what the assignments were asking of me and had ideas and thoughts even way beyond what were the bare minimum needed to complete the assignment. However, more often than not, I struggled to get what I had in my head to run down my arm and pop out of the pencil correctly.

(01:00:54):

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. 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. As I matured into a young adult, my homocystinuria was always on the back of my mind when dating, as at the time I had been told I'd be too high of a risk to have kids and was aware that the science at the time had indicated the average lifespan of individuals with my condition was only to the age of 30-something. I didn't necessarily feel like I was the ideal catch, but I knew that part of my non-negotiables in searching for Mr. Right had to include someone open to the idea of adoption and that would understand the potential risks involved, meaning that I may not be the person he'd get lucky to grow old with.

(01:02:03):

My husband and I met and started dating in our senior year of high school. Five years later, after finally marrying Mr. Right, I made sure one of the first things my husband understood was how to spot the signs of a stroke, as I knew that this was one of the most serious potential risks I faced as someone with homocystinuria. I made sure to review our plan often of what he was to do if he saw those signs. In July 2009, we adopted a six-year-old boy with special needs who is now 21. As the years progressed and we battled with my son's special needs, I continuously worried about how my husband would manage the complexities of our son's needs by himself if something happened to me. In 2015 when my son was 12 and I was 30, that fear was tested as close to reality as I could have ever predicted.

(01:02:56):

I woke up on the morning of December 26th, the day after Christmas, and jumped in the shower. I had a sharp charley horse in the bottom of my left boob that didn't ease up. "Weird," I thought. "Maybe I slept wrong," and continued my shower. Then, I had a sudden onset of severe nausea and became sick immediately in the shower, followed by dizziness so overwhelming that I had to sit on the floor of the bathtub. At that point, I knew time was of the essence. I summoned my husband to help me get to the car and take me to the emergency room. At first, the medical team waved it off as holiday stress induced, a 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. They informed my husband he most likely wasn't going to get to take me home, as they didn't think I'd make it before they could get me transferred to a different hospital and into surgery.

(01:03:53):

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. This traumatic experience pushed me to confront the complexities of managing my

condition. I started on blood thinners, however the blood thinners they put me on ended up becoming subtherapeutic, and in November of 2021, 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. I had awoke in the middle of the night to let the dog out and had been stumbling around, had impaired speech, and my smile had gone completely crooked.

(01:04:42):

The emergency squad was there within 15 minutes. 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. Today, we are officially in the process of trying to get pregnant for round number two for our parenting journey. We've had to assemble a VIP team of medical professionals to craft a meticulous plan of preparation and treatment during and after our entire process.

(01:05:17):

I'm unable to get off of my Plavix due to there not being an alternative option that is truly safe. Therefore, my team of doctors have asked that I remain on it for now and possibly through any pregnancy due to my medical history. So, I am simply only able to give over my worries to prayer that this medication won't cause to harm to a future baby. 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 endured.

Pamela P. (01:06:03):

I am Pam. I am 66 years old, and 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. One of my first signs of trouble was poor eyesight and later many visual complications. I received my first pair of glasses at the age of two, along with a diagnosis of dislocated lenses. Since this is something that doesn't occur in very many conditions and no one knew about homocystinuria, I was also diagnosed with Marfan syndrome. Marfan syndrome and homocystinuria share a lot of commonalities. I was extremely nearsighted and needed to sit in the front row in elementary school in order to see the board. By junior high, I was wearing contact lenses and had 20/25 vision for the first time in my life. As I grew older, I developed retinal detachments in both eyes at separate times.

(01:07:06):

The surgical repair in my left eye went well, but the one in my right eye was more difficult. It required a second revision, which eventually resulted in the loss of most of my sight in that eye. By my 40s, my dislocated lenses were hanging by threads, and I needed more surgery to remove them. In the past few years, my vision has sharply declined. I have glaucoma, myopic degeneration, peripheral vision issues, and a visual acuity of 20/60. Because of these issues, I can no longer drive, and I'm dependent on others for transportation. 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.

(01:08:03):

I was told once I stopped growing, my scoliosis would be taken care of, and for a long time, it was. When I was 46, I suffered a stroke. Luckily, it was mild, but my right internal carotid artery was 100% occluded

and remained so to this day. Shortly thereafter, I was hospitalized twice with blood clots in my lungs. This was a turning point for me in my life and prompted me to do my own research. I had learned a lot about Marfan syndrome, but nothing I read had described strokes or blood clots. By chance, I found out about homocystinuria online with strokes and blood clots as being possible symptoms. I wondered if I might have been misdiagnosed all this time. After a few phone calls, blood tests, and finally a genetic test, my suspicions were confirmed. I was diagnosed with classical homocystinuria in 2011, needing to start a strict low protein diet for life.

(01:09:05):

Now, I need to put all foods on a gram scale, so I know I am meeting my 20 grams of protein allowance and not going over. I need to check menus ahead of time online when dining out for appropriate foods. Now in my 60s, I continue to face challenges as I 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. My scoliosis has returned, causing pain and trouble with mobility. I find I can no longer walk or stand for long periods of time like I used to. Because of my history of blood clots and my advancing age, doctors have advised me against surgery. I continue to have major struggles with my vision as well.

PART 2 OF 9 ENDS [01:10:04]

Pamela P. (01:10:03):

I continue to have major struggles with my vision as well. Since February of this year, I have noticed a problem with the color perception in my left eye. Pictures appear blurred and reading and watching television has become difficult. I'm currently being evaluated for cone-rod dystrophy. It is terrifying to think I may lose my vision due to the complications of this disease. I have trouble with my depth perception and find it necessary to take my husband's arm whenever we are in public. He helps me to navigate things I cannot see, such as curb steps and things in dimly lit rooms. Although, homocystinuria research has come a long way, much more needs to be done. I am hopeful that new therapies will be developed and approved, so I may have a better quality of life.

Brooklyn P. (01:10:55):

Hi, my name is Brooklyn and I'm 37 years old. Homocystinuria is still considered a child's disease, yet it is a full-time job that is mentally and physically exhausting. We hear all around us, "Take care of your mental health and practice mindfulness." What is mindfulness? It's living in the present moment. As someone living with homocystinuria, I can't do that. 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. My parents considered me a careful child until I fell in a sandbox, breaking my arm. Someone noticed I might need glasses. Age three I got my first pair, but my vision was continued to get worse. By age seven, my [inaudible 01:11:41] completely dislocated, and the other one was attached, but did not yet to require surgery.

(01:11:46):

I was in severe pain. I vividly remember the awful pain and part of the ambulance ride. A few years after my [inaudible 01:11:52] dislocated, I started to wear contact lenses and it was long afterwards I started experiencing migraines. The migraines began once I started wearing contact lenses and continued even though I stopped wearing them. We were trying to seek answers. My mother and I sat in a lot of waiting rooms to see lots of different doctors before finally I saw an ophthalmologist who said, "The only

disease I've ever seen where the vision deteriorates this fast is homocystinuria." The day I was diagnosed, the doctor said, "As long as you take your formula and follow the diet, you'll be fine." And of course, celebration and food go hand in hand, I quickly learned this is an incredibly difficult diet to maintain, especially as the only kid that had to have different food than everyone else.

(01:12:35):

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. When I started school, I was unable to go to preschool because I was so far behind the other kids. Certain tasks like tying my shoes and problem solving I learned to do much later than my peers. As I entered school, I was often taken out of my classes to do occupational therapy to try to close some gaps.

(01:13:06):

As I continued on, I struggled with learning disabilities and needed an individual education plan or IEP in school in order to provide me more time and assistance to complete my work, even though I was going to a special education school. I was a shy and quiet kid because there was no one else remotely like me and I always felt like I didn't fit in. Around age 11, I was diagnosed with scoliosis. At the time, doctors first wanted me to stop growing before having surgery. A back brace stopped my growth, but did not stop my curvature in my spine. But at age 22, I had scoliosis surgery.

(01:13:42):

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. 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. Even just reading through a job description often leaves me exhausted. If I do find a job, how am I supposed to retain it with these issues?

(01:14:32):

I want what everyone else wants, a job that allows me to support myself financially, that I'm passionate about, and can retain without the risk of burnout. Unfortunately, due to all the struggles that I'm facing, I've not been able to find a job. From before my diagnosis to now, I continue to wait countless hours to see doctors because as I age, I require more care. I live alone, so the impact that HCU sometimes feels as invisible as a disease or when I talk about my condition to friends, family, and new people I meet, I realize I have an ever-growing list of doctors, medical problems that need solving. Homocystinuria is a lot like playing whack-a-mole. You think you solved the problem and then boom, another one pops up. It's really hard to tease out which issues are compatible with you and which it's just a normal result of aging. And as much as my doctors want to help me solve the problem that aging with issue presents, they don't have all the answers. This invisible child's disease impacts my adult reality.

Anna C. (01:15:41):

My name is Anna. My daughter Juana has classical homocystinuria and we are from Uruguay. Juana is 11 years old and was diagnosed at age six due to a variety of symptoms, extreme myopia, and movement in her lenses being the most noticeable. 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. Because of her eye problems, Juana has been using contact lenses since age five to be able to achieve only 70% vision. It was a necessary solution for her to be able to have a chance to attend school and learn to write and read, which at some point wasn't a given.

(01:16:35):

Apart from that, the fragile structure of her eye is at high risk of length detachment, which would need a major surgery that we have no assurance would work or would cause her to lose her eyesight completely. To avoid as many risks as possible, 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. Instead, she has to go to weekly appointments of physical therapy because of her arced feet, knock knees, and posture to prevent it getting worse and manage the pain in her feet and legs. Adding to this already difficult reality, she also has behavioral issues and learning difficulties, which drives an never bigger wedge between her and her peers.

(01:17:32):

Juana has struggled with schoolwork from the very beginning. It takes her twice the time to complete assignments and often needs a lot of support. She's always a few steps behind what's expected of her age. Having these diagnoses does not make living in society any easier. 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. 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. 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 [inaudible 01:18:30] frequently. We've gotten to a point where 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. Even on her best days, we are always reminded that she suffers from a rare disease and as such, she's greatly different from the rest. Juana is extremely social and cheerful, but because of the impact homocystinuria has had on her, she relies on me always 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 [inaudible 01:19:24].

(01:19:26):

First thing in the morning, I put in her contact lenses because she can't see well enough to do it on her own. 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. Even though I am well aware that many of Juana's symptoms are because of her late diagnosis, it is important to clarify that with our current treatment, there is no guarantee that homocysteine levels won't ever go up, putting her at risk to develop any number of health issues. Because of this, 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.

(01:20:21):

Being an extremely positive girl, what hurts Juana the most is not her dietary restrictions, drinking foul-smelling formula, or having to see doctors more often than any other person. It's missing out on so much. It's sitting out through a football match, it's not being able to share experiences with friends or family. 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.

James Valentine, JD, MHS (01:21:02):

Wow, thank you so much, Anna, for sharing you and your daughter's journey with HCU, as well as to all of our panelists who were so brave to share first this morning and help us understand some of the symptoms and daily impacts of this condition. So, now it's our first opportunity today to broaden the discussion to all of you, our individuals living with classical HCU, and their direct caregivers who are live in the audience and have you share your experiences with this condition. We invite you now to begin calling in if you have certain symptoms or impacts on daily lives you'd like to share. You can do so now and any time during the program by dialing in at +1 703-844-3231. Again, that phone number is +1 703-844-3231. If you call in, you'll talk to our operator and we'll be able to get you into the queue to bring into the discussion. You can also write in with your experiences. There's a live comment box under the live stream player on the webpage you're following along today. So, you can submit written comments and we'll be sharing those throughout the program as well. But to get us thinking about this topic and get a sense of the experiences of our audience, we're going to start off with a pair of polling questions. So, you can go back to that webpage if you were with us earlier or if you are just joining us, you can go to www. pollev.com/hcupfdd, again, you can do this on your phone in a browser, on a new tab on your web browser on your computer. Go to www.pollev.com/hcupfdd. You can keep this up throughout the entire program as we go to different questions throughout the session. You'll be able to answer those as they'll appear automatically there. So here we want to know which of the following classical HCU-related health concerns that have you or your loved one ever had, and you can select all that apply. The options are, A, blood clot, stroke, and pulmonary embolism, B, optic lens dislocation, C, severe nearsightedness, D, osteoporosis or broken bones, E, tall stature or long legs or arms, F, curved spine or scoliosis, G, pain, H, digestive issues, I, cognitive issues or learning problems, J, developmental delays, K, anxiety or depression or, L, some other health concern that's a result of your classical HCU or your loved ones that you've experienced that isn't otherwise listed on this slide. I want to point out that this is our first question where our audience can select more than one option. So, you'll be seeing percentages on the right side of the results here, those represent a percentage of total responses, not the percentage of individual people selecting any one given response. So, I like to think of this as looking at the size of the different bars. You can kind of use that as a little bit of a relative ranking across these different response options.

(01:24:22):

So, we'll give everyone a few more moments here. As it stands, it looks like optic lens dislocation and anxiety or depression have kind of been the flipping back and forth as one or two. We also see tall stature and long legs or arms up at the top. Along with those up in that upper echelon, we see osteoporosis and broken bones, as well as curved spine and scoliosis all being reported very frequently by our audience. We see then pretty consistent... Quite a few people selecting each of the other different symptoms and health effects to a large degree, including some others that we haven't had listed. So, I think we're seeing that there's quite a few different symptoms and health concerns people with classical HCU are living with.

Danae Bartke (01:25:16):

This really does also reflect, I think, what we would expect looking at Dr. Chapman's presentation from this morning. I think she had quite a few of these things on her slide itself. It would be interesting to hear what the other ones are that people are experiencing too. So, those are great ones for people to call in with or submit their comments with too.

James Valentine, JD, MHS (01:25:41):

Absolutely, so we can go to our second polling question. So, here you'll recognize the response options. Here, we want to know, thinking about those, which though would you say are the most troublesome of these classical HCU-related health concerns that you or your loved one have ever had, and here we want you to select the top three that represent those most troublesome health concerns. So the options are, again, A, blood clot, stroke, or pulmonary embolism, B, optic lens dislocation, C, severe nearsightedness, D, osteoporosis or broken bones, E, tall stature, long legs, or limbs, F, curved spine or scoliosis, G, pain, H, digestive issues, I, cognitive issues or learning problems, J, developmental delays, K, anxiety or depression or L, again, there's other health concerns that aren't listed.

(01:26:33):

But here as you're picking your top three, I want you to think about why it is you're making these selections. What came to your mind that helped inform that decision to say... We saw on the previous question how many different symptoms people are living with, how did you make the selection of what rose to the top three for you? And we'd encourage you to call in and write in to share that.

(01:26:58):

So, I think we saw that anxiety and depression was one of the most common reported health concerns, and here perhaps then no surprise, it's also rising to the top as one of the top three most troublesome aspects of living with classical HCU. After that, we're seeing the blood clot, stroke, and pulmonary embolism reported also up there right at that top tier, and optic lens dislocation being perhaps the third up with those other two. However, what really stands out to me is that we see every single one of these other ones except for digestive issues in some number of people's top three. So, while some of these may be the top two or three, for some number of people, these other things are the things that are most troublesome to them. And so again, we really want to hear about what that looks like and why you selected what you did, even if you're picking one of those things that maybe wasn't selected by as many people. So, I want to thank everyone for participating in these polling questions. Again, you can keep this website up. As we go to different questions throughout the day, you'll be able to see those there and just be able to answer them as we go along. So again, if you would like to share maybe some of your most troublesome health concerns, I encourage you to call in.

(01:28:20):

You can do so at +1 703-844-3231, if you'd like to share what you chose in that polling question. Again, you can do so at +1 703- 844-3231, but to get us started in this discussion, I'd like to welcome a panel of your peers living with classical HCU and other caregivers who have joined us today via Zoom. So, welcome to the program. It's great to see you all. As we're thinking about this first topic of maybe what are the most troublesome direct symptoms and health effects. Pam, maybe we can start with you today thinking about that. What was maybe the top one or two that you picked out of that polling question and can you tell us a little bit about why you selected that? Oh, Pam, you're on mute.

Pamela S. (01:29:15):

I'm so sorry. I'm new to this. Hi, my name is Pam Stallings and I'm from Louisville, Kentucky, and can you refresh some specifics that you'd like to have me answer?

James Valentine, JD, MHS (01:29:27):

Yeah.

Pamela S. (01:29:27):

I'm sorry, I'm not in the poll.

James Valentine, JD, MHS (01:29:29):

Oh, no worries, Pam. So, the question here is there's so many different direct symptoms and health effects of living with classical HCU. If you had to pick just one or two of those that you would say are the most troublesome or most burdensome, what would that be? And can you tell us a little bit about why?

Pamela S. (01:29:50):

Well, I'm a parent of a 31-year-old who was diagnosed when she was 23. So as Danae knows, we have had 15 surgeries, and when you talk about the stresses and everything in her life, I guess it has to be all of the surgeries and the symptoms stemming... Which I have not heard from you all talk about is she had Chiari. She is tall, she's actually 6'3", her feet are substantially different in size because of all the surgeries. She was born premature, but I think she would say that it's the food. She is a first grade school teacher and she just struggles with the daily routines, learning how to reboot her life.

(01:30:46):

She was in a body brace for a complete year due to her surgery with the Chiari malformation and with that, it was a little bit different from the spinal stenosis and all of that, and the other diagnosis because when they went in to correct her Chiari, they also found when they were doing the fusion, she had very brittle and porous bones. And so, instead of taking part of her rib and putting it in to hold the OC3 fusion, he couldn't do that because of the bones. They were too very brittle, and so that was one of the things. My daughter was also diagnosed with Loeys-Dietz, and that's when we found out that she also had a homocystinuria.

James Valentine, JD, MHS (01:31:39):

Sure, so Pam, you kind of mentioned that-

Pamela S. (01:31:42):

I know I kind of skirted it.

James Valentine, JD, MHS (01:31:45):

It's totally okay. There's a number of really important things that you described. One thing for those of us that aren't part of this community, you talked about the number of different surgeries and how that's been really difficult. Can you tell us about what was driving the need for surgeries? What things specifically, and when did that occur? Was that something that is more recent? Are these in the... Years ago? Can you describe that a little bit?

Pamela S. (01:32:18):

Well, unfortunately she was born premature. So, she was in ICU and they immediately diagnosed her with a clubfoot, so what they thought. In Louisville, Kentucky 31 years ago, we did not have any pediatric specialties. So, immediately we started going to the orthopedic, and one thing after another... When she was in second grade, she was actually perfectly normal to us. We weren't seeing anything other than possibly she had some struggle with being in crowds. Now that I look back, she definitely had some brain fog.

(01:33:09):

We did private pay some OTPT after everyone masked her surgeries with the diagnosis. We were told till probably about the second grade that there was nothing wrong with her, and then once she started having those surgeries, they sent her to a neurologist and the neurologist couldn't figure out what was going on. We were sent through the genetics protocol as well. Samantha had been tested twice genetics and nothing came up.

(01:33:46):

Loeys-Dietz is relatively new. Danae knows a little bit about Loeys-Dietz as well and how we're a little bit different than everybody else, but in 2006 is when Dr. Dietz and Dr. Loeys came up with that. It was undiagnosed, misdiagnosed, we had Ehlers Danlos, we had Marfans. And when we were tested, we had none of those. And like I said, she started feeling really sick her senior year in college and to the fact that she couldn't get out of bed, her headaches, all of that. So, we quickly got her back to the pediatric specialty clinic in Iowa City and he went through just to see if it was the Chiari related or anything, and it was none of that, and that's when she was diagnosed with the HCU.

James Valentine, JD, MHS (01:34:34):

Wow. Well, thank you so much, Pam, for sharing a lot of that journey and a number of the things that she experienced over that time, from the earliest stages through kind of adulthood. Karen, I'd like to bring you into this conversation. Again, thinking about there's such a wide range of different symptoms and health effects, what maybe stands out as the one or two most troublesome things in your experience?

Karen L. (01:34:57):

Hi, I'm Karen Lewis. Mark and I have three children. Two of them have homocystinuria, classical. My son Ben is 32 and Gabbi is 22, and you saw Gabbi on the video, which I had to get a few tissues for that. So, Ben was diagnosed through newborn screening, which we were very lucky because he was just a smidge above the cutoff. He was very sick and we just didn't know what was wrong. So, he was diagnosed about a month of age.

(01:35:33):

And then Gabbi was actually, I believe, the first baby diagnosed through amnio. So, she was diagnosed before she was born. I think some of the most troubling things that I find are Gabbi's scoliosis. She's gone through two very traumatic, severe spinal fusion surgeries, which were probably one of the most traumatic things we've ever experienced as a family. And I feel like 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.

James Valentine, JD, MHS (01:36:28):

Sure.

Karen L. (01:36:28):

And I think just socially it can be extremely difficult for HCU patients. I feel the world revolves around food, so it can be very difficult.

James Valentine, JD, MHS (01:36:43):

So Karen, you mentioned a few things that I want to follow up on, but one thing you mentioned was the worry about blood clots and stroke. Is that something where there's already been some experience with that or is that something that's just more of a worry for the future for you all?

Karen L. (01:37:02):

We haven't had an experience, thank goodness. I will say through Gabbi's surgeries, that was one of the most stressful situations and why she was in ICU for eight days with each surgery was because of the unknown because after her surgery, she wasn't able to really keep down any formula, wasn't eating. Her HCU levels were very high and her homocysteine levels were very high. So, that was a worry at all times in the hospital of whether she would have a blood clot or a stroke. And I think just knowing that that is a possibility just stays with you, and I think it stays with my children too, no matter how old they are, they still worry about that because it still... Even though you're diagnosed early, it's still a possibility forever.

James Valentine, JD, MHS (01:38:03):

Right, very helpful to understand that. The other thing I wanted to follow up was you mentioned that there's impacts on her ability to be social and her social life. I guess my question there, as we're exploring the direct symptoms and health effects of HCU, is there one symptom? Is there multiple things that make that difficult? Could you maybe share a little bit about what you meant when you said there were some social limitations and what about HCU makes that hard?

Karen L. (01:38:42):

I find that it is difficult socially, and Gabbi explained some of it, where I'll take college, for instance, where most students can eat in the dining hall. For the first year with Gabbi, we thought we had it under control for the dining hall, but it didn't work out. So, Gabbi would have to plan her meals in the morning of what she wanted to have a dinner, and then she would have to let them know, and then by the time she would get there with her friends, her food usually wasn't cooked yet and they can just go up to the dining hall and pick whatever they want. So by the time her food was prepared, her friends had already eaten, so she would eat alone because there's many times that friends aren't very sympathetic to what you have and they're busy, so they go do their own thing, and Gabbi was left alone eating.

(01:39:44):

If she had too much protein during the day and they wanted to go out for dinner or if they changed their mind and they said, "We're not eating in the dining hall, we're going to want to go out to dinner," Gabbi wouldn't be able to go because she wouldn't be able to eat the protein amounts for dinner. So different things like that, birthday parties, it's hard because say you're invited to a birthday party, you have to contact your friend or the family and ask what they're having at the birthday party, can you eat the food? And it's just different. So, it definitely always seems to put in extra effort or work to be able to do the fun things that you want to do.

James Valentine, JD, MHS (01:40:24):

Right, and one thing we saw in the polling was the number one thing rated was anxiety and/ or depression, which of course is not necessarily the direct manifestation always of a condition, but the fact that you have to live with all of these things. And so, I guess just for you as a mother, have you and Gabbi had those types of conversations? Do you have any kind of perspectives on the impact that this condition has on people's mental health?

Karen L. (01:40:56):

I definitely think it causes anxiety. I know that Gabbi... I don't feel as much with my son Benjamin, but maybe he has a little bit of anxiety, but I think Gabbi definitely deals with anxiety more than Benjamin does. And I think she worries a lot about the effects or if her levels are high or if she's had too much protein. I do think that that does weigh on her.

James Valentine, JD, MHS (01:41:33):

Well, thank you for being willing to speak to that and share that, Karen. I do see we have a phone caller that I'd love to bring into this conversation. We have Joanna from Oregon who is living with HCU and wants to speak to some of the top symptoms that have been impacting her. So Joanna, I'd like to welcome you to the program. Are you with us?

Joanna (01:41:54):

Yes.

James Valentine, JD, MHS (01:41:55):

Hi, welcome.

Joanna (01:41:57):

Thank you.

James Valentine, JD, MHS (01:42:00):

So we'd love to hear... Go ahead, please.

Joanna (01:42:03):

Oh no, what were you saying?

James Valentine, JD, MHS (01:42:05):

I was just going to say we'd love to hear on this topic of symptoms and health effects. Are there certain symptoms or things you'd like to highlight and share with us?

Joanna (01:42:16):

Sure, I was diagnosed when I was three years old. I had trisodium phosphate down on my hands, I rubbed into my eyes, and I noticed my lenses had dislocated. And since then at that time, I became at the age where I didn't believe in the condition because nobody took the time to look it up, my doctors, except for the geneticists. And eventually I ended up having some B12 deficiencies, which they thought were strokes because they start out with your face numb and then they will go into panic attacks, urine balance problems, and then it goes into dementia if it goes far enough.

(01:43:29):

And I came to the point with the second one, where I couldn't even trust myself without going into layers. And eventually that cleared up after I started with the B12 shots again and the folic acid, and the second one was after my major stroke, which paralyzed my left side. And currently I have everything back again, thanks to a lot of physical therapy, occupational therapy. They sent me home with a walker and a wheelchair, which at that time I refused to use. And I had my parents walk me around and gait belt until I learned how to walk. And so, it is through sheer persistence that I am able to walk and everything right now. My father passed away the same year as my stroke, and so he's no longer alive, but going off diet, this really gives you anxiety. It is my biggest regret ever, and it's added anxiety that you will never have if you are on diet because it makes you worry about everything you eat-

PART 3 OF 9 ENDS [01:45:04]

Joanna (01:45:03):

... because it makes you worry about everything you eat. It's constantly, even if I have a shot where I can have more protein, I'll be worried for the rest of my life if I go over.

James Valentine, JD, MHS (01:45:23):

Right. Yeah. I can't even imagine. I think this anxiety clearly is top of many people's minds and hearing what is behind that now for a few people, including you, Joanna, has been really helpful. And of course, thank you for sharing that experience with stroke, I'm glad to hear that you were able to rebound from that, but still a tremendous experience to have to go through. One thing that you had mentioned was, or maybe earlier on in your journey with HCU, were some of the visual issues, and I'm just curious, have those persisted? What has that looked like for you and how would you describe how that impacts your life?

Joanna (01:46:12):

So with my first B12 deficiency, it happened when I was 19 years old, and that one I was started on a medication called cystadane. That was back in the nineties, early nineties. And that medication is super, super bitter. If you're familiar with warheads, it's kind of like that and can be described as a bitter salt. It kind of looks like cocaine, but it's not. And hence the reason why we have to have it rubbed down every single time we're in an airport because they're worried about it being a drug, an illegal drug. And even the formula, the foods, everything is a problem when you take it to the airport. But ... I forgot your question.

James Valentine, JD, MHS (01:47:28):

I was just curious about the visual impacts and-

Joanna (01:47:32):

Oh, the visual issues. Okay. Yes, so the main thing, my major stroke, it had protruded my right eye, which is still protruded, but my visual issues got better after I started taking the medications and following the diet again, cystadane I consider is my gold.

James Valentine, JD, MHS (01:47:57):

Yeah. When you said they got better, Joanna, can you describe what that looked like for you? Put in a little bit of context for someone like me that might not know.

Joanna (01:48:09):

Yes. Before I started taking the medications, following the diet, I was legally blind. Now I have close to perfect vision.

James Valentine, JD, MHS (01:48:24):

Oh, okay. Very significant improvement though, so glad to hear that. Well, Joanna, thank you so much for calling in and sharing a number of these different really important symptoms and health effects of your journey with living with classical HCU. I'd like to come back and check in with our panel here and maybe bring in Melanie on this topic. So we were initially focusing on some of those top symptoms and health effects, so certainly if that comes to mind, would be eager to hear that. But as you're thinking about any symptom or health effect you might want to share, would be interested to kind of understand what that actually looks like from a day-to-day basis. So Melanie, is there anything you'd like to share on this topic?

Melanie (01:49:13):

Hi, my name is Melanie. I'm from Vancouver, British Columbia in Canada. I have a 10-year-old little boy Mason who has classical homocystinuria and he was unfortunately missed at birth, so he was not diagnosed until about two years ago when he was eight years old. As far as your question, I can kind of go into 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. So day-to-day, that's quite difficult for a little boy to have to get up and essentially have somebody put his eyes in for him in order for him to see. He has to rely a lot on us and he just doesn't have the ability to put those in yet.

(01:50:08):

It's very hard for him to see and he also doesn't have those motor skills to really get that job done. So that affects him daily. I would say that's the number one thing. And the other thing that I would say is much so what Karen had mentioned, the fact that foods in everyday part of life, you're not getting around that. And to not necessarily be able to enjoy that every day, that can take a huge effect on a person, I believe. And the formula as well. Having to force yourself to drink something that tastes so gross every single day with no end in sight, I think that that's a very difficult thing for any person to have to do just to remain healthy.

James Valentine, JD, MHS (01:50:54):

Yeah, no, thank you for sharing both of those impacts. Maybe starting with the first one with the visual issues, you mentioned that it still can be difficult for him to see obviously the burden of needing his parents to put kind of his eyes in as you described it, but then you also mentioned that that is further complicated due to some motor issues that he has. Could you kind of speak more to that? What were you describing there?

Melanie (01:51:26):

Yeah, I think for most of Mason's life as a baby and growing up into a toddler, he always reached his milestones, but he reached them a little bit later than most babies and most little kids, which didn't

really cause any huge alarm among any professionals and he always did catch up. So it hasn't been any sort of a huge problem, but it's certainly an issue that's there. And I think that being able to do something like pick up a little contact lens and focus enough to get it into your eye when you can't even see, it's almost an impossible task at this point for him.

James Valentine, JD, MHS (01:52:08):

I see. Sure. No, that's very helpful to understand. And are there any other examples, just to understand the range or scope of motor, that's a very fine motor kind of activity, being able to grip a contact lens. Is there example that maybe you could share of what this impact looks like in daily life for him?

Melanie (01:52:37):

I think that's the main one that we see, but from starting kindergarten onwards, we were always sort of told that he didn't quite pick up with the printing and holding the pencil the proper way and things that maybe a lot of other kids might actually deal with as well. But I do believe that it's because of the late diagnosis that these things sort of continued on a little bit longer for him and we weren't ever, ever really be able to fully fix the issue because we didn't know what the problem was.

James Valentine, JD, MHS (01:53:10):

Right. And then obviously on the concerns around navigating the diet and what that looks like and the burden. I guess one question is maybe this is relevant given his age, has that been more or less difficult at different ages or over time. Can you maybe speak a little bit to that?

Melanie (01:53:35):

Yeah, so as I had mentioned, he wasn't diagnosed till eight years old, so I'm sure you can imagine that every 8-year-old child has a lot of favorite foods. We took away 90% of those. Chicken, hamburgers, eggs, he loved fish. So the change in his life with respect to diet was huge. Then having to kind of switch our way of thinking, we thought we were feeding him so healthily all this time, And unfortunately we were not and we didn't know. So it was a huge mental shift for our entire family to have to do that and for him to have to ... For us to explain to him in an age appropriate way why he can't eat these foods without scaring him was also really, really difficult for us. And it still is. He's only 10, so we don't want to add any stress, but we also do understand that it's important to be honest with him. So it's kind of a battle as he grows up as to how much we start to expand and educate him.

James Valentine, JD, MHS (01:54:40):

Right. And given what you just described of striking that balance and being transparent in an age appropriate way, was he able to handle that maybe initial transition compared to where he's at today in terms of coping with the fact that he has these dietary restrictions?

Melanie (01:55:03):

Well, I mean, I'll brag and say my son is a rock star. He works really, really hard and I'm really, really proud of him. But not to sugarcoat it at all because it's extremely sad and it's extremely difficult. If you can imagine being a little kid and you're excited to have breakfast and let's just say he picks an egg and he can have one, we can work that into his day. It's one of his favorite foods. But then later that night, 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. It's like, "Well, unfortunately buddy, you already

had an egg today and you've had lunch and you've had this snack," and now he can't go and enjoy those types of things with his friends. He does his best to cope with these types of disappointments a lot. It's just part of what he has to deal with and it's really unfair and it's really sad.

James Valentine, JD, MHS (01:55:59):

No, it really is. So Melanie, thank you so much for letting me probe a bit there and really understand. I do see we have another phone caller, which I'd like to bring into this conversation. We have Liz from South Carolina who's a caregiver that wants to speak to some of the top symptoms or health effects. So Liz, I'd like to welcome you to the program. Are you with us?

Liz (01:56:21):

Yeah, I'm here. Hi James, and Danae, and everybody listening.

James Valentine, JD, MHS (01:56:25):

Welcome.

Liz (01:56:25):

As you said. I'm Liz, I'm in South Carolina. My little guy is seven years old. He was missed at newborn screening, so at age two and a half he got sick and we learned he was having seizures. He was put into a medically induced coma and doctors determined that he was having seizures as a result of extensive clotting throughout the brain and he'd had an area of stroke as well. So doctors told us they had no idea what was causing it and that we could lose Elliot, but it turns out 10 days later we got the diagnosis of classical HCU and started treatment. And that was really the first way that classical HCU manifested in Elliot.

James Valentine, JD, MHS (01:57:15):

My goodness.

Liz (01:57:18):

Yeah, today, he still has random seizures that fire off that are really unexplained. The best that we've been told is that there are result of kind of like with a traumatic brain injury, the initial clotting that happened in his brain created a seizure focal point. And so these seizures can happen at any time and kind of show up very unwelcome and unexplained at this point.

James Valentine, JD, MHS (01:57:44):

Wow. And have there been any ... I know you said that's unexplained, so maybe it may or may not relate to those initial blood clots, but have there been any other lasting effects of that initial set of seizures and the associated blood clots that were caught and what led to his diagnosis?

Liz (01:58:08):

So we've been very lucky. Elliot went through a lot of physical and occupational therapy to overcome some of the challenges initially that those things presented. It has not had any major lasting effects other than, like I said, the seizures and the extreme anxiety and fear that it's caused as kind of a side effect and not knowing when something might occur when we might have another seizure event. So yeah, it's created a lot of stress and anxiety as you can imagine.

James Valentine, JD, MHS (01:58:42):

Sure. And you mentioned that initially there was some PT and OT that was needed and was helpful. Can you maybe just give us an example of what that was helping address, just so we have an idea of that?

Liz (01:58:57):

Yeah, I think because he was laying in an ICU bed for 29 days in the hospital and during that time was not able to walk, wasn't talking for a while, so we really didn't know what the outcome would be for Elliot. So the PT and OT kind of just helped to, 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.

James Valentine, JD, MHS (01:59:28):

Yeah. So a range of things, the gross and fine motor, but also speech. So I appreciate you expanding on that a little bit. And then you talked about anxiety and worry of seizures happening. Can you maybe just describe for us how frequently is he experiencing seizures? What does that look like? Is that pretty constant these days or consistent in how frequently they occur?

Liz (01:59:59):

So they're unpredictable, 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. He had one at school not too long ago and I was out of town traveling for a work trip. And of course that's always when these things happen and I got a call from his teacher and she was in utter panic and they had called an ambulance and he was having a seizure at school. And so yeah, it's just kind of unpredictable. Thankfully, not super frequent, but again, like I said, we just kind of live in a constant fear because they don't seem to really be triggered by anything other than, like I said, just the initial trauma that he sustained from the clotting.

James Valentine, JD, MHS (02:00:49):

I see.

Liz (02:00:49):

So, It's kind of unknown at this point.

James Valentine, JD, MHS (02:00:51):

Yeah. Well, Liz, I really appreciate you calling in and sharing some of these things and helping us understand something we haven't heard a lot about, which is blood clots and seizures. And of course anxiety I think we're hearing is really a theme that's really crosscutting now across a number of these different symptoms and health effects. I do want to recognize we've been getting a number of written comments that have been coming in, so would like to check in with Danae, what are we seeing?

Danae Bartke (02:01:16):

Yeah, I am looking at a comment here from Samantha from Ontario, Canada, and it goes well right along with what Liz was talking about with those initial seizures. So Samantha writes, "At age two years old, I began having seizures. Once I was diagnosed and being treated, the seizures stopped. Also, eyesight I could not see, but my parents didn't know that for the longest time, I went backwards on my

milestones. I went from sitting up to not sitting up on my own. I also didn't speak until around four years old," which we do sometimes see in patients, let me see here, I'm going to move down here. Samantha also shared, "On my bad days, I would start to stutter. I have always believed this is my body's way of telling me I've gone over my protein limit. As a child, you could tell when my bad days were as I would get super angry and not only stutter, but also would intensely scratch my face out of frustration. As a child, if I went over my protein alignment, my mom could easily tell."

(02:02:33):

I know I've had many conversations with parents where they can see the high levels in their kids, not so much the patients, but the parents can definitely see behavior changes in their child. And anger outbursts are definitely one of them. Let's see, one more comment here. We have Angela from California. "It's frightening as a parent to see all the things they could go through, skin issues, emotional dysregulation, vision and hearing issues, poor growth, and to wonder if our treatments course is the right one, will symptoms get worse? Are they all related? Is this just the calm before the storm? I can't even find educational resources related to my boy situation and gene mutations. Why don't we know more? Why don't we have more treatment options?" So a lot of fear from parents about what is to come, and I think that happens in our older patients as well. So it's regardless of time.

James Valentine, JD, MHS (02:03:37):

Well, thank you for everyone who has been writing in. We'll continue to share those written comments throughout the program. And if we don't get to reading yours today, just remember we will have all of these comments to help incorporate into that voice of the patient summary report. So I do want to broaden the discussion a little bit. We'll continue to explore what it is to live with classical HCU, but I want to explore a bit around how these different impacts or symptoms and health effects of the disease actually impact your daily lives and activities that are important to you. So to get us thinking around this topic, we're going to go to another polling question. So you can pull out your phone, go to that browser, open up that tab in your browser, go to wwwpollEV.com/HCUPFDD. Again, you can keep this open throughout the day as we go to new questions, they'll automatically appear.

(02:04:33):

So here, we want to ask what specific activities of daily life that are important to you or your loved one are you or they not able to do or maybe struggle to do as a result of classical HCU? And you can select up to your top three. The options are A, attending school. B, biking or playing sports. C, sleeping. D, going to restaurants. E, working or having a career. F, attending social events with family and friends. G, participating in hobbies. Or H, some other activity of daily life that's important to you or your loved one that is either not able to be done or it's difficult or a struggle to do as a result of classical HCU that's not otherwise listed here as a response option. And as you're thinking about and making your selections, we want you to think about what is it about your HCU that makes these activities difficult? Is it one symptom or health effect? Is it kind of a constellation or multiple of these things? We really kind of want to understand what is making these activities hard or impossible.

(02:05:56):

So I see just a few results still are trickling in. So we'll just give you another moment here as it stands. And I think as we've already started to hear from our discussion this morning that going to restaurants is really difficult or impossible. So we're seeing that as our top response followed by attending social events with family and friends being right up there as well. However, we're seeing all of these other activities of daily life also being impacted for numbers of people, again, hobbies, playing sports and biking, working, having a career, sleeping, attending school, and other things all being impacted for a

number of people in this community. So we do want to hear about not just the most common things, but even some of those things that are less commonly reported but are still very important things to talk about.

(02:06:53):

So thank you for everyone for speaking to this question. I'd like to maybe start the discussion here with our Zoom before we bring them into the discussion though, if you do want to share your thoughts around impacts on activities of daily life, you can share your thoughts via phone. So we encourage you to call in at +1 703-844-3231. Again, that's +1 703- 844-323. We'd love to hear your perspectives on some of these impacts on daily life. So coming to our Zoom panel here, Ben, we haven't had a chance to speak with you yet. As you're thinking about the range of different impacts of HCU, what stands out in your mind as maybe a top impact?

Ben M. (02:07:42):

Well, just a little introduction. My name is Ben, I live in Georgia. I was diagnosed with newborn screening. And just for the record, I'm not Karen's son, Ben. I'm a different Ben. So anyways, 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. They may have vegetarian options, but a lot of times that includes a different source of protein. The impossible meats and things like that are still super high in protein.

(02:08:28):

So we are having to scour menus online thinking, "Okay, well, if I order this dish without the cheese and without whatever other ingredient," it's a constant struggle trying to see the things that we can eat. And it causes a lot of frustration and as an adult it's not as difficult. But I can remember being a kid with HCU and everybody's already spoken to the anxiety that you feel, but going out to eat with friends, it was embarrassing as a kid, it was embarrassing because I was different and it gets better as you get older, but I feel bad for the kids that are having to go through that now because I know what that's like and it's very difficult.

James Valentine, JD, MHS (02:09:21):

Yeah. Well, you mentioned that it does get a little easier as you get older, is that you're just able to cope with it a little differently. Can you kind of speak to that?

Ben M. (02:09:32):

Yeah. As a kid, you're always worried about what other people are going to think about you. As an adult, it's a little easier to say, it doesn't matter. Everybody's so preoccupied with themselves, nobody's really looking at what you're doing or your eating habits. But as a kid, it's like I'm at this birthday party and everybody has a huge slice of this birthday cake and I'm sitting here with my little individually packaged little Debbie snack cake, or I'm going to a friend's house for a cookout and I have to ask their parents to cut my hot dog in half long ways. So it still fits on the bun, but it's not quite as much protein. It was embarrassing and isolating and it just gets easier as you get older because you don't care so much about what people think.

James Valentine, JD, MHS (02:10:24):

Right. And kind of just wondering, in addition to maybe not being so worried about what other people think, have you as an adult been able to at all shift what maybe social activities you're doing with

friends? So it's maybe not as food focused or can you just tell us a bit about how social relationships maybe have evolved too?

Ben M. (02:10:51):

Yeah, so thankfully my protein allotment is higher than a lot of what I hear from other patients. I'm allowed 40 grams of protein per day, which makes it a little bit easier for me to manage. If I know that I'm going to do something with friends later in the evening, I'll hold off on eating.

James Valentine, JD, MHS (02:11:10):

I see.

Ben M. (02:11:12):

I may skip breakfast and lunch and just save all of my protein allotment for that event at night. And I'm very thankful that I'm able to do that. But I understand that some patients are limited to eight grams of protein a day or 10 grams of protein per day, and they can't do that. So it is very difficult and I'm thankful for the allotment that I have.

James Valentine, JD, MHS (02:11:39):

Right. Well, thank you so much for sharing all of that, Ben. Chris, I'd like to bring you into this discussion as well. As you maybe think about your family's experience. Are there ways in terms of activities in daily life that you've had to modify or maybe even remove altogether as a result of HCU?

Chris (02:12:01):

Well, thank you James, and thanks for the opportunity to be here today. I'm Chris Hummel, I'm from Mechanicsburg, Pennsylvania, and my 18-year-old son Will, who I'm sure many of you online have met at some point at one of the conferences, he suffers from classical HCU, so I think that Will was also diagnosed at birth. So he doesn't have a lot of the symptoms that many others on the call have, and we are absolutely blessed with that. So looking at the list and the polling questions, the top two that you mentioned, going to restaurants and the social events are the ones that jumped out at me. And for the same reasons that Ben mentioned, Will's a little younger than Ben, but same kind of thing growing up with it, it has gotten easier, but two things. One, I worry that now that he's a freshman in college, he's out on his own. He eats some meals at home, eats some meals in the dining hall, but I worry that as he gets older and somebody else mentioned, as your kid gets older, you've lost control over what they do.

(02:13:12):

So 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 can watch him as closely as we used to. So that's one of those things, and I forget what the second point I was going to make. Oh, the second point was that one thing that Ben alluded to, as you get older, it just becomes easier. People care or you care less about what people think and so forth. But I haven't really checked in with Will with where he is right now in school to see how he's doing because he was anxious about his diet and how that was perceived by his friends and family members and so forth. And I think maybe I've taken it for granted that he's been in compliance and doing well, that maybe he's feeling anxiety that I'm not sure is there. So I will check in with him on that.

James Valentine, JD, MHS (02:14:10):

Yeah. And just because the anxiety around complying with the low protein diet has been such a prominent thing for him. Can you talk about are there periods of time where that anxiety has been greater? You mentioned one being wondering about going off to college and I mean that's generally a whole new part of life and a lot of anxiety about going off to a different setting and starting that level of schooling. But as you reflect back over the years, has anxiety been something that's been around and are there times where maybe it's worse than others?

Chris (02:14:56):

Well, I think that the reason why I'm thinking about it more now is the anxiety was more as he would enter a new situation like college like he's doing right now. So when he would go from elementary school when 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.

James Valentine, JD, MHS (02:15:27):

I see. That makes a lot of sense. So thank you for sharing that, Chris. I do see we have a caller I'd like to bring into the discussion. We have Jamila from Miami, Florida who is living with classical HCU Jamila. I'd like to welcome you into the program. Are you with us?

Jamila (02:15:46):

Hi, thank you for taking my call.

James Valentine, JD, MHS (02:15:48):

Yes, well, we can hear you loud and clear. We'd love to hear maybe some of the top impacts that you've experienced as a result of HCU.

Jamila (02:15:57):

Okay. I'm Jamila and I was diagnosed with HCU through the newborn screening. I wanted to piggyback on some of the comments the other panelists have been speaking about related to concerns about healthcare or the progression of symptoms as their loved one's age. Right now, I'm in the mix of actually experiencing that myself and as a patient and as a healthcare provider. It's something that is acutely on my mind to try to differentiate what are normal signs of aging through the lifespan and what are signs of aging that are compounded by HCU, whether the HCU is controlled or uncontrolled and the spectrum of patients and our experiences and the level of protein that we're able to intake is variable.

(02:17:04):

So I think that we all have some form of anxiety or depression related to our condition and food, and I think that can be complicated by those various developmental stages. I don't know if the symptoms or the management necessarily becomes easier, but I think that there becomes new challenges as you go along and that management of care might look a little bit different as the patient and the family are experiencing some of what the lasting effects of HCU will ultimately be, which there aren't that many studies related to that. So It's challenging in that fact.

James Valentine, JD, MHS (02:17:50):

So Jamila, as you kind of talked about them as being some of the symptoms of aging, are there specific ones that you're thinking of when you say that the ones that are hard to distinguish for you, that you're experiencing or are worried about kind of onsetting? Would just love to hear a little bit more about that.

Jamila (02:18:13):

Well, I think from a female perspective, some of the most concerning things might be osteoporosis and osteopenia, which are already factors for patients, female patients that are aging, compounded by the fact that HCU already makes you susceptible to those conditions. So that is a perfect example of one of the diseases that is on the forefront of something that I think about and it also changes the landscape and how I navigate things that I might do in the future. Health-wise, related or quality of life related to lifestyle.

James Valentine, JD, MHS (02:19:00):

Are certain things that are important to you, activities in your life that are already impacted by osteoporosis or are there ones that you're worried about?

Jamila (02:19:14):

I think that when you're discussing with your provider about maybe what kind of medications you're going to use or how you're going to go about maybe family planning or things like that, those are some of the things that are the forefront of those discussions and impact what you're going to take or how you're going to change your dietary regimen to facilitate the needs of those anticipatory diagnoses.

James Valentine, JD, MHS (02:19:47):

Right. Well, Jamila, thank you so much for calling in and sharing on these topics, some that we haven't heard much about yet. So really appreciate you doing that. I want to check in with our panel. So I think we've focused a lot and heard a lot about ...

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James Valentine, JD, MHS (02:20:03):

the impacts that the diet, the protein restricted diet has on social impacts on being able to go out to restaurants. I wonder maybe, and we can see if the little show of hands, if there are other symptoms or health effects of HCU that have impacted either activities in daily life or that you're worried may make aspects of quality of life a little bit more difficult. Anything come to mind for any of you on our panel? If not, I do see that we have ... Oh, yes, Pam. Oh, and you're on mute, Pam.

Pamela S. (02:20:53):

I still going to mention ... Another panel earlier mentioned how difficult it was to travel and when you're traveling, for instance, with a medical condition, a lot of us have to travel to get to our doctors and people with formulas and stuff, and that alone is very difficult because I know a lot of the panels that I speak with too is when you go through TSA, they specifically want to open up the formulas and smell it, and we carry all of the information that Danae sends and we're so buttoned up, but still people don't trust us.

James Valentine, JD, MHS (02:21:34):

Right. Yeah, that's really kind of a different difficulty of traveling with the medications. We heard about some other medications from a caller earlier that kind of get caught up in screening. And so certainly the formula too, also making that more difficult. I do see-

Pamela S. (02:21:54):

Other thing too, the other thing too is every single one of us, I'm pretty sure is on the similar, I know Samantha takes 20 supplements every morning before she goes to work. So that's another quality of life because she's waking up at 6:00 AM to leave the house at seven.

James Valentine, JD, MHS (02:22:14):

Right. Wow.

Pamela S. (02:22:14):

So anyway, thank you.

James Valentine, JD, MHS (02:22:15):

Yeah, no, thank you, Pam. So I see that we also have been getting some written comments about different impacts on activities in daily life. So again, Danae, what are we seeing from our written commenters?

Danae Bartke (02:22:28):

Yeah. A lot about anxiety and the mental health aspects here. So we have Avin from Dublin, Ireland. She writes in, "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." And then we have a patient who recalls what it was like as a child, Judah from Maryland, "During physical education I was slower than my peers. They teased me and made fun of me." I think some of the parents had shared some of the developmental delays. And then we have Danielle, who's an adult patient from Florida, "As a professional, having HCU has impacted my career choices and trajectory. While most think physical activity limitations are present, anxiety of always ensuring I'm employed with a company that provides affordable and functional healthcare that meets my needs, brings challenges, anxiety and unrealistic expectations of academic and business acumen, perfection." So we see quite the gamut from parents with newborns to adult patients and the mental health impact.

James Valentine, JD, MHS (02:23:44):

Yeah, absolutely. Again, thank you to everyone who has been writing in and sharing and again, encourage you to keep doing that. We will continue to read out these quotes and if we don't get to yours, I promise we will also be using those in the voice of the patient report. Karen, I think you had something to add on this topic of impacts on daily life.

Karen L. (02:24:05):

I think one thing that I just wanted to talk about, because we often talk about the diet and the food and how difficult and restrictive that is, but the other thing that is a huge impact, I believe is the formula. And I think the formula is a struggle for almost every patient or child that I've met and 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 bringing it to work or college, it's also having to travel with it. But 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 the taste to a different formula. So that is another huge, huge issue I believe in the everyday life of the patients with HCU.

James Valentine, JD, MHS (02:25:15):

Yeah. Well, thank you for sharing and adding that, Karen. I do want to make sure we have time to cover our last topic of this morning, which is shifting gears a little bit towards thinking about the future. So we've covered a lot of what people are currently living with and going through or have in the past. We've already heard a lot about anxiety and anxieties, maybe pertaining to day-to-day life and what worries you may have. So I want to kind of more explicitly ask about what maybe your worries and concerns are for the future. And again, to get us started on this topic, we have one final polling question for the morning. So you can pull out your phone, go to that tab in a new browser, go to www.pollEV.com/HCUPFDD. You can keep this open into the afternoon when we'll have some additional polling questions then. So here we want to know what worries you the most about you or your loved one's condition in the future. And you can select the top three.

(02:26:16):

The options here are A, struggling with diet. B, needing surgery. C, that my symptoms will get worse. D, stomach problems. E, Needing to quit my job. F, worsening impaired thinking or memory. G, blood clots leading to stroke or heart attack. H, dying prematurely. I, ability to start my or loved one's own family. Apologies. One second. We're refreshing polling here in the studio. So I, ability to start there or my own family. J, who will be able to care for my child after I pass away? Or K, some other worry or concern you have for you or your loved one's condition in the future that isn't listed here but represents one of the top three greatest worries or concerns that you have.

(02:27:17):

So we give everyone a few moments here. I know it may be hard to narrow this down to just the top three greatest worries that you have, but as always, I want you to think about why you're selecting these as your greatest worries given that there are so many concerns that you all may have. As it stands, it looks like blood clots leading a stroke or heart attack is kind of the top of the list here, followed by struggling with the diet into the future. We see that there's great worries about symptoms getting worse, dying prematurely and worsening impaired thinking or memory, but interestingly, we're seeing most everything here besides stomach issues listed as a top three concern that our audience here today has.

(02:28:16):

So we'd love to continue to hear about the wide range from you all of different worries and concerns that you might have. So thank you for participating in this final polling question for the morning. As we go to think about this topic and worries for the future. I want to start with our Zoom panel here. Chris, maybe we can start with you on this one. You kind of described your family's situation as kind of currently not having many of the different symptoms that maybe others have. As you all think about the future, what worries and concerns do you have?

Mehul Desai, MD (02:28:58):

Well, the ones I picked were the ones that you read off. It was struggling with diet, it was the blood clots and it's dying prematurely. And I feel like we've built up a little pool of good health, but there's no guarantee. Somebody else earlier in the call said there aren't any guarantees for what's going to happen in the future. And that's 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. So that's our big concern.

James Valentine, JD, MHS (02:29:33):

Yeah, yeah. Thank you so much, Chris, for sharing that. Melanie, I'd like to bring you in on this as well. Anything that stands out to you as maybe the top worry or a couple of worries that you all have?

Melanie (02:29:47):

I think what Chris touched on earlier, being that Mason's still a child and fully in our care, it's that lack of control that you know is coming. 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 and 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 and a diet meaning food, something you eat every single day, they're at risk of making a very big mistake every single day. So as a parent, that's a huge worry to think about sending them out into the world and preparing them the best that you possibly can in order to do that.

(02:30:34):

I think that's my number one for sure that I think about a lot. And then, yeah, secondly, I think it's the quality of life that he's going to have. I know a lot of thoughts are ... Well, it's a diet and it's formula, you can do it's fine. And it's like it's not really fine. It's not just a diet, it's not just formula. These are huge impacts in daily life and while we're grateful that they exist and that we can utilize them to keep our kids and all of these people healthy, as healthy as we can, it's not a solution. It's not a long-term solution that is sustainable for everybody and it's not an easy life and they deserve better.

James Valentine, JD, MHS (02:31:19):

Absolutely. Thank you, Melanie. Chris, I'll come back to you quickly, but then I'll come to you to bring you into this discussion as well.

Chris (02:31:29):

So just one other quick thing to add, which is just the worry about insurance. And I don't want this panel discussion to be about insurance, but as we'll turn from 17 to 18, all the insurance changed and he has to deal with that stuff. And my wife is a healthcare professional who deals with insurance companies every day, dealing with insurance companies with HCU has led to numerous phone calls where she leaves in tears and she navigates this on a day-to-day basis. So to think that now Will is going to be able to do that is terrifying because the impact of not getting things through properly, the costs, all of that, the impacts can be huge for his health, his wallet, all that stuff. So I just wanted to add that insurance. I'm sure everybody on the panel and in the audience can relate to that, but that's a big worry.

James Valentine, JD, MHS (02:32:32):

Those things we know are very real experiences that add to the burden of already living with the condition. We do recognize that that's a little bit outside of the scope for today's discussion, but do want to recognize that that's a very valid experience. Ben, on this topic of worries for the future, we'd love to get your thoughts and perspectives here.

Ben M. (02:32:57):

So just me personally, we have a daughter who's two and we have another one on the way, a boy on the way, and it is my biggest fear ... Sorry.

James Valentine, JD, MHS (02:33:16):

It's okay.

Ben M. (02:33:22):

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.

James Valentine, JD, MHS (02:33:45):

Right. Yeah. Thank you Ben, so much for raising that. And it is a very real concern and I know we've heard a little bit today about kind of brain fog, but even perhaps more severe cognitive impairment and a worry of losing your memories and your sense of self and all of that is very real. So I just want to really acknowledge you and thank you, Ben, for raising that. I do want to go to a phone caller that we have. We have Brie who's living in Missouri and is a caregiver and we'd like to see Brie, what you might have to share on some of the topics we've been exploring this morning on what it is to live with HCU or worries for the future. So Brie, are you with us?

Brie (02:34:41):

I am. Can you hear me?

James Valentine, JD, MHS (02:34:43):

We can. Welcome.

Brie (02:34:46):

Perfect. Yeah, I'm sitting here listening and I'm like, I echo everything. So we have two kids with homocystinuria. Jacob is 11 and Clara is nine. They were diagnosed when Clara was four. So it took about a year for diagnosis for her and then after her then Jacob. And our biggest struggles, and I'll touch on the base of the future too, but just like everybody else has said, it's like the diet's a pain and as much as you're trying to teach them in check and teach them and show them how to read labels and show them what a serving size looks like and try not to sound like a nag or get stressed out when you see that they're starving and you're like, "Well, these ..." For example, Jacob's 11 that he's growing so much, he just passed me up and he's constantly hungry and he's drinking his formula, reluctant ... And at this point he's embraced it because he knows, he's like, "It fills me up," but he hates it.

(02:35:55):

And that fatigue of having to drink something that they don't like is frustrating because you wish that there was a better option for them. And then just the fear is they're going to be leaving the house. They're going to need to be making these choices. And I'm trying to teach him that autonomy as they're young and still in our household in middle school. Now with him, I'm trying to give them some freedom and just kind of checking in when we get to see what his levels are, it's like how is that going for us? But it's a scary experiment because you're trying to give him that freedom and you know that from what you're hearing from him, he's staying within his level or staying underneath his protein intake or within his range. But it's like handing him that trust is really hard because he's 11 year old boy.

(02:36:49):

And with our daughter, she gets frustrated too. And with her, with both of them, it's memory, it's the mental fog. And then you're going, "Well, is that anger outburst and that memory issue and your forgetfulness, is that because of your levels being up right now or is that because you're just having an off day?" And it's hard to know because it's not exactly easy to drag them both to the lab. That's monthly or every six weeks that we're checking those levels. But it would be nice to be able to have an easier way of testing where those levels are so that you can see what the direct correlation is between their diet and their mood and their levels.

(02:37:39):

Where are we at on a day-to-day basis instead of once every six weeks? And for Clara, I'm terrified of when she wants to become a mom and she wants to have a baby. What does that look like for her? I know she's at higher risk for blood clots. I know that she's a higher risk for miscarriage, but I also know it's possible to carry the term with a healthy baby because that has happened several times I know in our community. But what does that look like for her? And I don't want her to be scared. I want her to go into that journey excited and just like any other potential mother would be. And I think I've kind of touched everything.

James Valentine, JD, MHS (02:38:22):

Yeah, no, I really appreciate you covering a number of the different topics we've talked about, including some of these worries and ability to kind of family plan is a big one and we haven't heard a lot about that so far, but that I'm really glad that you raised that with us, Brie. So thank you so much for sharing. I see we have another phone caller that I would like to speak with. We have Alex, who is from Brooklyn, who is living with HCU. And so Alex, I'd like to welcome you to the program. Are you with us?

Alex (02:39:05):

Yes, I'm here. Can you hear me?

James Valentine, JD, MHS (02:39:05):

We can. Welcome.

Alex (02:39:08):

Hi. So it's been very great discussion. I'm really liking what everybody is saying and it's all very true. I was diagnosed with HCU at newborn screening here in New York. I'm 36 years old. So basically I'm of the first generation living kind of controlled and all of that childhood psychology, psychological stuff, feeling isolated at pizza parties and just feeling different. Very, very true. I want to talk about just as you grow older, what that kind of transforms into and what that kind of looks like as you start to become an adult with a very rare disease that's fairly new.

(02:40:07):

It sometimes feels like there is no system in place because we are kind of writing history as we go. So a lot of the times I go to a pediatric place to get checkups, which is weird, makes you feel strange. There's no entrance into adulthood, but your kind of childhood anxieties transform into this, like how long am I going to live? What does the adult version of this 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. One thing I just want to say is that there's not that much research because there isn't that much of a pool because It's so rare. So how does this ... We're on cystadane, we're on

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. I was diagnosed with a very rare cancer recently.

(02:41:19):

I've been going through chemotherapy and radiation. Is this connected to HCU? We don't know. Can there be horrible dental problems in the longterm that could also contribute to cancers or any whole host of random other medical things? Yes. We don't know. We need more research. We need a way to find out what the levels of homocysteine and methionine in our blood kind of at all times easier, in an easier way. And we need a new form of treatment, really. What does that look like and where is the cure? That's what we're all waiting for. And this has been really great so far. I'm super grateful for it, but most of the things that we have, most of the treatments are about 30 years old. And what does the future look like for adults? Because it's all very geared towards children, and if you're controlled from birth, you're good, but then what happens? That's what we want to know.

James Valentine, JD, MHS (02:42:28):

Yeah. Well, Alex, I mean, you've made so many helpful points here, at least for me to understand as an adult, as you're thinking about your future and the uncertainty is what I'm really hearing from you loud and clear about so much of what is to come across so many of these different symptoms and health effects and what's related to HCU, what's not some of the things that we've heard as things that are related to HCU, whether or not that's likely to happen or what it might look like for you. And then of course the important unmet needs that exist to address this, including in adulthood. So I really appreciate you sharing that. I do want to check in. I know that we've gotten some written comments on this as well. So Danae, what are we hearing?

Danae Bartke (02:43:19):

Yeah, I know we will kind of go backwards here. Samantha also has written in. It was a Brie who had mentioned her daughter Clara. She worried about the future. Samantha from Ontario, also Canada had wrote in, "I worry about having children and how that could affect my body. I also worry about the potential for brittle bones." Definitely common themes for women in our community when they approach childbearing age. Judah, "My concern as I age is the lack of information and help to correct things as they happen." So echoing what Alex had to say too.

James Valentine, JD, MHS (02:44:01):

Yes.

Danae Bartke (02:44:02):

And Pam. Pam is one of the oldest patients in our community. She's from Nevada. "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. More research needs to be done on aging with HCU." So a lot of notes about aging with HCU.

James Valentine, JD, MHS (02:44:26):

Yes, and the great uncertainty that comes with that. So I want to just thank everybody. I want to thank our Zoom panel. You have been incredible at helping share throughout this whole session this morning, and then to everyone who's called in and written in, we've learned so much from you about what it is to

live with HCU. We're about to head into a break, but when we come back, we're really going to try to build on this topic and focus more in on current treatment approaches and what you are looking for from future treatments. So for now, we're going to sign off. We'll return at 1:00 PM Eastern on that topic of current and future treatments.

PART 5 OF 9 ENDS [02:55:04]

James Valentine, JD, MHS (03:12:13):

Good afternoon, and welcome back to the externally-led patient-focused drug development meeting on classical homocystinuria. I am James Valentine, your meeting moderator, and I'm here with my co-host, Danae Bartke, from HCU Network America, and we're pleased to have everyone join us as we build on the wonderful morning discussion that we had really understanding what it is to live with classical HCU as we now shift gears a bit to focus on current and future treatment approaches. It's my pleasure to turn it over to Danae to introduce our afternoon clinical speaker. Danae.

Danae Bartke (03:12:47):

Yeah, thanks, James. It's my pleasure to introduce our next speaker, Margie McGlynn. Margie is the HCU Network America co-founder and board president. She'll provide a treatment overview of classical homocystinuria, which will serve as a scientific foundation for this afternoon's discussion. Margie, over to you.

Margie McGlynn, R.Ph., Hon DSci (03:13:12):

Well, thank you for that introduction, Danae. I became involved in homocystinuria as a young child. In the mid-60s, I had two sisters diagnosed with classical HCU. One passed away at age 14 of a stroke, and one in age nine of a pulmonary embolism. I vowed that someday I'd do something about it. So after a long career in the pharmaceutical industry, I started a research fund in their honor, and I co-founded HCU Network America with Danae. So I'm now pleased to give you an update of how far the research pipeline has come, but I will first set up the current treatment overview.

(03:13:55):

So I'm going to take you through the current treatments for classical homocystinuria. First, about half of patients, as you heard this morning, have a mutation that's responsive to vitamin B-6 or pyridoxine, which is a co-factor. So those patients are obviously given that treatment because it can lead to a significant reduction in homocysteine levels. But the mainstay of treatment is really dietary approaches. Patients are prescribed a low protein or, in some cases, a low-methionine diet, and the intent there is to decrease levels of methionine so it cannot be converted to homocysteine, which I refer to as HCY and methionine is referred to as MET.

(03:14:43):

But these patients also then need to receive a methionine-free amino acid supplement to support their growth. About three-fourths of patients are also given betaine to donate a methyl group to convert homocysteine back to methionine. But many of these same patients are also on dietary approaches and or pyridoxine. Patients often get supplements of folic acid and vitamin B12. Both are important for the remethylation pathway. And if patients have low cystine levels, they will also receive supplements for that because that compound is not made if the CBS enzyme is defective. But despite all of these therapies, homocysteine is often not controlled.

(03:15:35):

In fact, the natural history study results were recently presented at the SSIEM meeting that showed that the average homocysteine level of patients in established metabolic centers was 112 micromoles per liter, and that's compared to the upper limit of normal of 15, and 45% of patients in this study had levels over 100 putting them at higher risk for thromboembolic events. So we need better treatment. In fact, there have been no new therapies introduced since 1996 when betaine was brought to the market. And since my sisters were diagnosed in 1964, betaine is the only treatment that has come onto the market, and none of these treatments are disease-modifying. And there are many issues with compliance and palatability, but there is hope for the future.

(03:16:36):

Let me now take you through the pipeline, but first, I'm going to take you back to the metabolic pathway that Dr. Chapman took you through this morning. I won't take you through it again, but I'm putting this up here because I'm going to come back and show you where all of the approaches that are in research affect this pathway. So there are five novel approaches being studied for classical homocystinuria, at least that we are aware of. The first is systemic enzyme replacement therapy, and this would replace the CBS enzyme so that you can degrade homocysteine. The second would be oral therapy that can prevent methionine absorption so it's not converted in the body to homocysteine.

(03:17:26):

The third approach would be gene therapy to deliver the DNA to liver cells so that they can produce the CBS enzyme, which then degrades homocysteine. The fourth approach, chaperone therapy, to stabilize the CBS enzyme to restore function, and lastly, to modify the metabolic pathway in a way that can help lower homocysteine levels. So let me now take you through each of these. But first, I'll show you the pathway and where each of these approaches are targeted at the pathway. So you can see here on the upper left preventing methionine absorption here, so it's now converted to homocysteine. You can see the metabolic pathway modification where Formate can also contribute to this conversion.

(03:18:19):

And then, these three approaches are all targeted at the CBS enzyme, either replacing it or enhancing its stability so that it can function better. So now, let me take you through enzyme replacement therapy. There is one product in development called Pegtibatinase, which is a pegylated version of the CBS enzyme. This was discovered by the late Jan Kraus at University of Colorado. This program has completed Phase 1/2A, and recent data presented on the highest dose cohort showed up to a 67% reduction in homocysteine levels. Travere, the company developing this therapy, has announced that they hope to initiate their Phase 3 trial in fourth quarter 2023.

(03:19:12):

The second approach, there are two products I'll talk about. Both are oral therapies to prevent the absorption of methionine so that you can convert methionine to homocysteine. The first is being developed by Synlogic, and it's an engineered probiotic bacteria that consumes methionine in the GI tract. This program has completed Phase 1, where they have achieved proof of mechanism in healthy volunteers. They do have modeling data that suggests it could lower plasma homocysteine by up to 58%, but obviously that has to be shown in patients with classical HCU. The company has not yet announced their timeline for beginning a Phase 2 trial.

(03:19:59):

The second product in this category is from Petri Bio, and it's a bacterially-derived methionase, an enzyme which degrades methionine in the gut so that it's not converted to homocysteine. This program has achieved preclinical proof of concept, where they showed a 35% reduction of homocysteine in a

mouse model. The next step would be IND-enabling studies so they can file the IND and begin the first phase of human testing. The next category, gene therapy, only has one active program, and that is an AAV vector that contains the DNA, which can then be transcribed to the CBS enzyme. It's a joint program of Warren Kruger and Ron Crystal.

(03:20:50):

This program has achieved preclinical proof of concept in a mouse model, and they are now determining the best path forward for IND-enabling studies and moving on to Phase 1, which will likely require an industry partner. The next category, chaperones, has one program currently active, although there have been other products in this category where data has been published in the past, preclinical data. The active program is at Newcastle University, Dr. Thomas McCorvie. This is at discovery stage, where there are screening for molecules that could bind to the CBS enzyme and restore its function.

(03:21:32):

The next step would be preclinical proof of concept. The last category, metabolic pathway modification. The only active program is Formate program being studied by Ken Maclean at the University of Colorado. Dr. Maclean has demonstrated preclinical proof of concept in a mouse model. First, showing that low-dose Formate can lower homocysteine levels and also showing that when you combine Formate with betaine, you can achieve near-normal levels of homocysteine in the mouse model. The next step would be IND-enabling studies and determining the appropriate dosage form. So this slide now shows you where each of these specific products affects the pathway.

(03:22:25):

In the upper left Synlogic and Petri Bio. Then you have Formate and then the enzyme replacement therapy, Pegtibatinase, gene therapy, chaperone therapy, all addressing the CBS enzyme. So the last topic I'll cover. What are the issues that arise in the development of new therapies for classical homocystinuria? And I did ask the researchers for all of the programs I discussed to provide input on this so this also reflects their thoughts. First, it is not yet confirmed what specific biochemical changes cause what specific clinical issues in patients. Certainly, it's been shown a correlation between overall homocysteine levels and thromboembolic effects, but what exactly is causing cognitive deficit, ophthalmic issues, et cetera, still is not confirmed.

(03:23:25):

Second, there could be an issue of availability of homocysteine for enzyme therapy to exert its effect because homocysteine forms dies sulfides, so therefore, the enzyme would not be able to clear it. On the other hand, the initial data we've seen would give us reason to believe that this may not be a problem. Probably the biggest problem is the difficulty of controlling diet during a clinical trial. While you can give patients instructions as to exactly what they should do, patient compliance with dietary therapy for HCU is very poor, and high variability could exist day to day. The next point. Some of the researchers, particularly at an early stage, are looking for greater clarity on what is the appropriate endpoint and the development path to get to market.

(03:24:17):

And if the endpoint is levels of homocysteine, what is the right target? Is it 100? Is it 50? And I'm sure as the earlier programs move through development, that will become clear. And the last issue is there may be enrollment challenges for clinical trials for classical HCU. Because of the small population versus other diseases and the proximity of many of the patients to metabolic clinics, this can be overcome by things like remote visits being allowed in clinical trials. So, in summary, the current treatment landscape leads to very poor compliance and lack of control of homocysteine.

(03:25:01):

And as you'll hear about from patients, there are many quality-of-life issues that result from this, but there is hope for the future. Many new treatments in development that could possibly offer greater control of homocysteine levels, potentially even allowing relaxation or no dietary treatment, which is the main goal of patients. They would love to be able to avoid the low-protein diet and the poor- tasting supplements that come along with that. So we are excited for the future, and I'm pleased to have been able to share this overview with you today. And now, I will turn it back to our moderators.

James Valentine, JD, MHS (03:25:51):

Thank you so much, Margie, for giving us that overview of both current treatments as well as the research pipeline. It was a perfect setup to launch us into our afternoon discussion, where we'll be asking those living with classical HCU and their caregivers to share their experiences with treatments and their views on what they would like to see from future treatments. To get us thinking about this topic and the types of things we'd like for you to share this afternoon, I'm going to go through some of the discussion questions we have for you. So in this afternoon, we're going to be addressing first your currently available treatments.

(03:26:28):

And when we use this term treatment, we mean this in the broadest sense. We don't just mean drugs and medications or even surgeries and medical procedures, but really the broader range of things that you do in your life to try to make living with HCU a little bit easier. This, of course, includes diet, but even more holistic approaches that maybe you take, and even lifestyle modifications. Again, anything that you do to try to help manage and live with HCU and make life with the symptoms of HCU a little bit easier. So as we think about that wide range of different things that we're kind of referring to in shorthand as treatments, we want to know what are those things that you're currently doing to try to manage your loved one's HCU symptoms.

(03:27:19):

We want to then get your assessment of how well those treatments are treating the most significant symptoms and health effects of HCU, and in addition to understanding how well things are working, knowing that whether or not they are working, they might come with some significant downsides. And so we'd like to know what those are for you or your loved one's current treatments and how those downsides affect daily life, whether that's side effects, the burden of keeping up with a particular treatment regimen, whatever those downsides may be for you or your loved one. Once we've spent some time covering the range of different current treatment approaches will shift gears towards the end of the session, and we're going to ask you to think about short of a complete cure.

(03:28:01):

Yes, we all want that complete cure for HCU, but in the meantime, we want to know from you what specific things would you be looking for in an ideal future treatment for your or your loved one's HCU. Another way to think about this is if a new product were to come along, what factors would be important to you in deciding whether to participate in a new research trial for that investigational product or if it were to get approved? What factors would be important to you to get us thinking about these topics and to share some of their experiences? It's my pleasure to introduce our afternoon panel. We have Janet, Kelly, Judah, Breun, and Jessica. Janet, why don't you take it away?

Janet S. (03:28:47):

My name is Janet, and I live in Central California. I am 31 years old, and I live with classical homocystinuria. I want to take you to the back to the year 2002. I was 10 years old, sitting with my parents in a tiny room at the Children's Hospital. Two doctors came into the room, who later turned out to be my dietician and genetics doctor. Hearing the word homocystinuria for the first time sounded like a voodoo spell. My parents looked just as confused as I did and had a million questions like, "Is it a terminal disease, and will I be able to live a full life?"

(03:29:24):

After getting some news from my doctors, my parents seemed more at ease but still worried. I had no clue what was going on. I couldn't even wrap my head around what was being said. I just knew that my life was going to completely change. As soon as we got home, my parents tried to make as many changes to my diet as they could, and I fought them every single step of the way. I couldn't understand why I was the only one in the family that had to change the way I ate. Remember, I was just 10 years old with no understanding of what homocystinuria was.

PART 6 OF 9 ENDS [03:30:04]

Janet S. (03:30:01):

... with no understanding of what homocystinuria was. To me, it was just a word that branded me as an outsider. I felt like I was put on display for not only my family, but my classmates as well. In the cafeteria, other kids would look at my lunch and would ask me why I was eating that instead of what they were having, and I could never explain it because I myself didn't know why I couldn't have a normal lunch. I didn't know what was going on within my body. I wanted nothing more than to have the foods that I have always eaten. The embarrassment was too much for me. I was tired of being looked at differently because of my food. I felt like I was being punished without knowing why. I was struggling so hard to stay within the guidelines of my diet. My levels were not going down at every doctor's visit and I would get scolded.

(03:31:05):

I vividly remember my doctor telling me by the age of five, a child develops most of their taste buds. I was 10 when I was diagnosed. She said I was pretty much set up for failure. Had I been diagnosed earlier, I would have not had struggled as much as I did. I still struggle heavily with the diet. The low-protein diet is incredibly stressful and difficult to maintain. I recently have tried to regain control of my diet, but ended up becoming even more anxious and scared to eat. I lost 10 pounds in a month in the process and felt miserable and isolated. I obsess over every morsel put to my mouth. The diet had consumed me entirely, having to constantly count my protein intake and check the nutrition facts on every box of food.

(03:31:55):

In any other situation where you were obsessing over nutrition labels and terrified of putting food in your mouth, they would consider it an eating disorder, but somehow this is the standard that we are prescribed and it's considered healthy. At the end of the month, I realized I couldn't do it anymore. I wanted to be happy, even if it cost me, I ended up paying the price. I developed a deep vein thrombosis in my left hand. As a result, I lost 60% of my arm function.

(03:32:29):

Being a first generation Mexican American and trying to navigate this disease took an extreme toll on me. Since the diagnose 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.

(03:32:58):

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. For Latinos, food and social gatherings are a core part of our culture. So when I stopped eating due to my diet, everyone was concerned and scared for my health. I felt like an outsider in my own family. While everyone was enjoying their Bistec con arroz, I was stuck eating salads.

(03:33:28):

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 celebration again.

Kelly W. (03:33:48):

Hello, my name is Kelly. I have classical homocystinuria and I was diagnosed at age five. In the musical Les Mis, there's a song called Empty Chairs at Empty Tables. The opening line state, "There's a grief that can't be spoken. There's a pain that goes on and on, empty chairs at empty tables." When I was in the '90s, I was one of two individuals caught late in the state of Michigan. There were no metabolic clinics, no social media groups or videos we could use to understand the complicated diet or make taking the medication tolerable. There were however teams of doctors and dieticians doing their best to navigate the issues with us and our caregivers.

(03:34:40):

I remember the medical formula I took from age six to 17 when pre-made medical formula in pouches became available. That was 2007, give or take a year. I vividly remember the smell of vomit, the taste and texture of the gritty, grainy, thick, pasty medical formula. I remember my mother trying to cover the taste by mixing it with salsa or chocolate, which resulted in me vomiting it back up. I remember running and hiding to avoid taking it daily. I remember the frustration of not understanding why all the foods I loved were now off limits. My parents remember me pushing food around my plate because I hated the medical food that was safe because it was difficult to cook and tasted like paper mache.

(03:35:41):

I remember teachers becoming an integral part of me gaining weight by bribing me with lunches out and Polly Pocket toys. I remember eating out and understanding that most of the fast food and restaurant menus being off limits because it was too high in protein, which meant it wasn't safe to eat. I remember when I was 16 years old, a statistic from the 1980s stating that undiagnosed patients will die before reaching 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, et cetera.

(03:36:34):

I was born in 1989 and since newborn screening in Michigan didn't screen for HCU until 2004, this unknowingly led me to eating foods that were poisonous to me for the first nine years of my diagnosis, which led to a change in my 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.

(03:37:18):

I often think about who I would've been, how differently my life would be had I been caught at birth and understood the diet from day one instead of struggling for decades. I wonder what complications and the severity would be in comparison. I wonder if I would be able to work or drive. I wonder if I would've been able to graduate college. I wonder if I would be able to safely have children without a major medical concern of clotting. I wonder what hospitalizations wouldn't have occurred because things hadn't reached near fatal endpoints. I wonder if my homocysteine levels would've been consistently lowered instead of higher despite best efforts. I wonder, would I have enough energy to be more physically active? I wonder.

(03:38:18):

The mental health stuff gets pushed aside because 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 from enduring everything I've had to.

(03:38:49):

I don't have a dream treatment. I gave up on wishing for stuff like that, like a once a day pill when I was seven years old. My inner child would probably still say, "I want a pill I can take once or twice a day and that's it." Liquids are often too acidic and give me heartburn, have crystals that get stuck in my throat, or just plain taste awful. As future treatments are being researched, I would like to see more testing sites throughout the country. Clinical trials are too far away and I am on a fixed income. 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.

Judah (03:39:51):

My name is Judah. I am 59 years old with B6 responsive classic homocystinuria. I was diagnosed in 1972 in Israel at the age of seven after a fall from a plastic blowup chair. I did not respond like a normal child, which would have been to simply get up. My parents took me to the hospital to be evaluated and it was discovered that I had HCU. I have had intensive HCU treatments throughout my life.

(03:40:32):

In the fall of 1972, I was sent to the U.S. to see a specialist. He confirmed that indeed I had classical homocystinuria. I was put on special protein diet during my stay. In addition, I was put on vitamin B6. The diet was very strict in the hospital. It was extremely difficult as a young child to survive to such a diet. Many times I did not care for the food and did not eat it.

(03:41:02):

When I went back to Israel, I was still on a low-protein diet, but I had other things to choose from. As an adult, I expanded my options by experimenting with cooking things that I liked and that had little to no protein. Over many years, I have been able to adjust to more vegetarian diet that mirrors a protein base. Still very hard, but more tolerable. The amount of protein is very limited. I count my proteins every meal, so I do not go over my allotment. After I return to Israel, my hair went from blonde to black as seen by my pictures. My motor coordination drastically improved and I was able to ride a gear bike.

(03:41:54):

I always had struggles. I had to work harder than my peers to accomplish my schoolwork and college courses. I graduated from college. 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. These days I am on vitamin B6, B12, folic acid and cytidine, as well as a low-protein diet. My protein allowance is enough, so I don't need medical formula. The current options for HCU patients simply do not work well for me. Cytidine, 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.

(03:43:14):

In addition to HCU, I have many diseases that overlap with each other, such as diabetes and rheumatoid arthritis, all have their diet restrictions, which makes eating even more complicated. It is important to look at all these complications when addressing alternative options for HCU patients. This makes things extremely difficult for me to balance with various diet restrictions. I struggle daily to balance all these issues. I take a huge amount of insulin every day with monitoring 24/7, 365. I take orals and shots for RA. I would love to be treated with one process for all my medical issues.

(03:44:06):

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 HCU and find better options for them. As far as trials, my whole life of over five decades has been a trial. Over the years and with great difficulties, I have found a balance on my own that has stabilized my medical conditions. My doctors are always amazed. At this time, I would not risk losing this balance. I cannot risk or jeopardize my health for new clinical trials. Therefore, I would not participate in them. 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.

Breun (03:45:10):

Hi, my name is Breun and I'm the parent of three beautiful children, two of which have homocystinuria. Our kids were diagnosed at the ages of four and six, and 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 and a bout of pancreatitis, we were told that she had classical homocystinuria. We then tested our other children and discovered that our oldest, Jacob, six at the time, also had HCU. He had had a lot of developmental delays and regressions over the years and his diagnosis helped gain understanding as to what his body had been enduring and how HCU had been affecting him throughout his young life.

(03:46:09):

Once they were diagnosed with homocystinuria, we began a low-protein diet immediately. They were given B12 injections, folic acid, and high doses of vitamin B6. The B12 injections were prescribed to be administered at home intramuscularly. We had a close friend of the family that was willing to come over and administer these shots for us. 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.

(03:46:59):

They then began to take Cystadane, sorry, excuse me. They then began to take Cystadane and the long journey of discovering a formula that they would actually drink began. As you may or may not be aware, the formula choices they have are limited and not very palatable. Five years later, at the ages of nine and 11, they still struggle to consistently drink the required amount of formula. They both complain of

upset stomach and the fatigue of needing to drink these shakes. They now complain of upset stomach after they take their Cystadane as well, which is frustrating because that is absolutely required for them to take to keep their HCU levels in line.

(03:47:50):

Maintaining the low-protein diet has challenges of its own, but the biggest challenge is social gatherings, parties, and just anytime where they're out and trying to be free with friends. We have certainly tried to set them up for success and educate them. We've showed them how to read labels, but imagine yourself at the ages of nine and 11 reading labels on snacks so that you understand the serving size and how much protein is in any given item. That being said, we have tried to set them up for success and we'll continue to educate them, but at some point they will consistently be making choices independently as they get older.

(03:48:37):

The things that worry me that are coming down the pipeline are adhering to their low-protein diet, consuming their formula, Cystadane, and the required vitamins. 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.

(03:49:09):

In addition, even when kids are doing perfect with their diet, medications and formula, the unpredictability of their HCU levels is beyond frustrating. There is no rhyme to reason to what can make their levels skyrocket at times. With no easy way to test at home, it is hard to understand what directly affects their levels. Other concerns that come to mind are specifically for my daughter. When she decides to become a mother, what does that look like for her? Though I do have the knowledge that bearing children to term under close monitoring from a physician as possible, I know she's at greater risk for complications and miscarriages. I would love for her to be able to have a pregnancy journey without these risks and complications.

(03:50:07):

When I think about putting my kids in clinical trials, there are many factors to consider. Ease of administering medications, transparency of potential long-term risk factors, the autonomy of themselves being able to decide whether a monthly in-clinic injection or infusion is right for them, or if more frequent in-home injections make sense. I have found that even though they are children, they do appreciate the power to be able to make their own decisions when the option is given. Development of medications as well as home blood tests to check HCU levels to be able to eliminate the requirement of a low-protein diet and the need for formula would offer so much freedom for my children. I would love to see the lowering of risk factors for serious complications and offer a safer and healthier future. Thank you.

Jessica K. (03:51:06):

My name is Jessica. I live in Michigan. I am 32 years old and 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. Over the years, I've done lots of physical and occupational therapy trying to manage these issues. At five years old, I had to change my diet to two grams of protein a day, which was devastating for a little girl who was trying to make sense of the new word homocystinuria for her. My current treatment for HCU is a low-protein diet of 10 to 15 grams protein per day and medical formula supplement that I take in pill

form and B6. I am unable to take betaine, which is commonly prescribed to patients with HCU because I am allergic to it.

(03:52:02):

At five years old, managing homocystinuria is complicated by the fact that I had been diagnosed with two other serious medical conditions, diabetes as well as MCAS or Mast Cell Activation Syndrome. Both conditions have made compliance with my current treatment incredibly complicated. For one, I have tried many different medical formulas, but due to my diagnosis of MCAS, which causes me to have very severe reaction or adverse reactions to certain food strengths and medicine, I developed severe allergies to some of them. After drinking them, I'd vomit and break out in hives. This, of course, made an impossible task for me to drink the amount of formula that I needed to provide my body with the additional protein and nutrients that I wasn't able to get through foods. I now take my medical formula and tablet form, but even these give me severe acid reflux.

(03:53:04):

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. 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. As I have mentioned, I'm supposed to stick to no more than 15 grams of protein a day to keep my homocysteine levels down. While this is a big enough challenge in itself, having diabetes, sticking to a low-protein diet is an impossible task. 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. How am I supposed to maintain a healthy weight and keep my diabetes in check when my treatment for HCU consists of so many carbs and calories?

(03:54:09):

It's an everyday struggle and there are days when it all proves to be too much and I find myself falling short of compliance. I know this puts me at risk for serious complications like blood clot strokes and additional eye issues and among other things, and this sends me into my already anxiety into high gear. I live in fear of something bad happening to me, and this is not a fun way to live. I feel like I'm in a no-win situation.

(03:54:42):

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 200. I feel like a new person, more energy, less fatigue, and much more able to manage my anxiety.

(03:55:02):

At a certain point, 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. My dream treatment would be a once a month injection that lowers homocysteine levels. I also wish there was a way to monitor homocysteine levels from home, similar to the way diabetes monitor their sugar. I feel that being able to monitor my levels from home on a more consistent basis would allow me greater control of my disorder. My hope is one day to live a life where I'm constantly not living in the unknown or the fear of what might happen if my homocysteine levels aren't better controlled.

James Valentine, JD, MHS (03:56:06):

Thank you, Jessica, and to all of our panelists for helping us get this discussion started around current treatments for classical HCU and importantly, your thoughts about what you would be looking for from future treatments, both that we're going to address now as we enter the second part of our day where we get to expand and bring all of you and our live audience into the discussion.

(03:56:29):

If you have treatment experiences that you'd like to share, we'd like to invite you to call in and bring your voices into the discussion. You can call in now and throughout this afternoon session by dialing in at +1 703-844-3231. Again, that number is +1 703-844-3231. If you call in, our operator will speak with you and get you into the queue so we can bring you into the discussion. But to get us all thinking about these topics initially on current treatment approaches, we're going to start out with a few polling questions.

(03:57:07):

So if you've just joined us this afternoon, you can participate in polling by pulling out your phone and opening a web browser or by opening a new tab on the web browser on your computer, and going to www.PollEV.com/HCUPFDD. Again, that's www.PollEV.com/ HCUPFDD. You can keep this website open for the remainder of the afternoon, and as we go to different polling questions, it will automatically appear there.

(03:57:42):

So to get us started this afternoon, we here want to ask you about certain medications and medical treatments, and we really are focusing on medical treatments. We're going to address in another polling question some more holistic approaches for symptom management. But here, what medications and treatments have you or your loved one used either currently or previously to treat symptoms associated with classical HCU, and you can select all that apply. The options are A, a low-protein or methionine diet. B, betaine or Cystadane. C, pyridoxine or B6. D, folate, folic acid or folinic acid or B9. E, cobalamin or B12. F, blood thinners. G, antihypertensive medication. H, pain medication. I, spinal surgery. J, antidepressants or antianxiety medication. K, some other medication or medical treatment that you or your loved one has used either currently or in the past to treat the symptoms associated with classical HCU or L, if you or your loved one have not used any medications or medical treatments. As a reminder, this is our first polling question of the afternoon, and we have the option for people to select multiple different response options. And so the percentages we're seeing are a percentage of total responses, not the percentage of people selecting any one response. So you can think of these bars as a little bit of a relative ranking. We'll give everyone just a few moments. Again, we want to make sure you get into the system, have the ability to follow along and answer the questions throughout the afternoon.

(03:59:35):

As it stands, it's looking like the diet is the top choice, perhaps not surprising with the feedback and input we've heard throughout the day so far, but we see Cystadane as the next highest option and B9 after that, followed by B6 and perhaps still in that top tier are blood thinners. We do see B12, others, which we'd be very interested to hear what those are. And really every single other one here is being used by some members of the audience with antihypertensive being maybe the one that's least used by our audience and no one is reporting that they have not used medications or medical treatments.

(04:00:21):

If we can go to our second polling question, so here we want to broaden it and we do want to think about your treatment regimens beyond just traditional medications and treatments, but other maybe

management strategies or options that you've tried to help make living life with classical HCU a little bit easier. So here you can select all that apply. The options include A, physical and occupational therapy. B, acupuncture. C, aquatherapy. D, CBD. E, counseling or psychotherapy. F, frequent homocysteine levels being checked, so monitoring. G, some other approach that's not listed here, or H, if you're not currently doing anything to help manage symptoms. We'll give everyone a few moments here to let us know beyond medications and treatments, what else are you or your loved one doing to help treat and manage living life a little easier with classical HCU.

(04:01:25):

It looks like at least as it stands, while additional results are trickling in here, counseling and psychotherapy is top of the list along with monitoring and PT and OT. After that, maybe as a second tier, we're seeing CBD and other things being listed, and then we do have some experience in our audience with acupuncture and aquatherapy, and then we are having a small number of people report that they're currently not doing anything to help manage symptoms. So we have one more polling question for you here. Here we want you to think about everything that you clicked off over the last two questions, and we want you to think and assess how well does that treatment regimen treat the most significant symptoms of your classical HCU or your loved one's condition. The options are A, not at all. B, very little. C, somewhat. D, to a great extent, or E, not applicable because you're not using anything. As you're making your selections, I want you to kind of think what made me pick this? It's a very personal kind of subjective answer here. And so we want to think about what are those most significant symptoms of HCU that you were expecting or hoping your treatment regimen to address, and how do you rate if you're one of the about 50% of people that said it helps somewhat, what did that mean to you? Where was it helping? What were the gaps and where it's not helping? For those of you that are saying, about a little under a third of you saying that it helps to a great extent, what things is it really helping with? Whichever aspects of the treatment regimen you're thinking of. And for those who are saying very little, similarly, where are those gaps? What is not being managed except for a little bit. We are not having anyone report that it's not helping at all and no one is saying that they've not used anything.

(04:03:33):

So I want to thank you all for participating in that first set of polling questions. If you would like to call in and share some of your experiences with those different treatment approaches that we've just covered in these polling questions, I invite you to do so by calling in at +1 703-844-3231. Again, one more time that's +1 703-844-3231.

(04:03:57):

I'd like to kick things off and welcome to the program our Zoom panel, some of your peers who will be joining us and sharing some of their experiences throughout the afternoon here. And so there's a lot to unpack with current treatment approaches. And so I think where we want to start today is maybe focusing on the things that have been the most helpful, and we saw from polling that there are a number of people who are saying... No one said that it's not helping at all, the different treatment approaches. So we kind of want to unpack that piece of it a little bit. So maybe Ruth, we can start with you. As you're reflecting on, it can be anything that falls under this broad umbrella of what we're calling treatments, what maybe has been the most helpful from your perspective?

Ruth (04:04:44):

Hi, my name is Ruth. I'm in Cincinnati, Ohio and I have four children and my third daughter, Josie, was late diagnosed at the age of six. So in thinking about her treatments, I know that the Cystadane is very effective and we base that I think-

(04:05:03):

I think it's easier for late diagnosed patients to see that because you see the huge drop in a very short amount of time from when she started the medication. Now that was in conjunction with a low protein diet, but I do feel that the cystadane is extremely helpful. And as far as treatment, I mean it's really inconvenient, but the low protein diet is a necessity and it's very hard. It limits your ability to travel, to go out, to eat, for her to play on sports teams, to spend the night at people's houses, to participate in school activities. You name it, it limits it. But its effectiveness cannot be overstated.

PART 7 OF 9 ENDS [04:05:04]

James Valentine, JD, MHS (04:05:48):

Yeah. Ruth, so you mentioned that it was very obviously effective when treatment and diet were started in conjunction and you were able to see that in her levels. Was there any kind of signs to you in terms of symptoms that maybe she was experiencing? Did that correspond with any changes that you were able to observe or was it all just from the monitoring that you were able to tell it was effective?

Ruth (04:06:18):

No, you're absolutely correct. In addition to the blood work, which showed an obvious numeric change, she also as a toddler, she had been very clumsy. And we would always say, "Oh, Josie's so kooky." She would say the oddest things. She was very uncoordinated, was in pt, OT, couldn't write to save her life. And I recall a physician, her geneticist, telling me that her levels of homocysteine were equivalent to a typical person not sleeping for four days. So, if you can imagine what you'd feel like after staying up for four days, that's how she slogged through her first six years of life.

James Valentine, JD, MHS (04:06:58):

Wow.

Ruth (04:06:58):

Within months of starting the cystadene and a low protein diet, she was a new child. It was like the fog had been lifted and she made more sense in what she said. She has developed a much better coordination now. It's taken years. And I don't believe she'll ever be at the level of her older siblings who do not have homocystinuria, and as far as coordination and athletic ability. But she has come such a long way. And academically there's been a huge improvement as well. And I think part of that is an improvement in her anxiety and just this overall brain fog. So, it's absolutely, you can see it not just clinically, but you can see it as a mother as well.

James Valentine, JD, MHS (04:07:40):

And just out of curiosity, as you're thinking back, whereas you kind of talked about a number of things that some have taken years to almost counteract some of where she was prior to treatment, is there an example that maybe you can share of one of the first things you noticed and how long did it take for you to notice that change that you could actually see?

Ruth (04:08:05):

I would say first would be the most obvious was just academically.

James Valentine, JD, MHS (04:08:10):

Oh, okay.

Gabbi L. (04:08:10):

In preschool, she really struggled with pretty much anything, letters, numbers, vowel sounds, rhyming, you name it. And so she started in kindergarten. It was January of her kindergarten years when we started on all this medication because they had thought she had had some type of learning disability. Well, it turns out it was just this. And so flash forward like a year, and she was reading and doing math and more engaged, and it was night and day, and that includes socially. It was almost like she had had like her handcuffs were taken off and she would talk to people, and engage with you more, and have eye contact with you. So, I would say though it was most obvious in a school setting.

James Valentine, JD, MHS (04:08:59):

Okay. That's very helpful. Thank you so much, Ruth, for sharing that.

Ruth (04:09:02):

You're welcome.

James Valentine, JD, MHS (04:09:03):

Barbara, I'd like to bring you in this conversation as well as we're kind of first focusing on the things that maybe have been most helpful or in some way made life a little bit easier. So would love to hear what you think.

Barbara Z. (04:09:15):

Right. I'm Barbara. My son is Alex. He called in this morning if everyone was on. He's now 36 and he was picked up on newborn screening. So, he's been treated since birth. I mean, he's on a low protein diet. He has been very restricted. 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 was. It always has been. 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 levels still fluctuated.

(04:10:18):

When he got into middle school, he obviously went off his diet somewhat because he was free to eat whatever he wanted, and he ate whatever he wanted. I think he ate pizza and bologna sandwiches. I'm not sure, but his levels were very, very high. And so we put him on cystadane. So, that was helpful at the time. It was really helpful for him. I think it decreased his anxiety about his condition, because had a lot of anxiety about his condition, even from a young age.

(04:10:52):

So the cystadane, although it decreases the homocysteine, it raises the methionine. And so that was always a concern. What does methionine do to you when your methionine levels are a hundred? But he needed it, so he was on it. And he took the formula. He's been on formula for his whole life. When he

was a kid, it was impossible to get it in. 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. And he was on this formula that we had to force bottle feed him, which after we got the whole thing down, he would vomit. And then we'd have to chase him around as a toddler to get it in. And then eventually he's picked it all up on his own and he did well.

James Valentine, JD, MHS (04:11:57):

Right. And Barbara, as you think about he's been on kind of this treatment regimen since birth. You mentioned that there still was fluctuations in his levels and there was periods of time where obviously compliance with all of that was harder, especially as he got older. How would you describe, I guess, any kind of breakthrough in terms of some of the symptoms or health effects that he's experienced despite being on this diet since birth? Are there any gaps or things that maybe have broken through in terms of symptoms that you could share?

Barbara Z. (04:12:40):

Well, as a kid, he was very hyper, very, very hyper. He had, I'm sure, ADHD, but was not treated. So, that was, I think, definitely related probably to his diet and not being controlled. He got much more organized as he got older and he took care of his own needs as far as his formula, et cetera.

(04:13:12):

The one thing that comes to mind now is that he's developed another rare cancer. It's very rare and it's adenoid cystic carcinoma. And there's two things about it. One is that 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. So, when your levels are really high diet, yeah, he's not even eating. So, cystadane is not going to really lower them quickly. So there's really very, very little as far as treatment options for these very high levels of homocysteine. That's one part of it. The other part of it is that 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. So, those things are in my mind.

James Valentine, JD, MHS (04:14:20):

Sure. Thank you so much for sharing that, Barbara. Mark, to bring you in on this as well, reflecting on the range of kind of broadly speaking treatment options that are available, is there anything you'd like to share that maybe has been helpful or useful for you all?

Mark L. (04:14:41):

Yeah, thanks. First of all, thank you for having me here. It's been actually quite an emotional day. I am Mark Lewis. I'm the proud father of three. My son Benjamin is 32, but he was diagnosed through newborn screening with classical homocystinuria. And then my youngest, Gabrielle, you met her earlier, she was actually diagnosed prior to birth. And both of our children have been on diet and managed through their years. But in terms of therapy, those things that are available to us, we've talked about it all day. There are oral supplements. 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.

(04:15:47):

These are the therapies available to us. And when you're handed a disease, a disorder, you have to use the tools that are available to you. Excuse me. And so that's what we've done over the years. That hasn't evolved much. We call it betaine, but the advent of betaine has been quite helpful. We sort of call it the backstop to this disease because we can essentially use it to try to mitigate and offset some of those highs and lows. But it's then all about the formula and all the things that go with the challenges of that. We've seen that industry evolve a little bit over the years. We've certainly seen our kids grow a lot over the years from adolescents, toddler, high school, college, and each of those phases have different challenges in life.

(04:16:36):

We've talked a lot about compliance right her., but what about the flu or the other medical events that you have that you can ingest your formula? And we're operating blind always, or mostly. When your child is sick, you don't know what their homocysteine levels are. You're concerned about them elevating to a point of a dangerous level. And 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. We talked about teenagers and doing what teenagers do. We didn't talk about puberty and all the things that kind of go with that. So, it's an ebb and flow, a push and pull, a give and take to try to really manage through what is required to keep, in our case, our children healthy.

James Valentine, JD, MHS (04:17:30):

Right. And I think you've given us a good lay of the landscape of a lot of what's been helpful, but also the difficulty of navigating those things with all of these different aspects, real aspects, of life from puberty to illness and everything in between. I'm just curious then when you were looking at that polling question that was asking to rate how well this worked, what was your rating to give me a sense of where you're putting this in totality?

Mark L. (04:18:03):

Yeah, easy for me to say, because I've lived with the disease, but I don't have it, but I've witnessed it for the past 32 years. I say somewhat because you try. In every instance, you try to support, in our case, our children. My son is off living his life now and doing quite well. But just making sure that his business trip, he's going to be able to do what he's got to do. I give it a somewhat because there's trade-offs. There's no silver bullet here, and everything you do is almost to a day-to-day type of decision. And the best you can do is somewhat. And my wife and I have embraced the fact that there's going to be these situations that you do the best you can to plan ahead. You call the parent. You call the dining hall and you just somewhat your way through this disease.

James Valentine, JD, MHS (04:19:00):

Wow. Really well said, Mark. Thank you so much. I do see that we've had some written comments come in on this topic of treatment successes. So Danae, what are we seeing?

Danae Bartke (04:19:12):

Yeah. We have a comment here from Samantha from Ontario, Canada. She says, "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." And then we have Melanie from Vancouver,

Canada, who was with us earlier today, and she had shared, "We manage his HCU with a strict diet protocol, betaine and formula among many other supplements to keep him healthy. Unfortunately, even doing these things peripherally doesn't always keep his levels in a safe zone. So, a little bit of a win, but there's always the uncertainty."

James Valentine, JD, MHS (04:20:14):

Absolutely. Well, thank you everyone who's been writing, and I want to encourage you to keep sending in those comments. We'll continue to read them throughout the program. But I do want to take a moment to broaden the discussion a bit to include other experiences with the treatments that we currently have available. And so if there's something that comes to mind of a treatment experience that maybe the treatment, it's unclear how it's working, I think we're hearing some of that, or maybe it clearly didn't work, or it's come with some important downside, topics that we've already started to explore, but I kind of want to formally bring them into the fold and get us also all thinking about that through a polling question. So, if you can pull out your phones, go to that browser or open that browser tab on your computer, go to www.PollEV.com/HCUPFDD.

(04:21:08):

Here we want to know what are the biggest drawbacks of your loved one's current treatment approaches? And you can select up to the top three. The options are here, are A, not very effective at treating the target symptom, B, not very effective at achieving target homocysteine levels, C, it only treats some, but not all of the symptoms, D, high cost or copay and not covered by insurance, E, limited availability or accessibility, F, the side effects, G, the route of the administration, which is the way that it's taken or administered, H, that it requires too much effort and or time commitment, I, some other drawback that you view as one of the biggest drawbacks of you or your loved one's current treatment approaches, or J, if this is not applicable because you or your loved one is not using any treatments. Again, select the top three that you report as the biggest drawbacks of current treatment approaches.

(04:22:07):

And as you're doing so, think about some of the why. How has this affected your life, these different drawbacks? I told you these would be harder as the day kind of went on to answer and think through as we're asking you to kind of narrow things down here to the top three. As it stands, and I would say pretty consistent with what we've been hearing, but we want to make sure that we're not missing anything here, which is it requires too much effort and or time commitment to keep up with the treatment regimen. If you have a personal take on that, something to share and add to the discussion, we definitely want to hear from you. We're seeing that high cost or insurance coverage is a top issue. Route of administration. Definitely want to hear more about that. I think maybe it-

Danae Bartke (04:23:00):

I think that could also tie in, sorry to interrupt, but I think that also can tie in, looking at some of the comments people have had about the taste, the taste and the grittiness of it, so.

James Valentine, JD, MHS (04:23:17):

Yes. Anything about the way that you have to take things right now and whether it's the taste of it, the volume and amount, anything like that, absolutely. We want to hear about that. Really, we're seeing everything here in some number of people's top three. Another top one is not effective at achieving target homocysteine levels. So, the things that maybe are rising to the top are things we've heard a bit about. Side effects though certainly would want to hear a little bit more about that. And I'll just point

out that no one again has reported that they're not using any treatments. So we want to explore some of these biggest drawbacks.

(04:24:05):

And if you would like to share some of your experiences, we welcome you to call in at 1-703-844-3231. Again, that phone number is 1-703-844-3231. And of course you can also use that comment box under the live stream to submit comments on this topic. To get us kicked off on this though, I'd like to go to our Zoom panel and maybe, Landon, we can start with you. As you're kind of thinking about the range of different treatment approaches that exist, is there something that stands out that maybe whether or not it's been helpful has some important drawback that you'd like to share?

Landon S. (04:24:46):

Hi. My name is Landon Skeens. I'm from West Virginia and I have had homocystinuria or been diagnosed with homocystinuria for almost 13 years now. 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. Also, the number of medications that we have to take. For me personally, I take over a hundred pills a day, so traveling with that is a big downside.

James Valentine, JD, MHS (04:25:32):

Can you tell us, maybe just to give us a sense of what all you're taking? That's a lot of pills to have to take in a day. Can you maybe mention what those are?

Landon S. (04:25:44):

So, I currently take 80 HCU pills. I pet 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.

James Valentine, JD, MHS (04:26:11):

Yeah, no, it's a lot. So, obviously you mentioned that it's hard to travel, keep all of that on you. Do you happen to experience any side effects from any of those medications or is that not something really that you have?

Landon S. (04:26:34):

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.

James Valentine, JD, MHS (04:26:43):

And are there things that make compliance easier or harder for you? Anything that comes to mind there?

Landon S. (04:26:52):

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.

James Valentine, JD, MHS (04:27:09):

And so it's like certain times of day when you're around peers that you need to take medications. Sometimes it's harder to maybe you skip or delay taking. Is that what it is?

Landon S. (04:27:23):

Definitely.

James Valentine, JD, MHS (04:27:25):

Okay. Well, Landon, this has been really an important downside that I think we haven't heard a lot about, which is just the pure volume of medication and other kind of treatments. So, thank you for sharing that. Danielle, would like to bring you in on this topic as we're still exploring current treatment approaches. Have there been things that have helped, maybe haven't helped, and any important downsides that have come with those?

Danielle B. (04:27:54):

Sure. My name is Danielle. I live in Winter Park, Florida. I was diagnosed with newborn screening for classic homocystinuria. The one thing that I would say is that there are many treatments, but all of these treatments are palliative care. And I guess it's a single sentence, but it does speak volumes. So, as we have described all of these things, most of the treatments that we do go through, it's just because the benefit outweighs the risk. So, with that said, I personally don't find any of these treatments as true treatments. They're just maintenance. And I think that's a big reason why we're here today.

James Valentine, JD, MHS (04:28:37):

Yeah. So, I kind of want to dig into your personal exploration of these current treatments. Hear you loud and clear that their kind of symptom management, palliative, not really treating the underlying condition. But at the same time you are mentioning that they have some effectiveness, at least at knowing that that's kind of the goal of those treatments. What kind of risks or downsides of these treatments have been maybe the biggest or most difficult to manage and deal with? And then can you maybe explain why you continue with those treatments, even though as you said, it's the benefits are kind of outweighing the risks. I just want to see what that looks like and how you think through that kind of decision-making personally.

Danielle B. (04:29:32):

Sure. So the first thing that I would say that I'm apprehensive about is the lack of information sharing of side effects. We have spoken extensively about the beauty of betaine, but it was many years before the downside of having high methionine surface to a public level where we could all come together as a community and openly speak about it. Because when things like this, when treatments first come to market, everybody's excited because it's just one step closer to the ideal goal. But then after everybody's starting to take it, you realize, "Hey, is it really outweighing it? Is it really preventing it? Is it stabilizing it?"

(04:30:10):

And I think that all comes down to your personal belief on where you are and your life journey on, if you're going to continue with that care. And that's why I said at the end, all of this is truly just palliative care. Because I decide to continue with that on my journey because it's fitting for my life in this moment. Now, if I was an extreme geriatric senior, I probably wouldn't because now I have more years behind me than in front of me. And if there was something that is truly meeting that marker, truly

promoting health and its benefits, I wouldn't have to ever have that deciding conversation at any stage of my life.

James Valentine, JD, MHS (04:30:46):

So, you're saying currently you're staying with that treatment despite the kind of risk or maybe even uncertainty that has surfaced from experience with use of it for you today, that's something that you still see as valuable?

Danielle B. (04:31:06):

100% just because of age-based. Like I said, if I was 80, 90, absolutely not. To me, there would be no need. If I lived 85 to 90 years under this treatment, it was successful. But the thing is, it's not a treatment because it's not providing a long-term source of success, and it's only providing a stabilized maintenance.

James Valentine, JD, MHS (04:31:26):

Sure.

Danielle B. (04:31:26):

So, I think we say it's a treatment, but it really is falling under a different realm. And yes, palliative care has treatments, but I think this is kind of where it lives not as a treatment of success and stability.

James Valentine, JD, MHS (04:31:39):

Sure. Well, thank you, Danielle, for helping us understand that a little bit more. I do see that we have a phone caller that I'd like to bring into the conversation. We have Dave from Vancouver, and shout out to all of our Canadian participants. Between written comments and callers, great to see those of you outside of the US participating actively. So, Dave is a caregiver, a grandfather in fact, of his grandson living with HCU. So, Dave, we'd like to welcome you into the program. Are you with us?

Dave (04:32:12):

Yes, I am. Thank you.

James Valentine, JD, MHS (04:32:14):

Yeah, so we'd love to hear. We're on kind of exploring different current treatment approaches, kind of the pros and cons that you or your loved ones have personally experienced. What would you like to share on this topic?

Dave (04:32:29):

Well, it's really heart-wrenching when you see things going on and Mason having to take the formulas and the pills and everything as a little boy. And if the taste could be better, I've heard that mentioned so many times, it would be so much better and easier for young people. It's hard for everybody. But one of the really side effects is, and it's been mentioned lightly a few times, is the effect on people's teeth. And dental care and dental health is very important to everybody's overall health period. So, seeing the side effect of the extra dental work that's required to maintain good teeth for a young person, for any person actually. But young people are still developing. Their baby teeth are coming out. Their other teeth are

forming. And it's a scary thought that one of the side effects of this is going to be possible real repercussions being your overall health because your teeth are starting to fail.

James Valentine, JD, MHS (04:33:36):

And has the preventative dental care helped Mason or has that not been fully successful for him?

Dave (04:33:48):

It's successful in the fact that you make many additional appointments and go and you get your teeth clean, polished, and the appearance looks better. But overall, with that kind of effect, the long-term, which we haven't seen yet, only been a few years, can be a lot more drastic. And that's a fear that we have.

James Valentine, JD, MHS (04:34:10):

Wow. Well, Dave, this is something we haven't talked a lot about today, so I'm glad that you kind of addressed it so directly, and shared your grandson's kind of experiences trying to help mitigate this risk. So, thank you so much for calling in. I see we have another caller. We have Kelly from Michigan who's living with classical HCU that wants to share some of her experiences with current treatments. So Kelly, I'd like to welcome you to the program. Are you with us?

Kelly (04:34:40):

Yes, I am. Thank you for having me.

James Valentine, JD, MHS (04:34:43):

Yeah, so would love to hear any kind of current treatment experience. What is top of mind for you?

Kelly (04:34:54):

So, I was in one of the videos leading up to this discussion. I know that I talked a little bit about some of the challenges that I had as a child. But the real challenge as an adult is trying to make taking your medication when you have to work, work for you. Because unfortunately, it's not something that you can do without a bunch of questions that are going to come around. And I know that a lot of times people will ask, "Well, why don't you just take it at this time or at that time?" And it's like, that's great in theory until you are working and you're trying to do your job, but you are starving and you're hungry.

(04:35:45):

And we already know that it's hard for kids to focus in school if they're hungry. That is very well-researched. But how do you do your job when all you can tell is like, "I'm hungry, I'm having brain fog. I'm having a hard time focusing on the task at hand." So, it can be very disruptive, unfortunately, to a workplace environment. And if you're dealing with the side effects of some of those treatments, like heartburn for example, you're going to end up having even more questions. 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.

(04:36:44):

And the other point I would like to make is that 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. The closest clinical trial site to me is in Indianapolis. And if I had to go there twice a week, well then it would not be possible. That's a 12 hour bus ride one way. So, at that point, you'd be better off moving to Indianapolis than actually taking the bus. So, 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.

James Valentine, JD, MHS (04:37:45):

Yeah. Well first, thank you for commenting on participating in trials, and in particular how visual impairment makes travel, and participating in trials difficult on top of everything else, that already makes that a big burden, a big ask. I did want to follow up on something you were commenting on a little earlier, which was impact on ability to work. And you kind of mentioned it's a bit about difficulty of taking treatments, but also being hungry and that kind of leading to maybe brain fog as well as just that feeling of hunger. I guess, is there an example you can share with us? Is that a daily thing that you struggle with? And can you give us an example of maybe how that in the real world impacted some aspect of your workday?

Kelly (04:38:48):

So, I can give you one very good example, and it was from a previous employment situation that I was in. So, this would've been about 10 years ago. I no longer work currently, as my disabilities have gotten to a point where holding a normal 9:00 to 5:00 job, it's just not possible.

(04:39:10):

But when I was trying to work, I worked at a local midwest grocery store chain. I'm not going to say which one, just for obvious reasons. But I was working as a cashier. I was on the lane. It was very hot. And I kept telling my supervisors, "Guys, I need to go take my medicine. I'm feeling really hot, really nauseous, and I know myself well enough to know when my body's trying to tell me something." They kept saying, "Oh, don't worry, the person ahead of you, they're coming. They're going to be back. They're going to be back." And this went on for like five minutes and eventually I looked at the cashier in the lane next to me and I told him, "You need to call a code." And next thing I know, I had slid myself down the carousel of grocery bags that would go in a circle, you know?

(04:40:02):

... grocery bags that would go in a circle, you know? And they came over and they're like, "Oh my God, are you okay?" And I'm like, "Yeah, I'm fine." They're like, "What can we do for you?" I'm like, "Go get my medicine, it's in the refrigerator in the break room." They're like, "Are you okay? Can we do anything?" I'm like, "No. Just go get that. Seriously."

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James Valentine, JD, MHS (04:40:25):

Yeah, yeah.

Kelly (04:40:26):

They're sitting there arguing with me and it's like, I've told you what you can do. They're like, "Next time Kelly says she needs a break, she gets a break." I'm like, "That's right, sunshine. You get the gold star."

James Valentine, JD, MHS (04:40:36):

Yeah.

Kelly (04:40:37):

So in a normal workplace environment, employers need to understand that this is in many ways along the same lines as somebody who has blood sugar issues needing to have their insulin.

James Valentine, JD, MHS (04:40:49):

Right. Yep, yep. No, that makes a lot of sense. And thank you for being willing to share that example with us, Kelly. I do see we also have a lot of comments that have come in on this topic of treatment downsides. So Danae, can you share some of those?

Danae Bartke (04:41:05):

Yes. Okay. Sorry, here. I'm going to circle back. I think it was Kelly who mentioned the acid reflux, and I think Jessica did in her video as well. But Samantha from Ontario, she's done a fantastic job with all her comments today, but she shared, "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."

(04:41:48):

Continuing with the trend of formula, we have Brooklyn from Montreal, Canada. "The downsides of current treatment is it acts as an anchor that weighs me down. I cannot be spontaneous. When traveling, it's advised all my medication be packed on my carryon. However, if I pack a hundred percent of my medication in my carryon, I'll have no space for anything else I need." And then shifting gears here, Judah from Maryland writes, "Due to the removal of my lenses, I need to wear thick glasses. In those days," So he's speaking of as a child, sorry, "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."

James Valentine, JD, MHS (04:42:38):

Wow. Yeah, so a number of different kind of downsides that we just heard from there. I know there were a lot of comments that have come in reiterating a lot of the anxieties and burdens related to the diet as well, but glad to have some of those highlighted there. So I do want to make sure that we spend some time shifting gears a little bit to the future treatments. Of course, if you have existing treatment experiences to share, we still welcome those. But I do want to go to our next and last polling question for the day to get us also thinking about what you all are looking for from future treatments. And so you can go to www.PollEV.com/HCUPFDD one last time here today to share your thoughts.

(04:43:31):

And here, again, knowing that we all would want a complete cure for HCU, we do want your perspectives on specific things that you would be looking for in an ideal future treatment. And you can select up to three. The options here are A, eliminate the need for a special diet. B, eliminate the need for medical formula. C, prevent disease progression. D, prevent blood clots. E, reduce pain. Or F, something else that's not listed here that you would look for from a future treatment that represents a top three most important thing to you.

(04:44:10):

And again, as always, as you're making your selections, we encourage you to think about what is driving your selections here and what you would view as a success here. What would this mean to you if a treatment were to be available that could help with one of these things? So we'll give everyone a few moments here to get in their responses. I think we can probably confidently say that the top pick here today is going to be eliminating the need for special diet. It has been a large focus of both the morning and afternoon discussions so far. And close behind that being the elimination of the need for medical formula and preventing disease progression. So on that preventing disease progression, I want to know what that means to you. What would it mean to prevent disease progression? What symptoms or health effects, or how do you kind of define that for yourself or your loved one?

(04:45:10):

We see after that preventing blood clots, and then some people have selected other and reducing pain. So we do want to hear about those things as well. So to get us started on this topic, well, first if you would like to call in on this final topic, you certainly can do so. We'd be happy to have you at 1703-844-3231. Again, that's 1703-844-3231. It will be our last opportunity of the day to have your voice heard by phone, but I do want to check in with our panel here. And Mark, maybe we can start with you. If you were to define what would be an important treatment goal from a next future treatment, what would be top of your list?

Mark L. (04:45:59):

Yeah, I'm going to put my parent hat on. But I have to go with the acute event. The thing that we worried most about and still do and still will is the risk of a medical event such as a clot, such as the things we heard this morning about some terrible situations. So as a parent, that's our number one. Long-term progression is certainly a concern. We've heard about that by some of the other community here. What ifs. My children were diagnosed at birth, they have hopefully a long life ahead of them. I like how Danielle put it where we're thinking about palliation and prevention. But what's that look like? Because even though you do as good as you can, there's still the complications. My children might kick me under the table for not picking eliminate a formula and food, but those are clearly absolutely important too for us to just be humans.

James Valentine, JD, MHS (04:47:03):

Absolutely. Thank you, Mark. Ruth, we will go around here and bring in each of you on Zoom. So I would like to ask you the same question. In terms of short of that cure, what would be top of the list or something that's really important for you all?

Ruth (04:47:22):

I echo what Mark says, the acute events. You can think about those all day long if you want to as a parent or as a patient, and it's a terrifying thing to think about. So while I echo those, I would also say just having more freedom in my daughter's life. I think that's what she would say is she would ask... She 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.

James Valentine, JD, MHS (04:47:56):

Absolutely. Thank you, Ruth. Just going around here, Barbara, your thoughts on what would represent a meaningful future treatment outcome?

Barbara Z. (04:48:07):

Well, of course no medical complications, that's number one. But just to have a day where you're not consumed by doing all these things, formula, everything, it's just constant and it would be nice to free them up. Also, some kind of monitoring system where they know what they're doing, like diabetes. Some kind of natural to your body like insulin is to diabetics would be nice. Betaine is, but it's in such high doses that it really isn't natural anymore. So something like that. And also a monitoring system like diabetes has so that the patients can know where they stand.

James Valentine, JD, MHS (04:48:58):

Yeah, no, that's a great idea. Thank you so much, Barbara. Coming around here. Danielle, I know you mentioned a little bit about treatment goals, but as you're thinking about this, what's top of your list? What would you say?

Danielle B. (04:49:14):

I'm going to agree with Mark as a patient though, and say we can put the diet and formula to the side. We can keep it, it's fine. But with keeping it, I do hope that things for the future come such as ease of use, ease of consumption, and ease of traveling. Because earlier this morning we heard a lot of things that could be scary for first time travelers and first time explorers as you're navigating the world on your journey. And then personally, another thing that I would really appreciate is a home monitoring system because as we know, most of the things that we are giving are natural forms that are now turning into toxic levels of natural forms, as Barbara was beginning to hint at. I think a way to monitor that. So if this is going to be our now and forevermore, having something that could monitor that experience definitely would reduce a lot of the things that were expressed this morning in regards to apprehension, anxiety, and things of the unknown.

James Valentine, JD, MHS (04:50:09):

Sure, yeah. Thank you for both of those things. And Landon, to kind of close out here on the Zoom panel. Last but certainly not least, very interested in what you are looking for from future treatments.

Landon S. (04:50:25):

Definitely a lesser risk of blood clots and stroke and all of those not so fun things, but also definitely a home monitoring system to measure those homocysteine levels and not be in the dark every day.

James Valentine, JD, MHS (04:50:39):

Yeah, absolutely. Well, I just want to thank all of you on Zoom for all of your thoughtful contributions throughout this afternoon's panel. We couldn't have done it without you. And we're going to turn to some phone callers here and written comments, but before we do that, I just wanted to make sure that we thanked you for everything that you've contributed this afternoon. So thank you.

Danae Bartke (04:51:03):

Thank you.

James Valentine, JD, MHS (04:51:03):

So I do want to get us to the phones here. I see that we have a caller, we have Alex who we spoke with earlier from Brooklyn who's living with HCU, who wants to comment on this final topic of some kind of

goals or improvements he'd like to see in future treatments. So Alex, I'd like to welcome you to the program. Are you with us?

Alex (04:51:28):

Yeah, I'm here.

James Valentine, JD, MHS (04:51:29):

Welcome back.

Alex (04:51:31):

So yes, just to sort of... Hi, it's good to be back. Just to sort of reiterate, the home testing for homocysteine and methionine levels would be amazing. A future treatment that looks something more than what we've had for the past 30 years, some form of injections or something to lower that is always ideal. What I wanted to talk to you about really quick was the formula and the food. So this is something I've been kind of harping on for a while, but I think it's very important. I think a lot of the formulas, with the exception of one company that makes an unflavored formula, just have an excess of sugar.

James Valentine, JD, MHS (04:52:21):

Okay.

Alex (04:52:21):

And an excess of just processed ingredients in the food. And I think that could lead to so many other health problems for especially kids. I mean, it could be a cause of some of these... Tooth decay and all of this stuff. I think that there needs to be a real switch in the pharmaceutical approach to this in terms of creating healthy treatments. I don't understand why there's so much processed food and sugar going into the formula. And I think this is, like Danielle said, a bandaid. This isn't really a treatment.

James Valentine, JD, MHS (04:53:07):

Right.

Alex (04:53:07):

But while it's there and while we have this, we can do something about that pretty quickly.

James Valentine, JD, MHS (04:53:14):

Right.

Alex (04:53:15):

And I would love to see that be improved. I do kind of a health tonic with my unflavored formula and it's changed my life. So that's it. I know we're running out of time, but I just wanted to say, the sugary formula and things like that.

James Valentine, JD, MHS (04:53:34):

No, it's important to hear. It's kind of as you said, while formula is a reality, it's important to know what your preferences are to make that something that is healthier for you and more acceptable to you. So

thank you so much for sharing. We have one more caller that we'll bring into the conversation here. We have Liz, who also is calling back from this morning's session from South Carolina. So Liz, I'd like to welcome you into this discussion of future treatments. Are you with us?

Liz (04:54:10):

Yeah, I'm here. So, hi again. As I mentioned, my seven-year-old little guy Elliot, his current treatment consists of vitamin B6, B12, folic acid, betaine, and of course the low protein diet. He's on 11 grams of protein a day, so it is incredibly restrictive. Just to illustrate how restrictive it is, just to tell a little anecdote on Elliot. Last winter, it snowed in South Carolina, which is something that does not happen often, and Elliot and his big brother wanted to make snow cream. So Elliot's watching the snow come down and he looks at me and says, "Mom, does snow have protein?"

James Valentine, JD, MHS (04:54:45):

Aww.

Liz (04:54:46):

And I said, "No, Elliot, it doesn't." And he got the biggest smile on his face. He said, "Good, then I can eat all the snow I want." And as his mom, my heart dropped because something as normal and simple and human as eating, it makes me sad that it always has to be at the forefront of his mind.

James Valentine, JD, MHS (04:55:05):

Yeah.

Liz (04:55:05):

So that being said, looking towards the future, we would love a treatment that would maybe be orally ingested that would allow for greater daily protein allotment, but we'd also absolutely consider an injection that regulates enzyme activity that would allow for that more normal diet and also no longer hopefully the need to drink the medical formula.

James Valentine, JD, MHS (04:55:28):

Right.

Liz (04:55:29):

With that being said, 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.

James Valentine, JD, MHS (04:55:55):

Absolutely. Well, I appreciate you calling back in here, Liz, and sharing some, well, first for sharing that anecdote, while cute, also very hard and your heart does sink hearing that, but also your perspectives on future treatments. To kind of close this discussion out, I do want to make sure we get to some of these written comments we've gotten again, and quite a few that have come in here. And so Danae, can you share some of those with us?

Danae Bartke (04:56:26):

Yeah, there are so many comments here. It is really hard to choose from. Melanie from Canada again writes, "Short of a complete cure, we would love to see treatments that'll allow less or no formula and the ability to eat more protein on a daily basis." We have Valerie from Arizona, "Approving a new form of a treatment will drastically change the quality of life for me and others who live with HCU. It will take away the anxiety, stress, and unknowns of when a complication could occur in one's life, releasing the fear for not only the individual with HCU, but the families and future generations who are diagnosed with this rare condition."

(04:57:11):

We have Chris who reiterates the need for a monitor. "So a call earlier this morning mentioned that blood levels of her kid are only taken every four to six weeks, and his son are taken every three to six 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 and change the course of treatment if levels are high." And Jamila wrote in from Florida, excuse me, "Access to a diverse array of medical treatments is not solely related to relaxing diet and lifestyle modifications. It is a matter of 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." I'm going to add just one more here.

James Valentine, JD, MHS (04:58:11):

Please do.

Danae Bartke (04:58:13):

Ben from Georgia shared, "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."

James Valentine, JD, MHS (04:58:41):

Wow. Yeah. Well, thank you everyone who's been writing in. Those were, I think we heard definitely some consistent themes, but also a variety of additional kind of preferences from this community on what they're looking for from future treatments. And it was so important that we heard all of those because it really helps drug developers and FDA as they consider clinical trial design and ultimately weigh the benefits and the risks of potential new products that are coming through the pipeline. So now we're at the end of the part of the program where we're seeking your input. We probably could have spent many more hours talking through all of these issues, but I think today has been tremendous and we have come such a long way in understanding what is important to this community in terms of the needs, the serious and urgent needs for new treatments.

(04:59:41):

As your meeting moderator, I just want to thank you so much for being so willing to share what really are very personal parts of your lives and your loved one's lives, allowing us to dig into those and really paint a picture of what it is to live with classical HCU. In many ways, I think we've really pulled back the curtain on what that means, and if we didn't do that, we wouldn't know how to help and what to try to

address. And so as the person who's been asking this of you throughout the day, I just want to thank you from the bottom of my heart for being so willing to do all of that.

(05:00:20):

So at this point we're going to move to some summary remarks. It is an impossible task to do a full summary of today's meeting, but these remarks, we have the perfect person to share some thoughts and reflections on what we've heard today, and that's my friend and colleague, Larry Bauer. To introduce Larry, he's a nurse by background. Started his career at the Cleveland Clinic, went to NIH where he researched rare diseases as a clinical research nurse for 17 years, and then moved to the FDA where he co-founded the Rare Diseases Program where he worked as a regulatory scientist for 10 years. And in private practice has been a key partner in helping plan this particular meeting. So Larry, without further ado, over to you.

Larry Bauer, RN, MA (05:01:14):

Thanks so much, James. It's been an incredible day and I will try to summarize it. And I do apologize in advance for any of the fine points that I've missed, but know that this meeting will be available online for any of you to go back to watch. So our meeting today was opened by Danae Bartke, who's the co-founder and executive director of HCU Network America and also someone living with HCU. This was followed with a presentation from Dr. Mehul Desai from the FDA's Division of Rare Diseases and Medical Genetics in CDER. Dr. Desai shared that the PFDD meetings, they're valuable to the FDA to learn from the experts, caregivers of people living with HCU, and people with HCU. And that what they learned will help facilitate treatment development, design clinical trials, and review new drugs for HCU.

(05:02:08):

Dr. Desai's talk was followed by a clinical overview presented by Dr. Kimberly Chapman, who's an attending physician in genetics and metabolism at Children's National and an associate professor of pediatrics and integrated systems biology at George Washington University. She shared with us that HCU is a rare disease affecting the processing of the amino acid methionine, leading to harmful buildup of homocysteine. It affects multiple body systems. There are CNS effects like mental health and intellectual disability, eye problems with severe myopia and ectopia lentis, skeletal issues including scoliosis, excessive height, osteoporosis, as well as vascular issues including thromboembolism. It affects about one in 900,000 people worldwide, with some parts of the world having much higher prevalence rates like Qatar. Newborn screening is there, but it misses up to 50% of the B6 responsive patients, and elevated total homocysteine levels is diagnostic for the condition.

(05:03:12):

Then we moved into hearing from our first panel that was focused on the morning topic of symptoms and the impacts of those symptoms on people's lives. We heard from Gabby, who's 21 years of age and was diagnosed via amniocentesis so very early. She said attending social events brought a lot of anxiety because of food issues. She developed scoliosis at age eight and also had osteoporosis, which limited her participation in sports. She had to have two scoliosis surgeries because of an allergy to the original metal implants. She often feels isolated and worries about her future and says HCU affects every second of every day.

(05:03:52):

Next we heard from Krista who's 38 and was diagnosed at three months of age. She had digestive issues from the formula. She struggled in school with ADHD and learning disabilities and had issues with executive functioning. When she was age 30, she had a blood clot in the lower left heart ventricle resulting from high homocysteine levels. Then this was followed up later by a massive stroke and

survived due to early emergency response. She worries about the future and possible future thromboembolic events.

(05:04:23):

Then we heard from Pam, who's 66 years old and was diagnosed at age 54, even though she had eye problems that started at age two. She was misdiagnosed with Marfan syndrome, which is fairly common. She has retinal detachments in both eyes. She suffered a stroke at age 46 and her right carotid artery is still a hundred percent blocked. She was hospitalized twice with blood clots in her lungs. She's terrified about losing her vision and struggles with depth perception, especially when trying to navigate being out in public.

(05:04:56):

Next we heard from Brooklyn who's 37 and says managing HCU is mentally and physically exhausting. She struggled early on with educational difficulties and learning activities of daily living. She had scoliosis at age 11. She said that brain fog impacts her life the most, and we heard this again and again. Word recall and anxiety are also impactful. And she says she cannot find a job. And as she ages, she requires more care.

(05:05:26):

And lastly, in the morning we heard from Anna who's mom to her daughter Juana, who was diagnosed at age six after having extreme myopia and movement in her lenses. Juana has limited activity and avoids sports due to the fragility of her eyes. She also has some behavioral issues and learning difficulties which have made school and her social life challenging. Her mom worries about what level of independence she will be able to reach as she gets older.

(05:05:53):

So some of the themes from the morning were that HCU is a chronic illness with broad life impacts. Its multisystem, affecting bones, including scoliosis and osteoporosis. There are multiple eye issues and development of venous emboli, which is the most life-threatening aspect of HCU. People also describe the effects of brain fog, learning disabilities, anxiety, depression, and almost everyone shared that the life impacts occur daily and many of them had worries for their future.

(05:06:24):

After our lunch break, we came back and we heard a treatment overview. So the whole afternoon focused on treatments and hopes for the future. The overview was provided by Margie McGlynn, who's a co-founder and board president for HCU Network America, as well as sister to two affected siblings. Current treatment options have poor compliance and often do not control homocysteine adequately. There are a variety of new treatments in development, including an enzyme replacement therapy. And the main goal of patients, which we heard even right up to the very end of the meeting, is to avoid the low protein diet and poor tasting supplements.

(05:07:05):

Our afternoon panel started out with Janet, who's 31, who was diagnosed at age 10. She felt like an outsider at school because of the dietary restrictions and felt like she was being punished. At one point she went off the diet to try and enjoy her life, but she developed a deep vein thrombosis in her hand, which resulted in 60% loss of her arm function. She longs for a day when she does not have to take 33 plus pills a day and to eat the diet. Kelly was diagnosed at age five. The diet and medical foods have been extremely challenging, resulting in vomiting at times. She's had years of therapy to help with anxiety, depression, and PTSD. She'd like to have a pill she could take once or twice a day and clinical trials that would be close to her home.

(05:07:48):

Next, we heard from Judah, who's age 59 with B6 responsive classical HCU. He eats a vegetarian diet low in protein, which he finds more tolerable. Takes B6, B12, folic acid, and Cystadane. His treatments cause stomach upset with unpleasant tastes and smells. And he would not want to risk his health to participate in a clinical trial.

(05:08:11):

Then we heard from Breun who has two children with HCU diagnosed at ages four and six. Clara began struggling with detached lenses at age four. They've been on a low protein diet and take B12 injections, folic acid, and high doses of B6. They struggled to drink the required amount of formula and complain of upset stomach after drinking them. The restricted diet profoundly impacts their social lives. And when considering clinical trial participation, they would need to consider the ease of medication administration, potential long-term risks, and they said the kids would need to weigh in on the decision to participate or not.

(05:08:52):

And lastly, we heard from Jessica, who's 32 and was diagnosed at age five. She had a lot of PT and OT to manage her symptoms. She is unable to take betaine because of an allergy. Her HCU is complicated by also having diabetes and mast cell activation syndrome. So trying to only eat 15 grams of protein a day and also limit carbs for the diabetes is incredibly challenging. She's in the open-label part of a clinical trial and has improved homocysteine levels and has more energy and better managed anxiety since being in the trial. She wishes there was a way to monitor homocysteine levels at home. That was another theme that came up repeatedly. People would like to be able to measure their homocysteine level the same way that diabetics measure blood sugar.

(05:09:44):

So in the afternoon we heard about the tremendous unmet medical needs in the HCU community with few FDA approved products. Strict diet control is extremely challenging and does not guarantee that homocysteine levels will be kept in range. Many talked about needing surgical interventions for eye issues and scoliosis, and thromboembolic events require emergency intervention and blood thinning medications. Many patients expressed willingness to participate in research, especially hoping for new treatments to eliminate the need for the special diet and excessive numbers of pills. So on that note, I'd like to say thank you and turn the meeting back over to Danae in the studio.

Danae Bartke (05:10:31):

Thank you so much, Larry, for that wonderful summary. Thank you Dr. Desai, Dr. Chapman, and Margie for taking the time out of their busy schedules to speak at the meeting today. We appreciate all that you do for the classical HCU community. Thank you to the FDA staff who tuned in today. We would also like to thank Will, Lou Allen, Ethan Gabor, Lena Mirzug, and Karen Jackler from the FDA's patient-focused drug development staff who guided us through this process. Thank you also to James Valentine and Larry Bauer from Hyman, Phelps & McNamara, whose assistance of planning and moderating today's meeting has been invaluable. Thank you to the Dudley Digital Works media team for the production planning and all the behind scenes work that they did today. A big thanks to my fellow HCU Network America Board members and volunteers, including Kristin Rapp, Margie McGlynn, and Danielle Benton. A special thanks to Liz Carter who was at my side every step of the way in preparing this meeting.

(05:11:38):

But a huge thanks goes out to you, the entire HCU community, from patients, caregivers, family members, and friends. Thank you for honestly sharing the lived experience of HCU. This meeting could not have been as impactful or enlightening without each of you. In the coming weeks, we'll compile all the information from today, including the polling data and comments into a voice of the patient report. This will be available on our website. Today's program will be available on demand immediately at the conclusion of this meeting. The form to submit comments for the report is open for another 30 days, so please submit additional comments for the voice of the patient report. We know that today has been emotional, so we have planned a future online meeting exclusively for patients, caregivers, and their friends. There we will gather to share our thoughts and feelings about this meeting. This will take place on November 5th at 4:00 PM eastern. A zoom link will be provided on our website.

(05:12:47):

Today's meeting will have a lasting impact on the future of HCU research and medical product development. So once again, to the entire HCU community, thank you for making your voice heard today.

PART 9 OF 9 ENDS [05:14:05]