Additional Patient Comments

Externally Led Patient-Focused Drug Development Meeting for Galactosemia

The Galactosemia meeting held on September 1, 2023 was hosted by the Galactosemia Foundation (GF) and the National Organization for Rare Disorders (NORD). The meeting represented an important opportunity for the galactosidase community to share patient, family and caregiver perspectives on the challenges and unmeet treatment needs of those who live with galactosidase every day. The patient and caregiver perspectives gathered from the meeting are summarized in an accompanying *Voice of the Patient* report.

To ensure that as many voices as possible were heard, patients and caregivers were invited to submit additional testimonies during and after the September 1 Galactosemia EL-PFDD meeting. The submitted comments are presented in this document, and respondents are identified by their first name only. Comments were edited only slightly (if at all) for spelling and punctuation. Selected quotes are included in the main body of the *Voice of the Patient* report.

Brian, Caregiver of a 29-year-old patient

My name is Brian Mannix. I only learned about this meeting after it had already started, so I apologize for being unprepared.

My son Chris was born with classic galactosemia 29 years ago. Our early experience was terrible. His heel stick test was positive, but the lab never reported the result to anyone. He was in and out of hospitals for five weeks until finally we got the correct diagnosis. At that point he was severely jaundiced, nearly comatose, and blind in both eyes due to severe cataracts and a retinal hemorrhage. An MRI showed serious damage to his brain. A genetic test showed that he had two zero-activity alleles, which matched those of the two siblings whose clinical outcome was the worst to be found in the medical literature.

This was all very discouraging. We did manage to save the vision in one of his eyes, although it still has a cataract; the other eye was a total loss. At two years old, Chris had made no progress learning to talk, and would only screech. Everyone we saw gave him a dismal prognosis.

But his story turned out much better than we expected. Although he couldn't speak, it seemed to me that he followed the conversations at the dinner table, between me, his mom, and his older brother. When we tried sign language (ASL), he picked it up immediately, because he already had a large receptive vocabulary; we simply had to tell him what a sign was, and he would get it. Within a few weeks he could sign well enough to tell me all about his day. And that opened up something in his brain, so that he began to say words along with signing, and within a few months stopped signing altogether and just talked.

Today, Chris is a fully functioning (and driving) adult, and has a job as the stage manager for a local Shakespeare Opera Company. If an actor is sick for a performance, Chris will step in as an understudy. He is articulate and clever, although he remains self-conscious about his blind eye and generally is socially withdrawn. But we are astonished about how well he has done, with no treatment other than dietary control.

My explanation for this is that there are secondary metabolic pathways for dealing with galactose, and their activity is highly variable across patients. In some individuals the level of activity is too low even to deal with endogenously produced galactose, and the disease will tend to be progressive. In others, like Chris, the secondary pathways are more active and a careful diet will keep galactose levels within the range they can deal with.

So my recommendation to other parents is not to despair, but emphasize a careful diet. And my recommendation to researchers, NIH, and FDA, is to try to characterize those secondary pathways and look for ways to enhance them. As long as the diet is well controlled, it may not take much to reverse the course of this disease.

For example, with the success of the mRNA covid vaccines (a form of human gene therapy), it should now be possible to test that platform for treating inborn errors of metabolism and other genetic diseases. After covid, most of the research dollars will be directed towards infections like influenza and towards immunotherapy for cancer. But, now that gene therapy is generally accepted as safe and effective, NORD should be an advocate for giving attention to diseases like galactosemia.

Kayla, Caregiver of a six-year-old patient

My name is Kayla Kloska. I am the mother to the sweetest and full of life 6-year-old named Kaden. In 2016, We received Kaden's Classic Galactosemia diagnosis late at night on day four of his life and it was one of the scariest moments of my husband's and my life. No one we knew had heard of this disease and our doctors weren't too familiar with it either. Learning about this disease and the side effects that can develop from the toxin build up such as apraxia, tremors, cognitive delays, cataracts, processing problems, etc. has always weighed heavily on our minds. We asked if the restricted diet will prevent these side effects from happening and were told that there will always be a build up of toxin in his body due to the endogenous production of galactose, regardless of maintaining the restricted diet. Being told that your child will probably have the above-mentioned side effects is a devastating feeling for a parent. I have prayed every night since he was diagnosed that a treatment would be developed in his lifetime in order to give him the best quality of life he can have.

Although Kaden is a healthy little boy with an appetite for knowledge, things do not come easy to him. Apraxia of speech has been his most consistent and most severe disability over the course of his life. I taught him sign language at 1 years old to ease the sense of frustration from knowing what he wanted to say but not knowing how to say it while we started the Apraxia

Diagnosis journey. He has worked hard in speech therapy for the past four years. His fine motor/ poor finger strength was a rough go about when he started pre-school at age three and could not hold the crayons properly to color. He also struggled with using utensils. Unfortunately, where we live Occupational Therapists are hard to come by so we did a small amount of therapy with a licensed OT but, most of his OT therapy was done by me watching YouTube videos and then teaching him. During his Pre-Kindergarten year, he struggled with processing the information he was learning at the same rate of speed as his peers. We do constant repetition of information at home after hours and now he is closer in performance toward his peers. He still has to work a little harder to retain the information.

Kaden is confident in most of his skills but is starting to notice that he is slightly behind his peers. Some days it doesn't bother him and some days it does. He will become self-conscious and shut down when it is taking him longer to understand new or previously learned concepts. He is noticing that his writing and picture drawings don't always look as accurate as his peers and always struggles when someone doesn't understand him clearly. As his mother, it is extremely hard to watch him be so down on himself and lose confidence when he works so hard to master skills and shrink the gap between his peers.

As Kaden has gotten older, he is maturing and understanding that some things will be difficult for him. We teach him that although he will always be successful, he will have to work harder than the rest of his peers to achieve that success and that it is ok if that pathway looks differently than others' pathways to success. Recently, he has struggled with not being able to consume the same foods as his friends at school, parties, and other social settings. It is hard to watch your child cry about not being able to have the pizza or cupcake. I try my best to always make sure there is a dairy free alternative for Kaden anywhere we go because I do not want him to feel left out. Sometimes I am not able to provide this and feel like I have let him down when he is disappointed that he has to have something different or go without. We never want him to feel this way, but it does happen. We have been teaching him that it is ok to not consume the same things as others, but it is a hard concept for a 6-year-old to grasp.

My biggest fear for Kaden as he gets older is that he regresses in the skills he has worked so hard to master and loses his self-confidence/full of life personality. Kaden is the sweetest boy with a kind heart. He loves social settings and meeting new people. I am afraid that he will not be able to function as an independent adult in society and create a family/life of his own. We are a very close family and our children bring us such joy. If Kaden were unable to experience that himself due to galactosemia-caused disorders, it would be devastating. I fear that his sunny disposition would disappear.

This community deserves to have access to pharmaceutical treatment. This disease has devastating effects and its heartbreaking that there is currently nothing available on the market to help manage the disease better.

Shelby, Patient, 31 years old

My name is Shelby Norris. I was born in New York City in 1991. I was born with jaundice and a high bilirubin, but the doctors were not sure what was causing my symptoms. I was placed in the Newborn Intensive Care Unit at three days old and after a few days, I was transferred to another hospital, which had more technology. I would have a better chance at a diagnosis, but would have to transported via ambulance. My parents followed the ambulance in their car, anxiously wondering what was going to happen to their first-born child. Upon being transferred to another hospital, a doctor took a look at me and decided to do a heel prick test. The results indicated that I did in fact have classic galactosemia. I stayed in the Newborn Intensive Care Unit for another week before being sent home with my frightened and confused parents. They quickly scheduled appointments with specialists in New York City, ranging from pediatricians, geneticists, and metabolic doctors. They learned all about galactosemia from the doctors at Mount Sinai Hospital system. I went to various appointments to have blood drawn every three months. I would get DEXA scans to check on my bones. I would go to the endocrinologist to check on my hormones and my progress with puberty. I went to physical therapy, speech therapy, and occupational therapy. Growing up with this disorder was difficult. As a child, I know that I could not eat many foods, but I saw my family members eating these things that would make me very ill. I was tempted by these cakes, ice cream cones, donuts, puddings, and myriad other items that my family members would eat. At school, when celebrating birthdays, I would usually be restricted to eating some pretzels or a piece of fruit while my peers ate cupcakes. I had to quickly learn how to advocate for my self and how to tell my peers and teachers that I had a special diet. In my eyes, it was not fair, and in my mother's eyes, it was very frustrating; she had to explain my special dietary restrictions to peers, her friends, doctors, teachers, and everyone else who asked. Not only did I struggle with the diet, but I also struggled with academics. I was an amazing student, but I had an Individualized Education Plan and required special attention in class. I hated math and would often need one-on-one tutoring and services, in order to enhance my understanding of various math concepts. In addition, my social skills suffered. In middle school, I was the odd one out, as I did not make eye contact when speaking and had tough time with making friends. My peers ridiculed me and ostracized me for most of my middle school days. I had about three close friends whom I could count on for support and laughs; however, it was tough to go to school when many peers would mock me or stare at me. Other females would gossip about me and threaten to beat me up for no reason. I felt like the black sheep of the grade, mainly confined to the outskirts of the yard at recess, watching everything go on around me, without a way in. I felt unseen, unheard, and misunderstood. I was grateful that the school guidance counselor was available often and I would often confide in her, when the days were especially difficult. High school was better for me. I made more friends and excelled in my courses, especially literature and science. I graduated and went to college, where I received my degree in Psychology.

Life as an adult with galactosemia was easier, but it still came with many challenges. For me, a big challenge is the mental aspect of the disorder. Galactosemia comes with many symptoms and complications, one of them being depression. I do put a great deal of effort into my mental well-being. I practice meditation and I am a big advocate for self-care. I see a therapist and I do what I can to help myself. I do journaling and I have tried Cognitive Behavioral Therapy, which

has proved helpful. But it would be great if there was a treatment for galactosemia. The depression is exhausting, and it can be so difficult to just keep pushing on, every single day. In addition, anxiety is another part of galactosemia. The anxiety is sometimes health-related. I worry about the potential decline of my health and the possibility that I may develop new or worsening symptoms as I age. Sometimes the anxiety is related to social events. But it is just draining to have to constantly be anxious about being social and worry about making friends or maintaining friendships. Sometimes I make plans and then on the night of the event, I get nervous and feel like I should cancel. This is partially because I get nervous about being social and whether I will be mocked by others, or if I will fit in at social gatherings. I find I usually wind up standing in a corner, just observing, trying to connect with others, but it continues to be difficult as an adult.

Another difficult part of Galactosemia is the fact that many females experience premature ovarian insufficiency (POI). I was diagnosed when I was only 13 years old, and I was devastated. Upon receiving this diagnosis, I played it off like I never wanted children, but that was just a defense mechanism, an attempt to shut off some of the pain. Even though, I was only 13, I had dreamt of being a mother and doing all the traditions that my mother did with me. When I heard that I likely would not be able to have children, I felt like a small piece of me died. I played it off like I didn't care. But in reality, I was wanting to have children and I felt it was so unfair that I likely wouldn't have the chance.

A treatment for galactosemia would help in so many ways. I know that it would likely not reverse the damage that has already occurred to my body and my vital organs, such as my brain and liver. But, for the many young people in the United States and around the world, a treatment could potentially be life-saving. We all deserve to get relief from these troubling symptoms and complications that are associated with this disorder, and in some cases, can be life-threatening. Thank you so much for reading and paying attention to this very significant cause.

Megan, Caregiver of a seven-year-old patient

Comment 1: I am a parent to a 7-year-old daughter with classic galactosemia. I am an Occupational Therapist by background. This condition affects every aspect of our lives. My daughter has learning impairments, impaired memory, cognitive impairment, sensory processing disorder, and anxiety. She receives in school services through her IEP as well as private tutoring, outpatient speech and outpatient occupational therapy services. I am terrified of what the future could bring as far as further impairments.

Comment 2: My daughter, Ava Lilja, is a seven-year-old girl who was diagnosed at three days old with Classic Galactosemia.

To say this disease, Classic Galactosemia, is devasting would be an understatement. It has and continues to affect all aspects of my daughter’s life as well as our family's. As a result of this disease and the damage it causes to the central nervous system my daughter also has sensory

processing disorder, anxiety, cognitive impairment, learning impairments, impaired memory, difficulty focusing, speech apraxia, impairments in gross and fine motor coordination and struggles with social skills. Constipation, cyclical vomiting, and nausea are also constant symptoms of this disease that my daughter endures daily.

Despite early intervention services, special education services in school, private and school outpatient occupational and speech therapy, and private tutoring, she continues to struggle and the gap between her and school aged peers continuously increases year after year. I am an Occupational Therapist by background. It is heartbreaking to see the effects of this disease on my daughter.

The reality is that the current treatments we use (Occupational and Speech therapy, tutoring, vitamin D, MiraLAX, supplements and vitamins) are not working as none of these target the root cause which is the daily damage to her central nervous system that is happening as a result of her body making endogenous galactose despite being on a dairy free diet. These treatments are not "fixing" anything. They are merely trying to manage the symptoms that result due to the neurological damage this condition causes, like putting a band aid on the problem versus targeting the root of the problem.

Between school, therapy, and private tutoring my daughter is mentally, physically, and emotionally exhausted. There is not time for "fun" extracurricular activities. In order to be able to bring her to all her therapy and tutoring appointments my mother has had to retire early. If we did not have my mother's help to bring our daughter to the appointments, my husband and I would not be able to work full time to provide for our family.

The fact that my daughter has so many medical, therapy, and tutoring appointments also means that our son who does not have classic galactosemia is affected as well. There simply is not enough time to bring him to the extracurricular activities he wants to attend. It is a difficult position for our family. Our son who does not have classic galactosemia does not have any of the impairments that Ava has.

Ava works so hard. Ava has been described by her private tutor as the hardest working child she has taught in her 40-year career. Ava wants to do well in school and aspires of going to college someday. It pains me to see her work so much harder in nearly every task than her school aged peers. Learning is harder, gross and fine motor skills are harder, social skills are harder. Despite her strong work ethic, special education services, private therapy and private tutoring, she continues to fall behind. She is almost eight years old and cannot ride a bike without training wheels, cannot skip, and cannot do a jumping jack. She also cannot write basic letters, read simple stories, and cannot spell simple words independently such as "Dad". She has difficulty sounding out words and difficulty with abstract concepts such as math. She cannot add simple numbers such as 1 + 1. She often asks me "Mom, why is it so hard for me to do things?" She sees her brother who does not have the disease and often compares herself to him. She has also made the comment "Why is homework easy for my brother but not me?" She frequently

makes statements such as “I just cannot remember things” and “Why do I feel sick all the time, I do not want to throw up at school anymore!”.

There are times I question having her participate in therapy and tutoring due to her exhaustion, but I know if she does not, she will only fall further behind and therefore can negatively affect her chance at being a functional adult someday.

I am having to constantly educate medical providers, therapists, and educators on my daughter’s condition. Most of them have never even heard of classic galactosemia yet alone understand the disease and the symptoms associated with it. It is exhausting as a parent to have this task on top of the daily demands for caring for my daughter with this condition.
The reality of this disease is it is progressive, I worry what will happen in the future. When will seizures and tremors start? Since she is a female, there is a high likelihood that if we stay on our current course of treatment that she will have primary ovarian insufficiency and will need to be on hormone replacement as a teenager. What will happen someday when my husband and I are no longer around to care for her? Who will help her? Will she be okay? Unfortunately, these are the sad and painful futures our family is dealing with right now with no FDA approved treatment on the market. Therefore, we are involved in a drug trial with hope that an approved FDA treatment will soon be on the market to give my daughter the chance at a better future.
Ava has been in a drug trial for over a year. It is not easy, and she does not fully understand the reasons for the drug trial. Ava has been through countless blood draws and tests. It is very difficult. It is exhausting on top of the daily impacts this condition already causes and what she already must endure daily. She must miss school, therapy and tutoring when we travel for the drug trial, and it is more time off work for my husband and myself. We participate in the drug trial in the hopes to have a treatment to help her and others like her. We do it in the hopes her future will be better due to an approved FDA treatment for Classic Galactosemia.
Time is of the essence; my daughter has daily damage to her central nervous system that cannot be reversed.

I am hopeful that the FDA will understand the realities of the struggles my daughter faces daily, and that the FDA will take steps to approve a treatment for Classic Galactosemia to give her and others a chance at a better life and more independent future.

Sincerely,
Megan Lilja, B.S., M.S., OTR/L
Mother to a sven-year-old child with classic galactosemia

Kelley, Caregiver of a 12-year-old patient

I am writing to add comments and concerns from a parent perspective to the discussion. I think one important thing to point out to start is that what we previously thought of as effects of galactosemia, particularly classic variant no longer hold true. As we know, there are very few researchers who study this disease. There are only small numbers of subjects in each study group and by human nature, there is always variability with people. We STILL don’t know what

genes and modifiers are interacting with each other. We still don't know how one genotype is different than another. The literature simply put, under-represents the deficits related to galactosemia. With the perspective that the effects are "only diet related" or mostly mild is simply false. The idea that all damage is done in utero and therefore there is nothing we can do is simply false. The effects of this disease are life long, progressive and drastically impact the patient's functioning, independence and survival in various ways.

We can list a multitude of areas of deficits and severity as well as tell you how these things impact our children and community members. What we are asking for is for someone to be willing to look at this disease differently than it has been thought of before. The diet for example, as early elimination of lactose/dairy in infancy reduces the rate of sepsis and death it does not fix anything. The body continues to produce galactose and we get galactose from everything we eat/drink in a typical diet whether it's in a bound or free form. You cannot eliminate galactose at this time and it's actually needed for a normal body to metabolize. With the inability to metabolize galactose it remains in toxic levels in their bodies. This is life-long. We have known that toxic levels of galactose cause various issues in the body. Why would that not be the case in someone with galactosemia? Why would we think that reducing it in a diet is just enough. We wouldn't say the same thing about someone with Diabetes or other metabolic disorders or people who struggle with excess of anything or too little of something else. Yet, there are treatments for those disorders. We know the science and expertise exists to produce something that is actually a treatment or even a cure. We need the FDA to hear this plea and understand that even if the total number of people living with galactosemia may be lower than other metabolic diseases, don't they all deserve the best science can offer? Don't they deserve a chance to live and live a healthy, productive life? There have been many challenges to the scientific study of this disease which is one reason the studies that previously represented galactosemia are out of date. As parents, as those living with galactosemia yes it's true, there is a spectrum of related issues. Some people manage those issues better than others. That would hold true for just about any disease. But, we know that those with galactosemia have many more medical, neurological, metabolic, social-emotional, cognitive-communicative and physical issues than same age peers. We know that these deficits harm their overall health, increase risks of additional severe diseases, impair their ability to be productive citizens and live independently. This is not just a burden to the patient and families.

Parents and patients may not share with you their challenges. We simple can't reach the entire community and their loved ones. I hope that the information yielded in the discussion will be enough for the FDA to make considerations for us. When children are young, it's not only the child but the parent that bears the burdens of this disease. As parents age themselves and leave their now adult children with galactosemia it's a societal and healthcare burden as well. From birth, these children demonstrate motor deficits and cognitive deficits noted very early on. There are issues with reaching physical milestones, cognitive milestones and speech-language milestones. There are a lot of associated medical issues including issues with immunity, digestion, growth, bone density, vision, dental health, bowel/bladder function, issues with blood cells, hormone deficiencies, seizures, tremors, ataxia, etc.. The list goes on. These

are things that if you only read and believed early published literature you would not understand comes with galactosemia. They simply weren't mentioned. Most of the people living with galactosemia suffer from some degree of apraxia as well as other speech impairments as well as language impairments. They struggle academically across subjects. They have various processing deficits and learning disabilities. They have anxiety and depression that greatly impact not only their emotional health but their physical health and functioning. They struggle socially trying to fit in with peers who are not experiencing their challenges. They are labeled, defined and reduced. Early on, they endure multiple doctor appointments which may include genetic doctors, metabolic doctors, endocrinologists, OBGYN specialists, neurologists, dieticians, physical therapists, occupational therapists, speech therapists and developmental specialists just to name a few. They have multiple blood draws in the first several years of life and throughout their life. Labs after labs. Our son also has a cardiac condition which we were told that children with developmental disabilities are at higher risk for. He continues to see doctor after doctor. Therapies, X-rays, bone density scans, brain scans, blood draws, echocardiograms, EKGs, EEGs, etc…. This is his reality.

Our son wants more than anything to be like his friends/peers at school. He doesn't want to have these issues. He wants to ride his bike, swim, play sports and keep up with kids at school like his friends. He doesn't want to be the kid in class needing so much more and struggling. He wants to be accepted and seen for his potential. He suffers from significant fine and gross motor issues. He still can't tie his shoes, snap, button, use a belt, loop a hole, cut shapes, draw to illustrate ideas, write like a typical 12-year-old or even go up/downstairs like a typical peer. He still can't ride the escalator places because he can't coordinate that quickly and he's terrified of falling on the escalator. He can't cut his food so we order things he can pick up with his fingers when we are out or we typically bring in food from home that is safe and appropriate for him so he doesn't always feel left out. He's the kid who has to do without time and time again as others are enjoying something delicious and he gets to explain for the millionth time that he just can't have it. He's the kid that gets the special pizza and cupcake at parties when we can plan ahead. He wants to grow up to be a soccer player and a police officer.

Our biggest fears are not only what he is currently dealing with but also what does the future hold for him? We tell kids to be dreamers and dream big that they can do whatever they put their mind to. But for kids with disabilities, that's not true. When we die as his caregivers and advocates, where will he be? He has a brother and a sister but we don't want to strap them with the burden of caring for their adult brother. We have to make plans now for when we die so that he isn't subject to living out his life in a nursing home. That's his reality if he can't live alone. There aren't a lot of resources for people like our son especially as they age and what's available is very costly. That's horrible to think that at 12, that is his potential future. We worry whether he will be accepted and loved and whether he can share his life with a partner. We know that people who feel loved and accepted and can partner with a significant other thrive and actually live longer. We worry that he won't make friends as he continues through school and he will feel even more isolated and start getting depressed. We worry that he will develop seizures, tremors, ataxia and other balance issues that will further impair him.

We know that things could always be worse and we are very, very grateful for everything that he can do. We are so grateful that he is the best little boy who everyone loves and is so hardworking. We try to stay positive and focus on the positives taking it one day at a time. We try to say things like, "you'll get there, it will be alright, just because you can't do it now doesn't mean you won't ever do it, you might not be able to do it YET but you will", etc… But in reality, we don't know. We can see some early signs of tremor starting. We know he has severe balance and motor planning issues now. We know he hasn't improved much with many of his issues despite regular, intensive therapy. The therapy is not a fix. It can help to mitigate some of the issues and improve outcomes but, it by far does not fix it. We need help from a medicine or a treatment. That's our only hope at this point. We are running out time to improve his potential outcomes.

To describe what galactosemia has caused is very difficult and doctors write things off all the time as not being related to galactosemia. That is simply not true. When you poll the majority of us caregivers, you will hear much of the same stories. This is a reality. It's not a minor disease. Our son has low tone, hypermobile joints and apraxia. He has motor planning and balance issues. These things fatigue him and cause him pain in his joints. He has difficulty holding his bladder and is still in pull-ups at night at 12. He can't go to sleep-overs because he's embarrassed about this. He wears glasses because his eyes didn't fully develop. He is in special education for all curriculum areas. He wears orthotics in his shoes to help stabilize his body and improve his movement as well as decease the pain in his feet. He uses a seating system at school to improve his posture so he can better write, read and participate. He has a pectoral deformity and as he was developing basically his hips, chest and trunk were trying to turn inward further impairing his movement. He has low bone density and has had a few small bone fractures as he is suspectable to falls and injury. He has a very high pain tolerance (part of severe processing issues) so at times when he has seriously gotten hurt he was not able to tell someone immediately about it. He was unintelligible for several years. He does have speech now but it's labored, misarticulated and impacts him in all of his communication needs. He has receptive and expressive language disorders that impact his communication and affect him across all his academics. He has learning difficulty even when we break things down step by step, allow extra time and provide tons and tons of repetition. He gains and loses throughout his abilities and it's very hard to generalize any information for him or build upon it. This manifests as a "memory" problem at school. It takes more effort on his part to process information and learn anything. Anything related to sequencing like sequencing sounds to make words, sequencing words to make sentences, sequencing sentence to produce connected speech or write a simple paragraph is very difficult. Sequencing a story for recall or sequencing numbers in math, etc… This is part of severe apraxia and processing issues. He has to work harder than anyone to gain very little. He has cognitive deficits, speech impairments, apraxia, language impairments, fine motor and gross motor impairments, processing deficits, vision issues, low bone density, muscle tone issues, and neurological damage related to galactosemia. He has social-emotional issues starting as he is becoming more aware of all of these differences and the amount he struggles with. He can't enjoy sports or hang out with same age peers doing

what they do. He also has a cardiac condition which we believe having galactosemia predisposed him to which involved two holes in his heart and mitral valve stenosis. He is also under the care of a cardiologist as we wait for him to continue to develop hoping that the mitral valve stenosis doesn't get worse leading to an open heart surgery which would then make him prone for further valve replacements in his lifetime. I was told once that having a genetic disorder is like a perfect storm and that it's very common to see other issues along with it. He is on the smaller size and through his toddler years, we struggled to get him to gain any weight. We had to supplement his diet further with items to put on weight and maintain muscle. Thankfully, he's starting to grow and his weight is fine now but he's still smaller in stature and very immature physically as well as mentally. He has dental issues as well. He is congenitally missing one of the front teeth and has demineralization/low enamel. He's had several spacers and such to try to organize the mouth to improve his bite and prepare the teeth for straightening. One issue we are concerned with is that if we get him the dental implant now that due to his low bone density the doctors are afraid the implant won't take well or that eventually he will have to have multiple different implants as he ages because the bone will recede. The solution is shifting a tooth into that place to "replace" the tooth but his teeth are in such poor condition that's not a great solution either. This has caused them to modify the plan for his bite, etc… We also know that his bite and dentition also impact his speech and breathing. None of the issues he is experiencing "run" in our family. Between our two large families, our son is the first to experience any of this. When he was an infant and toddler, I could smell a sweet smell in his urine and on his skin. The doctors would say it must be because of the soy formula and tell me not to worry about it. I recently learned that other galactosemic children also had the same thing even those on non-soy formula. Our son is also borderline anemic. I have often wondered if the kidney function is being affected by galactosemia and what the role of EPO in the kidney might be with galactosemia since it has a role with bone marrow and red blood cells. To my knowledge this has never been studied. Since most of our providers have never seen or heard of galactosemia, they are not knowledgeable in identifying related concerns.

In terms of treatments, we do what we can to provide him with as much support as possible at home. We make appointments, take him to appointments and try to carry over all the recommendations the professionals give us. He has speech therapy both privately and in school, OT, and intermittent PT. As most have mentioned, therapy does not cure any of the issues but does improve his abilities to some degree. Without it, we know he would be even worse. Most patients are in therapy for the duration of their adolescent lives. Like some other disorders or delays that receive therapy for short periods, these patients needs are more extensive. Second, insurance caps out each year at about 30 visits combined so we pay out of pocket the majority of the year. Insurance does not cover the additional costs of seeing specialists or certain labs. We end up paying quite a bit out of pocket on medical expenses each year. Even though you pay for insurance you still have to pay a portion of every visit, every lab, etc… Our son has an school IEP (individual education plan for special education) and is in special education with support as well as he goes into general education with support and or is pulled out for additional resource. There is also a lot of social stigma with this. He uses an AT device

(previously used an AAC device along with sign language) and has tutoring. He also does a neuro-listening program for 30 mins per day and has around 4 hours of homework each night to try to catch up. There is no time for him to play sports or join in clubs outside of school. Fatigue is a real issue. He fatigues at the end of the school day so even after school it's so hard for him to do what he has to do. He has to work and process harder than other children so he fatigues easily. I equate this to me having a very intense course I have to get through and I'm tired at the end of one day and my son has to do this every single day. He has mental and physical fatigue. He works twice as hard as his peers but he continues to fall further and further behind. The gaps are not closing. We provide him all the supplements that are available to try to treat low bone density and hopefully impact his speech and neurological functioning. He has seen specialist after specialist in attempt to manage the side effects of galactosemia and monitor all of his issues. We don't expect him to suddenly be able to take dairy, honestly managing the diet is the easiest part of this. We don't expect him to suddenly not need any help but, we are hopeful for a treatment to make things better for him across the board. We are hopeful for something to protect him from further damage.

As we talk about all the cognitive and physical effects of this disease, we can't underscore the social emotional impact, financial impact and the impact this disease has on the family unit either. There are real implications of managing this disease. I think us caregivers and patients with severe disease we are willing to make sacrifices and put the effort into pursuing a cure or a treatment because our loved ones need it now. We would want a treatment that prevents further neurological damage and protects their current neurological functioning. There was suggestion that the galactose literally "pokes" holes in the myelin which is suspected to be part of the motor and processing issues they face. We don't yet understand why the neurological functioning is so impaired and continues to progressively get worse leading to tremor, seizures and additional motor functioning deficits. We know that biproducts and metabolites are likely playing a role. We would want a treatment that would help our son communicate, think better and faster and support him as he continues to try to learn. We would want a treatment with no harmful or adverse side effects and only tolerable side effects if any. We would want something that would not interrupt his daily routine significantly like having to stop throughout the day to take multiple doses. He doesn't swallow pills and lot of our community members can't swallow pills so it would need to come in a different method of delivery. We would want it NOT to be injectable as this would be very hard and painful for him. We would want something that does not further restrict his diet. We know there has been concern mentioned about a potential drug only being effective if given in early stages of life. But the body continues to produce galactose throughout the lifespan and continues to receive it from the diet. There is no reason to indicate it would not be helpful. There may be less progress noted than in a younger, developing child however, we know in the world of neurological study that neuro-plasticity is a real thing. There is always hope that the brain can change if presented with the appropriate intervention. There is always hope that damage can reverse to some degree. There is always hope that you can stop or prevent further damage from disease. We would want something that older children would be a candidate for as well. For us at his age, his speech-language, cognitive, neurological and motor functions are paramount.

Bottom line, we need a therapy that potentially addresses the unmet needs or we need a cure. The implications of this disease are real, severe, impactful to health and function, impactful to social-emotional needs and progress through life. It is not a disorder of diet. It is a real disease that impacts multiple organs in immense ways. The World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". We need to look at galactosemia from a larger lens. These children and adults are in a health crisis.

Thank you for the opportunity to tell you about our son's story and listen to our plea for help. Thank you for your time and consideration.
Sincerely,
Kelley Foley (parent/caregiver)

Natasha, Patient

Title of email: I hate having galactosemia because I feel low because I can't have kids and IVF using egg donor hasn't worked on NHS.

I don't feel normal at all because the fact that I am not able to conceive on my own and that I'm getting too old now. I'm 32 years old now, I'm running out of time becoming a parent. I get very frustrated when I see other women out there not being good mothers. It makes me feel angry and upset there are times where I feel as though I want to end my life and that I'm letting my boyfriend down and that my boyfriend deserves a lot better than me! I wish I was never diagnosed with galactosemia and just wished I was like everyone else. I blame myself when my fertility treatment hasn't worked. I get very emotional and I feel as though I want to end my life because I'm not getting pregnant and I feel very low and ashamed of myself after a second unsuccessful cycle of IVF treatment and it's not fair that I can't be like other women and just be pregnant that's all I would want. I'm scared that I'm running out of time to be a parent.
Kind regards Natasha

Debbie & Perry, Grandparents

I was so blessed by tuning into your symposium. I learned so much and am so hopeful for the future with such efforts behind this rare disease which impacts so few directly but indirectly thousands more by association through family and friends.
I am hopeful that sharing the following info that follows could help.

I have been studying neuromovement therapy with AnatBanielMethod.com and following her guidelines I've been learning with her book, "Move into life" and then followed this by reading "kids without limits" better understanding the challenges our first grandson might face with Class 1 Galactosemia.

I have a personal story of the benefits of this therapy for pain after a fall in 2021. I am hopeful with the next few months with my grandson to work with some of these lessons and share it with his parents.
The science behind the power of neuroplacticity might be what is needed to help people keep their children healthier. I truly believe this and perhaps falling of a ladder last year was my way to discover this hope.

I sincerely believe this therapy approach to the type of challenges you all shared with us in this emotional symposium could be ground breaking as you wait for the genetic cure that is so badly needed. I encourage your families to read and practice the subtle wonderful lessons you can incorporate into daily life yourselves. There are therapist throughout the world who have been trained by Anat which you can access a list through her website.
Perhaps you can share this with others once you check it out yourselves.
Happy to chat with anyone!
Sincerely
Debbie Ekstrand

Mike, Caregiver

As a caregiver for a child with CG, we appreciate the comments that were made. I would like to stress the importance of Applied and Jaguar working toward the betterment of our kids either through medicine or gene therapy.

This is really our only hope for a normal life for our child and as each day passes, it becomes more out of reach. We need a speedy resolution.

Thanks for your time.

Joah and Ashley, Caregivers of two patients

Voice of the Patient - Galactosemia

Quality of life is a major concern - not only for our two children with classic galactosemia - but for our child without galactosemia. As parents, we wish for our children to ultimately become happy, productive members of society. Addressing various outcomes of Galactosemia that continue to manifest, however, have often made our daily lives an on-going struggle.

In addition to diet, some challenges tied to galactosemia can be lessened with on-going behavioral, educational, and medical supports. A seemingly endless list of appointments, procedures, and interventions often only serve as a band-aid on a large wound, however, since those with galactosemia cannot convert galactose - which the body naturally produces - to glucose. The goal posts are constantly shifting for those with galactosemia and it is exhausting for patients and caregivers alike trying to mitigate some of the many challenges.

A therapy/intervention/cure which addresses the source of the issues for those with galactosemia - the body's inability to convert galactose to glucose - would be a godsend for our entire family. It is frankly what gives us hope as we navigate life with this rare condition.

Josh & Ashley Weber
Franklin TN

Lineidy, Patient

I wasn't able to speak on Zoom on the day of the FDA event because I was at work. I wanted to say that I'm a little slow at work and people get upset. Also, it's hard for me to maintain a good diet and stay healthy. Another thing that is hard for me is speaking up at work. I would like to speak up more but it's hard for me with galactosemia. Another thing that is hard for me is time management with galactosemia.

Lineidy

Timothy, Grandparent of two children, ages three years and 20 months old

To whom it may concern,

I am writing this letter as a physician and grandparent of two children, ages 3 years old and 20 months, with classic galactosemia in response to the recent NORD virtual meeting with the Galactosemia Foundation and the FDA. As a pediatrician, I see the benefits daily of therapeutic interventions in the lives of my patients with serious chronic disease. These interventions often range from coordinated subspecialty care to cutting edge medical interventions such as surgery and new therapeutic medications. I have seen the impact that new treatments can have on my patients, short and long term, as well their families. The time commitment, financial impact, and the emotional stress of caring for a child with chronic illness is often overwhelming. Fortunately, medicine continues to evolve to treat previously untreatable diseases and offer patients and their families hope.

Classic galactosemia (CG) is one of these rare chronic diseases with variable outcomes that progresses with age. As you know, it is caused by the absence of galactose-1-phosphate which causes accumulation of galactose and it's toxic metabolites. There is no way of predicting the eventual level of deficits both cognitively and medically. These include speech and gross/fine motor delays, cognitive impairment, neurologic complications such as tremors and seizures. In the past, the only believed treatment was dietary and aggressive therapy. However, neither has proven to be effective in preventing progression of symptoms or significantly altering outcomes due to the endogenous production of galactose and its metabolites. Both of my grandchildren are exhibiting the common early symptoms of CG including speech delay, sensory integration problems, and are in appropriate early intervention programs. As previously mentioned, there is no way to predict the ultimate severity of disease progression, but it is heartbreaking to realize the possible but likely problems my grandchildren will face in the future.

As a physician, I am always in hope of treatment for devastating diseases and now personally affected by two grandchildren with CG, I was excited to learn of Applied Therapeutics study of AT-007. Unfortunately, my grandchildren were to young to be enrolled in the study as there would not have been any hesitation from my family. This potential treatment can be life altering for my grandchildren as well all children/adults with CG. My analysis of the available data from the study is very positive with no known significant side effects. I was very disappointed to learn that the FDA was going to require clinical outcomes data for an undetermined length of time. It is my belief that this drug with potential benefits of preventing disease progression, reversing symptoms, and offering hope to those families dealing with CG should become available to all patients. Each day potential treatment is delayed, toxic metabolites and the negative effects increase.

I understand the FDA's need for clinical data and to determine the potential risks and benefits. As is the case of most rare disease with no current treatment, I believe therapeutic interventions with new drugs should be advanced/approved to all those interested through EUA or orphan drug approval. I urge the FDA to continue their collection of clinical outcomes data but with allowing patients with CG to have access to AT-007. My hope is that this drug along with other possible future treatments will allow my grandchildren to live normal/productive lives. Thank you for your consideration in this matter.

Allie, Caregiver of a two-year-old patient

My name is Allie Diebold and my two-year old son, Noah, has classic galactosemia. His twin sister, Emma, has the Duarte variant.

We had been discharged and home from the hospital for one day when I received a call from the on-call pediatrician telling me to immediately stop breastfeeding my newborn twins, start them on soy formula, and get them to the emergency room for bloodwork, as they both tested positive for galactosemia on their newborn screens. My husband, Eric, and I had no idea what it was or that we were both carriers. Nothing breaks a new momma's heart more than hearing something is wrong with her babies.

It was a few days after that phone call that Noah was admitted to the NICU with a bleeding disorder and then found that his liver was not functioning correctly, related to issues with galactosemia and the brief few days he was breastfed. After 10 days in the NICU, we were lucky to bring our sweet boy back home. During those 10 days we met with numerous medical professionals and learned more about galactosemia than I ever could have imagined. We continue to learn more and more all the time.

The problem is, there isn't much information about galactosemia because it is so incredibly rare and there are no treatment options. The Applied Therapeutics trial (AT-007) has been a sign of hope for Noah and our family that he and others with galactosemia will have a treatment option and the potential to live a "normal" life. At this time with Noah we are seeing speech

and development delays. We know these may just be the start of issues he may face as he continues to grow and are willing to do whatever we need to do to help him. Our hope for a treatment option is to prevent any ongoing speech, cognitive and developmental delays and reduce the risk of seizures and other neurological disorders. I do feel it is also important to mention the benefits this would have for caretakers and other family members. As a mother of a young child battling this rare disease, my anxiety has greatly increased due to constantly reading labels, trying to decipher conflicting information about what is allowed and what is not, juggling appointments and blood draws, and managing the fear of going out to eat because you don't know how a restaurant prepares their food and may not understand the questioning that comes from a parent. Many people do not understand that saying your child is "dairy-free" is not a choice we are making for him -- it is to save his life.

As a mom, I will do anything I can to help my children. That is why it was so important for me to participate in the Voice of the Patient report and the externally-led patient focused drug development meeting. Please help give those affected by Galactosemia a chance.

Jenny, Caregiver of two patients

My husband and I have three children, the younger two have classic galactosemia. In 2007 our son was tentatively diagnosed on his seventh day of life through newborn screening. His symptoms were vomiting, frequent urination, poor feeding and substantial weight loss. Our doctor called me that afternoon saying his test results came back abnormal and to stop breastfeeding immediately but that that was all she knew about it. What?! That is not a phone call any new mother wants to receive. My husband's response when I gave him the news was "Don't Google it!" Thank goodness he was able to filter through the very limited and very dismal information he could find online. We underwent many exhausting days of blood work and tests to confirm his diagnosis. In 2010 our daughter was born. Since we now had an idea of what we could be facing, we asked that her newborn screening be rushed. Unfortunately, due to where we lived, it wasn't until about a week later that our Genetic doctor was able to call the lab for results. It was heartbreaking. Looking back I can say that I'm glad they have each other on this rare journey because they can share the burden together.

As our children get older the more we see how galactosemia's effects are changing them. It is sad to watch your 10-year-old blowing bubbles with her 3-year-old bestie and she has to ask the 3-year-old to put the bubble wand back in the container because her tremors are too bad. And know that that friendship at 12 years and 5 years is the only real friend she has. While our two children with classic galactosemia present different symptoms wildly different now, we are worried for what the future holds.

We have been participating in the only pediatric drug trial from it's inception in 2021. It is hard. The participants in this trial are tugged from sleep to endure long days of testing, too many blood draws to count and absolutely too much stress than a child shouldn't have to take on; especially when they are either too young and/or don't have the cognitive ability to fully

understand what is being asked of them. Daily I wake my children at 5:20 in the morning to give them the trial medication so that they can follow protocol and wait the prescribed two hours before eating and head off to school. For over two years they have traveled long days across time zones, missed many days of school, have even more food restrictions and certain times they can and can't eat to participate in this trial that they may or may not even be on drug or with the uncertainty of said drug collecting enough data because of the small population to even get out of the trial stage. Imagine the waiting and watching for other families to see if the possibility of a potential drug will be available to help their children. Then there are the parents of the children in the drug trial who also have the hardship of waiting and watching to make sure this new drug is not going to harm their children further, make their outcomes worse, looking for any sign that maybe this drug could be helping or wondering if they are on placebo and putting their child through this for nothing. Taking countless days off work, traveling with children during a pandemic, counting hours, documenting data, making appointments, reading food labels for more ingredients to avoid and praying that they are doing the right thing for their children. This is not easy for anyone.

Our hopes for the future of new drugs for rare diseases in small numbers would be for trials to not be compared with and lumped into large trial rules. We hope that new drugs and research can continue quickly so that our children can lead long healthy productive lives independently. Improve their cognitive ability to make and maintain meaningful relationships. Have clear speech and effective communication so that they too can be understood. To not have to ask for help putting bubble wands into the container or having to drink through a straw so you don't spill your drink. And most importantly, give our children the opportunity to have their own children instead of ovarian failure and potentially forced puberty with the use of more drugs.

It is impossible and unnecessary to point out all the complications that come with Galactosemia and other rare diseases. It is individual. We are rare. We are strong. We will not give up when it comes to our children and their future. We need your help.