Spring 2023

Preferences of Adults With Turner Syndrome Regarding Disclosure of Potential Neurodevelopmental And Psychiatric Features

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PREFERENCES OF ADULTS WITH TURNER SYNDROME REGARDING DISCLOSURE OF POTENTIAL NEURODEVELOPMENTAL AND PSYCHIATRIC FEATURES

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Bachelor of Science
Ball State University, 2021

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in

Genetic Counseling

School of Medicine

University of South Carolina

2023

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ACKNOWLEDGMENTS

I would like to thank my committee members, Crystal, Ashley, and Emily for all their dedicated time, work, and effort toward this project. Your helpful ideas, thoughts, and feedback demonstrated immense care and support towards my project and individuals with Turner Syndrome.

To my mom and dad, thank you for supporting my academic endeavors, including this project. You have never stopped listening to my ideas and encouraging me. You have been great examples my entire life of two hard-working, incredibly smart individuals.

Thank you to my genetic counseling cohort for being a supportive group, providing ideas and necessary breaks in this process. I could not have done this program without you.

I am grateful for Julianna, Kayla, Liz, and my three brothers, Will, Theo, and Drew, who all motivated me throughout my entire master's degree. Thank you for reminding me of the light at the end of the tunnel.

ABSTRACT

This study aimed to assess preferences of adults with Turner Syndrome (TS) regarding provider disclosure and discussion of potential neurodevelopmental or psychiatric features.

Fifty-six individuals with TS completed an online survey. Questions were asked about their TS diagnosis and provider involvement, neurodevelopmental and psychiatric diagnoses, and preferences concerning providers' disclosure regarding these possible non-physical features.

Sixteen individuals reported a formal neurodevelopmental diagnosis. Furthermore, 46 respondents reported personal suspicion of ADHD, math difficulties, weaker non-verbal or visual-spatial skills, intellectual disability, or autism spectrum disorder. Thirty-five individuals had a formal diagnosis of at least one psychiatric condition. The preferred providers to initiate this conversation were pediatricians or primary care providers, endocrinologists, or genetic providers. Most individuals preferred that this discussion happens around the time of diagnosis or in late childhood/early adolescence. Lastly, 75% of participants stated that genetics providers should be involved in these conversations.

Participants desired an age-appropriate discussion surrounding possible neurodevelopmental or psychiatric features. This study suggests that several different providers can initiate this conversation. Genetics providers should be

involved by giving a complete overview of the condition and providing ongoing care or referrals to other specialists.

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CHAPTER 1: LITERATURE REVIEW

1.1 Turner Syndrome Overview

Turner syndrome (TS) is one of the most common chromosomal aneuploidies, affecting 1 in 2,000 to 1 in 2,500 liveborn females worldwide. It is most commonly characterized by short stature, primary ovarian insufficiency, infertility, heart defects (i.e., coarctation of the aorta), and other physical features (i.e., webbed neck, broad chest, etc.). However, the features of TS are variable, and some individuals go undiagnosed for many years. For example, if an individual is not diagnosed by the first year of life, the median age at diagnosis is 9.3 years old (Swauger et al., 2021). As the use of Non-Invasive Prenatal Screening (NIPS) and prenatal diagnostic testing increases, more individuals may be diagnosed earlier, either prenatally or in infancy.

TS is caused by partial or complete loss of genetic material on the X chromosome. Up to 50% of individuals with TS have a complete absence of their second X chromosome, referred to as Monosomy X (45,X). The missing X chromosome is often paternal in origin (Gravholt et al., 2017). Approximately 30% of females with TS are mosaic for this condition, which can include various cell lines. In addition to a 45,X cell line, some individuals may have cell line(s) such as 46,XX, 47,XXX, 46,XY, ring X, or other variations (Gravholt et al., 2017; Swauger et al., 2021). The mosaic TS phenotype can vary widely, and some individuals may go undiagnosed for many years or their lifetime depending on

present features. Therefore, a mosaic TS diagnosis can be made incidentally (Tuke et al., 2019). Approximately 20% of TS diagnoses may be due to an isochromosome Xq (i(X)q) or a deletion on the X chromosome (Gravholt et al., 2017).

1.2 Physical Features of TS

The only clinical feature consistent among virtually all individuals with Monosomy X is short stature, typically under five feet without growth hormone therapy. With mosaic TS and other forms of TS (i.e., deletions or isochromosomes), short stature is still common but may not be as severe. While not universally observed in all individuals with TS, typical dysmorphic features may include widely spaced nipples/broad chest, a short, webbed neck, micrognathia or high palate, a low posterior hairline, multiple moles, edema in the hands and feet, nail dysplasia and/or short metacarpals, and cubitus valgus (Akalin et al., 2021).

Primary ovarian insufficiency (POI) is another major feature of TS, although the onset may vary depending on the karyotype. Those with Monosomy X typically have no pubertal development and primary amenorrhea. However, some individuals have normal or delayed puberty but later develop secondary amenorrhea (Negreiros et al., 2014). Spontaneous menarche occurs in about 25% of females with Monosomy X and is more common in females with mosaic TS. The ovaries typically consist of small amounts of connective tissue and no follicles or streak gonads, causing infertility (Calanchini et al., 2020; Negreiros et al., 2014).

Cardiac defects and cardiovascular disease are also common manifestations of this condition. About 44.5% of females with TS will have a cardiac defect. An aortic valve abnormality (i.e., primary bicuspid aortic valve) or aortic arch abnormality (i.e., coarctation) are the most common (Cramer et al., 2014). In addition, adults with TS are at increased risk of coronary artery disease, aortic dissection, hypertension, and heart failure (Gravholt et al., 2017). It is estimated that the risk for aortic dissection is four times higher than the general female population, and pregnancy and delivery can increase this risk (Falsey et al., 2022; Quezada et al., 2015).

Other features of TS include renal anomalies such as collecting duct abnormalities, horseshoe kidneys, and malrotation. In addition, recurrent ear infections and conductive hearing loss are more common in individuals with TS than in the general population, as well as autoimmune conditions, including hypothyroidism and irritable bowel syndrome (Akalin et al., 2021).

1.3 Neurodevelopmental and Psychiatric Features of TS

Non-physical features of Turner Syndrome are less commonly studied and discussed in a clinical setting. Just like physical features, neurodevelopmental and psychiatric implications are variable and depend on a combination of genetic (haploinsufficiency), hormonal (reduced estrogen and androgen production), and environmental (i.e., educational opportunities) factors. Most individuals with TS have normal intelligence; intellectual impairment/disability is typically only seen in individuals with a ring X chromosome (Leppig et al., 2004). It is unclear if there is increased risk of an autism spectrum disorder (ASD) diagnosis in individuals with

TS. Some studies describe an association, while others do not (Lepage et al., 2014). Most recently, Wolstencroft et al. (2022) collected mental health and neurodevelopmental data in children and adolescents with TS. Using parental reports from the Developmental and Well-Being Assessment (DAWBA) and Social Responsiveness Scale (SRS-2), approximately 20% of the females met diagnostic criteria for ASD (Wolstencroft et al., 2022). However, the association between ASD and TS requires more research, so it is not often clinically discussed with patients and families.

Up to 75% of females with TS have learning disabilities, usually math-related, and may require special education services (Davis et al., 2020). Individuals typically have weaker visual-spatial skills, which impacts adaptive skills, including learning how to drive or ride a bike. Executive functioning, which includes planning, organization, attention, motivation, working memory, and processing speed may also be slightly impaired. Poor performance in these areas typically emerges in childhood and persists through adulthood (Jordan et al., 2023). Despite difficulties in these areas, individuals with TS perform similarly to peers in auditory-verbal tasks (Anaki et al., 2018). About 25% of children and adolescents with TS meet the criteria for Attention Deficit/Hyperactivity Disorder (ADHD), which is significantly higher than the general population, estimated at 6% (Bitsko et al., 2022; Green et al., 2015).

Concerning psychiatric diagnoses, it is estimated that about one-third of children/adolescents with TS have at least one mental health disorder, which is over two times higher than the general population. However, there is some

discrepancy in the literature regarding rates of anxiety and depression in the TS population. Some studies estimate that over 50% of individuals have symptoms of either anxiety, depression, or both (Davis et al., 2020). Other studies claim no association between TS and anxiety or depression or estimate an only slightly increased risk of developing anxiety or depression than the general population (Ertl et al., 2018; Jordan et al., 2023). Obsessive-compulsive disorder (OCD) or OCD-like behaviors may also be more common in individuals with TS, though it is likely underdiagnosed or underrecognized (Moonga et al., 2017). It remains unclear if mental health diagnoses like anxiety and depression should be considered independent risk factors of the condition versus secondary complications due to physical features like infertility or short stature (Liedmeier et al., 2020).

Social development and maintaining friendships and relationships tend to be areas of difficulty. For example, Liedmeier et al. (2020) found that women with TS are less likely to have partners and/or marry. A decreased desire to engage in social activities often makes building and maintaining friendships more difficult (Björlin et al., 2021). This difficulty may also be related to weaker non-verbal skills like recognizing others' emotions and aberrant eye gaze processing (Jordan et al., 2023). While not fully explained, some individuals with TS may struggle with alexithymia. Emotional arousal may be lower, and it may be difficult to define the nature of their emotions or reasons for emotional reactions (Roelofs et al., 2015). Low self-esteem is common in the TS population, contributing to

social anxiety. Fortunately, despite social difficulties, women with TS do not report impairment in their work life (Liedmeier et al., 2020).

1.4 TS Diagnosis

A TS diagnosis can be made prenatally or postnatally, typically through a karyotype. Some individuals are diagnosed via chromosomal microarray (CMA), which may provide a higher resolution for detecting microdeletions and microduplications less than 1-2 MB. However, CMA may not detect low-level mosaicism or structural rearrangements. Given the technical limitations of CMA, karyotype remains the first-line test for diagnosing TS (Tulay et al., 2020).

Swauger et al. (2021) analyzed medical records of patients with TS at a clinic in Cincinnati between 1997 and 2016. Prenatal TS diagnoses through NIPS, chorionic villi sampling (CVS), or amniocentesis accounted for 37% of all diagnoses. Almost half of all diagnoses were made before one year, and the median age was 1.5 years. However, excluding prenatal or neonatal diagnoses, the median age was seven years, and excluding diagnoses made by one year, the median age was 9.3 years (Swauger et al., 2021). Therefore, unless the diagnosis is provided by one year of age, it tends to be delayed by several years, impacting care. A diagnosis must be provided as early as possible for this population, as it is vital for growth hormone treatment, implementing neurocognitive and psychological support, and inducing puberty at the right time. Decreased quality of life is also more likely when the individual is diagnosed at an older age (Swauger et al., 2021).

Another consideration for providers is that while a diagnosis can be made prenatally, it is difficult to predict the phenotype, even though this is a common concern for parents and families. Furthermore, if the diagnosis is mosaic TS, this is an added challenge for the counseling session due to the increased phenotypic variability (Tokita & Sybert, 2016). Postnatally, the most common indications that lead to a TS diagnosis are short stature (35%), nonspecific prenatal testing (11%), lymphedema (10%), dysmorphic features (9%), cardiac abnormalities (6%), incidental (5%), and pubertal delay (4%) (Swauger et al., 2021). Therefore, pediatric genetic counselors and geneticists need to consider the variable TS phenotype and choose the most appropriate genetic test when there is suspicion of this syndrome.

When providing a TS diagnosis, it can be challenging to know or assess how much information is appropriate to provide a patient and/or their family. The most common (and physical) features of TS are usually provided; however, there is limited research on when neurodevelopmental and psychiatric features are disclosed.

Clinicians' primary goal of the disclosure appointment is typically to succinctly convey essential comorbidities of TS accurately. However, only disclosing brief, essential information can leave families feeling inadequately informed (Sutton et al., 2006). Therefore, with a disclosure appointment, providers should plan to spend enough time with patients or families to explain the diagnosis and answer any questions. In addition, it has been suggested to have a second appointment to discuss TS in more detail after the family has had

time to process the initial information. Health implications and standards of care may also be provided in a written form (Sutton et al., 2006). Pediatric endocrinologists are likely to have the most expertise on TS; however, genetic counselors are valuable providers and resources, especially when discussing the genetics and natural history of the condition.

1.5 TS Management

Management of TS depends on the type (i.e., mosaic TS versus Monosomy X) and age at diagnosis. Clinical practice guidelines (CPGs) for managing patients with TS were established in 2016 at an international Turner Syndrome meeting. For growth and puberty, growth hormone treatment, estrogen replacement therapy, and progesterone may be recommended at different points in childhood, adolescence, and adulthood (Gravholt et al., 2017).

Fertility is a major concern for this population. The probability of spontaneous pregnancy is low and continues to decrease with age. Oocyte donation is an option to promote fertility. Family planning should involve significant medical counseling for the individual. During pregnancy, a person with TS must have a multidisciplinary team, including maternal-fetal medicine specialists and cardiologists, due to a high risk of complications (Gravholt et al., 2017).

Upon diagnosis, a cardiovascular evaluation with imaging/scans is recommended. If no notable defects or diseases are present, follow-up studies should be conducted every few years, depending on the individual, or before pregnancy. Hypertension should be treated if present. Other evaluations at

diagnosis or throughout the lifetime can include audiology, hypothyroidism screening, metabolic screening, ophthalmological exams, scoliosis clinical evaluations, and a renal ultrasound (Gravholt et al., 2017).

For neurodevelopmental and psychiatric aspects of the condition, there are six recommendations/suggestions as described by Gravholt et al. (2017). “Recommendations” are considered strong recommendations, while “suggestions” are considered weak recommendations. In addition, the quality of evidence behind these recommendations or suggestions is labeled as very low, low, moderate, or strong (Gravholt et al., 2017).

1) Neuropsychology and allied behavioral health services as a part of care (recommendation, moderate evidence).
2) Annual developmental and behavioral screenings until adulthood with referrals as necessary (recommendation, moderate evidence).
3) Neuropsychological assessments at vital transitional stages in schooling (suggestion, low evidence).
4) Adjustments in academics and occupations to accommodate for learning or performance issues (recommendation, moderate evidence).
5) Aiming for on-time puberty and managing indicators of hearing loss to enforce positive psychosocial and psychosexual adaptation (recommendation, low evidence).
6) Adapted (if necessary) evidence-based cognitive or psychosocial interventions created for non-TS populations to meet the needs of

females with TS (suggestion, very low evidence) (Gravholt et al., 2017).

Since these guidelines were published, it still needs to be determined if and how the recommendations have been implemented. Davis et al. (2020) surveyed pediatric endocrinologists that provide care for individuals with TS and found that 42% of respondents said their patients receive some form of neurodevelopmental screening, while 37% said their patients receive mental health screening. However, only 26% reported that their patients receive both as recommended by the CPGs (Davis et al., 2020).

1.6 Study Rationale

Starke et al. (2002) surveyed parents' perspectives on receiving a TS diagnosis and found that the information from the doctor providing the diagnosis was problematic. For example, the syndrome's name or associated comorbidities were not defined. Also, the parent did not understand the information or too much was given at once. Information received was mainly about physical features (i.e., heart issues, short stature). Only some providers explained potential problems like math challenges, concentration difficulties, and developmental delays. When providing suggestions to healthcare providers, parents preferred that the diagnosis be delivered in person by a doctor knowledgeable about TS and to balance the positive and negative implications of TS. In addition, the provider should be empathic and inspire hope (Starke et al., 2002).

While the Starke et al. (2002) paper is helpful for providers, it has been over twenty years since it was published, and we now know more about TS,

especially neurodevelopmental and psychiatric implications. There are CPGs for the medical care of children and adults (Gravholt et al., 2017), but there is limited research on how neurodevelopmental and psychiatric factors are discussed with patients. It still needs to be studied if or how genetics providers (genetic counselors and geneticists) disclose these potential features, even though genetics providers often diagnose TS. Furthermore, there is limited research surveying or talking to individuals with TS directly. It is valuable to hear perspectives directly from an affected population when determining best care practices. Therefore, this study focuses on adults with TS because they can directly attest to their own neurodevelopmental and psychiatric history and discuss their disclosure preferences. This promotes person-centered care and gives individuals a stronger voice in their healthcare.

1.7 Purpose of Study

This study assessed healthcare experiences and preferences of individuals with TS. There were four main objectives.

1) Evaluate the neurodevelopmental and psychiatric history of individuals with Turner Syndrome;
2) Assess provider disclosure of possible neurodevelopmental and psychiatric features of Turner Syndrome;
3) Understand the preferences of adults with Turner Syndrome regarding discussion of these diagnoses;
4) Make recommendations to genetics providers and/or other medical providers regarding the disclosure and discussion of these features.

Individuals with TS were invited to take an online survey through three TS Facebook groups. The survey consisted of quantitative and qualitative questions. First, we hypothesized that individuals with TS have heard of many of the potential neurodevelopmental and psychiatric features; however, a medical provider may not have been the one to disclose them initially. Second, we predicted that most individuals would likely have at least one neurodevelopmental and/or psychiatric diagnosis. Third, we hypothesized that individuals with TS would prefer a disclosure/discussion surrounding these non-physical features at diagnosis and again during adolescence. Finally, we predicted that an individual with TS may have only seen a genetics provider once or twice in their lifetime (unless care was through a TS clinic), which may be due to limited access to these providers. Therefore, their provider preference for this discussion may be someone other than a genetics provider.

CHAPTER 2

PREFERENCES OF ADULTS WITH TURNER SYNDROME REGARDING DISCLOSURE OF POTENTIAL NEURODEVELOPMENTAL AND PSYCHIATRIC FEATURES[1]

[1] Pancake, E., Hill-Chapman, C., Lowell, E., and Wong, A. To be submitted to *Patient Education and Counseling*

2.1 Abstract

2.1.1 Objective

This study aimed to assess preferences of adults with Turner Syndrome (TS) regarding provider disclosure and discussion of potential neurodevelopmental or psychiatric features.

2.1.2 Methods

Fifty-six individuals with TS completed an online survey. Questions were asked about their TS diagnosis and provider involvement, neurodevelopmental and psychiatric diagnoses, and preferences concerning providers' disclosure regarding these possible non-physical features.

2.1.3 Results

Sixteen individuals reported a formal neurodevelopmental diagnosis. Furthermore, forty-six respondents reported personal suspicion of ADHD, math difficulties, weaker non-verbal or visual-spatial skills, intellectual disability, or autism spectrum disorder. Thirty-five individuals had a formal diagnosis of at least one psychiatric condition. Preferred providers to discuss these potential neurodevelopmental and psychiatric features were pediatricians or primary care providers (39.3%), endocrinologists (26.8%), and genetics providers (17.9%). Most individuals preferred that this discussion happens around the time of diagnosis or in late childhood/early adolescence. Lastly, 75% of participants stated that genetics providers should be involved in these discussions.

2.1.4 Conclusions

Participants desired an age-appropriate discussion about non-physical features. Several different providers can be involved in this discussion.

2.1.5 Practice Implications

This study suggests that providers should initiate an age-appropriate conversation with patients with TS regarding possible neurodevelopmental or psychiatric features. Genetics providers should be involved by giving a complete overview of the condition and providing ongoing care or referrals to other specialists.

2.2 Introduction

Turner syndrome (TS) is one of the most common chromosomal aneuploidies, affecting 1 in 2,000 to 1 in 2,500 liveborn females worldwide. It is commonly characterized by short stature, primary ovarian insufficiency, infertility, heart defects (i.e., coarctation of the aorta), and variable physical features (i.e., webbed neck, broad chest, etc.). Other physical complications may include renal anomalies, hearing loss, and autoimmune conditions. Due to the variable expressivity of the syndrome, it is difficult to predict the features an individual will have, even though this is a common concern for families (Tokita & Sybert, 2016).

TS is caused by partial or complete loss of genetic material on the X chromosome. Up to 50% of individuals with TS have a complete absence of their second X chromosome, also called Monosomy X (45,X). Approximately 30% of females with TS are mosaic for this condition, which can include various cell lines, such as 45,X, 46,XX, 47,XXX, 46,XY, ring X, or other variations (Gravholt

et al., 2017; Swauger et al., 2021). The mosaic TS phenotype can vary widely, and some individuals may go undiagnosed for many years or their lifetime depending on present features (Tuke et al., 2019). The remaining 20% of diagnoses are due to an isochromosome Xq (i(X)q) or a deletion (Gravholt et al., 2017).

Some neurodevelopmental and psychiatric diagnoses are more common within the TS population; however, they are less commonly studied and discussed in a clinical setting. Most individuals with TS have normal intelligence; intellectual impairment/disability is typically only seen in individuals with a ring X chromosome (Leppig et al., 2004). It is unclear if there is increased risk of an autism spectrum disorder (ASD) diagnosis in individuals with TS. Some studies describe no increased risk (Lepage et al., 2014), while other studies found that approximately 20% of individuals met the diagnostic criteria for ASD (Wolstencroft et al., 2022).

Up to 75% of females with TS have learning disabilities, usually math-related, and may require special education services (Davis et al., 2020). Individuals typically have weaker visual-spatial skills and slight executive functioning impairment (Jordan et al., 2023). Despite difficulties in these areas, individuals with TS perform similarly to peers in auditory-verbal tasks (Anaki et al., 2018). About 25% of children and adolescents with TS meet the criteria for Attention Deficit/Hyperactivity Disorder (ADHD), which is higher than the general population, estimated at 6% (Bitsko et al., 2022; Green et al., 2015).

Concerning psychiatric diagnoses, it is estimated that about one-third of children/adolescents with TS have at least one mental health disorder, which is over two times higher than the general population (Wolstencroft et al., 2022). Regarding anxiety and depression, some studies estimate that over 50% of individuals have symptoms of either anxiety, depression, or both, while other studies discuss little to no increased risk compared to the general population (Davis et al., 2020; Ertl et al., 2018; Jordan et al., 2023). Obsessive-compulsive disorder (OCD) or OCD-like behaviors may also be more common in individuals with TS (Moonga et al., 2017). However, it remains unclear if mental health diagnoses like anxiety and depression should be considered independent risk factors of TS versus secondary complications due to physical features like infertility or short stature (Liedmeier et al., 2020).

Social development and maintaining friendships and relationships are often areas of difficulty. For example, Liedmeier et al. (2020) found that women with TS are less likely to have partners and/or marry. A decreased desire to engage in social activities often makes building and maintaining friendships more difficult (Björlin et al., 2021). This difficulty may also be related to weaker non-verbal skills like recognizing others' emotions and aberrant eye gaze processing (Jordan et al., 2023). Lastly, low self-esteem is common in the TS population, contributing to social anxiety (Liedmeier et al., 2020).

A TS diagnosis can be made prenatally or postnatally, typically through a karyotype (Tulay et al., 2020). Swauger et al. (2021) analyzed medical records of patients with Turner Syndrome and found that 37% of diagnoses were made

prenatally. Almost half of all diagnoses were made before one year, and the overall median age was 1.5 years. However, excluding prenatal or neonatal diagnoses, the median age was seven years, and excluding diagnoses made by one year, the median age was 9.3 years (Swauger et al., 2021). Therefore, unless the diagnosis is provided by one year of age, it tends to be delayed by several years. This can decrease the quality of life and impact vital care, which includes providing appropriate neurocognitive and psychological support. (Swauger et al., 2021).

Clinicians' primary goal of the disclosure appointment is typically to succinctly convey essential comorbidities of TS accurately. However, only disclosing brief, essential information can leave families feeling inadequately informed (Sutton et al., 2006). Therefore, in a disclosure appointment, providers should plan to spend enough time with patients or families to explain the diagnosis and answer any questions. In addition, it has been suggested to have a second appointment to discuss TS in more detail after the family has had time to process the initial information (Sutton et al., 2006).

Parents have previously voiced that information from the doctor providing the TS diagnosis was problematic (Starke et al., 2002). For example, the syndrome's name or associated comorbidities were not defined. Also, parents did not understand the information or too much was given at once. Information received was mainly about physical features, and only some providers explained potential neurodevelopmental concerns. Parents suggested that a doctor knowledgeable about TS should provide the diagnosis with empathy and hope

(Starke et al., 2002). Pediatric endocrinologists are likely to have the most expertise on TS; however, genetic counselors are valuable providers and resources, especially when discussing the genetics and natural history of TS.

After a diagnosis, there are management guidelines available (Gravholt et al., 2017). To summarize, for neurodevelopmental and psychiatric features, it is recommended or suggested that neuropsychology and behavioral health services should be a part of comprehensive care, including screenings or assessments throughout childhood/adolescence. In addition, adjustments should be made in school and work to accommodate for learning or performance issues as needed. Finally, providers should adapt psychosocial interventions created for non-TS populations to meet the needs of individuals with TS (Gravholt et al., 2017).

Since these guidelines were published, it is yet to be determined if and how the recommendations have been implemented. The most recent study surveyed pediatric endocrinologists that provide care for individuals with TS, and 42% of respondents said their patients receive some form of neurodevelopmental screening, while 37% said their patients receive mental health screening. However, only 26% reported that their patients receive both as recommended by the guidelines (Davis et al., 2020).

Neurodevelopmental and psychiatric features of TS have been studied more often in the last few years; however, there is limited research on how and when these potential features are discussed with patients (Starke et al., 2002). It is also not yet understood if or how genetics providers disclose these potential

features, even though they often diagnose TS. Additionally, there is limited research surveying individuals with TS directly. Therefore, this study aimed to evaluate the neurodevelopmental and psychiatric history of individuals with TS and assess provider disclosure of these features. We also asked for their preferences regarding this discussion to make recommendations to genetics providers and other medical providers.

2.3 Material and Methods

2.3.1 Participants and Recruitment

Participants eligible to participate in this study were individuals with a diagnosis of TS who were 18 years old or older. They were invited to participate in an online survey and doing so served as their consent to participate (Appendix A). An invitational social media flyer was created and posted in three TS Facebook groups (Appendix B). Individuals were not eligible for the study if they did not have a TS diagnosis, had a TS diagnosis but were under age 18, or were parents or other family members of an individual with TS.

2.3.2 Research Methods

An original survey was created through Qualtrics® to assess the neurodevelopmental and psychiatric history of those with TS and their preferences for disclosure and discussion of these potential features (Appendix C). The survey consisted of multiple-choice, Likert scale, and open-ended items. The respondents remained anonymous; no identifying information was collected on the survey.

Participants were asked about their TS diagnosis and level of provider disclosure about potential neurodevelopmental and psychiatric implications. They answered questions about formal neurodevelopmental or psychiatric diagnoses or personal suspicion for these conditions without a formal diagnosis. They were asked questions regarding the disclosure of potential neurodevelopmental and psychiatric features, including their preferred medical provider for this discussion, the most appropriate age to discuss these features, and the genetics providers' role in the process. Lastly, they had the option to answer general demographic questions. The study was reviewed and approved by the University of South Carolina Institutional Review Board (ID: Pro00122597).

2.3.3 Data Analysis

Descriptive statistical analysis using Microsoft Office Excel software was used to address the objectives. The quantitative information was categorized, and frequencies and percentages were calculated. Thematic analysis was used for the qualitative data. Responses were first coded and categorized into themes by the principal investigator (EP). These categorizations and themes were reviewed by a research committee member until consensus was obtained.

A total of 75 surveys were submitted. Of those, eighteen surveys were excluded from data analysis due to incompletion (less than 80% completion, excluding demographic information). Furthermore, one survey was excluded because the participant was under 18. Therefore, a total of 56 responses were included in the data analysis.

2.4 Results

2.4.1 Participant Demographics

Participants were not required to answer the demographic questions. Participant demographic information can be seen in Table 2.1.

2.4.2 Participants' Diagnoses

Participants were asked to indicate their karyotype results. Twenty-six (46.4%) respondents indicated they were diagnosed with non-mosaic TS. Of those responses, twenty-three indicated they had a 45,X karyotype, two did not select a type, and one specified they had a deletion. Twenty-five (44.6%) participants selected mosaic TS; the specified types can be seen in Figure 2.1. Lastly, five respondents (9%) did not know their karyotype.

For age at diagnosis, zero respondents indicated they were diagnosed prenatally. Twelve individuals (21.4%) reported that the diagnosis occurred in infancy. Out of this group, seven individuals specified that their diagnosis occurred at birth. Twenty participants (35.7%) reported a diagnosis in childhood (1-11 years). The average age of the childhood group was 6.1 years, ranging from 2-11 years, excluding four respondents who did not specify an exact age. Sixteen individuals (28.6%) indicated a diagnosis in adolescence (12-17 years). The average age was 13.4 years, ranging from 12-15 years. Three respondents did not specify their ages. Finally, eight participants (14.3%) reported a diagnosis in adulthood (18+ years). The average age of this group was 30.4 years with a range of 19-46 years, excluding one respondent who did not specify their age.

All respondents selected providers that have been a part of their healthcare team, as seen in Table 2.2. Concerning disclosure/discussion by a medical provider about potential neurodevelopmental and psychiatric features, the number of respondents that selected each feature is reported in Figure 2.2.

2.4.3 Neurodevelopmental History

Participants were asked if they had a formal diagnosis of ADHD, learning disability, intellectual disability, or ASD. Ten individuals (17.9%) indicated they had a diagnosis of ADHD. Eleven participants (19.6%) reported a learning disability, and the types of learning disability can be seen in Figure 2.3. Four respondents indicated they were diagnosed with ASD (7.1%). No one reported a diagnosis of intellectual disability. Most individuals (40/56, 71.4%) reported they did not have any of the formal diagnoses listed. Furthermore, eleven individuals (19.6%) reported needing an individualized education plan (IEP) through high school. Of note, some individuals reported an IEP but did not report a formal diagnosis or reported a diagnosis but did not report an IEP. Lastly, respondents indicated if they suspected having any listed neurodevelopmental features without a formal diagnosis, as reported in Table 2.3.

2.4.4 Psychiatric history

Thirty-five individuals (62.5%) reported a formal diagnosis of at least one mental health condition. Twenty respondents (35.7%) indicated they had two or more diagnosed mental health conditions. The specific breakdown of anxiety and depression diagnoses or personal suspicion of these conditions can be seen in Table 2.4. Participants were also asked about any other formally diagnosed

psychiatric conditions. Four respondents (7.1%) reported other diagnoses, which included eating disorders (3/56, 5.4%), bipolar disorder 2 (1/56, 1.8%), mixed anxiety/depression disorder (1/56, 1.8%), and suicidal intent (1/56, 1.8%). The remaining fifty-two individuals (92.9%) did not report any other formally diagnosed conditions.

Seven respondents (14.2%) suspected they had a condition other than anxiety and depression without a formal diagnosis. The conditions mentioned included bipolar disorder (1/56, 1.8%), OCD or Obsessive-Compulsive Personality Disorder (OCPD) (3/56, 5.4%), and gender and sexuality issues (1/56, 1.8%). Two individuals did not specify the condition. One individual wrote about several concerns, including relationships, neurodevelopmental or academic concerns, and self-esteem issues. This was categorized as “other.”

2.4.5 Provider Preferences

Participants were asked a series of Likert scale questions about their preferences regarding the disclosure of potential neurodevelopmental and psychiatric conditions. Responses to each statement can be seen in Figures 2.4 and 2.5. In addition, respondents were asked which provider they would have preferred first discuss possible neurodevelopmental or psychiatric diagnoses with them. Twenty-two individuals (39.3%) chose a pediatrician or primary care provider (PCP). Fifteen participants (26.8%) selected an endocrinologist. Ten respondents (17.9%) chose a genetics provider (genetic counselor or geneticist). Four individuals (7.1%) specified a psychologist. The remaining five participants

(8.9%) selected a cardiologist, fertility specialist, OB/GYN, or any provider. These were all classified under “other.”

Participants were also asked why they chose their selected provider, and associated themes are reported in Figure 2.6. Themes included knowledge or qualifications, rapport, and anticipatory guidance. For “knowledge or qualifications,” responses emphasized that the provider they chose either knew the most about TS, provided their diagnosis of TS, or was/is their primary doctor. Responses in the “rapport” theme discussed how their chosen provider knew them best and they felt most comfortable with them. Finally, responses categorized into “anticipatory guidance” wrote about how this provider would have been able to provide suggestions on what to look for regarding these conditions and ensure proper care (i.e., referrals to specialists).

The second free-response question addressed opinions regarding the best or most appropriate age for a provider to discuss potential non-physical diagnoses. Percentages of each type of response can be seen in Figure 2.7. The “other” category included nine participants, which included “unsure” or “depends” responses, as well as not answering the question. Of note, twelve respondents (21.4%) mentioned that providers should discuss these topics in an “age-appropriate way.” An example of a response emphasizing age-appropriate discussions was as follows:

> *“If the individual is a child, I believe the parents should be consulted at the earliest opportunity. The child should be told the information when they are old enough to have questions or if it has some impact on them (e.g*

additional appointments/medication) - information should be given at an age-appropriate level."

Next, participants were asked if knowing about these potential features would have been helpful during adolescence. Forty-eight respondents (85.8%) disclosed that it would have been beneficial, and themes can be found in Figure 2.8. Those under the "knowledge of diagnosis and self" theme wrote how this discussion would have helped them understand themselves or TS better. Responses in the "anticipatory guidance" theme suggested a desire for this information so that they would have known what symptoms may indicate a neurodevelopmental or psychiatric concern, and therefore know how to prepare or what to expect. One respondent wrote: *"Yes, while I didn't have any significant impacts I feel as though knowing I could help strengthen any aspects of concern."*

"Earlier treatment/support" was also a major theme. Responses in this category discussed that not knowing about these potential features made treatment difficult later. This information would have provided avenues for support, earlier medication, and better management of their symptoms. Lastly, "relief of guilt/shame and coping" was a theme among several responses. Many individuals expressed that they felt different from their peers growing up. Knowledge about these potential features may have helped them feel less different, odd, or "broken." It could have also increased their understanding of why some tasks (i.e., riding a bike or driving a car) were more difficult for them.

As one respondent wrote:

> *"Absolutely. I personally experienced a lot of shame in school due to my difficulties in math, as well as my social anxiety. And as I was learning to drive I felt shame that it was so difficult for me to master. To this day I still do not drive on the highway. If I had known these were related to my Turner's syndrome when I was younger, it would've taken a lot of that shame and embarrassment off my shoulders."*

Four individuals (7.1%) had "maybe" or "yes and no" responses or did not respond to the question. Four individuals (7.1%) responded that this would not have been helpful. Instead, they reported that discussing these possible diagnoses would have made them feel different and possibly caused them to be treated differently by others (i.e., teachers or clinicians). For example, one participant wrote: *"Worried about the label negatively affecting teachers opinion of my potential, since I did very well without intervention (wasn't diagnosed until 38)."* They also felt they would have focused too much on those diagnoses and not pushed themselves to succeed in certain areas (i.e., math).

Lastly, respondents were asked to comment on genetics providers' role in discussing possible neurodevelopmental or psychiatric features with a newly diagnosed individual. Forty-two respondents (75%) wrote that genetics providers should be involved, and four main themes were identified. Some responses fit multiple themes. Twenty-four responses (42.3%) discussed providing a "general overview or anticipatory guidance" so that families know what signs or symptoms indicate a neurodevelopmental or psychiatric concern for their child with TS. For

example, one participant wrote: *"Yes! Since they're the ones that often give the diagnosis and order the Karyotype, they should do some counseling with the kiddos and families about what to potentially expect later in life, especially teen years."* Furthermore, several individuals emphasized that genetic providers should discuss variable expressivity. One respondent wrote:

> *"Yes. I think they should make the parents aware that it is common for women with TS to suffer anxiety and depression and here's some signs to look out for. Remind them that not everyone has every single symptom of TS and it doesn't mean their child will automatically have anxiety or depression…"*

Additionally, eight participants (14.3%) noted that genetics providers should provide "ongoing care," such as being available to answer questions, offering themselves as a patient resource, or providing another, more in-depth discussion later. Another theme among six responses (10.7%) was providing "referrals to specialists" for any concerning symptoms.

Four responses (7.1%) mentioned "age-appropriate" discussions. Individuals wrote about genetics providers being available to have more discussions with the child as they develop or encouraging parents to talk to their children at their comprehensible level. Lastly, four responses (7.1%) were categorized as "other." Responses in this theme were about providers needing to be trained on the subject first or not personally having a genetics provider. Nine individuals (16.1%) commented "yes" without an explanation.

Six individuals (10.7%) were still determining if genetics providers should be involved. Four participants (7.1%) did not answer this question. Four respondents (7.1%) commented that it would not be helpful for them to be involved. Some felt it would be too overwhelming to discuss at diagnosis, while other individuals in this group felt that genetics providers are not the most appropriate specialists to discuss neurodevelopmental or psychiatric features.

2.5 Discussion and Conclusion

2.5.1 Discussion

This study aimed to evaluate neurodevelopmental and psychiatric histories of individuals with TS, assess preferences regarding provider disclosure/discussion of these potential features, and make recommendations to genetics providers and other medical providers.

In this sample, reported formal neurodevelopmental diagnoses were lower than in previous research. However, several more participants suspected they had one or more of these disorders, even if they were never diagnosed. For example, only 10/56 individuals had a formal diagnosis of ADHD, but eight more suspected ADHD. Therefore, 32.1% of participants had a concern or a diagnosis of ADHD, which is higher, but comparable to results found by Green et al. (2015), who reported that 25% of adolescents with TS met ADHD diagnostic criteria. Similarly, almost 20% of participants reported a diagnosed learning disability; however, several more individuals suspected math difficulties, weaker non-verbal communication skills, or weaker visual-spatial skills. This suggests that these

neurodevelopmental concerns may be underdiagnosed in this population, or some concerns may be present but not constitute a full diagnosis.

Concerning psychiatric diagnoses, over 50% of individuals had a formal diagnosis of anxiety, and 44.6% had a depression diagnosis, supporting the findings from Davis et al. (2020), who found that over 50% of individuals with TS had symptoms of anxiety and/or depression. While there were no formal diagnoses of OCD, 5.4% of individuals suspected this condition, supporting the hypothesis that it is often underrecognized (Moonga et al., 2017). Interestingly, 5.4% of participants reported an eating disorder diagnosis. Bjorlin et al. (2021) reported that individuals with TS were twice as likely to have an eating disorder (2.3% of individuals with TS compared to 1.16% of the general population). This study supports that eating disorders are more common in this population with a higher percentage than observed by Bjorlin et al. (2021).

This study reveals that most individuals desire an age-appropriate discussion with a medical provider surrounding non-physical features. Thirty-three participants (58.9%) reported that a medical provider discussed at least one of these features with them. Difficulties with math, weaker visual-spatial skills, and social anxiety were the most commonly discussed, which was expected since these features have been well-studied. Most individuals strongly agreed that knowing about possible neurodevelopmental and psychiatric features at the time of their TS diagnosis would have been helpful. These implications are typically something they want to avoid discovering on their own.

Furthermore, most participants recommended a discussion either at or soon after diagnosis or in late childhood/early adolescence. The median age of diagnosis is 9.3 years (Swauger et al., 2021), excluding prenatal or neonatal diagnoses, and this study group did not have any prenatal diagnoses. Therefore, for many individuals, a late childhood/adolescence discussion may have occurred within a couple of years of their diagnosis, and this retrospective thinking may have contributed to their answers.

On average, participants somewhat disagreed or felt neutral about it being overwhelming to talk about these features at diagnosis. Some individuals (5%) said it should only be discussed if a concern arises, emphasizing how it could exacerbate problems. This suggests that not every individual will want to discuss these non-physical features after diagnosis and that feedback should be tailored to the individual.

Regardless of the preferred age, many individuals emphasized that the discussion must be age-appropriate and understandable to the patient. Parents should also be involved. This may look like providing parents with signs or symptoms that indicate their young child with TS may have one of these diagnoses so they can find the appropriate specialists. Parents may further explain these concepts to their child on their own to help normalize TS and encourage their child's knowledge of their condition. Regardless, individuals want to be involved in their appointments and care, even from a young age.

Most participants felt that knowing about these possible features would have been helpful in adolescence. Interestingly, "relief of guilt or shame" was the

most common theme. Many individuals experienced negative feelings about perceived weaknesses or mental health and did not know that some symptoms could be attributed to TS. It may be vital for them to understand these implications to help normalize their diagnosis and mitigate “feeling different.”

Most individuals felt their healthcare team was responsible for discussing these possible diagnoses (instead of their parents). They also wished their providers had discussed these potential diagnoses more, as they judged non-physical features as equally important to physical features. Additionally, several participants did not think their provider adequately discussed these features. This study supports previous research that found that provided information was primarily about physical features, and families were dissatisfied with the information they were provided (Starke et al., 2002; Sutton et al., 2006).

Most participants chose either their pediatrician/PCP or their endocrinologist as their preferred provider for discussing these possible diagnoses. This was expected, as these providers are likely the most involved in their care. Additionally, because these providers may provide a diagnosis, have an established relationship with their patient, or see this patient for much of their pediatric life, they need to discuss these features and provide the necessary follow-up based on medical guidelines.

For genetics providers specifically, themes were split depending on the chosen provider. Participants felt genetic counselors would have prepared them and their parents well and helped them cope with the new information. This was not surprising as one of the roles of a genetic counselor is to provide accurate,

well-rounded information and initial psychosocial support for patients. On the other hand, some participants preferred to review their diagnosis with geneticists whom they felt would be able to provide accurate information and be a resource for natural history-related questions and concerns. Finally, psychologists can give specific expertise on neurodevelopmental and psychiatric diagnoses, which supports the guidelines stating that neuropsychology services should be a part of comprehensive care (Gravholt et al., 2017).

Most participants (75%) stated that genetics providers (i.e., genetic counselors or geneticists) should be involved in this discussion with a newly diagnosed individual. A broad overview of the condition that includes these implications is helpful. Furthermore, some participants discussed genetics providers' unique ability to explain the variable expressivity of TS. They should provide a balanced discussion and explain that not every possible feature of TS is seen in every individual. They can also advocate for their patients by referring them to other specialists as needed.

2.5.2 Conclusion

While there are guidelines regarding the neuropsychological care of individuals with TS, there needs to be more research on how these recommendations have been implemented (Davis et al., 2020). In the past, parents and individuals with TS have felt inadequately informed about their diagnosis, and only some providers have discussed possible neurodevelopmental implications (Starke et al., 2002; Sutton et al., 2006). This study supports previous research in those findings. Participants felt it is their

healthcare team's responsibility to discuss these features at an age-appropriate level, around the time of diagnosis or late childhood/early adolescence. Preferred providers included pediatricians or PCPs, endocrinologists, or genetics providers. Genetics providers should be involved by giving a broad and balanced overview of the condition, providing ongoing care, and making referrals to other specialists.

2.5.3 Practice Implications

Based on the results of this study, patients with TS would benefit from an initial discussion surrounding potential neurodevelopmental or psychiatric features at diagnosis and/or in late childhood/early adolescence. This discussion should be with a provider who is most involved in their care or has the most expertise on TS. Often, all the information provided at diagnosis is not retained, as a diagnosis can be overwhelming. Continuing conversations throughout childhood, adolescence, and even adulthood may be beneficial in providing well-rounded care for an individual with TS. This allows the opportunity for these individuals and families to know possible symptoms or behaviors, relieve guilt, and increase knowledge of their diagnosis.

The results suggested that genetics providers should be involved by providing a general overview of TS, including physical, neurodevelopmental, and psychiatric features. They should also offer follow-up and referrals as needed.

2.5.4 Limitations and Further Research

The sample size of this study was small and may not be representative of all individuals with TS. The use of additional resources (like the TS registry) to recruit for future studies may provide further insight. Participants overwhelmingly

identified as white, and only those 18 years and older were allowed to participate. Future research should include a more diverse sample and adolescents. As research regarding non-physical features of TS is somewhat new, younger populations may be more likely to receive information on these features.

Furthermore, mosaic karyotype had to be interpreted for a few surveys. For example, individuals may have only marked “45,X” or “46,XX,” among other answers. It was interpreted that the other cell line was 45,X or typical 46,XX; however, this cannot be confirmed.

Finally, participants emphasized “age-appropriate discussions”; however, the preferred content of these discussions is not yet understood. Further studies should seek to better understand what information is desired. Additionally, it may be prudent to survey providers to understand the information they are trying to convey compared to the information individuals receive. Parental surveys may also give a different perspective.

Table 2.1 Patient Demographics

Characteristic	Total (n)	Percent (%)
Age		
18-30	17	30.3
31-40	14	25.0
41-50	13	23.2
51-60	6	10.7
61-69	3	5.4
No response	3	5.4
Race/Ethnicity*		
African American/Black	1	1.8
East Asian/Southeast Asian	2	3.6
Hispanic/Latinx	2	3.6
White	51	91
No response	1	1.8

Gender		
Female/woman	52	92.8
Non-binary, genderqueer, or not exclusively male or female	2	3.6
Prefer not to say	1	1.8
No response	1	1.8
Sexual Orientation		
Straight or heterosexual	43	76.7
Lesbian, gay, or homosexual	1	1.8
Bisexual	4	7.1
Queer	1	1.8
I use another term		
Asexual	3	5.4
Prefer not to say	3	5.4
No response	1	1.8
Relationship Status		
Single, never married	31	55.3
Serious relationship or engaged	3	5.4
Married or domestic partnership	18	32.1
Separated or divorced	3	5.4
No response	1	1.8
Children		
Yes		
Adopted	4	7.1
Biological children (Conceived with your own egg)	3	5.4
Children through an egg and sperm donor	2	3.6
No	46	82.1
No response	1	1.8
Highest Level of Education		
High school	5	9.0
Technical/trade/vocational school	2	3.6
Some university	7	12.5
Bachelor's degree	23	41.0
Master's degree	13	23.2
Doctoral degree	4	7.1
No response	2	3.6

*This characteristic is a question for which participants could select multiple answers. Therefore, the percentages do not reach a sum of 100%.

Table 2.2 Providers Involved in Care

Provider*	Total (n)	Percentage (%)
Endocrinologist	47	83.9
Cardiologist	46	82.1
Dermatologist	27	48.2
ENT/Audiologist	36	64.3
Fertility Specialist	16	28.6
Gastroenterologist	18	32.1
Genetic Counselor	9	16.1
Geneticist	15	26.8
Obstetrician/Gynecologist	40	71.4
Ophthalmologist/Optometrist	35	62.5
Pediatrician/Primary Care Provider	47	83.9
Psychiatrist	13	23.2
Psychologist	24	42.9
Turner Syndrome-specific Clinic	12	21.4
Other		
Urologist	1	1.8
Nutritionist	1	1.8
Occupational Therapist	1	1.8
Physical Therapist	1	1.8
Speech Therapist	2	3.6

*This is a question for which participants could select multiple answers. Therefore, the percentages do not reach a sum of 100%.

Table 2.3 Suspected Neurodevelopmental Features

Neurodevelopmental Feature*	Total (n)	Percentage (%)
ADHD	8	14.2
Difficulties with math	25	44.6
Weaker non-verbal communication skills	18	32.1
Weaker visual-spatial skills	27	48.2
Intellectual disability	3	5.4
ASD	10	17.9
No response	10	17.9

*This is a question for which participants could select multiple answers. Therefore, the percentages do not reach a sum of 100%.

Table 2.4 Reported Anxiety and Depression

Psychiatric Diagnosis	Total (n)	Percentage (%)
Anxiety		
Formal Diagnosis*		
Generalized anxiety	24	42.9
Social anxiety	5	8.9
PTSD	3	5.4
Panic disorder	3	5.4
OCD	3	5.4
Don't know	2	3.6
No Formal Diagnosis		
Personal suspicion of anxiety	12	21.4
No personal suspicion of anxiety	15	26.8
Depression		
Formal Diagnosis	25	44.6
No Formal Diagnosis		
Personal suspicion of depression	12	21.5
No personal suspicion of depression	18	32.1
No response	1	1.8

*This is a question for which participants could select multiple answers. Therefore, the percentages do not reach a sum of 100%.

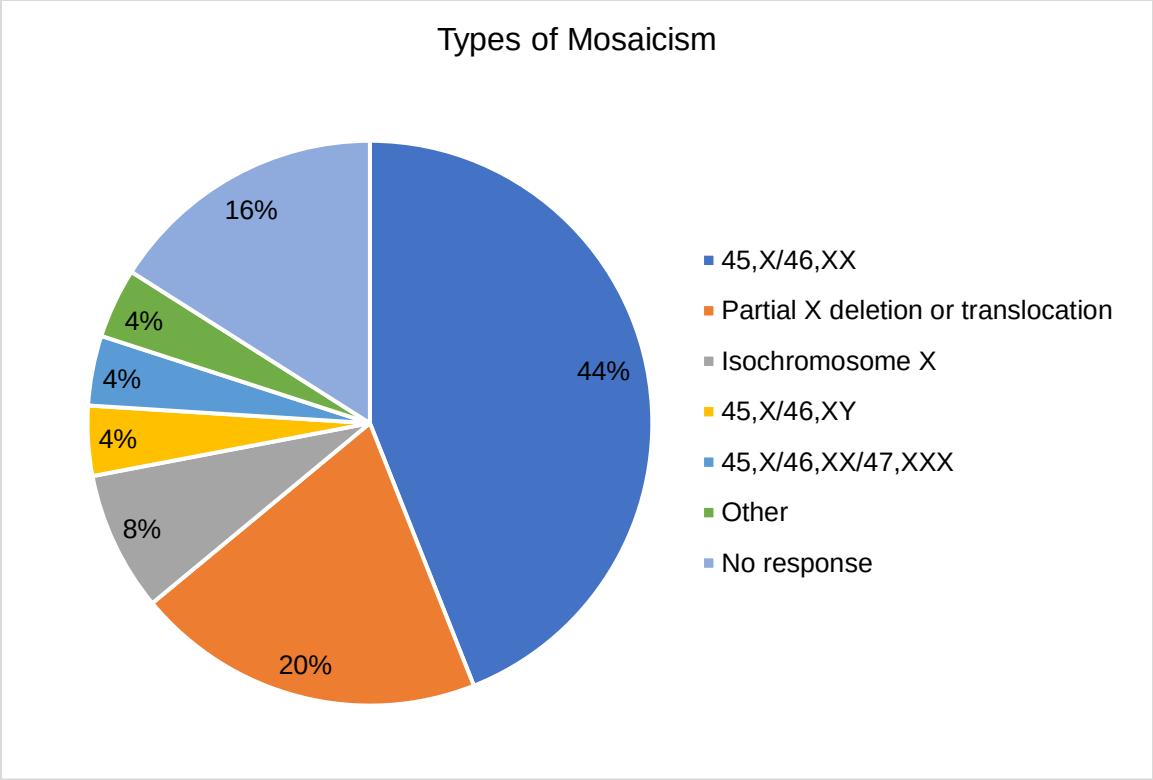

Figure 2.1 Percentages of reported types of TS mosaicism.

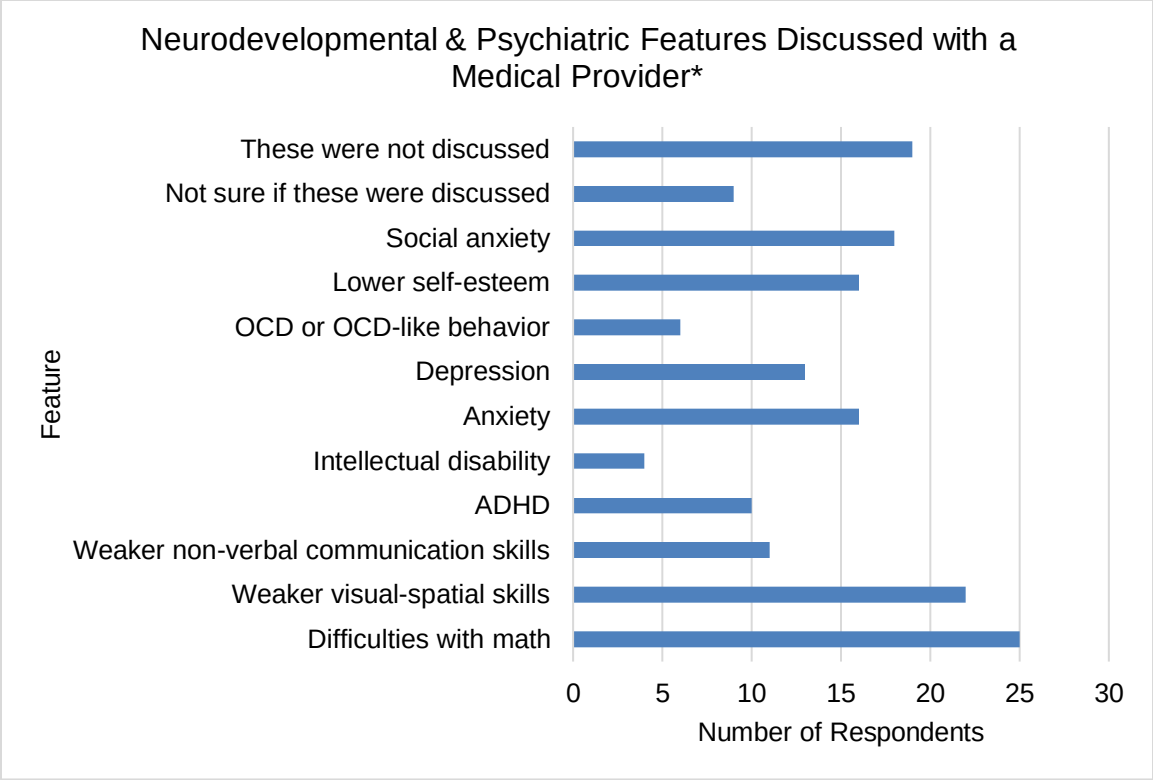

Figure 2.2 Number of respondents who reported a discussion with a medical provider regarding the listed neurodevelopmental and psychiatric features. *This is a question for which participants could select multiple answers. Therefore, the total is not 56.

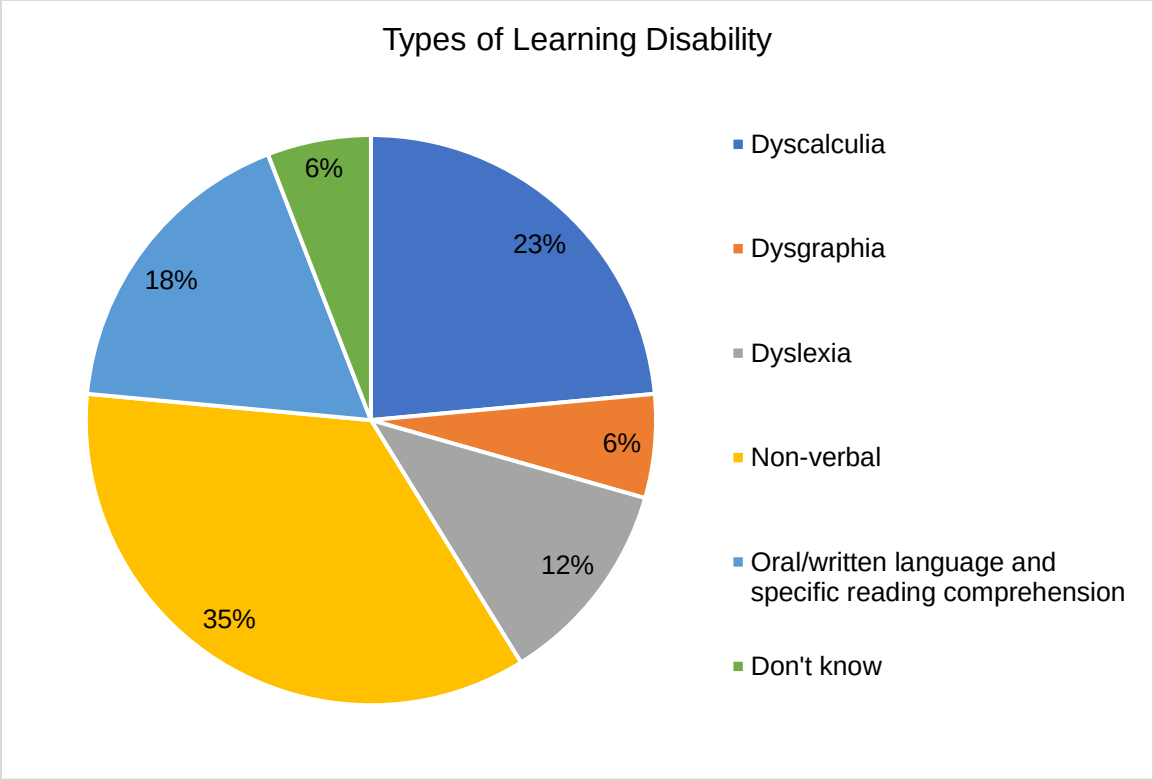

Figure 2.3 Frequencies of reported types of learning disability.

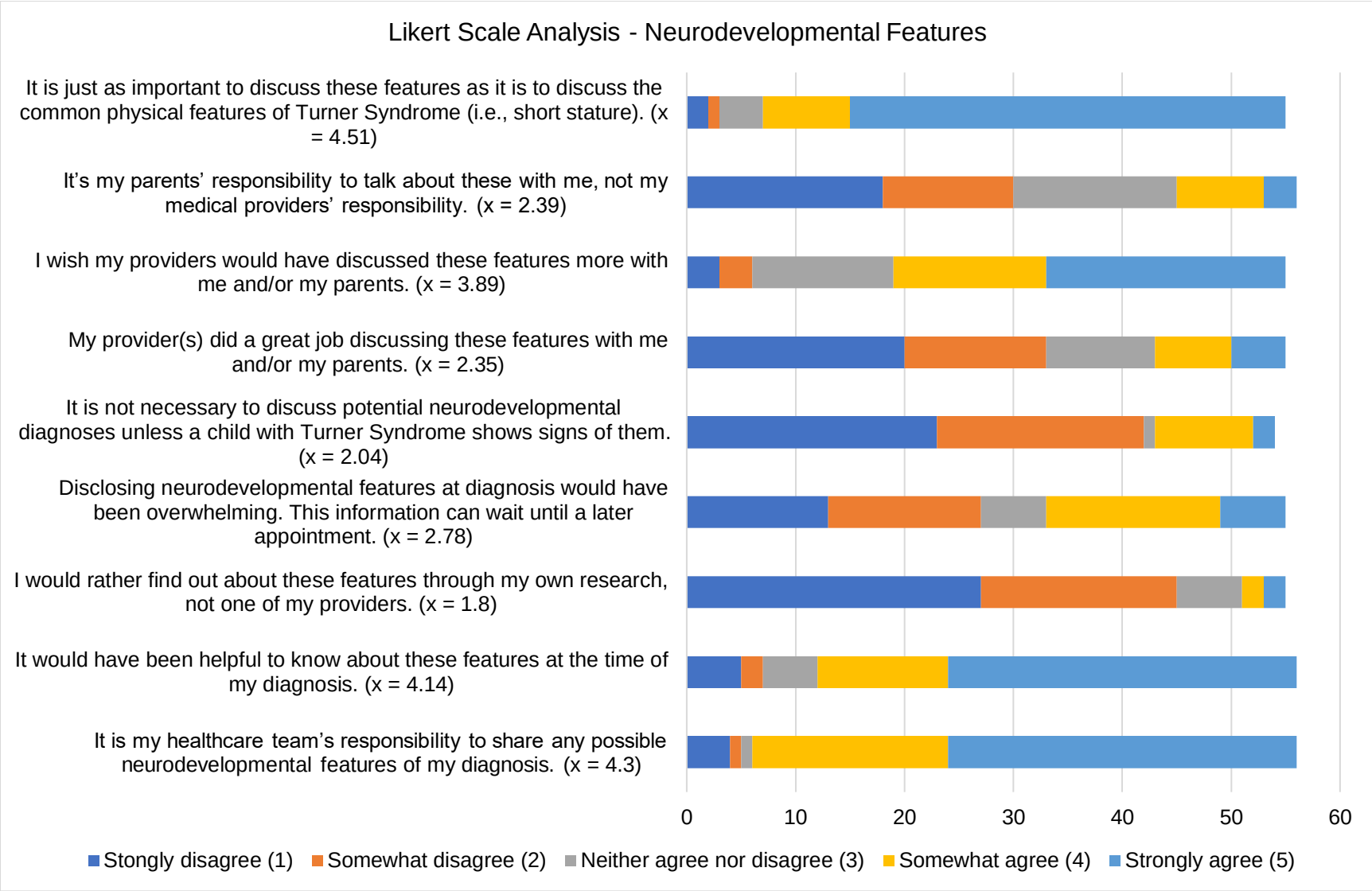

Figure 2.4 Likert scale analysis on preferences regarding disclosure and discussion surrounding neurodevelopmental features.

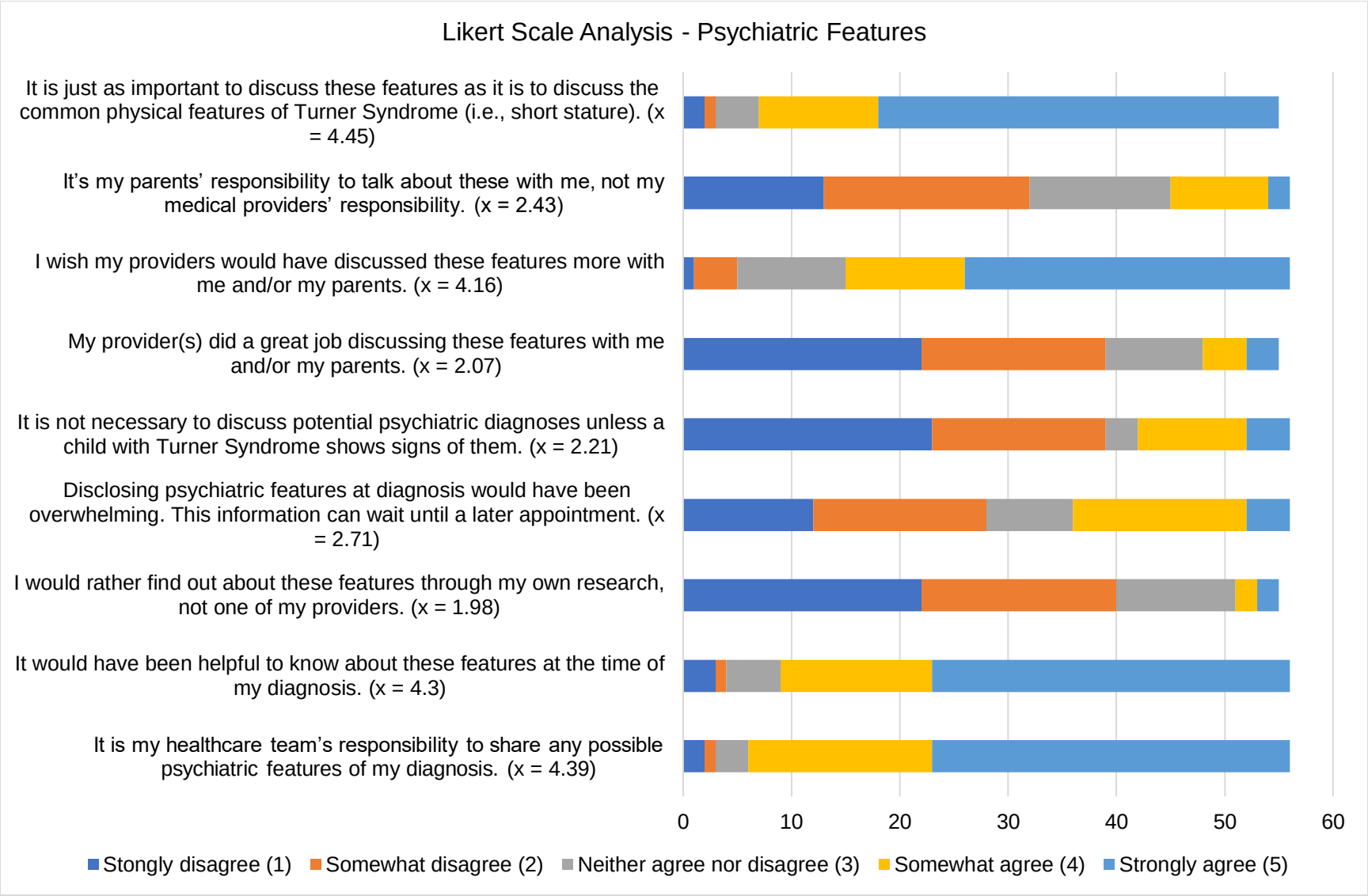

Figure 2.5 Likert scale analysis on preferences regarding disclosure and discussion surrounding psychiatric features.

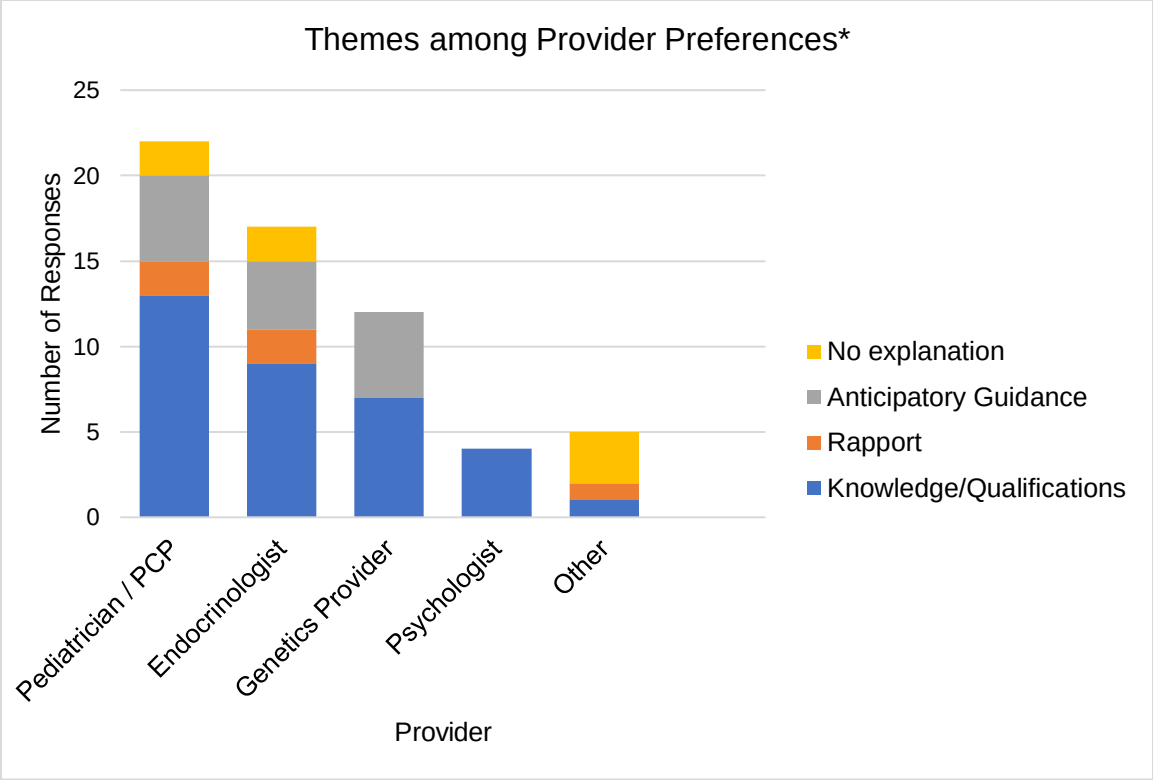

Figure 2.6 Themes regarding the reason for the chosen provider for discussing possible neurodevelopmental and psychiatric conditions. *This is a question for which multiple themes could fit one response. Therefore, the total is not 56.

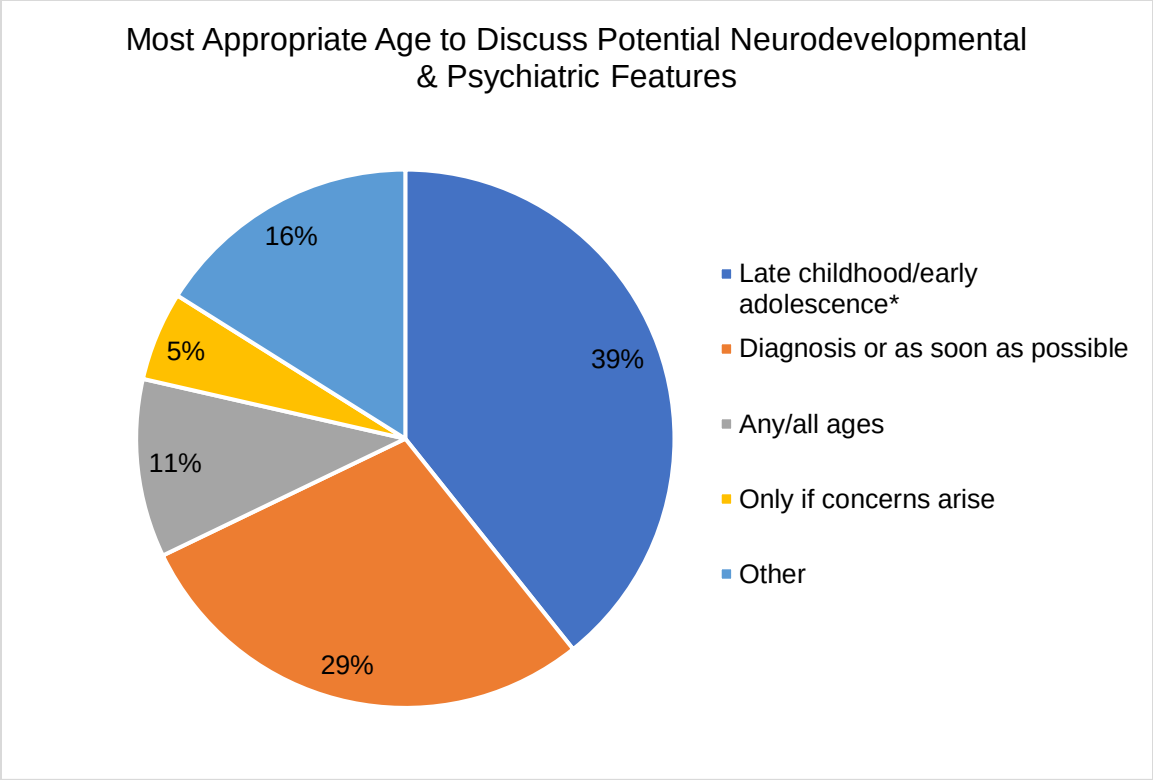

Figure 2.7 Participants' opinions regarding most appropriate age to discuss potential neurodevelopmental or psychiatric conditions. *Late childhood/early adolescence is defined here as 10-14 years old.

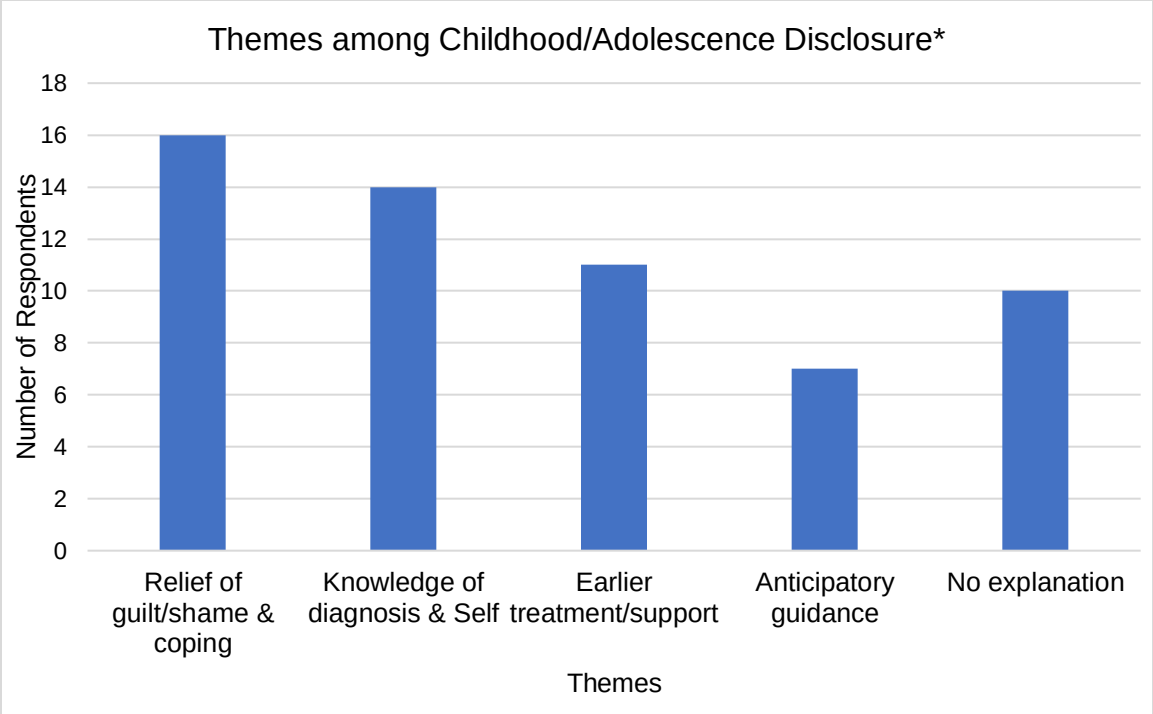

Figure 2.8 Themes regarding the value of discussing potential neurodevelopmental or psychiatric features during childhood/adolescence. *This is a question for which multiple themes could fit one response. Therefore, the total is not 48.

CHAPTER 3: CONCLUSIONS

While there are published care guidelines about neurodevelopmental and psychiatric features of TS, there needs to be more research on how these recommendations have been implemented. This study evaluated the neurodevelopmental and psychiatric history of individuals with TS and assessed preferences on provider disclosure of these potential diagnoses. Results support previous research, indicating that individuals with TS need to receive education about potential neurodevelopmental and psychiatric features consistently. Participants believed it is their healthcare team's responsibility to discuss these features at an age-appropriate level, around the time of diagnosis and/or in late childhood/early adolescence. Commonly preferred providers include pediatricians or primary care providers, endocrinologists, and genetics providers. Genetics providers can give a broad and balanced overview of the condition, provide ongoing care, and make referrals to other specialists.

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APPENDIX A: STUDY CONSENT FORM

University of South Carolina School of Medicine
Genetic Counseling Program

Dear Potential Participant,

My name is Liz Pancake. I am a graduate student working on my thesis in the Genetic Counseling program at the University of South Carolina. You are invited to participate in a graduate research study focusing on individuals with Turner Syndrome and their preferences regarding provider disclosure of potential neurodevelopmental and psychiatric features of Turner Syndrome. The research involves completing one online survey.

The goal of this survey is to gather information on your neurodevelopmental and psychiatric medical history, understand your diagnostic and medical experience, and provide the opportunity for stating your preferences regarding discussion about these potential features. Eligibility for this survey includes 1) you have been formally diagnosed with Turner Syndrome, and 2) you are 18+ years old.

Participation is anonymous. We do not ask for your name or contact information. The results of this study may be published or presented at academic or professional meetings, but your identity will not be revealed.

Your participation in this research is voluntary. By completing the survey, you are consenting that you have read and understand this information. If you do not wish to answer a certain question, you can skip it and continue with the survey, and at any time, you may withdraw from the survey. The survey should take 15-20 minutes. Compensation will not be provided upon survey completion.

Thank you for your time and consideration to participate in this survey. Your responses may help inform recommendations for counseling patients with Turner Syndrome in the future. If you have any questions regarding the research, you may contact either myself or my faculty advisor, Crystal Hill-Chapman, Ph.D., using the contact information below. If you have any questions about your rights as a research participant, you may contact the Office of Research Compliance at the University of South Carolina at (803) 777-6670.

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APPENDIX B: SOCIAL MEDIA POST

Hi everyone! I am a genetic counseling student with the University of South Carolina. Please see the flyer attached to this post for information on a survey I have created for my thesis! If you are interested in participating, please click the link below. The survey will be open until October 31st. Thank you for taking the time!

Link to survey: https://uofsc.co1.qualtrics.com/jfe/form/SV_bPf7rpy1vWJznBI

APPENDIX C: QUESTIONNAIRE

1. Have you been diagnosed with Turner Syndrome? (yes/no)
2. Are you 18 years or older? (yes/no)

(If answered yes to both, continue into survey)

<u>Diagnostic Background</u>

1. What is your karyotype (chromosomes) result?
    a. Non-mosaic Turner Syndrome
        i. Please specify type (optional)
            1. 45,X (monosomy X)
            2. Other, please specify _____ (fill in)
    b. Mosaic Turner Syndrome
        i. If you know which cell lines you are mosaic for, please specify (Optional, check all that apply)
            1. 45,X
            2. 46,XX
            3. 47,XXX
            4. 46,XY
            5. Ring X
            6. Isochromosome X
            7. Partial chromosome X deletion or translocation
            8. Other, please specify _____ (fill in)
    c. I don't know my karyotype
2. Around how old were you at diagnosis?
    a. Prenatal (before birth)
    b. Infancy (0-1 month – 12 months)
    c. Childhood (1-11 years)
    d. Adolescence (12-17 years)
    e. Adulthood (18+ years)
3. Do you know your **exact** age at diagnosis? If so, please specify. (Fill in, optional)
4. In your lifetime, which of the following providers have been a part of your healthcare team? (Check all that apply)
    a. Obstetrician/Gynecologist (OB/GYN)
    b. Pediatrician/primary care physician
    c. Endocrinologist
    d. Geneticist
    e. Genetic counselor
    f. Turner Syndrome-specific clinic
    g. Cardiologist

h. Fertility specialist
i. Dermatologist
j. ENT/audiologist
k. Ophthalmologist/optometrist
l. Gastroenterologist
m. Psychologist
n. Psychiatrist
o. Other, please specify _____ (fill in)

5. Which of the following neurodevelopmental and psychiatric features did a medical provider discuss with you as features some individuals with Turner Syndrome can have? *Note: These features vary broadly and are not seen in all individuals with Turner Syndrome.* (Check all that apply)
    a. Difficulties with math
    b. Weaker non-verbal communication skills – difficulty interpreting nonverbal behavior such as body language, facial expressions, etc.
    c. Weaker visual-spatial skills (i.e., difficulty riding a bike or driving)
    d. Attention deficit/hyperactivity disorder (ADHD)
    e. Intellectual disability
    f. Anxiety
    g. Depression
    h. Obsessive compulsive disorder (OCD) or OCD-like behavior
    i. Lower self-esteem
    j. Social anxiety – difficulty making friends or decreased desire to engage in social activities
    k. I'm not sure if my provider(s) discussed any of these with me.
    l. My provider(s) did not discuss any of these with me.

<u>Neurodevelopmental History</u>

1. Have you ever received a formal diagnosis of the following? (Check all that apply)
    a. Attention deficit/hyperactivity disorder (ADHD)
    b. Learning disability
    c. Intellectual disability
    d. Autism spectrum disorder (ASD)
    e. None of the above
    f. I don't know
2. If you were diagnosed with a learning disability, what was the diagnosis? (Optional, check all that apply)
    a. Dyscalculia – difficulties with math
    b. Dysgraphia – trouble with handwriting and fine motor skills
    c. Dyslexia – difficulties with reading and language-based skills
    d. Non-verbal – trouble with interpreting body language and facial expressions, as well as visual-spatial challenges (i.e., difficulty riding a bike or driving)

e. Oral/written language and specific reading comprehension – difficulties understanding written or spoken language or expressing verbal language
f. I don't know

3. Up through high school, did you ever have an individualized education plan (IEP) or receive special education services?
    a. Yes
        i. What was the disability category? (Optional, check all that apply)
            1. Specific learning disability
            2. Autism spectrum disorder
            3. Emotional disturbance
            4. Speech or language impairment
            5. Visual impairment
            6. Deafness
            7. Hearing impairment
            8. Deaf-blindness
            9. Orthopedic impairment
            10. Intellectual disability
            11. Traumatic brain injury
            12. Multiple disabilities
            13. Other health impairment (i.e., ADHD), please specify ____ (fill in)
            14. I don't know
    b. No
4. Have you suspected that you've had any of the following **without** a formal diagnosis or discussion with a provider? (Optional, check all that apply)
    a. ADHD
    b. Difficulties with math
    c. Weaker non-verbal communication skills – interpreting nonverbal behavior such as body language, facial expressions, etc.
    d. Weaker visual-spatial skills (i.e., difficulty riding a bike or driving)
    e. Intellectual disability
    f. Autism spectrum disorder

<u>Psychiatric History</u>

1. Have you ever had a psychological or medical diagnosis of anxiety or an anxiety-related disorder (generalized anxiety, social anxiety, PTSD, panic disorder, or OCD)?
    a. Yes
        i. What was the diagnosis (Check all that apply)?
            1. Generalized anxiety
            2. Social anxiety
            3. Post-Traumatic Stress Disorder (PTSD)
            4. Panic disorder
            5. Obsessive Compulsive Disorder (OCD)

6. I'm not sure

b. No
    i. Do you suspect you've had a history of anxiety or an anxiety-related disorder? (yes/no)

2. Have you ever had a psychological or medical diagnosis of depression?
    a. Yes
    b. No
        i. Do you suspect you've had a history of depression? (yes/no, optional)
3. Are there any other mental health conditions that you have been psychologically or medically diagnosed with?
    a. Yes
        i. What mental health condition have you been diagnosed with? (Free response, optional)
    b. No
4. Are there any other mental health conditions you have been concerned about throughout your lifetime that did not result in a diagnosis or were not discussed with a medical provider? (Optional, free response)

<u>Medical Services Preference</u>

1. Please give your opinion regarding disclosure of potential **neurodevelopmental** features of Turner Syndrome. These can include difficulties with math, weaker non-verbal and visual-spatial skills, ADHD, intellectual disability, and autism spectrum disorder. *Note: These features vary broadly and are not seen in all individuals with Turner Syndrome.* (Likert: 1 – strongly disagree, 2 – slightly disagree, 3 – neither agree nor disagree, 4 – slightly agree, 5 – strongly agree)
    a. It is my healthcare team's responsibility to share any possible neurodevelopmental features of my diagnosis.
    b. It would have been helpful to know about these features at the time of my diagnosis.
    c. I would rather find out about these features through my own research, not one of my providers.
    d. Disclosing neurodevelopmental features at diagnosis would have been overwhelming. This information can wait until a later appointment.
    e. It is not necessary to discuss potential neurodevelopmental diagnoses unless a child with Turner Syndrome shows signs of them.
    f. My provider(s) did a great job discussing these features with me and/or my parents.
    g. I wish my providers would have discussed these features more with me and/or my parents.
    h. It's my parents' responsibility to talk about these with me, not my medical providers' responsibility.

    i. It is just as important to discuss these features as it is to discuss the common physical features of Turner Syndrome (i.e., short stature).
2. Give your opinion regarding disclosure of potential **psychiatric** features of Turner Syndrome. These can include anxiety or social anxiety, depression, OCD or OCD-like behavior, and lower self-esteem. *Note: These features vary broadly and are not seen in all individuals with Turner Syndrome*. (Likert: 1 – strongly disagree, 2 – slightly disagree, 3 – neither agree nor disagree, 4 – slightly agree, 5 – strongly agree)
    a. It is my healthcare team's responsibility to share any possible psychiatric features of my diagnosis.
    b. It would have been helpful to know about these features at the time of my diagnosis.
    c. I would rather find out about these features through my own research, not one of my providers.
    d. Disclosing psychiatric features at diagnosis would have been overwhelming. This information can wait until a later appointment.
    e. It is not necessary to discuss potential psychiatric diagnoses unless a child with Turner Syndrome shows signs of them.
    f. My provider(s) did a great job discussing these features with me and/or my parents.
    g. I wish my providers would have discussed these features more with me and/or my parents.
    h. It's my parents' responsibility to talk about these with me, not my medical providers' responsibility.
    i. It is just as important to discuss these features as it is to discuss the common physical features of Turner Syndrome (i.e., short stature).
3. In hindsight, which medical provider would you have preferred discussed possible neurodevelopmental and psychiatric features of Turner Syndrome with you and/or your parents?
    a. Obstetrician/Gynecologist (OB/GYN)
    b. Pediatrician/primary care physician
    c. Endocrinologist
    d. Geneticist
    e. Genetic counselor
    f. Turner Syndrome-specific clinic
    g. Cardiologist
    h. Fertility specialist
    i. Dermatologist
    j. ENT/audiologist
    k. Ophthalmologist/optometrist
    l. Gastroenterologist
    m. Psychologist
    n. Psychiatrist
    o. Other (please specify) _____

4. Why would you have preferred the medical provider you chose above to discuss these topics with you? (Optional, free response)
5. When (or at what age) do you think it is appropriate for a provider to talk to an individual with Turner Syndrome about potential neurodevelopmental and psychiatric diagnoses? (Free response)
6. Do you believe knowing about these possible features would have been helpful during your childhood/adolescence? Why or why not? (Free response, opriontal)
7. Should genetic providers discuss these factors when talking to a patient with a new diagnosis? How do you recommend they should be involved? (Free response)

<u>Demographics (Optional)</u>

1. What is your current age? (Fill in)
2. What is your race/ethnicity? (Check all that apply)
    a. African American/Black
    b. East Asian/Southeast Asian
    c. South Asian
    d. Hispanic/Latinx
    e. Middle Eastern/North African
    f. Native American/Alaskan Native
    g. Native Hawaiian/Pacific Islander
    h. White
    i. Other, please specify ____ (fill in)
3. What is your gender?
    a. Female/Woman
    b. Male/Man
    c. Non-binary, genderqueer, or not exclusively male or female
    d. I use another term, _____ (fill in)
    e. I don't know
    f. Prefer not to say
4. What is your sexual orientation?
    a. Straight or heterosexual
    b. Lesbian, gay, or homosexual
    c. Bisexual
    d. Queer
    e. I use another term, _____ (fill in)
    f. Prefer not to say
5. What is your relationship status?
    a. Single, never married
    b. Serious relationship or engaged
    c. Married or domestic partnership
    d. Separated or divorced
    e. Widowed
6. Do you have any children?
    a. Yes

        i. Do you have biological children, adopted children, stepchildren, children through an egg donor, or children through a sperm donor? (Check all that apply)
            1. Biological children (Conceived with your own egg)
            2. Adopted children
            3. Stepchildren
            4. Children through an egg donor
            5. Children through a sperm donor
            6. Children through an egg and sperm donor
    b. No
7. What is the highest level of education you have completed?
    a. Elementary/middle school (Kindergarten-8th grade)
    b. High school
    c. Technical/Trade/vocational school
    d. Some university
    e. Bachelor's degree
    f. Master's degree
    g. Doctoral degree

APPENDIX D: SUPPLEMENTAL DATA

Individualized Education Plan	Total (n)
No	45
Yes	
Speech or language impairment	3
Hearing impairment	2
Specific learning disability	4
ASD	1
Other health impairment	
Non-verbal learning disability	1
Low-processing IQ	1
ADHD	1
No response	2