REPRODUCTIVE DECISION-MAKING FOR X-LINKED HETEROZYGOTES: UNEXPLORED COMPLEXITIES

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ABSTRACT

Background: Reproductive decision-making (RDM) is known to be a complex process, especially for heterozygotes with a pathogenic X-linked genetic variant. While studies of carriers of genetic conditions with various inheritance patterns have identified some personal values and concerns relevant to reproductive decisions, the ways in which X-linked heterozygotes (XLHs) integrate personal values, concerns, and the influence of social relationships into their decision-making process has not been fully understood, especially in the context of rare diseases.

Objective: This study aims 1) to characterize what is currently known about RDM for XLHs, and 2) to further our current understanding by exploring experiences of RDM in heterozygotes from a community with a rare X-linked disease community, Barth syndrome.

Methods: The first objective was met by conducting a scoping review of the values and psychosocial experiences that influenced the RDM process for XLHs. To address the second objective, previously conducted semi-structured interviews with 27 women with X-linked tafazzin variants recruited through the Barth Syndrome Foundation were analyzed. While these interviews included questions about psychological challenges, RDM experiences, and support systems of XLHs, secondary data analysis primarily addressed decisional conflict (DC) during RDM.

Results: 84 articles met inclusion criteria for the scoping review. Analysis of these articles showed that negative emotions like guilt, fear, and anxiety often accompanied RDM. Values like spirituality, conservation of personal resources, and a desire to avoid causing suffering were especially influential. Secondary data analysis made clear that

XLHs are highly susceptible to DC during RDM due to extra reproductive considerations related to the possible transmission of a genetic variant. Facing these considerations could lead to negative emotions and DC when personal values conflicted with other personal values or the opinions of others. To resolve the conflict, heterozygotes re-prioritized their values, reconsidered the extent to which they allowed certain values to influence reproductive decisions, and altered the content of their values.

Discussion: Many of the values identified in the scoping review were also named by Barth heterozygotes, suggesting that the manuscript findings are generalizable to other XLHs. Genetic counselors should offer decisional and emotional support to XLHs at multiple points throughout the RDM process.

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TABLE OF CONTENTS

ABSTRACT ..... *ii*

ACKNOWLEDGEMENTS ..... *iv*

LIST OF TABLES ..... *vi*

LIST OF FIGURES ..... *vii*

PART ONE: INTRODUCTION *1*

Background Information **1**
Terminology 1
Unique concerns 2

Scoping Review **3**
Spirituality 5
Personal resources: finances, time, and emotional energy 6
Avoid causing suffering 8

Decisional conflict **9**

Current study **10**
Theoretical Framework 10
Barth syndrome 11
Secondary Data Analysis 12

References **13**

PART TWO: MANUSCRIPT *17*

Abstract **17**

Introduction **19**

Methods **21**
Participants 21
Instrumentation 22
Procedures 22
Data Analysis 25

Results **26**
Answering reproductive questions 26
Question 1: Do I want to have a child? 27
Question 2: Do I want to intentionally avoid transmission of a TAZ variant? 29
Question 3: Do I want to use assisted reproductive or abortion technologies? 32
Emotional and social experiences of DC 35

Discussion **37**
Generalizability 42
Practice Implications 43
Limitations 45

Conclusion **46**

References **48**

LIST OF TABLES

Table 1.1: Frequency of Emotional and Social Experiences……5

Table 2.1: Participant Characteristics ……23

Table 2.2: Interview Guide Topics and Sample Questions ……24

LIST OF FIGURES

Figure 1: Theoretical Model of DC during RDM for XLHs ……..38

PART ONE: INTRODUCTION

Background Information

Reproductive decision-making (RDM) can be a complex and long process in which individuals learn about and contemplate different reproductive options and then choose one. For individuals who have one or more pathogenic genetic variants, RDM can be further complicated by decisions around whether or how to avoid transmitting the variant to offspring. In the context of genetic diseases, different inheritance patterns can lead to different challenges and considerations for individuals during the RDM process. Academic literature has shown that women who have a heterozygous pathogenic variant in a gene on the X chromosome face challenges that might be different than those who have variants associated with autosomal dominant or autosomal recessive conditions.

Terminology

Traditionally, women who have such X-linked (XL) variants are not thought to experience any symptoms related to the disorder. For this reason, these women are often referred to as 'X-linked carriers'. However, studies have shown that some XL genetic conditions can affect heterozygous females as well as hemizygous males, and some support organizations are working to raise awareness of this issue (van Galen et al., 2021; Choi et al., 2021; Viggiano et al., 2019; Battersby et al., 2013; "Remember the Girls", 2022). Barth syndrome, the XL condition studied in this thesis, is not known to cause any symptoms for heterozygous females. However, in an effort to support the awareness that 'carrier females' are not always 'carrying' a variant without experiencing

symptoms, the terminology ‘X-linked heterozygote/s’ will be used in place of ‘carrier female/s’ throughout this thesis.

Unique concerns

X-linked heterozygotes (XLHs) who do not have an affected relative may not learn of their genetic status until giving birth to an affected child. However, women with relatives who are affected by an XL condition are often aware of their potential to carry a pathogenic variant from a young age due to knowledge of genetic inheritance patterns (von der Lippe et al., 2017). This knowledge that one carries a pathogenic variant can have a significant impact on the way that an individual thinks about and arrives at a reproductive decision.

For example, fear and guilt were seen to accompany thoughts around passing on an X chromosome with a pathogenic variant to one of their children. In semi-structured interviews with nine adolescent girls who were sisters of males with CGD and were unaware of their carrier status, James, Holtzman, and Hadley found that even the prospect of grappling with these reproductive implications can be daunting and can generate a sense of fear around genetic testing (2003). Kay and Kingston’s qualitative interviews with 14 XLHs at a reproductive age showed that carriers without affected children forecasted a sense of guilt around different reproductive outcomes even before they occurred (2002). These women often compared the guilt they would feel at having an affected child with the guilt they would feel over having multiple terminations as a way to help make or prepare for reproductive decisions. Guilt is also frequently present in XLHs with affected children, as James et al. found in their surveys of families with CGD, DMD/BMD, and spinal muscular atrophy types II and III (2006). This guilt seems

to be especially troublesome for mothers of children with XL conditions, since mothers in this study more commonly experienced guilt in the context of XL inheritance patterns as compared to AR inheritance patterns.

In addition to the negative emotions that carriers experience around reproductive decisions, some XLHs have difficulty talking about their concerns related to the decision-making process with others. James, Holtzman, and Hadley's study of adolescent sisters at risk of being CGD carriers found that these girls avoided discussing experiences around the condition with their parents for fear of upsetting them, despite the girls' confidence in their parents' abilities to answer questions and provide emotional support (2003). These sisters also considered peers a poor choice for discussion because their peers might stigmatize or make fun of them or their brothers. In Kay and Kingston's study, it was found that XL carriers with affected family members also limit their conversations, even excluding partners from discussions about RDM (2002). Together, these two studies suggest that many XLHs engage independently with some or all aspects of the RDM process, including the emotions that can accompany it. While RDM in the context of genetic risk may always be difficult, this evidence suggests that the decision-making process for XLHs is especially fraught.

Scoping Review

To explore the current evidence on RDM in XLHs, a scoping review on XL RDM was conducted according to the guidelines outlined by the Joanna Briggs Institute (Joanna Briggs Institute, n.d.; Peters et al., 2015). For this study, a scoping review was chosen over a systematic review in order to allow the study question to remain broad

and encompass the entire range of personal values, concerns, and psychosocial experiences that pertain to reproductive decision-making in XL carriers. The review was focused mainly on two questions:

1. What personal values and concerns influence reproductive decisions and impact the reproductive decision-making process in carriers or at-risk carriers of XL disorders?
2. What positive and negative psychosocial experiences do XL carriers or at-risk XL carriers have in relation to reproductive decision-making?

467 articles were identified as possibly meeting inclusion criteria, and were read briefly in order to make final inclusion decisions. 84 articles met inclusion criteria, and were then uploaded to Mendeley software and read thoroughly. Findings from each article were written down on data extraction sheets. These thematic findings, such "anxiety" or "blamed by others", were inductive and not based on previously identified categories of results.

Overall, the scoping review made clear that current research on XL RDM has identified many different decisional factors that are important in reproductive decision-making. Most of this research has been based on samples from more common XL disorders Fragile X syndrome, hemophilia, and Duchenne muscular dystrophy (DMD). The decisional factors most commonly identified in this review related to spirituality, personal resources, and a desire to avoid causing suffering. Findings from the scoping review also suggest that the majority of emotions identified in the literature around XLH RDM are negative, with guilt, fear, anxiety, sadness, and general distress being the

most common. In addition, social relationships were seen to be important in the RDM process, especially when XLHs received direct instruction from others or talked with their spouses about their RDM. Social interactions had the capability to complicate or improve the RDM experience. Findings on important decisional factors are discussed below, and findings on emotional and social experiences during RDM are summarized in Table 1.1.

TABLE 1.1: Frequency of Emotional and Social Experiences

Emotional Experiences: n (%)		**Social Experiences: n (%)**	
Anger	5 (6)	Blamed by others	5 (6)
Anxiety	18 (21)	Concerned about what others will think about decision	9 (11)
Fear	20 (24)		
General distress	17 (20)	Desire for input from others on decision	5 (6)
Guilt*	28 (33)		
Hopelessness	4 (5)	Partnership difficulties	9 (11)
Isolation	4 (5)	Partnership grows closer	2 (2)
Regret	5 (6)	Receive disapproval of decisions	4 (5)
Relief	3 (4)	Receive support and help in coping from others	14 (17)
Sadness	16 (19)		
Shame	10 (12)	Spouse influences decisions	19 (23)
Stress	6 (7)	Told what to do by others	22 (26)

Frequency is based off of the number of articles that demonstrated the experience at least once.
* Guilt may refer to guilt over unknowingly having an affected child, as well as guilt over processes that an XLH was in control of.

Spirituality

Many XLHs mentioned the influence of religious convictions on reproductive decisions, often tying their thoughts to discourses of control. Some described their sense that they should not be the ones exercising control over whether they had an affected child, believing that forgoing some reproductive options and “leaving it in God’s

hands" was preferable (Thomas et al., 2007). In other studies, women emphasized how their spirituality brought them peace through the belief that a divine being had control over the outcome (Raspberry & Skinner, 2011b; McConkie-Rosell et al., 2012). Specifically, many found solace in the belief that a deity would protect them from circumstances they couldn't cope with, and would purposefully choose the best possible reproductive outcome for them and their families. Practically, this narrative of giving up control often resulted in decisions to avoid pregnancy termination (Schaller et al., 2007; Michie & Skinner, 2010). For those seeking to carry children, some wrestled with whether certain reproductive technologies like pre-implantation genetic diagnosis (PGD) aligned with their faith or not (Thomas et al., 2007).

Whether or not spirituality is a reproductive decision-making factor for a large number of individuals or simply a select few is not clear from the current literature. Both Balak et al.'s survey of hemophilia heterozygotes in the Netherlands (2012) and Bong's survey of DMD heterozygotes in the USA (2020) found that only a minority of their research participants identified religious convictions as the determining factor for their reproductive decisions. However, Gillham et al.'s interviews with hemophilia heterozygotes in South Africa found that a majority of their participants relied on their religious views to shape their reproductive decisions (2015). It is possible that the number of individuals who rely heavily on spirituality to make decisions may vary depending on their cultural background.

Personal resources: finances, time, and emotional energy

Another factor that influenced XLHs reproductive decisions was personal resources, particularly finances. Many individuals stated that their decision to have

children or refrain from having children was influenced by a consideration of their financial preparedness (Raspberry & Skinner, 2011a; Raspberry & Skinner, 2011b; Bailey et al., 2003; Kadir et al., 2000). Some discussed this specifically in light of the possibility to have a child with an XL disorder, while others mentioned this while discussing the possibility of having a child in general. Financial concerns around IVF/PGD were frequently mentioned, with many XLHs stating that the costs of this reproductive technology made it inaccessible or a less desirable option to them (Lavery, 2002; Schaller et al., 2007; Bong, 2020). In more recent studies, XLHs have also mentioned their hesitations around having a child with an XL disorder that would incur costs to society, and not just themselves (van Dijke et al., 2021; Severijns et al., 2021).

Time was another resource that influenced XLHs' reproductive decision-making process. For women who already had other children, concerns about one's ability to devote enough to time to both the existing child and another child who might have an XL disorder made them hesitate to move forward with pregnancies (Fanos & Puck, 2001; Bailey et al., 2003). In addition, quantitative studies with XLHs showed that age was associated with different reproductive decisions, suggesting that an individual's sense of their reproductive timeline was also factored into the decision-making process (Xunclà et al., 2010; Naicker et al., 2016; Bong, 2020).

Many XLHs also weighed their emotional energy when considering different reproductive decisions (McKee, 2017; Raspberry & Skinner, 2011b). Different individuals expressed different emotional concerns about having a child, including availability of emotional support, emotional capacity to parent multiple children, and bearing with stigma (Leuzinger-Bohleber & Teising, 2012; Huyard, 2012; Raspberry &

Skinner, 2011a; Bailey et al., 2003; Clarke, 2016). Some individuals also factored in the emotional toll that having a pregnancy termination and avoiding an affected child would have on them (Kay & Kingston, 2002). However, not all personal assessments of emotional capacity resulted in concern or fear. Women mentioned feeling able to both cope with and provide emotional support to a child with an XL condition, with some drawing on personal experience or divine support to feel assured of this (Naicker et al., 2016; McConkie-Rosell et al., 2012; Thomas et al., 2007).

Avoid causing suffering

A third common consideration that was factored into XLHs' reproductive decisions was a desire to avoid causing suffering. This was primarily related to the suffering of an affected child; namely, how living with an XL condition would bring great difficulties. Many women reflected on the experiences of affected relatives when discussing their desires to prevent suffering for a child of their own (Bong, 2020; McConkie-Rosell et al., 2012; Leuzinger-Bohleber & Teising, 2012; Lewis et al., 2012; Kay & Kingston, 2002; Parsons & Atkinson, 1993). Statements about avoiding suffering were often coupled with assertions that preventing suffering was a moral obligation or that heterozygotes would feel guilty believing they had knowingly allowed harm (Zuckerman et al., 2020; Bong, 2020; von der Lippe et al., 2017; McConkie-Rosell et al., 2012). However, there was a spectrum of opinions about how awful the suffering might be, with some considering the suffering tolerable and others forecasting that a child with an XL condition would have very low quality of life (Zuckerman et al., 2017; Kay & Kingston, 2002; Parsons & Atkinson, 1993). This spectrum may be related to the perceived severity of the condition, since those who predicted lower quality of life for

affected individuals did so in the context of conditions that significantly affect multiple body systems and activities of daily life, like Duchenne muscular dystrophy. Many XLHs who were very concerned about causing suffering for their child decided to avoid having a child with an XL condition.

In addition to concern for the suffering of an individual with an XL disorder, many XLHs also considered how their reproductive decisions might have a negative impact on other members of their family. This included the possibility for emotional harm to siblings, partners, and even grandparents who had previously endured difficulties raising children of their own with an XL condition (Boardman, 2021; Bong, 2020; von der Lippe et al., 2017; Fanos & Puck, 2001; James et al., 2003; Kay & Kingston, 2002; Parsons & Atkinson, 1993).

Decisional conflict

The Ottawa Decision Support Framework, which was used to help guide the development of the research proposal for this thesis, defines decisional conflict as "a state of personal uncertainty about which course of action to take when choice among options involves risk, loss, regret, or challenge to one's personal values" (Stacey et al., 2020). Decisional conflict is most commonly identified via verbal expression of uncertainty, but can also be accompanied by psychological, emotional, and even physical distress (Stacey et al., 2020).

Though current literature on XLH RDM illuminates many important decisional factors, very little attention has been paid to how these factors individually and collectively contribute to decisional conflict. Based on the findings from the scoping

review, it is clear that reproductive decision-making is a process that may easily lead to decisional conflict. There are many instances in which it appears to be evident across different XL conditions and different sets of values, which are discussed in the manuscript below. However, the lack of explicit focus on this concept limits our understanding of how XLHs experience it. It is important to explore instances of decisional conflict like these, since they influence both the experience of reproductive decision-making and the decision itself. A deeper understanding of what decisional factors tend to conflict, when decisional conflict is likely to be present, and how such conflict impacts XLHs during the reproductive decision-making process is crucial to healthcare professionals' ability to provide adequate informational and psychosocial support throughout the reproductive decision-making process.

Current study

Theoretical Framework

This study's analysis is guided by the Pregnancy Decision-Making Model (PDMM) developed by Klann & Wong (2020). The PDMM asserts that an evaluation of personal resources and values, personal narratives, barriers to access, and social influences all interact to influence three decisional outcomes: what decision is made, decisional certainty, and decisional satisfaction. This model aligns well with the data since an overarching narrative about heterozygote experiences with Barth syndrome is provided in addition to data on the reproductive decision-making experience. Following the PDMM, analysis aimed to further explore which decisional factors contribute to decisional conflict, as well as how these factors and this conflict relates with one's

personal life narrative. The PDMM was developed based on academic literature and author experience regarding unintended pregnancies, and has little empirical evidence as of yet, likely due to its recent publication. However, the model appears to align with this study's data and goals in multiple ways. For these reasons, this study aims to use the PDMM as a guide while being attentive to the ways in which the data support or contradict the model.

Barth syndrome

The XLHs who participated in this research project all had heterozygous pathogenic variants in the *TAZ* gene, which encodes the tafazzin protein and is known to be associated with Barth syndrome. Barth syndrome is a disorder associated with cardiomyopathy, skeletal myopathy, delayed growth, neutropenia, and high levels of 3-methylglutaconic acid in the urine (Clarke et al., 2013). While lifespan can vary, as of 2011 only 36% of known living individuals with Barth syndrome were older than 15 years of age (Clarke et al., 2013). However, recent research shows that the lifespan of Barth syndrome patients is becoming longer with earlier diagnosis and improved management of cardiac and immune complications (Taylor et al., 2021).

Approximately 13% of *TAZ* variants are thought to arise spontaneously in affected boys, meaning that most mothers of affected sons are heterozygotes, but not all (Clarke et al., 2013). Despite the predominance of inherited variants over spontaneous ones, learning of *TAZ* variants can still come as a surprise to families since XLHs are unaffected and affected males may lack a diagnosis due to early death or the rarity of the condition.

The life-limiting nature of Barth syndrome, as well as its variable expressivity, likely influence how XLHs perceive the condition and think about having a son or daughter with a *TAZ* variant. In addition, Barth syndrome's rarity (affecting an estimated 1 per 1,000,000 males worldwide) may limit access to resources and social support during RDM (Miller et al., 2020). These factors influence the RDM process as a whole and may contribute to decisional conflict, which makes Barth syndrome a very relevant condition for the purposes of this study.

Secondary Data Analysis

The interviews analyzed in this study were originally conducted as part of a broader study of psychosocial well-being, reproductive decision-making, and social support in women with heterozygous *TAZ* pathogenic variants. However, the second aim of the current study aligns very closely with two aims of the original study, which focused on describing psychological challenges for heterozygotes and their experiences with reproductive decision-making. In addition, the current study's analysis was done in close collaboration with researchers from the original study team. Results from the original study have never been published. For these reasons, the manuscript in this thesis is written in the format of a primary data analysis.

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PART TWO: MANUSCRIPT

Abstract

Reproductive decision-making is known to be a complex process, especially for heterozygotes with a pathogenic X-linked genetic variant. Studies of X-linked heterozygotes have identified various personal values and concerns that influence reproductive decisions, but these studies provide limited insight into decisional conflict during the reproductive decision-making process. This study aims to explore how heterozygotes with variants known to cause Barth syndrome, a rare X-linked disorder, navigate and experience decisional conflict during reproductive decision-making. Semi-structured interviews were conducted with 27 Barth heterozygotes recruited through the Barth Syndrome Foundation. Special attention was paid to narratives of high and low decisional conflict and the values around which decisional conflict occurred. Findings showed that decisional conflict was a result of conflicts in value systems. To resolve the conflict, heterozygotes re-prioritized their values, reconsidered the extent to which they allowed certain values to influence reproductive decisions, and altered the content of their values. Value systems could also be reshaped over time by personal experiences, and thus influence levels of decisional conflict in subsequent reproductive decisions. Decisional conflict often induced feelings of stress and guilt, and could be exacerbated by the opinions of others. Genetic counselors are well-equipped to provide decisional and emotional support to X-linked heterozygotes during reproductive decision making, and their services may help reduce decisional conflict and the negative emotions that accompany it. Counselors should help heterozygotes identify factors that are contributing to conflict and decide if and how they want to restructure their value

systems. This kind of support may be needed at multiple different points to accommodate for shifts in value systems over time.

Keywords:

decision making, reproduction, X-linked, decisional conflict, value, genetic counseling

Introduction

Reproductive decision-making (RDM) involves the process of thinking about whether and how to have a child and making a decision between different reproductive options. In the context of genetic risk, this decision is not thought to be a simple one, but rather involves a complex process that can vary over time and include individual and interpersonal deliberation (Raspberry & Skinner, 2011b). RDM for individuals who have one or more pathogenic variants has been studied in a wide variety of conditions, with most research focused on common autosomal dominant (AD) or recessive (AR) conditions. There is less literature focused on X-linked (XL) conditions, but current studies suggest that XL heterozygotes (XLHs) experience certain parts of the RDM process differently. James et al. found that XLHs experienced more guilt over passing on pathogenic variants than female carriers of AR conditions (2006). In addition, XLHs may learn of their possible heterozygous status at a young age if a relative is diagnosed (von der Lippe et al., 2017). As a result, XLHs may grapple with reproductive concerns far before they want to initiate any reproductive efforts, knowing that the potential for any future children to be affected with the XL condition in question rests solely on their own genetic status and is not dependent on a partner's status. These emotional and cognitive factors set XLH RDM apart from other RDM processes and suggest a need for focus on RDM in XLH populations specifically.

The current knowledge around XLH RDM encompasses an understanding of what values and decisional factors are used to make reproductive decisions. These include but are not limited to a desire to have children, a desire to avoid causing suffering, a fear of devaluing the lives of affected individuals, finances, spirituality, and a

consideration of the impact on both the mother and other existing family members (Zuckerman et al., 2020; Bong, 2020; von der Lippe et al., 2017; Kay & Kingston, 2002; Clarke, 2016; Raspberry & Skinner, 2011a; Kadir et al., 2000; Raspberry & Skinner, 2011b; McConkie-Rosell et al., 2012; Thomas et al., 2007; Boardman, 2021; Fanos & Puck, 2001). These values and factors are present in a variety of XLHs, though most of the findings are drawn from populations with more common XL conditions like Fragile X, Duchenne or Becker muscular dystrophy, and hemophilia. Thus, the voices of XLHs from rare disease communities are underrepresented in this literature.

In addition, current studies on XLHs provide a very limited understanding of how the values and factors named above interact with each other and influence levels of decisional conflict (DC). DC describes an individual's uncertainty around what option to choose when given multiple options. It is more common when one faces decisions that require them to choose between competing values, or that can have significant consequences and uncertain outcomes (O'Connor, 1995). Experiencing DC is especially likely when individuals lack information, support, or clarity around their values and how to apply them in novel situations (Garvelink et al., 2019). Reproductive decisions can be highly consequential, and XLHs making such decisions often must learn about new and complex reproductive options that may challenge their values and provide limited certainty about a future child's health. Thus, DC is very likely to occur for some XLHs during their RDM process.

Quantitative studies of DC in RDM confirm that high and low levels of DC are present in a variety of different genetic conditions (Severijns et al., 2022; Reumkens et al., 2021; Gietel-Habets et al., 2018). In addition, qualitative explorations of RDM and

genetic conditions show many instances in which DC appears to be evident. These instances involve conflicts between many of the values named above that have been shown to be important in XLH RDM (McConkie-Rosell et al., 2012; James et al., 2003; Parsons & Atkinson, 1993; Decruyenaere et al., 2007; Henneman et al., 2002).

While these findings are helpful for beginning to characterize DC, they are limited and likely do not fully characterize all the ways in which DC can arise during RDM for individuals who may pass on a genetic variant. In addition, the lack of an explicit focus on DC in many qualitative publications leaves gaps in our understanding of why individuals experience DC, how individual value systems and interpersonal relationships influence DC, and what the emotional and psychological effects of DC during RDM are. Finally, many of the studies that have contributed to our current understanding were conducted before reproductive technologies like non-invasive prenatal testing were clinically available and thus cannot provide insight on how heterozygotes experience DC around these options.

This study aims to address these gaps through a qualitative exploration of DC during the RDM process for XLHs from a rare disease community, Barth syndrome. Barth syndrome is a rare X-linked disorder caused by pathogenic variants in the *TAZ* gene associated with cardiomyopathy, neutropenia, and a shortened lifespan.

Methods

Participants

Adult women ($\geq$18 years) with a known deleterious *TAZ* mutation (based either on clinical genetic testing or obligate heterozygote status per family history) were invited to participate in this study. Participants were recruited via convenience sampling

through the Barth Syndrome Foundation (BSF), an international organization that provides services to families with Barth syndrome and promotes research and awareness about the condition. Overall, 28 individuals who met inclusion criteria agreed to participate. One interview from the original dataset was excluded from this study due to failure to audio record, leaving 27 participant interviews for coding and analysis. Most participants were mothers, and nearly half (13/27) resided in countries other than the United States at the time of the interview. Most participants had experienced a death in their family that was either definitely or likely due to Barth syndrome. Participant characteristics are summarized in Table 2.1.

Instrumentation

An interview guide was developed by multiple genetic counselors who all had expertise on the experiences of XLHs, either through counseling experience or research endeavors. Interview questions aimed to characterize the nature, frequency, severity, and predictors of psychological and reproductive challenges of Barth syndrome heterozygotes. Interview guide topics and sample questions were approved under the Johns Hopkins School of Medicine IRB, and are listed in Table 2.2.

Procedures

Participants provided informed consent prior to their participation in the study. Semi-structured telephone interviews were then completed with each participant, ranging from 24 minutes to 65 minutes (46 minutes average). One genetic counselor with no clinical engagement with any of the participants served as the interviewer. All interviews were audio recorded and transcribed. In addition, post-interview field notes were recorded by the interviewer and were shared with the rest of the study team.

TABLE 2.1: Participant Characteristics

	N (%)
Age	
18-30	3 (11)
31-40	12 (44)
41-50	4 (15)
51-60	5 (19)
61+	3 (11)
Nationality	
Australia	1 (4)
Belgium	4 (15)
Canada	2 (7)
France	1 (4)
UK	5 (18)
USA	14 (52)
Family history of Barth syndrome*	
Mother – confirmed Barth syndrome	20 (74)
Sister – confirmed Barth syndrome	4 (15)
Sister – likely Barth syndrome	3 (11)
Aunt – confirmed Barth syndrome	5 (18)
Grandmother – confirmed Barth syndrome	3 (11)
Niece – confirmed Barth syndrome	1 (4)
Niece – likely Barth syndrome	1 (4)
	2 (7)
Family deaths from Barth syndrome	
Yes – confirmed Barth syndrome	6 (22)
Yes – likely Barth syndrome	14 (52)
No	7 (26)
Timing of heterozygote genetic testing	
Before childbearing	5 (18)
While family building	16 (60)
After reproductive choices complete	6 (22)

TABLE 2.2: Interview Guide Topics and Sample Questions

Topics	Sample Questions
Family History	*Can you tell me a little bit about how Barth was first diagnosed in your family? What was learning the diagnosis like for you?* *Who did you tell about the diagnosis? How did they react?*
Impact of Barth Syndrome on Family	*How has living with Barth syndrome affected your family?* *People sometimes say that while there are certainly very hard parts of living with a medical condition in the family there can be benefits as well. Has this been true for your family? In what ways?*
Carrier Testing	*How did you first find out you were a Barth syndrome carrier? Was it something you had considered before that?* *Was it hard to decide whether to have carrier testing?* *What was the experience of learning carrier result like? Who did you tell? Was there any response that was particularly helpful?*
Impact of Carrier Test Results	*Have there been benefits and/or emotional downsides to learning you are a carrier?* *Who do you talk to about being a carrier? Are there people who are particularly helpful or unhelpful to talk to?* *Do you think there is an age that is particularly good or bad for carrier testing? What advice would you give to someone considering TAZ carrier testing?*
Reproductive Plans	*Have your plans for having children been affected by being a TAZ carrier? How?* *Have you ever had a pregnancy that you knew was at-risk for Barth syndrome? What was that experience like?* *If you think about possibly having a child in the future, do you worry about the baby having Barth syndrome or being a carrier?* *Have you considered using genetic testing to diagnose Barth syndrome prior to birth? How do you weigh these choices?* *Is there anyone you talk to about issues related to future pregnancy and use of genetic testing? Are any of these conversation partners particularly helpful or unhelpful? Why?*

Data Analysis

This study's analysis was guided by the Pregnancy Decision-Making Model (PDMM) developed by Klann & Wong (2020). The PDMM asserts that an evaluation of personal resources and values, personal narratives, barriers to access, and social influences all interact to influence three decisional outcomes: what decision is made, decisional certainty, and decisional satisfaction. Attention was paid to all four of these precipitating factors to better understand how they contributed to decisional conflict (DC) and affected RDM as a whole.

Before beginning coding, transcripts were uploaded to MAXQDA, which is a software designed to aid in qualitative data analysis. The first author then wrote one-page summaries of each interview to familiarize herself with the overall narrative of each participant and to increase study validity. Following this, the entire transcript for each interview was coded and analyzed by the first author. Regular discussions with genetic counselors who helped develop the interview guide and had a history of frequent interaction with this population were held to discuss the student's coding, analysis, and interpretations of the data.

Each transcript was coded with attention to factors involved in reproductive decision-making, DC or lack thereof, influences of social support on the decision-making process, and emotional and psychological aspects of decision-making. DC codes were applied to instances in which participants questioned their personal values, delayed decision making, and described vacillating. DC codes were also applied any time a participant expressed that making reproductive choices were very easy or instantaneous to allow for comparison between individuals with higher and lower levels

of DC. Instances of decisional conflict or lack thereof were then compared between participants and considered as a whole, which allowed for broader themes to be developed. Positive and negative emotion codes were developed inductively and applied when participants explicitly mentioned or demonstrated emotions like guilt, stress, anxiety, sadness, and relief. Codes relating to social interactions were also applied when XLHs mentioned feeling pressured by others about what decision to make, receiving judgment for decisions they made, or receiving any form of support from others that positively impacted their RDM experience. Overall, analysis was guided by Braun & Clarke's guide for conducting thematic analysis (2006). When presenting the data, minimal modifications to the quotes were made in order to clarify the intended meaning of the participant. These modifications are present in brackets within the quotes.

Results

DC during RDM impacted XLHs in a variety of ways. Psychologically, XLHs had to wrestle with multiple reproductive questions in order to arrive at a conclusion about whether and how they wanted to have a child. Grappling with these questions often brought up negative emotions like stress and guilt. Social interactions between XLHs could exacerbate one's DC and make them question the reproductive conclusions they had arrived at.

Answering reproductive questions

In order to make a reproductive decision, XLHs asked themselves different questions, including: 1) Do I want to have a child? 2) Do I want to intentionally avoid transmitting a pathogenic *TAZ* variant? 3) Do I want to use assisted reproductive or

abortion technologies? Answering these questions required XLHs to reflect on their personal values and to what extent they should influence reproductive decisions. Changes in the prioritization and content of these values resulted from grappling with DC or from new personal experiences, and could then influence the extent to which XLHs experienced DC later in RDM.

Question 1: Do I want to have a child?

As XLHs engaged in the RDM process, they needed to assess whether they wanted to have a child at all. Knowing their heterozygous genetic status could complicate this question by connecting the concept of having a child to the possibility of passing on a variant that could cause disease. One XLH who learned her genetic status before she was ready to have children found that this complication made it difficult for her to think clearly about her reproductive desires.

> If I wasn't a carrier for Barth Syndrome, I think my mind would think quite rationally about did I or did I [not] want to have children. I think the fact that I know that I'm a carrier for Barth Syndrome makes my mind play tricks on me and about what I actually do and don't think.
>
> - Participant 21

Participant 21, who learned about Barth syndrome through her nephew's diagnosis, felt that knowing her genetic status skewed her reproductive views and made it difficult to 'rationally' discern what her reproductive desires would be if she was not a Barth heterozygote. Her fear of causing suffering for future generations of her family caused her to question her values around having children, as well as her confidence in her ability to discern what she truly wanted.

Other XLHs were more confident in their personal desires to have children, but experienced DC as they attempted to balance them with concerns for possible negative personal repercussions. For some, the main repercussion they desired to avoid was exhaustion. Thinking about parenting another child, especially one who may require non-traditional support and resources, made some women question whether they were too old or had enough stability in their current lives to add another child to the family dynamic. Participant 26, who learned of her heterozygosity after her son was diagnosed with Barth syndrome, focused primarily on the latter.

> **Interviewer:** And so [expanding your family] was something you had been planning to do? Are you still planning to do?
>
> **Participant 26:** Yes, no, probably not. I would probably be willing to-- I mean that's still something we battle with every day. You know, [my son] has had a heart transplant and so our lives still haven't recovered from that completely. And so that's another aspect.
>
> - Participant 26

In addition to a fear of exhaustion, XLHs also considered the mental stress that came with pregnancy. For those who chose to get pregnant naturally, the psychological burden of waiting to learn the child's genetic status was especially difficult. Attempting to reconcile a desire to have a child with a desire to avoid such a mentally taxing experience could lead to DC.

> Due to the high anxiety and the high stress that I experienced with the pregnancy of [my affected son], with [a later pregnancy] I didn't want to go back for the third one, because I just didn't know if I could go through that or put myself through

that again, even though at the very start we both said “Oh, we want three kids, we want three kids.”

- Participant 10

These three participants’ statements show that the way XLHs thought about their reproductive futures was highly influenced by their circumstances and personal experiences. The timing of learning one’s genetic status, the severity of Barth syndrome in affected children, and prior pregnancy experiences all shaped their thoughts around having children and whether to prioritize their desire for more kids over other values. Because of this, reproductive goals were subject to change over time.

Question 2: Do I want to intentionally avoid transmission of a TAZ variant?

For Barth heterozygotes, deciding whether to intentionally avoid having a child with a *TAZ* variant was another key step in the RDM process. As with the first question, the values that shaped answers to this question could be re-prioritized over time as circumstances changed and new personal experiences were gathered. This, in turn, could lead to different levels of DC. Participant 17’s RDM experience is one example of this. She explains how her focus shifted over time from the fear of passing on a pathogenic variant to the benefits of having another child:

> And then when [my son] was diagnosed, carrier guilt kicked in. I [couldn’t] possibly imagine even passing this on to somebody else. Even if it's a girl, I don't want her to have to deal with this burden. And so I still think I would like to [have another child], but a lot of it is now, because I know that [my son] would benefit from having a sibling, and that was kind of what tipped the scales for me. It was like, I wanted two, I wanted him to have a sibling, but I don't know if I can do it,

and then seeing him interact with other kids and knowing how much he would grow from having a sibling, it was like, “Okay, maybe I can do this."

- Participant 17

In the immediate aftermath of learning about her son’s Barth diagnosis, Participant 17’s feelings of guilt caused her to feel strongly that any possibility of transmitting a *TAZ* variant again should be avoided. However, the passage of time and her experience of watching her son grow up caused her to question her prior decision to avoid pregnancy, and thus to experience DC. This questioning and DC was brought on by a re-prioritization of her values, as changes in the circumstances of her life led her to place a higher priority on having another child.

Not every XLH who thought about whether to avoid transmission of a pathogenic variant experienced DC around their desire to have children. Rather, some who also initially considered avoiding having children with Barth syndrome wrestled with the ethics of this choice instead. The primary ethical concern named by these XLHs was a fear that choosing to avoid the birth of a child with Barth implied that unaffected children were better or preferable. Participant 9, mother of an affected son, experienced significant and distressing DC around this ethical question.

And it was the whole thing in your head of, ‘Am I saying that a boy is not good enough? Am I saying that I want just a daughter? Am I saying that another [affected] child, no, no, I don’t want that?’ It was quite horrible actually for me and my husband. It wasn’t nice because it was almost as if he was saying that what we have – eh, let’s see what else we can have.

- Participant 9

Most XLHs who named this concern were mothers of affected children. Notably, these participants' ethical dilemma was not framed in an impersonal manner. Rather, multiple XLH mothers talked about the decision to avoid variant transmission in reference to their current affected son.

> And then as I gave it more time and more thought, I would feel – I felt like I would feel guilty and wrong going down [the IVF] route, because I would never have done that with [my son], and he's been such a blessing. I wouldn't have chosen that then.
>
> - Participant 3

Though Participant 3 discussed her concerns in relation to IVF, her primary qualm did not lie in the use of the technology itself but rather its use for the purpose of avoiding having a child with the condition her son had. She, along with other mothers, wrestled with the difficult question of whether a desire to avoid Barth syndrome was synonymous with a desire to reject the child with Barth syndrome she already had. While hopes of preventing future suffering from the condition led them to consider alternative reproductive options, a desire to affirm the value and goodness of the lives of their sons made some XLHs question to what extent the desire to prevent suffering should influence reproductive decisions.

The experiences of these three XLHs demonstrate again the power of personal experiences, and how mothering a child influenced their reproductive values and views on the ethics of avoiding variant transmission. Like the examples previously mentioned, Participant 17 experienced a re-prioritization of values. However, both Participant 9 and Participant 3 found themselves questioning not the relative importance of preventing

suffering compared to other values, but rather what its larger implications were if used as a motivation to avoid transmission of a *TAZ* variant. Their stories show that DC for XLHs can involve more than just a tradeoff between values, but also a reconsideration of how to live out certain values and the extent to which these values should influence their reproductive decisions.

Importantly, the mothering experiences of Participants 9 and 3 were not the initiators of change in their value systems. Rather, it was the experience of DC that led these two to reflect on their value systems and then re-prioritize. Their narratives stand in contrast to those explored earlier, which showed how new circumstances and personal experiences led XLHs to create shifts in their value systems. Participants 9 and 3's RDM processes show that not only personal experiences and circumstances but also DC itself can instigate changes in one's values system and how one lives it out. Thus, DC and shifts in value systems share a reciprocal relationship in which each is capable of affecting the other.

Question 3: Do I want to use assisted reproductive or abortion technologies?

The final question involved in XLHs' RDM process was whether to use the assisted reproductive or abortion technologies available to them. With reproductive technologies like IVF, cost was a barrier for some that completely prevented their consideration of it. However, for those who were not impeded by cost, the physical demands of the procedure could create DC around whether the perceived benefits of the technology made its use worth it. Participant 13, mother of a daughter conceived through IVF, struggled with this in her attempts to become pregnant again. She

experienced DC as she tried to decide whether she would undergo another IVF cycle should the final embryo saved from a previous cycle fail to implant.

> One embryo, yeah, we are going to try this first, and then, if it's not, if it's saving, then thinking about another treatment, that maybe I won't do the treatment again, even if I want another child. … It would be heavy to do it again.
>
> – Participant 13

Despite the fact that she still had one embryo left, Participant 13 still found herself wrestling with DC around her desire to have a child and her desire to avoid undergoing treatment again. Aware of her competing values and the possibility that implantation would not succeed, she began the mental work of RDM before she was certain that she would need to make a decision about whether to use the reproductive technology another time. Her narrative shows that RDM and the experience of DC is not limited to the time frame in which XLHs are ready to make and then immediately act on reproductive decisions. Rather, knowing one's heterozygous status and reflecting on the reproductive questions needing to be answered can begin the RDM process and lead to DC at any point.

Other XLHs' stories also demonstrate a long-term involvement with DC and RDM, though their struggles with reproductive and abortion technologies revolved less around physical demands and more around spiritual values. Participant 7, whose son was severely affected by Barth syndrome, explained how she grappled for years with her spiritual beliefs and the ethics of reproductive options like IVF.

> And that was something I really wrestled with for several years and just never was able to come to terms with that for me, I just really have very strong faith and

> my belief is that life begins at conception and I feel like an embryo has already been conceived and therefore destroying an embryo was not the right thing for me.
>
> - Participant 7

Her statement revels the prolonged DC she experienced before arriving at a conclusion, though Participant 7 eventually settled on a personally prohibitive stance towards IVF. Other XLHs who mentioned spirituality in their discussions around RDM and the use of technologies often shared her perspective that pregnancy termination and the discarding of embryos were not compatible with their moral convictions. However, since these spiritual values were formed over time, they also had to capability to change as XLHs underwent new personal experiences and faced new circumstances. This is seen clearly through Participant 27's RDM journey. Initially, her spiritual views led her to feel sure that she would never terminate a pregnancy. However, after Participant 27's son with Barth syndrome passed away, she found herself questioning her original stance on RDM. Reflecting on the suffering her son endured made her think differently about her faith and the boundaries it set for her RDM.

> Having seen what [affected son] went through and the suffering that he went through in the months before he died … suddenly I could see shades of gray and we both decided-- and it was a very personal decision, and not something that we shared with anybody else at all-- that we would just try naturally and see what happened, and then in the event of an affected pregnancy, I would have a termination. So yeah, things changed for me quite a lot.

- Participant 27

As Participant 27's personal experience with Barth syndrome changed, her values that informed RDM shifted as well. Unlike the value-shifts explored earlier, Participant 27's changes in her value system involved both re-prioritization and reshaping of the content and influence of her values. New personal experiences led her to place a higher priority on avoiding suffering for her future children and her family, which conflicted with her desire to have more children in a way that aligned with her original spiritual values. Rather than placing less importance on her faith or questioning how much a spiritual conviction against abortion should influence her reproductive decisions, she instead reconsidered the very content of her spiritual values and whether or not they created a black and white framework for thinking about different reproductive options. This demonstrates the profound impact that experiencing DC can have on one's values, leading not only to re-prioritization or re-evaluation of impact, but also to changes in the values themselves.

Emotional and social experiences of DC

DC during RDM was accompanied by difficult emotional and social experiences for XLHs. Most of the emotions related to DC were negative and tied to the psychological difficulty of wrestling with different personal values. For example, many participants found that navigating the various reproductive options presented to them generated a sense of stress, including whether to test and how to utilize the results.

Guilt was also highly prevalent in XLH narratives of their RDM process. Some XLHs described feeling guilty as they wrestled with sincere desires that threatened other important values. This was true for Participant 26, who felt guilty for how strongly

she wanted to have another child while knowing that IVF was financially unfeasible and thus fulfilling her desire may mean having another affected child.

> I guess I feel more guilt because I do want another baby so bad but then why would I do this to another child? That's when I would feel guilty.
>
> - Participant 26

DC around the values of avoiding variant transmission and having a child even if they knew they might be affected created a sense of guilt for other XLHs as well. However, some experienced guilt more as a result of what others thought about their reproductive values and DC than how they felt about their own DC.

> So [my family and significant other] made me feel quite selfish for even thinking about children and things like that. So I've always felt quite alone with it really.
>
> - Participant 21

Though Participant 21 avoided talking about her genetic status and RDM with her family, their unspoken opinions still had quite a large impact on her and generated a sense of guilt around considering having a child. This, along with other family dynamics, made her feel isolated during the process of RDM and contributed to her difficulties in coming to a reproductive conclusion.

Other XLHs who did engage in active conversations about RDM with others still found themselves feeling guilty and questioning their choices. Even after they had arrived at a reproductive decision they were satisfied with, the opinions of others could unsettle XLHs and make them wonder whether they had truly made the right decision, creating the possibility for DC to arise.

> The only thing [is] that it is somewhat difficult or painful, even within the Barth Foundation [support group] and sometimes with your own family to discuss this because there's different points of view. … People that don't agree with you makes it difficult to deal with sometimes, and makes you even though you're okay with your decisions, you talk to yourself about it, you know, your immediate family is okay, anytime somebody questions it or has a different view, you question yourself and you don't-- so you feel some guilt there. Like am I wrong?
>
> - Participant 18

These narratives reveal how the opinions of family members, friends from support groups, and significant others could make XLHs doubt themselves and their desires, thus generating more DC instead of helping to resolve it. These negative social experiences also limited the support network available to XLHs during RDM, adding a sense of isolation on top of the stress and guilt that already could accompany DC.

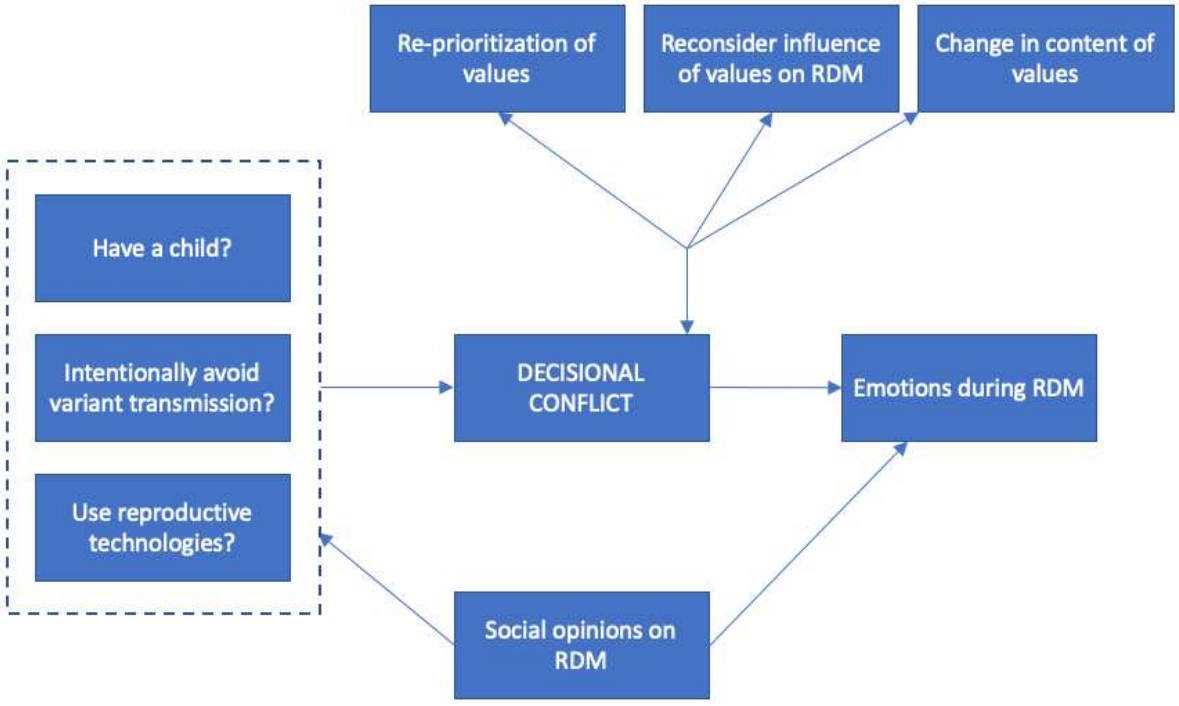
Discussion

Barth heterozygotes thinking about RDM had to ask themselves multiple reproductive questions, including whether they wanted to have a child, intentionally avoid transmission of a *TAZ* variant, or use assisted reproductive and abortion technologies. These three questions led XLHs to reflect on their values and could lead to DC when values did not align. DC could be influenced by shifts in one's value system over time, and could also initiate re-prioritization or changes in the content of one's values. Wrestling with DC often produced negative emotions like stress and guilt, and created a need for social support from others. However, some interactions with members of a social support system or attention to their opinions could exacerbate the

problem by generating additional DC as well as a sense of isolation during RDM. Figure 1 depicts the relationship between concepts described here, demonstrating how these factors influence DC during RDM and interact with each other.

Our results show that RDM for XLHs is a process uniquely susceptible to DC. Many individuals who are not XLHs and are considering having children need only ask themselves the first question named in this manuscript: Do I want to have children? Those who struggle with infertility or feel that having a child is not in the best interests of themselves or their family may also ask themselves if they want to use assisted reproductive or abortion technologies. However, only individuals who have a pathogenic genetic variant must ask themselves all three questions listed above in order to arrive at a reproductive decision. Though the questions were numbered in this

FIGURE 1: Theoretical Model of DC during RDM for XLHs



manuscript for the sake of clarity, it is important to remember that these questions were not necessarily addressed by XLHs in a sequential order. Many XLHs grappled with all three questions at once, and used their thoughts and answers from one question to influence the way they thought about and answered another. Facing so many reproductive questions at one time created much more opportunity for DC for XLHs than would be expected for other prospective parents.

Asking these questions and experiencing DC pushed XLHs to re-evaluate their value system. This reflection and experience of DC led some XLHs to change which values they prioritized most. However, the values XLHs considered most important were also subject to change as XLHs moved through different life circumstances and gained new personal experiences. For example, the reproductive desires and concerns that were most salient immediately after learning one's carrier status or receiving a Barth diagnosis were not always the same as those considered most important after having other children or experiencing the death or suffering of a child. This re-prioritization of value systems over time could in turn influence how much DC XLHs experienced and what reproductive decisions they made.

As an alternative to re-prioritizing values, some XLHs changed their thoughts on how values should influence RDM. This was primarily exemplified as parents who held a desire to avoid causing suffering for future children questioned whether this desire should lead them to avoid bringing a life with Barth syndrome into the world at all. Other XLHs changed the very content of their values, like whether their spiritual framework had space for "gray" and ethical possibilities for termination or not. These changes in the actual values and their influence on RDM demonstrates that resolving DC can be

more complex than making simple value tradeoffs (O'Connor, 1995). While these tradeoffs are certainly present, DC can also lead to changes in core values and how XLHs choose to live them out. The complex nature of value re-organization and re-shaping gives insight into why resolving DC can be such a difficult process for some XLHs and why one's reproductive values and experience of DC can change from one reproductive decision to the next.

DC was tied not only to psychological difficulties, but also to emotional and social complications. Stress and guilt were the two most common emotional experiences, and arose as a direct consequence of DC. Navigating different reproductive technologies and knowing how to maximize their utility was a particular source of stress for some XLHs. This finding is notable, since the number and availability of these technologies expanded between the time previous studies on XLH RDM were completed and the time these interviews were completed. These options will also likely continue to increase in the future. Providing clear and concise information on these options and helping XLHs decide which technologies would be most useful for their families may help alleviate some of the stress and DC associated with the RDM process.

Feelings of guilt for XLHs were brought on as some wrestled with conflict around personal desires and desires for the wellbeing of future children. This is not surprising, as guilt is known to be a common emotion that XLHs experience during RDM (Kay & Kingston, 2002). However, this study's findings add to what is currently known by demonstrating that guilt can center around the presence of a desire or the criticism of others and not just around the result of a reproductive decision. The forms of guilt identified in this study may be more difficult to resolve since they do not stem from

personal and conscious choices. Traditional tactics used by genetic counselors to alleviate guilt, like forgiveness, may not be effective for these forms. Alternative methods for addressing guilt like normalization, reframing, limiting liability, and an exploration of how personal and societal expectations contribute to the feeling may better help XLHs adapt during their RDM process (Kessler et al., 1984).

Finally, this study's findings demonstrate that social relationships can have the ability to exacerbate DC. These findings have important implications for genetic counseling practice. Feeling supported is known to help alleviate DC, and many genetic counselors encourage patients to rely on members of their social support network while adapting to the difficulties of living with a genetic variant (Garvelink et al., 2019). While it is also known that social interactions can help XLHs during RDM, our findings show that interactions with individuals in that support network like family members, support group members, and significant others can actually contribute to DC when their opinions differ and are known to the XLH (Leuzinger-Bohleber & Teising, 2012; Dunn et al., 2008). Genetic counselors should be aware of this possibility when counseling individuals around social support, and consider providing anticipatory guidance around the potential for increased DC after talking to others. Our results also show that negative interactions with others can make XLHs feel isolated during RDM and leave them with minimal support. As an alternative or additional form of support, healthcare providers should make sure XLHs are aware of genetic counseling services and able to access them. Genetic counselors are impartial professionals with expertise in facilitating decision-making and adapting to genetic conditions, and thus are well-equipped to support XLHs through DC and RDM.

Generalizability

The values mentioned by Barth syndrome heterozygotes do not differ significantly from those mentioned by other XLHs in current literature. A desire to have children, a desire to avoid causing suffering, a fear of devaluing the lives of affected individuals, spirituality, and the impact on the mother were all identified in the narratives of XLHs from other disease populations (Zuckerman et al., 2020; von der Lippe et al., 2017; Zaccaro & Freda, 2014; Thomas et al., 2007; Kay & Kingston, 2002). In addition, these values were seen to contribute to instances of DC during RDM in XLHs as well as individuals with genetic variants that caused AD or AR conditions (McConkie-Rosell et al., 2012; James et al., 2003; Parsons & Atkinson, 1993; Decruyenaere et al., 2007; Henneman et al., 2002). Finally, evidence of reproductive mindsets changing over time, especially when influenced by personal experiences parenting affected children or a positive prenatal diagnosis, was also present in a study with carriers of variants associated with AR conditions (Frigon et al., 2022). For these reasons, it is likely that the findings of this paper relating to how Barth heterozygotes alter their value systems to address DC are generalizable to other XLHs, and possibly to individuals who may pass on AD or AR conditions. Because this experience of challenging and altering value systems led to emotional difficulties, it is reasonable to expect such emotional challenges in these populations when facing DC as well.

The social experiences described by Barth heterozygotes in this paper, like being concerned about others opinions and receiving disapproval of the reproductive conclusions arrived at, were also mentioned by other XLHs (Zaccaro & Freda, 2014; Raspberry & Skinner, 2011b; Leuzinger-Bohleber & Teising, 2012). While this is the

first study to explicitly address the connection between these social interactions and DC, it is probable that this connection is not limited to Barth heterozygotes. Other XLHs also likely experience prolonged or exacerbated DC as a result of isolation and difficult social interactions, and may need additional support throughout the RDM process. One possible exception to the generalizability of these findings is the influence of support groups, as mentioned by Participant 18. The participants in this study were all members of the Barth Syndrome Foundation, which is an especially close-knit group of families who are affected by Barth syndrome. It is possible that high value placed on relationships between members and on a sense of belonging in the Foundation made XLHs more concerned about other members' opinions than would be true for XLHs involved in other support organizations. Further research on the role of support groups during RDM is needed to clarify to what extent recruitment from the Barth Syndrome Foundation limits the generalizability of this finding.

Practice Implications

Genetic counselors working with XLHs should fully appreciate the complexity of DC during RDM, and allow this understanding to bear on their practice. DC during RDM should be normalized in XLH populations, and decisional support should be provided throughout the RDM process. To do this, genetic counselors must help XLHs consider what value tradeoffs they want to make. Counseling techniques used in solutions-focused counseling, like miracle questions and scaling questions, as well as techniques used in motivational interviewing are known to help individuals clarify their values and should be considered when discussing this aspect of DC (Biesecker, Peters, & Resta, 2019; Miller & Rose, 2015). However, genetic counselors must also help XLHs think

about how they may want to reshape or reconsider the content of their values and how to apply them during RDM. This could involve a deeper exploration of the values that XLHs hold and how they envision living them out. Techniques based on narrative therapy, existential counseling, and multicultural counseling may be appropriate for these discussions, as they help individuals reflect on how their personal values and expectations are shaped by their personal identities and by the cultures they have been a part of.

Given that values can be reshaped over time, genetic counselors should also consider offering XLHs a chance to meet at multiple points over the course of their pregnancy or lives. Genetic counselors practicing in the prenatal sphere are best situated to carry out these conversations during life stages in which XLHs are making active reproductive decisions since they will be most informed about current reproductive options and their utility. However, our data shows that XLHs may need to process life events and their impact on their reproductive views even when they are not imminently ready to have another child. In this case, understanding how the condition can affect people's lives and how specific family dynamics may influence a certain XLH's views may be more important for helping an XLH process changes in reproductive values. For this reason, genetic counselors who have more familiarity with the XL condition or with the XLH's family, possibly through contact with affected relatives, may be better positioned to have these discussions. It is key that such genetic counselors working with individuals with XL disorders reach out to family members who are XLHs or possible XLHs early to make them aware of their availability for support and to develop rapport. Doing this may lead to more frequent and open

discussions around personal values, which could help resolve DC or the negative emotions and isolation that can accompany it during RDM for XLHs.

Finally, the potential for limitations in an XLH's social support network and increased DC brought on by conversations with others points to a clear need for additional support felt by some XLHs during the RDM process. Genetic counselors working with such individuals should provide such support by offering an opportunity to explore both the decision-making process and the emotions that accompany it. The use of counseling techniques like the ones outlined above and proven educational strategies should also be considered to help XLHs adapt. Referrals to other unbiased professionals like therapists may be preferable to recommending reliance on family members, support groups members, or significant others who have personal investment in RDM for heterozygotes.

Limitations

This study was limited by the lack of diversity in participants' relational ties to individuals with Barth syndrome. Though some women were related to an individual with Barth syndrome in multiple different ways, the majority of participants were mothers of affected individuals. Given that values that influence DC can be shaped by the number of children one has and experiences parenting affected children, the scarcity of individuals who did not have affected children of their own may have limited our understanding of how other important personal experiences may or may not reshape reproductive values. In addition, only 5 participants (18.5%) learned of their heterozygous genetic status before actively making their first reproductive decisions. Women who learn their status before beginning any active decision-making may have

longer to wrestle with their values and reshape them based on many different life experiences and identities. Thus, the relative scarcity of such participants in this data set may mean that findings unique to them were absent from the data. Finally, though the Barth Syndrome Foundation is an international organization with member who speak many different languages, only XLHs who spoke English were asked to participate in interviews. Placing limitations on language may have limited the range of cultural views represented, though XLHs from multiple different nations did participate in this study.

Conclusion

RDM for Barth heterozygotes can involve DC, especially when considering the questions of whether to have a child and whether to intentionally avoid transmission of a pathogenic *TAZ* variant. This DC leads some XLHs to re-prioritize their values, while others reshape their values and how they want them to impact RDM. Because of this, DC levels and experiences with RDM are not static, but rather can change as values and circumstances shift over time. Living with and attempting to resolve DC can be stressful and emotionally taxing. In addition, people that may traditionally be part of an XLH's support system may actually exacerbate DC, leaving some XLHs in need of additional decisional and emotional support. Genetic counselors interfacing with XLHs should help them navigate value tradeoffs and changes in values themselves using appropriate counseling techniques. Discussions around the negative emotions and social experiences that can accompany DC are also relevant to genetic counseling appointments, and may help XLHs adapt to the challenges of RDM. Prenatal genetic counselors as well as genetic counselors who have contact with XLHs or possible XLHs

should make them aware of the support available to them and offer multiple appointments over time to be sure XLHs receive adequate support throughout their RDM process.

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