Genetic testing for Autism Spectrum Disorder (ASD): Evaluating the challenges of genomic translation

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Abstract

Genetic testing for Autism Spectrum Disorder (ASD): evaluating the challenges of genomic translation

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Genetic testing for ASD is a new, complex and evolving aspect of healthcare, occurring in the setting of substantial challenges to the diagnosis and treatment of this group of conditions (Jeste & Geschwind, 2014). To date there has been little focused research examining what families experience through the genetic testing process and what they see as the benefits and or harms of genetic testing for ASD. There also has not been any research exploring health care provider views about genetic testing for ASD. My research focuses on three aspects of genetic testing for ASD: guidelines, parent's experiences, and provider and parent perspectives.

In Chapter 2, a guideline review tool was used to analyze five professional guidelines, identifying similarities and differences both in their content and in the process used to develop them to determine where there is and is not consensus in regard to genetic testing for individuals with ASD and to evaluate the guideline creation process.

Chapter 3 examines, through qualitative interviews and exploration of diagnostic services for ASD, what genetic testing is being offered to families with ASD and what the path from a clinical ASD diagnosis to genetic testing looks like. Currently the pathway from an ASD diagnosis to genetic testing is messy, expensive, sometimes random and, the interviews in this study suggest, often puzzling or dissatisfying to both patients and providers so efforts to create a clearer and more transparent approach would benefit all involved.

Chapter 4 examines provider and parent attitudes about genetic testing for ASD, identifying their concerns and motivations to obtain testing and their thoughts on the benefits and barriers to testing. There is variability in provider attitude and practices toward genetic testing for ASD, as well as parent uncertainty about the value of testing. When providers recommend testing, parents generally follow their advice but they do so primarily to ensure that they are providing all recommended care.

In conclusion, there is a broad range of opinion in the medical community when it comes to offering genetic testing for individuals with ASD and these divergent perspectives extend to the clinical guidelines. As a result, offering genetic testing to individuals with ASD is disorganized and as a result, confusing for parents. Finding a way to make the process understandable and easy for families to navigate would be most beneficial to parents. Providers involved in the diagnosis, treatment, and care of individuals with ASD should focus on transparency for families, more research on benefits and outcomes of genetic testing related to ASD, and movement towards clinician consensus on testing recommendations.

Table of Contents

List of Tables

Table Number **Page**

Chapter 1: An Introduction to Autism and Chromosomal Microarray

Autism

Autism spectrum disorder (ASD) is used to describe a group of developmental disorders with behavioral symptoms that are seen on a continuum ranging from mild to severe expression (Lauritsen, 2013). ASD has been controversial for several reasons: there has been a remarkable increase in prevalence in recent years (King & Bearman, 2009; Silverman & Brosco, 2007), the understanding of its etiology is mixed and evolving as technologies improve (Jiang et al., 2014), and the search for specific medical interventions has been largely unsuccessful (McPheeters et al., 2011). First described in the medical literature by Leo Kanner in 1943 (Silverman & Brosco, 2007) the essential features of ASD are persistent impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities (Neurodevelopmental Disorders, 2013) with varying degrees of severity (Silverman & Brosco, 2007). To qualify for a diagnosis of ASD, symptoms must be present in early childhood and symptoms must limit and impair everyday function (Lauritsen, 2013; "Neurodevelopmental Disorders," 2013). Diagnosis is based on behavioral observation (Freitag, Staal, Klauck, Duketis, & Waltes, 2010) and management of autism involves educational, behavioral, and medical therapies to promote conversational language and social interactions while mitigating self-stimulatory behaviors, tantrums, aggression, and self-injurious behavior (Miles, McCathren, Stichter, & Shinawi, 2010). Studies estimate the prevalence of ASD at around .5-1%.(Freitag et al., 2010; Hallmayer et al., 2011; "Neurodevelopmental Disorders," 2013; Silverman & Brosco, 2007). The apparent rise in the number of cases of autism suggests an environmental component of the etiology, but these shifts also may be accounted for by differences in study methodology, greater physician and public awareness, and an increasingly broad definition of autistic disorders in the Diagnostic and statistical manual (DSM) ("Neurodevelopmental Disorders," 2013; Singh, Hallmayer, & Illes, 2007). The reasons for the increase in ASD prevalence rates are still not fully resolved.

Historical Review of Etiological Hypotheses

From the very beginning, parents have been involved and essential to the advancement of autism research. Kanner gave credit to the parents of his patients for their meticulous notes on their children as a primary source of his research, but also criticized the parents for their "cold" demeanor in his field notes and in public presentations (Silverman & Brosco, 2007). This criticism was just the beginning of the medical community's focus on parental blame. Through the 1950s autism was considered to be caused by psychological influences (Silverman & Brosco, 2007; Tabor & Lappe, 2011) such as bad parenting and "cold" mothering. Autism researchers, such as Bruno Bettelheim, developed a Freudian explanation that autism arose in infancy in response to rejection by an emotionally distant, although typically well-educated parent (Baker, 2008), an idea that became known as the "refrigerator mother" hypothesis. Parents and some experts in the field challenged this hypothesis, and by the 1960s, medical professionals began to seriously consider non-psychological frameworks for understanding autism. In 1964, Bernard Rimland, worked to dispel the concept of the "refrigerator mother" and described infantile autism as a neurological disorder with a strong genetic component (Silverman & Brosco, 2007). This paradigm shift gave rise to two different explanatory frameworks; the "mainline" and "alternative" models (Baker, 2008).

The majority of autism researchers view autism as a neurodevelopmental condition (Baker, 2008) and focus on the biology of the disease. The first twin studies in autism, conducted in 1977 (Folstein & Rutter, 1977; Silverman & Brosco, 2007; Singh et al., 2007) by Michael Rutter and Susan Folstein, showed a high degree of concordance (Folstein & Rutter, 1977; Freitag et al., 2010) indicating that shared genetic factors played an important role in the disease (Folstein & Rutter, 1977; Schaefer, Mendelsohn, & Professional Practice and Guidelines Committee, 2008). As a result of this study and similar studies in the 1980's through the mid 1990's, most researchers in the field subscribed to the view that autism was a highly heritable genetic neurological disorder (Silverman & Brosco, 2007). Modeling a strategy that

had been successful for single-gene diseases, in the early 1990's researchers began recruiting families with children diagnosed with autism to participate in large genetic family studies called linkage studies (Tabor & Lappe, 2011). Linkage studies were successful in confirming an overall contribution of genetics to autism but did not identify specific causal genes on a consistent basis (Tabor & Lappe, 2011). These studies have shown that autism is a "complex" disorder with many genes of small effect and variable models of inheritance (Tabor & Lappe, 2011).

An alternative community viewed autism in biomedical terms with the hope that at least some forms of autism are curable with a focus on treatments (Baker, 2008). This view was spearheaded by advocacy groups in the late 1990s who first presented the notion of an "autism epidemic" and the idea that the cause of autism was not only biological, but also environmental (Baker, 2008). In 1998, following insistence from parents for further investigation on physical symptoms in their children (Silverman & Brosco, 2007) Andrew Wakefield published a study indicating a possible link between bowel inflammation and developmental regression, with a brief mention of a possible temporal association between the measles-mumps-rubella (MMR) vaccine and autism (Singh et al., 2007). Over the following decade, this study drew enormous attention from parents and the media ,even though epidemiological studies consistently found no evidence for a link between the MMR vaccine and autism (Godlee, Smith, & Marcovitch, 2011). Vaccination rates fell in the UK starting in 2002 and there was a large upsurge of measles incidence (Leask, Booy, & McIntyre, 2010). The impact was also apparent in the United States, where Wakefield's theory augmented unsubstantiated fears about thiomersal (a mercury-based preservative) in some vaccines leading to autism. Thiomersol was eventually removed from vaccines, but further research has not revealed a link between thiomersal and developmental delays (Baker, 2008). In 2004, The US Institute of Medicine Report on Vaccines and Autism was published stating that vaccines didn't cause autism (Singh et al., 2007) and 10 of the coauthors from the Wakefield study partially retracted the research. However, Wakefield, continued to state that the research was accurate. In 2010, 12 years after publication in *The*

Lancet, Wakefield was found to have falsified data and the Wakefield paper was finally retracted by the UK's General Medical Council (GMC) (Godlee et al., 2011).

Although Wakefield's studies have been discredited, an environmental contribution to autism remains a possibility, potentially influenced by genetic susceptibility factors. The early twin studies, mentioned above had very small sample sizes; they found high monozygotic twin concordance and low dizygotic twin concordance, indicating strong genetic heritability (Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989). However, a recent study provides evidence that the rate of concordance in dizygotic twins reported in those studies may have been underestimated and the influence of genetic factors on the susceptibility to develop autism, overestimated (Hallmayer et al., 2011). The study by Hallmayer, et al. also concludes that both genes and environment play significant roles in susceptibility to ASD and the non-genetic risk factors that may indicate environmental influence include parental age, low birth weight, multiple births, and maternal infections during pregnancy (Hallmayer et al., 2011).

Genetic Causes of Autism

Autism spectrum disorder (ASD) aggregates in families, but the genetic risk in a specific individual or family and the extent to which autism is caused by genetic factors or shared or non-shared environmental factors remains unresolved (Sandin et al., 2014). Previous twin and family studies, obtained mainly in the UK and in Northern Europe in the early 1990s, indicated that ASDs are predominantly genetically determined disorders with heritability around 90% (Freitag et al., 2010; Persico & Napolioni, 2013; Silverman & Brosco, 2007). More recent studies estimate a much lower rate of heritability of ASD and autistic disorders, approximately 50% by Sandin et al, 2014 and 38% by Hallmayer, et al 2011. However, the related increase in sibling recurrence risk and the presence of mild autistic traits in many first-degree relatives of patients with autism still indicate a strong genetic component in ASD (Persico & Napolioni, 2013). The clinical heterogeneity of ASD is believed to be due to both the complexity of its genetic

underpinnings (with various modes of inheritance) as well as gene-gene and gene-environment interactions (Persico & Napolioni, 2013).

Some genetic contributors are associated with heterogeneous presentations across the spectrum of disorders and include several rare, most likely, monogenetic disorders, “contiguous gene syndromes” (disorder due to deletion of multiple gene loci that are adjacent to one another) and common variants that increase the risk for autistic traits (Freitag et al., 2010). Currently a genetic cause or contributor is identified in 6-15% of individuals with a clinical diagnosis of ASD (Schaefer, Mendelsohn, & Professional Practice and Guidelines Committee, 2013). Initially, many researchers had hoped for “a gene” for autism, or a few genes with strong effect (Scherer & Dawson, 2011), but linkage and association studies have identified numerous susceptibility genes, located on various chromosomes, especially 2q, 7q, 15q and on the X chromosome (Devlin & Scherer, 2012; Persico & Napolioni, 2013). Only about 10% (Devlin & Scherer, 2012; Persico & Napolioni, 2013) of ASD cases are associated with known genetic syndromes and include Fragile X Syndrome, *PTEN* Macrocephaly Syndrome, Tuberous Sclerosis Complex, Rett Syndrome, Timothy Syndrome, Joubert Syndrome, Neurofibromatosis, untreated Phenylketonuria, Angelman, Cornelia de Lange and Down syndrome (Miles, 2011; Persico & Napolioni, 2013). These disorders can stem from either (a) genomic DNA mutations, triplet repeat expansions, or rare chromosomal abnormalities, or (b) rare de novo and some inherited copy number variants (CNVs) (Persico & Napolioni, 2013).

The advent of microarrays to screen genomes for variations in single bases or larger segments of the DNA has led to a shift in the genetic approach to both autism research and diagnostics (Scherer & Dawson, 2011). This research has revealed that rare alleles and genomic copy number variants (CNVs) contribute to ASD predisposition, some with enough evidence to support causation (Scherer & Dawson, 2011). CNVs are submicroscopic deletions, duplications, insertion, inversions, and complex recombinations affecting many loci and rare *de novo* or inherited copies of CNV’s are observed in 5-10% of ASD cases (Devlin & Scherer,

2012). The most common autism-related CNVs are the 15q11.2-11.3 duplications and reciprocal 16p11.2 microdeletions and duplications (Miles, 2011). Different CNV's will exhibit different phenotypic expression (i.e., "penetrance") for ASD depending on dosage sensitivity (if gene is dosage sensitive the number of copies will impact level of expression) and the function of the gene they affect (Devlin & Scherer, 2012). The high variability in CNV penetrance makes it difficult to determine whether in a given patient, a CNV is the sole cause of autism, confers vulnerability to the disease, or represents a chance finding. In fact, the majority of CNVs are inherited from either one of the parents, who may or may not display some autistic traits but have not been diagnosed with autism, and many CNVs found in ASD patients are also in patients with other psychopathologies, especially intellectual disability and schizophrenia (Persico & Napolioni, 2013). Researchers and clinicians may not always agree on whether a genetic aberration (e.g., certain type of CNVs) is "causal," "pathogenic," or "clinically significant" so an abnormal variant can include variants of uncertain significance (VOUS) and therefore may not give a clear etiology.

The increased detection of CNVs in autism has paved the way for identification of a number of new autism candidate genes (Miles, 2011). As new candidate genes are being reported, authoritative reviews and new web-based searchable lists (like SFARI gene created by the Simons Foundation), of candidate genes associated with ASD are available and constantly expanding (Miles, 2011). Of particular recent interest are the synaptic cell adhesion and associated molecules (neurexin 1, neuroligin 3 and 4, and *SHANK3*) which implicate glutamatergic synapse abnormalities in ASDs (Miles, 2011), chromatin Architecture genes (MECP2), and morphogenetic and growth-regulating genes (HOXA1, PTEN, EIF4E) (Persico & Napolioni, 2013).

Genetic Testing for ASD in Clinical Settings

Chromosomal microarray (CMA), also referred to as array comparative genomic hybridization (aCGH), is a technique enabling high-resolution, genome-wide screening of segmental genomic CNVs (Pinkel et al., 1998; Shinawi & Cheung, 2008; Solinas-Toldo et al., 1997; Vissers et al., 2003). In CMA, equal amounts of labeled genomic test DNA and reference sample DNA are cohybridized to an array containing DNA targets (Oostlander, Meijer, & Ylstra, 2004; Shinawi & Cheung, 2008). This allows for comprehensive interrogation of hundreds of discrete genomic loci for DNA copy number gains and losses and facilitates the identification of the molecular basis of many genetic diseases (Shinawi & Cheung, 2008). This technology was introduced in 1992 (Oostlander et al., 2004) and has evolved and been adopted in clinical genetics at a very fast rate; new platforms are being developed faster than clinical studies can define their use (Schaefer et al., 2008). Physicians have placed a lot of hope and value in these new technologies as evidenced by a statement in a Practice Guidelines from the American College of Medical Genetics and Genomics (ACMG): “Currently, CMA has emerged as a powerful new tool that promises further revolution of clinical genetic testing” (Schaefer et al., 2013)**.**

CMA is now being offered in the clinical setting to children diagnosed with autism (Miller et al., 2010) because it is possible to detect deletions, duplications, and mosaicism, missed by cytogenetic analysis (Shinawi & Cheung, 2008). The advantages of CMA as compared to conventional cytogenetics are increased resolution and throughput with the possibilities for automation, robustness, simplicity, high reproducibility, and precise mapping of aberrations (Shinawi & Cheung, 2008). The detection of pathogenic imbalances is about 3% by karyotype but 10% by array (Schaefer et al., 2013) and recent consensus statements suggest diagnostic yields of 15-20% for genetic testing of individuals with unexplained developmental delay or ASD (Miller et al., 2010). It is also better at detecting duplications compared to fluorescent *in situ* hybridization (FISH) and can detect small atypical deletions not detected by FISH. In addition

turn-around time is faster than cytogenetic methods (Shinawi & Cheung, 2008). According to Miles et al, CMA has replaced high-resolution chromosome analysis as the test of choice for the evaluation of any child with ASD (Miles et al., 2010).

The ACMG guidelines from 2013 state that due to the increase in diagnostic yield with clinical genetic testing for ASD, genetic testing should be discussed with all patients and families with ASDs. The ACMG guideline document provides very specific recommendations on how to proceed when discussing and offering testing to families (Schaefer et al., 2013). This will be discussed in greater detail in subsequent chapters. Although the ACMG guidelines and many providers are supportive of CMA testing as a first tier test, at this time, genetic testing for ASD is not consistently implemented in the clinical setting. A qualitative study published in 2013 found that although genetic testing for ASD has been offered for more than a decade in the clinical setting, the majority of participants in their study had never heard about such testing (Chen, Xu, Huang, & Dhar, 2013). Although this was a small study (N=42), they concluded that better education for parents and training for healthcare providers in communicating ASD genetic testing procedures and results with patients was needed. Some clinicians may not be discussing genetic testing with their patients at all, while other clinicians discuss or order tests that they are more comfortable with, such as karyotypes and fragile X testing, and CMA is done depending on the situation and/or available resources (Bauer & Msall, 2011).

Issues with CMA in a Clinical Setting

Like all clinical diagnostic methods, CMA technology has limitations. CMA is not able to identify balanced rearrangements, such as translocations and inversions, or detect polyploidy (Shinawi & Cheung, 2008). Although CMA can uncover numerous variations in the number of DNA copies scattered throughout the human genome, there is a continuum from a normal to pathogenic variants and in the middle are variants of uncertain significance (VOUS) (Shinawi & Cheung, 2008). Factors that impact whether a variant is normal or pathogenic include whether

or not it is inherited (Shinawi & Cheung, 2008) size, information about type of CNV, and location (Girirajan, Campbell, & Eichler, 2011). Approximately 65-80% of individuals carry a CNV that is at least 100 kbp in size, 5-10% of individuals harbor a CNV at least 500 kbp, and 1% of individuals carry a CNV at least 1 Mbp in size (Girirajan et al., 2011). Interpretation of microarray data is complicated by the presence of both novel and recurrent CNVs of unknown significance (Shen et al., 2010). Larger variants (> 500 kbp) if de novo are usually considered pathogenic (Girirajan et al., 2011), but some of the aberrations that are detected are benign so although the results of CMA testing are binary (there either is or is not a CNV), understanding the results is complex. Parental DNA is often needed to first determine if the CNV is inherited from a parent. If identical alterations are found in either one of the unaffected parents, or in independent normal controls, the CNV most probably has no direct phenotypic consequence; however low penetrance and variable expressivity of the phenotype may complicate the analysis (Shinawi & Cheung, 2008). Ongoing research on CNVs has led to the development of a group of databases that are slowly and continuously growing to assist in making decisions about the clinical significance of imbalances detected by microarrays. For translational research, a major challenge is to know whether a given variant is pathogenic and contributing to the clinical phenotype, or is an incidental observation (Scherer & Dawson, 2011). Translation of genomic information into the clinical setting is even more complex because the information that is obtained from a genetic test is not necessarily applicable knowledge that can be explained to families or can be used to inform treatment decisions (Scherer & Dawson, 2011). Clinicians need detailed information about how families will use CNV results in the treatment of their child or family planning (Scherer & Dawson, 2011) to ensure that the information gathered in the future is important to families.

Parental Perspective and ASD Genetic Testing

Parents of children with ASD often report mistrust of the medical community based on past experiences and because of apparently contradictory reports that appear in medical literature as new ASD studies are reported (Gupta, 2010). Some of this comes from inaccurate beliefs about ASD etiology. A recent survey found that one in four US parents believed that some vaccines cause autism in healthy children (Leask et al., 2010). The impact of Wakefield's fraudulent publication has had longstanding consequences on immunizations, but as Godlee expresses, "perhaps as important as the effect on infectious disease is the energy, emotion, and money that have been diverted away from efforts to understand the real causes of autism and how to help children and families who live with it" (Godlee et al., 2011). The qualitative study discussed previously found that parents were in favor of ASD genetic tests and a major reason for this is their hope that it will aid ASD research (Chen et al., 2013). This is not surprising given the long history of parental activism in the ASD community. Also not surprising is the finding that there is disparity in awareness and access to ASD genetic testing and pervasive misunderstanding of genetic testing (Chen et al., 2013). In that study, interviews were conducted with 42 parents of autistic children with diverse racial/ethnic backgrounds. The authors found that individuals with lower socio-economic status tended to be less familiar with and had less access to genetic testing.

Another study surveyed parents about their interest in a genetic risk assessment test for ASD and found the majority of parents would be interested in genetic testing to determine the risk of ASD in younger siblings of affected children in order to reduce their anxiety levels (Narcisa et al., 2013). However, in another study looking at the parental experience of genetic referral, parental guilt persisted even after a mutation was found to be the most likely cause. Feelings of guilt were not eliminated even if the genetic mechanism was understood (Skirton, 2006). Although strong evidence is lacking that finding an etiology for ASD has a positive impact on families, scientific journals make claims such as, "an early and efficient diagnosis by CMA

reduces the cost and stress of a long and fruitless workup, improves anticipatory guidance, and empowers the family with accurate genetic counseling" (Henderson et al., 2014).

Research Focus

Genetic testing for ASD is a relatively new, complex and evolving aspect of healthcare, occurring in the setting of substantial challenges to the diagnosis and treatment of this group of conditions (Jeste & Geschwind, 2014). The literature on the genetics of ASD speaks of the hope that genetic testing will disentangle the heterogeneity of ASD and the promise of future treatment (Jeste & Geschwind, 2014). The benefits associated with determining an etiology and the value of information are supported in the ACMG guidelines by anecdotal accounts of how this information can be useful to families. Unfortunately, to date there has been little focused research examining what families experience through the genetic testing process and what they see as the benefits and or downsides of genetic testing for ASD. Nor has research explored health provider views about genetic testing for ASD.

There is very little discussion about the implications of offering these tests, about which many questions remain, or the views of parents and clinicians about the realities of the testing process. A paper published in 2011, discussing the scientific, ethical, policy and communication aspects of translating genomic discoveries into clinical and diagnostic tools for promoting the well-being of individuals and families with ASDs, concluded that "there is a critical need for empiric study of the concerns and attitudes regarding genetic testing of persons with ASD and their families" (Scherer & Dawson, 2011). My research focuses on three aspects of genetic testing for ASD: guidelines, parent experience, and provider and parent perspectives. In chapter 2, through a guideline review, I identify the similarities and differences among guidelines to determine where there is and is not consensus in regard to genetic testing for individuals with ASD and to evaluate the guideline creation process. Chapter 3 focuses on the many pathways to genetic testing and the challenges families and providers face. Chapter 4 examines provider

and parent attitudes about genetic testing for ASD, identifying their concerns and motivations to test and their thoughts on the benefits and barriers to testing.

Chapter 2: Review of Guidelines for Genetic Testing for Autism Spectrum Disorder (ASD)

Introduction

Autism spectrum disorder (ASD) refers to a heterogeneous group of conditions. This presents a substantial challenge to diagnosis and treatment (Jeste & Geschwind, 2014). The variable clinical expression of ASD is due to its genetic heterogeneity and multiple gene-gene and gene–environment interactions (Persico & Napolioni, 2013). ASD has been controversial for several reasons: there has been a remarkable increase in prevalence in recent years (King & Bearman, 2009; Silverman & Brosco, 2007), the understanding of its etiology is mixed and evolving as technologies improve (Jiang et al., 2014), and the search for specific medical interventions has been largely unsuccessful (McPheeters et al., 2011). The diagnosis of ASD is based on clinical manifestations and cognitive and developmental assessment. Individuals with ASD are diagnosed, evaluated and followed by pediatricians, neurologists, psychologists and psychiatrists and some are referred to geneticists for evaluation (McGrew, Peters, Crittendon, & Veenstra-Vanderweele, 2012). The purpose of genetic testing in children with ASD is to identify a genetic etiology, (Agency for Healthcare Research and Quality, 2014) with the goal that discovering etiology can help guide management for the individual, and facilitate provision of an explanatory cause and accurate recurrence risk for families (Vande Wydeven, Kwan, Hardan, & Bernstein, 2012).

Genetic tests currently available can identify the underlying genetic etiology in a small subset of children with a clinical diagnosis of ASD (Narcisa et al., 2013). There are 6-15% of cases where a genetic cause or contributor is identified (Schaefer et al., 2013). Table 2.1 lists the most common tests offered to families with an ASD diagnosis (Schaefer et al., 2013). Chromosome microarray (CMA) is a technique that allows the identification of copy number variants (CNVs) throughout the genome (Manning & Hudgins, 2007; Miller et al., 2010; Schaefer et al., 2008; Teutsch et al., 2009). Studies reporting diagnostic yield for CMA define it as the number of patients with abnormal variants divided by the total number of patients tested (Miller

et al., 2010). However, researchers and clinicians may not always agree on whether a genetic aberration (e.g., certain type of CNVs) is “causal,” “pathogenic,” or “clinically significant” so an abnormal variant can include variants of uncertain significance (VOUS) and therefore may not give a clear etiology. Fragile X syndrome, PTEN Macrocephaly syndrome, and Rett syndrome (MEPC2 test) are three of the known single gene disorders commonly associated with ASD (Shen 2010, Persico 2013) for which there are specific genetic tests available. Table 2.1 shows the approximate diagnostic yields expected in the genetic evaluation of ASDs (Schaefer et al., 2013).

Table 2.1. Diagnostic yields of reported approaches and tests offered

Approach	**Test/s**	**Diagnostic Yield**
Microarray(CMA)	Array comparative hybridization (aCGH) and single-nucleotide polymorphism arrays	10%
Single gene tests	Fragile X syndrome	1-5%
	MECP2	4% of females
	PTEN	5% of those w/head circumferences >2.5 SDs that are tested
Chromosomal analysis	Karyotype	3%
Genetic evaluation	Other*	10%

*May include targeted gene testing, neuroimaging, metabolic and/or mitochondrial testing. (Schaefer et al., 2013)

Besides Fragile X, PTEN, and MECP2, there are a number of other single genes that are associated with ASD. ASDs are referred to as syndromic if the autistic diagnosis is part of the clinical presentation of a known genetic syndrome (Jiang et al., 2014). Table 2.2 is a current list of syndromic ASD genes that have been identified (Jiang et al., 2014). Testing for these genes is sometimes indicated after a genetic diagnostic evaluation reveals a suspicion of one of these syndromes (Schaefer et al., 2013). The most commonly cited are Fragile X syndrome (~1–2% of ASD cases), tuberous sclerosis (~1%), and Rett syndrome (~0.5%), with all of the ASD-related syndromes accounting for approximately 10% of the cases of ASD (Devlin & Scherer, 2012).

Table 2.2. Syndromic ASD genes

Chromosome Locations	Genes	Syndromes
2	MBD5	2q31 microdeletion syndrome
2	SOS1	Noonan syndrome
5	CDKL5	Rett-like syndrome
5	NSD1	Sotos syndrome
7	CHD7	CHARGE
7	CNTNAP2	Cortical dysplasia-focal epilepsy syndrome
7	RAF1	Noonan syndrome
7	BRAF	Noonan syndrome
9	TSC1	Tuberous sclerosis complex
12	CACNA1C	Timothy syndrome
12	PTPN11	PTEN associated disorder
12	KRAS	Noonan syndrome
14	PTEN	PTEN associated disorders
14	FOXG1	Angelman-like syndrome
15	UBE3A	Angelman syndrome
15	MAP2K1	Noonan syndrome
16	TSC2	Tuberous sclerosis complex
17	RA1	Smith-Magenis syndrome
18	TCF4	Pitt-Hopkins syndrome
22	SHANK3	Related to Phelan-McDermid syndrome
X	MECP2	Rett syndrome
X	FMR1	Fragile X syndrome
X	SLC6A8	Creatine transporter
X	SLC9A6	X-linked Angelman-like syndrome
X	HPRT1	Lesch-Nyhan syndrome
X	ARX	ARX related disorders
X	MED12	Lujan-Fryns syndrome

(Jiang et al., 2014)

The data in Table 2.1 suggest that, “the diagnostic yield increases with technological advances, targeted genetic testing, and the clinical expertise of examiners” (Bauer & Msall, 2011). With more testing, more genes associated with ASD are identified, as seen in Table 2.2, and the hope is that “children with ASD who have definitive etiologies may be able to access more specific resources, they may be spared long, emotionally and financially exhausting diagnostic journeys, and associated medical conditions and comorbidities can be managed proactively” (Lintas & Persico, 2009).

There are many arguments for and against routine genetic testing for ASD at this point in time. Clinical practice guidelines are the mechanisms for making consensus arguments based on a combination of reviews of clinical evidence, expert opinion and professional practice

standards (Institute of Medicine, 2011). The goal of clinical practice guidelines is to identify and promulgate best practices and serve as a framework for clinical decision making. Despite an abundance of published guidelines, the methodology by which the guidelines have been developed is often poorly defined and varies greatly within and among organizations (Rosenfeld, Shiffman, Robertson, & Department of Otolaryngology State University of New York Downstate, 2013).

In 2008, The U.S. Congress, through the *Medicare Improvements for Patients and Providers Act*, asked the Institute of Medicine (IOM) to undertake a study on the best methods used to develop clinical practice guidelines. The IOM then formed a committee to develop standards for organizations to follow when developing their own guidelines. The IOM expert committee established eight standards necessary to create rigorous, trustworthy clinical practice guidelines (Table 2.3).

Table 2.3. IOM Criteria for Trustworthy Clinical Practice Guidelines

1. Establish transparency
2. Manage conflict of interest
3. Indicate how group composition was determined
4. Be sure that the clinical practice guideline reflects a systematic review
5. Establish and describe the evidence used and for rating the strength of the evidence
6. Articulate the recommendations clearly
7. Subject the recommendation to external review by a defined panel
8. Develop the criteria and schedule for updating.

(Institute of Medicine, 2011)

This chapter examines guidelines from five different professional communities and the recommendations that they make with respect to genetic testing for ASD. To date there has not been a systematic review of the guidelines from these five professional organizations. This chapter will identify the similarities and differences among the guidelines and their recommendations in order to determine where there is and is not consensus in regard to genetic testing for individuals with ASD and to evaluate the guideline creation process.

Material and Methods

The first step of this analysis was to identify the current existing professional guidelines that address genetic testing for individuals with ASD. Two strategies were employed for the search: a literature search in PubMed and asking providers who I interviewed for my dissertation project about guidelines they are aware of and how they use them to guide their practice. For PubMed, I used the terms “genetic testing”, “autism”, and “guidelines”, which yielded 22 articles in December 2014. Of these, only two were guidelines from professional organizations on this topic and both were created by the American College of Medical Genetics and Genomics (ACMG): one from 2008 and an updated guideline in 2013. (Schaefer et al., 2008, 2013) I reviewed the remaining articles and found seven articles that included a discussion of the guidelines for genetic testing and ASD in the introduction or discussion portion of their manuscript (Bauer & Msall, 2011; Jeste & Geschwind, 2014; Lintas & Persico, 2009; McGrew et al., 2012; McLennan, Huculak, & Sheehan, 2008; Roesser, 2011; Shea, Newschaffer, Xie, Myers, & Mandell, 2014). This resulted in a list of nine guidelines.

I interviewed multiple providers including geneticists, neurologists, psychologists, psychiatrists, generalists and developmental pediatricians, and genetic counselors who are involved in the diagnosis and care of children with ASD (see chapters 3 and 4 for recruitment strategy). Providers interviewed mentioned eight guidelines that they followed in their clinical practice. Seven of these were already on the compiled list, adding the other guideline mentioned in these interview brought the total to ten possible guidelines for this investigation.

For the analysis, guidelines were excluded for four reasons: 1) if there was a more recent updated version of the guideline from the same professional organization; 2) if the guideline addressed genetic testing for developmental delay, but did not specifically mention ASD; 3) if the guideline was not from a professional organization and was not mentioned by any of the providers; and 4) if it was an adaptation of other guidelines already included in the study. The five guidelines that remained after these exclusion criteria were applied were issued from a

variety of stakeholder groups including: geneticists and genetic counselors (American College of Medical Genetics [ACMG], 2013), neurologists (American Academy of Neurology and Child Neurology Society [AAN], 2000), child psychologists and psychiatrists (American Academy of Child and Adolescent Psychiatry [AACAP], 2014), clinical cytogeneticists and laboratory professionals (International Standard Cytogenomic Array Consortium [ISCA], 2010), and pediatricians (American Academy of Pediatrics [AAP], 2007).

Review criteria

Each guideline was reviewed using a tool created by the Center for Genomics and Healthcare Equality (CGHE) at the University of Washington to evaluate: a) compliance of the guideline with IOM criteria for trustworthy guidelines; and b) the degree to which the guideline address implementation in resource-poor, medically underserved or rural environments. Two CGHE investigators created a list of questions based on the IOM recommendations, to which three questions were added addressing implementation in resource-poor, medically underserved and rural environments. The tool was reviewed by a third investigator for consistency with IOM criteria. Each question is scored “Yes” (guideline is compliant), “No” (guideline is not compliant), and “Partial” (guideline is partially compliant, meaning it contains some but not complete information). Applying the tool to the guidelines and generating the data allows comparisons of similarities and differences between the guidelines and the process used to generate them. The tool comprises five main categories described below along with details about rating.

I. *Preliminary components*. The first category in the tool has four subsections that are divided to detail the procedures established in the guideline development process. This category includes: a) Description of the deliberative process; b) Disclosure of funding; c) Description of the process for assigning author order and attribution; and d) Plans for training patient/consumer representative in evidence appraisal. The second section included categories to identify who was involved in the recommendation process and included: a) Methods expert(s), b)

Clinician(s), c) Patient/consumer or patient/consumer representative from target populations. The third subsection detailing conflicts of interest (COIs) and management strategies, including: a) description of the guideline development group (GDG) membership (name, affiliation, area(s) of expertise, and role(s) on GDG); b) statement defining what is being considered a COI (e.g., financial, intellectual, research, etc.); c) disclosure statement indicating any COI, d) management plan for any COI; e) statement of proportion of members with COI,;and f) statement of status of COI for chair(s). The fourth and final subsection for the preliminary components, detail evidence for evaluation strategies, was about identifying an evidence evaluation group or a process of evidence evaluation.

II. *Creation and justification of recommendations*. This category has two subsections. The first subsection, select and justify the evidence, includes: a) describe the methods to identify, select, grade, and assess the evidence; b) identify, select, and assess the evidence that will be considered; c) grade the quality of the evidence; an d) identify gaps in the evidence. The second subsection, make and justify the recommendations, includes: a) Clear definition of topic; b) Clear definition of scope of guidelines (area of practice; target population); and then c) looks at whether for each recommendation the guideline does the six things listed in Table 2.4.

III. *External review*. This category looks at the following questions: a) Has the guideline undergone external review? b) Are reviewer areas of expertise specified? c) Have reviewers included consumers/patients from target population? d) Have they maintained a written record of review and the rationale for responses to reviewer comments? e) Have they provided reasonable notice to public stakeholders of the comment period?

IV. *Updating plans*. This category includes specific plans and a date for when the guideline will be reviewed again and update.

V. *Dissemination and publication plans*. This category includes documenting a publication date, plans for disseminating to target audience, easy-to-read version for non-professionals, and publicly available funding source and guideline development process.

Scoring process

Each guideline was reviewed and given an overall score. These score ratings were calculated based on whether the section from the CPG tool had been fully addressed (Yes, value = 1) or not (No, value = 0). Some of the sections were scored as "partial" (value = 0.5) if there was some (but not complete) information in the guideline that addressed the criterion. I also coded the guidelines as "unclear" if it was not clear whether or not that component had been addressed. Instances when there was no information about external review processes were coded as "not stated." These latter two responses were scored with a value of 0 because there wasn't enough information to make a determination. As a measure of overall completeness, the scores across the 15 items were summed to compute a total score which is helpful for comparing across the guidelines.

Results

Content and timing of guidelines

Table 2.4 lists the five guidelines reviewed related to genetic testing for ASD, the sponsoring organization, the year published and the recommendations for genetic testing for ASD. Overall, there are three recommendations: 1) those recommending karyoptype and Fragile X testing only (AAN and AAP); 2) those recommending CMA as a first tier test (ISCA and ACMG); and 3) those allowing clinician discretion to determine which tests to order of those three (AACAP). The first two guidelines, AAN and AAP, both suggest karyotype and Fragile X testing for ASD individuals, with the only difference being that the AAN guidelines list three criteria for ordering the test, while the AAP suggests these tests for all individuals plus additional evaluation in the presence of mental retardation or global developmental delay. Neither of these guidelines suggest CMA as a testing option for ASD.

Table 2.4. Current Guidelines around Genetic Testing for ASD

Guideline	Sponsoring Organization	Year	Recommendation
Practice parameter: Screening and diagnosis of autism	American Academy of Neurology (AAN) and Child Neurology Society (CNS)	2000	•High resolution chromosome analysis (karyotype) and Fragile X testing performed in the presence of: -mental retardation (or if MR cannot be excluded) -family history of Fragile X or undiagnosed MR -dysmorphic features
Identification and Evaluation of Children With ASD	American Academy of Pediatrics (AAP)	2007	•High-resolution chromosome analysis (karyotpype) and Fragile X testing •Etiologic workup of children with both ASD and Global Developmental Delay/MR
Consensus Statement: Chromosomal Microarray is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disability or Cognitive Anomalies	International Standard Cytogenomic Array (ISCA) Consortium	2010	• CMA as the first-tier genetic test for patients with: -unexplained DD/ID, ASD, or multiple congenital anomalies
Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions	American College of Medical Genetics and Genomics (ACMG)	2013	• Genetic evaluation offered to every person with ASD • CMA is recommended as a first tier test over karyotyping • Fragile X syndrome, MECP2, and PTEN testing for all and: -Fragile X testing in females with ASDs when: -a phenotype compatible with Fragile X -a family history positive for X linked neurodevelopmental disorders -premature ovarian insufficiency, ataxia, or tremors in close relatives -MECP2 testing of males with autism with drooling, recurrent respiratory infections, hypotonic facies -PTEN testing for head circumference > 98% • Chromosomal analysis when third-party payers will not cover CMA testing • X-linked intellectual disability gene panel when family history consistent with X linked inheritance and patient has cognitive impairments • Testing for mitochondrial disorders when supporting symptoms or laboratory abnormalities present • Other genetic tests if etiologic evaluation indicates
Practice Parameter for the Assessment & Treatment of Children and Adolescents with ASD	American Academy of Child and Adolescent Psychiatry (AACAP)	2014	• Medical exam that includes genetic testing, which may include -G-banded karyotyping -Fragile X testing -Chromosomal microarray

The ISCA guidelines were the first to suggest CMA as a first tier test in 2010. This was followed by the ACMG issuing an updated set of guidelines in 2013 recommending genetic testing for all patients with ASD that some providers interpret as defining the standard of care. The ACMG guidelines are the most extensive guidelines to date with the most recommendations specific to genetic testing for ASD. According to the ACMG Guidelines:

> The rationale for a genetic evaluation is based on the goal of identifying a unifying diagnosis for a patient. A definitive diagnosis facilitates acquisition of needed services and is helpful in many other ways for the family. Many families are greatly empowered by knowing the

> underlying cause of a relative's disorder. Depending on the etiology, associated medical risks may be identified that lead to screening and the potential for prevention of morbidity. Specific recurrence-risk counseling—beyond general multi- factorial information—can be provided, and targeted testing of at-risk family members can be offered. Finally, an established diagnosis will help in eliminating unnecessary diagnostic tests. In light of these expected benefits, a genetic evaluation should be offered to every person with an ASD (or his or her family). (Schaefer and Mendelsohn, 2013, p.400)

The ACMG guidelines not only go into detail about the recommendations (as seen in Table 2.4), but also the proposed benefits and purpose of testing. The AACAP guidelines are the only ones written after ACMG and although they mention CMA as an option, the recommendation is not specific and leaves the decision-making up to the provider's discretion.

Guideline review

Table 2.5 lists the five categories used in the CPG tool to evaluate the guidelines and the process of guideline development. Table 2.5 also includes the evaluation of how well each of these categories met the IOM and CPG tool goals based on the scoring criteria described in the methods section. In general, the guidelines made clear recommendations, by specifying the definition of the topic and scope of the guidelines (i.e. area of practice, target population). All the guidelines provided a justification for the recommendations, with some providing more evidence than others in support of their reasoning. However, none of the guidelines met all of the criteria of the guideline development process and the five categories from the CPG tool. The AAP and the ACMG scored the lowest (5.5) because there were only 3 criteria that they addressed completely: making clear recommendations; their justification for the recommendations; and wording these recommendations so compliance can be measured. The other three guidelines, AAN, ISCA, and AACAP, all scored considerably higher, 9.5, 9.5, and 10 respectively. These guidelines scored higher because they all partially fulfilled the preliminary component criteria, evaluated the strength of the recommendation, and summarized relevant evidence and gaps in recommendations.

Table 2.5. Guideline Review using the CPG Tool

Criteria / Guidelines (year)	AAN (2000)	AAP (2007)	ISCA (2010)	ACMG (2013)	AACAP (2014)
I. Preliminary components					
Detail the procedures established to direct the guideline development process	Partial	No	Partial	No	Partial
Detail the composition of guideline development group (GDG)	Unclear	Unclear	Partial	No	Partial
Detail conflicts of interest (COIs) and management strategies	Partial	No	Partial	No	Partial
Detail evidence evaluation strategies	Yes	No	Partial	No	Yes
II. Creation and justification of recommendations					
Select and justify the evidence	Yes	Partial	Yes	Partial	Partial
Make clear recommendations	Yes	Yes	Yes	Yes	Yes
For each recommendation does the guideline**:**					
1. Provide a justification for the recommendation	Yes	Yes	Yes	Yes	Yes
2. Evaluate the strength of the recommendation	Yes	No	Yes	No	Yes
3. Summarize the relevant evidence and gaps	Yes	Partial	Yes	Partial	Yes
4. Describe whether or not cost-effectiveness was considered and why	Partial	Partial	Yes	Partial	No
5. Discuss the incorporation of patient values	Partial	Partial	No	Partial	Yes
6. Word so compliance can be measured	Yes	Yes	Yes	Yes	Partial
III. External Review	Not Stated	Not Stated	Not Stated	Not Stated	Yes
IV. Updating Plans	No	No	No	No	No
V. Dissemination and publication plans	Partial	Partial	Partial	Partial	Partial
Total Score (maximum 1 point per item = 15)	**9.5**	**5.5**	**9.5**	**5.5**	**10**

AAN: While no guideline met all of the criteria, there are some that were more complete then others. The AAN guideline details the guideline development process and their thorough process of evaluating the evidence. Additionally, they are the only guideline that may have fulfilled the criteria of having a patient/consumer representative on their guideline development group (GDG), although it was not completely clear due to the lack of detailed data on each members' role. They are also the only guideline that includes a statement defining what is being considered a conflict of interest (COI). They indicate that a COI is, "Ownership, equity position, stock options, patent-licensing arrangements, consulting fees, or honoraria associated with this publication or its products" (Filipek et al., 2000). There is also a discussion of cost effectiveness and its importance, but nothing specifically about the cost-effectiveness of genetic testing for ASD. This guideline was written in 2000 so it is now out of date and there were no stated plans to update.

AAP: The AAP guideline fails to meet the IOM standards in many categories, but stands out in two main ways. First, it is the only guideline that addresses the evidence gaps in

answering the question, “should genetic testing be offered to individuals with ASD in a clinical setting?” Their recommendations are based on the fact that there is not enough evidence to support making a recommendation for offering CMA to every individual in a clinical setting. They briefly discuss ordering the test (as opposed to ordering no tests) in terms of cost effectiveness and not just in comparison to other tests, “the availability of technology, the need for and feasibility of sedation, managed care cost/benefit guidelines, and physician motivation each may play a role" (Johnson, Myers, & American Academy of Pediatrics Council on Children With Disabilities, 2007). While this is the only guideline that explores cost-effectiveness in terms of conducting the test versus abstaining from any testing, it is still a very brief discussion of cost-effectiveness.

ISCA: The ISCA Consortium “guideline” is actually written as a consensus statement instead of a guideline. However, it scored higher than the ACMG or the AAP guidelines on the tool, and is more detailed in the explanation of the deliberative process and in defining the roles of the group. This guideline involved method experts in the process; seventeen clinical lab geneticists and nine genome scientists and bioinformaticians were part of the guideline development group. However, this also meant a large number of the GDG had conflicts of interest, which they thoroughly noted, but did not develop a management plan for. They mention cost-effectiveness in the statement, “offering CMA as a first tier test is more cost effective then G-banded karyotyping and FISH analysis and several other examples” (Miller et al., 2010). This is an improvement over some of the other guidelines that do not mention cost-effectiveness at all, but they still do not really discuss a true cost effectiveness model since they are only comparing it to other tests. Finally, this consensus statement gives an algorithm that serves as a useful tool for clinicians and an easy way to measure compliance.

ACMG: The ACMG guidelines are dedicated to focusing specifically on genetic testing for ASD and have the most recommendations for clinicians to follow. They are very detailed in the recommendations that they make, have justifications for those recommendations and word

their recommendations so that compliance can be measured. However, in every other category assessed by the tool, they are lacking information. The ACMG guidelines are not transparent in that they do not discuss the guideline development process, the group that developed the guidelines, or the evaluation strategies. They also fail to state whether an external review was done or if they have plans to update their guideline. The original guideline which addressed this issue was written in 2008 and then revised in 2013; the revised version was scored in this analysis.

AACAP: The AACAP was most thorough in explaining the guideline development process; however, the published version provided only partial detail, with the reader referred to the AACAP website for further information (which I did). The AACAP almost entirely meets the requirement of detailing the composition of the GDG (although the roles on GDG is not completely explained), but it does identify how each person was involved and there were a large number of people participating in this process. The authors also try to thoroughly list all conflicts of interest for each member and they have the most extensive evidence evaluation process, describing methods used to identify, select, grade, and assess the evidence. The areas where the AACAP guidelines are lacking are that they fail to identify gaps in evidence and they do not word their recommendation so that compliance can be measured. This stems from the fact that the specific recommendation regarding genetic testing for ASD is actually under the main recommendation stating, “Clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD” (Volkmar et al., 2014), so the genetic testing portion is worded as a suggestion of something that might be part of that assessment based on the clinicians’ decision.

Discussion

Content and timing of guidelines

Given the lack of evidence and definitive answers, coupled with strong support for the benefits of testing from many providers, different specialties have taken separate stances in their professional guidelines on what tests should be offered and in what circumstances. The literature demonstrates that few patients who receive genetic tests for ASD obtain clinically useful information, based on the low to modest rates of detection of associated syndromes or risk variants, different perceptions of clinical utility and the value of this information, and uncertainty of how to translate the knowledge to clinical interventions. Although the definitive answers that many had hoped for with genetic testing for ASD do not exist, many clinicians, especially those with a vested interest in genetic evaluation and testing, are pushing to increase genetic testing for children with ASD in order to "raise the clinical management of these patients and their families beyond current standards" (Lintas & Persico, 2009). However, there is conflicting evidence that raising the standard would produce a benefit that would apply to families.

Lack of definitive evidence seems to be the cause of differences in judgments about the significance of genetic testing for ASD. However, there may be other distinct reasons for these differences. There is a wide timespan in the dates when these guidelines were written (2000-2014), which is important to consider in terms of their processes and quality, especially given the fast-paced changes taking place in regard to genetic testing technology. As Jeste and Geschwind (2014) explain, "The evolution in recommendations for clinical genetic testing reflects the scientific advances made in our understanding of genetic etiologies of ASD." Thus we see here that in the first two sets of guidelines, AAN (2000) and AAP (2007), the recommendation is for karyotype and Fragile X testing only. CMA and specifically aCGH was first developed in 1992, but early applications were directed at the detection of genetic abnormalities in cancer (Oostlander et al., 2004) so CMA was not clinically available when the

AAN guidelines were written. By 2004, discussions in the literature began proposing other applications of CMA in human genetics (Oostlander et al., 2004). In later guidelines (ISCA [2010] and ACMG [2013]), CMA is recommended as a first tier test. The AACAP (2014) also mentions CMA as a testing option to consider. Many have made the argument that there is disagreement among professional organizations about what test is recommended, but it is unclear if it is disagreement or if the AAN and AAP are just outdated guidelines, and that they were being conservative with respect to the technologies available because of the process and delay in their issuance. Some providers feel that AAP is in agreement with ACMG in regard to genetic testing and are supportive of CMA as a first tier test based on the joint publication from AAP and ACMG about predictive genetic testing of children (Committee on Bioethics et al., 2013). In addition, there have been publications in the AAP Journal that support CMA as a first tier test (Grody, Thompson, & Hudgins, 2013; Shen et al., 2010). However, as it stands the AAP guidelines from 2007 are the only guidelines that make a specific recommendation about genetic testing and ASD and therefore are the only guidelines that can be evaluated. If the AAP and/or the AAN wants or thinks that different recommendations should be implemented by their providers, they are currently not taking that stance and providing their clinicians with the guidelines to support that.

Guideline review

The CPG tool and the IOM guidelines evaluate compliance with standards set by the IOM and the result from this review is that the norm is far from that standard at this point. In fact, none of the guidelines are meeting all of the IOM criteria. Areas that are odds with the criteria for trustworthy practice as defined by the IOM include updating plans, detailing components of the process, considering cost effectiveness and patient values. Transparency and external review are also lacking. The guidelines are inconsistent in how they meet the criteria with no clear pattern on how or why certain components are or are not being addressed. In contrast, all five guidelines are consistently clear in their recommendations and justifications for those

recommendations. In addition, all of the guidelines at least partially addressed the evidence gaps surrounding genetic testing for ASD so they are all acknowledging the lack of definitive evidence to some degree.

Although many providers described the AAP and AAN as outdated, with no plans to update, they were still two of the three guidelines most cited in the literature and referenced by the providers interviewed, with ACMG being the other. As stated in the introduction, the goal of clinical practice guidelines is to serve as a framework for clinical decision making. Therefore it seems logical that the most important criteria of the guideline for the practicing clinician is that there are detailed recommendations with justifications for those recommendations, worded so that compliance can be measured. These areas of the IOM criteria were completely met by the AAP, AAN and ACMG.

Limitations

There are limitations with this analysis of the guidelines addressing genetic testing and ASD. First, the CPG tool was created to help evaluate guidelines and the development process. However, this is a new tool and the point system was developed as a way of organizing the information for discussion purposes in this paper. While the tool is useful for determining if the IOM standards are being met, a limitation and recommendation for future use is that different criterion be given a point value that is consistent with importance or value to the providers that will be utilizing the guidelines.

Another limitation of this study is that the IOM criteria were published in 2011. All but two of these guidelines were published prior to the release of the IOM recommendations. Therefore, it is a difficult to evaluate a guideline's adherence to criteria that were not established at the time they were drafted.

Conclusions

This guideline review demonstrates that the guidelines focusing on genetic testing and ASD differ substantively in their recommendations, and that no guideline meets all the CPG tool criteria for trustworthiness as adapted from the IOM standards. It is not clear if this variety is due to a difference of opinion by providers and clinical specialties on what the standard of care should be, or if the difference is simply due to the variable publication timing of each specialty's guidelines. Because of the lack of definitive evidence about the clinical utility of genetic testing for ASD, the most logical conclusion is that it is not merely the year of publication, but the differences in values and judgments by the variety of medical providers involved in ASD care that results in the lack of an established standard of care.

Although the AACAP guideline comes the closest to meeting the IOM standards, genetic testing for ASD is only a small portion of this document and therefore the recommendation is not well defined, comprehensive, nor worded so compliance can be measured. While some genetics professionals and other healthcare providers I interviewed would like the ACMG guideline to be seen as the standard of care because it is the most comprehensive in terms of recommendations for genetic testing in ASD, it fails to meet many of the criteria outlined in the IOM standards. If all clinicians involved in the diagnosis, evaluation and care of individuals with ASD could be included in the guideline development group, as well as methods experts and patient/consumer representatives, it would provide a chance to educate individuals from different backgrounds and help practitioners from different disciplinary perspectives to understand all the advantages and limitations of different forms of testing in different populations. A process that involves all of these players might create a more transparent course of development with a clear explanation of the methods and comprehensive evaluation of evidence. Adding an external review process with a plan to update the guidelines in the future would meet all the IOM standards. Although these may seem like lofty goals, in a case like genetic testing for ASD, where there are multiple specialties involved in diagnosis, testing and

treatment, there needs to be movement towards collaboration and consensus among these providers in order to work towards a standard of care in clinical practice that maximizes benefits and minimizes harms. Working cooperatively to clarify and identify areas of agreement and areas of disagreement may help to define potential points of consensus and limit the proliferation of divergent guidelines. This in turn could result in more cost effective decisions about testing and more consistent insurance coverage.

Chapter 3: The Pathway from Autism Spectrum Disorder (ASD) Diagnosis to Genetic Testing

Introduction

Autism spectrum disorder (ASD) represents a heterogeneous group of conditions that present a substantial challenge to diagnosis and treatment (Jeste & Geschwind, 2014). "Currently, the diagnostic process typically includes a clinical developmental history, assessments of speech, language and intellectual abilities, and of educational or vocational attainment" (Walsh, Elsabbagh, Bolton, & Singh, 2011). This comprehensive evaluation, conducted by multidisciplinary expert clinical teams, is viewed as necessary not only to establish or to confirm a clinical diagnosis of ASD but also to inform and tailor the service provisions that are required for different individuals. However, these so-called 'gold-standard diagnostic tools' have not been widely adopted in community services because they are laborious, expensive and resource intensive (Walsh et al., 2011). Diagnosis of ASD is based on clinical manifestations and cognitive and developmental assessment using standardized measures. In this context, the purpose of genetic testing in children with ASD is to identify a genetic etiology (Agency for Healthcare Research and Quality, 2014). Defining the genetic etiology of ASD is distinct from genetic testing for other conditions in that there is strong evidence for complex genetic factors comprised of different forms of genetic variation (or architecture) in the etiology of ASD (Devlin & Scherer, 2012). Current research indicates that a very small population-attributable risk of ASD is explained by known genetic causes: about 5–15% of individuals with ASD have an identifiable genetic etiology corresponding to known chromosomal rearrangements or single gene disorders; in addition, rare *de novo* or inherited copy number variations (CNVs) are observed in 5–10% of idiopathic ASD cases (Devlin & Scherer, 2012). For these reasons, and in part because there is no standardized protocol of treatment to follow once a diagnosis of ASD has been made, offering genetic testing to individuals who have been diagnosed with ASD is a complex issue.

Very few studies have focused on the parent experience and interest in genetic testing for individuals with ASD, thus the benefits and struggles that families encounter during the genetic testing process are relatively unknown. Even without strong evidence that finding an etiology for ASD has a positive impact on families, scientific journals make claims such as, “an early and efficient diagnosis by CMA [Chromosome Microarray] reduces the cost and stress of a long and fruitless workup, improves anticipatory guidance, and empowers the family with accurate genetic counseling” (Henderson et al., 2014).

Genetic testing for ASD is complicated by the variability in providers, guidelines, tests, insurance, and parent motivations involved in ASD. An ASD diagnosis can be made by a variety of providers and there are competing guidelines regarding genetic testing for ASD that vary by specialty: chapter two focused in depth on the five guidelines referenced most in the literature and by the providers in this study. Guidelines from the American College of Medical Genetics and Genomics (ACMG) focus exclusively on genetic testing for ASD and strongly support genetic testing (specifically CMA) for ASD at this time. However, offering CMA for individuals with ASD it is not consistently implemented in the clinical setting. In a 2012 qualitative study, the majority of families had never heard about genetic testing for ASD despite the availability of testing in the clinical setting for more than a decade (Chen et al., 2013). This finding suggests that many providers are not discussing genetic testing with their patients. In fact, a study by Amiet, Couchon, Carr, Carayol, & Cohen (2014) stated that 60% of parents from the US reported that no genetic testing was recommended for their children with ASD. When genetic testing is discussed with families there is also inconsistency among providers about what testing to offer due to the variety of tests available in the context of genetic testing for ASD. Although CMA is the test recommended by ACMG as the first tier test, some clinicians order karyotypes and Fragile X testing (to exclude Fragile X as the diagnosis) first, and CMA is done depending on available resources (Bauer & Msall, 2011). This chapter focuses on characterizing the variable pathways to genetic testing and the challenges families and providers face.

Material and Methods

Study design and participants

I conducted a qualitative study with 15 health care providers and 14 parents of children with ASD to elicit their perspectives regarding genetic testing for ASD. Parents with at least one child diagnosed with ASD were eligible to participate. Parents were recruited in two ways. First, parents of children with scheduled appointments at the Center on Human Development and Disability (CHDD) Autism Genetics Clinic at the University of Washington were mailed letters in advance of their appointment. I approached these families at their initial genetics clinic visit and gave them additional information about the study, answered any questions and enrolled six interested parents (Families 1-6 in Table 3.2). Second, I recruited eight parents (Families 7-14 in Table 3.2) through two listservs that serve as discussion forums for families living with ASD. One listserv is called Families for Effective Autism Treatment (FEAT) of Washington, and is a non-profit organization founded by families for families who have children with ASD. I contacted the FEAT Family Resource Coordinator and asked her to post a request for participants to their Yahoo group. I also posted the same request for participants through a parent who was part of a group at Microsoft called the "Autism Information Exchange" for parents who had children with ASD. For both listservs, interested parents were invited to contact me via email if they were interested in the study and willing to do a phone interview. I do not know how many individuals are members or what the average readership is for either of these listservs, therefore it is impossible to calculate a response rate.

Multiple types of providers are involved in the diagnosis and care of children with ASD including geneticists, neurologists, psychologists, psychiatrists, generalist and developmental pediatricians, and genetic counselors. A snowball sampling technique was used to contact all of these provider types, beginning with names proposed by Dr. Holly Tabor, an associate professor in bioethics with expertise in ASD, who works collaboratively with providers involved with diagnosing ASD. She provided me with an initial list of local geneticists, psychologists, and

pediatricians involved in ASD care. At the end of my interviews with these providers, I asked if they had recommendations of other providers who I should include. I continued recruitment until I had a diverse group of perspectives and no new names were being mentioned. I contacted a total of 23 providers (4 psychologists/psychiatrists, 5 pediatricians/ developmental pediatricians, 4 geneticists, 4 genetic counselors, and 6 neurologists) of which 15 (4 psychologists/psychiatrists, 4 pediatricians/developmental pediatricians, 3 geneticists, 2 genetic counselors, and 2 neurologists) agreed to be interviewed. This study was approved by the University of Washington Institutional Review Board and all participants signed consent forms.

Data collection

For the six families recruited through the UW clinic, I obtained written informed consent and then observed the conversation with their clinicians during their initial appointment at the UW genetics clinic with the goal of learning how genetic testing options were discussed. Each of these six sessions was recorded and transcribed and contact information was obtained for follow-up. I then contacted these six parents for a follow up interview, of whom three agreed to participate (Families 2, 3, and 5 in Table 3.2). With the addition of the eight parents who were recruited through the listservs, I was able to conduct interviews with 11 parents in total. Fifteen of the 23 providers I contacted agreed to be interviewed. All of these providers are involved with the ASD diagnosis and/or genetic testing and represented the following clinical specialties: 3 geneticists, 2 neurologists, 4 psychologists/psychiatrists, 4 pediatricians/developmental pediatricians, and 2 genetic counselors. Interviews were conducted face-to-face (2 parents, 9 providers) or by phone (9 parents, 6 providers). All interviews were recorded and transcribed.

Parents were asked about their experience with the genetic evaluation process for their child, their motivations for seeking genetic testing, their decision-making surrounding genetic testing, and their overall thoughts and feelings regarding genetic testing. The average length of interview time for parents was 21 minutes (range 6-44 minutes). Providers were asked questions about the genetic testing process at their facility, their own personal thoughts and

practices regarding genetic testing, the potential effects of genetic testing, communicating with families, and returning results. The average length of interview time for providers was 40 minutes (range 16-66 minutes).

To assess the parent experience of finding a provider to diagnose a child who may have ASD, I conducted an internet search using Google to identify diagnosing providers in the Puget Sound area. The first link available was for *Autism Speaks* so I used this as the main source. Under the *Autism Speaks* resources page there was a map and a hyperlink under WA with a list of resources. One of the choices under the list of resources is "Where to get an autism diagnosis." Using this as a starting point to identify ASD services in the Seattle area, I systematically went to each hyperlink of listed providers, reading through their website about what is offered, and calling if I had any questions or for clarification about whether diagnosis was a service that was provided. A few centers were added to the list after the interviews were conducted because a family or provider mentioned a center where a child was diagnosed and through internet search and phone calls I confirmed that the center offered ASD diagnosis as a service.

Data analysis

I employed content analysis (Hsieh & Shannon, 2005) for the interview data and developed a coding scheme with the assistance of a second coder. Both coders independently coded the first three provider interviews and the first four family interviews. The coders met to compare reoccurring themes across the transcripts, discuss any divergent codes and review transcripts to reach an agreement about the meaning and application of codes. Once the coding scheme was established, I completed coding all transcripts using Dedoose software. The coded data were then analyzed to identify emerging themes and interpret patterns. In this chapter I report on the interview findings related to ordering and accessing genetic testing. Additional data from this analysis will be reported in Chapter 4.

Results

The individuals interviewed in this study described experiencing three steps to genetic testing for ASD. The first step is the diagnosis of ASD. Once a diagnosis is made, the second step involves offering genetic testing (or not) to find a possible cause. In the third and final step, the decision has to be made to accept and complete the testing. While this may seem like a simple process, parents and providers described a number of complicating factors and the path to testing is usually not straight forward or necessarily the same for any two families.

Step 1: Initial diagnosis of ASD

A diagnosis of ASD can be made in several diagnostic centers in Washington by several different types of providers, including psychologists, psychiatrists, developmental pediatricians, neurologists, and pediatricians. Table 3.1 lists the 14 diagnostic centers in the greater Seattle/Tacoma area that offer the majority of diagnostic services for ASD in Washington State. According to the providers interviewed, a large number of the ASD diagnoses in Washington are made at the larger tertiary centers. Two representative comments were: “I think that in my experience there are very few non-autism program centers that are willing to commit to a diagnosis” (Provider #4) and “Most pediatricians aren’t going to make a diagnosis of autism. Most pediatricians, the vast majority refer out to a tertiary center” (Provider #3). Even though the majority of ASD diagnoses are made at a few centers, these centers employ different types of providers who work either together as part of a multidisciplinary team, or as individual providers to make the diagnosis.

Table 3.1. Diagnosis Centers in Greater Seattle Area

Diagnosis Centers, Location	Providers (n)
Seattle Children's Autism Center, Seattle	Multidisciplinary team-Neurologists (3), Developmental Pediatricians (4), Psychiatrist (5), Psychologist (14), Nurse Practitioner (8), Nurses and other therapists (14).
UW Autism Center-CHDD, Seattle	Diagnostic Evaluation by Psychologists (3), Medical Evaluation by Developmental Pediatrician (1)
Mary Bridge Neurodevelopmental Program, Tacoma	Multidisciplinary team: Psychologists & Developmental Pediatricians *
Mary Bridge Pediatric Psychology, Tacoma	Neuropsychologist
Sendan Services, Bellingham	Psychiatrist, Psychologist, and therapists (2)
Neurodevelopmental Program at Seattle Children's, Seattle	Multidisciplinary team-Neurodevelopmental Physicians(6), Neurologist (1), Nurses (11), Social worker (1), Dietitian (1), and Physical (4) and Occupational Therapists (3)
Lakeside Center for Autism, Lakeside	Team led by Psychologist*
Woodinville Psychological Associates, Woodinville	Psychiatrist
Ryther Autism Diagnostics and Assessments, Seattle	Psychologists*
The Center for Family and Lifespan Development, Federal Way	Psychologists (2)
Madigan Medical Center, Tacoma	Developmental Pediatrician, Psychologist and Social Worker
Boyer Children's Clinic, Seattle	Team led by a Developmental Pediatrician*

*More specific information about providers was not available on website or by phone

Some families' journey ends after step 1

For some of the families (and for 3 families in this study) the pathway to genetic testing ends after the ASD diagnosis is made. There are a number of recommendations that may or may not be given to the families of individuals with an ASD diagnosis. These recommendations can include medical recommendations, educational recommendations, therapy recommendations, and community recommendations. Genetic testing is just one possibility in the category of medical recommendations that can be offered to families and this may be discussed at the same appointment when they are discussing seeing additional specialist, having other testing done (i.e. hearing test) or other clinical interventions. As one provider explained:

> In autism we can look for diagnostic evaluation, you come on in and say, great we got a diagnosis of autism and what you end up with is a list of 15 things you could try this, you could do this, try this, try this, here you go. And it's a very different process for families and

> that kind of makes me sad a little bit in terms of we're not as clear because we don't know how to indicate which treatment we think is going to be best for a particular kid. (Provider #3)

Some families talked about all the choices they were given about different therapies to try, different specialists to see or different tests to have done, but did not mention genetic testing as an option. Other parents felt that they were given very little direction about the next steps to take after a diagnosis of ASD was made. One parent said we were "just given that big three ring binder and some book recommendations and told to find an ABA [Applied Behavior Analysis] provider pretty much" (Parent #10). Genetic testing will not occur if the provider does not offer genetic testing or refer to another provider who will make that recommendation. Three families in this study were never offered genetic testing or discussed it with their providers.

Step 2: Offering genetic testing

The second step in the pathway is offering genetic testing to families. This step is complicated by deciding what type of tests to offer, under what circumstances to offer them, and who decides. Table 3.2 below outlines the pathway to testing taken by the 14 families involved in this study. For some families, the path seems direct at first glance. For example, family #1 first saw a neurologist who referred them to a geneticist who then ordered genetic testing. However, this was done when the individual was 20 years old, so it may not be as simple as it seems. I was not able to learn more about this family's path as they dropped out of the study after the initial clinic visit. For those I did interview, the path to testing often took many turns, and families may be offered genetic testing multiple times in their lives. For some families this is because they have adult children who may or may not have been offered testing when they were first diagnosed, but are now being offered testing again because of evolving technology. However, even families who are newly diagnosed often are not offered genetic testing at diagnosis, but are offered testing later or are offered testing by several different providers. If families were offered testing at different times, the first offer is labeled "1" and the second "2" in Table 3.2, as in the case of family #2. Their child was diagnosed many years prior to the

appointment in the ASD clinic. After diagnosis, they were referred to and saw many specialists, one of which was a genetic counselor who offered and ordered a karyotype. Now, years later, they were again in a situation where their child was struggling so they sought recommendations from a variety of specialists. Their neurologist referred them to a geneticist who offered and ordered CMA testing, fragile X testing and testing for Prader-Willi syndrome.

The variability in who is diagnosing ASD, what is recommended to families, and when it is recommended complicates the pathway to testing. When one adds the variability of genetic testing to the equation it becomes difficult to determine any pattern or commonalities in practice or path. Different providers will order/recommend different tests based on their judgments about test utility (potentially influenced by associated findings in the patient such as dysmorphic features, history of seizures, family history of ASD, etc.), which guidelines they are following, family motivations, and insurance coverage.

Who is offering genetic testing

According to both the families and providers interviewed in this study, families may be offered genetic testing by the provider who diagnosed them or they may be referred to another specialist who may or may not offer testing. However, many providers do not order or recommend genetic testing, either because they are unfamiliar with the tests that are available or because they do not see the utility of testing. Those providers who cannot order the test themselves but believe that testing would be beneficial (e.g. psychologists), must refer to another provider who can order the test. Medical geneticists and developmental pediatricians are the providers who order the test most often, but as shown in Table 3.2, there are many different pathways to testing and to the providers who ordered their test.

Providers often choose to refer to a medical genetics clinic instead of recommending or ordering the tests themselves. This was the case in the first six families listed in Table 3.2. All six families had been referred to the same geneticist and all of them were offered genetic testing. Based on my interviews with providers, some providers choose to refer to a genetics

clinic in all circumstances, but some only refer in certain circumstances. This choice is based on a number of factors such as how comfortable providers are with respect to ordering and interpreting the tests themselves, how accessible the genetics clinics are to the family, and the wait time to see a geneticist. Providers often assess the situation and then make a decision. As one developmental pediatrician explained:

> There's a couple of different strategies – I can't say that we have a consistent methodology. If I see a child with a number of risk factors, dysmorphic features, unusual head size, unusual family history, my preference would be to send that child to a geneticist to determine the most cost efficient way to do the genetic evaluation. (Provider #4)

Among the different types of providers I interviewed, the developmental pediatricians seemed to feel the most comfortable ordering the testing themselves. As one of these providers stated:

> I mean a geneticist doesn't need to see the ones that are negative. So I sometimes think that's kind of where I feel like I'm doing everybody and I'm doing the system a service by knowing enough about the recommendations, ordering the test and if it's negative it's done. (Provider #12)

However, not all developmental pediatricians offer testing to every family with a child who has ASD or refer to geneticists for testing. Based on the family interview data, developmental pediatricians were involved in the care of five of the families, but only three of those providers discussed genetic testing with the families. Two families (#6 and #11) were diagnosed by a developmental pediatrician but were never offered genetic testing. Family #8 discussed it with a developmental pediatrician after the initial diagnosis, but only after the mother asked about testing; it was only after her request that the testing was ordered because she was very concerned about recurrence risk. Family #5 had discussed genetic testing with a developmental pediatrician when their child was 10 years old, which was years after their initial diagnosis, at which time they had chromosomal testing. In a more recent follow-up appointment with a nurse practitioner 10 years after the karyotype, they were referred to a geneticist for additional genetic testing. Family #14 discussed genetic testing with their developmental pediatrician when the child was first diagnosed at age six and decided not to have the testing at that time. However, a few years later, they discussed it again with a neurologist and at that time

the family decided to have testing because the child was going to be sedated for other tests and the family thought that this would be a good time to draw blood and do the genetic tests.

Table 3.2. Pathway to Genetic Testing

Family	Offered testing	Had testing	Patient's age	Pathway from initial diagnosis (ID) to testing (T) offered	Who ordered genetic test	What test was offered
1[a]	Yes	Yes	20	Neurologist ⇨ Geneticisit (T)	Geneticist	CMA & Fragile X
2	Yes	Yes	35	1.Autism Clinic (ID) ⇨ Genetic Counselor (T) 2. Neurologist ⇨ Geneticist (T)	Geneticist	1. Karyotype 2.CMA, Fragile X, & a test for Prader-Willi Syndrome
3	Yes	No[c]	22	1.Pediatrician(ID) ⇨ ? (T) 2.Neurologist ⇨ Geneticist (T)	Geneticist	1. Karyotype 2. CMA
4[a]	Yes	No	26	1.Autism Clinic (ID) 2.Neurologist ⇨ Geneticist (T)	Never ordered	CMA & Fragile X
5	Yes	Yes	10 20	1.Pyschologist (ID) ⇨ Developmental Pediatrician(T) 2. Nurse Practitioner ⇨ Geneticist(T)	Geneticist	1. Karyotype 2. CMA & Fragile X
6[a]	Yes	Yes	20	1. Pediatrician ⇨ Developmental Pediatrician (ID) 2. Neurologist ⇨ Geneticist (T)	Geneticist	1. Karyotype and Fragile X 2. CMA
7	Yes	Yes[b,c]	3	Nurse Practitioner (ID) ⇨ Genetic Counselor (T) ⇨ Researcher(T)	Research study[b]	Fragile X & 2 others[d]
8	No	Yes	2	Developmental Pediatrician (ID)(Parent came in requesting test)	Developmental Pediatrician	Fragile X first (NEG) then FISH array
9	Yes	Yes	4	1. Psychologist (ID) ⇨ Geneticist(T) 2. Naturopath (T)	Naturopath	MTHFR & 23andme
10	No	No	8	Psychologist (ID)	Never ordered	N/A
11	No	No	6 (ID)	Developmental Pediatrician (ID)	Never ordered	N/A
12	Yes	No[c]	6	1. Pediatrician(ID) 2. Pediatrician(T)	Never ordered	Genetic testing[d]
13	No	No	3 (ID) 15	Pediatrician (ID)	Never ordered	N/A
14	Yes	Yes	6 (ID) 10	1. Psychologist(ID) ⇨ Developmental Pediatrician(T) 2. Neurologist (T)	Neurologist	CMA & Fragile X

[a] Parents dropped out of the study
[b] Parents did not receive results
[c] Insurance would not cover the cost of the test
[d] Parents were not sure what the tests were

Clinical practice of selecting ASD patients for testing based on clinical criteria

From the provider interviews, it appears that many refer ASD patients for genetic testing on a case-by-case basis, especially in the presence of certain clinical triggers. Triggers that providers mentioned included dysmorphic features, multiple systems affected, severe developmental delay, or multiple family members being affected. As one developmental pediatrician explained:

> If the child is intellectually impaired, if the child comes from a family with genetic disorders of intellectual impairments, or if a child has unusual physical findings such as a dysmorphic, unusual facial features, for example, something that may look genetic, or sometimes even syndromic, those would be strong indications for genetic testing. (Provider #8)

Many of the providers referenced a 2012 study that challenged the common clinical practice of selecting ASD patients for genetic testing based on dysmorphology, seizures and intellectual disability, which the researchers claimed "are not major independent risk factors in the ASD population and should not be used to screen patients for [genetic] testing" (McGrew, et. al, 2012). However, providers I spoke with were not convinced by these findings. One developmental pediatrician stated, "we were always taught that the more severe developmental delay that a child has, the more likely you are to find the genetic etiology and I still believe that's true" (Provider #12).

Some providers stated that they turned to testing when they couldn't make sense of a clinical finding. One neurologist explained that he orders testing "either when they have intellectual disability/global development delay, which is another indication for genetic testing, or when they have a neurologic issue that we think could be genetic and we don't have an explanation of it" (Provider #15).

Lack of consensus about guidelines and test utility

As discussed in chapter 2, there are a number of professional guidelines, including those by the ACMG, to help inform provider decision-making, but there is no single guidelines that all providers follow. One geneticist explained how he handles the ACMG guideline recommendation to offer CMA testing to all families diagnosed with ASD, keeping in mind the families' needs: "So I like to give them a choice and I'm willing to be criticized that I'm not delivering the standard of care if the family believes this is not in their best interest or they can't tolerate the information that may come from there" (Provider #13).

Although some providers consider the ACMG guidelines to represent standard of care, recommendations from other specialties differ, and there is little provider consensus across

different specialties on what constitutes the standard of care. Thus, although many providers (all the geneticists and developmental pediatricians interviewed, as well as some of the others) reported feeling obliged to comply with the ACMG guidelines, they are not being adopted by all providers and are not being translated into institutional protocols. One geneticist stated:

> I feel a little manipulated by the national standards that this is the standard of care because I'm not sure if it really influences the management. I'm not sure I agree with that statement and I'm not sure where I stand on those – and my personal point of view is it's good to know as much as you can about something and if this requires information that you can't currently interpret, I'm okay with it but I recognize that the patients and their families are not always of the same mind. (Provider #13)

A developmental pediatrician stated:

> I think so many things subconsciously go into our minds about how strongly or how ambivalently we make a recommendation, we actually – regardless of what we write down in the report and we know what we're supposed to write down because the clinical guidelines are pushing us to write those things down, but how we convey that information in person I think is determined by so many different things than any other lab test that we do for this testing. (Provider #12)

If geneticists and developmental pediatricians feel ambivalent about genetic testing for ASD, providers from other specialties may be even more so. One psychologist simply stated, "I think that the background rate of adherence to guidelines is low" (Provider #6).

Among providers at a given treatment center, there may be disagreement regarding which guidelines to follow or how to best translate the recommendations from guidelines into institutional protocols. As one psychologist explained:

> We don't have a standard protocol here at all and we've talked about that a lot… if we should have standard protocol. That's more of a bigger issue for [our] center in general because we have nurse practitioners, neurology, pediatrics, psychiatry and psychology and speech all seeing kids and there are different guidelines for different disciplines for all kinds. (Provider #3)

Many providers still question the utility of different genetic tests (including CMA) used in the context of ASD and are waiting for better testing before they commit families to the genetic evaluation process. A genetic counselor explained:

> I've been fortunate enough to be able to go and meet with the neurodevelopment/autism clinic providers as part of their conversations related to autism, genetic testing and a paper that was put out in the last year about the recommendations for what genetic testing should

> look like in this cohort of patients. It was really intriguing to hear those providers talk about their approach to testing because many of them really question the value of testing in this population……meaning that $2,000 for this chromosomal microarray test which may or may not give you an answer. (Provider #11)

Providers expressed concerns about offering these tests in a clinical setting due to the fact that the science and technology seem premature. One psychologist seemed frustrated that "we're going to move it forward into clinical deployment before it's ready for prime time" (Provider #6). One geneticist was aware of the way this testing was being perceived by psychologists, stating," I think basically [the psychologists] themselves are uncomfortable with genetic testing and I think that they also—a lot of them still think of it as being purely in the research realm" (Provider #7)..

Providers recognized that there may be a societal value to testing, but not necessarily to individual families. As one psychologist put it, "It's better for moving the science forward as opposed to actually being most helpful for families. So there's some clinical utility but that's limited for a small portion of kids with autism" (Provider #3).

These quotes indicate that many providers find that the benefits mentioned in the ACMG guidelines are questionable and are concerned about the added burden of time and energy that is placed on families. A developmental pediatrician stated, "So I think I waffle around it because of my concern about the burden that I'm imposing on these families. And I think we have moved too quickly to clinical practice" (Provider #10).

<u>Step 3: Getting the test:</u>

The third and final step in the pathway from a diagnosis of ASD to getting a genetic test is actually having the test done. Families interviewed in this study do not always choose to follow through with testing once the testing is offered to them. Chapter 4 discusses the motivating factors and barriers that drive a family's decision to have or not have testing, but for this chapter it is important to note that among parents who choose to pursue testing, a major barrier is getting the test paid for by insurance. Six parents in this study did not have testing

done and three of them cited lack of insurance coverage as the main reason. Family #3 had been referred from the autism clinic and had hoped to have testing done, but did not proceed once they learned their insurance would not cover it. Family #7 had discussed genetic testing with their nurse practitioner and the family was referred to medical genetics, but when insurance would not pay for it, the family went on to have testing through a research study. However, the research protocol did not include return of results, so they did not receive their results. For family #12, the child was diagnosed with ASD at 1½ years of age and had a twin brother with Down syndrome. The twin brother had genetic testing at 4 months and that is when he was diagnosed with Down syndrome. The child diagnosed with ASD was offered genetic testing 5 years after the diagnosis, but insurance would not cover the cost of testing so parents chose not to pursue it, noting that if genetic testing had been offered at diagnosis they probably would have pursued it at that time.

The providers I interviewed also mentioned that in their experience, genetic testing for ASD is being covered less frequently by insurance companies. One provider said, “It seems that most of the insurance plans are increasingly rejecting requests to pay for microarrays. Our lab here has implemented a policy in which unless there is pre-authorization, they are not going to proceed with the test” (Provider #4). The reason providers believe that insurance is not paying for it is that “some insurers still specifically consider it investigational and won’t pay for it” (Provider #7). When insurance companies are not paying for the test, providers begin to question the benefit of testing and its utility. One provider explained, “to get funding for those tests that’s tightened up quite a bit recently and it’s forced me to rethink the value of it” (Provider #4).

Discussion

The ACMG guidelines state that everyone diagnosed with ASD should have a genetic evaluation, but provider and parent interviews demonstrate considerable variability in the

approach to genetic testing for ASD. There is variability in providers who are making the initial ASD diagnosis and differences in their belief in and authority to order genetic tests. No two patients will necessarily have the same experience, as each patient's journey depends on who makes the initial diagnosis, where they are seen, what kind of insurance they have, where they live, what kinds of questions the family asks, the nature of their symptoms and the family's response to them. Lack of consensus among providers, related at least in part to the different guidance offered by other professional guidelines, is one of the reasons that genetic testing is not consistently implemented. There are recent publications that try to address this issue, e.g., "Diagnostic Yield of Chromosomal Microarray Analysis in an Autism Primary Care Practice: Which Guidelines to Implement?" (McGrew et al., 2012). Even more recently the Agency for Healthcare Research and Quality drafted a technical brief titled, "Genetic Testing for Developmental Disabilities, Intellectual Disability and Autism Spectrum Disorders" to promote useful information for understanding the current landscape of genetic testing and identify evidence gaps in the hope of guiding future research for addressing genetic tests' clinical utility (Agency for Healthcare Research and Quality, 2014). Interview data from this study suggest that currently there is variability in provider attitude and practices about the utility and purpose of testing, as well as evidence that parents express confusion and misunderstanding regarding these issues.

Without consensus, many providers choose not to offer testing to families and many families are unaware of the option for genetic testing. According to Chen et al. (2013),"the majority of the participants [from their study], who had not taken their children for ASD genetic testing, had never heard about such testing." Of those parents interviewed in our study, six parents did not have genetic testing and three families had never been offered or even discussed genetic testing with their providers. This aligns with findings from another study published in 2014: "60% of the parents from the US reported that no genetic testing was

recommended, the low rate of genetic testing reported for the children from the US (28%) may be mainly attributed to a lack of healthcare provider's referral" (Amiet et al., 2014).

Interview data revealed that testing decisions by parents frequently appear to be influenced primarily by providers and secondarily by insurance carriers. This is consistent with the literature stating that often "health insurance companies do not provide reimbursement for CMA for patients with ASD" (Henderson et al., 2014). Among the parents I interviewed, eight chose to pursue testing, but only five completed testing because for three of the eight families it was not covered by insurance. The interviews in this study also demonstrate that lack of insurance coverage may cause providers not to order the test; for one interviewee the lack of coverage also raised questions about the clinical utility of testing. Better insurance coverage would likely lead to more testing. An example is the higher rates of this testing in other countries: "it is likely that free access to care in France may in part explain the better accordance with genetic testing recommendations in ASD found in this country" (Amiet et al., 2014).

Three things are clear from the interviews about genetic testing for ASD: there is a lack of consensus amongst providers about its utility, a lack of insurance coverage, and a lack of parental awareness. The absence of provider support, insurance coverage, and parent knowledge has resulted in disorganization and confusion in the process of ordering and receiving genetic testing, but it is unclear if this is detrimental for families who have a child with ASD. There seems to be an urgency in the literature to have all individuals with ASD undergo genetic testing. As Cuccaro et al. (2014) state in their conclusions, "The need to understand and improve on referral to genetic services for individuals with ASD is becoming more pressing." However, the variability in ASD presentations, the lack of definitive treatment or of impact on treatment from most genetic test results, and the complexity all raise questions about the clinical utility of routine genetic testing for ASD.

Four of the five families interviewed that had genetic testing done stated that it had no impact on their lives. If a positive result is obtained from genetic testing, it may point to an etiology for a child's ASD, but finding an etiology is rare. One family that had genetic testing in this study received a positive result (20%, roughly consistent with the 6-15% reported by Schaefer et al., 2013) and according to that family it made a huge difference in their lives. That child was found to have a clinically identifiable syndrome which resulted from a duplication of chromosome 15q11.2-13.1. After testing, the family now has a support group of parents who have children with this same genetic condition and they are aware of certain medical conditions associated with this syndrome, certain medications to avoid, and clinicians who specialize in providing for these kids. The mother of that child is an advocate of genetic testing for all kids with ASD because of the impact that a confirmed etiology had on her and her child.

Conclusions

The pathway from a diagnosis of ASD to genetic testing is complicated and difficult for families to negotiate, suggesting that improvements could and should be made. It is not clear whether improvements should include promotion of routine genetic testing for ASD. Guidelines about genetic testing are inconsistent, particularly the role of CMA tests (see Chapter 2). Some of the inconsistency may reflect the rapidly changing technology, given that some guidelines were published more than 8 years ago. The varied experience of families reported in interviews, and varied opinions about testing in provider interviews, indicate there is also a lack of a clear standard of care. Before future protocols or guidelines are developed, building consensus about the best approach to genetic testing for ASD and whether or not there should be a standard pathway for all individuals diagnosed with ASD should be the focus. One way to address this would be to promote more comprehensive discussions with the inclusion of all provider specialties involved in the diagnosis and care of individuals with ASD (geneticists, genetic counselors, pediatricians, neurologists, psychologists, ASD care providers, etc). Other key

stakeholders who should be included are experts on test methodology who can speak to the utility of performing these tests, insurance providers, and parent/family representatives. Taking the time to think through a potential approach that all or most providers could follow would be helpful. Such a pathway would not necessarily involve uniform genetic testing for individuals with ASD, but the rationale and criteria for offering testing should be clarified, including the delineation of areas of consensus and areas of persistent disagreement among different stakeholders. This is a process that will take time and energy and may be a moving target, as treatments and access to diagnosis of ASD are changing, as is insurance coverage. However, currently the pathway from an ASD diagnosis to genetic testing is messy, expensive, sometimes random and, as the interviews in this study suggest, often puzzling or dissatisfying to both patients and providers so efforts to create a clearer and more transparent approach would benefit all involved.

Chapter 4: Where's the Benefit? Views on Genetic Testing for ASD

Introduction

Genetic testing for ASD is being offered in a clinical setting and parents often rely on their healthcare provider to guide them in making a decision about whether or not to have their child tested. In turn, providers often rely on practice guidelines or other professional statements to inform them about the standard of care for particular healthcare concerns. However, as reviewed in chapters 2 and 3, there is no consensus about the standard of care with respect to genetic testing for individuals diagnosed with ASD. Some professional groups recommend genetic services to families of children with ASD, citing substantial benefits to testing. Current guidelines from the ACMG and other professional societies (ISCA) recommend genetic testing for all individuals diagnosed with ASD, using chromosomal microarray analysis (CMA), as the first tier test. Other guidelines suggest a more selective approach to genetic testing (AAP, AACAP, and AAN guidelines). These guidelines make conflicting clinical recommendations about genetic testing for ASD (Shea et al., 2014) and have been met with "a surprising mix of apathy and controversies" (Cuccaro et al., 2014). Some providers have embraced genetic testing for individuals with ASD and are recommending it to all of their patients. Besides geneticists, genetic tests are most often ordered by pediatric neurologists and developmental pediatricians (Cuccaro et al., 2014), while other providers are ambivalent about genetic testing for ASD.

There are several scientific concerns raised about applying the ACMG guidelines to all individuals with ASD: a) the populations in most of the studies conducted thus far may not be representative of the primary ASD population; b) diagnostic criteria for ASD and information on the clinical characteristics of the patients is not comprehensive in some studies; and c) the cost and cost-effectiveness of CMA testing (McGrew et al., 2012). Clinical utility is also in question because genetic testing for ASD rarely leads to an improvement in outcomes for the patient (Jordan & Tsai, 2010). Incorporating genetic testing and services as part of routine care for

individuals with ASD has ethical and social implications given the complexity of ASD diagnosis, phenotypic expression, and etiology, combined with the range of testing options and the difficulty interpreting CMA test results, including the potential for results of unknown significance and incidental findings (Cuccaro et al., 2014; Jordan & Tsai, 2010; Manning & Hudgins, 2007; Miller et al., 2010; Scherer & Dawson, 2011; Walsh et al., 2011).

Despite the questions surrounding genetic testing for ASD, there remains a strong push to move forward with universal genetic testing for individuals with ASD (Cuccaro et al., 2014).The benefits cited include: 1) disease management (including identifying potential or existing comorbidities) (Schaefer et al., 2008; Shen et al., 2010; Vande Wydeven et al., 2012; Walsh et al., 2011); 2) determining recurrence risk (the frequency of ASD in siblings born after the first diagnosed child) (Bauer & Msall, 2011; Shen et al., 2010; Vande Wydeven et al., 2012; Walsh et al., 2011); 3) help accessing resources and support (Bauer & Msall, 2011; Shen et al., 2010), and 4) finding an explanatory cause (Scherer & Dawson, 2011; Shen et al., 2010; Vande Wydeven et al., 2012).

However, the majority of children with ASD are not receiving genetic services (Vande Wydeven et al., 2012). As discussed in chapter 3, genetic testing for ASD is not consistently implemented in the clinical setting, in part because healthcare providers often utilize their experience and beliefs about the value and utility of genetic testing for ASD to inform a case-by-case approach. Those who do not offer genetic testing for every individual with ASD will often refer to genetics only if the child has significant functional impairment (Cuccaro et al., 2014). Some providers neither offer testing nor refer to genetics in any case.

The research about parent views and experiences is limited, but some research suggests that parents may value genetic information that provides a causal explanation of ASD in their child (Miller et al., 2010). Yet, many parents are confused about what genetic testing is and what value it could have for them. In a study by Cuccaro et al. (2014) when asked about whether their child would benefit from seeing a genetics professional, nearly half of the parents

were unsure. In addition these same parents were unclear about ASD etiology and recurrence risk. One survey indicated that some parents of children considered a clinical diagnosis more useful than a rare, specific etiological diagnosis (Makela, Birch, Friedman, & Marra, 2009) and that often the intensity of the need for an etiologic diagnosis diminished over time. These factors likely contribute to low uptake rates of genetic testing by parents of children with ASD (Cuccaro et al., 2014; Mercer, Creighton, Holden, & Lewis, 2006; Selkirk, McCarthy Veach, Lian, Schimmenti, & LeRoy, 2009; Vande Wydeven et al., 2012). When parents are offered genetic testing for their child with ASD the most common reasons to decline testing are concerns about cost or the lack of perceived benefit for testing (McGrew et al., 2012).

Developments in technologies used to identify genetic causes of ASD have generated enthusiasm and hope for the future, but little effort has been made to explore the practical, ethical, and social implications of delivering these services to parents and families (Cuccaro et al., 2014). This research focuses on how navigating the landscape of ASD and genetic testing impacts providers and parents. This chapter specifically examines provider and parent attitudes about genetic testing for ASD, identifying their concerns and motivations to test and their thoughts on the benefits and barriers to testing.

Material and Methods

Study design and participants

I conducted a qualitative interview study with fifteen health care providers and eleven parents of children with ASD to elicit their perspectives regarding genetic testing for ASD. The details of recruitment are described elsewhere (chapter 3) and summarized here. Parents with at least one child diagnosed with ASD were eligible to participate. Eligible parents were recruited in two ways: 1) through the Center on Human Development and Disability (CHDD) Autism Genetics Clinic at the University of Washington with scheduled appointment with a clinical geneticist (three families); and 2) through two listservs that serve as discussion forums

for families living with ASD (eight families). Clinic-based recruitment was done by mailing letters describing the study in advance of scheduled appointments and then meeting families on the day of their visit to explain the study and obtain written consent. The two listservs included Families for Effective Autism Treatment (FEAT) of Washington, a non-profit organization founded by families for families who have children with ASD, and a group at Microsoft called the Autism Information Exchange for parents who had children with ASD. For both listservs, a member of the group posted a description of the study that invited interested parents to contact me via email if they were interested in the study and willing to do a phone interview.

For the provider interviews, I used a snowball sampling technique to contact a range of providers who are involved in the diagnosis and care of children with ASD. A first set of names was proposed by Dr. Holly Tabor, an associate professor in bioethics with expertise in ASD, who works collaboratively with providers involved with diagnosing ASD. She provided an initial list of local geneticists, psychologists, and pediatricians involved in ASD care. At the end of my interviews with these providers, I asked if they had recommendations of other providers who I should include. I continued recruitment until I had a diverse group of perspectives and no new names were being mentioned. I contacted a total of 23 providers of which 15 (4 psychologists/psychiatrists, 4 pediatricians/developmental pediatricians, 3 geneticists, 2 genetic counselors, and 2 neurologists) agreed to be interviewed. This study was approved by University of Washington Institutional Review Board and all participants provided written consent.

Data Collection

Six families were originally recruited through the UW clinic. I obtained written informed consent and then observed during their initial appointment at the UW genetics clinic. Each of these six sessions was recorded and transcribed and contact information was obtained for follow-up. I then contacted these six parents for a follow up interview, of whom three agreed to participate. Including the eight parents recruited through the listservs, I was able to conduct

interviews with 11 parents in total. In addition, I interviewed 15 clinicians from different specialties involved with ASD diagnosis and/or genetic testing. Interviews were conducted face-to-face (2 parents, 9 providers) or by phone (9 parents, 6 providers). All interviews were recorded and transcribed.

Parents were asked about their experience with the genetic evaluation process for their child, their motivations for seeking genetic testing, their decision-making surrounding genetic testing, and their overall thoughts and feelings regarding genetic testing. The average length of interview time for parents was 21 minutes (range 6-44 minutes). Providers were asked questions about the genetic testing process at their facility, their own personal thoughts and practices regarding genetic testing, the potential effects of genetic testing, communicating with families, and returning results. The average length of interview time for providers was 40 minutes (range 16-65 minutes).

Data Analysis

I employed content analysis (Hsieh & Shannon, 2005) of the interview data and developed a coding scheme with the assistance of a second coder. Both coders independently coded the first three provider interviews and the first four family interviews. The coders met to compare reoccurring themes across the transcripts, discuss any divergent codes and review transcripts to reach an agreement about the meaning and application of codes. Once the coding scheme was established, I completed coding all transcripts using Dedoose software. The coded data was then analyzed to identify emerging themes and interpret patterns. This chapter reports interview findings related to provider and parental views on genetic testing for ASD, specifically focusing on concerns, motivations and thoughts on benefits or barriers.

Results

Providers interviewed were either supportive or ambivalent about offering genetic testing for individuals with ASD. Those that support testing contend that benefits include recurrence risk

information and the benefit of knowledge, and also express the possibility of improved outcomes based on future treatments informed by genetic research. Those that are ambivalent cite a number of concerns including burden to family, complexity and uncertainty of the results and the difficulty conveying this information to families, and the lack of information to inform clinical care. Because of these different perspectives on genetic testing some providers offer genetic testing routinely or refer patients to medical genetics while others do so rarely or not at all.

For the most part, parents pursued testing in order to "cross it off the list" of things recommended by their provider. In some cases, parents had independent motivating factors for testing such as helping the ASD community or searching for answers. Often, even after testing was done, they expressed confusion about reasons for testing but nevertheless felt good about complying with their providers' recommendation. The most common reason parents did not have testing was lack of awareness, but other barriers included the cost/lack of insurance covering the test and the child's difficulty with blood draws.

Providers: two views on genetic testing for ASD

In interviewing providers it became clear that there were two distinct ways they thought about genetic testing for ASD. Providers were either very supportive of testing, specifically chromosomal microarray analysis (CMA), or they are ambivalent about testing (Table 4.1). The providers were evenly divided between those who were supportive (n=8) or felt that genetic testing should be offered to all individuals with ASD, and those who were ambivalent (n=7) and questioned offering genetic testing to all individuals with ASD.

All but one of the neurologists and genetic professionals were in the supportive group. When talking about genetic testing for individuals with ASD, supportive providers stated simply, "I think it is a must" (Provider #1) and "The goal is to get it done at some point in time" (Provider #2). All four pediatricians were ambivalent about testing. These providers did not feel that there is an accepted standard of care recognized by all providers who diagnosis ASD: "Unless we're saying with clear conviction that we should be going in this direction, are we in fact being

ambivalent to these families? I think that's where providers are right now. We don't know what the right answer is either" (Provider #10). Psychologists were evenly split in their opinions about testing. Both of the two psychologists in support of genetic testing had additional training and/or conducted research involving genetic testing and ASD. One of these psychologists had a very clear view: "I think it's an absolutely necessary sort of procedure and it should be considered standard of practice" (Provider #9). He elaborated stating, "it's helpful as a clinician sometimes where you know there's a sustained genetic event – we do have autism database[s] out there and you kind of look and see what goes for what, you know, so it's always kind of nice for me in terms of prioritizing the a kid's treatment needs which are often quite large. If we have some additional information based on their genotype, we can plan around that" (Provider #9).

Table 4.1. Providers Views on Genetic Testing for individuals diagnosed with ASD

#	Provider Type	Supportive or Ambivalent
4	Developmental Pediatrician	Ambivalent
8	Developmental Pediatrician	Ambivalent
10	Developmental Pediatrician	Ambivalent
12	Developmental Pediatrician	Ambivalent
13	Geneticist	Ambivalent
1	Geneticist	Supportive
7	Geneticist	Supportive
11	Genetic Counselor	Supportive
14	Genetic Counselor	Supportive
2	Neurologist	Supportive
15	Neurologist	Supportive
5	Psychologist	Ambivalent
6	Psychologist	Ambivalent
3	Psychologist	Supportive
9	Psychologist	Supportive

Concerns Expressed by Providers

Provider ambivalence stemmed from a number of concerns, including that testing is too complex for families to understand, especially variants of unknown significance and incidental findings; testing is evolving; testing might create guilt, blame or stigma; and the fact that results do not change treatment. Table 4.2 gives the percentage of providers in this study who mentioned each of these concerns. The bottom line for many of the providers who were

ambivalent about testing was that with all these concerns and no change in treatment, the benefits of genetic testing for individuals with ASD are rare and minimal.

Table 4.2. Concerns with testing

CONCERN	% of Providers (n)
Complexity and Uncertainty	**53% (8)**
Too Complex for Families	13% (2)
Variants of uncertain clinical significance	47% (7)
Incidental findings	13% (2)
Field is changing too quickly	**27% (4)**
Stigma/Guilt	**27% (4)**
Stigma	13% (2)
Guilt or blame	13% (2)
Lack of Benefit	**33% (5)**
Will not change treatment	20% (3)
Burden to the Family	6% (1)
Only beneficial for a small number of people	20% (3)

Complexity and Uncertainty

The complexity, or all of the complicated aspects of testing from discussing it to ordering the test, to interpretation, was a real concern for many of the providers. Just ordering the test can be complicated. As one developmental pediatrician explained:

> I have gotten phone calls and emails from primary care providers that have said this is not a test that I can order out of my clinic. I don't have authorization. I don't know how to go about getting authorization. Most importantly the test results are going to come back to me and I don't know what to do with the test results unless I call you and you're only here once a month, etc. (Provider #12)

This developmental pediatrician continued to explain the complexity in terms of returning test results to families:

> We're not talking about just high resolution chromosomes anymore. Now we're getting down into copy number variants with very complicated technology. I think parents don't understand it and how a genetic finding could be the cause of their child's autism and not be the cause of somebody else's who both look the same. So I think this whole thing has just gotten so complex and there are so many variations of answers or I guess genotypes are coming up for the one thing called autism that parents don't know what to do with it and I think they're overwhelmed by CGH testing. (Provider #12)

Providers were also concerned about variants of unknown significance. Provider #10 summed it up by saying, "There is also the problem with all the grey zone, copy number variants of uncertain clinical significance, which I think can be confusing and not helpful for the family."

Provider #13 found that this was a huge barrier to offering testing: “so I found that pretty hard to recommend especially when there's unlikely to be [a] 100% clear cut answer because of the lack of penetrants of some of these variants.” The complexity and uncertainty of testing is a major factor in whether or not a provider discusses or offers testing. Another provider explained:

> Questions come up when you say “I think your child should have a genetic test,” when we bring it up and those questions might be, what are you going to learn and why are you going to learn that? And what's going to be the advantage to me for learning that? I always say the majority of families are not sophisticated enough to really kind of ask those questions. They’re kind of still in the shock of dealing with a whole lot of other stuff. (Provider #4)

These quotes illustrate the concerns that some clinicians have when helping families in their clinic and how they handle communicating the uncertainty and complexity of these tests. As one provider pointed out, when dealing with ASD in clinical settings, genetics is “such a small piece of the autism puzzle” (Provider #3). Incidental findings, defined as findings emerging from the test that are unrelated to the presenting diagnosis of ASD, add another layer to the complexity of the issue. Providers thought incidental findings were definitely a concern when discussing genetic testing for ASD.

Evolving technology

Many providers noted difficulty keeping up with the changes in the current technology. As a genetic counselor explained, “So I think that the testing has evolved quite quickly and providers may be having a harder time keeping up with it particularly if it’s not something that they do periodically” (Provider #11). Some providers believed and hoped that the technology is still evolving and that a better test will come along to clear up some of the issues. Provider #4 explained, “I think the other problem is the technology keeps changing. I mean it’s almost hard to say let’s do this test now and we know that in two years there's going to be a different test.” This sentiment was shared by several providers, including Provider #12 who said:

> I think a lot of us are even more ambivalent now about going through all these steps because we’re thinking if they're saying [in] 2 or 3 more years exome sequencing is coming out and the likelihood of picking up something that was negative on CGH, just like likelihood now that we currently have of chromosomes versus CGH, then why not just wait another couple years and get the exome sequencing?

Stigma and guilt

Additional concerns from providers included creating stigma and guilt for parents. One provider reflecting about a specific family pointed out that "it could be stigma [to find a genetic etiology] I suppose with kids that are high functioning" (Provider #9). Regarding the guilt issue, one provider explained "if there's a genetic finding that's attributed to the mother or the father side. Sometimes it's hard to predict how people respond once they find out that information" (Provider #5).

Lack of benefit and added burden

Without a clear clinical care benefit it is hard for some providers to impose what they feel is an added burden for the family, with possible waste of time, energy and financial resources. As provider #12 explained, "I think I waffle around it because of my concern about the burden that I'm imposing on these families." The one geneticist who was ambivalent about testing expressed:

> The standard of care is to do an array CGH for every child with autism. And I personally feel the information that's generated from it is unlikely to influence management and unlikely to cast for sure good information on the etiology of the autism in that family unless it's a very well known variant, very well known cause. (Provider #13)

Provider #3 stated, "that's something that we have to be frank and honest about. Often it doesn't affect the management directly." As Provider #6 explained, "You know, it's a tiny fraction, a really tiny fraction where you've got something that you can take to the bank right away."

Benefits of testing

Although half of the providers expressed concern over testing, those who are supportive believe that there is a real benefit to genetic testing for ASD. The benefits listed in Table 4.3 were mentioned in the interviews by providers and parents, with percentages listed. The first four listed are those that were most often discussed by providers. The benefits brought up most

often by parents were recurrence risk and helping the ASD community, followed by feeling good about doing all that was recommended and finding an explanatory cause.

Table 4.3. Benefits to testing

Benefits to testing	% of Providers (n=15)	% of Parents (n=11)
Future benefits (Disease Management)	40% (6)	18% (2)
Recurrence Risk/Reproductive decision-making	40% (6)	45% (5)
Resources and Support	27% (4)	9% (1)
Knowledge (Explanatory Cause)	53% (8)	27% (3)
Parent feeling good about doing all they could (all that was recommend)	13% (2)	27% (3)
Help the ASD community	6% (1)	36% (4)

Future benefits

Many providers identified potential benefits and hope for the future in offering genetic testing: future treatment informed by genetic research, potential improved health outcomes in the future, and potential benefits of knowledge. Several of the providers I spoke with were honest about this, stating "so I'm for it totally 100% but realizing that it's not probably as helpful given a particular family in the moment as it will be five years from now" (Provider #3)**.** Providers also identified the use of genetic testing as a mechanism for achieving the future benefits:

> There's little doubt that we're going to understand what autism is about, to a large extent by understanding the genetics of it and understanding how those thousand genes that are involved in autism actually interact with pathways may lead actually to specific therapies. (Provider #4)

Treatment for ASD patients based on a known genetic etiology is not yet a reality. Provider #6 explained, "theoretically it might be that one could really fine tune some behavioral interventions too or to be more vigilant about screening for neurobehavioral language or other abnormalities if you knew what the underlying genetic risk factors were." Another provider stated:

> The other reason to look is something can be identified that were there a known associations of something that we might intervene or be able to predict that we need to monitor heart functioning or there's something where we know that we potentially – there's a higher association of certain health problems or that sort of thing. (Provider #5)

Another provider talked about the value of identifying a genetic disorder associated with ASD:

> Some of these things [genetic disorders] have medical implications that are either immediate or in the future they need to be monitored so they can help prevent you know, medical complications that may otherwise be overlooked. (Provider #8)

Recurrence risk

Establishing recurrence risk was mentioned frequently by the providers as a benefit to testing. According to providers #7 and #8, "the family wants to know the recurrence risk for healthy siblings for their children to have autism" (Provider #7) and genetic testing "might provide some tremendous utilities to the family in terms of family planning" (Provider # 8). However, one provider brought up the difficulty in parsing out recurrence risk when you are looking at genetic variation due to copy number variants as opposed to recurrence risk for syndromic ASD. Provider #6 stated, "one of the problems is that these genes don't cause autism. So although we can talk about recurrence risks in families, I don't think that we can directly connect those recurrence risks to the presence of a single copy number variant or even single gene defect." Provider #3 talked about how relevant recurrence risk is for pregnant women or women intending to get pregnant, but explained that, "generally that's not a driving feature for them. Usually I put it to them and they don't often always think of this. I would say 50% of the time only how will it affect the management of their child."

Resources and support

In terms of accessing resources and support, providers felt that the support that was most helpful for families was being connected with other families whose child has the same genetic diagnosis. As Provider #5 explained:

> Families may be part of a group that surrounds particular genetic findings or other groups around the world that are coming together around certain genetic findings and I think that can be a great support to parents to not feel they're the only one that has a child with a particular difference.

One parent described experiencing the benefits of joining a support group. She stated that she found comfort in "knowing hey I can call up any of these other seven people in the area

and we'll get together no matter what our kids do, we don't have to explain it to each other" (Parent #8).

Benefit of knowledge

Finding a possible explanatory cause for ASD may or may not be beneficial, especially when the information that parents are getting regarding the cause of their child's ASD is rarely straightforward. However, many providers believed that families benefit from this knowledge. A genetic counselor explained, "having worked with families it is being able to provide an answer that's the why to that question. …I think is hard to quantify but it's so valuable" (Provider #11). A geneticist described how this knowledge could assuage the guilt in some circumstances:

> I think a lot of families carry with them all of their lives that it's their fault that they did something that they caused this. And to have a genetic test result and say 'you know this is just something that happened, it wasn't under your control and it's not your fault' is very powerful for people." (Provider #7)

One psychologist described how this knowledge was a way for families to work through the diagnosis: "I think some of the benefits are that for families that would feel comforted knowing, just having the knowledge of a cause that can give them some peace of mind, that can be helpful." (Provider #5)

Providers make the decisions on a case-by-case basis

Given the number of concerns and possible benefits, providers often use their clinical judgment and make the decision to offer testing on a case-by-case basis. As one provider explained,

> If the child is intellectually impaired, if the child comes from a family with genetic disorders of intellectual impairments, or if a child has unusual physical sightings such as a dysmorphic, unusual facial features for example something that may look like a genetic syndrome, those would be strong indications for genetic testing. (Provider #8)

Another provider went into detail about what was referred to as the diagnostic clarification process:

> So sometimes what we'll do is talk about the fact that the child has no dysmorphic features, has no microcephaly, has no other neurologic findings except for the autism diagnosis or if it's mild intellectual disabilities or mild global delays especially in a young child who hasn't

had any services, we'll often say at some point in this evaluation if these symptoms persists with despite intervention, we would obtain this, this and this. So we don't necessarily make it an immediate requirement. We kind of make it its part of the process, the diagnostic clarification process over time. (Provider #12)

Some providers base the decision more on the needs of the family than on the clinical findings. As Provider #5 stated:

> I think that depends on what the needs of the family are in terms of whether they – I think if they can offer some information that people are looking for possible explanations for what's going on with their child or their family member."

Other providers said that they spend time with families to ascertain their goals and motivations.

> If the family's pushing for it, we would have no hesitation about doing it as long as they understand the financial implications that they may be faced with a significant bill and that the results might be very confusing in terms of risk. (Provider #4)

However, if two-way communication is not taking place, families may simply do what is recommended by their healthcare provider.

Some providers described being directive in their approach to recommending testing and touting the benefits. For example, one geneticist explained:

> I discuss what testing has been done if any, and then what testing is available or appropriate given the whole evaluation. It usually includes array because most of the patients that I see have not had array before and that is now, like I said, part of the first line genetic testing. (Provider #7)

However, others may discuss the pros or cons or may not discuss testing at all. Provider #13, explained, "So I don't push it upon them because I try to explain the pluses or minuses of the testing and I would say 50% of the families are lead not to have testing." The following statement suggests that the provider's own thoughts on testing have an impact on offering the test:

> I don't know that I would necessarily suggest it in a situation where there wasn't overwhelming clinical need to. It would be a really hard conversation to have to commit someone to a couple of thousand dollars so that we might learn something really cool. (Provider #6)

Parental views and motivations are shaped by providers and how they frame the issue

In chapter 3, I reported that many parents were not aware of testing and therefore they had no opinion about it. Parents who discussed testing with their provider generally knew little or nothing about the testing until that discussion and trusted their providers' information and recommendation. Table 4.2 listed the concerns providers had about testing. Because parents generally did not express concerns about genetic testing, Table 4.2 is limited to provider concerns. As one of the neurologists pointed out, educating families about the benefits and harms of testing is the key:

> I think that it's important to offer genetic testing because of the potential benefits for it. I think it's not right for every family and I always try to go through reasons to and reasons not to do it or to kind of give them a choice. (Provider #15)

Although seeking a causal explanation for ASD or information for reproductive decision making were the two biggest motivators for parents, parents also wanted to do what was recommended. As parent #2 explained, "Well [our doctor] had guided us in the genetics direction to cross it off the list" of things tried." Some parents expressed confusion about the test and reasons for conducting it: "I don't even know what a geneticist would test for" (Parent #9) and, "I don't really know that much about it in terms of what the information would be that we would get" (Parent #13). Despite this lack of knowledge, if their provider recommended testing they were willing to have it done to ensure that they were doing "all they could" for their affected child. As a result, parents often prioritized testing based on what they heard from their provider. One parent who had seen a geneticist and had testing stated, "I've done what I can as a parent that I've taken advantage of what's out there." (Parent #5) Another parent who didn't initially have testing, but later had testing through a research study stated, "That wasn't as important to us as getting the therapies in place and our goal was to have successful experience in school and things like that" (Parent #7).

Families in this study expressed wanting and needing help with their child's ASD. One parent was very emotional as she explained that her daughter

> …needs help but I don't know right now other than what we are doing, what we would do and if she had gotten diagnosed with some kind of syndrome, then what would change? Would there be another medication? I think what we're doing and what we're pursuing is what we can do for her now. There isn't that much. We have to be not in a big hurry and that's very difficult when she's struggling so much. And I'm not done yet. It's just so hard. Life is hard. (Parent #2)

Parents expressed a hope that genetic testing will somehow help them by either giving them an answer, help them get better treatment, or help them get things paid for by insurance: "If there was an identifiable syndrome it could open up new avenues and new doors for him in terms of speaking styles, learning styles, and possibly more services from the state" (Parent #5). Another parent explained, "We've been advocates and you know, that's what we could do. That's all we can do" (Parent #13). Parents also expressed the feeling that in their opinion there is no harm to testing so why not. One parent stated, "she'll be under for the MRI so why not just get it out of the way" (Parent #14). Another said, "if insurance would have covered it we probably would have done it just to have the information, it would never hurt" (Parent #7).

<u>Independent motivators or barriers to testing for parents</u>

Information about future prognosis and personalized medicine or treatment were things that were brought up by many providers (Table 4.2), but these points were mentioned by only two families. However, four of the 11 parents talked about helping the ASD community: "I would have them tested if it helped research for you know, future kids" (Parent #10). A couple of parents had very strong feelings about wanting to find a causal reason for their child's ASD, for example: "Before I die I just want to know what caused his autism" (Parent #13) and "Hopefully in my lifetime we'll get some answers about autism" (Parent #11). In most cases, recurrence risk was something parents listed as a benefit after speaking with their provider, but in one family it was the driving factor that had them pushing for genetic testing:

> I really wanted to have genetic testing done for him just to rule anything out. I had wanted to have a second child and I wanted to make sure that if there was something that I needed to be aware of that we had that sorted out first. (Parent #8)

Interestingly, none of the parents mentioned guilt as a motivation for having the genetic test. However, the one parent who got the test and found a genetic "answer" said,

> You know, I think with autism you're always wondering you know, was it environmental, did I get something, did I get sick, did I get a shot that I shouldn't have or you're going through every single thing. You know, did I eat something, was I exposed to something and before we had the genetic diagnosis you know you're also thinking can I cure this, can I rapidly change his diet, can we eliminate every chemical in the house. I mean you're going through everything trying to figure out how to help your child and once you have the genetic diagnosis, there's relief like I didn't do anything. (Parent #8)

For parents, the biggest barrier to having genetic testing done was lack of knowledge because the test had never been offered as an option. Replies from two parents when asked about genetic testing included, "We didn't know it was available" (Parent #11), and "it wasn't something that our doctor offered to us" (Parent #13). If testing was offered, the second barrier parents faced was that their insurance would not cover it. These issues were discussed in more detail in chapter 3, but are relevant here in contrast to providers' view that often genetic testing is not a priority for families of individuals with ASD. While this was sometimes true, for many families genetic testing was not an option, either because testing was not offered or because of lack of insurance covering it. One provider explained, "And so without pre-authorization, we don't know for sure if it's going to get paid for and we definitely don't want the family to have to be charged" (Provider #12). Another provider stated simply, "The other reason I no longer routinely request it, is it's expensive" (Provider #10). A third provider said, "If cost weren't a factor, I would say that we should do it every time. But cost is clearly a factor." (Provider #4)

The final barrier to testing mentioned by families was difficulty in conducting the blood draw. As parent #14 stated, "we didn't do it because there was just too much going on and then trying to think about scheduling a blood draw…. It often didn't seem like there was much advantage of knowing."

Discussion

Currently there is variability in provider attitudes and practices toward genetic testing for ASD, as well as parental uncertainty about the value of testing. Because there is no perceived standard of care and providers often offer genetic testing or referrals to genetic counseling on a case-by-case basis, the parental perspective is likely to be determined by what their provider says and does. If the provider was ambivalent, parents may have set a low priority on testing; conversely they may be motivated to test if their provider tells them that genetic testing could provide a causal explanation or help with reproductive decision making. When providers recommended testing, parents generally followed their advice but they did so primarily to ensure that they were providing all recommended care or to "cross it off the list". "Crossing it off the list logic" is expressed in the literature as well:

> If the results of high resolution karyotype, CGH, and DNA determination for fragile X syndrome are negative, we can reassure ourselves that we have done our best to sort out potential etiologies. In all scenarios, we can celebrate that quality medical, developmental, educational, and community support interventions can optimize child and family well-being." (Bauer & Msall, 2011)

This philosophy of doing everything possible to find an answer is prevalent in medicine, likely fueled in current medical genetics practice by the belief that greater understanding of contributing genetic factors creates hope for the future:

> The rapid advances in genetics have facilitated an understanding of developmental trajectories, comorbidities and biological mechanisms underlying the deficits in ASD which, in turn, will open the door to the development of more mechanism- based, phenotype-specific treatments for these children. (Jeste & Geschwind, 2014)

None of what I heard from providers sounded very definitive which speaks to the fact that so much is unknown when dealing with ASD and although the hope is that genetic testing can help to establish a developmental or medical trajectory for these patients, currently that is unrealistic.

The search for "the answer" is something that seemed important to both parents and providers. The value of an answer has been emphasized in the literature: "…a clear genetic diagnosis also spares the patient and family a diagnostic odyssey involving multiple rounds of

diagnostic testing" (Shen et al., 2010). Yet the benefits of genetic testing for ASD are less clear cut because genetic testing and counseling can be stressful (Muhle, Trentacoste, & Rapin, 2004), interpreting genetic testing results are challenging (especially for a disorder like ASD that is complex and heterogeneous), and even when the results implicate a known genetic cause, at this point they do not inform intervention choices (Muhle et al., 2004; Schaefer et al., 2008). In the absence of providing answers that will directly impact the treatment of their child some parents are comfortable with searching for answers that will help future individuals with ASD. As the Chen at al (2013), study noted, "when asking parents' willingness in taking their children for ASD genetic testing, aiding ASD research was a most frequently mentioned reason."

Families stated that they wanted to do everything they could to help their children and they were seeking guidance from providers to help them. Therefore, if providers gave them a suggestion of a test that may give them another "diagnosis" or an etiology they might agree in the hope that the information could change things or make life easier. Education about the genetic tests and the benefits and concerns is necessary for parents to make informed decisions about whether to pursue testing. If this education were taking place, parents would express similar concerns as providers, but this doesn't seem to be the case. Instead it seems as if parents don't remember discussing genetic testing with their provider or they talked about the benefits of testing if they spoke with a provider who was supportive of testing and explained the benefits. For these reasons, if genetic testing was recommended to them, most families pursued it, but these interview data suggest that often they did not understand the test or what the results would mean for the future of their child. The bottom line is that parents are searching for ways to help their children and they turn to testing for those answers because that is what their provider recommended.

It is clear that the reason many clinicians are ambivalent about genetic testing for individuals with ASD is that they see ethical concerns with routinely offering genetic testing to all ASD patients. The information derived may be of uncertain clinical significance, and the benefits

touted in the literature such as recurrence risk are limited. In the rare instance of finding a syndromic diagnosis for ASD this information will provide a prognosis, some guidance for medical management and a more accurate recurrence risk. However, a positive finding from CMA is not as definitive and the state of the science is such that "the limited information regarding specificity, sensitivity, penetrance and phenotypic expression of these variants means that accurate prediction of recurrence risk and developmental outcomes is not yet possible in most cases" (Walsh et al., 2011).

The predominant view in the US is that knowledge is an unambiguous good, however poor quality medical information can be harmful; as Jiang et al. point out "concern over incidental findings may indeed increase rather than decrease anxiety" (Jiang et al., 2014). The limitation of array-based testing of children with ASD is that the findings, although interesting scientifically for identification of genetic changes associated with ASD, fail to provide specific guidance on treatment. Although a number of benefits were identified by clinicians, treatment guidance was cited only as a future rather than a current benefit of testing. Until genetic testing for ASD can provide information to guide the use of beneficial interventions, the clinical use of testing will be of limited value.

Conclusion

Further discussion among stakeholders is needed to clarify the purpose of genetic testing and its appropriate use in ASD care. Such efforts could identify limited areas of consensus, for example, additional patient characteristics that increase the likelihood that a genetic syndrome is present and therefore increase the value of genetic testing. These efforts could also inform communication efforts that allow parents to understand that genetic testing for their children with ASD is an evolving technology that currently lacks robust evidence for clinical utility but may provide other benefits. This chapter focused on provider and parent attitudes about genetic testing for ASD, examining the benefits, concerns, and motivations. While it

succeeded in gathering a good fund of information on provider attitudes, concerns, and motivations, further exploration into parental perspectives is necessary. Because of the complexity of this issue, the approach to including parents in this discussion to elicit their thoughts and feelings needs to be more extensive then was possible in this project. Providers have a wealth of knowledge on this topic, which allows them to express their thoughts and feelings in a very comprehensive way. Parents may need more education to fully address the potential benefits and concerns noted by clinicians. Fundamentally, however, the data from parental interviews in this study provided only limited support for informational benefits of CMA testing for ASD (e.g., identifying a genetic "cause" for ASD or informing parents about the risk of a future child with ASD). Instead, parents were focused on helping their child; in that respect, their uncertainty and lack of focus on genetic testing is an accurate reflection of the lack of treatment guidance provided by current testing. Parents who pursued testing often did so as a responsible parent, simply because their provider recommended it. Others did not pursue testing because their provider never mentioned it. In this context, parents do not seem to be getting the information they need to make an informed decision regarding whether or not to pursue testing.

Chapter 5: Summary and Implications

There is a broad range of opinion in the medical community when it comes to offering genetic testing for individuals with ASD, and these divergent perspectives extend to the clinical guidelines. In interviews with providers about discussing CMA testing for individuals with ASD, opinions ranged from “I think it’s an absolutely necessarily sort of procedure and it should be considered standard of practice” (Provider #9) to “I think we’re not far enough down the process of these tests before we opened it up to the whole world to order these lab tests.” (Provider #12) There are also differences of opinion about what is the best technology, whether there is clinical benefit, and accordingly, what types of genetic tests to offer and to whom in the clinical setting.

This broad range of opinion stems from the lack of definitive evidence. While the medical literature offers studies describing which test has the highest diagnostic yield, there seems to be a major gap in evidence about the clinical utility of genetic tests for ASD, as reflected in a technical brief by the Agency for Healthcare Research and Quality (2014) that examined 132 case of ASD in which only a few reported changes being made in patient management due to the findings of genetic tests:

> No consensus has been reached on the usefulness of diagnostic yield studies in assessing a genetic test’s clinical utility (impact on health outcomes). Improved diagnostic yield may not necessarily lead to a positive change in clinical management or in health outcomes.

Clinicians arguing that genetic tests for ASD have clinical utility acknowledge that only a small subset of patients receive actionable results, “so there’s some clinical utility but that’s limited for small portion of kids with autism”(Provider #3).

The lack of an established standard of care and of physician consensus creates a situation that is confusing and difficult for parents. A qualitative study found that there is disparity in awareness and access to ASD genetic testing and pervasive misunderstanding of genetic testing (Chen et al., 2013). My interviews with parents supported these findings and indicated that parents don’t know much about the test, what they would learn from the test.or even remember is tests were done. Currently, offering genetic testing to individuals with ASD is

inconsistent and as a result, confusing for parents. Families dealing with a diagnosis of ASD are already dealing with a lot of unknowns and face many challenges. Genetic evaluation and testing is unfortunately an additional confusing component of care for families who are already struggling.

Some providers feel that genetic testing for ASD moved from research into the clinical setting too quickly, while ACMG and other professional organizations are making recommendations to offer genetic testing to all patients with ASD and some providers are offering these tests routinely. Thus, although some providers characterize genetic testing for ASD as premature translation, others, including an influential professional organization, are committed to continuing this testing approach. Moving forward, there needs to be a way to assist families in negotiating the difficult terrain of an ASD diagnosis and the multitude of tests and services that are available. In this context, genetic testing for ASD should ideally be presented in a way that is transparent to families. The current complicated and fragmented approach to offering genetic evaluation and testing results in ambiguity and disparity with some families being offered services and not others, with little or no discussion about the options and pros and cons of testing.

The implications of this research are threefold. First, parents are likely to benefit from healthcare providers working cooperatively to address the gaps in evidence and differences of opinion, in order to create movement towards consensus. At this point creating a standard of care approach to testing for individuals with ASD seems unrealistic, given the genuine professional disagreements about test use. The first step towards a consensus development process would be to define the areas of agreement and disagreement. Current guidelines and consensus statements from ACMG and ISCA suggest that CMA should be offered to every individual who has been diagnosed with ASD, and other guidelines suggest that genetic counseling and/or genetic evaluation should be offered as well. However, a common sentiment from providers interviewed in my study was that if every individual with ASD was offered testing

and counseling, there would not be enough genetic counselors and geneticists to see these patients. One provider explained that healthcare providers involved in diagnosis of ASD include:

> "…psychiatrists, neurologists, developmental pediatricians and psychologists. So if you think about all of them and then the few geneticists that are available there's no way the geneticists can handle the workload that would be generated by all of those services making the diagnosis" (Provider #12).

I also heard repeatedly that there is no system in place for storing new or unusual findings, no infrastructure for storing data, and no system for follow up. Recommendations from one professional organization that are not fully consistent with other professional groups are not likely to lead to a consensus. If professional organizations could start by clarifying areas of agreement and disagreement this effort might help to define potential points of consensus, for example, agreement on which patients are most likely to benefit from genetic testing and which are least likely (together with a clarification on how benefit is defined). This sentiment is reflected in the conclusion of a study by Scherer and Dawson (2011):

> We need to walk cautiously down this accelerated translational pathway of genomic research into clinical benefit, mindful not just of what we know with some confidence, but also the limits of our knowledge and how to communicate this to the individuals with ASD and families who will be affected.

The second recommendation is for movement towards transparency when discussing genetic testing for ASD with families. The goal should be to develop readily accessible information sources that explain to parents the evolving nature of the testing technology with no standard of care at the present time. The information sources could summarize different professional recommendations in lay language and offer reasons to consider or not to pursue testing, emphasizing the importance of parents determining their preferences. This aligns with the conclusion by Chen et al in their 2013 study:

> As parents hold different attitudes, policymakers should thoroughly consider the perspectives of both parties when developing relevant regulations and recommendations. For example, should health-care providers recommend all parents with ASD children to take their affected children for such testing? How do we ensure that testing results will benefit the affected families without causing them further harm and/or burden?

Developing effective educational materials and talking points to disseminate to parents of children diagnosed with ASD about the pros and cons of testing would help parents make an informed decision. Providers need to work cooperatively to agree to be clear about what the issues are and why testing is an option or why it may not be an option. Providers interviewed in this study agree that genetic testing for ASD is complex and difficult to explain and they admit that they are not always fully invested in it. This needs to change and there needs to be a concerted effort to alleviate the confusion and help families. One provider stated:

> It's hard to explain it. It's hard as the provider to explain it in a way that makes sense to families I think. I think we don't do a good job explaining microarray and the reality is we're ambivalent as providers. (Provider #12)

Parents in my study repeatedly spoke about looking to their provider for direction, "her father and I aren't sure what to do so that's why we've been pursuing anything that [our doctor] thinks might be helpful." (Parent #2) Data from previous studies has shown that both parental and provider knowledge is lacking in terms of genetic services for individuals with ASD (Cuccaro et al., 2014). Developing an effective communication strategy that is clear and accessible should be a goal so that providers are trained and prepared to assist parents in decision making and so that all parents have the same opportunities, education, and choices.

The third recommendation for change is to conduct more research on the implications of universal testing among individuals with ASD. Currently, there is no research on the feasibility of universal testing, which is needed, especially given that the current health system is ill-prepared to follow the ACMG guidelines. The recent technical brief titled, "Genetic Testing for Developmental Disabilities, Intellectual Disability and Autism Spectrum Disorders" by the Agency for Healthcare Research and Quality (2014) was conducted to provide useful information for understanding the current landscape of genetic testing and identify evidence gaps in the hope of guiding future research for addressing genetic tests' clinical utility. This seems like a step in the right direction to determine exactly what changes need to be made, but

I suggest an even greater research focus on the impact testing has on families and how to best address the needs of families. Scherer and Dawson (2011) stated this same idea:

> There is a critical need for empiric study of the concerns and attitudes regarding genetic testing of persons with ASD and their families, its impact, and how persons with ASD and families understand and use this kind of information.

This research could inform training for professionals who order the tests and return results, inform insurance companies faced with determining test coverage, support creation of data storage systems for new, emerging and unusual findings, and contribute to the development of a protocol for follow up that minimizes the burden on the families.

The current pathways to genetic testing are inconsistent, sometimes costly and often confusing for parents. There is also an absence of systematic input from the community affected by ASD and of research about perspectives of various stakeholders (Walsh et al., 2011). ASD and genetic testing is a complex issue with these and other major challenges to overcome. In this study, I heard from many clinicians who have thoughts on ways to improve the system in order to make some of their hopes for the future a reality. However, these individuals with diverse backgrounds, thoughts, and feelings are not in conversation with each other. There is a need for professionals with diverse views to come together to discuss genetic testing and ASD, so that the promise of the future has a chance of becoming a reality. For now, finding a way to make the process transparent and easy for families to navigate is what would be most beneficial to parents and should be the focus of providers involved in the diagnosis, treatment, and care of individuals with ASD.

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