University of Cincinnati

Date: 3/11/2021

I, Kaylee Crossen, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:

Parent experiences with newborn screening and medical management for late-onset Pompe disease

Student's name: **Kaylee Crossen**

This work and its defense approved by:

Committee chair: Melanie Myers, Ph.D.

Committee member: Lisa Berry, M.S

Committee member: Nancy Leslie, M.D.

Committee member: Cecilia RajakarunaMS

38197

Parent experiences with newborn screening and medical management for late-onset Pompe disease

A thesis submitted to the

Graduate School

of the University of Cincinnati

in partial fulfillment of the

requirements for the degree of

Master of Science

in the Department of Pediatrics,

Division of Human Genetics

of the College of Medicine

March 2021

by

Kaylee Crossen

B.S. Allegheny College, May 2019

Committee Chair: Melanie Myers, PhD, MS, LGC

Committee Members:

Cecilia Goueli, MS, LGC

Lisa Berry, MS, LGC

Nancy Leslie, MD

Abstract

Pompe disease was added to the recommended uniform screening panel to avoid diagnostic delay and implement prompt treatment, specifically for those with infantile-onset Pompe disease (IOPD). However, two-thirds of newborns with abnormal newborn screening (NBS) for Pompe disease have late-onset Pompe disease (LOPD). An early diagnosis of LOPD raises the question of when symptoms will arise which is challenging for parents, patients, and providers managing an LOPD diagnosis.

This study aimed to characterize parents' experiences of their child's LOPD diagnosis and medical monitoring to understand patient-provider relationships and adherence challenges. A qualitative descriptive approach was chosen to gain an in-depth understanding of parental experiences. Eight mothers were interviewed to assess their experiences. Interview questions were designed around experiences with positive NBS and diagnosis, experiences with living with the diagnosis, and experiences with medical monitoring. Parents were asked what they reported as their child's monitoring plan, and what changes they wanted regarding monitoring. Interview transcripts were analyzed through conventional content analysis.

Results of this study found that negative emotions like fear were more frequent with communication of the NBS. Parents expressed uncertainty surrounding age of symptom onset and the future. The medical monitoring experience increased worry but parents expressed that being vigilant with management reassured them. In summary, this study suggests parental emotions shifted to thankfulness and reassurance with time and education about the condition and monitoring plan. These findings can guide providers on how to care for this patient population and be sensitive to the psychosocial implications of receiving a positive NBS and an LOPD diagnosis.

Keywords: Pompe Disease, Late-Onset Pompe Disease, Newborn Screening, Pre-symptomatic Patients, Parent Perspectives, Medical Management

(page intentionally left blank)

Acknowledgments

This study was conducted when the first author was enrolled in the Genetic Counseling Graduate Program, College of Medicine, University of Cincinnati and Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Thank you to my research advisory committee for your time, support, and commitment to this project.

Table of Contents

Tables and Figures

Introduction

Pompe disease occurs when two pathogenic variants in the *GAA* gene cause a deficiency of the lysosomal enzyme acid alpha-glucosidase, causing an accumulation of glycogen in muscle cells. The two sub-types of Pompe disease differ by their age of onset and initial presentation. Infantile-onset Pompe Disease (IOPD) occurs within the first year of life, and symptoms include cardiomegaly, respiratory failure, and hypotonia. Late-onset Pompe Disease (LOPD) can develop any time after the age of one year with the onset of proximal muscle weakness and difficulty breathing. Late-onset Pompe disease is highly variable in age of symptom onset and disease severity, even within families (Alandy-Dy et al., 2019; Papadopoulos et al., 2014).

Early treatment for Pompe disease with enzyme replacement therapy (ERT) extends life expectancy and improves cardiomegaly, cardiomyopathy, respiratory capacity, and physical endurance (Chien et al., 2013). ERT is most effective when patients are diagnosed early and treatment is initiated before extensive and irreversible damage occurs in the tissues (Chien et al., 2011). Therefore, an early diagnosis is key to improving outcomes, especially for infants with IOPD. Currently, twenty states and Washington DC have added Pompe Disease to their newborn screening (NBS) panels since its introduction in 2013 (Frank, 2020). State-based NBS is based on the Wilson and Jungner criteria (1966) which explain that screening for diseases should only occur when there is a known natural history of the disease, a recognizable early disease stage, an accurate diagnostic test, and a proven and accepted treatment plan. However, two-thirds of Pompe disease patients identified from NBS are diagnosed with LOPD, which does not occur at a recognizable early stage (Ross & Clarke, 2017).

Diagnosing LOPD at birth cannot predict age of onset and some consider it similar to testing minors for adult-onset conditions (Alandy-Dy et al., 2019; Papadopoulos et al., 2014; Ross, 2012). Early diagnoses come with benefits and drawbacks. Benefits include improving health outcomes by avoiding a diagnostic delay and the associated uncertainty, anxiety, and turmoil for patients and families living without a diagnosis (Carmichael et al., 2015; Lisi et al., 2016; Lisi & McCandless, 2016; Saich et al., 2020; Weinreich et al., 2012). On the other hand, disadvantages discussed and agreed on are increased

healthcare and treatment costs, uncertainties about treatment coverage by insurance, parental uncertainties and anxieties about the diagnosis and prognosis, medicalization of the asymptomatic child, lack of the child's autonomy for knowing the diagnosis and screening, and concerns about patient insurability and employability (Lisi & McCandless, 2016; van El et al., 2014; Wilcken, 2010). However, there is limited research on the long-term benefits and drawbacks of pre-symptomatic LOPD diagnoses as NBS for Pompe disease is still fairly new.

Many children with LOPD diagnosed following NBS remain asymptomatic and may be considered "patients in waiting", a term introduced to describe the number of asymptomatic patients diagnosed through NBS who live not knowing when or if their symptoms will arise (Timmermans & Buchbinder, 2010). Close monitoring of patients with Pompe disease is important to identify early symptoms for the best ERT outcomes (Ficicioglu et al., 2020). However, parents of children considered "patients in waiting" may experience fear, anxiety, and uncertainty about their child's diagnosis, the future, and treatment (Pruniski et al., 2018). They may become hypervigilant and constantly question whether symptoms are present and whether their children are reaching developmental milestones (Pruniski et al., 2018).

The Pompe Disease Newborn Screening Working Group recommendations for symptom screening include visits and tests every 3-12 months depending on a patient's age (Kronn et al., 2017). Visits include multiple tests and labs including ECGs, echocardiograms, hearing tests, blood tests for CK levels, urine samples for Hex4 levels, feeding and swallow tests, physical examinations, and developmental assessments (Kronn et al., 2017). However, as more diagnoses of LOPD are made following NBS, it is unknown whether medical providers are recommending and following proposed guidelines or less stringent guidelines when patients are asymptomatic. It is also unknown whether families follow provider recommendations when their child is healthy. Understanding parents' experiences when their child has an LOPD diagnosis can provide insight into adherence and parents' relationships with their providers and child. We interviewed parents to explore their experiences receiving a diagnosis of LOPD through NBS as well as their experiences with medical monitoring of an

asymptomatic child. The aim of our study is to describe parental experiences and psychosocial implications of their children being "patients in waiting" as a result of a diagnosis of LOPD and document their current monitoring plan to provide insight to providers who care for this patient population.

Methods

This study was reviewed and approved as exempt by the institutional review board at Cincinnati Children's Hospital Medical Center (CCHMC) (2020-0655).

Research Team

The research team includes one genetic counseling student, genetic counselors and a geneticist who provide care for children with LOPD and researchers with experience in qualitative methodology. Our study team is made up of all females. Two of our research team members follow patients at the STAR Center for Lysosomal Disease at CCHMC.

Recruitment

We recruited participants from CCHMC, outside institutions, and a Pompe Facebook group. Eligibility criteria included primary caregivers of children with LOPD diagnosed following NBS who speak English. Exclusion criteria included parents of children with LOPD on ERT and parents of children who have Pompe disease related cardiac manifestations such as cardiomegaly and cardiomyopathy. LB identified patients followed at the STAR Center for Lysosomal Disease at CCHMC who met eligibility criteria. We sent invitations to participate by mail or email to six families identified. Emails that contained our recruitment letter to be shared with eligible participants were also sent to genetics providers at five other medical institutions known by the research team in Ohio and Kentucky that follow children with LOPD. KC posted an invitation to participate on a Pompe Facebook group. The invitation explained our study and asked for interested eligible participants to reach out to KC by email. The invitation was posted three times.

Interviews

The research team created an interview guide to assess parents' experiences receiving a diagnosis of LOPD following NBS, what parents report about their child's medical management including details regarding providers, evaluations, laboratory studies, and the frequency of each, parents' experiences with medical monitoring when their child is asymptomatic, and what changes parents want regarding monitoring their child from LOPD symptoms (Appendix A). A medical management checklist was based on the review of recommendations by the Pompe Disease Newborn Screening Working Group (Kronn et al., 2017) (Appendix A). The interview guide also included demographic questions about both the parent and their child to better understand the population of participants. The interviewed guide was pretested with the research team and peers not related to the study to assess question quality and flow of the interview (Kallio et al., 2016). Adjustments to questions after pretesting were made as needed. KC was also trained on interviewing and probing through pretesting the interview guide with members of the research team.

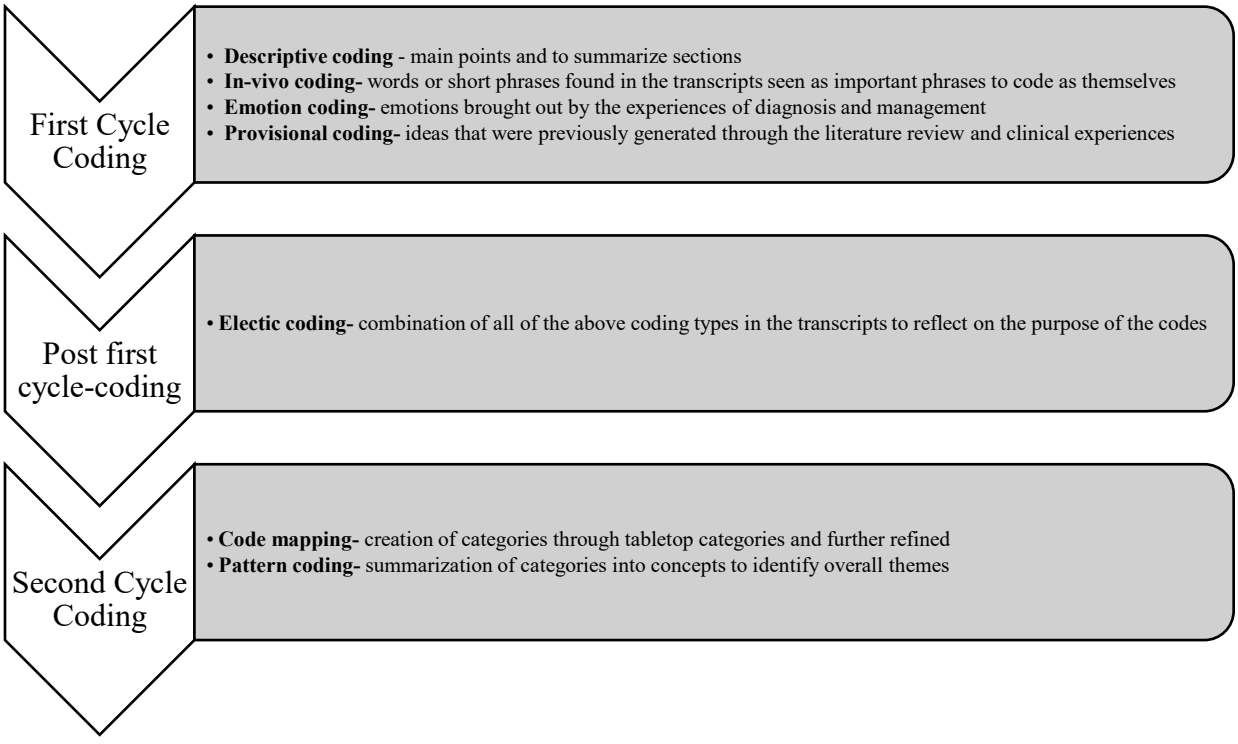
Participants provided verbal consent at the start of each interview. KC conducted interviews via Skype voice calls. Interviews were audio recorded. CG was present for five interviews and MM was present in the first two interviews to observe KC and ask participants additional follow-up questions. No participants knew the interviewer before the study. The members of the research team present on each call took notes during each interview for reference and to be analyzed alongside transcripts. Interviews lasted about an hour per participant. Families were recontacted after interviews to thank them for their time and to request their child's genetic testing results to record their genotypes to identify if there are differences in monitoring experiences. Recruitment ended with no additional interested participants and data saturation was achieved (no new themes emerged during the coding process).

Analysis

Audio recordings were transcribed through Descript, an online transcription software. KC reviewed transcripts for accuracy. The transcripts were entered into ATLAS.ti version 8.0 for coding. A qualitative description approach was taken (Sandelowski, 2000, 2010). Conventional content analysis was

used to code transcripts with codes based straight from the text by reading transcripts word for word (Hsieh & Shannon, 2005). KC and CG created and organized a codebook that included deductive codes based on questions in the interview guide and inductive codes that emerged from the transcripts (Appendix B). Data collection and data analysis occurred simultaneously (Hsieh & Shannon, 2005). A coding plan was made that included adding the deductive and inductive codes to transcripts as first cycle coding, combining codes post first cycle coding, and creating categories and themes in second cycle coding (Figure 1). KC and CG coded the first transcript together as a training session. Remaining transcripts were coded independently by KC. KC sent CG the transcripts after first cycle coding with highlighted quotes. CG reviewed the coded transcripts for coding agreement. KC and CG met weekly to discuss each transcript and addition of new codes as well as come to consensus on coding disagreements. Through conventional content analysis, codes were grouped into categories by KC and LB through second cycle coding (Hsieh & Shannon, 2005) (Figure 1). Findings represent a direct descriptive summary of the categories.

Figure 1: Coding Process



Results

Participants

Eight participants were interviewed. Six of the eight participants were recruited from a Pompe Facebook group and two were recruited from CCHMC. All eight participants were mothers between 29 and 38 years old, married, Caucasian/white, and had at least some college education (Table 1). Their children with LOPD diagnosed following NBS screening ranged from three months to three years at the time of interviews (Table 2). Of the seven known genotypes for the children, five were homozygous for c.-32-13T>G (Table 2).

Table 1
Parent Demographics

		n
Age		
	Range	29-38
Gender		
	Female	8
Race		
	White/Caucasian	8
Marital Status		
	Married	8
Highest Education		
	Some College	1
	College Degree	2
	Some Graduate	1

Table 2
Child Demographics

Participant	Child's Age	Child's Genotype
1	5 months	c.-32-13T>G homozygous
2	3 months	c.-32-13T>G homozygous†
3	2 years	c.-32-13T>G and 2242dupG
4	2 months	c.-32-13T>G and c.2481+110_2646+39del
5	2 years	c.-32-13T>G homozygous*
6	1 year	c.-32-13T>G homozygous†
7	9 months	Unknown
8	3 years	c.-32-13T>G homozygous

*taken from parent's results
† by parental report

Experiences with NBS and Diagnosis

Communication of NBS and Diagnosis

Seven parents learned of their child's initial abnormal NBS from their child's primary care provider (PCP)/Pediatrician or a nurse of their PCP/pediatrician (Table 3). One mother reported learning the NBS results from the health department (Table 3). All participants learned results via phone within a few days to two weeks after leaving the hospital. Parents subsequently met with geneticists and genetic counselors for additional testing to determine if their child had Pompe disease and if so, which type, IOPD or LOPD.

Table 3
Parent reports of learning about NBS result

Participant	Caller with NBS Result	NBS Result Timing after Birth
1	Pediatric Nurse	8 days
2	Pediatric Nurse	3-4 days
3	Pediatrician	7 days
4	Primary Care Physician and member of genetics team	7 days
5	Pediatrician	2 weeks
6	Pediatrician	7 days
7	Primary Care Office	10 days
8	Health Department	7 days

Waiting between NBS results and diagnosis

The wait for the initial genetic appointments, additional information, and the specific diagnosis after receiving the abnormal NBS were all described as sources of stress and anxiety for parents. During this time, parents reported that they did not cope well. When parents reported on the way they coped, they described focusing on their newborn and other children. The waiting time for the return of confirmatory

testing and diagnosis ranged from a few days after the initial call to a few months to receive genetic testing results.

"The waiting game is so hard just to figure out if it's late-onset or if it's [infantile]-onset. I think that waiting game just about did me in. It was very, very hard to do…." Participant 1

During periods of waiting, parents sought information from Google. Parents stated that when they received the initial news, they were told not to google it, but every parent reported they googled Pompe disease which produced devastation, fear, and uncertainty.

"I know [the nurse] told me not to Google and I'm so grateful that she told me that, but I had idle hands and an anxious heart, and I had to." Participant 1

"It is really scary to be honest because you just don't know what you don't know and all you know is what you read on Google." Participant 7

"We Googled Pompe disease and literally the first thing that comes up is these babies don't live past their first birthday and obviously that was super heartbreaking. I don't think I'll ever forget that moment of seeing that and thinking that's the possibility." Participant 8

Emotions

Parents provided descriptive examples of the emotions that came with the initial news about the NBS result and during the waiting period between NBS results and initial visits and molecular test results (Table 4). All parents experienced uncertainty about which form of Pompe disease their child had which produced anxiety. The stories from parents described trauma from the news, stress related to the possibility that their child could have a genetic disease, devastation related to the unexpected information about the newborn screen, and fear of the future. A period of sadness was described by some parents when they received the diagnosis of LOPD. However, all parents felt relief when their child was diagnosed with LOPD rather than IOPD.

Table 4
Emotions related to the initial NBS result, waiting period, and diagnosis of LOPD

Emotion	Quotes
Grief	*"At first, I feel like I went through all the stages of grief, probably three times over" Participant 1*
Fear	*"We were terrified because they just said Pompe disease…They didn't say what types and the more we Googled, the more we found out that the life expectancy isn't long. We're looking at this baby that they just said is completely fine, healthy, and everything was great and then had this just hanging over us. It was probably the hardest week of our lives, to be honest." Participant 6* *"It was a rough go for a bit because you have the happiness of having a child and that happiness just drops into fear." Participant 6*
Traumatized	*"We didn't really have a super great experience at first because it's like our doctor's office was just kind of like 'I'm sorry we don't know anything about it, but your child could die in a year'… I know they do not have to know everything, but they did not know anything before they called us. So, it was kind of traumatic, to say the least." Participant 7*
Devastation	*"We were just constantly devastated in the first month." Participant 8*
Relief	*"We were slightly more relieved just because the infantile-onset one causes more issues and they have to receive treatment sooner, whereas with the late-onset one the treatment could be held off until much later in life and I don't believe it causes many issues with the heart and respiratory system as it does with [infantile-onset]." Participant 5* *"I guess obviously very relieved that if you had to have some type of the disease, that was the best kind to have, but also just heartbroken he'd have to go through this in his life." Participant 6* *"I remember feeling relieved that it was late-onset Pompe, but at the same time, thinking now I'm going to have to worry about this for the rest of her life." Participant 8*

Three mothers reported they felt that being postpartum at the time of the newborn screen call and during the period of waiting for a first visit exacerbated their feelings of grief and stress.

> *"Seven days postpartum with your sixth child and somebody is telling you to go home and love your baby, because literally there is no hope, awful, awful, awful…." Participant 3*

"It was an extremely stressful time when I first found out, especially since you're extremely hormonal after you give birth in the first place and then to basically add to my plate that something is wrong with my child was a lot." Participant 5

Siblings

Parents became worried about their older children who were not screened for Pompe disease on NBS when they received a diagnosis of LOPD for their newborn. Cascade testing diagnosed two older siblings in one family (participant 3), aged 15 and 10, who subsequently began being monitored for symptoms.

Experiences with Living with the Diagnosis

Uncertainty

Parents expressed uncertainty living with the diagnosis, specifically in terms of symptom onset and the variability of LOPD. Parents also expressed uncertainty about the future, including insurance coverage for treatment and their child's career (Table 5).

Table 5
Uncertainties related to parents having a child living with an LOPD diagnosis

Uncertainty Theme	Quotes
Symptom Onset	*"I think it is kind of hard since it's such a spectrum and it's such a wide spectrum. It's kind of hard because I wanted to plant my feet firmly on what it was going to look like." Participant 1* *"Sometimes you don't even know what you don't know and that's what's kind of scary." Participant 6*
Future Insurance Coverage of Treatment	*"I think maybe the biggest worry I have is when we get there is insurance going to [cover treatment]. What's their criteria for making a payment on a very, very expensive drug? What does a kiddo have to show? Like if they don't have abnormal CK values, but they're showing physical decline, like what?" Participant 2*
College and Career Choices	*"You want to say to your kid you can be whatever you want, but then in the back of your head you have that nagging of what if they make a career choice they can't [physically] do, then what? You don't want them to struggle." Participant 6*

Emotions

Parents described many emotions relating to living with the diagnosis of LOPD (Table 6). Parents expressed gratitude that their child was diagnosed early but they also experienced anticipatory grief and worry related to development and symptoms onset.

Table 6
Emotions related to parents having a child living with an LOPD diagnosis

Emotion	Quotes
Anticipation	*"I just feel like, someone used the word, anticipatory grief, when we're going to see symptoms and how we're going to handle it when it gets here kind of a thing." Participant 1*
Sadness	*"I'm not devastated anymore. I think me and my husband both say that we have days where it's still kind of hard, like it hits us and we're just having a bad day about it." Participant 1*
Gratitude	*"We're thankful that we have the best end of the deal versus the other side, which I couldn't imagine having the infantile-onset, but still we would still fight and do whatever it takes to get the best care that we can." Participant 4* *"Being in [a support group], there's people that are misdiagnosed with things well into their thirties and forties and their muscles deteriorate and they can't get that back. They start enzyme replacement, but it's too late, so I'm very thankful that it's added to the newborn screen because that gives us a jump start on things." Participant 4*

Hypervigilance

Parents became hypervigilant after their child's diagnosis. They paid extra attention to their child's milestones and worried that a finding could be a symptom of Pompe disease.

> *"I noticed a little bit that she's always had her tongue out, which for a baby to have their tongue out it's normally cute. Instead of me just being able to see it as cute, I got really nervous because I remembered in my research that tongue enlargement was something that was a Pompe symptom, so, then I automatically went there…. When she is trying to hold her weight on her feet flat-footed, she has like a little quiver in her leg, so instead of me being able to just relax and think like, well, she is a baby, she is gaining strength, but she has to learn all this stuff. I*

automatically thought it was Pompe related. I think, I am probably overanxious about small things that may or may not even be an issue. I think just because I'm on high alert for symptoms that I think into the things that are very much more than likely unrelated. So as far as seeing her differently, I think that it's like maybe [being] more protective, more high alert." Participant 1

"… being a PT, I'm looking for even just little signs of him being behind in his development…. He's got some allergies right now, and I know a lot of the moms talk about, oh, you don't want your kid with Pompe to get sick because they tend to stay sick for a while. So I think I've been a little more worried with him than I was my oldest just because I do know that he has it." Participant 2

"You try not to nitpick and say what is this going on; are your calves hurting because you just ran and you're a crazy kid out at recess or are your knees and calves hurting because of Pompe disease…. However, you just keep that little information in the back of your head. Our ten-year-old has been complaining of lower leg pain and everybody was brushing it off as growing pains… so we kind of troubleshoot a little bit without running to the doctor every little chance we are calling or emailing the doctor." Participant 3

"… you start overanalyzing everything and that's what I've been doing with her. Anytime she chokes, is that the respiratory part of the Pompe or is it just her being a normal newborn? Her legs kind of twitch every now and again, is that Pompe or is it just her being a normal newborn…. So, yeah, I guess I do look at her a little bit more fragile than I do the other kiddos." Participant 4

Coping

Parents indicated they coped with the diagnosis in many ways (Table 7). Many parents adjusted their focus on their family and daily life to cope with the diagnosis and avoided thinking about it until doctor visits approached. Two parents focused on trying to stay positive to cope.

Table 7
Methods of coping reported by parents through diagnosis period and after

Coping Method	Quotes
Avoidance	*"We don't feel that it's something that needs to hinder him from doing anything. We feel that if we bring it up or the more that it's brought up to our family, it just causes more stress and more anxiety. And it's not something that we typically try to do." Participant 5* *"I definitely don't want her to feel limited because of [her diagnosis], especially when presently she's not. She doesn't need to be limited by that because her muscles are fine and her motor skills are great. It sort of comes up around the times when we go to the doctor, otherwise, we just don't really talk about it." Participant 8*
Positivity	*"We try to do positive at our house, positive vibes, positive faith. We try to say, guess what? You may have this lab draw and I know they have to take quite a few tubes of blood from you... do you want to go over to a friend's house afterward… just making that a special thing. [We say] this day stinks, I know you have all day doctor's appointments at 10 years old, and you have to miss school on your birthday. You know what? I think he deserves a new nerf gun…. We just want to normalize doctor appointments. When [they] go off to college, I still want them to feel like this is just normal. Yes. I'm going to stay with my appointments. Yes. I'm going to keep this up. Yes. This kind of does stink as a young adult, but you know what? I can still ride a bike. I can still play sports. I can still do all these things." Participant 3*

Parents valued having support systems for emotional support as well as for informational resources (Table 8). The most common support system discussed by parents was the Facebook parent group as they stated it provided hope and quick answers to questions. Parents listed family, friends, religion, and other communities as some of their main sources of support. Providers also provided support in different ways such as educating themselves, addressing psychosocial concerns, and providing reassurance.

Table 8
Support systems reported by parents through diagnosis period and after

Support System	Quotes
Facebook Parent Group	*"I got in contact with all those moms on the Facebook page, that helped probably more than anything, just knowing that kids can be normal and okay with the disease. Then also seeing how variable it is, well it's just so all over the board what it can do to your body, so I don't know. It's a scary thing, but I feel better with the knowledge I have now." Participant 2* *"Its really nice to jump onto the group and just quickly ask a question and you get 54 responses or comments to this one question…it makes you feel like it's a bigger community than what we are because we are such a rare thing here." Participant 3* *"I went on Facebook and got on some different support groups. That really seemed to help the most because getting people's actual life experiences was much better than Google." Participant 4* *"Whenever you get on the Facebook groups, you're like, oh my gosh, there's pictures of these little boys or girls doing so good and that just gives you hope." Participant 7*
Family/Friends	*"I feel like it's really important to have your family close to you in things like this. Just because you have your older kids who need picked up from school. Like just getting everything lined up whenever you do have appointments and things like that. And then emotionally, when you go through it all, it's nice to have everybody there and just some people to lean on when you go through it." Participant 7*
Religion/ Spirituality	*"I had posted on my personal Facebook page asking my friends and family for prayers for her. We were going to something and we were waiting; that we received a diagnosis and we were waiting on more details about the diagnosis. I said that we wanted everybody to pray for us." Participant 1*
Providers	*"Just knowing that [my pediatrician] had done his homework on this to learn more, made me feel very supported." Participant 1* *"… I was by myself doing all the appointments with [a social worker], so having somebody so upbeat and positive really, really, really helped me." Participant 3* *"Whenever we are anxious, and we get [to the research center], and we see the doctors, the doctor's kind of ease our mind. They remind us treatment is an option. There's some kids out there that have genetic diseases that we can't do anything about and there's therapy and he's going to be okay. They reassure us that everything's going to be fine and I guess that's how we cope." Participant 7* *"I remember as clear as day the genetic counselor said. 'Well, your job is to love her and you're going to leave the worrying about that to the experts because we're going to follow her and keep track of her CK levels and keep track of her development. And we're going to be the ones to worry about that. And your job is to just love her' I'll never forget that either. It totally changed my perspective on the whole thing." Participant 8*

Acceptance and Normalization

Some parents needed time to grieve before they were able to reach acceptance. Many families referred to their child as a normal kid and did not try to label their child because of their diagnosis as they gained acceptance and gained more information about the diagnosis.

> *"He doesn't have any of the symptoms and we're not having to do any of the treatments, so to us, he is a normal kid who does normal things." Participant 5*

One parent described the diagnosis as a risk factor rather than an actual diagnosis.

> *"I don't want people to treat my son differently because he's got a disease. I do understand the importance of monitoring for the signs of the disease, but to me, I think my genetics counselor put it really well and she said it's a risk factor for getting the disease." Participant 2*

Three parents explained early diagnosis helped monitoring become normalized in their family.

> *"I think what's nice about being diagnosed so young, this'll just be his normal, whereas you're not taking a six year old and taking them out of the normal routine of life and having them go every three months or every six months, whatever. It's just going to be normal for them." Particiapnt 7*

Family Planning

Some parents indicated that receiving their child's diagnosis of LOPD after NBS influenced their family planning. One family (participant 8) chose prenatal testing in a future pregnancy to feel prepared. Others decided not to have more children because their experience with receiving a diagnosis of LOPD was very traumatic. Still others interrupted a 25% recurrence risk as low and were reassured by autosomal recessive inheritance and chose to have more children.

Experiences with Medical Monitoring

Reported Monitoring Plans

Participants were asked to describe their medical monitoring using a checklist designed from the Pompe Disease Newborn Screening Working Group recommendations (Kronn et al., 2017). Parents

reported their children had received a number of tests and examinations since their diagnosis (Table 9). All eight children received CK levels, Hex4 levels, and an echo. CK levels, Renal/Hepatic panels, and Hex4 levels were performed routinely at visits, typically with the genetics team. All children received a baseline echo and seven received a baseline ECG. Some children received secondary Echos or ECGS at one year. Three children received chest X-rays. One child received a baseline chest x-ray and was followed up with an echo due to an abnormal finding that was a thyroid concern. Three had follow up hearing screens after their newborn hearing test. Seven children received a physical therapy assessment. Other assessments include vitamin D levels, feeding/ swallowing assessments, neurology assessments, muscle ultrasounds, vision screens and spirometry.

Three parents reported that their children were also involved in research studies related to LOPD which led to increased monitoring and assessments for research purposes (Participants 3, 6, and 8).

Parents reported that while geneticists conducted the majority of physical exams for their child which is important for assessment of muscle tone, other providers also conducted routine physical exams, including pediatricians, physical therapists, and neuromuscular physicians. Parents expressed the highest comfort with specialists and experts in Pompe disease conducting their child's physical exams because of their experience with the patient population.

Table 9

Assessments received by LOPD patients to date

Participant	CK Level	Renal/ Hepatic Panel	Vitamin D Level	Hex4 Level	ECG	Echo	Chest X-ray	Physical Therapy Assessment	Hearing Screen	Feeding/ Swallowing Assessment	Neurology Assessment	Muscle Ultrasound	Vision Screen	Spirometry
1	X	X		X	X	X		X						
2	X			X	X	X	X	X						
3	X	X	X	X	X	X		X	X	X	X			
4	X	X		X		X								
5	X			X	X	X	X	X						
6	X	X		X	X	X		X		X		X		
7	X			X	X	X		X	X			X		
8	X	X		X	X	X	X	X	X	X			X	X

Providers

Parents were also asked to describe the providers their children see based on the recommendations from the Pompe Disease Newborn Screening Working Group (Kronn et al., 2017). Parents reported their child was followed by a variety of providers. All eight children met with geneticist with or without a genetic counselor. Parents reported their child would be or has been seen every six months in the first two years of life and then annually for seeing the genetics teams and most reported they saw genetics more than once in the first three months.

More than half the children were seen by a cardiologist to assess for cardiomegaly and cardiomyopathy. Cardiologist visits varied between one initial visit, two visits, and routine follow ups. One parent reported her child follows with cardiology every year for an unrelated heart concern (participant 1). Two children were seen by a pulmonologist, one for a baseline visit and one is followed yearly. Two children were receiving physical therapy every two weeks. One other mother reported a physical therapist was present at each clinic visit with their multidisciplinary team. A metabolic physician was involved in this child's care. A neuromuscular doctor was involved in one child's care. A neurologist was involved in one child's care. All eight children were being followed on a typical well-child visit schedule with their pediatricians or PCPs with no additional visits for LOPD.

Parental advocacy and collaboration

Parents described being proactive about requesting more monitoring based on the Pompe Disease Newborn Screening Working Group recommendations from their providers. For example, one mother (participant 3) changed providers for her three children with LOPD because they were not be as vigilant as she wanted.

> *"We are really [our children's] advocates, so us speaking up for children has been something that has not come naturally, but has been a needed asset for us." Participant 3*

Parents also indicated that providers listened to their suggestions to alter medical monitoring to provide the best care for their child.

"[My pediatrician] knows that I want to do anything and everything. Pulmonologists, bring it on, if she thinks that I need it. Swallowing study, let's do it. If it's out there, I want to do it. I mean, obviously not anything too invasive like surgery or something like that, but if it's out there and available, I want to take advantage of it." Participant 4

"That's actually us telling [our providers] what we feel and then we go off of recommendations from [other specialists] and say, hey, are you comfortable with doing an echo and EKG every two years? Are you comfortable with seeing us every year and we would be seen yearly anyways. So it was more of us saying, okay, these are the recommendations we're bringing to you. What do you think about this? It was more of us telling them and asking them what they thought." Participant 3

Telehealth due to COVID-19

Our study took place during the COVID-19 pandemic, during which medical monitoring appointments were delayed or conducted by telehealth. Many felt telehealth was a challenge because they wanted the providers to physically see and touch their child to do a physical assessment. Specifically, the assessment of muscle tone was challenging via telemedicine.

"The [early intervention program] who do physical therapy has done Zoom assessments. It's very difficult. It's on webcam essentially and they have me do these things with her while they watch and they try and have me explain what I'm feeling or what I'm assessing… I'm thankful that they're following her, but it's hard. It's hard to put a lot of confidence in what they're assessing when it's on camera." Participant 1

" [Telehealth] is definitely not the same as having a physician physically examine your child, but she was able to perform all the tasks that they asked to do through the telemedicine medicine visits. Maybe that's the way it's going to be in the future, I'm not sure, but for the visit, we had it worked out really well for us. I can't complain." Participant 3

"They want to do everything over the phone and through telemedicine and that's hard. I really want somebody to put their hands on her and make sure that we're doing everything possible that we can do right now because obviously, any mom would want that." Participant 4

Benefits

Parents reported the biggest benefit of monitoring was that it helped comfort and ease their minds because monitoring would allow early detection of symptoms and initiation of treatment without a diagnostic delay.

"[Our doctor] said it's the ethics of in [adulthood] by the time they get diagnosed and get put on enzyme replacement therapy, it's almost too late. They have the symptoms that nothing is going to reverse, and it just stabilizes the diseases, if that. I think the monitoring is important because if things do start to go south, I think most every parent with an LOPD kiddo would tell you they want to get them on treatment so that they don't have to live with that for the rest of their life, the weakness and the things that can happen from that." Participant 2

"It kind of eases some worries on our end of what if we miss something happening and we don't know it. It is kind of comforting to have these consistent appointments." Participant 6

"I don't need to be constantly worrying about what's going on and whether their CK levels are starting to be abnormal. I feel like knowing that there's like a very specific thing that can tell when this is off, we're going to need to start talking about therapy, ERT. It helps me to relax, so that to me is a huge benefit. Just the idea that we aren't waiting for physical symptoms or physiological symptoms." Participant 8

Barriers and Drawbacks

The mothers in this study did not report any barriers to monitoring their children's health, but they did speak about drawbacks. Drawbacks include disagreements about monitoring with spouses and providers.

"My husband doesn't really want to continue the monitoring until we start seeing symptoms. For me, it's kind of like a peace of mind to make sure that all his levels were normal." Participant 5

"We actually ended up switching our neurologist and our cardiologists because we as parents did not feel like they were trying to be as proactive….. We've kind of had to fight a little bit to get baseline testing done for our older kids... We have switched the neurologist and we switched the pediatric cardiologists, the cardiologist that told us to go home and love our baby instead of actually digging a little bit deeper… We were very happy with the team we have here now locally." Participant 3

Parents explained medical monitoring of their asymptomatic children yielded many emotions, both positive and negative. Parents felt frustrated when disagreements occurred with providers. Parents also worried between visits and about upcoming visits.

"If the doctor was constantly reordering all these tests, it would make me feel like they are expecting something to go wrong a lot sooner than it may. So, it maybe creates unnecessary worry that there is going to be health issues early on." Participant 2

"When we have appointments, it gets a little anxious and our minds go places we shouldn't let them but other than that…. You just get nervous that their levels are going to go up or his heart's going to show enlargement or anything like that. There's anxiety of having to start treatment because then it feels real. Right now, you go through day to day and it just does not feel real, but then whenever you have to go [to the hospital] and you walk into [the hospital], you have to run all these tests and it just kind of brings back memories and then it also reminds you that he actually has this. We could have to do treatment starting next week if his numbers aren't how they should be." Participant 7

Time for medical visits was another drawback noted by participants. In particular, the amount of time they had to take off work, travel for appointments, and wait for visits. Scheduling multiple appointments if more than one child had LOPD was also a challenge.

Suggestions

Parents were asked about changes they wanted in management. They explained they would like to see providers prepare more before visits and that the specialists should communicate more with the PCP or pediatrician.

> *"If something's going to be put on newborn screening in that state, then have some kind of training in it so that they can help the families. I had one of my pediatricians, and they're great, but they even said 'is there anything that we should be looking for that [our specialists] said'. This is not how it should be working. I just think more knowledge for the providers, the pediatrician part aspect of it." Participant 6*

Parents made suggestions for families such as being proactive about monitoring, advocating for their child, and joining support groups such as the one found on Facebook with other parents who have children with Pompe disease.

> *"I would say as crazy as it sounds, find a Facebook group, get involved with them because they're the people I can look at it and that gives you hope." Participant 7*

Parents made suggestions for delivering the initial NBS news. They suggested hearing the information from someone with more expertise would be beneficial and that during the initial visits that providers should be mindful of the stress the parents are going through. Every parent said they were told not to google Pompe disease, however, since parents will still google the condition, they recommended that providers describe the types of information they may see on the internet.

> *"I wish that she just would have said that there was stuff off with her blood that we needed to see somebody, to kind of look more into it and discuss it more. I think I would have been anxious in the waiting period anyways, but I so hope, I so wish that she wouldn't have told me something that I could have Googled because the first thing that popped up when we Googled it was that people with this diagnosis don't live past a year or two. It's just hard to even get through that like that's not even our reality and it's still hard for me to talk about." Participant 1*

Parents explained they hoped that new information on genotype phenotype correlation will tailor treatment plans.

> *"What's kind of amazing is that they are part of what is changing these protocols. Newborn screening for Pompe is so new that the protocol is changing as it goes. I know before they were born kids were being checked every three months or every two months and now it is six months. My hope is that it eventually with these mutations we are really fine to check once a year or once every two years or whatever, but that is a wish, I don't know if that's possible."*
>
> *Participant 8*

Discussion

Newborn screening for conditions with both early-onset and late-onset forms, like Pompe disease can result in challenges for families and providers. Parental emotions are intense through the diagnosis period and living with an asymptomatic child. These emotions change from the initial NBS result to living with the diagnosis. More positive emotions are present after acceptance and normalization. Uncertainties were present after the NBS results, during the waiting period for a diagnosis, during living with an asymptomatic child, and relating to monitoring. Parent reported monitoring plans varied for each of their children.

Experiences with NBS and Diagnosis

We found that parents voiced profound effects after receiving their child's abnormal NBS and diagnosis, specifically heightened anxiety, fear, and uncertainty. Similar qualitative research by Pruniski et al. (2018), who interviewed nine parents with children with both IOPD and LOPD diagnosed following NBS also found that parents experienced increased anxiety, fear, uncertainty, and gratefulness in response to a diagnosis of LOPD. Our findings suggest that negative emotions may be heightened during the postpartum period as this is a time of intense emotions and transitions for a family.

Parental fear and anxiety were most intense during the waiting period between the initial NBS result call and meeting with the genetics team for both our study and Pruniski et al.'s (2018) parents.

During the waiting period, parents explained that googling Pompe disease was traumatic. Parents see IOPD first on the internet, however, their child could have LOPD, be a carrier for Pompe disease, or have a pseudodeficiency. These other outcomes may not be clearly described on the internet.

Mostly pediatrician offices called out the initial NBS result to families. Other studies have reported limited awareness about NBS among both parents and providers (Davis et al., 2006). Continuing updated medical education programs on Pompe disease and other conditions on NBS will aid in better communication of this sensitive information to families, especially since they may not be gaining all the appropriate information from the internet.

A positive experience with initial news can help build rapport and trust between the family and health care providers (Evans et al., 2019).

Experiences with Living with the Diagnosis

We observed that parents were hypervigilant about their child's development as a result of the uncertainty about symptom onset. The parents we interviewed were also uncertain about what the future would hold for their child. The increased hypervigilance noted by parents in our and other studies may lead to medicalization of the asymptomatic child with LOPD supporting the notion of "patients in waiting." (Bouwman et al., 2013; Pruniski et al., 2018)

Timmermans and Buchbinder (2010) introduced "patients in waiting" when describing how NBS would increase the number of diagnosed asymptomatic patients that do not need treatment. "Patients in waiting" live not knowing when or if their symptoms will arise which causes a high amount of uncertainty for pre-symptomatic patients and their families (Timmermans & Buchbinder, 2010). A patient diagnosed with LOPD at one year old described having a burden of knowledge living asymptomatic for 20 years. (Kwon & Steiner, 2011)

The parents in our study coped with negative emotions and uncertainty by seeing other families with children who have Pompe disease on social media groups. This helped parents gain a more realistic idea of what the diagnosis would look like and provided hope. Parents also reported that this group has been helpful to make them feel like a member of the Pompe disease community as they live with the

diagnosis. These findings contrast to other parents interviewed by Pruniski et al. (2018) who reported isolation and loneliness in social media support groups, particularly if their child had no symptoms compared to others in the group.

Experiences with Medical Monitoring

Medical monitoring for asymptomatic children also impacts parents as parental anxiety and uncertainties increased related to medical visits. Participants described increased stress and anxiety that symptoms or changes in health will be found during medical monitoring visits.

Despite the increased negative emotions, parents expressed gratefulness for monitoring because it provided reassurance that their child would be able to start ERT as soon as symptoms arise. Routine follow-up and checkups have been found to provide security to "patients in waiting" (Timmermans & Buchbinder, 2010). The multiple visits and lab tests may help reassure parents that they are doing everything they can, but they may also be creating unnecessary stress and anxiety, or like one participant describes "anticipatory grief". Recognition by providers of the psychosocial implications of medical monitoring of asymptomatic patients and collaboration between parents and providers will be important to find a balance that eases stress and anxiety for parents.

Parents reported many differences between their children's medical monitoring plans to date (Table 9). Most of the parents in our study wanted to be as proactive as possible and found it frustrating when plans were not clear. Newborn screening for Krabbe disease (KD) has also led to similar uncertainties for families whose children are at risk of developing later-onset KD, another lysosomal storage disease for which early treatment can lead to improved outcomes. When New York initiated screening in 2006, monitoring plans for asymptomatic children diagnosed with KD through NBS were still evolving, which increased uncertainty for providers and families (Wasserstein et al., 2016). Providers suggested some intensive follow-up for KD. Some families were not willing to subject their children to invasive assessments when they were asymptomatic, thus increasing risk for loss-to-follow up (Duffner et al., 2009; Ross & Clarke, 2017; Wasserstein et al., 2016).

Genotype-Phenotype Correlation

Most of the children of parents in our study were homozygous for the c.32-13 T>G splice site variant (62.5%, 5/8) which is commonly associated with the mild LOPD phenotype, but recent evidence shows a more classical LOPD phenotype in some patients with this variant, and modifiers could explain childhood symptom onset for some patients (Bergsma et al., 2019; Herbert et al., 2018; Kroos et al., 2012; Kroos et al., 2007; Musumeci et al., 2015; Rairikar et al., 2017). Thus, symptom onset is expected to occur later in life but may be earlier. As we learn more about genotype-phenotype correlation, we may have more specific medical management suggestions for individuals based on their genotype. Providers may also be able to help provide anticipatory guidance for families.

Telehealth

As our study occurred during the COVID-19 pandemic, many clinical encounters were through telehealth. When asked about telehealth visits, participants said they made the best of it but many preferred to have in-person physical examinations to provide more reassurance. Telehealth can be a challenge for families to use under certain circumstances such as receiving abnormal test results on their newborn from a new provider, being unfamiliar with the technology, and communication issues using the platform.

The COVID-19 pandemic has expanded telehealth infrastructure that can aid in providing faster, more efficient care to families. Telehealth can limit the need for travel to follow-up appointments and potentially decrease the wait for initial visits with providers so that parents can gain more education about the NBS results. Telehealth visits can decrease the wait time between the initial NBS results and meeting with the genetics team. Providing families NBS information from geneticists and genetic counselors through telehealth sooner could decrease the negative emotions brought on by the waiting period and deter parents from seeking more information on their own.

Conclusion

The parents made many suggestions for both providers and other families. Parents were all thankful for an early diagnosis as it allowed them to be proactive about their child's medical care,

however, they stated they had intense emotional responses and uncertainty when pediatricians provided abnormal NBS results. They recommended that it would be helpful if these providers had increased knowledge and more information about Pompe disease when communicating NBS results to families. Increased education to primary care providers can help to decrease these responses. Parents also suggested that other families be proactive, advocate for their children and NBS, and seek support from other LOPD families. Parents said being a part of support groups was beneficial to see other experiences and find hope.

Continuing to explore parents' experiences with NBS for Pompe disease as their children age could help identify areas where families could benefit from more support from providers. Further exploration of the benefits and limitations of monitoring asymptomatic patients from the parental perspective could help inform future practice and policies regarding communicating NBS Pompe disease results and follow-up medical monitoring plans.

Limitations

Our study consisted of eight participants, a small sample size, which limits generalizability to all parents with children with LOPD diagnosed because of NBS. The participants in our study were all mothers, were all white/Caucasian, and had an education level of some college or above. These findings may not be generalizable to all parents of children with LOPD diagnosed following NBS. In addition, six of the eight participants were recruited through a Pompe disease Facebook group, suggesting participants may have had a bias towards using social media as support. Specifically, the mothers in this may be more likely to use social media for support, information, and anticipatory guidance about LOPD than other parents of children with LOPD.

Newborn screen for Pompe disease is relatively new so the asymptomatic patients were all ages three and under. Longitudinal studies that follow the natural history of children diagnosed with LOPD on NBS and the monitoring they receive overtime will inform updates to management of patients with LOPD.

Bibliography

Alandy-Dy, J., Wencel, M., Hall, K., Simon, J., Chen, Y., Valenti, E., Yang, J., Bali, D., Lakatos, A., Goyal, N., Mozaffar, T., & Kimonis, V. (2019). Variable clinical features and genotype-phenotype correlations in 18 patients with late-onset Pompe disease. *Annals of Translational Medicine*, *7*(13), 276. https://doi.org/10.21037/atm.2019.06.48

Bergsma, A. J., In 't Groen, S. L. M., van den Dorpel, J. J. A., van den Hout, H. J. M. P., van der Beek, N. A. M. E., Schoser, B., Toscano, A., Musumeci, O., Bembi, B., Dardis, A., Morrone, A., Tummolo, A., Pasquini, E., van der Ploeg, A. T., & Pijnappel, W. W. M. P. (2019). A genetic modifier of symptom onset in Pompe disease. *EBioMedicine*, *43*, 553-561. https://doi.org/10.1016/j.ebiom.2019.03.048

Bouwman, M. G., de Ru, M. H., Linthorst, G. E., Hollak, C. E., Wijburg, F. A., & van Zwieten, M. C. (2013). Fabry patients' experiences with the timing of diagnosis relevant for the discussion on newborn screening. *Molecular Genetics and Metabolism*, *109*(2), 201-207. https://doi.org/10.1016/j.ymgme.2013.03.008

Carmichael, N., Tsipis, J., Windmueller, G., Mandel, L., & Estrella, E. (2015). "Is it going to hurt?": the impact of the diagnostic odyssey on children and their families. *Journal of Genetic Counseling*, *24*(2), 325-335. https://doi.org/10.1007/s10897-014-9773-9

Chien, Y. H., Hwu, W. L., & Lee, N. C. (2013). Pompe disease: early diagnosis and early treatment make a difference. *Pediatrics and Neonatology*, *54*(4), 219-227. https://doi.org/10.1016/j.pedneo.2013.03.009

Chien, Y. H., Lee, N. C., Huang, H. J., Thurberg, B. L., Tsai, F. J., & Hwu, W. L. (2011). Later-onset Pompe disease: early detection and early treatment initiation enabled by newborn screening. *The Journal of Pediatrics*, *158*(6), 1023-1027.e1021. https://doi.org/10.1016/j.jpeds.2010.11.053

Davis, T. C., Humiston, S. G., Arnold, C. L., Bocchini, J. A., Bass, P. F., Kennen, E. M., Bocchini, A., Kyler, P., & Lloyd-Puryear, M. (2006). Recommendations for effective newborn screening communication: results of focus groups with parents, providers, and experts. *Pediatrics*, *117*(5 Pt 2), S326-340. https://doi.org/10.1542/peds.2005-2633M

Duffner, P. K., Caggana, M., Orsini, J. J., Wenger, D. A., Patterson, M. C., Crosley, C. J., Kurtzberg, J., Arnold, G. L., Escolar, M. L., Adams, D. J., Andriola, M. R., Aron, A. M., Ciafaloni, E., Djukic, A., Erbe, R. W., Galvin-Parton, P., Helton, L. E., Kolodny, E. H., Kosofsky, B. E., Kronn, D. F., Kwon, J. M., Levy, P. A., Miller-Horn, J., Naidich, T. P., Pellegrino, J. E., Provenzale, J. M., Rothman, S. J., & Wasserstein, M. P. (2009). Newborn screening for Krabbe disease: the New York State model. *Pediatric Neurology*, *40*(4), 245-252. https://doi.org/10.1016/j.pediatrneurol.2008.11.010

Evans, A., LeBlanc, K., Bonhomme, N., Shone, S. M., Gaviglio, A., Freedenberg, D., Penn, J., Johnson, C., Vogel, B., Dolan, S. M., & Goldenberg, A. J. (2019). A Newborn Screening Education Best Practices Framework: Development and Adoption. *International Journal of Neonatal Screening*, *5*(2), 22. https://doi.org/10.3390/ijns5020022

Ficicioglu, C., Ahrens-Nicklas, R. C., Barch, J., Cuddapah, S. R., DiBoscio, B. S., DiPerna, J. C., Gordon, P. L., Henderson, N., Menello, C., Luongo, N., Ortiz, D., & Xiao, R. (2020). Newborn Screening for Pompe Disease: Pennsylvania Experience. *International Journal of Neonatal Screening*, *6*(4). https://doi.org/10.3390/ijns6040089

Frank, G. (2020, February). *20 States and DC Screening Newborns for Pompe as Efforts Continue for More, MDA Says*. BioNews Services. Retrieved April 20, 2020 from https://pompediseasenews.com/2020/02/20/newborn-screening-pompe-active-20-states-dc-efforts-continue-for-more-mda-says/

Herbert, M., Cope, H., Li, J. S., & Kishnani, P. S. (2018). Severe Cardiac Involvement Is Rare in Patients with Late-Onset Pompe Disease and the Common c.-32-13T>G Variant: Implications for Newborn Screening. *The Journal of Pediatrics*, *198*, 308-312. https://doi.org/10.1016/j.jpeds.2018.02.007

Hsieh, H.-F., & Shannon, S. E. (2005). Three Approaches to Qualitative Content Analysis. *Qualitative Health Research*, *15*(9), 1277-1288.

Kallio, H., Pietilä, A. M., Johnson, M., & Kangasniemi, M. (2016). Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. *Journal of Advanced Nursing*, *72*(12), 2954-2965. https://doi.org/10.1111/jan.13031

Kronn, D. F., Day-Salvatore, D., Hwu, W. L., Jones, S. A., Nakamura, K., Okuyama, T., Swoboda, K. J., Kishnani, P. S., & Group, P. D. N. S. W. (2017). Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum. *Pediatrics*, *140*(Suppl 1), S24-S45. https://doi.org/10.1542/peds.2016-0280E

Kroos, M., Hoogeveen-Westerveld, M., van der Ploeg, A., & Reuser, A. J. (2012). The genotype-phenotype correlation in Pompe disease. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *160C*(1), 59-68. https://doi.org/10.1002/ajmg.c.31318

Kroos, M. A., Pomponio, R. J., Hagemans, M. L., Keulemans, J. L., Phipps, M., DeRiso, M., Palmer, R. E., Ausems, M. G., Van der Beek, N. A., Van Diggelen, O. P., Halley, D. J., Van der Ploeg, A. T., & Reuser, A. J. (2007). Broad spectrum of Pompe disease in patients with the same c.-32-13T->G haplotype. *Neurology*, *68*(2), 110-115. https://doi.org/10.1212/01.wnl.0000252798.25690.76

Kwon, J. M., & Steiner, R. D. (2011). "I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients. *Neurology 77*(6), 522–523 https://doi.org/10.1212/WNL.0b013e318228c15f

Lisi, E. C., Gillespie, S., Laney, D., & Ali, N. (2016). Patients' perspectives on newborn screening for later-onset lysosomal storage diseases. *Molecular Genetics and Metabolism*, *119*(1-2), 109-114. https://doi.org/10.1016/j.ymgme.2016.07.009

Lisi, E. C., & McCandless, S. E. (2016). Newborn Screening for Lysosomal Storage Disorders: Views of Genetic Healthcare Providers. *Journal of Genetic Counseling*, *25*(2), 373-384. https://doi.org/10.1007/s10897-015-9879-8

Musumeci, O., Thieme, A., Claeys, K. G., Wenninger, S., Kley, R. A., Kuhn, M., Lukacs, Z., Deschauer, M., Gaeta, M., Toscano, A., Gläser, D., & Schoser, B. (2015). Homozygosity for the common GAA gene splice site mutation c.-32-13T>G in Pompe disease is associated with the classical adult phenotypical spectrum. *Neuromuscular Disorders*, *25*(9), 719-724. https://doi.org/10.1016/j.nmd.2015.07.002

Papadopoulos, C., Papadimas, G., Michelakakis, H., Kararizou, E., & Manta, P. (2014). Highlighting intrafamilial clinical heterogeneity in late-onset Pompe disease. *Molecular Genetics and Metabolism Reports*, *1*, 2-4. https://doi.org/10.1016/j.ymgmr.2013.10.002

Pruniski, B., Lisi, E., & Ali, N. (2018). Newborn screening for Pompe disease: impact on families. *Journal of Inherited Metabolic Disease*, *41*(6), 1189-1203. https://doi.org/10.1007/s10545-018-0159-2

Rairikar, M. V., Case, L. E., Bailey, L. A., Kazi, Z. B., Desai, A. K., Berrier, K. L., Coats, J., Gandy, R., Quinones, R., & Kishnani, P. S. (2017). Insight into the phenotype of infants with Pompe disease identified by newborn screening with the common c.-32-13T>G "late-onset" GAA variant. *Molecular Genetics and Metabolism*, *122*(3), 99-107. https://doi.org/10.1016/j.ymgme.2017.09.008

Ross, L. F. (2012). Newborn screening for lysosomal storage diseases: an ethical and policy analysis. *Journal of Inherited Metabolic Disease*, *35*(4), 627-634. https://doi.org/10.1007/s10545-011-9435-0

Ross, L. F., & Clarke, A. J. (2017). A Historical and Current Review of Newborn Screening for Neuromuscular Disorders From Around the World: Lessons for the United States. *Pediatric Neurology*, *77*, 12-22. https://doi.org/10.1016/j.pediatrneurol.2017.08.012

Saich, R., Brown, R., Collicoat, M., Jenner, C., Primmer, J., Clancy, B., Holland, T., & Krinks, S. (2020). Is Newborn Screening the Ultimate Strategy to Reduce Diagnostic Delays in Pompe Disease?

The Parent and Patient Perspective. *International Journal of Neonatal Screening*, *6*(1), 1. https://doi.org/10.3390/ijns6010001

Sandelowski, M. (2000). Whatever happened to qualitative description? *Research in Nursing & Health*, *23*(4), 334-340. https://doi.org/10.1002/1098-240x(200008)23:4<334::aid-nur9>3.0.co;2-g

Sandelowski, M. (2010). What's in a name? Qualitative description revisited. *Research in Nursing & Health*, *33*(1), 77-84. https://doi.org/10.1002/nur.20362

Timmermans, S., & Buchbinder, M. (2010). Patients-in-waiting: Living between sickness and health in the genomics era. *Journal of Health and Social Behavior*, *51*(4), 408-423. https://doi.org/10.1177/0022146510386794

van El, C. G., Rigter, T., Reuser, A. J., van der Ploeg, A. T., Weinreich, S. S., & Cornel, M. C. (2014). Newborn screening for pompe disease? a qualitative study exploring professional views. *BMC Pediatrics*, *14*, 203. https://doi.org/10.1186/1471-2431-14-203

Wasserstein, M. P., Andriola, M., Arnold, G., Aron, A., Duffner, P., Erbe, R. W., Escolar, M. L., Estrella, L., Galvin-Parton, P., Iglesias, A., Kay, D. M., Kronn, D. F., Kurtzberg, J., Kwon, J. M., Langan, T. J., Levy, P. A., Naidich, T. P., Orsini, J. J., Pellegrino, J. E., Provenzale, J. M., Wenger, D. A., & Caggana, M. (2016). Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. *Genetics in Medicine*, *18*(12), 1235-1243. https://doi.org/10.1038/gim.2016.35

Weinreich, S. S., Rigter, T., van El, C. G., Dondorp, W. J., Kostense, P. J., van der Ploeg, A. T., Reuser, A. J., Cornel, M. C., & Hagemans, M. L. (2012). Public support for neonatal screening for Pompe disease, a broad-phenotype condition. *Orphanet Journal of Rare Diseases*, *7*, 15. https://doi.org/10.1186/1750-1172-7-15

Wilcken, B. (2010). Expanded newborn screening: reducing harm, assessing benefit. *Journal of Inherited Metabolic Disease*, *33*(Suppl 2), S205-210. https://doi.org/10.1007/s10545-010-9106-6

Wilson, J., & Jungner, G. (1966). *Principles and practice of screening for disease*. World Health Organization. https://apps.who.int/iris/handle/10665/208882

Appendix A: Interview Guide

Hello, my name is Kaylee Crossen. I am a genetic counseling graduate student at the University of Cincinnati and Cincinnati Children's Hospital.
We are conducting a research study to learn parents' experiences receiving a diagnosis of late-onset Pompe Disease (LOPD) on newborn screening and their experiences with their child's medical monitoring. Thank you for your interest in this study.
This interview will be conducted in a private setting and will be audio-recorded. The recording will be transcribed. To protect your privacy, we will assign a study ID that will be associated with the information you provide. We will remove your name and your child's name and any other identifiers from the transcripts. Only the research team will have access to the documents linking your study ID number and your name. The deidentified transcripts will be kept on a password protected computer when the study is completed with the possibility of using the data in future research by the study team.
Interviews will take approximately 1 hour. Demographic questions and open-ended questions will be asked during the interview. Participation is voluntary. There are no right or wrong answers. You do not have to answer every question. You may withdraw from the study at any time if you do not wish to participate.
The answers you provide will help us understand parents' experiences of having a child with LOPD. While there is no direct benefit to you, the information you provide may help other families of children with LOPD or providers.
In order to participate in this study, you must meet the eligibility criteria. I have a few questions to ask you to help determine this.
Are you a parent or legal guardian of a child who was diagnosed with LOPD on newborn screening?
Are you at least 18 years of age?
Has your child started ERT (enzyme replacement therapy) for their LOPD?
Does your child have cardiomegaly and cardiomyopathy?
(If they meet criteria, continue. If they do not meet criteria, "Thank you for your interest, but unfortunately we cannot continue with the interview.")
The interview will take approximately one hour. Is this a good time for you?
(If no, ask for a better date and time)
Do you consent to participate in the interview?
Do you have any questions for me before we begin?
Okay to start, I am going to ask you for brief demographic information to get to know you better.

Demographics:

1. How old are you?
    a. Enter age
2. What gender do you identify with?
    a. Male
    b. Female
    c. Prefer not to answer
3. What is your race?
    a. Caucasian
    b. African American
    c. Asian
    d. Hispanic
    e. Other
4. What is your marital status?
    a. Married
    b. Divorced
    c. Single

    d. Widowed
    e. Other
5. What is your highest level of education?
    a. Some High School
    b. High School Degree
    c. Some College
    d. College Degree
    e. Some Graduate School
    f. Graduate Degree or More
6. How many people, including yourself, live in your household?
    a. Enter Size
7. Does your child with LOPD have public or private insurance?
    a. Public
    b. Private
    c. Unknown
8. How old is your child who was diagnosed on newborn screening with LOPD?
    a. Enter Age
9. If you have older children than your child with LOPD, how many were screened for LOPD?
    a. Enter number
10. Of your other children screened for LOPD, how many were diagnosed?
    a. Enter number
    b. How old are they?
        i. Enter age
11. Which state do you live in currently?
    a. Enter State:
12. Which state was your child with LOPD born in?
    a. Enter State:
13. How far do you live from the center where your child receives care for LOPD?
    a. Enter distance (in miles):

Interview:

Diagnosis questions:

Now I am going to ask you about your experience with the diagnosis of LOPD for your child. These questions will be open-ended, and you can share as much or as little as you would like.

Can you first tell me a little bit about your family such as who makes up your family?

Next, I will ask you about your experiences with LOPD.

I understand your child was diagnosed with LOPD. I would like to know more about how you learned about the diagnosis. Can you tell me more about your experience receiving the diagnosis?

- Probes:
    - How did you learn about the diagnosis?
    - What were you feeling?
        - Compared to now

What does this diagnosis mean to you?

What does the diagnosis mean for your child? – (depending on child's age)

Has this experience influenced how you see your child and their health?

Medical Monitoring Plan Questions:
I will now ask you some specific questions about how your child is monitored for LOPD. The following may not all be familiar to you and in no way is this an extensive list of how your child should be followed, as some of these items may not be appropriate for your child and others with LOPD.

1. What providers follow your child for LOPD?
    - ☐ Geneticist
        i. How often in person? _____
        ii. How often by telemedicine? _____
    - ☐ Cardiologist
        i. How often in person? _____
        ii. How often by telemedicine? _____
    - ☐ Pulmonologist
        i. How often in person? _____
        ii. How often by telemedicine? _____
    - ☐ Pediatrician
        i. How often in person? _____
        ii. How often by telemedicine? _____
    - ☐ Other
        i. _____
        ii. How often in person? _____
        iii. How often by telemedicine? _____

Often when your child sees a provider for LOPD, they perform a physical exam, specifically they want to look at their muscle strength. Typically, they look at sitting, head control, walking, and climbing stairs. The next few questions will ask who performs these examinations.

2. Who conducts physical exams for your child for LOPD?
3. How often does your child receive a physical exam for LOPD?
    - ☐ Once a year
    - ☐ Once every 6 months
    - ☐ Once every 3 months
    - ☐ Other_____
4. How comfortable are you with this provider conducting a physical exam for LOPD?
5. Do you think other providers should be assessing muscle strength?

Now I will ask you about a few more tests your child receives such as blood and urine screening, heart monitoring, and other assessments.

6. Has your child received blood tests?
    - ☐ Yes
        i. Is your child currently receiving blood tests?
            - ☐ Yes
            - ☐ No
                a. How many blood tests has your child had in the past?
                    i. _____
        ii. Are they checking for:
            - ☐ CK/CPK levels (Creatine Kinase)
            - ☐ Kidney/Liver function (Renal/Hepatic function)
            - ☐ Other _____
            - ☐ Unknown
        iii. How Often?
            - ☐ Once a year
            - ☐ Once every 6 months
            - ☐ Once every 3 months
            - ☐ Other_____

- ☐ No
- ☐ Unknown

7. Has your child received urine tests?
   - ☐ Yes
     i. Is your child currently receiving urine tests?
        - ☐ Yes
        - ☐ No
          a. How many urine tests has your child had in the past?
             i. _____
     ii. Are they checking for:
        - ☐ Hex4 (Glucotetrasaccharides)
        - ☐ Other _____
        - ☐ Unknow
     iii. How Often?
        - ☐ Once a year
        - ☐ Once every 6 months
        - ☐ Once every 3 months
        - ☐ Other_____
   - ☐ No
   - ☐ Unknown
8. Has your child received ECGs or EKGs?
   An ECG/EKG measures the heartbeat and can identify differences in heart rhythm.
   - ☐ Yes
     i. Is your child currently receiving ECGs/EKGs?
        - ☐ Yes
        - ☐ No
          a. How many ECGs/EKGs did your child have in the past?
             i. _____
     ii. How Often?
        - ☐ Once a year
        - ☐ Once every 6 months
        - ☐ Once every 3 months
        - ☐ Other_____
   - ☐ No
   - ☐ Unknown
9. Has your child received an echo?
   An echo is an ultrasound of the heart which helps identify the shape and parts of the heart.
   - ☐ Yes
     i. Is your child currently receiving echoes?
        - ☐ Yes
        - ☐ No
          a. How many echoes did your child have in the past?
             i. _____
     ii. How Often?
        - ☐ Once a year
        - ☐ Once every 6 months
        - ☐ Once every 3 months
        - ☐ Other_____
   - ☐ No
   - ☐ Unknown
10. Has your child received a Chest X-rays?

- ☐ Yes
    i. Is your child currently receiving Chest X-rays?
        - ☐ Yes
        - ☐ No
            a. How many Chest X-rays has your child had in the past?
                i. _____
    ii. How Often?
        - ☐ Once a year
        - ☐ Once every 6 months
        - ☐ Once every 3 months
        - ☐ Other_____
- ☐ No
- ☐ Unknown

11. Has your child received a Physical Therapy (PT) assessment?
    - ☐ Yes
        i. Is your child currently receiving PT assessments?
            - ☐ Yes
            - ☐ No
                a. How many PT assessments has your child had in the past?
                    i. _____
        ii. How Often?
            - ☐ Once a year
            - ☐ Once every 6 months
            - ☐ Once every 3 months
            - ☐ Other_____
    - ☐ No
    - ☐ Unknown
12. Has your child had a sleep study?
    - ☐ Yes
        i. Is your child currently receiving sleep studies?
            - ☐ Yes
            - ☐ No
                a. How many sleep studies has your child had in the past?
                    i. _____
        ii. How Often?
            - ☐ Once a year
            - ☐ Once every 6 months
            - ☐ Once every 3 months
            - ☐ Other_____
    - ☐ No
    - ☐ Unknown
13. Has your child received hearing screening?
    - ☐ Yes
        i. Is your child currently receiving hearing tests?
            - ☐ Yes
            - ☐ No
                a. How many hearing tests has your child had in the past?
                    i. _____
        ii. How Often?
            - ☐ Once a year
            - ☐ Once every 6 months

- ☐ Once every 3 months
- ☐ Other_____

☐ No
☐ Unknown

14. Has your child received feeding and swallowing testing?
    ☐ Yes
        i. Is your child currently receiving feeding and swallowing tests?
            ☐ Yes
            ☐ No
                a. How many feeding and swallow tests has your child had in the past?
                    i. _____
        ii. How Often?
            ☐ Once a year
            ☐ Once every 6 months
            ☐ Once every 3 months
            ☐ Other_____
    ☐ No
    ☐ Unknown
15. What other tests, assessments, or examinations has your child received?

Thank you for that information. I am now going to ask you more questions about the monitoring plan that has been recommended for your child, specifically about your experiences. Can you tell me more about your experiences with monitoring your child's health?

How do you feel about how your child is monitored for LOPD?

What are your thoughts about the benefits of how your child is currently monitored?

- Probe on whether benefits are tangible and/or emotional

What are your thoughts about the drawbacks of how your child is currently monitored?

- Probe on whether drawbacks are tangible and/or emotional

What barriers do you and your family face with monitoring your child?

- Probe on culture and distance and trust

Tell me about the support you have for managing the diagnosis, your child's health, and monitoring plan. I am going to continue to ask about the monitoring plan but now I would like to get insight on what you think will work best for your family and child.

Are there any changes you would like to see in how your child is followed? If so, what, and why?

Do you have any suggestions you would like to pass on to other parents or to the healthcare providers who follow children with LOPD?

Is there anything else you would like to share that you think is important for providers to know that I have not asked you?

Would it be okay if we contacted you after this interview if we need additional information or have remaining questions?

Thank you for your time and participation in this interview!

Appendix B: Codebook

Category	Code	Subcode	Description
Diagnosis	Experience	Difficult News	The family reported they received difficult news
		Dx Communication	Ways in which parents were communicated with about diagnosis
		Experience	General experience parent went through
		Sibling Testing	Experience with testing other children
		Waiting	Family discussed the wait it took for diagnosis
	Knowledge	Better Understanding	Parent has better understanding from beginning
		Child Knowledge	Knowledge that the child has about visits/Pompe
		Genetic Terms	Parent discuss specific terms related to genetics
		Google	Parent gained knowledge from google
		Lack of Understanding	Parent had a lack of understand about diagnosis process
		Parent Knowledge	Knowledge about Pompe that parent has or lack of knowledge they had/have and what they have researched
		Partner Communication	Parent relays information to partner
		Provider Knowledge	Knowledge providers knew about Pompe
	Labeling	Label	Parent talks about labelling diagnosis in general
		Label: risk factor	Parent sees diagnosis as a risk factor
Hypervigilance		High Alert	in vivo to explain hypervigilance
		Hypervigilance	Parent pays extra attention to child between visits and pays extra attention to their child's health and development
		Protective	Parents are more protective of child
Anxiety/Worry		Anxiety	General anxiety
		Anxiety: future	Parent is anxious about future for their child
		Anxiety: heart	Parent has anxiety for child's heart involvement
		Anxiety: information	Parent feels that too much information is anxiety inducing
		Anxiety: labs	Parents have anxiety about labs
		Anxiety: milestones	Parents worry about if child will meet milestones
		Anxiety: onset	Parents have anxiety about when symptoms will occur
		Anxiety: telling children	Parents are nervous about telling child and siblings
		Anxious Heart	in vivo
		Unnecessary Worry	Parents worry more than they should while child is asymptomatic
		Worry: insurance	Parent fears what criteria insurance will cover ERT
		Worry: more intervention	Parent is worried child needs more monitoring or interventions
		Worry: older children	Parent worries other children may be affected after initial diagnosis on NBS
		Worry: symptom onset	Parent worries about disease onset
Uncertainty		Anticipatory Grief	Parent experience grief with asymptomatic children
		Uncertainty	General uncertainty
		Uncertainty: dx	Parent has uncertainty about what diagnosis would be
		Uncertainty: standard of care	There is uncertainty about the standard of care and what is recommended
Emotions	Negative Emotions	Desperation	Parents feel desperate
		Devastation	Parents are devasted and feel devastation
		Disheartening	in vivo, response to provider knowledge
		Exhausted	Parents were exhausted during diagnosis process
		Frustration	Parents feel frustration
		Grief	Parents grieve with new diagnosis and while waiting
		Heartbroken	Parent feels heartbroken (in vivo)
		Scared	Parents were scared
		Shock	Parent felt shock
		Stressful	Parent was stressed
		Traumatic	Parents report experience of diagnosis to be traumatic
	Positive Emotions	Confident	Parent feels confident with care and future
		Hope: no progression	Parent has hope from child being asymptomatic
		Hope: other PD children	Parent has hope from seeing other PD children doing well
		Hope: research	Parent has hope that research will bring better surveillance and treatments
		Hopeful	Parent has hope
		Peace	Parent was able to gain peace
		Relief	Parent is relieved about Late onset vs Infantile onset
		Thankful	Parent is thankful and grateful
	Emotion Changes	Emotional Improvement	Parent has better emotions since beginning
		Reassurance	Parent has been reassured

Monitoring	Physical Exam Opinions	Geneticist Confidence	Parent is confident with geneticist performing physical exams
		Geneticist Doubt	Parent is not confident with geneticist performing physical exams
		Neuromuscular Confidence	Parent is confident with neuromuscular doctor performing physical exams
		PCP Doubt	Parent is not confident with PCP performing physical exams
		PT Confidence	Parent is confident with PT performing physical exams
	Experiences with Monitoring	Advocacy	Parent advocates for child and their care
		Collaboration	Parent and Provider collaboration for their child's monitoring
		No Monitoring	Parent does not want to monitor while asymptomatic
		Normalization	Parent feels that monitoring is just a part of their normal life
		PCP Educated	PCP educated themselves on Pompe
		Preparedness	Parents feel prepared and know what will happen during visits
		Telehealth	General experience with telehealth
Benefits of Monitoring	Emotional	Comfort	Comfort comes from monitoring child for symptoms
		Safety	Safety comes from monitoring child for symptoms
	Tangible	Benefit: early detection	Parents see the benefit of early detection and starting treatment early
		Benefit: multiple providers	Parents like that there are multiple providers following child
		Benefit: providers	Providers make the appointments easier and provide information well
		Minimization	Parent's providers are eliminating unnecessary tests
Drawbacks of Monitoring	Emotional	Drawback: asymptomatic	There is many visits while asymptomatic
	Tangible	Drawback: older children	Older children have difficulties going to appointments and missing school
		Drawback: provider understanding	Some providers do not understand their need for Pompe
		Drawback: repeated tests	There are many tests that are repeated while normal
		Drawback: schedule	Between multiple kids, appointments and school it is difficult to schedule
		Drawback: time	The time appointments take is a drawback
		Drawback: waiting	Parent does not like waiting for initial visit of other visits
		Drawback: worry	Parents worry about every visit
Barriers and Challenges		Barrier	Parent discusses what barrier they face
		Challenge: insurance	Parent had difficult with testing or monitoring being covered
		Challenge: provider	Parents did not agree or work well with providers
		Challenge: telehealth	Telehealth is challenge for parent to inform specialist
		Challenge: work	Parent takes off work for visits
Desires	Changes for Diagnosis	Recommendation: initial news	Parents would like to see change in how the initial news is given
		Recommendation: join community	Parents would like to get involved with support groups sooner
		Recommendation: mindful	Parents would like providers to be mindful of situation (trainee was not experienced)
	Changes for Monitoring	Change: less visits	Parents would like less visits to decrease how overwhelming they will be if child is still asymptomatic
		Change: provider communication	Parents would like providers to communicate more about child
		Recommendation: anticipatory	Parents would like more information about other older children with LOPD
		Recommendation: Duke	Parent recommends that other parents follow with Duke
		Recommendation: prepare	Parent would like providers to be more prepared to see child
		Recommendation: proactive	Parents would like other parents to be proactive about child's health
		Recommendation: prognosis	Parents would like more prognosis information
Coping Strategies		Coping: distraction	Parents distract themselves to cope
		Coping: focus	Parents do not focus on the disease to cope, they resume as if life was normal
		Coping: information	Parents cope by having more information
		Coping: monitoring	Parents find monitoring their health is a way of coping
		Coping: no coping	Parents could not cope with information
		Coping: positivity	Parent remains positive
		Coping: prognosis	Parents think knowing prognosis will help to cope
		Coping: risk factor	Parents think not labeling with a disease is a way to cope
Support Systems for Families		Support: facebook groups	Parents find support from Facebook Support Groups
		Support: family	Parents say that their family offers emotional support
		Support: other medical parent	Parent finds support from another parent who had a child who went through a different disease
		Support: other PD parents	Parents find support from other PD parents
		Support: PCP	Parents feel supported by their pediatrician
		Support: religion	Parents feel supported through their religion
		Support: social work	Parent had social worker for support
		Support: work	Parent feels supported by bosses and coworkers
Other/Uncategorized		Change In Behavior	Parent's behaviors has changed since diagnosis
		Change In Lifestyle	Parent's lifestyle has changes from diagnosis
		COVID	Parent talks about COVID-19 and pandemic
		Crutch	Parent thinks child may use diagnosis as crutch
		Curse	in vivo, parent says diagnosis is like a curse
		Difficult Days	in vivo, Parents still have difficult days of coping
		Family Planning	Parent discusses their decisions having more children
		Idle Hands	in vivo, Parent had idle hand during wait for diagnosis to google information
		Infantile	Parent talks about infantile form
		Medical Background	Parent has medical background which influences understanding and self monitoring
		Postpartum Effects	Parent expressed emotions were stronger due to postpartum effects
		Proactive	Parent is proactive with children's health and monitoring
		Research	Child is in a research study