NEWBORN SCREENING FOR X-LINKED ADRENOLEUKODYSTROPHY:
IMPACT ON FAMILIES AND RECOMMENDATIONS
FOR HEALTHCARE PROVIDERS

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By
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CERTIFICATION OF APPROVAL

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder. It is caused by gene variants in the ABCD1 gene and results in elevated very long chain fatty acids (VLCFA) that lead to a varied clinical spectrum. Males with X-ALD may present with symptoms ranging from isolated adrenal insufficiency and slowly progressive myelopathy to severe cerebral demyelination. Females who are heterozygous for X-ALD will typically develop symptoms by age 60. X-ALD was added to California’s newborn screening (NBS) panel in 2016 in large part due to existing treatment in the form of stem cell transplantation. California is one out of 10 states currently screening for X-ALD. This study examines the impact of receiving a positive NBS result for X-ALD on families in California. In-depth qualitative interviews were conducted with mothers of 10 children (6 males and 4 females) identified via NBS for X-ALD to explore their experience with the NBS process, interactions with the healthcare team, understanding of X-ALD, coping skills, and impact on family life. The interviews lasted between 50 and 99 minutes with an average length of 65 minutes. Interviews were transcribed verbatim by an online professional transcription service. The transcribed interviews were independently analyzed using thematic analysis by two coders (Vaismoradi, Turunen, & Bondas, 2013). Overall, mothers felt strongly that X-ALD should be included on California’s NBS panel; however, the majority of mothers expressed concerns over varying aspects of the NBS experience. Common themes included high stress and anxiety at initial phone call, difficulty managing ambiguity and living with uncertainty, varied
healthcare support concerns, and desire for more resources including treatment information, clinical trials, and financial support. Mothers predominantly exhibited impressive resiliency, relying on religious beliefs, family support, and the ALD community as coping strategies. Mothers’ recommendations for healthcare providers involved in X-ALD patient care included: educate HCPs making initial phone call on ALD, provide resources and contact information for specialists with ALD experience, offer information on ongoing research, and streamline care coordination. Mothers’ advice for parents of children with X-ALD primarily focused on maintaining hope and appreciating the time they have with their children.
CHAPTER I

INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) is a metabolic disorder that disrupts the function of peroxisomes. It is caused by a pathogenic gene variant in the ABCD1 gene that maps to Xq28 and results in a broad phenotype, including adrenal insufficiency and cerebral demyelination, leading to neurological deficits and progressive paralysis of the lower limbs. The disorder affects approximately 1/42,000 males, and approximately 1/28,000 females are heterozygous for the ABCD1 gene variant (Kemper et al., 2017).

As is typical of X-linked inheritance patterns, hemizygous males are the most severely affected. However, even among males, the disorder varies widely. Patients with X-ALD are asymptomatic at birth; however, approximately 80% of males will develop adrenal insufficiency during their life, usually before adulthood. It is estimated that all males and many females with X-ALD will develop progressive myelopathy. This may present as spastic gait, spastic paraparesis, and sensory ataxia (Huffnagel et al., 2018). The most severe form of X-ALD is cerebral ALD (cALD), which affects approximately 38% of males with the ABCD1 gene variant (Engelen, Kemp, & Poll-The, 2014). Symptoms usually appear between 5-10 years of age followed by death or severe disability within several years. When cerebral manifestations appear in childhood, the earliest symptoms are typically related to cognitive dysfunction such as declining school performance and behavioral issues. Other symptoms may follow, including visual and sensory agnosia, decline in motor...
skills, and epileptic seizures (Huffnagel et al., 2018). It is estimated that more than 80% of females with the ABCD1 gene variant may develop symptoms of myelopathy or neuropathy by age 60. Females are usually not impacted by adrenal insufficiency or cALD (Engelen et al., 2014).

For boys with early-stage cALD, allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established treatment proven to halt cerebral demyelination. In boys with more advanced disease, HSCT may actually result in more rapid decline and thus is recommended only for boys with abnormal brain MRIs not yet presenting neurological symptoms. Transplant related mortality is less than 5%; however, there are significant morbidity concerns including graft rejection, graft-vs-host disease, and associated long-term immunosuppression (Engelen, et al., 2014; Moser & Fatemi, 2018).

Given the potential benefit of HSCT in asymptomatic males with early brain lesions, several states added X-ALD to their newborn screening (NBS) panel. New York was the first, followed by Connecticut, California, Minnesota, and Pennsylvania. Ten states are now screening for X-ALD and multiple others plan to begin screening in 2019/2020 (Salzman & Kemp, 2019). Figure 1 shows X-ALD NBS program by state and current implementation status.
Newborn screening for X-ALD in California utilizes a two-tiered approach.
The first tier measures the ALD biomarker, C26:0-lysophosphatidylcholine (LPC). If
this very long chain fatty acid (VLCFA) is elevated, the second-tier test re-analyzes
the C:36:0-LPC VLCFA using alternative technology. Positive samples from the
second-tier testing are referred for confirmatory gene sequencing of the ABCD1 gene
(Kemper et al., 2017; Neogi et al., 2019). Newborn screening programs may identify
all infants, both male and female, with an ABCD1 gene variant, as well as infants
with other, usually fatal, metabolic disorders, such as Zellweger syndrome.
Additionally, there is a risk of falsely identifying infants without the condition, i.e.,
false-positive results (Kemper et al., 2017).

*Figure 1. X-ALD NBS by State (Salzman & Kemp, 2019)*
To date, there are no evaluations of existing state NBS programs for X-ALD, including California. This is likely due to the recent addition of X-ALD to most states’ NBS panels. The New York X-ALD screening program, which has been in existence since 2013, also has not published data on long-term clinical outcomes of children identified through X-ALD NBS, nor on the impact that positive screening results had on families. To determine X-ALD NBS guidelines, California utilized preliminary data from New York’s screening program and conducted an extensive literature review. A brief overview of potential harms associated with X-ALD NBS included direct clinical harm of HSCT treatment following early diagnosis, risk of false-positive results leading to over-diagnosis, identification of female heterozygotes, and identification of newborns with other untreatable peroxisomal disorders (Kemper et al., 2017). No further research is available on these harms and how they specifically relate to X-ALD.

Newborns identified through X-ALD NBS may have a known pathogenic gene variant in the ABCD1 gene, a variant of unknown significance (VUS) in the ABCD1 gene, or elevated very long chain fatty acids (VLCFA) with no identifiable gene variant. In the case of a VUS or unidentified gene variant, the diagnosis may be unclear. Furthermore, even in patients, particularly females, with a known gene variant, symptoms may not develop until later in life, if at all. These individuals may be considered patients-in-waiting, living in a gray zone between sickness and health, as they await a diagnosis and symptomatic treatment (Timmermans & Buchbinder, 2010). Some may argue that the potential for offering life-saving treatment to boys
with cALD nullifies the possibility of negative associated impacts on identity formation and emotional stability. Nevertheless, it is important to explore families’ experiences with the X-ALD NBS process to identify where these disruptions in development may occur and to offer patients and their families care that goes beyond treating only the medical expressions of this diagnosis.

It is important to note that families affected by X-ALD championed the addition of X-ALD to state NBS panels. In a study surveying 128 individuals with a family history of X-ALD, 93% would test sons at risk for inheriting the familial ABCD1 gene variant; 43.4% of these respondents would have liked this testing in the newborn period and 45.9% would have liked testing in the prenatal period. Similarly, 89% of respondents would test an at-risk daughter; 23.6% would have liked testing in the prenatal period and 27.6% in the newborn period. Overall, 90% percent of respondents supported NBS of X-ALD for both males and females (Schaller, Moser, & Edwards, 2007).

As California continues in its fourth year of screening for X-ALD, it is essential that the existing program be evaluated. This evaluation should include the impact that X-ALD newborn screening has on families that received a positive screening result. The goal of this study was to determine whether current considerations used in implementing newborn screening for X-ALD in California adequately considered the full spectrum of clinical and psychosocial impacts on families that receive a positive screening result. Information garnered from this study may be useful to healthcare providers for the improvement or modification of
California’s NBS program and consequent care offered to families. This is the first study that explored families’ experiences with the X-ALD NBS process by asking about perceived benefits and limitations about the NBS program, family dynamics, coping strategies, and recommendations.
CHAPTER II

METHODS

Participants

Eligible participants were mothers and fathers of children who participated in California’s newborn screening program for X-ALD between September 2016 and January 2019 and received a positive screening result. This included parents of males and females with a known pathogenic gene variant in the ABCD1 gene, males and females with a variant of uncertain significance (VUS) in the ABCD1 gene, and males and females with elevated very long chain fatty acids (VLCFA) only. Eligible participants were over the age of 18 and willing and able to participate in an audio-recorded interview in English.

Recruitment

To recruit for this study, the principal investigator (PI), KS, worked directly with genetic counselors and nurse coordinators at certified metabolic clinics across California. The five sites involved in this study were: University of California, San Francisco (UCSF); University of California, Davis; Sutter Medical Center, Sacramento; Valley Children’s Hospital (Fresno); and University of California, Los Angeles (UCLA). Each site submitted a letter of support detailing their agreement to help recruit for this study.

Recruitment was from September 2018 through January 2019. Genetic counselors and nurse coordinators identified eligible parents whose children were patients at their respective institutions and distributed a recruitment letter explaining
the goals of the study, the PI’s contact information, and a consent form. Interested family members reached out to KS directly, by phone or email, who screened participants for eligibility status. Eleven individuals, all of whom met the eligibility criteria, were enrolled in the study. One was enrolled as a pilot, the remaining ten were included in the analysis. A mutually agreed upon time for the phone interview was established. Prior to the interview, KS emailed an electronic copy of the consent form that explained the purpose of the research, description of interview questions, estimated length of the interview, potential risks of participating in the study, rights as a research participant, and contact information for a licensed and certified genetic counselor, should participants wish to speak to a professional counselor regarding questions or concerns that arose during the interview. Consent was obtained over the phone and recorded by KS, with permission granted by the participant, prior to the interview. All participants received a $25 visa gift card. The research study was reviewed and approved by the Institutional Review Board of California State University, Stanislaus (protocol #1819-004).

Data Collection

A semi-structured, open-ended interview guide was created with the collaboration of 4 investigators (KS, JF, JY, JK). The interview guide covered approximately 50 questions, both qualitative and quantitative, to gather demographic information and to learn about families’ experiences with California’s newborn screening program. The interview guide contained questions focusing on 1) understanding of newborn screening result and X-ALD diagnosis; 2) experience
receiving the newborn screening result; 3) family relationships and communication; 4) coping; 5) clinical care issues; and 6) participant recommendations for health care providers, policymakers, and other families going through a similar experience. The interview guide was pilot tested with the first eligible participant who reached out to KS. The pilot participant provided feedback on the flow, structure, and questions of the interview guide. Adjustments to the interview guide were made as recommended.

All phone interviews were conducted by KS and were digitally recorded. The interviews lasted between 50 and 99 minutes with an average length of 65 minutes. Interviews were transcribed verbatim by an online professional transcription service. All identifying information from participants was removed to ensure confidentiality. Names of probands in the transcripts were changed to pseudonyms.

Data Analysis

The transcribed interviews were independently analyzed using thematic analysis by KS and RW, with the goal of identifying overarching themes and patterns within the data. In the first round of coding, KS and RW evaluated the first two interviews separately to identify major recurrent concepts. A preliminary codebook was established by both coders based on mutually agreed upon findings. In a second round of coding, the remaining eight transcripts were analyzed independently by both coders using the preliminary codebook as a guide. These data were also compared for inter-coder reliability. Discrepancies in codes were noted and adjusted based on coder agreement, resulting in a final, comprehensive codebook. Codes were sorted into overarching themes: 1) Communication of results; 2) Understanding of results; 3)
Emotional reaction and progression; 4) Coping; 5) Impact on relationship with partner; 6) Impact on parenting; 7) Cascade testing; 8) Overall opinion on NBS and follow-up care; 9) Recommendations for healthcare providers (HCPs); and 10) Recommendations for families going through a similar situation.
CHAPTER III

RESULTS

Participant and Proband Characteristics

Eleven eligible mothers were interviewed on their experience with California’s newborn screening program for X-ALD, 10 of whom are represented in this study. The majority of participants had sons (6/10) who were originally identified on newborn screening, as compared to daughters (4/10). Notably, five identified children were found to have a variant of uncertain significance (VUS), while four were found to have a known pathogenic gene variant (positive result) and one had no gene variant identified but presented with elevated VLCFAs only. Given that population level genetic testing is relatively new for the ABCD1 gene, the 50% VUS rate identified in this study is not altogether surprising. As more newborns are tested and identified in California and across the United States, it is likely that the VUS rate will decrease. Demographic information is summarized in Table 1.
Table 1

Demographic Information

<table>
<thead>
<tr>
<th>PARTICIPANT DEMOGRAPHICS</th>
<th>RESPONSE</th>
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<td>Ethnicity</td>
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<tr>
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<tr>
<td></td>
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<tr>
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<td></td>
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<td>High School Degree or GED</td>
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<td>Career/Employment</td>
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</tr>
<tr>
<td></td>
<td>Homemaker</td>
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<td>Proband’s Gender</td>
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<tr>
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<td>Family Members of Proband</td>
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<td>TRICARE (Veterans Insurance Program)</td>
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This study explored myriad facets of the NBS experience for X-ALD to provide a diverse and comprehensive narrative to guide HCPs and policymakers in establishing holistic patient-and-family care protocols. Mothers shared their experience on the initial communication of the NBS result, the waiting period to see a specialist, and the in-person meeting with the specialist. Mothers’ understanding of their child’s result, emotional reactions and progression regarding the result, impact
on dynamics with their partner and children, cascade testing, as well as varied coping abilities were also explored. Lastly, mothers described their overall opinion on the NBS process for X-ALD and their satisfaction with follow-up care provided to their children and other, affected family members. The study concludes with mothers’ recommendations for healthcare providers involved in X-ALD patient care and for families in similar situations.

**Initial Communication of Positive NBS Results**

All parents received an initial phone call regarding the NBS screening result. The majority of parents (6/10) received the NBS results from a non-genetics provider, usually a pediatrician and in one case a nurse, while 3 families received the news from a trained genetics provider, usually a geneticist. One family was unsure of the role of the individual who conveyed the initial results over the phone. One family was aware of X-ALD in the family and thus prepared for possible results found on NBS. The remaining nine families had no prior knowledge of X-ALD and limited or no understanding of NBS. Multiple mothers reported a lack of understanding or familiarity with X-ALD by the healthcare provider conveying the results.

“I was shocked. I was in tears. She [the pediatrician] didn't seem like she knew anything. So it wasn't like I could ask her any questions.”

Given the limited information some HCPs provided over the phone, many mothers left the initial phone call with immense fear as well as confusion on how their child was affected. One mother recalled believing that her newborn daughter may die of ALD.
“The initial phone call, the very first one, I was a mess. I was crying and sobbing and I had no idea what was going on. I'd had so little information and all I knew was my daughter has this thing and she's gonna die. That's all I knew.” 

The majority of mothers responded negatively to hearing this news. Mothers described feeling “shock”, “fear”, “anxiety”, and “confusion”. Additionally, the majority of parents (80%) reported searching the internet for X-ALD after hearing the NBS screening results over the phone. This internet search yielded overwhelmingly disturbing results which often catapulted families into further distress.

“Yeah, we got a call over the phone. The doctor had no clue what ALD was either, just that it is a genetic disease, and told us the name, and told us that we'd be getting a call from a state doctor, a specialist, to make an appointment… She had no clue what it was. It was not explained to me whatsoever. I ended up going on Google, and it terrified me.”

**Waiting Period Between Phone Call and Seeing Specialist**

Typically, once a family is notified of the NBS results, they are referred to a specialist, usually a geneticist, for confirmatory biochemical testing and to discuss the results in detail. The amount of time between receiving the phone call and seeing a specialist varied significantly. Four families were seen by a specialist within 1-2 days, two within two weeks, and four families had to wait a month or more before seeing a geneticist. Typically, boys identified on NBS were seen more quickly than girls, unless girls had older brothers. In one circumstance, a family moved homes during
this time period, which may have led to the long wait time. Other factors that may lead to longer than expected wait times are limited genetics providers in the area and insurance issues. Regardless of the amount of time spent waiting, parents reported feeling “panicked”, “stressed”, and “concerned”. Some mothers spent the time waiting to speak with a specialist trying to learn more about the disease and familiarizing themselves with symptoms and disease progression while others coped with the uncertainty by resorting to denial of the NBS result.

**Meeting with the Specialist**

Unlike with the initial phone call, the majority of mothers (70%) reported that the information provided by the genetics provider was “sufficient”. In particular, mothers reported appreciating time with the geneticist and genetic counselor at the same time. The geneticist was generally viewed as the medical specialist and the genetic counselor was considered a resource that translated the geneticist’s words into patient-friendly language and provided psychosocial support.

“I think that it was awesome to be paired with a doctor and a genetic counselor at the same time so that as [the doctor] was explaining to us what ALD was, [the genetic counselor] was kind of doing the leg work behind to make sure that we understand everything, that we were processing it all okay.”

The three mothers who reported that the information provided by the geneticist was “not sufficient” all had sons with a VUS in the ABCD1 gene; therefore, these families may inherently have experienced more uncertainty. Nevertheless, a number of these
mothers reported frustration that the geneticist had limited first-hand experience with X-ALD and thus was unable to offer more nuanced information.

“Then the genetic specialist came in. He was wonderful, but essentially him and the counselor just gave us a print-out of adrenoleukodystrophy. I don't remember if it was exactly from the Mayo Clinic, but it was essentially just the definition of adrenoleukodystrophy. Again, not to speak to the quality of our meeting. But it was very ... It was a Google search. Like, the specialist didn't know what adrenoleukodystrophy was before Jeremy came up. We were the first.”

Several mothers reported feeling most reassured after meeting with specialists involved in the ongoing care of patients with ALD, in particular neurologists.

“I think it's been explained as good as science allows as of right now. We are confident in the neurologist that we meet with. He is one of the experts on ALD, so if there's things that he doesn't know, they're probably not out there to be known.”

Numerous mothers expressed a desire for the initial in-person consultation to include not only the geneticist and genetic counselor, but also the neurologist and endocrinologist.

“If my kids are going to be seeing neurology and endocrinology for the rest of their lives, I want one of those team members in that room with genetics, because those questions should have been answered. You shouldn't have let
me walk out with so much fear and so much … I couldn't even go back to
work because of the anxieties that I left there with.”

**Understanding the NBS Result in Males**

The majority of mothers with sons who were identified on NBS understood
their son’s diagnosis and prognosis. Regardless of whether the son was found to have
a VUS or a known pathogenic gene variant, all boys were followed as though they
have X-ALD and thus there was no significant difference in how HCPs described X-
ALD, how parents perceived and understood the description of X-ALD, and
recommended follow-up care. The majority of mothers reported struggling with the
characteristic ambiguity of the disease and not knowing if, when, or how their son
might be affected. Although multiple mothers reported understanding the lack of a
genotype/phenotype correlation in this disease, fewer mothers seemed to be aware of
this fact, or did not acknowledge it in their assessment of their child’s risk.

“All the men on my mother's side have lived very long lives so I don't know.
It could have been only passed down from mother to mother, but all the boys
have lived long. So I'm hoping that we have a good ALD chain.”

**Understanding the NBS Result in Females**

Mothers of daughter’s conceptually understood that their children were not at
risk for developing the cerebral form of X-ALD but that risk for certain neurological
symptoms in adulthood remained. Nevertheless, concern about lack of follow-up for
heterozygous females and possible symptoms in childhood were mentioned by
multiple mothers, suggesting additional support and reassurance may be necessary for
parents of females identified on NBS. Additionally, a major cause for concern reported by mothers was the need to one day discuss the meaning of being heterozygous for a variant in the ABCD1 gene with their daughters and possible impacts on future children. A number of mothers voiced discomfort or worry about initiating this conversation with their daughters.

“My immediate thought was how do I have the conversation with my daughter about her having children. I think that that was the biggest thought for me. Because now I have to explain to her that she has this gene that she could possibly give to all of her children, but most importantly her sons, if she ever were to become a mother.”

**Emotional Reaction and Progression**

Given that 9/10 mothers had never heard of X-ALD prior to receiving their child’s NBS results, the initial state of shock and confusion described by the majority of mothers would be expected. Interviews took place between 4 and 26 months after receiving the initial phone call. By this time, 60% of mothers reported feeling moderately to very hopeful about their child’s future and 70% reported a positive progression in their emotions about their child’s diagnosis, even though much sadness and uncertainty remained.

“Well the initial phone call, I thought I was gonna need to get ready for a funeral. And then now it's kind of like, let's just be happy and if we live, we have one more day.”
One mother reported that she was able to accept her son’s diagnosis and move forward after reaching a specific milestone in his medical care, specifically a clear brain MRI, which is usually not done until 12-18 months of age in affected boys.

“It took a good year for me to understand this thing. For a year, I was walking around in anxiety and depression about this… I've just been able to get over this hump, you know what I mean? You know when I got over the hump was when my baby, when he had his first MRI, because they couldn't even get my baby to have an MRI until 18 months. So the whole first year and a half of his life, I've been walking on egg shells thinking, what is that brain scan gonna show me?”

Of the mothers who were having difficulty adjusting to their child’s diagnosis, many reported struggling with not having concrete answers on how their child could be affected. Additionally, the possibility of having a special needs child with potential long-term health implications felt overwhelming to some mothers.

“I think that's the worst part, because you don't know. So it's like either they told me they expect her to have a normal childhood, but then what if she doesn't? And it's like she goes all her life and she does have a normal childhood and then what if they hit in her adult years and she can't live the way that she wants to live. As a parent, you already have a lifetime responsibility. But, now, I've created a long-term responsibility for myself.”
Thinking about an affected child’s future was particularly distressing for mothers, and some reported denial of potential future health impacts to better manage the painful emotions associated with this train of thought.

“I try not to think about the future too much because it freaks me out. I mean, I try to envision positive things but it's just if I think too far in the future sometimes my mind goes, oh, what if he's in a wheelchair? Or what if he's dead? Or those kind of things. So I just, I really don't think about it very often. I guess that's the way that I deal with it.”

Learning about this NBS result shifted how many mothers envisioned their child’s future. Mothers reported focusing on the present and creating a fun and meaningful experience, regardless of the length of their child’s life.

“Again, no longer am I trying to raise a nice person. I'm trying to make sure he has a full life and that we give him a lifetime of experiences in potentially 15 years. To the best of our ability.”

**Coping with the NBS Result**

Mothers whose emotional progression around their child’s NBS result followed a positive evolution, utilized varied coping approaches, including: relying on one’s faith, information seeking, and maintaining hope. Half of mothers mentioned the importance of faith in their ability to adjust to their child’s diagnosis. In particular, sentiments such as trust in God, the afterlife, and a supportive Church community was especially helpful to some of these families.
“Religiously, I don't believe that just because you die it’s the end of that life, so it's not as much of a loss.”

“I would say our faith is definitely the main thing. Our trust in God, that he is in control of all things. And then, just the support that we have from our church, from our family, from our friends.”

Other mothers reported feeling empowered to delve more deeply into the X-ALD community and to educate themselves. Information seeking was reported by 7/10 of mothers as a major coping strategy. This included going back to school, actively engaging with the ALD community, attending conferences, researching and participating in clinical trials, and gaining an in-depth understanding of their child’s disease, possible progression, and outcomes.

“Well actually, I've always wanted to get into nursing and definitely these results gave me a push and I went back to school. Because it gave me the strength to do things and somehow help Forrest or other kids.”

At the time of these interviews, none of the children identified on NBS were symptomatic, although some had siblings or fathers who were showing symptoms of adrenal insufficiency. No one had been diagnosed with the cerebral form of X-ALD. Thus, although the uncertainty of this condition was often mentioned as a major source of stress, it also offered parents hope; hope that their child may never develop the fatal form, as well as hope that given their young age, better treatments and potential cures would be available by the time their children did develop symptoms.
“In 10, 20 years there may be a medication. I'm banking on it, that there's a medication for AMN. And Leo will be fine and he won't ever even have to go through that. Or the gene therapy is going to be the gold standard and we're good. So I do feel lucky in the sense that he is so young and we have time on our side.”

Multiple mothers also mentioned denial/distancing, problem-solving and leaning on friends and family as ways a means of managing their child’s screening result.

**Impact on Relationship with Partner**

All participants reported being in a relationship with a male, either married or partnered. The impact on the relationship with their partner/spouse varied broadly among participants. Of the ten mothers interviewed, four reported that having this X-ALD diagnosis in the family negatively impacted the relationship with her partner, three reported a positive impact, two reported no impact, and one was undecided. Of the mothers who reported a negative impact, three have daughters who were initially identified on NBS. In two of those families, the father was found to have the ABCD1 pathogenic gene variant and was therefore diagnosed with X-ALD. As a result, mothers found themselves concerned not only about their child’s health, but also about their partner’s health.

“So this has most definitely been the hardest year and a half of our entire marriage, our entire time together. I think just in finding out his [husband] diagnosis originally, it kind of sent me into a whirlwind.”
“With my husband, I'm scared every day that one day he's just gonna be like, "I can't walk." You know? It's scary.”

Blaming one another for the diagnosis in the family, the burden of juggling general life responsibilities along with countless medical visits, denial of the diagnosis on behalf of male partners, and deciding to stop trying for more children were also reported as factors that negatively influenced the relationship. One mother pointed out that the inequality between mothers and fathers taking on the role of health advocate for the affected child created distance in her own marriage.

“I think it's a huge burden. I noticed almost immediately upon reaching out to support groups and talking to other people that it's all about the mom. It's all about ALD moms for some reason. And it is. I became my son's health advocate, a role that I never really anticipated playing. My husband is excellent at keeping up the norm. He keeps a positive attitude, he's extremely hopeful that this won't affect Jeremy. But I'm of a very different thought process, so it has changed our dynamic significantly, just that most of the stress falls on me. I schedule all his appointments. I have all the conversations. I'm a member of the support groups on Facebook, so connecting to other ALD people. And he just doesn't. So that's a wedge, because it's very much a part of my everyday. I mean, there's not a day that goes by that I don't have some interaction with something ALD-related.”

Of the mothers who report a positive impact, all mentioned that receiving this diagnosis bonded the family together and increased appreciation for one another.
Additionally, an important influencing factor was the husband’s participation in the child’s healthcare needs. Mothers reporting a team-based approach to raising their children felt more positive about their relationship with their spouse.

“We've been together for a really long time and we're a team and we've always been that way and I think this just sort of puts our skills as a team into full force.”

**Impact on Parenting**

Most mothers reported that learning about the NBS result impacted the way they parent their affected child, particular in comparison to older children. The eight mothers who adapted their parenting describe their parenting as more protective, loving, lenient, and attentive. Seemingly minor health concerns may be a greater source of anxiety for parents, given the potential association with X-ALD.

I mean, I'm a little bit more stressed if he gets a rash and I'm concerned already. When Justin would get a rash, I would be like, "Oh it will go away", but when Forrest [has] a little bit like fever or anything, it's really alarming.”

Although most parents did not express favoritism among their children, many did acknowledge that affected children received more attention and were disciplined less harshly than older siblings might have been. Most parents expressed a deeper appreciation for their children, both affected and unaffected, as a result of the X-ALD diagnosis.

“Sometimes I think, I let him get away with more things than I let my older son get away with because that's always in the back of my mind. But it's also
changed the way that I think of my older son too. Anything can happen to him… Just live every day like it means something, because it does.”

“So we try to make today and tomorrow count. That's saying “yes” to things maybe we would ordinarily say “no” to. We discipline him differently. I'm not as hard on him. It's just different. It's trying to be more joyful, because today and tomorrow are going to be okay. Life has the probability of getting much harder.”

**Cascade Testing**

Nine out of ten mothers reported cascade testing in the family to identify other, potentially affected family members. The one family that was unable to access cascade testing cited insurance coverage issues. In two families, the father was tested and found to have X-ALD; in the remaining seven families, it was found or assumed that the X-ALD in the family was inherited from the mother. Generally, mothers who were heterozygous were not concerned about their own health or the health of other females identified through cascade testing. However, mothers with partners who were identified as having X-ALD reported significant concern and worry about their partner’s health. One mother shared the difficulty her husband was having dealing with his own diagnosis.

"I think he [husband] just flat out asked the doctor, "Okay, you're telling me all this medical stuff. But are you telling me that it's a possibility that it could me?" At which he [the doctor] said, "Yes." He went into a depression. And we didn't have any means of communication. I eventually got him to go to
therapy, but even during his time in therapy, he wasn't coming home and talking to me. There was this wall up around him and him by himself. And his family didn't understand. His grandparents are calling, asking why he wasn't answering calls and why he wouldn't text back. It's been a rough almost two years.”

Three mothers clearly voiced that finding this genetic disease in the family impacted their decision to have more children; a decision made despite the desire to grow their families.

“We were hoping to have a girl, and we honestly don't even want to try again because of this. That's sad in any marriage.”

**Overall Opinion on NBS Process and Follow-up Care**

Overwhelmingly, all participants agreed or strongly agreed that X-ALD should be included on the newborn screening panel for both males and females; however, the timing of when testing should be offered varied. Sixty percent of mothers believed that testing for X-ALD in males should be offered prenatally and 40% believed it should be offered at birth. For females, 30% believed that testing should be offered prenatally and 70% believed it should be offered at birth.

Of nine families in whom a gene variant for X-ALD was identified in a male, either a son or father, seven mothers were satisfied with the follow-up care their sons or husbands were receiving. All affected males were followed by endocrinology and neurology in 6 to 12-month intervals. Females were generally not offered follow-up
care after the initial genetics appointment unless symptoms arose. One mother reported feeling anxious about this lack of follow-up for her daughter.

“I'm just curious if Clarissa does need to be seen more often. I feel like because she's female and she's not, as far as they're concerned, presenting right now, they just pushed her to the back burner. And then I'm left over here as a parent kind of wondering well, what if she is presenting and I don't know?”

Four families participated in clinical trials and found these helpful for coordinating care and managing their sons’ multiple medical appointments. In the six families not participating in a clinical trial, mothers reported handling all the responsibility around scheduling appointments and tracking follow-up care. For some, this felt burdensome and additional help would be a welcome reprieve.

**Recommendations for Healthcare Providers**

The most common advice families had for HCPs was for pediatricians to educate themselves prior to calling families with the NBS results.

“I think that's the one thing that needs to change is having the regular pediatrician call to try to explain something that they have no background knowledge on or specialty knowledge on. I think that was probably one of the most difficult parts because she called and kind of told me what it was and then blatantly let me know, "I don't know what it is. But here's how you spell it so that you can educate yourself on it."
Alternatively, families believed the initial phone call should be made by a specialist with more knowledge of the condition.

“I would have liked a doctor who knew about the disease to call me. I would have wanted the specialist to call me and say, "Look, we got your results. We are the state doctors. We know exactly what we're dealing with, and we're gonna get you in on X, Y, and Z date." Instead of having a doctor call me and tell me, "Your kids have this thing. We don't know what it is, but we know he didn't pass the state screening. And you know, here it is, and this doctor will call you. You're up in the air." That was the biggest thing I would have changed from all this.”

Additionally, several families mentioned the lack of provision of mental health services. Beyond offering cascade testing, no other medical resources were offered to parents or other family members impacted by this result.

“I just think that there's that hole, that we have genetic specialist counselors, neurologist, endocrinologists, but we're missing the support piece, the mental health support piece.”

Having genetic counselors present for the meeting with the geneticist was appreciated by a number of families. However, multiple mothers would have preferred to see other specialists at the first in-person visit, in particular a neurologist. Multiple mothers desired further guidance on how to speak to their affected and unaffected children about the diagnosis in the family. Several families mentioned a desire for more patient-friendly resources on X-ALD, including information on disease
progression, clinical trials, and contact lists for specialists with experience in X-ALD.

Additionally, several mothers asked for information on financial resources for cascade testing and other services not fully covered by their insurance, such as MRI’s. Lastly, many families felt that the time from initial NBS result to official diagnosis was far too long, although several accepted the inherent limitations of available genetic testing and screening technologies. Nevertheless, many families felt that the waiting period between the initial phone call and seeing a specialist for confirmatory testing should be shortened. Table 2 summarizes mothers’ recommendations for the HCPs.

Table 2

Recommendations for Healthcare Providers

1. Education of HCPs, particularly pediatricians, on X-ALD
2. Shorter wait times between initial phone call and meeting with specialist
3. Faster turnaround times for confirmatory genetic testing result
4. Meeting with specialists to include geneticist, genetic counselor, neurologist, and endocrinologist
5. Resources and support in coordinating follow-up care
6. Referrals and/or resources for mental health services
7. Additional resources on X-ALD, including printed materials, online materials, and support groups
8. Information on clinical trials
9. Contact list for specialists with experience in X-ALD
10. Guidance/resources on discussing ALD diagnosis with children
11. Financial resources for cascade testing and other medical care if limited insurance coverage

Recommendations for Families

Normalization was common advice that mothers offered to other families. They felt it was important to recognize that X-ALD is a disease like any other and
that parents should focus on accepting this and appreciating the time they have with their children, regardless of how long or short that might be.

“Remember that we're all in the same boat. This disease doesn't make us any different than anybody else. We're all going to die, we're all going to get something or whatever happens and just to be in the moment as much as possible because that's all we have.”

One mother expressed concern that learning this diagnosis so early in a child’s life may impact bonding between parents and their newborn and encouraged parents to actively develop loving relationships with their affected children.

“I worry that there are some people who don't bond with their children or have these amazing relationships because they're afraid they're going to lose them… I would just want them to know that it's completely possible, it's completely worthwhile to invest in a relationship with these boys, because they are okay today and they will be okay tomorrow.”

Finding the positive in such a frightening situation was another common piece of advice offered to other families going through this process.

“[Your] baby is perfectly and wonderfully made and having knowledge of a genetic mutation doesn't change how perfectly they were designed. Do not be discouraged and know that God does knit all babies together perfectly and for a purpose, and so [don’t] think of it as such a terrible thing, but definitely something to see the good in.”
Other mothers recommended that parents educate themselves about X-ALD, accept the condition and then let their children live as normal a life as possible. Parents wanted to remind other families that this condition does not define their children.
CHAPTER IV
DISCUSSION

This study addresses a significant gap in the literature by elucidating the unique psychosocial and clinical experiences of parents with children identified on X-ALD NBS. These research findings have important implications for clinical practice and policy interventions.

Educating Healthcare Providers on X-ALD

Given the high anxiety and confusion experienced by many parents upon learning their child’s positive screening results, HCPs who work with these families should be aware of the factors that contribute to a positive, informative, and supportive NBS experience, in the context of a potentially devastating diagnosis. Specifically, pediatricians and other HCPs making the initial phone call need to be well-versed in the clinical aspects of X-ALD, including disease progression, prognosis, and treatment. This sentiment is not unique to families of this study. Pruniski, Lisi, & Ali researched families’ perspectives on NBS for Pompe disease (PD). The results of this study are strikingly similar to ours. As with X-ALD, many parents of children identified with PD felt the HCP making the initial disclosure was not fully informed on the condition. These families also emphasized education on the disease as an important recommendation for both HCPs and parents (2018).

For X-ALD, this information must be presented in a manner that is both truthful and realistic but laced with hope, given that at the early stages of this disease little is known on how it will affect the child. Emphasizing currently available
treatment and possible future treatment may be beneficial, as well as pointing out that newborns identified on NBS are not at any immediate risk for health issues. Parents may find comfort in knowing that although future risks are serious, at the time of NBS they need not worry about any sudden changes in their child’s health. For females, parents should understand that their daughter is not at risk for the cerebral form of this condition and that any future symptoms would be on the milder side and not until adulthood. Thus, it is of great importance that families are given sufficient information to understand the diagnosis while also appreciating that this is not a death sentence. Emphasizing hope in treatment and research as well as hope that their child may never develop the cerebral form should be features of that early message.

In a study exploring primary care physician’s (PCPs) experience notifying parents of positive cystic fibrosis NBS results, physicians reported that state NBS program could provide more resources to aid them in “breaking bad news” to patients, including training on having these difficult conversations, an information sheet that PCPs could distribute to families, as well as a FAQ sheet for physicians with sample responses (Finan, Nasr, Rothwell & Tarini, 2015). These types of interventions would likely benefit pediatricians revealing X-ALD results as well and could aid in streamlining the initial disclosure process across the state.

**Patient-in-Waiting: Affected Child and Parents**

Uncertainty is an overarching theme mentioned by all participants. Some reconciled themselves with the uncertainty of the prognosis of their child, while others continued to struggle to understand their child’s disease state, given the lack of
guidance. For most parents, the fear and uncertainty that this NBS result produced is profoundly intertwined into their everyday.

Most mothers had accepted their son’s diagnosis of X-ALD, but fewer were able to reconcile themselves with the ambiguity of what that meant. Unlike other conditions on NBS, X-ALD is unique in that there is no infant presentation. Up until age two or even later, these boys will be healthy, developing and growing as any other child. Therefore, it is particularly difficult for mothers to accept that their vibrant young boy could have a potentially fatal disease. The ongoing medical appointments only further underscore that these boys have a major medical concern, yet again, most won’t show any symptoms for several years. This phenomenon, described as patients-in-waiting by Timmermans & Buchbinder seems to be a common aspect of the NBS experience (2010). For many diseases on NBS, acute onset of disease occurs in infancy or a diagnosis of a condition is more definitive; thus the patient-in-waiting experience may be limited to the early diagnostic process of NBS. For X-ALD, this waiting period can last years. Of additional importance is recognizing that while the newborn is the patient, parents may become patients themselves. Not only do they take on the role of care advocate for their child, but in the case of mothers, they often learn they are heterozygous for ABCD1 variants, or in the case of fathers, diagnosed with X-ALD. Regardless, there are possible medical implications of this diagnosis for the parent identified.
Supporting Healthy Coping

Szulczewski, Mullins, Bidwell, Eddington, & Pai found that caregivers of children with pediatric chronic diseases showed decreased psychological functioning, which included anxiety, depression, and psychological distress, when uncertainty was high. Similarly, the study authors found that less uncertainty around a child’s illness was associated with improved coping mechanisms, and vice versa (2017). Although our study found that most parents had developed healthy coping mechanisms, uncertainty around the diagnosis and disease progression resulted in significant fear and distress in mothers. Therefore, reducing anxiety, as much as possible, should be an integral aspect of counseling around X-ALD. While physicians cannot predict disease outcome, uncertainty can be better managed by assuring families that X-ALD NBS follow-up care is designed to catch symptoms early when treatment will be most effective.

Additionally, HCPs are uniquely positioned to support parents in continuing and adopting healthy coping mechanisms, particularly around information seeking. This search for knowledge is an integral step in the process of adapting to a child’s diagnosis. By providing accurate and patient-friendly resources, parents may feel more confident in their ability to care for their child. Additionally, by providing information on support groups and clinical trials, parents may grow their social network by engaging with other families in similar situations. Lastly, as seen in this study, reliance on faith and God is one of the strongest predictors of healthy coping. Most hospitals provide chaplains or other HCPs who can engage with patients’
spiritual and religious convictions to aid them in managing distress and anxiety (Leite et al., 2013).

**Unexpected Findings: Diagnosing Fathers**

X-ALD is a unique disease given its variable phenotypic presentation and the inability to predict, even in families, how any one individual may be impacted. Adult males learning about their diagnosis of X-ALD as a result of a daughter’s positive NBS result is a notable possible outcome of this screening program. In this cohort of 10 families, two fathers were found to have X-ALD after cascade testing. Thus, it can be assumed that this is not an uncommon result that needs to be part of the initial discussion and follow-up with parents who receive a positive NBS result for a daughter.

For some fathers, this diagnosis is mild and may result in little, if any, serious symptoms. Although nearly all men will experience some form of adrenal issues and myelopathy in their lifetime, some may be spared the more disabling symptoms of neurological dysfunction. However, for many males, this diagnosis could be far more devastating. Approximately 20% of affected males may develop more severe symptoms after age 18 that could include progressive adrenomyeloneuropathy with cerebral manifestations, resulting in behavioral, cognitive, and sensory-motor deficits (Engelen et al., 2012). As represented by one of the males diagnosed in this study, an X-ALD diagnosis in an adult male could lead to depression, among other mental health concerns. This is an incredibly important and under-examined consequence of X-ALD NBS.
Impact on Unaffected Siblings

All children identified on NBS in this cohort had siblings. It is striking that 80% of mothers described a change in their parenting style after the NBS result. Typically, this primarily extended to the affected child; however, in numerous families, changes in parenting also impacted siblings. While these adjustments were usually described as positive, such as purposefully spending more time together as a family, it is important to note that many mothers also described more vigilant parenting styles. While this is not inherently negative, studies examining parenting described as overbearing found an association with lower self-efficacy and alienation from peers (Ingen et al., 2015). Additionally, studies examining dynamics in families with children with disabilities found a number of positive as well as negative implications for the families. Similar to what was expressed by numerous families in this study, on the positive side, it can increase family awareness of individuals’ strengths, enhance family cohesion, and encourage building relationships outside the immediate family, such as with community organizations or religious groups. On the negative side, the time, energy, and cost of raising a child with a disability can impact parent and sibling mental and physical functioning. Parenting practices, including parental expectations of healthy siblings regarding achievements as well as short and long-term responsibilities to the family and the affected child may contribute to sibling health and development (Reichman, Corman, & Noonan, 2008).

The boys identified in this study were all 3 years old or younger and are not yet showing signs of X-ALD. Thus the experiences of any older sibling would be
markedly different from those that have spent years coping with their brother’s diagnosis. Nevertheless, it is important to be aware of the potential impacts on siblings. Malcolm, Gibson, Adams, Anderson, & Forbat found that siblings of children with rare life-limiting conditions often felt isolated from peers due to limitations in social activities as a result of their sibling’s condition, pervasive worry about their sibling’s health status, and an awareness of the burden placed on their parents (2014). These aspects may all be relevant to siblings of boys with X-ALD. Therefore, these siblings may benefit from ongoing care that addresses their mental and emotional needs as they relate to their brothers’ diagnosis.

**Providing Mental Health Support**

All members of a family may be impacted by positive NBS results for X-ALD. Current clinical follow-up for boys includes meetings with the geneticist and genetic counselor to confirm a diagnosis, followed by annual or bi-annual visits with a pediatric neurologist, endocrinologist, and often the primary care physician. After the initial genetics visit, few girls are followed by specialists. Mental health support is not part of the follow-up process for these children, their parents, or their siblings.

Even though nearly all participants in this study were struggling with some aspect of their child’s NBS result, only one mother reported receiving mental health counseling. However, this was a resource she had utilized prior to receiving her son’s NBS result. Thus, this clearly essential aspect of medical care must be added to the established X-ALD NBS follow-up care plan. X-ALD is unique in that the NBS process does not end once a diagnosis is confirmed. Having this diagnosis in the
family may signify a drastic change in family and individual identity that requires ongoing, supportive, and effective services that address the varied mental and emotional health concerns. An increased focus on providing these resources could benefit parents, affected children, and their unaffected siblings.

**Limitations**

This study was limited to ten mothers of children identified on NBS for X-ALD in the state of California. Participants were primarily Caucasian and English-speaking, and most reported some form of college education. Recruitment for this study was limited to families who were seen by one of the five metabolic centers that participated in this study. In addition, classification of the gene variant and diagnosis as known pathogenic, VUS, or elevated VLCFA stemmed from parent report and was not confirmed with medical records. No parents of children with a false-positive result or parents of children diagnosed with an untreatable peroxisomal disorder participated in this study, although these individuals are also identified through X-ALD NBS. Additionally, given that NBS for X-ALD was only added to California in 2016, these families were still in the early stages of their experience with X-ALD with no symptomatic children identified as of yet. Thus, the results of this study may not be generalizable to families who have older children diagnosed with X-ALD through NBS in other states, specifically New York, and who have started showing symptoms of the disease. Additionally, there is the possibility of participation bias playing a significant role in this research study. Presumably, given the small sample size, many families were contacted and chose not to participate, perhaps because they
were coping less effectively with their child’s screening result or some other striking factor.

**Research Recommendations**

Future studies that include the paternal perspective as well as the first-hand experience of fathers diagnosed with X-ALD as a result of their daughter’s NBS result would yield revealing information on the impact of cascade screening and the opinions of fathers. Studies exploring the impact on siblings, particularly siblings of symptomatic brothers, would also provide deeper insight into the impact on family dynamics after a positive X-ALD NBS result. Furthermore, considering the diversity of California’s population, it is important that future studies on this topic explore non-English speakers’ experience with NBS, as well as those of parents with more diverse backgrounds in terms of socioeconomic status, education, race, and ethnicity. A follow-up study interviewing families whose children are further along in their disease course may uncover additional psychosocial and medical concerns not elucidated in this early study. Lastly, this study is unique to California’s NBS screening process, protocols, and patient experience and future studies looking at the NBS experience in other states will likely yield different informative data.
CHAPTER V

CONCLUSION

This qualitative study explored the experience of families, specifically mothers, with California’s NBS process for X-ALD. This is the first study that elicits the stories of families with children, both males and females, who received a positive NBS result for X-ALD to learn about the potential psychosocial and clinical consequences. Overwhelmingly, all parents participating in this study were proponents of newborn screening for X-ALD; however, certain aspects of the program can be improved.

Our findings suggest that the initial phone call revealing the positive results to parents had a strong influence on parental emotional reactions and understanding of the result. Thus, educating HCPs, in particular non-genetics providers, on X-ALD prior to revealing the NBS result was the most widely declared recommendation. Ongoing visits with specialists, particularly neurologists, provided some clarity on the diagnosis, and more importantly, a critical anchor for navigating the unfamiliar X-ALD landscape. Nevertheless, resources addressing the mental and emotional needs of parents, siblings, and affected children were rarely available or offered. A greater emphasis on providing mental health support services to all members of the family needs to be considered as an essential part of follow-up care for X-ALD; particularly as cascade screening is expanded to parents, siblings, and distant relatives for whom these results could have serious clinical and emotional consequences. Ultimately, mothers were coping well with their child’s result and many have a deeper
appreciation for their children, their families, and their community. Hope, religious attachment, and personal education were particularly helpful to a mother’s positive emotional progression in managing her child’s NBS result.

This study contributes to the limited literature that exists about NBS for X-ALD, and its findings may be used by geneticists, genetic counselors, pediatricians, neurologists, endocrinologists, and even policymakers to tailor the support, counseling, and clinical needs of these unique patients and their families. Additionally, this study is meant to provide a narrative of the diverse experiences of families with a positive NBS result for X-ALD, which may be helpful to other families in a similar situation.
REFERENCES
REFERENCES


adrenoleukodystrophy: evidence summary and advisory committee recommendation. *Genetics in Medicine, 19*, 121-126.


APPENDIX A

DEMOGRAPHICS AND FAMILY QUESTIONNAIRE

**Demographic Information**

1. I am the (mother / father) of a (boy / girl) who received a positive newborn screening (NBS) result for X-linked adrenoleukodystrophy (X-ALD).

2. Date of birth: ___________________________

3. Ethnic/Racial background: ___________________________

4. Marital Status: a. single  b. married  c. divorced  d. separated  e. partnered

5. Education
   a. Graduate degree  e. High school degree or GED
   b. College degree  f. Some high school, no diploma
   c. Associate degree  g. less than high school
   d. Some college, no degree

6. Occupation: __________________________________________

7. City of Residence: ______________________________________

8. Center that provided NBS result: __________________________

9. Date NBS result received: ________________________________

10. Type of insurance:
    a. Private (e.g. Kaiser, Anthem, etc. / HMO or PPO): _________________
    b. Medical
    c. Medicare
    d. Tri Care
    e. Uninsured/Self-Pay

11. Children (affected and unaffected)
    Name; Date of Birth; M/F; X-ALD Status (known pathogenic mutation, variant of uncertain significance, elevated VLCFAs only, unknown)

**Family Questionnaire**
For parents with a son who has a known pathogenic mutation only:
1. If your son has a known pathogenic mutation for X-ALD, which of the following could be true (check all that apply)?
   a. Your son may develop symptoms in childhood
   b. Your son may not live into adulthood
   c. Your son may develop symptoms later in life
   d. Your son may live into adulthood
   e. Your son is not affected by X-ALD

For parents with a son who has a variant of uncertain significance only:
2. What best describes your son’s “variant of uncertain significance (VUS)” result based on what his medical care team has explained?
   a. A mutation is found in the gene that is known to result in symptoms of X-ALD and could lead to severe disability and potentially death
   b. A mutation is found in the gene but we do not know if it is associated with X-ALD
   c. No mutation is found and your son is not at risk for developing symptoms of X-ALD

For parents with a daughter who has a known pathogenic mutation only:
3. If your daughter has a known pathogenic mutation for X-ALD, which of the following could be true (check all that apply)?
   a. Your daughter may develop symptoms in childhood
   b. Your daughter may not live into adulthood
   c. Your daughter may develop symptoms later in life
   d. Your daughter may live into adulthood
   e. Your daughter is not affected by X-ALD

For parents with a daughter who has a variant of uncertain significance only:
4. What best describes your daughter’s “variant of uncertain significance (VUS)” result based on what her medical care team has explained?
   a. A mutation is found in the gene that is known to cause symptoms of X-ALD
   b. A mutation is found in the gene but we do not know if it is associated with X-ALD
   c. No mutation is found and your daughter is not at risk for developing symptoms of X-ALD.

5. Which of the following is true for X-ALD? (check all that apply)
   a. Males with a known pathogenic mutation have X-ALD and will develop symptoms
   b. Females with a known pathogenic mutation have X-ALD and will develop symptoms
c. Males with a known pathogenic mutation are carriers for X-ALD and may never develop symptoms
d. Females with a known pathogenic mutation are carriers for X-ALD and may never develop symptoms

6. If a boy has X-ALD, what is most likely true?
   a. The mother is a carrier for the genetic mutation for X-ALD
   b. The father has the genetic mutation for X-ALD
   c. Both parents have X-ALD
   d. Neither parent has X-ALD

7. If a father has X-ALD, which of the following is true?
   a. A son would definitely inherit the genetic mutation for X-ALD
   b. A daughter would definitely inherit the genetic mutation for X-ALD
   c. No children would inherit the genetic mutation for X-ALD
   d. All children would inherit the genetic mutation for X-ALD

8. On a scale of 1-5, how strongly do you agree that males should be tested to determine if they have a genetic mutation for X-ALD?
   1. Strongly disagree
   2. Disagree
   3. Neutral
   4. Agree
   5. Strongly Agree

9. In your opinion, when should males be tested to determine if they have a genetic mutation for X-ALD?
   a. Prenatally (during pregnancy)
   b. At birth
   c. When symptoms arise
   d. 18 or later
   e. Never

10. On a scale of 1-5, how strongly do you agree that females should be tested to determine if they have a genetic mutation for X-ALD?
    1. Strongly disagree
    2. Disagree
    3. Neutral
    4. Agree
    5. Strongly Agree

11. In your opinion, when should females be tested to determine if they have a genetic mutation for X-ALD?
    a. Prenatally (during pregnancy)
b. At birth

c. When symptoms arise

d. 18 or later

e. Never
APPENDIX B

QUALITATIVE INTERVIEW GUIDE

Receiving the NBS Result

1. Prior to receiving the NBS result, were you or your doctor concerned about (child’s name) health?

2. How did you learn about (child’s name) NBS results?
   - Phone, in person?
   - How many days old was (child’s name) when you learned the results?
   - From whom did you receive your results?
   - How did they tell you about the results?
   - What was your reaction to the results?

3. What was your experience like waiting to meet with the specialist/geneticist after learning about (child’s name) NBS result?
   - How long did you have to wait between getting the positive result and seeing a specialist?
   - Did you research X-ALD in the time you waited? Do you remember researching symptoms? What did you learn?

4. How did the specialist/geneticist describe X-ALD to you?
   - How did this compare to your research?
   - What was your reaction to his/her description of X-ALD?
   - What questions or concerns, if any, came up for you at this time?

5. What is your understanding of (child’s name) NBS result and his/her diagnosis, if he/she has one?
   - Was it a known pathogenic mutation or a variant of uncertain significance?
   - What does that mean to you? Do you have any remaining questions about this result? Do you have any concerns or worries about this result?

Family Relationships and Communication

6. When you received the NBS results, with whom did you share that information and what was that conversation like?
   - What were the reactions of those that you told?

7. Has your experience with X-ALD affected or impacted your relationship with your spouse/partner?
8. How has your experience with X-ALD affected or impacted your relationship with [child’s name]?
   - **If applicable**, with unaffected children?

9. How has your experience with X-ALD affected or impacted your relationship with other family members, friends, or your community?

10. **If applicable**, how has your family’s experience with X-ALD changed relationships between [child’s name] and his/her siblings?

11. **If applicable**, have you thought about how you will talk to your other children about (child’s name) diagnosis?

12. How would you describe your parenting style with (child’s name)?
   - Has your experience with X-ALD impacted or affected the way you parent [child’s name]?
   - **If applicable**, how does it compare to how you parent(ed) your other children?

13. How has this NBS result impacted the way you think about [child’s name] future?

**Coping**

14. How have you been handling this result? What resources, if any, have been helpful to you during this time? (e.g. professional therapy, support groups, advocacy groups)?

15. How have your feelings about the NBS result changed over time, from initial diagnosis to now?

**Clinical Care Issues**

16. Can you tell me about your child who had the positive NBS result? How is your child doing now?
   - How is their health? If male, have they started developing any symptoms (muscle spasms, seizures, impaired vision, hearing loss, cognitive decline, behavior changes?)
   - Are there brain findings? (decrease in brain’s white matter?)
   - Are there any adrenal findings (poor appetite, weight loss?)
   - Any other major health issues?
17. What kind of follow up care or specialty care is (child’s name) receiving now?
   • What kind of follow up care or specialty care will your child need in the future?
   • Who is helping you coordinate this follow-up care?
   • Did your child need any additional biochemical or genetic test, or imaging?

18. Has anyone else in the family received genetic testing for X-ALD?
   • If yes, for whom and what were the results?
   • Has this information impacted you and your family in some way? How?
   • Who is helping coordinate follow-up care for these family members?

19. Are you aware of any available treatments? What do you know about them?
   • If yes, are you interested in pursuing these? Why or why not?

20. Do you have any remaining questions about your child’s healthcare needs that haven’t been answered?

Recommendations

21. How would you describe your experience going through the NBS process, specifically from the time of the heel prick to meeting with specialist to discuss your child’s result?
   • What could have been improved?
   • Was there information you wish you had been given prior to receiving the result?

22. How would you describe your experience so far with the healthcare team taking care of (child’s name), including doctors, genetic counselors, nurses, etc.?
   • What has been helpful in your interactions with the healthcare team?
   • What could be improved?
   • In retrospect, is there anything else you wish they had addressed / other information or resources they had provided?

23. Did you receive any kind pamphlets or brochures about NBS or ALD?
   • If yes, from whom did you receive it, when, do you remember what the pamphlets or brochures said? Was it helpful?
   • Do you remember receiving the “ALD in Babies” brochure?
   • If yes, from whom? Did you read it/find it helpful?
24. What would you tell a family that is going through a similar experience?

25. Is there anything else you would like to share about your experience?